Increases in Cerebral Atherosclerosis According to $CHADS_2$ Scores in Patients With Stroke With Nonvalvular Atrial Fibrillation

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Background and Purpose—The $CHADS_2$ score is used for risk stratification of ischemic stroke in patients with nonvalvular atrial fibrillation and high $CHADS_2$ scores are associated with increased risk of stroke. Most components of the $CHADS_2$ score are also risk factors for atherosclerosis. Therefore, high $CHADS_2$ scores can be associated with concomitant cerebral atherosclerosis and subsequently atherothrombotic stroke. The aim of this study was to determine whether there are differences in the presence and burden of concomitant cerebral atherosclerosis according to $CHADS_2$ scores in patients with stroke with nonvalvular atrial fibrillation.

Methods—We included 780 consecutive patients with nonvalvular atrial fibrillation who had undergone angiographic studies at index stroke between August 1994 and March 2010 in the present study. We investigated the relationships between the $CHADS_2$ score and the presence, severity, and pattern of cerebral atherosclerosis and stroke mechanism.

Results—Of the 780 patients, concomitant arterial stenosis (≥50%) was found in 231 patients (29.6%). The number of arteries with atherosclerosis increased as the $CHADS_2$ score increased ($P<0.001$) as did the proportion of combined extracranial and intracranial atherosclerosis ($P<0.001$). Multivariate analyses showed that high risk based on the $CHADS_2$ score was an independent predictor of concomitant cerebral atherosclerosis (OR, 3.121; 95% CI, 1.770 to 5.504) and the presence of proximal stenosis at the symptomatic artery (OR, 3.043; 95% CI, 1.458 to 6.350).

Conclusions—The $CHADS_2$ score can predict the presence of concomitant cerebral artery atherosclerosis. Increased risk of stroke in patients with high $CHADS_2$ scores may be partly explained by increased frequency and burden of cerebral atherosclerosis. **(*Stroke*. 2011;42:930-934.)**

Key Words: atherosclerosis ■ atrial fibrillation ■ $CHADS_2$ score ■ stroke

Nonvalvular atrial fibrillation (NVAF) is a well-known risk factor of stroke, and maintaining an optimum intensity of anticoagulation is highly effective for stroke prevention.[1] However, serious bleeding complications, including intracerebral hemorrhage, are related to warfarin use,[2,3] which limits its routine use in patients with NVAF. Risk stratification schemes have been developed to identify patients with high risks for ischemic stroke or systemic embolic events and also to identify patients eligible for anticoagulation.[4,5]

Currently, the $CHADS_2$ index is widely used to stratify patients with NVAF who are eligible for anticoagulation. Increases in $CHADS_2$ scores are associated with worsening intracardiac thrombogenic conditions and increased risk of embolic events.[6,7] However, it is also possible that increased risk of stroke with high $CHADS_2$ scores is caused by atherothrombotic mechanisms as well as cardioembolic mechanisms, because most components of the $CHADS_2$ score are also risk factors for atherosclerosis. Although previous studies indicated that approximately 20% to 50% of patients with NVAF have severe stenotic lesions at the carotid artery,[8–10] few data are available regarding the relationship between the presence of cerebral atherosclerosis in the entire cerebral arterial beds and the $CHADS_2$ score.

The aim of this study was to investigate whether there are differences in atherosclerotic burden in cerebral arterial beds according to risk levels based on $CHADS_2$ scores and to assess the relationship between $CHADS_2$ scores and stroke mechanisms.

Methods

Study Sample

Between August 1994 and March 2010, a total of 6059 consecutive patients with acute brain infarction or transient ischemic attack within 7 days after symptom onset were admitted to our hospital and

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registered to the Yonsei Stroke Registry. During admission, all patients were thoroughly investigated for demographic data, medical history, vascular risk factors, and clinical manifestations.[11] They all underwent brain CT and/or MRI, 12-lead electrocardiography, and standard blood tests. The presence of cerebral atherosclerosis was investigated by digital subtraction angiography, MR angiography (MRA), or CT angiography (CTA) during hospitalization. Stroke subtypes and the presence of any abnormalities on angiographic studies were determined prospectively at a weekly stroke conference based on neuroradiologist reports and consensus of stroke specialists and were entered into the stroke registry.[11] This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, and the requirement for informed consent was waived.

Among 6059 patients, we excluded patients without atrial fibrillation (n=4995) or those with atrial fibrillation and valvular heart disease (n=144). For analyses of concomitant cerebral atherosclerosis, 140 patients who had not undergone angiographic studies were further excluded. The final study sample consisted of a total of 780 patients with NVAF.

Clinical Variables

The CHADS$_2$ score was calculated for each patient with 1 point assigned to patients with a history of congestive heart failure, hypertension, age ≥75 years, or diabetes mellitus and 2 points for a history of stroke or transient ischemic attack. For this study, the CHADS$_2$ score was based on the previous diagnosis or clinical history before the index stroke. The study sample was divided into 3 groups: low risk (CHADS$_2$ score of 0), moderate risk (CHADS$_2$ score of 1 or 2), and high risk (CHADS$_2$ score of 3 to 6) based on previous studies.[4,5]

The complete history of medication before admission was available for 697 patients. Information regarding prior use of antithrombotics, statins, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers was collected. Data for the international normalized ratio at admission, smoking history, history of ischemic heart disease, and hypercholesterolemia were also collected.

