의학석사 학위논문

Risk of ischemic stroke in patients with suspected coronary artery disease, according to coronary computed tomographic angiography and myocardial single-photon emission computed tomography findings

관상동맥질환 의심 환자에서 관상동맥 조영 CT 와 심근 SPECT 를 통해 살펴본 허혈성 뇌경색의 위험도

2015 년 2 월

서울대학교 대학원

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지도 교수 김 용 진

이 논문을 의학석사 학위논문으로 제출함.

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이 희 선

이희선의 의학석사 학위논문을 인준함.

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ABSTRACT

Background Coronary artery disease (CAD) is considered an important cause of morbidity and mortality in patients with ischemic stroke. However, risk for ischemic stroke in patients with CAD remains unclear. We evaluated the risk of ischemic stroke according to the presence, severity, and extent of CAD evidenced by coronary computed tomographic angiography (CCTA) and single-photon emission computed tomography (SPECT) in patients with suspected CAD.

Methods We studied 1137 patients with suspected CAD, but without a history of CAD or stroke, who underwent both CCTA and SPECT for the evaluation of CAD between 2004 and 2011.

Results During a median follow-up period of 26 months, ischemic stroke was observed in 25 of 1137 patients (2.2%). The presence of coronary atherosclerotic plaque on CCTA was associated with a > 4-fold hazard increase for ischemic stroke (unadjusted hazard ration [HR] 4.38; 95% confidence interval [CI] 1.03–18.64; p = 0.046). Plaque in ≥ 2 vessels was associated with a >3-fold further increase in the risk of ischemic stroke compared with plaque only in one vessel (unadjusted HR 3.68; 95% CI 1.57–8.62; p = 0.003), whereas plaque of ≥ 50% diameter stenosis was not associated with increased risk compared with plaque of < 50% diameter stenosis (unadjusted HR 1.03; 95% CI 0.43–2.46; p = 0.943). The presence and extent of perfusion defect, and summed stress score on SPECT were not associated with ischemic stroke.

Conclusions The risk of ischemic stroke was associated with the presence and

extent of coronary atherosclerosis evidenced by CCTA, but not with the presence and extent of myocardial ischemia evidenced by SPECT. CCTA may provide additional information with regard to the risk of ischemic stroke in patients with suspected CAD.

Keywords: Ischemic stroke; Coronary artery disease; Computed tomography; Single-photon emission computed tomography;

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ACS = acute coronary syndrome

CACS = coronary artery calcium scores

CAD = coronary artery disease

CCTA = coronary computed tomographic angiography

CI = confidence interval

DS = diameter stenosis

HR = hazard ratio

PD = perfusion defect

SPECT = single-photon emission computed tomography

SSS = summed stress score

INTRODUCTION

Ischemic stroke and coronary artery disease (CAD) share common risk factors and pathophysiology (1,2). In patients with ischemic stroke, CAD is considered the most important cause of morbidity and mortality (3-5). Thus, the American Heart Association and American Stroke Association currently recommend comprehensive cardiovascular risk assessment and management for all patients with ischemic stroke (1). However, the risk of stroke in patients with CAD is not well understood. Although several studies have described the occurrence of stroke after acute coronary syndrome (ACS) (6,7), the risk of ischemic stroke in patients with stable CAD has not been evaluated.

Noninvasive cardiac imaging is being used increasingly for the evaluation of CAD (8). Myocardial single-photon emission computed tomography (SPECT) and coronary computed tomographic angiography (CCTA) have been widely utilized for the evaluation of CAD with excellent diagnostic value (9,10). Myocardial SPECT demonstrates stress-inducible myocardial ischemia, whereas CCTA detects coronary atherosclerosis with providing the anatomic information of stenosis (10,11). Additionally, the prognostic values of CCTA and SPECT for adverse cardiovascular events have been well evaluated (12,13). However, to date, the association of CCTA or SPECT findings with the risk of ischemic stroke has not been investigated. In the present study, we investigated the risk of ischemic stroke according to the presence, severity, and extent of CAD evidenced by CCTA and SPECT in patients with suspected CAD.

METHODS

Study population

We reviewed the medical records of 1818 patients who underwent both CCTA and myocardial SPECT for the evaluation of CAD within 90 days at Seoul National University Hospital and Seoul National University Bundang Hospital between November 2004 and November 2010. Among them, 516 patients with a history of CAD (defined as stable angina or ACS with or without coronary revascularization) and 148 patients with a history of stroke (defined as a diagnosis of ischemic, hemorrhagic, or transient stroke recorded in medical history or documents) were excluded. Thus, 1154 patients remained for the study analysis (Figure 1). The Institutional Review Board of the Seoul National University Hospital and Seoul National University Bundang Hospital approved this retrospective study and waived the requirement for written informed consent.

