

The association between asymptomatic  
coronary artery disease and  
CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> scores in  
patients with stroke

Myoung-Jin Cha

Department of Medicine

The Graduate School, Yonsei University

The association between asymptomatic  
coronary artery disease and  
CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> scores in  
patients with stroke

Myoung-Jin Cha

Department of Medicine

The Graduate School, Yonsei University

The association between asymptomatic  
coronary artery disease and  
CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> scores in  
patients with stroke

Directed by Professor Ji Hoe Heo

The Master's Thesis  
submitted to the Department of Medicine,  
the Graduate School of Yonsei University  
in partial fulfillment of the requirements for the degree  
of Master of Medical Science

Myoung-Jin Cha

June 2013

This certifies that the Master's Thesis of  
Myoung-Jin Cha is approved.

-----  
Thesis Supervisor: Ji Hoe Heo

-----  
Thesis Committee Member: Kyung-Yul Lee

-----  
Thesis Committee Member: Hyo Suk Nam

The Graduate School  
Yonsei University

June 2013

## ACKNOWLEDGEMENTS

Though there was a problem about how I started and the long distance, I was able to finish the course of master's degree with the help of many grateful peoples. First of all, I thank professor Ji Hoe Heo for giving me grateful advices and encouragement. I respect his passion and effort in studying and researching persistently and outstandingly. It was a good experience for me and it made me to study more and more and to enjoy the step to the learning

I also thank professor Hyo Suk Nam and professor Young Dae Kim for giving me valuable teaching and guidance and professor Kyung-Yul Lee to give me advices about this thesis.

I thank the colleagues in interpretation room of neurovascular ultrasound lab of Severance hospital who welcome me with a big smile though my frequent visits.

I owe this victory to my attentive parents-in-laws who support and help me, my beloved husband, Yong Ro Lee who picked me up at the early dawn every week rubbing his sleepy eye and my lovely daughter, Ju Eun Lee who played well during absence of her mommy.

## <TABLE OF CONTENTS>

ABSTRACT	1
I. INTRODUCTION	3
II. MATERIALS AND METHODS	4
1. Patients and enrollment	4
2. Calculation of CHADS <sub>2</sub> and CHA <sub>2</sub> DS <sub>2</sub> -VASc scores	5
3. MSCT Coronary Angiography	5
4. Risk factors	7
5. Data and statistical analysis	7
III. RESULTS	8
1. Demographic characteristics	8
2. Association between the presence and severity of CAD and CHADS <sub>2</sub> /CHA <sub>2</sub> DS <sub>2</sub> -VASc scores	12
3. Association between the presence and severity of CAD and CHADS <sub>2</sub> /CHA <sub>2</sub> DS <sub>2</sub> -VASc scores in AF patients	14
4. Factors associated with coronary artery disease	16
IV. DISCUSSION	22
V. CONCLUSION	24
REFERENCES	25
ABSTRACT(IN KOREAN)	30
PUBLICATION LIST	32

## LIST OF FIGURES

Figure 1. Flowchart showing patient inclusion and exclusion	9
Figure 2. Association of the presence and severity of CAD with the CHADS <sub>2</sub> score or CHA <sub>2</sub> DS <sub>2</sub> -VASc score	13
Figure 3. Association of the presence and severity of CAD with the CHADS <sub>2</sub> score or CHA <sub>2</sub> DS <sub>2</sub> -VASc score in patients with atrial fibrillation	15
Figure 4. The predictability of the presence of CAD using AUC analysis between the CHADS <sub>2</sub> and CHA <sub>2</sub> DS <sub>2</sub> -VASc scores and between the components of CHADS <sub>2</sub> and CHA <sub>2</sub> DS <sub>2</sub> -VASc scores	21

## LIST OF TABLES

Table 1. Characteristics of patients with and without coronary artery disease at baseline	10
Table 2. Characteristics of patients with and without atrial fibrillation at baseline	11
Table 3. Association between risk factors and components of CHADS <sub>2</sub> /CHA <sub>2</sub> DS <sub>2</sub> -VASc scores and coronary artery disease (univariate analysis)	17
Table 4. Association between risk factors and components of CHADS <sub>2</sub> score and coronary artery disease (multivariate analysis)	18
Table 5. Association between risk factors and components of CHA <sub>2</sub> DS <sub>2</sub> -VASc score and coronary artery disease (multivariate analysis)	19

## ABSTRACT

### **The association between asymptomatic coronary artery disease and CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> scores in patients with stroke**

Myoung-Jin Cha

*Department of Medicine  
The Graduate School, Yonsei University*

(Directed by Professor Ji Hoe Heo)

**Background:** CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are measurement tools that stratify thromboembolic risk in patients with nonvalvular atrial fibrillation, and are predictive of cerebral atherosclerosis, fatal stroke, and ischaemic heart disease. Patients with higher CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are more likely to have had an akinetic/hypokinetic left ventricular segment, or a recent myocardial infarction, all of which are associated with coronary artery disease (CAD). Most of the CHADS<sub>2</sub> score components are also risk factors for atherosclerosis. Thus, CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores may be predictive of CAD.

**Methods:** We enrolled 1733 consecutive patients with acute ischaemic stroke who underwent multi-slice computed tomography coronary angiography. We investigated the association of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores with the presence and severity of CAD.

