의학석사 학위논문

Prevalence and risk factors of silent ischemic brain lesion in patients with atrial fibrillation: A brain MRI study

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2013 년 2 월

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A thesis of the Master’s degree

심방 세동 환자에서 MRI로 확인되는 무증상 허혈성 뇌병변의 유병률 및 위험인자에 관한 연구

Prevalence and risk factors of silent ischemic brain lesion in patients with atrial fibrillation: A brain MRI study

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학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 제공하는 것에 동의합니다.

1. 동의사항

① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

2. 개인(저작자)의 의무

본 논문의 저작권을 타인에게 양도하거나 또는 출판을 허락하는 등 동의 내용을 변경하고자 할 때는 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.

3. 서울대학교의 의무

① 서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

② 서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문 제목: 신기능 감소 환자에서 관상동맥 컴퓨터 단층 촬영과 심근 관류 단일 광전자 방출 전산화 단층술의 예후 예측력에 관한 연구

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ABSTRACT

Introduction: The various prevalence of silent ischemic stroke (SIBL) in atrial fibrillation (AF) has been reported. Stroke history is point of two in CHADS2 scoring system, thus probably unknown portion of patients with CHADS2 score of zero or one has been undertreated in terms of stroke prevention. We investigated the risk factors for SIBL using magnetic resonance imaging (MRI) and its impacts on the clinical outcome in AF population.

Methods: Total 1200 individuals (400 with AF and 800 with sinus rhythm), who have done brain MRI for the purpose of routine health-check-up, were analyzed. Clinical outcomes including symptomatic stroke, dementia and cognitive disorder were also evaluated in AF patients (follow-up duration: 66.7±35.9, range 10-162 months).

Results: SIBL was observed in 113 (28.3%) of AF patients, which is higher than sinus rhythm individuals ($p<0.001$, OR 5.549). Independent risk factors for SIBL in AF patients were age (OR=1.049), hypertension (OR=2.086), dyslipidemia (OR=2.073), and valvular AF (OR=3.157). Symptomatic stroke incidence during the follow-up was higher in AF patients with SIBL (5.6%/y) than those without SIBL (2.7%/y). Among 374 non-valvular AF patients, the thromboembolic risk of 61 (23.6%) patients with SIBL among 259 patients with manifest

CHADS2 score under 1, were underestimated and only 16 (26.2%) patients were taking warfarin.

Conclusions: SIBL is observed in more than a quarter of AF population, especially in patients with valvular AF, old age, dyslipidemia, and hypertension. Screening brain MRI could be considered for risk stratification for AF patients with these risk factors to avoid underestimation of thromboembolic risk.

Keywords: silent ischemic brain lesion, atrial fibrillation, MRI
Student Number: 2011-22023

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LIST OF ABBREVIATIONS

AF: Atrial fibrillation

CHF: Congestive heart failure

CKD: Chronic kidney disease

CT: Computed tomography

DM: Diabetes

HTN: Hypertension

NVAF: Non-valvular atrial fibrillation

SR: Sinus rhythm

SS: Silent ischemic stroke

MRI: Magnetic resonance imaging

VAF: Valvular atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is associated with an increased risk of cerebral infarction.(1) To determine optimal anticoagulation therapy for AF patients we use scoring system such as $CHADS_2$ or CHA_2S_2-VASc scores. The CHADS2 risk index is useful and simple for stroke risk classification; 2 points are assigned for a history of stroke or TIA, and 1 point each for the presence of congestive heart failure, hypertension, age of 75 years or older, or diabetes mellitus. The ESC guidelines for AF suggested a new scoring system, CHA2DS2–VASc, in which 2 points are assigned for a stroke or TIA history, or age ≥75, and 1 point each is assigned for age 65–74 years, hypertension, diabetes, recent cardiac failure, vascular disease, and female sex. To assess the score we use multiple tools that are echocardiography for diagnosing heart failure, measuring blood pressure for hypertension and laboratory test for diabetes. However it is sometimes overlooked that silent ischemic brain lesion (SIBL) is frequently seen in asymptomatic patients with atrial fibrillation.(2) Therefore history of stroke could be underestimated in AF patients. History of stroke or transient ischemic attack is point of two in above scoring systems, thus probably significant but unknown portion of patients with $CHADS_2$ score of zero or one has been undertreated in terms of stroke prevention.