Concomitant Cerebral Atherosclerosis

The presence of steno-occlusive lesions of the cerebral artery was investigated using the results of digital subtraction angiography in 265 (34.0%) patients, contrast-enhanced MRA in 386 (49.5%) patients, and CTA in 129 (16.5%) patients among 780 patients enrolled. Arterial stenosis was identified when the degree of stenosis was ≥50% based on the North American Symptomatic Carotid Endarterectomy Trial[12] or Warfarin versus Aspirin for Symptomatic Intracranial Disease method.[13] The presence of arterial stenotic lesions was determined for each arterial segment, including the extracranial or intracranial internal carotid artery, the anterior cerebral artery, the middle cerebral artery, the extracranial or intracranial vertebral artery, and the posterior cerebral artery on each side as well as the basilar artery. When multiple stenotic lesions were observed in 1 arterial segment, data from the most severe stenotic lesion were used. In patients with data for both digital subtraction angiography and contrast-enhanced MRA or CTA, the results of digital subtraction angiography were used for analysis, and in patients with data for both contrast-enhanced MRA and CTA, the results of CTA were used for analysis.

For the analysis of concomitant cerebral atherosclerosis, we included only steno-occlusive lesions after excluding symptomatic arterial lesions to infracted areas. However, if a patient had a stenotic lesion at the proximal carotid bulb or the orifice of the vertebral artery, this lesion was considered the concomitant cerebral atherosclerotic lesion. Likewise, in cases with tandem stenotic lesions (distal and proximal steno-occlusive lesions), we considered only the proximal arterial lesion to be a concomitant cerebral atherosclerotic lesion. After exclusion of the symptomatic arterial lesions, the stenotic lesions were divided into isolated extracranial, isolated intracranial, and combined extracranial and intracranial lesions. The total number of stenotic arterial lesions was also calculated.

Table 1. Baseline Characteristics of the Study Sample

Characteristics	Numbers or Means
Age, years	69.5±10.5
Sex, male	446 (57.2)
Paroxysmal atrial fibrillation	101 (12.9)
Congestive heart failure	137 (17.6)
Hypertension	569 (72.9)
Age ≥75 years	252 (32.3)
Diabetes mellitus	186 (23.8)
Hypercholesterolemia	73 (9.4)
Previous ischemic stroke or transient ischemic attack	128 (16.4)
Smoking	
Current smoker	102 (13.1)
Exsmoker	136 (17.4)
Previous ischemic heart disease	141 (18.1)
CHADS$_2$ score	
0	104 (13.3)
1	243 (31.2)
2	231 (29.6)
3	133 (17.1)
4	51 (6.5)
5	16 (2.1)
6	2 (0.3)
Prior medication*	
Antiplatelet	291 (41.8)
Anticoagulant	144 (20.7)
Statin	120 (17.2)
Angiotensin-converting enzyme inhibitor	91 (13.1)
Angiotensin receptor blocker	151 (21.7)

Data are given as the no. (percentage) or mean±SD.

*Data were analyzed for 697 patients whose complete medication history was obtainable.

Statistical Analyses

Statistical analyses were performed using the Windows SPSS software package (Version 18.0; Chicago, IL). Continuous variables were compared with independent sample *t* tests, Mann-Whitney *U* tests, Kruskal-Wallis tests, or analysis of variance, and categorical variables with χ^2 tests, as appropriate. Post hoc analyses were conducted with the Scheffe test. The increasing proportions of clinical variables according to the CHADS$_2$ score were compared using the Mantel-Haenszel test. The relationship between numbers of lesions and CHADS$_2$ scores was determined by Spearman rank test. Multivariate logistic analysis was used to compute the ORs of covariates, including the CHADS$_2$ score, when determining independent factors predicting concomitant cerebral atherosclerosis or the presence of proximal arterial stenosis.

Results

The baseline characteristics of the 780 patients enrolled in this study are provided in Table 1. Among 697 patients for whom a complete medication history was obtainable, warfarin use with optimum intensity (international normalized ratio, 2 to 3) was observed in only 32 patients (4.6%). According to CHADS$_2$ scores, there was an increasing trend of having the components of the CHADS$_2$ index ($P<0.001$) and receiving prior cardiovascular medications, except for anticoagulants.

Table 2. The Distribution of Cerebral Arterial Lesion

Arterial Segment	Arterial Steno-Occlusive Lesion	
	Nonsymptomatic Arterial Lesion	All Arterial Lesion
Extracranial internal carotid artery	56 (7.2)	95 (12.2)
Intracranial internal carotid artery	21 (2.7)	45 (5.8)
Anterior cerebral artery	35 (4.5)	47 (6.0)
Middle cerebral artery	57 (7.3)	237 (30.4)
Extracranial vertebral artery	76 (9.7)	86 (11.0)
Intracranial vertebral artery	34 (4.4)	47 (6.0)
Basilar artery	13 (1.7)	38 (4.9)
Posterior cerebral artery	50 (6.4)	76 (9.7)

Data are given as the no. (percentage).

Concomitant Cerebral Atherosclerosis According to the $CHADS_2$ Score

In total, 231 patients (29.6%) were found to have atherosclerosis (≥50%) in ≥1 arteries at any cerebral arterial bed. Among these, isolated intracranial stenosis (47.6% [110 of 231]) was the most commonly involved location followed by isolated extracranial stenosis (33.8% [78 of 231]) and combined extracranial and intracranial stenosis (18.6% [43 of 232]). If we included all steno-occlusive lesions with the baseline angiographic studies, involvement of the middle cerebral artery was most common. However, after exclusion of the symptomatic arterial lesion, the extracranial vertebral artery was the most common artery involved followed by the middle cerebral artery and the extracranial internal carotid artery (Table 2).