**Results:** Among 1733 patients, 1220 patients (70.4%) had any degree of CAD,

and 576 (33.3%) had significant CAD ( $\geq 50\%$  stenosis in at least one coronary artery). As the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores increased, the presence of CAD also increased ( $p < 0.001$ ). The severity of CAD was correlated with CHADS<sub>2</sub> (Spearman coefficient 0.229,  $p < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (Spearman coefficient 0.261,  $p < 0.001$ ). In multivariate analysis, after adjusting for confounding factors, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores  $\geq 2$  were independently associated with CAD. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was a better predictor of the presence of CAD than the CHADS<sub>2</sub> score on area under the curve analysis.

**Conclusion:** CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were predictive of the presence and severity of CAD in patients with stroke. When a patient has high CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, physicians should consider coronary artery evaluation.

---

Key words : coronary artery disease, CHADS<sub>2</sub> score, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, stroke

**The association between asymptomatic coronary artery disease and  
CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in patients with stroke**

Myoung-Jin Cha

*Department of Medicine  
The Graduate School, Yonsei University*

(Directed by Professor Ji Hoe Heo)

I. INTRODUCTION

CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are simple and sound tools that stratify embolic risks in patients with nonvalvular atrial fibrillation (NVAf) <sup>1,2</sup>.

CHADS<sub>2</sub> score also predicts cerebral atherosclerosis, fatal ischaemic stroke, fatal ischaemic heart disease and early neurologic outcome in stroke patients with NVAf <sup>3-5</sup>. We recently have shown that concomitant potential cardiac sources of embolism (PCSE) were more frequent in stroke patients with higher CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, which may, in part, account for the increased risk of stroke in patients with high CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores <sup>6</sup>. Of note, among PCSE, an akinetic left ventricular segment, a hypokinetic left ventricular segment, and a myocardial infarction <4 weeks prior were associated with higher CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores <sup>6</sup>. These PCSE are associated with coronary artery disease (CAD). Most components of the

CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are also risk factors for atherosclerosis, and clustering of those factors is associated with cardiovascular mortality<sup>7-11</sup>. Thus, CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores may be predictive of CAD. Therefore, we investigated the association between CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and the presence and severity of asymptomatic CAD in patients with stroke.

## II. MATERIALS AND METHODS

### 1. Patients and enrollment

We enrolled consecutive patients with acute ischaemic stroke or transient ischaemic attack (TIA) who were admitted to the neurology department from July 2006 to June 2011 and who had undergone multi-slice computed tomography (MSCT) coronary angiography. All patients underwent brain CT scan and/or magnetic resonance imaging (MRI) and a cerebral angiographic study (digital subtraction angiography, CT angiography, or MR angiography). Every patient was evaluated with 12-lead electrocardiography, chest x-ray, and standard blood tests including lipid profile. Transesophageal echocardiography was a part of standard evaluation except in patients with poor cooperation due to decreased consciousness, impending brain herniation, swallowing difficulty, tracheal intubation, or lack of informed consent<sup>12</sup>. Transthoracic echocardiography and Holter monitoring were performed in the selected patients. Patients who were admitted to the stroke unit were monitored

continuously with electrocardiography during their stay in the stroke unit.

Ankle-brachial index was also performed as screening for peripheral artery disease (PAD). This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, and all patients provided informed consent.

## **2. Calculation of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores**

The CHADS<sub>2</sub> score was calculated as the sum of points assigned to each of the following items: one point each for congestive heart failure (CHF), hypertension, aged  $\geq 75$ , diabetes mellitus, and two points for a history of stroke or TIA. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was also calculated as the sum of points assigned to each of the following: one point each for a history of CHF, hypertension, aged 65-74 years, diabetes mellitus, female sex, vascular diseases [previous myocardial infarction, PAD, or complex aortic plaques] and two points for aged  $\geq 75$  and a history of stroke or TIA. Index stroke or TIA was not considered for the calculation of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.

## **3. MSCT Coronary Angiography**

Patients underwent MSCT coronary angiography during admission when they had at least one of the following: (1) angiographically confirmed atherosclerosis in intracranial or extracranial cerebral arteries or peripheral arteries; (2)  $\geq 2$  risk

factors for CAD, such as hypertension, diabetes mellitus, dyslipidemia, smoking, and central obesity; and (3) age (female >55 years, male >45 years). Exclusion criteria for MSCT coronary angiography included: (1) known CAD (angiographically confirmed CAD, unstable angina, coronary artery stent, or prior angioplasty or coronary artery bypass graft); (2) heart rate >64/min at the time of test; (3) poor general condition; (4) impaired renal function; (5) failure to obtain informed consent <sup>13</sup>.

Coronary CT angiography was performed using 64 multi-slice CT (Sensation 64; Siemens Medical Solutions, Forchheim, Germany) as reported previously <sup>13</sup>. Experienced cardiac radiologists, who were blinded to the clinical information, reviewed and interpreted all MSCT coronary angiographies. The severity of atherosclerosis was evaluated by the degree of stenosis. CAD was diagnosed when any degree of coronary artery stenosis was present at any of the three main coronary branches, including the left anterior descending, left circumflex, and right coronary arteries. Atherosclerotic stenosis was classified as no CAD (no plaque), mild CAD (<50% stenosis in at least one coronary artery), and significant CAD ( $\geq$ 50% stenosis in at least one coronary artery). The significant ( $\geq$ 50%) CAD was further categorized into 1-vessel disease, 2-vessel disease, and 3-vessel disease.