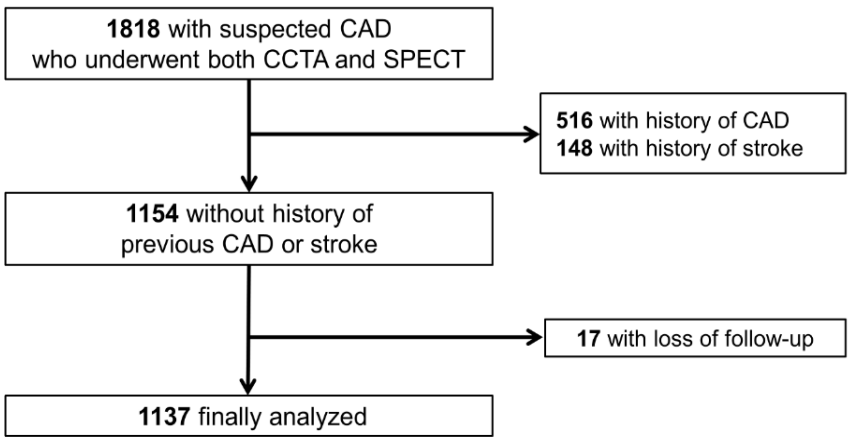

Figure 1. Flow chart of the study population

CCTA image with coronary artery calcification acquisition and analysis

CCTAs were performed using 16- or 64-detector row CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany; Brilliance 16 or 64, Philips Medical Systems, Best, the Netherlands). A ß-blocker (metoprolol or esmolol) was administered intravenously or orally to reduce the heart rate in patients with heart rate ≥70 beats/min. Sublingual nitroglycerin was given to all subjects immediately before scanning. Unenhanced scan for calcium scoring was performed in 952 of 1154 (82.5%) patients using prospective electrocardiography (ECG) triggering (section collimation 64 × 0.625 mm, rotation time 0.42 s, tube voltage 120 kV, tube current 150 mAs). CCTA was performed in all subjects using standard retrospective ECG gating with ECG-gated dose modulation (section collimation 64 × 0.625 mm, rotation time 0.42 s, tube voltage 120 kV, tube current 800 mAs). A bolus of 60–80 mL of contrast (Iomeron 400, Bracco Imaging SpA, Milan, Italy) was injected (4 mL/s), followed by a 50-mL saline flush. Unenhanced CT scans and contrast-enhanced CT angiograms were reconstructed retrospectively with a non-overlapping slice thickness of 3 and 0.6 mm, respectively.

All CCTA results were transferred to an external three-dimensional workstation and analyzed by two investigators who were blinded to patient clinical information. Plaque was represented by lesions >1 mm^2 within or adjacent to the vessel or adjacent to the vessel lumen but distinct from the pericardial tissue, epicardial fat, and the lumen itself. Patients were categorized as no plaque, plaque of <50% diameter stenosis (DS), and ≥50%

DS. Coronary artery calcium scores (CACS) were measured using the scoring system previously described by Agatston et al (14). Based on the CACS, patients were categorized in the following manner: 0, 1–399, and ≥400 (15).

SPECT image acquisition and analysis

Rest-stress myocardial SPECT (CardioMD, Philips Medical Systems; Vertex-60, Philips-ADAC, Hanover, Cleveland, USA) was performed with pharmacologic stress, using either technetium-99m tetrofosmin or sestamibi as the radiotracers (16). Rest images were acquired 1 h after administration of 8–10 mCi technetium-99m. Then, stress images were obtained while pharmacologic stress was induced by an infusion of adenosine (0.14 mg/kg/min for 6 min) or dipyridamole (0.142 mg/kg/min for 3 min) and the radiotracer (25 mCi technetium-99m for 3 min) at peak stress in sequence. Gated images were obtained 90 min after stress was induced. Imaging processing generated 3 planes of tomographic slice images of the left ventricle, the short axis, long vertical axis, and long horizontal axis, which were reconstructed with ECG synchronization (17).

Interpretation of SPECT images was carried out by two investigators who were blinded to patient clinical information, and it was based on polar maps of perfusion using a 17-segment model in accordance with the recommendations of the American Society of Nuclear Cardiology (18). Patients were categorized according to the presence or absence of perfusion defects (PDs). PDs were assessed on the stress image (segmental tracer activity <75% of the maximum) and divided into reversible (≥10% increase in

tracer uptake on the resting phase) and fixed (irreversible change on the resting phase) PD (17). For quantification of perfusion scintigraphy, a numerical value was visually assigned to each segment by checking radiotracer activity in stress phases according to a 5-point scale (0: normal; 1: mild; 2: moderate; 3: severe; or 4: absent). A summed stress score (SSS) was calculated by adding all the segmental scores during stress and was utilized for the analysis. The severity of myocardial ischemia was classified according to SSS ≤8 or >8 (19). The extent of coronary vascular territories was used for the analysis: 1- or ≥2-vessel territory. Although it is well recognized that the anatomy of the coronary tree can be variable, coronary vascular territories were assigned fixedly by general assumptions about the most frequent vascular distribution (20).