There was a positive correlation between the $CHADS_2$ score and the number of arteries affected by concomitant cerebral atherosclerosis (r=0.187, P<0.001). The burden of the concomitant cerebral atherosclerosis increased in an incremental fashion according to the $CHADS_2$ score when the number of stenotic arteries was divided into 4 groups such as 0, 1, 2, 3, or ≥4 (P<0.001; Figure A). An increasing tendency for concomitant cerebral atherosclerosis was observed in all cerebral arterial beds as the $CHADS_2$ score increased (Figure B). Concomitant cerebral atherosclerosis was observed in 20 patients (19.2%) in the low-risk group, 128 (27.0%) in the moderate-risk group, and 83 (41.1%) in the high-risk group. In particular, the proportion of combined extracranial and intracranial stenoses was relatively larger in the high-risk group than in the low- or moderate-risk group (Figure B).

The factors related to concomitant cerebral atherosclerosis were determined. Univariate analysis identified age (71.7±10.4 years with atherosclerosis versus 68.6±10.5 years without, P<0.001), hypertension (P<0.001), diabetes mellitus (P=0.017), and previous stroke or transient ischemic attack (P=0.019) along with belonging to the high-risk group (P<0.001) were associated with the presence of concomitant cerebral atherosclerosis. Multivariate logistic regression analysis revealed that belonging to the high-risk group with $CHADS_2$ scores of 3 to 6 was a significant and independent predictor for concomitant cerebral atherosclerosis (Table 3). Among components of the $CHADS_2$ score, hypertension, age ≥75 years, and previous ischemic stroke were determinants of cerebral atherosclerosis in patients with NVAF. When we further analyzed the data of digital subtraction angiography only, the high-risk group was also an independent and significant predictor for concomitant cerebral atherosclerosis (Supplemental Table I, http://stroke.ahajournals.org).

Stroke Mechanism According to the $CHADS_2$ Score

Of 780 patients, 21 patients had transient ischemic attack without a relevant acute ischemic lesion on brain imaging studies. The stroke mechanism was investigated in 759 patients who had neurological symptoms and clinically relevant ischemic lesions on brain imaging.

In this sample, 128 patients (16.9%) had a proximal stenotic lesion at the symptomatic artery, which suggests that the atherothrombotic mechanism could be a possible cause of ischemic stroke. Proximal atherosclerotic lesions were most frequently found in the high-risk group (24.0% [46 of 192]) followed by the moderate-risk (15.5% [72 of 465]) and low-risk groups (9.8% [10 of 102]), and these differences were significant (P=0.001). Among components of the $CHADS_2$ score, hypertension (P<0.001) and previous ischemic stroke (P=0.001) were associated with the presence of proximal atherosclerotic lesions. Other variables including age ≥75 years, diabetes mellitus, smoking, hyperlipidemia, previous ischemic heart disease, and prior medication before

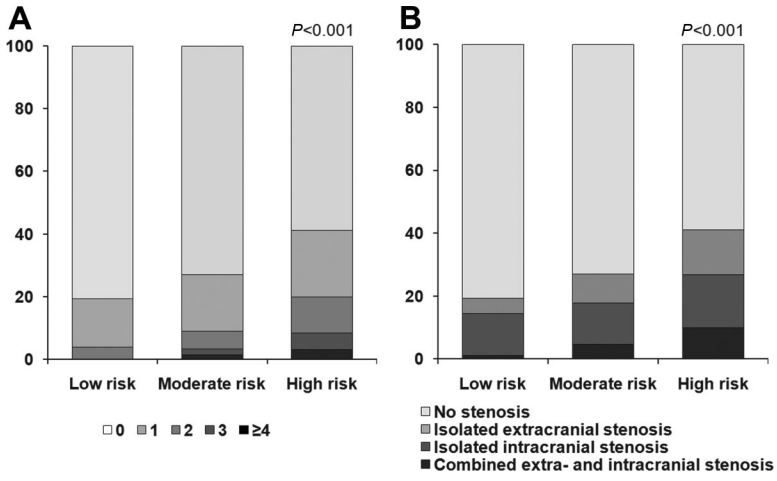

Figure. The increasing trend of cerebral atherosclerosis according to the risk level based on the $CHADS_2$ score. A, Total number of the atherosclerotic lesions; (B) distribution of cerebral atherosclerosis.

Table 3. Multivariate Analysis Regarding Concomitant Cerebral Atherosclerosis

	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	1.416 (1.027–1.951)	0.034	1.558 (1.117–2.173)	0.009
CHADS$_2$ score				
Low risk, 0	Reference		. . .	. . .
Moderate risk, 1–2	1.625 (0.956–2.764)	0.073	. . .	. . .
High risk, 3–6	3.121 (1.770–5.504)	<0.001	. . .	. . .
CHADS$_2$ score component				
Hypertension	. . .	. . .	1.859 (1.254–2.755)	0.002
Age ≥75 years	. . .	. . .	1.990 (1.419–2.791)	<0.001
Diabetes mellitus	. . .	. . .	1.423 (0.994–2.036)	0.054
Previous ischemic stroke before index stroke	. . .	. . .	1.527 (1.017–2.294)	0.041

the stroke were not significant determinants in univariate analysis. Multivariate analysis revealed that high risk based on the CHADS$_2$ score was associated with the presence of proximal arterial stenosis compared with the low-risk group. Among components of the CHADS$_2$ score, hypertension and previous ischemic stroke were significant predictors of proximal atherosclerotic lesions (Table 4).