#### **4. Risk factors**

Hypertension was defined as resting blood pressures with high systolic pressure  $\geq 140$  mmHg or diastolic pressure  $\geq 90$  mmHg on repeated measurements during admission or a history of having used any antihypertensive drug after diagnosis of hypertension <sup>14</sup>. Diabetes mellitus was defined as a fasting plasma glucose  $\geq 7.0$  mmol/l or a history of having used oral hypoglycemic agents or insulin <sup>15</sup>. Hyperlipidemia was defined as fasting serum total cholesterol level  $\geq 6.2$  mmol/l, LDL-cholesterol  $\geq 4.1$  mmol/l, or a history of having used lipid-lowering drugs after a diagnosis of dyslipidemia <sup>16</sup>. CHF was defined as a previous history of CHF or detection of CHF during admission based on the medical records or a hospital diagnosis code (*International Classification of Disease, 10<sup>th</sup> Revision ICD-10-CM* codes I50). Current smoking was defined as having smoked a cigarette in the year prior to admission. PAD was defined at ankle-brachial index  $< 0.9$ . Aortic plaques were diagnosed based on the findings of transesophageal echocardiography.

#### **5. Data and statistical analysis**

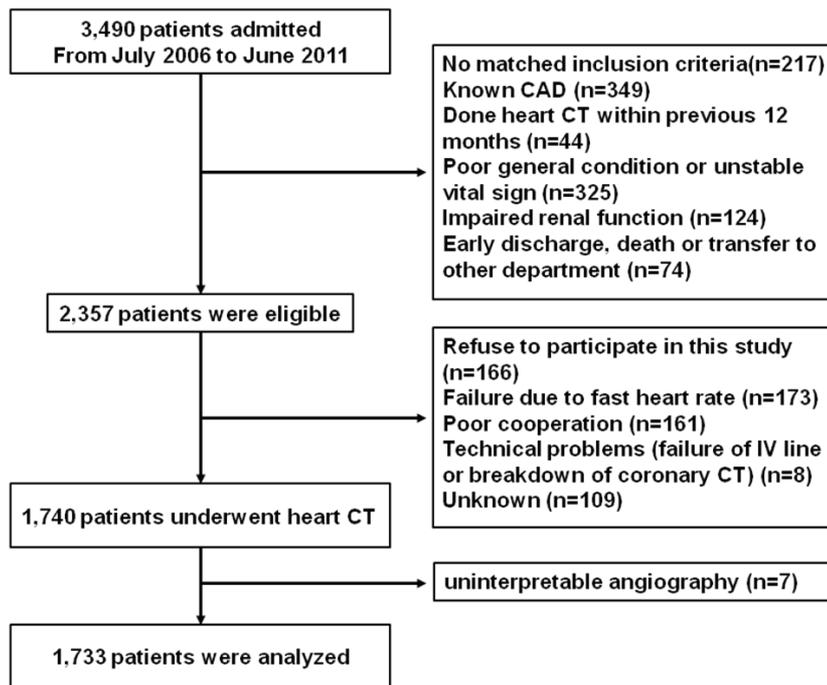
The Windows SPSS package version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Variables were expressed as mean  $\pm$  standard deviation or median [interquartile range (IQR)] as appropriate. Demographic characteristics and risk factors were compared using independent sample t-tests

or chi-square tests for categorical variables between the CAD and non-CAD groups. The association of CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores with the presence of CAD was analyzed using linear by linear association (Chi-square for trend). Correlation between the severity of CAD and CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores was assessed using the Spearman rank correlation coefficients. Confounding factors such as age, sex, smoking, AF, hyperlipidemia, and the components of CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were analyzed by univariate analysis, and the variables with p values <0.10 were entered for multiple logistic regression. The results were presented as odds ratio (OR) and 95% confidence intervals (CI). We compared the ability to predict presence of CAD between the CHADS<sub>2</sub> score and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score as well as their components using area under curve (AUC) analysis.

### III. RESULTS

#### **1. Demographic characteristics**

There were 3490 patients with acute cerebral infarction or TIA during the study period. Among them, 2357 patients were eligible for MSCT coronary CT angiography. After excluding 617 patients who could not complete coronary CT angiography due to various reasons and 7 patients with uninterpretable images, 1733 consecutive patients were included in this study. The complete numbers and reasons of exclusion were illustrated (Fig. 1).



**Figure 1** Flowchart showing patient inclusion and exclusion.

Among them, 1220 (70.4%) patients had any degree of CAD [mild CAD in 644 patients (37.2%), and significant CAD in 576 patients (33.3%)]. Of those with significant CAD, there were 320 patients with 1-vessel disease (18.5%), 166 patients with 2-vessel disease (9.6%), and 90 patients with 3-vessel disease (5.2%). When compared to patients without CAD, those with CAD were older, more likely to be male and smokers, and more frequently had hypertension, diabetes, PAD, TIA/ infarction and aortic plaques (table 1). When compared to patients without AF, patients with AF were older and less frequently smokers (table 2).