Follow-up information

Follow-up information was obtained from hospital records described by the attending clinical physicians. Ischemic stroke was regarded as the clinical end point, and hemorrhagic stroke was excluded due to the different mechanism. Ischemic stroke was diagnosed by typical neurologic signs and symptoms assessed by neurologists and noninvasive brain imaging such as brain CT and/or magnetic resonance imaging (21). Cases of ischemic stroke occurring within 24 h after coronary catheterization were excluded from the final analysis because they may have resulted from the procedure itself (22).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are presented as absolute values and their proportions. Differences between continuous variables were compared by the Student's *t* test for independent samples, and those between categorical variables were analyzed by the χ^2 test or Fisher's exact test, as appropriate. A value of $p < 0.05$ with 95% confidence interval (CI) was considered significance. To estimate the risk of ischemic stroke according to CCTA and SPECT findings, Kaplan–Meier survival curves were drawn. Differences between time-to-event curves were compared with the log-rank test. Cox proportional hazard model was used to estimate the risk of a given variable as expressed with a hazard ratio (HR) and corresponding 95% CI. All analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Of 1154 patients, 17 (1.5%) patients were lost to follow-up. Thus, 1137 subjects (711 men; mean age, 62 ± 10 years) remained for the final analysis (Table 1). A total of 817 (71.8%) patients had coronary atherosclerotic plaque on CCTA; 318 (39.9%) patients had plaque of <50% DS and 499 (61.1%) had plaque of ≥50% DS. Of these, 603 (73.8%) patients had plaque in one coronary vessel, and 214 (26.2%) in ≥2 vessels. Patients with atherosclerotic plaque on CCTA were more likely to be men, smokers, and those with a history of hypertension, diabetes mellitus, or hyperlipidemia. In 952 patients whose CACS were calculated, 271 (28.5%) patients had a CACS of 0; 537 (56.4%), of 1–399; and 144 (15.1%), of ≥400. Of 1137 patients, 349 (30.7%) had any type of PD by myocardial SPECT; of these, 287 (82.2%) and 62 (17.8%) patients had reversible or fixed PD, respectively. Of these, 271 (77.6%) patients had SSS ≤8, and 78 (22.3%) had SSS >8; 274 (78.5%) patients had PD in 1-vessel territory, and 75 (21.5%) had PD in ≥2-vessel territories. Patients with any type of PD were more likely to be men and smokers.

During a median follow-up period of 26 (interquartile range, 14–43) months, ischemic stroke was observed in 25 (2.2%) of 1137 patients. The occurrence of ischemic stroke during follow-up is summarized in Table 2. While 23 (2.8%) of 817 patients with plaque on CCTA experienced ischemic stroke, only 2 (0.6%) of 320 without plaque experienced ischemic stroke (*log-rank p* = 0.029). When we compared the risk ischemic stroke in patients with plaque on CCTA, there was no significant difference between patients with

plaque of <50% DS (9/318, 2.8%) and those with plaque of ≥50% DS (14/499, 2.8%; *log-rank p* = 0.943). Whereas, the incidence of ischemic stroke was significantly increased in patients with plaque observed in ≥2 vessels (13/214, 6.1%) compared with that in patients with plaque in only 1 vessel (10/603, 1.7%) (*log-rank p* = 0.001). In 952 patients whose CACS was calculated, ischemic stroke was significantly increased in patients with a CACS of ≥400 (6/144, 4.2%), compared with those with a CACS of 1–399 (9/537, 1.7%) and those with a CACS of 0 (2/271, 0.7%; *log-rank p* = 0.017, and 0.037, respectively). Kaplan-Meier curves, stratified by the presence of plaque, DS of 50%, multi-vessels involvement, and CACS are illustrated in Figure 2.