Discussion

We have demonstrated that cerebral atherosclerosis is more common in patients with higher CHADS$_2$ scores and that these patients also have higher risks of atherothrombotic stroke as well as cardioembolic stroke.

In our study sample, approximately one third of the patients demonstrated significant atherosclerotic lesions in the cerebral artery other than the steno-occlusive lesion in the symptomatic arteries. The frequency and burden of cerebral atherosclerosis increased with increases in the CHADS$_2$ score. Among components of the CHADS$_2$ score, older age, hypertension, diabetes, and previous ischemic stroke are well-known vascular risk factors for atherosclerosis and first-ever or recurrent ischemic stroke. The frequency or burden of cerebral atherosclerosis escalates with increasing numbers of vascular risk factors,[14] and such increases may also occur in patients with NVAF. Along with the known contributory roles of the components of the CHADS$_2$ score on atherosclerosis, our findings indicate that the risk of cerebral atherosclerosis increases as the CHADS$_2$ score increases.

A previous study showed that the frequency of the left atrial or left atrial appendage thrombus increased with the ascending CHADS$_2$ score, which suggests that the components of the CHADS$_2$ score may enhance the thrombogenic milieu in the intracardiac chamber.[6,7] Such changes in the intracardiac chamber may increase the risk of cardioembolism. However, the risk of atherothrombotic stroke in patients with NVAF may also increase in patients with higher CHADS$_2$ scores. In patients with NVAF, not only cardioembolic, but also noncardioembolic ischemic stroke can occur.[9,15] In our study, patients included in the high-risk group more frequently had combined extracranial and intracranial stenosis and proximal stenotic lesions of the symptomatic artery. The incidence of ischemic and total cerebrovascular events was greater in patients with combined extracranial and intracranial stenosis than in patients with only isolated extracranial or intracranial stenosis.[14] Given that artery-to-artery embolism from the proximal atherosclerotic plaques is the main stroke mechanism in atherothrombotic stroke,[9] the proximal arterial lesions may actually cause stroke in some patients with NVAF. In this regard, increased risk of stroke in patients with higher CHADS$_2$ scores may be associated with increased risk of atherothrombotic stroke in addition to preexisting atrial fibrillation-related risk of cardioembolic stroke.

Patients with higher CHADS$_2$ score may require additional measures for prevention of ischemic stroke because concomitant cerebral atherosclerosis was frequent in those groups. The measures may include combined use of an antiplatelet

Table 4. Multivariate Analysis Regarding the Presence of Proximal Arterial Stenosis

	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	1.339 (0.903–1.987)	0.146	1.390 (0.926–2.085)	0.112
CHADS$_2$ score				
Low risk, 0	Reference		. . .	. . .
Moderate risk, 1–2	1.747 (0.866–3.524)	0.119	. . .	. . .
High risk, 3–6	3.043 (1.458–6.350)	0.003	. . .	. . .
CHADS$_2$ score component				
Hypertension	. . .	. . .	3.043 (1.720–5.382)	<0.001
Age ≥75 years	. . .	. . .	1.392 (0.922–2.102)	0.115
Previous ischemic stroke before index stroke	. . .	. . .	1.930 (1.213–3.070)	0.005

drug and warfarin as well as strict risk factor controls. However, in case of combined use of an anticoagulant and antiplatelet drugs, increased risks of hemorrhagic complications also should be considered, in particular in Asian patients who are vulnerable to intracranial hemorrhage. Alternatively, combined use of antiplatelet agents and a direct thrombin inhibitor, 110 mg Dabigatran, which had less hemorrhagic complications than warfarin,[16] or closure of the left atrial appendage may be considered.

There are some limitations in this study. First, this is a retrospective study and angiographic results with various modalities were used for the investigation of cerebral arterial stenosis. Although contrast-enhanced MRA had higher sensitivity than other imaging modalities such as CTA or MRA,[17,18] Contrast-enhanced MRA also might produce an artifactual overestimation of arterial stenosis in some patients.[19] Second, in our study, stenotic lesions were more common in the intracranial artery than in the extracranial artery, possibly due to ethnic characteristics. Intracranial atherosclerosis, especially isolated intracranial artery stenosis, is more common in East Asians than in Westerners.[20–23] Stenosis or occlusion of the symptomatic intracranial artery can be either due to embolism from the heart or in situ thrombosis/arterial embolism from the atherosclerotic lesion. These lesions often cannot be differentiated on angiographic studies. Therefore, steno-occlusion of the symptomatic intracranial artery was not considered as an atherosclerotic lesion in our analysis. This definition in our study might lead to an underestimation of the frequency of intracranial artery atherosclerosis and the atherothrombotic mechanism attributed to intracranial artery atherosclerosis.

Conclusions

The results of our study suggest that the presence and burden of cerebral atherosclerosis can be predicted by $CHADS_2$ scores. Our findings also suggest that atherothrombosis should be considered to be a potential stroke mechanism in patients with high $CHADS_2$ scores. Approximately 40% of high-risk patients ($CHADS_2$ score ≥ 3) have significant stenosis of the large artery that may necessitate interventional treatment in some patients for improved stroke prevention. These patients may also require additional antithrombotic treatment. In this regard, strict evaluation of cerebral atherosclerosis should be considered in patients with higher $CHADS_2$ scores.