**table 1** Characteristics of patients with and without CAD at baseline.

	CAD (N=1220)	Non-CAD (N=513)	p-value
Age, yr, mean $\pm$ SD	66.02 $\pm$ 10.37	57.82 $\pm$ 12.74	<0.001
Sex, men	827 (67.8)	278 (54.2)	<0.001
Hypertension	970 (79.5)	317 (61.8)	<0.001
Diabetes mellitus	434 (35.6)	103 (20.1)	<0.001
Atrial fibrillation	168 (13.8)	74 (14.4)	0.720
Smoking	545 (44.7)	181 (35.3)	<0.001
Hyperlipidemia	119 (9.8)	37 (7.2)	0.091
History of PAD	32 (2.6)	1 (0.2)	<0.001
Aortic plaques	543 (44.5)	164 (32.0)	<0.001
Previous TIA/infarction	218 (17.9)	63 (12.3)	0.004
CHADS <sub>2</sub> score			<0.001
0	126 (10.3)	143 (27.9)	
1	457 (37.5)	211 (41.1)	
2	374 (30.7)	107 (20.9)	
3	137 (11.2)	37 (7.2)	
4	115 (9.4)	12 (2.3)	
5	11 (0.9)	3 (0.6)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc score			<0.001
0	33 (2.7)	55 (10.7)	
1	114 (9.3)	130 (25.3)	
2	259 (21.2)	115 (22.4)	
3	298 (24.4)	106 (20.7)	
4	269 (22.0)	64 (12.5)	
5	143 (11.7)	28 (5.5)	
6	77 (6.3)	7 (1.4)	
7	26 (2.1)	8 (1.6)	
8	1 (0.1)	0	

Numbers in parentheses are percentages. CAD, coronary artery disease; PAD,

peripheral artery disease; TIA, transient ischaemic attack.

**table 2** Characteristics of patients with and without AF at baseline.

	AF (N=242)	Non-AF (N=1491)	p-value
Age, yr, mean $\pm$ SD	66.91 $\pm$ 9.81	63.05 $\pm$ 11.93	<0.001
Sex, men	150 (62)	955 (64.1)	0.535
Hypertension	178 (73.6)	1109 (74.4)	0.785
Diabetes mellitus	63 (26.0)	474 (31.8)	0.072
Smoking	71 (29.3)	655 (43.9)	<0.001
Hyperlipidemia	16 (6.6)	140 (9.4)	0.161
Aortic plaques	104 (43.0)	603 (40.4)	0.457
Previous TIA/infarction	43 (17.8)	238 (16.0)	0.480

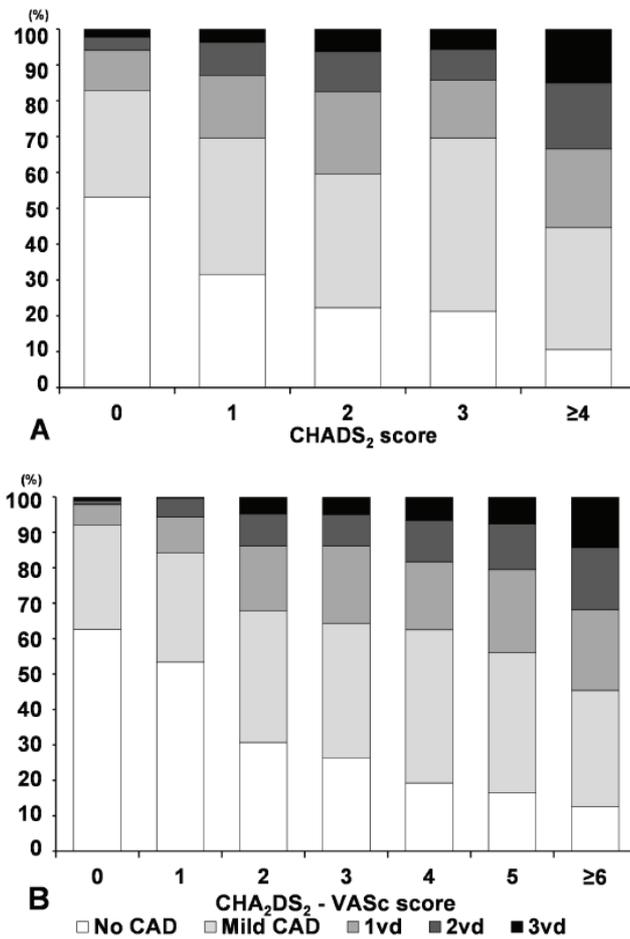
Numbers in parentheses are percentages.

AF, atrial fibrillation; TIA, transient ischaemic attack.

## **2. Association between the presence and severity of CAD and**

### **CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores**

The median CHADS<sub>2</sub> score was higher in the CAD group (2, IQR 0-2) than in the non-CAD group (1, IQR 1-2,  $p<0.001$ ). As the CHADS<sub>2</sub> score increased, the presence of CAD increased ( $p<0.001$ ). The number of patients with significant CAD also increased as the CHADS<sub>2</sub> score increased ( $p<0.001$ ). The median CHA<sub>2</sub>DS<sub>2</sub>-VASc score was higher in the CAD group (3, IQR 2-4) than the non-CAD group (2, IQR 1-3,  $p<0.001$ ). As the CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased, the presence of CAD increased ( $p<0.001$ ). The severity of CAD was correlated with CHADS<sub>2</sub> (Spearman coefficient 0.229,  $p<0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (Spearman coefficient 0.261,  $p<0.001$ ) (Fig. 2).