SIBL was defined as a cerebral infarction that is evident on brain imaging but is not associated with a clinical symptom.(3) It has been reported that the prevalence of SS in the general population was from 8% to 28%, with the

differences mainly explained by age.(3) According to the Framingham study, SIBL occurs fairly frequent (10%) among subjects from a general population investigated for acute stroke symptoms.(4) A population-based autopsy series revealed that SIBL was found in 12.9% of the 966 subjects who had undergone autopsy, and diastolic blood pressure and AF appear to be strong predictors of silent cerebral infarction in the Japanese general population.(5) In patients with AF, the various prevalence rates of SIBL (13%(6)~48%(2)) have been reported (Table 1). In contrast, the incidence of silent ischemic brain lesion was around 3% per year among elderly people in two large population-based studies.(7, 8)

Table 1. Previous studies

Year	Authors	N	modality	SIBL prevalence
1987	P Petersen et al.(2)	29 AF* : 29 NSR†	CT	14 (48%) : 8 (28%)
1990	WM Feinberg et al.(9)	141 AF	CT	36 (26%)
1995	MD Ezekowitz et al.(10)	516 AF	CT	76 (14.7%)
1995	Hara M.(11)	72 AF	MRI	32%
2009	P Petersen et al(12)	30 AF : 30 NSR	CT	4 (13%) : 3 (10%)
2012	A Kobayashi et al(13)	71 AF : 71 NSR	MRI	74.6% : 57.7%

* AF, atrial fibrillation, †NSR, normal sinus rhythm

Recent studies reported that the presence of SIBL can predict not only clinically overt future stroke,(14, 15) but also dementia or cognitive function decline.(16, 17) In the Cardiovascular Health Study, participants underwent a brief neurological evaluation, and SIBL were associated with visual field defects, extremities disturbances, frailty, and a decline in physical function.(16, 18-21) Furthermore, the presence of silent infarct-like lesions was associated with depressive symptoms.(22, 23)

Previous research reported that dementia might be related to AF even if no clinically overt stokes have occurred.(24) Therefore we could assume that silent infarctions may underlie the relation between dementia and AF. However AF researchers have been shown relatively low concerns about SIBL. Most previous studies for AF and SIBL usually used computed tomography (CT) scan as their tool for detection of SIBL. The sensitivity to detect infarcts is better for MRI compared to CT, so that studies using CT to detect SIBL will, therefore, report lower frequencies than those using MRI.(3)

Herein, we examined prevalence of silent cerebral infarction with MRI in patients with AF without clinical neurologic symptom, and investigated the risk factors and prognostic impact of SIBL in AF patients.

MATERIALS AND METHODS

1. Study population

We reviewed total 400 patients with AF (AF group) and 800 individuals with sinus rhythm (SR group) who have done brain MRI (from January 2000 to May 2012) in Seoul National University Hospital or Healthcare System Gangnam Center in Seoul for the purpose of routine health check-up without clinical neurologic symptom, or with atypical symptom like dizziness or general weakness having determined no association with the neurologic problem. If an expert neurologist decided that patients' symptom could possibly be associated with old cerebral infarction on MRI, the subjects were excluded before matching the cases. The two groups (AF group and SR group) were matched with age, sex, and history of hypertension, dyslipidemia, and diabetes. Matched 400 AF patients were extracted from 1,959 patients with electrocardiogram documented AF, 800 individuals for SR group from 17,358 individuals with normal sinus rhythm.

2. Silent ischemic brain lesion

SIBL was defined as high-intensity areas identified on a T2 weighted image coinciding with low-intensity areas on a T1 weighted image on MRI. MRI images were interpreted by more than two clinical neuroradiologists.

3. **Manifest or true $CHADS_2$ / CHA_2DS_2-VASc scores**

Manifest $CHADS_2$ / CHA_2DS_2-VASc scores indicate calculated scores irrespective of presence of SIBL. True $CHADS_2$ / CHA_2DS_2-VASc scores indicate the scores regarding SIBL as history of stroke that is point 2.

4. **Definition of variables**

Hypertension (HTN) was defined as a systolic blood pressure over 140 mmHg, a diastolic blood pressure over 90 mmHg or current medication for the treatment of hypertension. A fasting blood sugar level over 126 mg/dL or a 2 hour blood sugar level over 200 mg/dL or the use of medications for the control of blood sugar level defined as diabetes (DM). The NCEP ATP-III definition was used to define the presence of dyslipidemia.(25) A transthoracic echocardiography data used for analysis were obtained within one year before or after MRI performed date. Congestive heart failure (CHF) was defined as left ventricular ejection fraction 35% or less. Valvular AF referred to cases with rheumatic mitral valve disease, prosthetic heart valve, or valve repair. Chronic kidney disease (CKD) was defined based on the presence of kidney damage or glomerular filtration rate (MDRD estimated GFR <60 ml/min/1.73m^2) for over 3 months, irrespective of the cause. Dementia and cognitive disorder were defined according to the neurologists' diagnosis in clinical practice.