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Disclosures

None.

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Supplemental material

Supplemental table. Multivariate analysis regarding concomitant cerebral atherosclerosis with the data of DSA

	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Male sex	1.268 (0.716 - 2.245)	0.416	1.292 (0.730 -2.286)	0.380
$CHADS_2$ score				
Low risk (0)	reference		-	-
Moderate risk (1-2)	0.805 (0.368 - 1.762)	0.588	-	-
High risk (3-6)	2.703 (1.140 - 6.410)	0.024	-	-
$CHADS_2$ score component				
Age ≥75	-	-	1.311 (0.696 - 2.472)	0.402
Diabetes	-	-	1.869 (1.002 - 3.486)	0.049
Previous ischemic stroke before index stroke	-	-	2.231 (1.111 - 4.481)	0.024

Original Contributions

非瓣膜性心房颤动卒中患者的 $CHADS_2$ 评分增加伴脑动脉粥样硬化的增加

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背景及目的：$CHADS_2$ 评分用于非瓣膜性心房颤动患者的缺血性卒中危险分层，较高的 $CHADS_2$ 分数与卒中风险增加相关。$CHADS_2$ 评分的大部分组成部分也是动脉粥样硬化的危险因素。因此，较高的 $CHADS_2$ 分数与脑动脉粥样硬化及相应的动脉粥样硬化血栓形成性卒中有关。本研究目的是了解不同 $CHADS_2$ 评分的非瓣膜性心房颤动卒中患者的脑动脉粥样硬化患病及严重程度是否有所不同。

方法：本研究包括 1994 年 8 月至 2010 年 3 月的 780 例连续的、接受血管造影检查的非瓣膜性心房颤动卒中患者。分析 $CHADS_2$ 评分与脑动脉粥样硬化的患病、严重程度、类型以及卒中发生机制的关系。

结果：780 例患者中，发现 231 例 (29.6%) 合并动脉狭窄 ($\geq$50%)。动脉粥样硬化的动脉数量随 $CHADS_2$ 分数增加而增加 (P<0.001)，颅内和颅外动脉粥样硬化的比例亦随评分增加而增加 (P<0.001)。多变量分析表明，基于 $CHADS_2$ 评分的高风险也是脑动脉粥样硬化 (OR，3.121；95% CI，1.770-5.504) 及症状相关动脉近端狭窄 (OR，3.043；95% CI，1.458-6.350) 的独立预测因素。

结论：$CHADS_2$ 评分可以预测脑动脉粥样硬化的存在。高 $CHADS_2$ 评分患者的高卒中风险可能部分原因是脑动脉粥样硬化的发生和严重程度增加。

关键词：动脉粥样硬化，房颤，$CHADS_2$ 评分，卒中

(*Stroke*. 2011;42:930-934.　上海交通大学医学院附属仁济医院神经科　余寿芬 译　李焰生 校)

非瓣膜性心房颤动 (NVAF) 是一个公认的卒中危险因素，持续有效的抗凝治疗对于预防卒中是非常有效的[1]。但是，华法林的使用可能导致颅内出血[2,3]等严重出血并发症，因而限制了其在 NVAF 患者中的常规治疗。建立危险分层方案，可以筛查缺血性卒中以及全身栓塞事件的高危患者，同时也可以决定是否需要抗凝治疗[4,5]。

目前 $CHADS_2$ 评分被广泛用于需要抗凝治疗的 NVAF 患者的危险分层。高 $CHADS_2$ 评分与心脏内血栓形成以及栓塞事件风险增加有关[6,7]。然而，因为 $CHADS_2$ 评分的大部分也是动脉粥样硬化的危险因素，高 $CHADS_2$ 评分之所以意味着卒中风险增加，可能与心源性栓塞的发生机制及动脉粥样硬化血栓形成机制相关。尽管早先已有很多研究表明大约 20% 至 50% 的 NVAF 患者存在严重的颈动脉狭窄[8-10]，然而关于整个大脑动脉床的动脉粥样硬化与 $CHADS_2$ 评分关系的数据却很少。

本研究目的是研究根据 $CHADS_2$ 评分所划分的不同风险水平者的大脑动脉床的动脉粥样硬化程度存在差异，同时评价 $CHADS_2$ 评分与卒中机制的关系。

方法

研究样本

收集 1994 年 8 月至 2010 年 3 月在我院住院治疗同时在 Yonsei 卒中登记中心 (Yonsei Stroke Registry) 登记的发病 7 天内的急性脑梗死或短暂性脑缺血

From the Departments of Neurology (Y.D.K., M.J.C., J.K., D.H.L., H.S.N., J.H.H.) and Preventive Medicine (H.S.L., C.M.N.), Yonsei University College of Medicine, Seoul, Korea.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.602987/DC1.