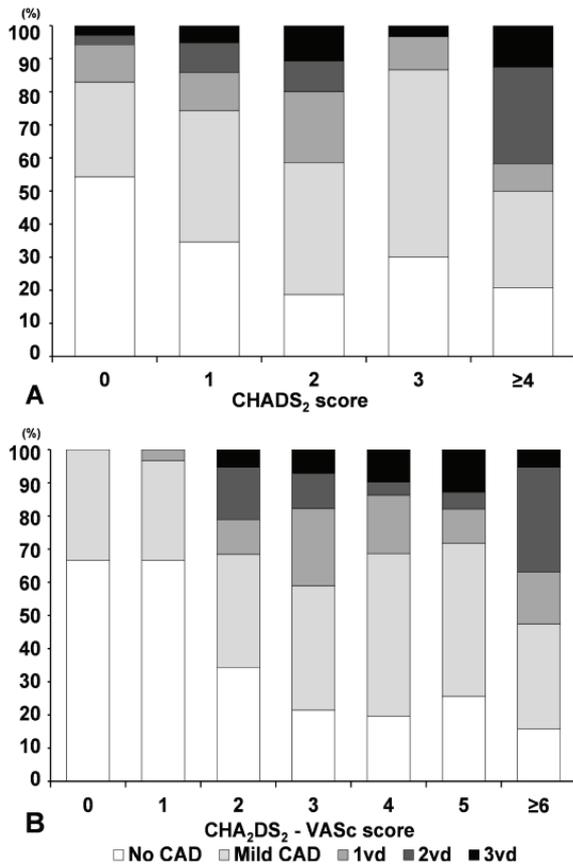
**Figure 2** Association of the presence and severity of CAD with the CHADS<sub>2</sub> score (A) or CHA<sub>2</sub>DS<sub>2</sub>-VASc score (B). As the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased, the presence of CAD increased ( $p < 0.001$ ). The severity of CAD was correlated with CHADS<sub>2</sub> (Spearman coefficient 0.229,  $p < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (Spearman coefficient 0.261,  $p < 0.001$ ).

### **3. Association between the presence and severity of CAD and**

#### **CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores in AF patients**

Because CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are used for stratification of embolic risks in patients with AF, we conducted subgroup analysis in patients with AF.

Among 1733 patients, 242 patients had AF. The presence of CAD increased as the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased ( $p=0.003$  and  $p<0.001$ , respectively). The severity of CAD was also correlated with CHADS<sub>2</sub> (Spearman coefficient 0.188,  $p=0.003$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (Spearman coefficient 0.237,  $p<0.001$ ) (Fig. 3).



**Figure 3** Association of the presence and severity of CAD with the CHADS<sub>2</sub> score (A) or CHA<sub>2</sub>DS<sub>2</sub>-VASc score (B) in patients with atrial fibrillation. As the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased, the presence of CAD increased ( $p=0.003$  and  $p<0.001$ , respectively). The severity of CAD was correlated with CHADS<sub>2</sub> (Spearman coefficient 0.188,  $p=0.003$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (Spearman coefficient 0.237,  $p<0.001$ ).

#### **4. Factors associated with coronary artery disease**

Univariate analysis showed that aged 65-74, aged  $\geq 75$ , female sex, hypertension, diabetes mellitus, stroke, vascular disease, aortic plaques, smoking, and CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were significantly associated with the presence of CAD (Table 3). On multivariate analysis, after adjustment for smoking and hyperlipidemia, higher CHADS<sub>2</sub> ( $\geq 2$ ) or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $\geq 2$ ) were independently associated with CAD. Among the components of the CHADS<sub>2</sub> score, hypertension, aged  $\geq 75$ , and diabetes mellitus were related to CAD (Table 4), and among the components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, hypertension, aged 65-74, aged  $\geq 75$ , diabetes mellitus, vascular disease, and female sex were associated with CAD (Table 5).

**Table 3** Association between risk factors and components of  
 CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and coronary artery disease  
 (univariate analysis)

	OR (95% CI)	p-value
Age I		
<75	Reference	
≥75	3.093 (2.160-4.430)	<0.001
Age II		
≤64	Reference	
65-74	2.524 (1.994-3.196)	<0.001
≥75	4.423 (3.059-6.396)	<0.001
Sex(Female)	1.779 (1.440-2.197)	<0.001
Congestive heart failure	1.389 (0.772-2.501)	0.273
Hypertension	2.399 (1.914-3.007)	<0.001
Diabetes mellitus	2.198 (1.719-2.810)	<0.001
Previous TIA/infarction	1.554 (1.149-2.101)	0.004
vascular disease	2.970 (2.390-3.690)	<0.001
Aortic plaques	1.707 (1.374-2.121)	<0.001
Smoking	1.481 (1.196-1.833)	<0.001
Atrial fibrillation	0.947 (0.705-1.273)	0.72
Hyperlipidemia	1.390 (0.947-2.042)	0.093
CHADS <sub>2</sub> score		
0	Reference	
1	2.458 (1.840-3.284)	<0.001
2	3.967 (2.876-5.473)	<0.001
3	4.202 (2.720-6.492)	<0.001
4-6	9.527 (5.300-17.123)	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score		
0	Reference	
1	1.462 (0.887-2.408)	0.137
2	3.754 (2.313-6.092)	<0.001

3	4.686 (2.884-7.611)	<0.001
4	7.005 (4.205-11.671)	<0.001
5	8.512 (4.709-15.384)	<0.001
6-8	11.554 (5.782-23.087)	<0.001

**Table 4** Association between risk factors and components of CHADS<sub>2</sub> score and coronary artery disease (multivariate analysis)