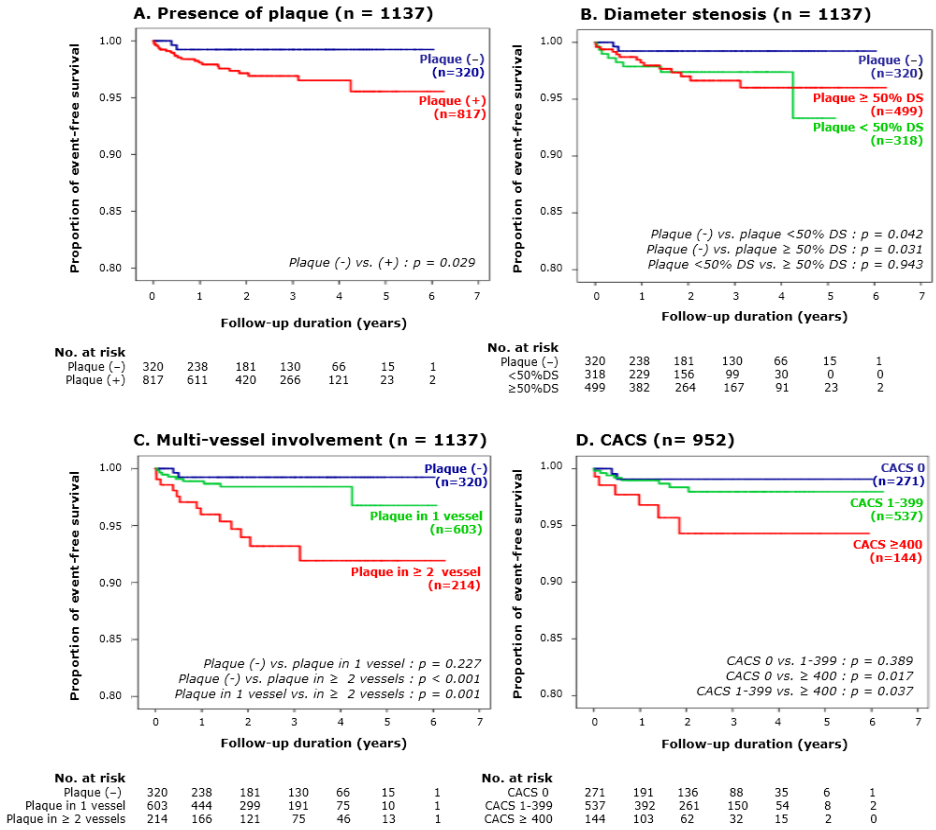

Figure 2. Kaplan–Meier survival curves according to coronary computed tomographic angiography findings Curves stratified by (A) the presence of coronary atherosclerotic plaque, (B) diameter stenosis of 50%, (C) number of vessels with plaque, and (D) coronary artery calcium scores.

When stratified by SPECT findings, ischemic stroke was observed in 7 (2.0%) of 349 patients with any type of PD and in 18 (2.3%) of 788 patients without PD (*log-rank p* = 0.768). When we compared the risk of ischemic stroke in patients with PD, there was no significant difference between patients with reversible PD (6/287, 2.1%) and those with fixed PD (1/62, 1.6%; *log-rank p* = 0.802), between patients with SSS ≤8 (6/272, 2.2%) and

those with SSS >8 (1/77, 1.3%; *log-rank p* = 0.636), and between patients with PD in 1-vessel territories (5/274, 1.8%) and those with PD in ≥2-vessel territories (2/75, 2.7%; *log-rank p* = 0.663). Kaplan–Meier curves, stratified by the presence of PD, reversible or fixed PD, SSS of 8, and multi-vessels involvement are illustrated in Figure 3.

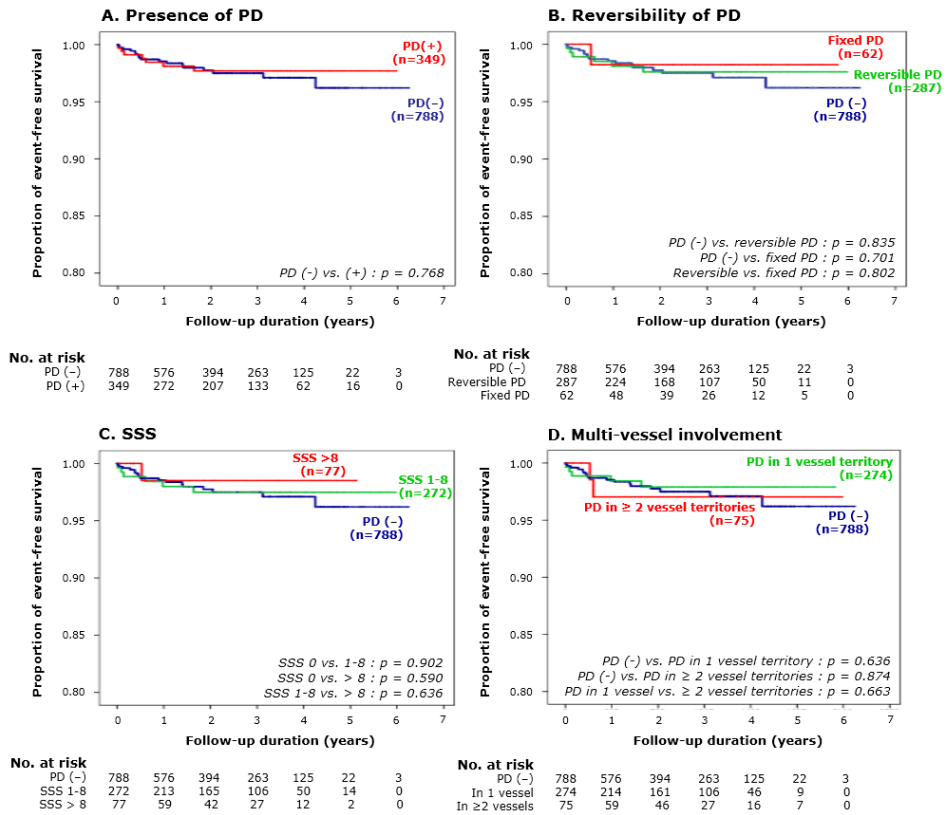

Figure 3. Kaplan–Meier survival curves according to single-photon emission computed tomography findings Curves stratified by (A) the presence of any perfusion defect, (B) fixed or reversible perfusion defect, (C) summed stress score, and (D) number of vessel territories of perfusion defect.