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发作 (TIA) 病例，共 6059 例。在住院期间，所有患者均彻底调查了人口学数据、病史记录、血管危险因素和临床表现 [11]，均接受头颅 CT 和 (或)MRI、12 导联心电图和标准的血液检验。住院期间，经数字减影血管造影 (DSA)、MR 血管成像 (MRA)、CT 血管成像 (CTA) 来检查大脑的动脉粥样硬化。卒中的亚型和血管影像检查的异常，均由神经影像学专家和卒中专家在每周的例会中提前决定，并在卒中注册表登记 [11]。这项研究通过了 Yonsei 大学卫生系 Severance 医院的伦理审查委员会的核准，并获得知情同意。

在 6059 名患者中，我们排除了非心房颤动者 (n=4995) 和合并瓣膜性心脏病者 (n=144)。为了分析大脑动脉粥样硬化，另外排除了 140 例没有行血管影像检查的患者。最终的研究样本包括 780 例 NVAF 患者。

临床变量

使用 CHADS$_2$ 评分评价每一位患者，评分中充血性心力衰竭、高血压病、年龄 ≥75 岁、糖尿病各记 1 分，既往卒中或 TIA 史记 2 分。在本研究中，CHADS$_2$ 评分是基于卒中发病前的诊断和临床病史。根据先前的研究方法，分研究样本为低危组 (CHADS$_2$ 评分 0 分)、中危组 (CHADS$_2$ 评分 1-2 分)、高危组 (CHADS$_2$ 评分 3-6 分)[4,5]。

有 697 例患者有完整的住院前的药物治疗史。收集既往使用抗栓药、他汀类药、血管紧张素转换酶抑制剂 (ACEI) 和血管紧张素受体阻滞剂 (ARB) 的信息。还收集入院时的国际标准化比率 (INR)、吸烟史、缺血性心脏病及高胆固醇血症的信息。

并存的脑动脉粥样硬化

在纳入的 780 例患者中，有 265 例患者 (34.0%) 的大脑动脉狭窄或闭塞是通过 DSA 来检查，386 例患者 (49.5%) 通过增强 MRA、129 例患者 (16.5%) 通过 CTA。根据北美症状性颈动脉内膜剥离术试验研究 (NASCET)[12] 和华法林对比阿司匹林治疗症状性脑血管疾病的临床试验 (WASID)[13]，动脉狭窄是指动脉狭窄程度 ≥50%。分析每一个动脉节段的狭窄病变情况，包括两侧颈内动脉的颅内段和颅外段、大脑前动脉、大脑中动脉、椎动脉的颅内段和颅外段、大脑后动脉和基底动脉。当某一动脉节段内有多个狭窄时，选用最严重者。当同时有 DSA、增强 MRA 或 CTA 检查时，选用 DSA 的结果。当同时有增强 MRA 和 CTA 时，选用 CTA 的结果。

表 1 研究样本的基线特征

特征	数目或均数
年龄，岁	69.5 ± 10.5
性别，男性	446 (57.2)
阵发性房颤	101 (12.9)
充血性心力衰竭	137 (17.6)
高血压	569 (72.9)
年龄≥ 75 岁	252 (32.3)
糖尿病	186 (23.8)
高胆固醇血症	73 (9.4)
既往缺血性卒中或短暂性脑缺血发作	128 (16.4)
吸烟	
目前吸烟	102 (13.1)
既往吸烟	136 (17.4)
既往缺血性心脏疾病	141 (18.1)
CHADS$_2$ 评分	
0	104 (13.3)
1	243 (31.2)
2	231 (29.6)
3	133 (17.1)
4	51 (6.5)
5	16 (2.1)
6	2 (0.3)
既往用药史 *	
抗血小板药物	291 (41.8)
抗凝药物	144 (20.7)
他汀类	120 (17.2)
ACEI	91 (13.1)
ARB	151 (21.7)

通过数目 (百分比) 或均数 ± 标准差给出数据。

* 对 697 例有完整的住院前药物治疗病史的患者进行的数据分析。

为分析共存的大脑动脉粥样硬化，在剔除了与梗死区域相关的症状性动脉狭窄病变后，选择狭窄 - 闭塞动脉。但当颈动脉球部近端或椎动脉开口处处在狭窄性病变，则该种病变也作为共存的大脑动脉粥样硬化。同理，在串联的狭窄病变中 (远端和近端狭窄性病变)，只认定近端的狭窄病变为大脑动脉粥样硬化病变。在排除了症状性动脉病变后，将狭窄病变分为孤立的颅外病变、孤立的颅内病变及颅内外合并病变。我们还统计了动脉狭窄病变的总数。

统计分析

数据统计分析采用 Windows SPSS 软件包 (18.0 版 ; Chicago，IL) 进行分析。连续变量采用独立样本的 *t* 检验、Mann-Whitney *U* 检验、Kruskal-Wallis 检验或方差分析。分类变量采用卡方检验。用 Scheffe 检验进行事后 (post hoc) 分析。用 Mantel-Haenszel 检验比较依据 CHADS$_2$ 评分所得的临床变量比例的增加。病变数量与 CHADS$_2$ 评分的关系用 Spearman

表 2 脑动脉病变的分布

	动脉狭窄 - 闭塞病变	
动脉节段	非症状性动脉病变	所有动脉病变
颈内动脉颅外段	56(7.2)	95(12.2)
颈内动脉颅内段	21(2.7)	45(5.8)
大脑前动脉	35(4.5)	47(6.0)
大脑中动脉	57(7.3)	237(30.4)
椎动脉颅外段	76(9.7)	86(11.0)
椎动脉颅内段	34(4.4)	47(6.0)
基底动脉	13(1.7)	38(4.9)
大脑后动脉	50(6.4)	76(9.7)

通过数目 (百分比) 给出数据。

等级检验分析。多变量的 logistic 回归分析是用来计算协变量的比值比 (ORs)，例如分析 $CHADS_2$ 评分是否为大脑动脉粥样硬化或近端动脉狭窄的的独立预测因素。