5. **Study design**

patients who underwent MRI for routine health check-up, we compared the prevalence of SIBL in AF to SR group. In AF group, risk factors for SIBL considered in the multivariate analyses including age, sex, medical history (CKD, dyslipidemia, and factors for $CHADS_2$ or CHA_2DS_2-VASc scoring system) and echocardiographic parameters. Clinical outcome data were also analyzed, including cerebral/cerebellar infarction, dementia and cognitive disorder. Each patients who complained of or were suspected to have neurologic symptom, they were referred to neurologist to be evaluated. The median follow-up period after MRI test was 65.0 months (range 10–162 months).

6. **Statistical analysis**

To reduce the effect of selection bias and potential confounding factors in this observational study, we performed adjustment for significant differences in the baseline characteristics between AF and SR group with the use of propensity-score matching with the R programming language. Comparison of characteristics among patients was performed with the use of the chi-square test with the Fisher's exact test for categorical covariates or Student's t-test for continuous covariates. Multivariate analysis was performed by multiple logistic regression. All data are expressed as mean value and standard deviation, if not specified further. Outcome data were compared between subjects by Cox-regression model. P value of less than 0.05 was considered to indicate statistical significance. All analyses except of group matching were performed with the use of SPSS version 19.0 (IBM Corporation, NY, USA).

RESULTS

Demographic features of the enrolled subjects

The baseline characteristics of 1200 individuals (400 in AF group and 800 in SR group) are described in Table 2.

Table 2. Patient characteristics (AF group versus SR group)

	AF group (n=400)	SR group (n=800)	p-value
Age	66.60±10.1	65.83±9..3	0.228
(range)	(26-90)	(26-88)	
25-39	3 (0.8%)	6 (0.8%)	
40-49	22 (5.5%)	40 (5.0%)	
50-59	70 (17.5%)	139 (17.4%)	
60-69	137 (34.3%)	300 (37.5%)	
70-79	134 (33.5%)	277 (34.6%)	
80-	34 (8.5%)	38 (4.8%)	
Female gender	131 (32.8%)	274 (34.3%)	0.650
HTN	229 (57.3%)	479 (59.9%)	0.384
DM	95 (23.8%)	184 (23.0%)	0.772
Dyslipidemia	72 (18.0%)	128 (16.0%)	0.411

CKD	68 (17.0%)	86 (10.8%)	0.003
CHF (EF<35%)	28 (7.0%)	1 (0.1%)	<0.001

In AF group, prevalence of CKD or CHF was significantly higher than SR group. Patients' characteristics of AF group are described in Table 3, and age, hypertension, dyslipidemia, CKD, LA size, medication status and manifest $CHADS_2/CHA_2DS_2$-VASc scores were significantly different between patients with SIBL versus those without SIBL.

Table 3. Characteristics of patients with AF

	Total (n=400)	SIBL positive* (n=113)	SIBL negative* (n=287)	*p*-value
Age	66.60±10.1	69.82±8.3	65.33±10.5	<0.001
25-39	3 (0.3%)	0	3 (1.0%)	
40-49	22 (6.0%)	1 (0.9%)	21 (7.3%)	
50-59	70 (17.5%)	10 (8.8%)	60 (20.9%)	
60-69	137 (34.3%)	43 (38.1%)	94 (32.8%)	
70-79	134 (33.5%)	47 (41.6%)	87 (30.3%)	
80-	34 (8.5%)	12 (10.6%)	22 (7.7%)	

Female	131 (32.8%)	39 (34.5%)	92 (32.1%)	0.360
Valvular AF	26 (6.5%)	11 (9.7%)	15 (5.2%)	0.081
Underlying ds.				
CHF (EF<35%)	28 (7.0%)	7 (6.2%)	21 (7.3%)	0.440
HTN	229 (57.3%)	79 (69.9%)	150 (52.3%)	0.002
DM	95 (23.8%)	29 (25.7%)	66 (23.0%)	0.329
Vascular disease	33 (8.3%)	10 (8.8%)	23 (8.0%)	0.462
CKD	68 (17.0%)	26 (23.0%)	42 (14.6%)	0.034
Dyslipidemia	72 (18.0%)	29 (25.7%)	43 (15.0%)	0.010
Echocardiography				
LVEF (%)	58.55±8.8	58.75±8.6	58.46±8.9	0.779
LA size (mm)	47±8.7	50±10.3	46±7.4	0.014
Medication				
None	173 (43.3%)	38 (33.6%)	135 (47.0%)	
Aspirin	124 (31.0%)	35 (31.0%)	89 (31.0%)	
Warfarin	103 (25.8%)	40 (35.4%)	63 (22.0%)	