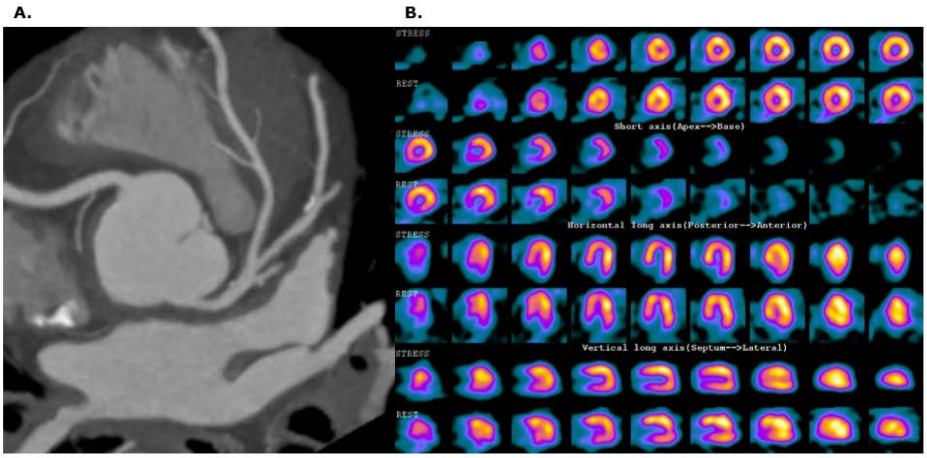

Figure 4. Coronary CT angiography and SPECT images in a 62-year-old man with chest pain who experienced ischemic stroke 1 year after coronary evaluation. (A) Thin-slap maximum intensity projection image of coronary CT angiography shows atherosclerotic plaques in the left main, left circumflex artery and diagonal branch. (B) Myocardial SPECT images demonstrate no perfusion defect.

Univariate analyses of factors associated with ischemic stroke are summarized in Table 3. The presence of atherosclerotic plaque on CCTA was a significant predictor of ischemic stroke with a >4-fold increase in the risk (unadjusted HR 4.38; 95% CI 1.03–18.64; p = 0.046). Plaque of ≥50% DS was also associated >4-fold increase in the risk of ischemic stroke compared with no plaque (unadjusted HR 4.44; 95% CI 1.01–19.52; p = 0.049), but was not associated with increased risk compared with plaque of <50% DS (unadjusted HR 1.03; 95% CI 0.43–2.46; p = 0.943). Coronary plaque observed in ≥2 vessels was associated with increased risk compared with no

plaque (unadjusted HR 9.17; 95% CI 2.07–40.65; p = 0.004) and plaque in 1 vessel (unadjusted HR 3.68; 95% CI 1.57–8.62; p = 0.003). In patients whose CACS was calculated (n = 952), CACS ≥400 showed increased risk of ischemic stroke compared with CACS 0 (unadjusted HR 5.72; 95% CI 1.16–28.37; p = 0.033) and CACS 1–399 (unadjusted HR 2.93; 95% CI 1.02–8.46; p = 0.046). The presence of any PD on myocardial SPECT was not associated with an increased risk of ischemic stroke (unadjusted HR 0.86; 95% CI 0.36–2.09; p = 0.747). Presence of fixed PD was not associated with an increased risk of ischemic stroke compared with reversible PD (unadjusted HR 0.76; 95% CI 0.09–6.34; p = 0.802) and no PD (unadjusted HR 0.68; 95% CI 0.09–5.11; p = 0.708). PD with SSS >8 also was not associated with the risk of ischemic stroke compared with PD with SSS 1–8 (unadjusted HR 0.60; 95% CI 0.07–5.01; p = 0.639) and no PD (unadjusted HR 0.58; 95% CI 0.07–4.28; p = 0.584). PD observed in ≥2-vessel territories was not associated with increased risk compared with PD in 1-vessel territories (unadjusted HR 1.43; 95% CI 0.27–7.38; p = 0.668) and no PD (unadjusted HR 1.13; 95% CI 0.26–4.89; p = 0.645).