	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Smoking	1.702(1.360-2.129)	<0.001	1.806(1.440-2.264)	<0.001
Hyperlipidemia	1.383(0.927-2.062)	0.112	1.431(0.959-2.136)	0.079
<b>CHADS<sub>2</sub> score</b>				
0	1			
1	2.520(1.880-3.379)	<0.001		
2	4.292(3.095-5.952)	<0.001		
3	4.547(2.929-7.059)	<0.001		
4-6	10.349(5.730-18.690)	<0.001		
<b>CHADS<sub>2</sub> score component</b>				
Congestive heart failure			1.562(0.842-2.897)	0.157
Hypertension			2.131(1.683-2.698)	<0.001
Age ≥75			3.392(2.342-4.913)	<0.001
Diabetes mellitus			2.190(1.699-2.824)	<0.001
Previous TIA/infarction			1.365(0.995-1.871)	0.054

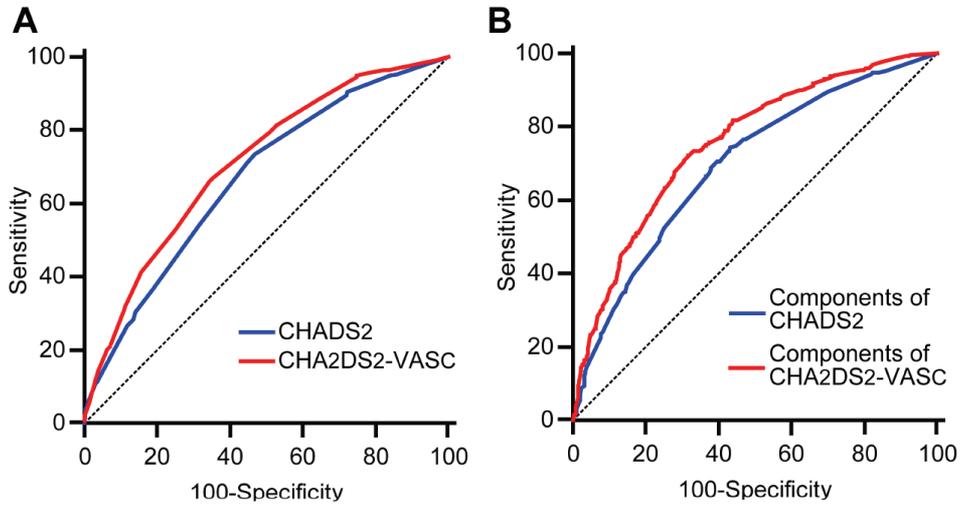
OR, odd ratio; CI, confidence interval; TIA, transient ischaemic attack.

**Table 5** Association between risk factors and components of CHA<sub>2</sub>DS<sub>2</sub>-VASc score and coronary artery disease (multivariate analysis)

	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Smoking	2.484(1.943-3.175)	<0.001	1.371(1.022-1.839)	0.035
Hyperlipidemia	1.357(0.902-2.041)	0.143	1.422(0.937-2.159)	0.098
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>				
0	1			
1	1.643(0.985-2.740)	0.057		
2	4.474(2.717-7.368)	<0.001		
3	6.640(3.996-11.032)	<0.001		
4	10.604(6.202-18.129)	<0.001		
5	13.489(7.270-25.028)	<0.001		
6-8	19.213(9.379-39.356)	<0.001		
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score component</b>				
Congestive heart failure			1.580(0.837-2.985)	0.158
Hypertension			1.924(1.498-2.470)	<0.001
Age 65-74			2.365(1.829-3.060)	<0.001
Age ≥75			4.918(3.315-7.296)	<0.001
Diabetes mellitus			2.113(1.622-2.752)	<0.001
Previous TIA/infarction			1.231(0.885-1.711)	0.217
Vascular disease			2.470(1.959-3.113)	<0.001
Female			0.519(0.387-0.695)	<0.001

OR, odd ratio; CI, confidence interval; TIA, transient ischaemic attack.

When we compared the ability to predict the presence of CAD between the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores using AUC analysis, the latter was a better predictor of the presence of CAD [CHADS<sub>2</sub> score AUC = 0.668 (0.641-0.696), CHA<sub>2</sub>DS<sub>2</sub>-VASc AUC = 0.710 (0.683-0.736),  $p < 0.001$ ]. Components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score also showed a better predictive value than those of the CHADS<sub>2</sub> score [CHADS<sub>2</sub> components AUC = 0.696 (0.669-0.723), CHA<sub>2</sub>DS<sub>2</sub>-VASc AUC = 0.755 (0.730-0.780),  $p < 0.001$ ] (Fig. 4).



**Figure 4** The predictability of the presence of CAD using AUC analysis between the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (A) and between the components of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (B). CHA<sub>2</sub>DS<sub>2</sub>-VASc score and components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score were better predictors of the presence of CAD [CHADS<sub>2</sub> score AUC =0.668 (0.641-0.696), CHA<sub>2</sub>DS<sub>2</sub>-VASc AUC =0.710 (0.683-0.7367),  $p<0.001$  and CHADS<sub>2</sub> components AUC =0.696 (0.669-0.723), CHA<sub>2</sub>DS<sub>2</sub>-VASc AUC =0.755 (0.730-0.780),  $p<0.001$ ].