Manifest CHADS2 score			1.34±0.84	1.05±0.89	0.003
	0	95 (26.0%)	15 (14.7%)	80 (29.4%)	
	1	164 (43.9%)	46 (45.1%)	118 (43.4%)	
	2	89 (23.8%)	32 (31.4%)	57 (21.0%)	
	3	24 (6.4%)	9 (8.8%)	15 (5.5%)	
	4	2 (0.5%)	0 (0.0%)	2 (0.7%)	
Manifest CHA_2DS_2-VASc score			2.50±1.15	2.03±1.33	0.001
	0	38 (10.2%)	1 (1.0%)	37 (13.6%)	
	1	88 (23.5%)	21 (20.6%)	67 (24.6%)	
	2	99 (26.5%)	31 (30.4%)	68(25.0%)	
	3	91 (24.3%)	29 (28.4%)	62 (22.8%)	
	4	43 (11.5%)	15 (14.7%)	28 (10.3%)	
	5	15 (4.0%)	5 (4.9%)	10 (3.7%)	
Follow-up duration[†]		66.7±35.9 (10-162)	65.9±34.8 (10-157)	66.9±36.4 (12-162)	0.779

(range)

* SIBL positive, patients with SIBL; SIBL negative, patients without SIBL

† months

3. Univariate analysis of risk factors

With the total 1200 AF and SR subjects, presence of AF was a risk factor of SIBL (p<0.001, OR 5.549, 95% CI 3.897-7.903). Age (p<0.001, OR 1.921 per 10 years, 95% CI 1.564-2.360), HTN (p=0.017, OR 1.524, 95% CI 1.077-2.157), DM (p=0.005, OR 1.677, 95% CI 1.172-2.399), dyslipidemia (p=0.021, OR 1.598, 95% CI 1.072-2.382) and CKD (p=0.002, OR 1.962, 95% CI 1.286-2.993) also showed higher risk of SIBL.

In SR group, Age (p<0.001, OR 1.615 per 10 years, 95% CI 1.271-2.052), HTN (p=0.001, OR 2.122, 95% CI 1.3347-3.375), dyslipidemia (p=0.013, OR 1.959, 95% CI 1.151-3.336) and CKD (p=0.0462, OR 1.743, 95% CI 1.009-3.012) were risk factors on univariate study.

In AF group, age (p<0.001, OR 2.698 per 10 years, 95% CI 1.803-4.037), hypertension (p=0.001, OR 2.122, 95% CI 1.334-3.375), dyslipidemia (p=0.013, OR 1.959, 95% CI 1.151-3.336), CKD (p=0.046, OR 1.743, 95% CI 1.009-3.012) were risk factors on univariate study. Age (p<0.001), manifest $CHADS_2$ (p=0.036) and CHA_2DS_2-VASc scores (p=0.005) showed linear association with SIBL prevalence by linear regression. Compared to age 25-59? group, age 60-69 (p=0.021, OR=10.979, 95% CI 1.438-83.816), age

70-79 (p=0.013, OR 12.966, 95% CI 1.700-98.879), age ≥ 80 (p=0.002, OR 13.091, 95% CI 1.571-109.110) showed increased risk of SIBL incrementally.

4. Multivariate analysis of risk factors

With the total 1200 AF and SR subjects, presence of AF was the most powerful risk factor of SIBL (p<0.001, OR 5.597, 95% CI 3.889-8.055) by multivariate analysis adjusted with HTN, DM, dyslipidemia, CKD and age. Age (p<0.001, OR 5.597 per 10 years, 95% CI 3.889-8.055) and diabetes (p=0.043, OR 1.817, 95% CI 1.459-2.263) were also significant independent risk factors.

In SR group, age (p=0.001, OR 1.527 per 10 years, 95% CI 1.186-1.968), HTN (p=0.028, OR 1.729, 95% CI 1.062-2.815) and dyslipidemia (p=0.032, OR 1.824, 95% CI 1.053-3.159) were independent risk factors by multivariate analysis including HTN, DM, dyslipidemia, CKD and age

In AF group, with the analysis of independent risk factors for SIBL, age (p<0.001, OR 1.609 per 10 years, 95% CI 1.237-2.091), HTN (p=0.016, OR 1.849, 95% CI 1.122-3.045), dyslipidemia (p=0.014, OR 2.062, 95% CI 1.155-3.682) and valvular AF (p=0.012, OR 3.157, 95% CI 1.287-7.741) were significantly associated with SIBL (Table 4). In 374 non-valvular AF patients, age (p=0.001, OR=1.609 per 10 years, 95% CI 1.223-2.116), hypertension (p=0.006, OR 2.086, 95% CI 1.230-3.538) and presence of dyslipidemia (p=0.016, OR=2.073, 95% CI 1.144-3.756) still had higher SIBL risk

significantly. Additional analysis was performed after the study subjects with non-valvular AF had been divided into 2 groups according to age: younger group (age < 65 years) and older group (age ≥65 years). In the younger group (n=149), history of hypertension (p=0.001) was the only significant independent risk factor of SIBL. In the older group (n=251), dyslipidemia (p=0.026) was the only significant risk factor rather than hypertension.