结果

研究纳入的 780 例患者的基本特点见表 1。在 697 例有完整用药史的患者中，恰当使用华法林 (INR 在 2-3) 者仅 32 例 (4.6%)。根据 $CHADS_2$ 评分，$CHADS_2$ 评分的增加与既往使用心血管药物治疗相关，但不含抗凝药物 (P<0.001)。

不同$CHADS_2$评分的共存的脑动脉粥样硬化

231 例患者 (29.6%) 在脑血管床中至少存在 1 处动脉粥样硬化 (≥50%)。其中，最常见者为孤立的颅内动脉狭窄 (47.6%，110/231)，其次是孤立的颅外动脉狭窄 (33.8%，78/232)，最后是颅内外合并动脉狭窄 (18.6%，43/232)。如果总括血管造影提示的所有狭窄 - 闭塞病灶，则大脑中动脉的病变最为常见。然而，在排除了症状相关的动脉病变后，则最常见的是椎动脉颅外段，其次是大脑中动脉和颈内动脉颅外段 (见表 2)。

$CHADS_2$ 评分与动脉粥样硬化性血管的数量呈正相关 (r=0.187，P<0.001)。当把狭窄动脉数量分为 0、1、2、3 或 ≥4 后，随着 $CHADS_2$ 评分的增加，脑动脉粥样硬化的程度也以渐进的方式增加 (P<0.001，图 A)。随 $CHADS_2$ 评分增高，脑动脉床共存脑动脉粥样硬化的倾向明显 (图 B)。在低危、中危和高危患者组中，分别有 20 例 (19.2%)、128 例 (27%) 和 83 例 (41.1%) 患者共存脑动脉粥样硬化。高危组有颅内外动脉合并狭窄的比例远高于低 - 中危组 (图 B)。

研究确定了与共存脑动脉粥样硬化相关的危险因素。单变量分析发现，与脑动脉粥样硬化相关的有年龄 (有动脉粥样硬化者 71.7±10.4 岁，不伴动脉粥样硬化者 68.6±10.5 岁，P<0.001)、高血压 (P<0.001)、糖尿病 (P=0.017)、既往卒中或 TIA(P=0.019)、高风险者 (P<0.001)。多变量 logistic 回归分析提示，$CHADS_2$ 评分 3-6 分的高危者是共存脑动脉粥样硬化的显著的独立预测因子 (表 3)。在 $CHADS_2$ 评分组成部分中，高血压、年龄 ≥75 岁、缺血性卒中病史是 NVAF 患者共存脑动脉粥样硬化的决定因素。仅对 DSA 的数据进行分析，发现高危组也是共存脑动脉粥样硬化的显著和独立的预测因子。

按照$CHADS_2$评分的卒中发生机制

780 例患者中，21 例患者为 TIA，其脑部影像学检查没有相关的急性脑缺血损伤。针对 759 例存在神经系统症状同时影像检查显示有临床相关的缺血损伤病灶的患者，研究其卒中发生机制。

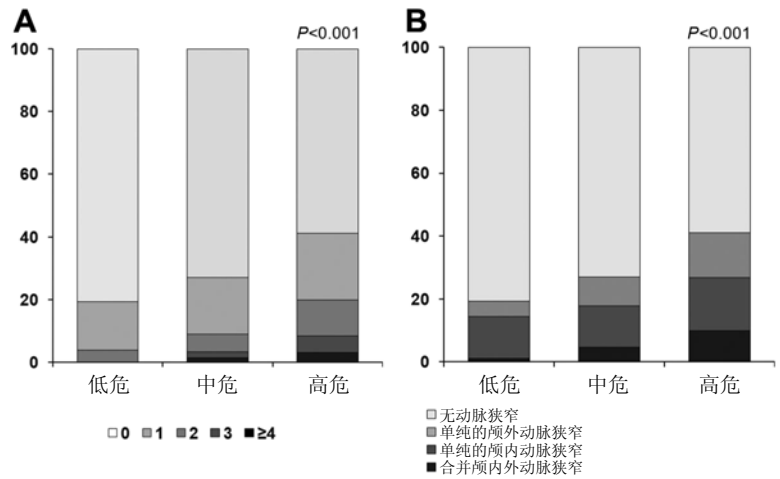

图 依据 $CHADS_2$ 评分确定的风险分层后的脑动脉粥样硬化增加趋势。(A) 动脉粥样硬化性病变的总数; (B) 脑动脉粥样硬化的分布。

表 3 关于共存脑动脉粥样硬化的多变量分析

	OR(95% CI)	*P*	OR(95% CI)	*P*
男性	1.416(1.027-1.951)	0.034	1.558(1.117-2.173)	0.009
CHADS$_2$ 评分				
低危，0	参考		…	…
中危，1-2	1.625(0.956-2.764)	0.073	…	…
高危，3-6	3.121(1.770-5.504)	<0.001	…	…
CHADS$_2$ 评分成分				
高血压	…	…	1.859(1.254-2.755)	0.002
年龄 ≥75 岁	…	…	1.990(1.419-2.791)	<0.001
糖尿病	…	…	1.423(0.994-2.036)	0.054
既往缺血性卒中	…	…	1.527(1.017-2.294)	0.041