Table 1. Baseline characteristics of patients with coronary artery disease

Characteristics	Total (n=1137)	Plaque on CCTA		*p* value	PD on SPECT		*p* value
		Yes (n=817)	No (n=320)		Yes (n=349)	No (n=788)	
Age, years	61.7 ± 10.3	63.2 ± 9.8	57.7 ± 10.6	0.052	62.2 ± 11.0	61.4 ± 10.0	0.132
Male, n (%)	711 (62.5)	542 (66.3)	169 (52.8)	0.000	245 (70.2)	466 (59.1)	0.000
BMI, kg/m^2	25.0 ± 3.4	25.0 ± 3.4	25.0 ± 3.4	0.878	25.1 ± 3.6	24.9 ± 3.3	0.175
Current smoking, n (%)	199 (17.5)	154 (18.8)	45 (14.1)	0.493	72 (25.0)	127 (22.7)	0.458
Diabetes, n (%)	568 (50.0)	433 (53.1)	135 (42.2)	0.001	177 (50.9)	391 (49.6)	0.699
Hypertension, n (%)	499 (43.9)	389 (47.7)	110 (34.4)	0.001	156 (44.8)	343 (43.5)	0.684
Hyperlipidemia, n (%)	587 (51.6)	447 (54.7)	140 (43.8)	0.001	176 (50.4)	411 (52.2)	0.591

CCTA = cardiac computed tomographic angiography; PD = perfusion defect; SPECT = single-photon emission computed tomography; BMI = body mass index

Table 2. The occurrence of ischemic stroke

	Ischemic stroke (%)	Log-rank *p*
CCTA findings		
In the entire cohort (n = 1137)		
Absence of plaque (n = 320)	2 (0.6%)	0.029
Presence of plaque (n = 817)	23 (2.8%)	
In patients with plaque (n = 817)		
Plaque <50% DS (n = 318)	9 (2.8%)	0.943
Plaque ≥50% DS (n = 499)	14 (2.8%)	
Plaque in 1 vessel (n = 603)	10 (1.7%)	0.001
Plaque in ≥ 2 vessels (n = 214)	13 (6.1%)	
In patients with CACS (n = 952)		
CACS 0 (n = 271)	2 (0.7%)	0.389
CACS 1-399 (n = 537)	9 (1.7%)	0.037
CACS ≥400 (n = 144)	6 (4.2%)	0.017
SPECT findings		
In the entire cohort (n = 1137)		
Absence of PD (n = 788)	18 (2.3%)	0.768
Presence of PD (n = 349)	7 (2.0%)	
In patients with any PD (n = 349)		
Reversible PD (n = 287)	6 (2.1%)	0.802
Fixed PD (n = 62)	1 (1.6%)	
PD with SSS ≤8 (n = 272)	6 (2.2%)	0.636
PD with SSS >8 (n = 77)	1 (1.3%)	
PD in 1 vessel territory (n = 274)	5 (1.8%)	0.663
PD in ≥2 vessel territories (n = 75)	2 (2.7%)	

DS = diameter stenosis; CACS = coronary artery calcium scores; SSS = summed stress scores; other abbreviations are same as Table 1.

Table 3. Univariate analysis of factors associated with ischemic stroke

Variables	Unadjusted HR (95% CI)	P value
Clinical variables (n = 1137)		
Age	1.04 (1.00 – 1.09)	0.063
Sex	1.82 (0.73 – 4.57)	0.200
BMI	0.92 (0.81 – 1.05)	0.216
Current smoking	1.51 (0.62 – 3.71)	0.367
Diabetes	1.26 (0.57 – 2.79)	0.569
Hypertension	0.93 (0.42 – 2.06)	0.865
Hypercholesterolemia	1.12 (0.50 – 2.48)	0.796
CCTA findings (n = 1137)		
Presence of plaque	4.38 (1.03 – 18.64)	0.046
Presence of <50% DS	1.03 (0.43 – 2.46)	0.943
Presence of plaque ≥50% DS	4.44 (1.01 – 19.52)	0.049
Plaque in 1 vessel	3.68 (1.57 – 8.62)	0.003
Plaque in 2 or more vessels	9.17 (2.07 – 40.65)	0.004
CACS (n = 952)		
CACS >0	2.38 (0.68 – 8.35)	0.176
CACS 1-399	2.93 (1.02 – 8.46)	0.046
CACS ≥400	5.72 (1.16 – 28.37)	0.033
SPECT findings (n = 1137)		
Presence of any PD	0.86 (0.36 – 2.09)	0.747
Fixed PD	0.68 (0.09 – 5.11)	0.708
Reversible PD	0.76 (0.09 – 6.34)	0.802
SSS 1-8	0.60 (0.07 – 5.01)	0.639

SSS >8	0.58 (0.07 – 4.28)	0.584
PD in 1 vessel territories	1.43 (0.27 – 7.38)	0.668
PD in 2 or more vessels territories	1.13 (0.26 – 4.89)	0.645

HR = hazard ratio; CI = confidence interval; other abbreviations are same as Table 1 and 2.