Table 4. Multivariate analysis of risk factors by multiple logistic regression

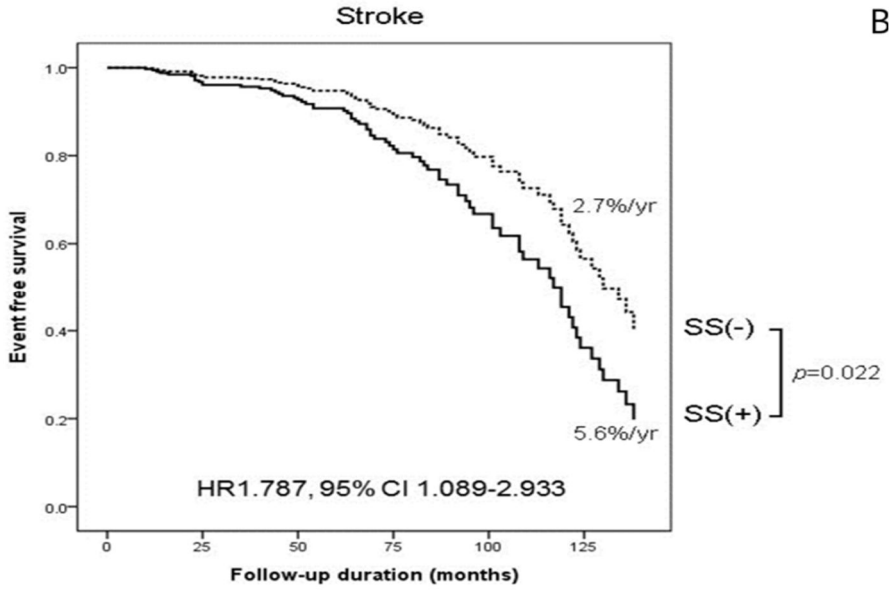
Risk factors	p-value	OR	95% CI
Age	<0.001	1.609*	1.237-2.091
Male sex	0.983	1.005	0.613-1.649
Valvular AF	0.012	3.157	1.287-7.741
CHF	0.330	0.629	0.248-1.598
HTN	0.016	1.849	1.122-3.045
DM	0.889	0.963	0.565-1.640
Vascular disease	0.390	0.689	0.295-1.611
CKD	0.467	1.252	0.683-2.294
Dyslipidemia	0.014	2.062	1.155-3.682
LA size	0.202	1.007	0.996-1.017

* per 10 years

5. Clinical outcomes in patients with atrial fibrillation and silent ischemic brain lesion

Follow-up duration for AF patients was 66.7±35.9 months (range 10 - 162, median 65.0 months). There were total 80 overt stroke events (3.6%/year) during follow-up period (65 cerebral infarction, 9 cerebellar infarction and 6 lacunar infarction). The annual stroke risk was elevated according to increase of manifest $CHADS_2$ or manifest CHA_2DS_2-VASc scores. Clinically overt stroke incidence was significantly higher in AF patients with SIBL (5.6%/yr, p=0.022, hazard ratio 1.787, 95% CI 1.089-2.933) than those without SIBL (2.7%/yr) when age, gender, CHF, HTN, DM, dyslipidemia, vascular disease and CKD were adjusted (Figure 1A). However dementia or cognitive disorder incidence were not associated with SIBL prevalence in our study (3.3%/yr versus 1.9%/yr, p=0.269, Figure 1B).

(A) stroke-free survival curve and annual stroke rate of each group



(B) dementia and cognitive disorder-free survival curve and annual event rate of each group