We also determined AUC in the subgroup of patients with AF and those without AF. When comparing with the CHADS<sub>2</sub> score, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was also better predictive of the presence of CAD in patients with AF [CHADS<sub>2</sub> AUC = 0.651 (0.578-0.725), CHA<sub>2</sub>DS<sub>2</sub>-VASc AUC = 0.704 (0.633-0.776),  $p < 0.001$ ], and in patients without [CHADS<sub>2</sub> AUC = 0.676 (0.646-0.706), CHA<sub>2</sub>DS<sub>2</sub>-VASc AUC = 0.715 (0.686-0.743),  $p < 0.001$ ].

#### IV. DISCUSSION

In this study, we demonstrated that CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were predictive of CAD in patients with stroke. As the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased, CAD was found more frequently and was more severe. These findings are in line with our previous observations demonstrating higher frequencies of an akinetic left ventricular segment, a hypokinetic left ventricular segment or a recent myocardial infarction in patients with higher CHADS<sub>2</sub> scores<sup>6</sup>, because those cardiac conditions are associated with CAD<sup>17,18</sup>.

CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were developed to stratify embolic risks in NVAF. However, accumulating evidence suggests that those scoring systems are also predictive of various cardiovascular and cerebrovascular outcomes. All causes and cardiovascular mortality were higher in AF patients with higher CHADS<sub>2</sub> score<sup>5, 19, 20</sup>. The mortality study in stroke patients with NVAF also

showed that CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were predictive of the occurrence of not only fatal ischaemic stroke but also fatal ischaemic heart disease<sup>5,21</sup>. In patients with acute coronary syndromes, CHADS<sub>2</sub> score was useful in identifying patients with a high risk of mortality and subsequent stroke<sup>22</sup>. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were a predictor of early neurological deterioration and correlated with early stroke severity<sup>3</sup>.

CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are also predictive of atherosclerosis. The frequency and burden of cerebral atherosclerosis increased as CHADS<sub>2</sub> score increased in patients with stroke<sup>4</sup>. Considering that some components of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are also risk factors for atherosclerosis, the association of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores with atherosclerosis in the cerebral and coronary arteries is expected<sup>7-9</sup>. In this study, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were predictive of the presence and severity of CAD in patients with stroke or TIA regardless of the presence of AF. Therefore, a predictive role of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores for cardiovascular outcomes and cerebral or coronary atherosclerosis is not limited to patients with AF but is also applicable to those without AF, as was shown in this study. Among components of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, age, hypertension, diabetes mellitus, vascular diseases, and female sex were associated with CAD. These are well-known risk factors for CAD. Though

previous TIA/infarction was given 2 points in both scores, it came borderline significantly with CHADS<sub>2</sub> score but not with CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Stroke and TIA develop not only due to atherosclerosis, but also due to non-atherosclerotic diseases including cardiac diseases, small artery disease, coagulopathy, dissection, etc. This may be responsible for borderline or no significance of the previous stroke/TIA with CAD. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score had a better predictive value for the presence of CAD than the CHADS<sub>2</sub> score, possibly because the CHA<sub>2</sub>DS<sub>2</sub>-VASc score contains more components that are associated with CAD than does the CHADS<sub>2</sub> score.

This study has limitations. The subjects of our study were patients with stroke. Therefore, it is uncertain whether the association of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores with CAD can be generalized to other populations. The diagnosis of CAD was based on MSCT coronary angiography, while conventional coronary angiography is the gold standard. Although MSCT coronary angiography has a sensitivity of >85% and a specificity of >90% to detect ≥50% CAD, as compared with conventional coronary angiography<sup>23,24</sup>, MSCT coronary angiography may overestimate stenotic lesions.

## V. CONCLUSION

Our study demonstrated that CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were

predictive of the presence and severity of CAD. Along with findings in previous studies, our findings suggest that the value of the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores may not be limited to their role in prediction for embolic risks in patients with NVAf. When a patient has a higher CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score, physicians should consider that that patient may also have high risks for other vascular outcomes, including CAD.

#### REFERENCES

1. Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285: 2864-70.
2. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; 137: 263-72.
3. Hong HJ, Kim YD, Cha MJ, et al. Early neurological outcomes according to CHADS<sub>2</sub> score in stroke patients with non-valvular atrial fibrillation. *Eur J Neurol* 2012; 19: 284-90.
4. Kim YD, Cha MJ, Kim J, et al. Increases in cerebral atherosclerosis according to CHADS<sub>2</sub> scores in patients with stroke with nonvalvular

- atrial fibrillation. *Stroke* 2011; 42: 930-4.
5. Kim YD, Cha MJ, Kim J, et al. Ischaemic cardiovascular mortality in patients with non-valvular atrial fibrillation according to CHADS(2) score. *Thromb Haemost* 2011; 105: 712-20.
  6. Cha MJ, Kim YD, Nam HS, Kim J, Lee DH, Heo JH. Stroke mechanism in patients with non-valvular atrial fibrillation according to the CHADS2 and CHA2 DS2 -VASc scores. *Eur J Neurol* 2012; 19: 473-9.
  7. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007; 69: 546-54.
  8. Goldman ME, Pearce LA, Hart RG, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. Reduced flow velocity in the left atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr* 1999; 12: 1080-7.
  9. Lane DA, Lip GY. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. *Thromb Haemost* 2009; 101: 802-5.
  10. Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). *Am J Cardiol* 2004; 93: 1422-5, A1410.