该样本中，128 例患者 (16.9%) 有症状相关动脉的近端狭窄，提示动脉粥样硬化血栓形成可能是缺血性卒中的发病机制。近端动脉粥样硬化最多见于高危患者 (24%，72/465)，其次是中危患者 (15.5%，72/465) 和低危患者 (9.8%，10/102)，差异有统计学意义 (*P*=0.001)。在 CHADS$_2$ 评分组成部分中，高血压 (*P*<0.001) 和缺血性卒中史 (*P*=0.001) 与近端动脉粥样硬化病变相关。单变量分析中，年龄 ≥75 岁、糖尿病、吸烟、高脂血症、缺血性心脏病史及卒中前相关药物治疗与动脉粥样硬化没有相关性。多变量分析提示，基于 CHADS$_2$ 评分的高危者较低危者与近端动脉狭窄相关。在 CHADS$_2$ 评分组成成分中，高血压和缺血性卒中史可以预测近端动脉粥样硬化。

讨论

我们证实高 CHADS$_2$ 评分的患者更易有脑动脉粥样硬化，故这些患者发生动脉粥样硬化性血栓形成性卒中和心源性栓塞性卒中的风险均高。

本研究样本中，近 1/3 的患者存在症状相关的动脉的狭窄闭塞之外的脑动脉粥样硬化。脑动脉粥样硬化发生和严重程度随 CHADS$_2$ 评分增高而升高。CHADS$_2$ 评分中的增龄、高血压、糖尿病和既往缺血性卒中是动脉粥样硬化以及首发或再发缺血性卒中的血管危险因素。脑动脉粥样硬化的频率及严重程度随血管危险因素数目的增加而增加 [14]，这也同样见于 NVAF 患者。除 CHADS$_2$ 评分中各危险因素对动脉粥样硬化有影响外，我们证实脑动脉粥样硬化的风险随 CHADS$_2$ 评分增高而增高。

过去的一项研究显示，左房和心房心耳中的附壁血栓的频率随 CHADS$_2$ 评分增加而增加，提示 CHADS$_2$ 评分的组成成分促进了心腔内的血栓形成 [6,7]。心腔的这些改变会增加心源性栓塞的风险。然而，CHADS$_2$ 评分愈高，NVAF 患者发生动脉粥样硬化性血栓形成性卒中的风险也愈高。NVAF 患者不仅可以发生心源性栓塞性卒中，也可以发生非心源性栓塞性缺血性卒中 [9,15]。在本研究中，高风险组患者更易有颅内外血管合并及症状相关动脉的近端狭窄。与孤立的颅内或颅外血管狭窄相比，颅内外血管合并狭窄的患者更易发生缺血性和总的脑血管事件 [14]。鉴于动脉粥样硬化血栓形成性卒中的主要发病机制是近端动脉粥样硬化斑块所致的动脉 - 动脉栓塞 [9]，近端动脉病变确实可以导致部分 NVAF 患者的卒中发生。因此，高 CHADS$_2$ 评分所致的卒中风险增加，可能与动脉粥样硬化血栓形成性卒中及心源性栓塞性卒中的风险增加有关。

高 CHADS$_2$ 评分患者易合并脑动脉粥样硬化，

表 4 关于近端动脉狭窄的多变量分析

	OR(95% CI)	*P*	OR(95% CI)	*P*
男性	1.339(0.903-1.987)	0.146	1.390(0.926-2.085)	0.112
CHADS$_2$ 评分				
低危，0	参考		…	…
中危，1-2	1.747(0.866-3.524)	0.119	…	…
高危，3-6	3.043(1.458-6.350)	0.003	…	…
CHADS$_2$ 评分成分				
高血压	…	…	3.043(1.720-5.382)	<0.001
年龄 ≥75 岁	…	…	1.392(0.922-2.102)	0.115
既往缺血性卒中	…	…	1.930(1.213-3.070)	0.005

故需增加其他的措施来预防缺血性卒中。这些措施包括联合应用抗血小板药物和华法林及严格控制危险因素。然而，联合应用抗凝药物和抗血小板药物会增加出血性并发症的风险，尤其是亚洲人群更易发生颅内出血。另一种方法是可以考虑联合应用抗血小板药物和直接的凝血酶抑制剂 (达比加群 110 mg) 以相对减少出血性并发症 [16]，也可考虑关闭左心耳。

本研究有一些不足。第一，这是一项回顾性研究，而且采用不同血管造影技术检查脑动脉狭窄。尽管与 CTA 或 MRA 相比，增强 MRA 敏感性更高 [17,18]，但在一些患者中，增强 MRA 可能高估了动脉狭窄 [19]。第二，本研究中，狭窄性病变在颅内动脉较颅外动脉多见，这点可能与种族有关。相对于西方人，颅内动脉粥样硬化，特别是孤立的颅内动脉狭窄在东亚人中更常见 [20-23]。症状相关性的颅内动脉狭窄或闭塞，既可归因于心源性栓塞，也可归因于原位血栓形成或动脉粥样硬化所致的动脉栓塞。这些病变在血管造影中很难区别，故在本研究中，并未把症状相关性颅内动脉狭窄或闭塞作为动脉粥样硬化病变。这种定义也许会造成对颅内动脉粥样硬化发生率以及颅内动脉粥样硬化性血栓形成的低估。

结论

本研究结果提示，可依据 $CHADS_2$ 评分预测脑动脉粥样硬化的发生及严重程度。同时也提示，动脉粥样硬化性血栓形成应该作为高 $CHADS_2$ 评分患者卒中发生的一种机制。近 40% 的高风险患者 ($CHADS_2$ 评分 ≥3) 有大动脉狭窄，可能需要一些干预治疗以提高对卒中的预防。对高 $CHADS_2$ 评分患者需要进行严格的脑动脉粥样硬化的评估。

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