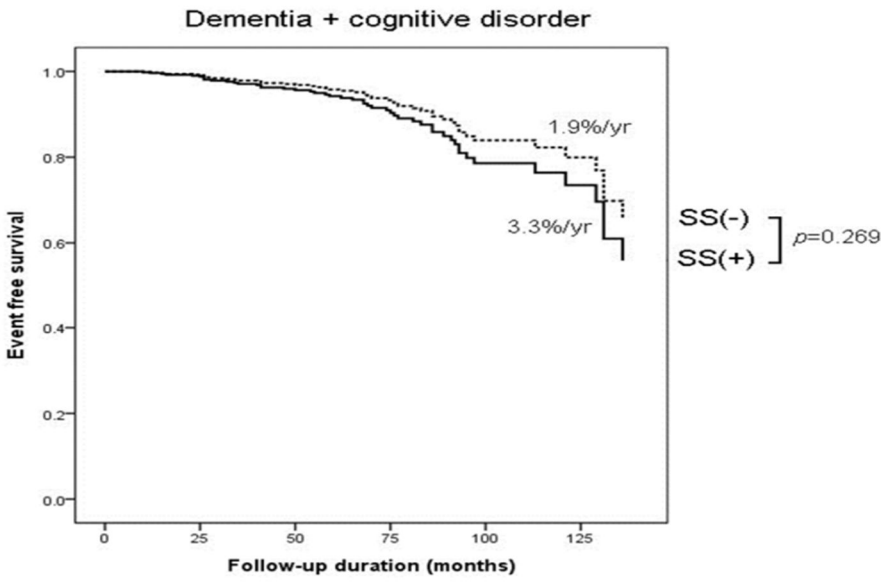


Figure 1. Clinical outcome of AF patients with or without silent ischemic

brain lesion.

The solid line indicates survival curve for patients with SIBL and the dotted line for those without SIBL. A, stroke-free survival curve and annual stroke rate of each group; B, dementia and cognitive disorder-free survival curve and annual event rate of each group. Symptomatic stroke risk was significantly higher in AF patients with SIBL (p=0.022, hazard ratio 1.787, 95% CI 1.089-2.933) than those without SIBL, but dementia and cognitive disorder risk was not different between two groups.

6. Manifest and true $CHADS_2$ and CHA_2DS_2-VASc scores

Among 374 non-valvular AF patients, there were 95 patients with manifest $CHADS_2$ score 0 and 164 patients with manifest $CHADS_2$ score 1. Among 95 $CHADS_2$ score 0 patients, SIBL were observed in 15 (15.8%) patients, whose true $CHADS_2$ score was 2. Among the 95 patients, total 13 (13.7%) patients experienced overt stroke event during the follow-up period, but 5 (33.3%) of 15 patients with true $CHADS_2$ score 2 had overt stroke events. Among 164 $CHADS_2$ score 1 patients, SIBL was found in 46 (28.0%) patients, whose true $CHADS_2$ score was 3. Among the 164 patients, total 24 (14.6%) patients experienced overt stroke event during the follow-up period, but 12 (26.1%) of 46 patients with true $CHADS_2$ score 3 had overt stroke events. To sum up, the thromboembolic risk of 61 (23.6%) patients among 259 patients with manifest $CHADS_2$ score 0 or 1, whose true score was 2 or 3, were underestimated and

only 16 (26.2%) patients were taking warfarin (Figure 2A).

There were total 38 patients with manifest CHA_2DS_2-VASc score 0 and 88 patients with manifest CHA_2DS_2-VASc score 1. Among 38 CHA_2DS_2-VASc score 0 patients, SIBL were observed in only 1 (2.6%) patients, whose true CHA_2DS_2-VASc score was 2. Among the 38 patients, total 4 (10.5%) patients experienced overt stroke event during the follow-up period. Among the 88 manifest CHA_2DS_2-VASc score 1 patient, SIBL was observed in 21 (23.8%) patients, whose true CHA_2DS_2-VASc score was 3. Among the 88 patients, total 14 (15.9%) patients experienced overt stroke event during the follow-up period, but 8 (38.1%) of 21 patients with true $CHADS_2$ score 3 had overt stroke events. To sum up, the thromboembolic risk of 22 (23.6%) patients among 126 patients with manifest CHA_2DS_2-VASc score 0 or 1, whose true score was 2 or 3, were underestimated and only 22 (31.8%) patients were taking warfarin (Figure 2B).