DISCUSSION

In the present study, we studied the risk of ischemic stroke in patients with suspected CAD who underwent both CCTA and SPECT. There were several important findings. Overall, we found that the presence of coronary atherosclerotic plaque on CCTA, but not the presence of PD on SPECT, was associated with the increased risk of ischemic stroke. Interestingly, disease severity as estimated by DS on CCTA was not associated with the risk of ischemic stroke, whereas disease extent as estimated by the number of vessels with plaque on CCTA and CACS allows further stratification of the risk of ischemic stroke. The presence of any PD on SPECT as well as the presence of fixed PD, SSS, and extent of PD were not associated with an increased risk of ischemic stroke.

CAD is considered an important cause of death in patients with ischemic stroke, and has resulted in the need for comprehensive cardiovascular risk assessment and management (1). However, to date, the occurrence of ischemic stroke in patients with CAD is not well known. Although several studies evaluated the risk of ischemic stroke in patients with CAD, most of the studies have focused on the incidence of stroke after ACS (6,23-25), and not on patients with stable CAD. These studies reported that the incidence of stroke after ACS is 0.5–2.5%. In a cohort of 18,151 patients with non-ST elevation ACS recruited by the Organization to Assess Strategies for Ischemic Syndromes (OASIS) study, the 6-month incidence of stroke was 1.3%, of which 89% were ischemic strokes (23). This study reported an almost 2-fold

higher incidence of stroke (2.5%) in patients who underwent coronary artery bypass surgery, a finding consistent with those of previous studies that have shown that stroke is a relatively common complication of coronary artery bypass surgery. In a cohort of 35,233 patients enrolled in the Global Registry of Acute Coronary Events (GRACE) with ACS, in-hospital strokes occurred in 310 (0.9%) patients (21). To our knowledge, we are the first to report an incidence of ischemic stroke of 2.2% during a median follow-up period of 26 months in patients with suspected CAD, without history of CAD or ischemic stroke.

Atherosclerosis is a systemic process that may involve more than one vascular bed in a substantial number of subjects (26-28). Thus, risk prediction would benefit from noninvasive measures of atherosclerosis (27,28). One current noninvasive measure of atherosclerosis is the assessment of coronary artery calcifications by CT. CACS is closely related to the coronary atherosclerotic plaque burden (29) and has been reported to predict adverse coronary events (30,31). There is also a close relation between coronary artery calcification and the extracoronary plaque burden (26,32). Several population-based studies reported the association between CACS and the risk of stroke (27,28,33). Recently, Hermann et al. demonstrated that CACS was an independent predictor of stroke in the Heinz Nixdorf Recall cohort that included 4180 subjects (28). In the current study, we examined the association between coronary atherosclerosis, evidenced by CCTA as well as CACS, and the risk of ischemic stroke. Stroke occurrence was significantly increased in patients with coronary atherosclerosis evidenced by CCTA (2.8%) compared

with that in patients without (0.6%), with a >4-fold hazard increase. Occurrence of ischemic stroke was further increased in patients with plaque in ≥2 vessels (6.1%) and in patients with CACS ≥400 (4.2%). However, the presence of significant coronary stenosis, defined as DS ≥50%, did not further increase the risk of ischemic stroke, which indicates that the increase in the risk of ischemic stroke was derived mainly from general atherosclerotic burden and not the presence of focal severe stenosis. We also evaluated whether myocardial ischemia burden evidenced by SPECT was associated with the risk of ischemic stroke. The presence of PD on SPECT was not associated with increased risk of ischemic stroke. Neither the extent of PD nor SSS was associated with the increased risk of ischemic stroke. These findings are in accordance with those currently reported, which stated that significant stenosis on CCTA was not associated with an increase in the risk of ischemic stroke.

Although CCTA has been demonstrated as an accurate noninvasive test for the anatomic diagnosis of CAD, CCTA has limited value for the detection of ischemia-causing lesions that require revascularization treatment (34). Current guidelines recommend evidence of the presence of ischemia prior to revascularization (35,36) because revascularization of a non-flow-limiting coronary stenosis does not benefit patient. Therefore, a substantial number of patients with CAD on CCTA need to be investigated by a subsequent functional test including myocardial SPECT. Nevertheless, the presence of coronary atherosclerosis evidenced by CCTA, either obstructive or nonobstructive, has been associated with increased cardiovascular events (37).

Additionally, CCTA provides incremental prognostic information for adverse cardiac events compared to functional tests (38,39). The current study is the first to demonstrate that the risk of ischemic stroke is associated with coronary atherosclerosis evidenced by CCTA, but not with myocardial ischemia evidenced by SPECT. These findings do not support the superiority of CCTA over SPECT for the prediction of ischemic stroke, but suggest the additive value of CCTA in the risk stratification of patients, not only in terms of adverse coronary events, but also cerebrovascular events in patients with suspected CAD. In this population, the role of CCTA was not limited to the detection of patients with obstructive CAD, but it extended to the identification of those with more extensive disease who required close monitoring for the increased risk of coronary and cerebrovascular events. However, further studies are required to evaluate whether aggressive treatment based on CCTA findings influences patient prognosis beneficially.