11. Wysokinski WE, Ammash N, Sobande F, Kalsi H, Hodge D, McBane RD. Predicting left atrial thrombi in atrial fibrillation. *Am Heart J* 2010; 159: 665-71.
12. Cho HJ, Choi HY, Kim YD, et al. Transoesophageal echocardiography in patients with acute stroke with sinus rhythm and no cardiac disease history. *J Neurol Neurosurg Psychiatry* 2010; 81: 412-5.
13. Yoo J, Yang JH, Choi BW, et al. The frequency and risk of preclinical coronary artery disease detected using multichannel cardiac computed tomography in patients with ischemic stroke. *Cerebrovasc Dis* 2012; 33: 286-94.
14. Jones DW, Hall JE. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and evidence from new hypertension trials. *Hypertension* 2004; 43: 1-3.
15. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26 Suppl 1: S5-20.
16. National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

- final report. *Circulation* 2002; 106: 3143-421.
17. Hoole SP, Heck PM, White PA, et al. Stunning and cumulative left ventricular dysfunction occurs late after coronary balloon occlusion in humans insights from simultaneous coronary and left ventricular hemodynamic assessment. *JACC Cardiovasc Interv* 2010; 3: 412-8.
  18. Barnes E, Hall RJ, Dutka DP, Camici PG. Absolute blood flow and oxygen consumption in stunned myocardium in patients with coronary artery disease. *J Am Coll Cardiol* 2002; 39: 420-7.
  19. Goto S, Bhatt DL, Rother J, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J* 2008; 156: 855-63, 863 e852.
  20. Khumri TM, Idupulapati M, Rader VJ, Nayyar S, Stoner CN, Main ML. Clinical and echocardiographic markers of mortality risk in patients with atrial fibrillation. *Am J Cardiol* 2007; 99: 1733-6.
  21. Henriksson KM, Farahmand B, Johansson S, Asberg S, Terent A, Edvardsson N. Survival after stroke--the impact of CHADS2 score and atrial fibrillation. *Int J Cardiol* 2010; 141: 18-23.
  22. Poci D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS2 Score in Acute Coronary Syndromes: Risk of Subsequent Death or Stroke in Patients With and Without Atrial Fibrillation. *Chest* 2012; 141: 1431-40.

23. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; 359: 2324-36.
24. Hamon M, Morello R, Riddell JW. Coronary arteries: diagnostic performance of 16- versus 64-section spiral CT compared with invasive coronary angiography--meta-analysis. *Radiology* 2007; 245: 720-31.

ABSTRACT(IN KOREAN)

뇌경색 환자들에서 무증상 관상동맥질환과 CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores와의 연관성

<지도교수 허지희 >

연세대학교 대학원 의학과

차명진

배경 : CHADS<sub>2</sub> 와 CHA<sub>2</sub>DS<sub>2</sub>-VASc score는 비판막성 심방세동 환자에서 혈전색전증의 위험을 분류하고, 대뇌의 동맥경화증, 치명적인 뇌졸중, 허혈성 심장 질환을 예측하는 측정 도구이다. 높은 CHADS<sub>2</sub> 와 CHA<sub>2</sub>DS<sub>2</sub>-VASc score를 가진 환자들은 관상동맥질환과 관련된 무운동/저운동 좌심실과 최근 발생한 심근경색을 더 많이 가지고 있다. CHADS<sub>2</sub> score 구성요소의 대부분은 동맥경화의 위험 인자이다. 그러므로 CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc score는 관상동맥 질환을 예측한다.

방법 : 본 연구는 다채널 전산화단층촬영 관상동맥조영술을 시행한 급성 허혈성 뇌졸중 환자 1733명을 대상으로 하였다. 우리는 CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc score와 관상동맥질환의 유무와 심각도와의 관련성을 연구하였다.

결과 : 1733명 중 1220명(70.4%)에서 정도와 관련없이 관상동맥질환을 보였고 575명 (33.3%)이 의미있는 관상동맥질환(적어도 하나의 관상동맥에서 50% 이상의 협착)을 보였다. CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc score가 증가할수록 관상동맥질환의 존재도 또한 증가하였다 ( $p<0.001$ ). 관상동맥질환의 심각도는 CHADS<sub>2</sub> score (Spearman coefficient 0.229,  $p<0.001$ )와 CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Spearman coefficient 0.261,  $p<0.001$ )와 관련이 있었다. 다변량 분석에서 혼란변수를 보정하였을 때 CHADS<sub>2</sub>와 CHA<sub>2</sub>DS<sub>2</sub>-VASc score가 2 이상인 것은 관상동맥질환과 독립적으로 관련이 있었다. CHA<sub>2</sub>DS<sub>2</sub>-VASc score는 area under the curve 분석에서 관상동맥질환의 존재에 있어서 CHADS<sub>2</sub> score보다 더 나은 예측인자였다.

결론 : CHADS<sub>2</sub>와 CHA<sub>2</sub>DS<sub>2</sub>-VASc score는 뇌졸중 환자에서 관상동맥질환의 존재와 심각도를 예측하였다. CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc score가 높은 환자의 경우에 의사들은 관상동맥평가를 고려해야 한다.

---

핵심되는 말 : 관상동맥질환, CHADS<sub>2</sub> score, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, 뇌경색

## PUBLICATION LIST

Cha MJ, Lee HS, Kim YD, Nam HS, Heo JH. The association between asymptomatic coronary artery disease and CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> scores in patients with stroke. *Eur J Neurol* 2013; Apr 5. doi: 10.1111/ene.12158. [Epub ahead of print].