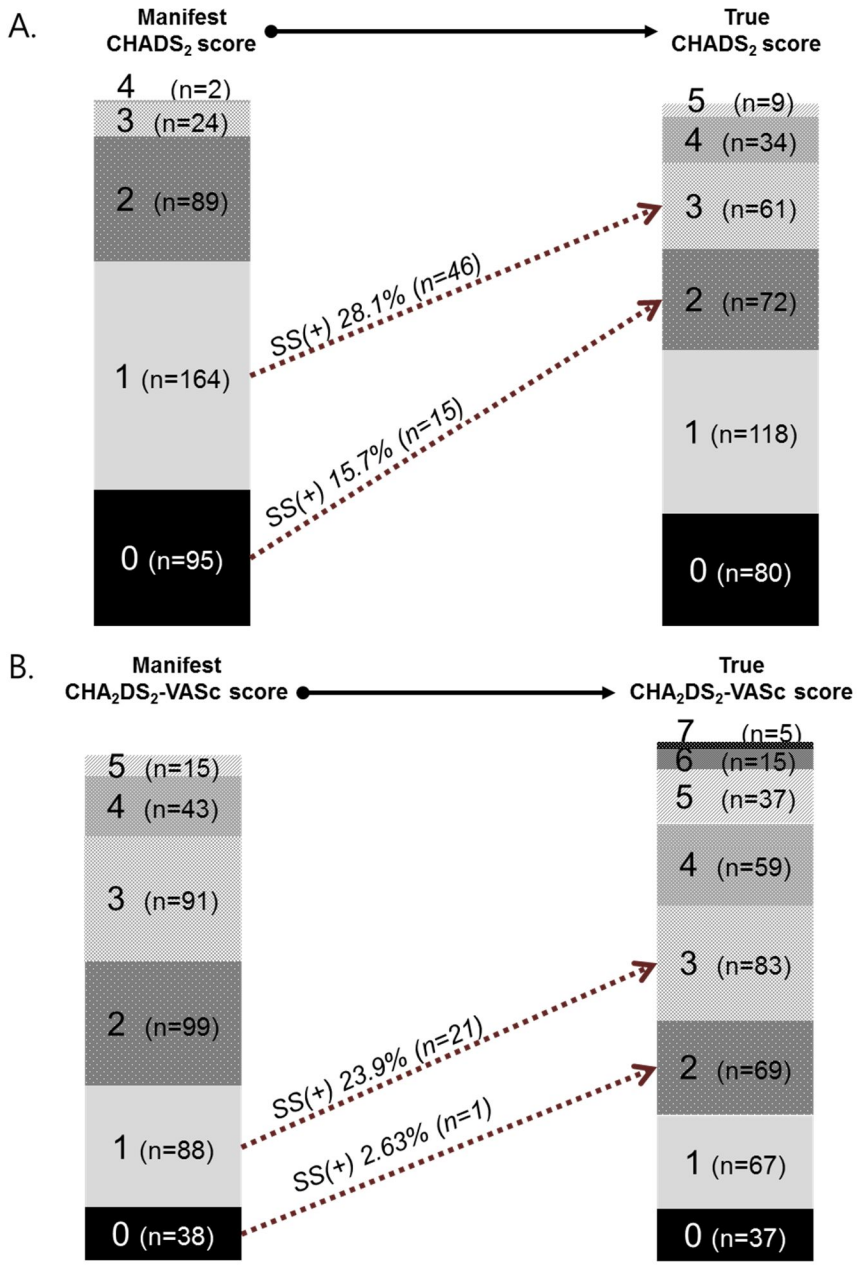


Figure 2. Distribution of manifest and true CHADS2 and CHA2DS2-VASc score. A. the thromboembolic risk of 61 (23.6%) patients among 259 patients with manifest CHADS2 score 0 or 1 were underestimated. B. the

thromboembolic risk of 22 (23.6%) patients among 126 patients with manifest CHA2DS2-VASc score 0 or 1 were underestimated.

DISCUSSION

SIBL is known to be a precursor of symptomatic stroke, dementia or cognitive disorder. There have been several previous studies on the prevalence of SIBL among AF patients (Table 1). Our study demonstrated that the prevalence of SIBL in AF patients is 28.3% on MRI data, that is significantly higher than normal individuals (6.6%) and the prevalence increased with age.

Risk factors for SIBL have not been studied yet in AF population. In clinically normal individuals, age and a history of hypertension have been the most consistent risk factors for SIBL in most of the studies.(26-28) A low plasma HDL-cholesterol level and a high degree of blood viscosity have also been reported as risk factors in studies dealing with hypertensive subjects.(29, 30) Risk factors for SIBL in symptomatic stroke patients would be more variable. Age had been the most consistent risk factor,(27, 31) and other risk factors were hypertension,(31, 32) male gender,(31-33) glucose intolerance,(4) ischemic changes on ECG,(32) and left atrial enlargement.(34)

In our study, old age, dyslipidemia, HTN, and CKD were significant risk factors on univariate analysis. However, multivariate analysis revealed that independent risk factors for SIBL were age, HTN, dyslipidemia and valvular AF. Valvular AF showed significantly higher risk of SIBL in multivariate analysis, but not in univariate analysis. . This might be because the patients age was significantly younger than non-valvular AF patients (62.1 versus 66.9 years, VAF vs. NVAF, p=0.024,) and HTN prevalence (11.5%) tended to be

lower in valvular AF patients (p=0.063).