There are several limitations to this study. First, this is a retrospective study and may have been influenced by selection or referral biases. In addition, subsequent treatment and risk factor management may have been affected by the CCTA and/or SPECT findings. However, such effects are inevitable in a study observing clinical diagnoses and treatment pathways. Second, there was lack of consideration for noncoronary cause of ischemic stroke, such as carotid artery stenosis, low cardiac output, left ventricular aneurysm related to old myocardial infarction, or atrial fibrillation in this study (40). Since the objective of this study was to determine the direct relationship between ischemic stroke and atherosclerosis which has been

known as one of the major mechanism of ischemic stroke, it is valuable itself. Hereafter, further validated study will be needed to solidify our result. Thirdly, in our study, the relatively small number of ischemic stroke events precluded a multivariate analysis for comparison of CCTA with other risk factors. However, to our knowledge, this is the first and the largest study which followed for the ischemic stroke in patients with suspected CAD without prior CAD or stroke. And, in this population, none of the clinical variables were associated with the risk of ischemic stroke.

CONCLUSION

In patients with suspected CAD, the risk of ischemic stroke was associated with the presence and extent of coronary atherosclerosis evidenced by CCTA, but not with presence and extent of myocardial ischemia evidenced by SPECT. CCTA may provide additional information with regard to the risk of ischemic stroke in patients with suspected CAD.

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국 문 초 록

서론 관상동맥 질환과 허혈성 뇌경색은 위험 인자와 병태생리를 공유한다. 특히, 관상동맥 질환이 허혈성 뇌경색 환자에서 가장 중요한 사망과 이환의 원인임은 잘 알려져 있다. 반면, 관상동맥 질환 환자에서 허혈성 뇌경색의 발병과 위험도에 대해서는 아직까지 불명확한 것이 사실이다. 이에 본 연구에서는 관상동맥 조영 CT와 심근 SPECT를 통해 평가한 관상동맥 질환과 허혈성 뇌경색 발병의 연관성에 대해 알아보고자 하였다.

방법 2004년부터 2010년까지 관상동맥 평가를 위해 관상동맥 조영 CT와 심근 SPECT를 모두 시행한 환자가 연구 대상이 되었으며, 이 중에서 관상동맥 질환 및 뇌경색의 과거력이 있는 환자는 제외되어 총 1137명의 환자를 대상으로 분석을 시행하였다. 추적 관찰 중 발생한 허혈성 뇌경색은 신경과 전문의의 검진 및 뇌 CT 혹은 MRI로 입증된 임상 사건으로 정의하였다. 관상동맥 조영 CT와 심근 SPECT의 이환, 중증도 및 범위에 따라 임상 사건 발생 위험도를 비교하였다.

결과 추적 관찰 기간(중간값; 26개월, 4분위 범위; 14−43개월)동안 허혈성 뇌경색은 25명의 환자(2.2%)에서 발생하였다. 관상동맥 조영 CT에서 죽상경화반이 관찰된 경우, 허혈성 뇌경색 발생의 위험은 4배 이상 증가하였다 (위험비 4.38, 95% 신뢰구간 1.03−

18.64, p = 0.046). 구체적으로, 2혈관 질환의 경우, 단혈관 질환에 비해 허혈성 뇌경색 발생의 위험비가 3배 이상 증가하고 (위험비 3.68, 95% 신뢰구간 1.57-8.62, p = 0.003), 관상동맥 석회화 수치가 400 이상인 경우는, 400 미만인 경우에 비해 3배 가량 허혈성 뇌경색 발생 위험이 증가하지만 (위험비 2.93, 95% 신뢰구간 1.02-8.46, p = 0.046), 직경이 50% 이상 감소된 중증 협착이 동반된 경우는 50% 미만의 협착이 동반된 경우에 비해 허혈성 뇌경색의 발생의 유의한 증가를 보이지 않았다(위험비 1.03, 95% 신뢰구간 0.43-2.46, p = 0.943). 반면, 심근 SPECT 결과는 본 연구에서 허혈성 뇌경색 발생과 어떠한 연관성도 보이지 않았다.

결론 허혈성 뇌경색의 발생 위험은 관상동맥 조영 CT에서 확인된 관상동맥 죽상경화증과 유의한 연관성을 보이는 반면, 심근 SPECT에서 확인된 심근 허혈과는 연관성이 없었다. 관상동맥 질환이 의심되는 환자에서 관상동맥 조영 CT는 허혈성 뇌경색의 발생 예측에 추가 정보를 제공할 수 있다는 점에서 의의가 있다.

주요어: 허혈성 뇌경색; 관상동맥 질환; 관상동맥 조영 CT(Coronary CT angiography); 심근 SPECT (myocardial SPECT);

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