As shown in our study, overt stroke risk was significantly higher in AF patients with SIBL than those without SIBL (2.7%/yr) regardless of age, sex, CHF, HTN, DM, dyslipidemia, vascular disease, and CKD. However, dementia or cognitive disorder incidence were not associated with SIBL prevalence in our study. This could be the counterevidence that clinicians did not usually pay attention to the patients' cognitive function, so that the diagnosis of dementia or cognitive disorder had been delayed in the real world practice.

In our study, 61 (23.6%) patients with SIBL had "manifest" $CHADS_2$ score of 0 or 1. However their "true" CHADS2 score were 2 or 3, and only 16 patients were taking warfarin. Among the 45 patients without anticoagulation, 10 patients experienced symptomatic stroke event during follow-up (4.0%/yr), which is similar to the adjusted stroke risk of $CHADS_2$ score 2 patients.(35) As it is, probably significant but unknown portion of patients with $CHADS_2$ score of zero or one has been undertreated in terms of stroke prevention. Therefore the imaging test of SIBL for patients with AF should be considered for stroke risk stratification.

This is the largest scale study about SIBL in AF patients using MRI data. Moreover this paper firstly investigated risk factors of SIBL in AF patients. The presence of SIBL on MRI is frequently observed in more than a quarter (28.3%) of AF population, especially in patients with valvular AF. Old age, hypertension and dyslipidemia were also potent independent predictors for SIBL. By using current scoring system without imaging test, clinicians have

underestimated the stroke risk, and many AF patients might not receive optimal anticoagulation treatment. In this study, the thromboembolic risk of about a quarter of patients with manifest $CHADS_2$ score ≤ 1 patients or manifest CHA_2DS_2-VASc score ≤ 1 were underestimated Screening MRI for detection of silent ischemic brain lesion could be considered for risk evaluation for patients with AF, especially valvular AF, elderly patients, and patients with dyslipidemia or hypertension.

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국문 초록

서론: 심방 세동 환자에서 발생하는 무증상 허혈성 뇌병변의 유병률은 다양하게 보고되고 있다. 뇌병변 병력은 심방 세동 환자의 허혈성 질환 발생 위험도를 측정하는 $CHADS_2$ 점수 체계의 항목으로 포함되기 때문에, 무증상 허혈성 뇌병변을 가진 환자들은 그 위험도가 과소평가될 가능성이 높다. 따라서 이 논문에서는 뇌 자기 공명 영상을 이용하여 심방 세동 환자에서 무증상 허혈성 뇌병변의 유병률을 조사함과 동시에 예후를 분석해본다.

방법: 심전도에서 심방 세동 (N=400) 및 정상 심장 리듬 (N=800)이 확인된 1200명을 대상으로 하였다. 이 환자들은 특별한 신경계 증상 없이 건강검진을 목적으로 뇌 자기 공명 영상을 시행하였다. 심방 세동 환자에서 검사 이후 발생한, 증상을 동반한 뇌경색, 치매 그리고 인지 기능 장애 발생 여부를 예후 분석에 포함하였다. 환자들은 평균 66.7개월의 (10개월 이상 162개월 이하) 경과 관찰 기간을 가지고 있었다.

결과: 심방 세동 환자에서 무증상 허혈성 뇌병변은 총 113명 (28.3%)에서 발견되었고, 이것은 정상 심장 리듬을 가진 환자에서보다 통계적으로 5배 이상 많은 것으로 나타났다. ($p<0.001$, OR

5.549)심방 세동 환자에서 무증상 허혈성 뇌병변의 위험인자로는 연령 (OR=1.049), 고혈압 (OR=2.086), 고지혈증 (OR=2.073), 그리고 판막성 심방세동 (OR=3.157)인 것으로 나타났다. 심방 세동 환자를 대상으로 한 예후 분석에서, 무증상 허혈성 뇌병변을 가지고 있는 환자에서 증상을 동반한 뇌경색은 발병은 유의하게 높아졌으나 (5.6%/연 대 2.7%/연), 치매와 인지기능 장애에 있어서는 차이를 보이지 않았다.

결론: 무증상 허혈성 뇌병변은 심방 세동 환자의 4분의 1이상에서 확인되며, 특히 고령, 고혈압 환자, 고지혈증 환자 그리고 판막성 심방 세동 환자일 경우 그 유병률이 높게 나타났다. 따라서 심방 세동 환자의 허혈성 질환 발병 위험도를 정확히 평가하기 위해서는 선별 검사 목적의 뇌 자기 공명 영상이 필요할 수 있겠다.

주요어: 무증상 허혈성 뇌병변, 심방 세동, 자기 공명 영상

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