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Increased Risk of Cardiovascular Events in Stroke Patients Who had Not Undergone Evaluation for Coronary Artery Disease

Young Dae Kim[1], Dongbeom Song[1], Hyo Suk Nam[1], Donghoon Choi[2], Jung-Sun Kim[2], Byeong-Keuk Kim[2], Hyuk-Jae Chang[2], Hye-Yeon Choi[3], Kijeong Lee[1], Joonsang Yoo[1], Hye Sun Lee[4], Chung Mo Nam[5], and Ji Hoe Heo[1]

Departments of [1]Neurology, [4]Biostatistics, and [5]Preventive Medicine, Yonsei University College of Medicine, Seoul;
[2]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul;
[3]Department of Neurology, Kyung Hee University College of Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Korea.

Purpose: Although asymptomatic coronary artery occlusive disease is common in stroke patients, the long-term advantages of undergoing evaluation for coronary arterial disease using multi-detector coronary computed tomography (MDCT) have not been well established in stroke patients. We compared long-term cardio-cerebrovascular outcomes between patients who underwent MDCT and those who did not.

Materials and Methods: This was a retrospective study in a prospective cohort of consecutive ischemic stroke patients. Of the 3117 patients who were registered between July 2006 and December 2012, MDCT was performed in 1842 patients [MDCT (+) group] and not in 1275 patients [MDCT (-) group]. Occurrences of death, cardiovascular events, and recurrent stroke were compared between the groups using Cox proportional hazards models and propensity score analyses.

Results: During the mean follow-up of 38.0±24.8 months, 486 (15.6%) patients died, recurrent stroke occurred in 297 (9.5%), and cardiovascular events occurred in 60 patients (1.9%). Mean annual risks of death (9.34% vs. 2.47%), cardiovascular events (1.2% vs. 0.29%), and recurrent stroke (4.7% vs. 2.56%) were higher in the MDCT (-) group than in the MDCT (+) group. The Cox proportional hazards model and the five propensity score-adjusted models consistently demonstrated that the MDCT (-) group was at a high risk of cardiovascular events (hazard ratios 3.200, 95% confidence interval 1.172–8.735 in 1:1 propensity matching analysis) as well as death. The MDCT (-) group seemed to also have a higher risk of recurrent stroke.

Conclusion: Acute stroke patients who underwent MDCT experienced fewer deaths, cardiovascular events, and recurrent strokes during follow-up.

Key Words: Stroke, coronary disease, outcome, multi-detector coronary computed tomography

INTRODUCTION

Ischemic stroke shares common risk factors with coronary artery occlusive disease (CAOD). Myocardial infarction is one of the leading causes of death during long-term follow-up in patients with an ischemic stroke.[1-4] CAOD was present in about 70% and significant (≥50%) stenosis was noted in about 30% of stroke patients without a history of CAOD in studies using autopsy or coronary catheter angiography.[5,6] However, evaluation of asymptomatic CAOD in stroke patients is not commonly

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Corresponding author: Dr. Ji Hoe Heo, Department of Neurology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemoon-gu, Seoul 03722, Korea.
Tel: 82-2-2228-1605, Fax: 82-2-393-0705, E-mail: jhheo@yuhs.ac

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undertaken in routine clinical practice.

Recently, multi-detector coronary computed tomography (MDCT) has been introduced for evaluating coronary arteries. MDCT accurately detects the presence of CAOD,[7] and is a convenient and safe test. MDCT-based coronary findings have been found to be strong predictors of future cardiovascular events or death in patients with or without known CAOD.[8-10] Previous studies using MDCT showed that CAOD was present in 48–70% and significant CAOD was present in 18–33% of ischemic stroke patients without a previous history of CAOD.[11,12] MDCT has additional benefits in stroke patients, as it can detect the potential cardiac or aortic sources of embolism.[13]

Diagnosis of asymptomatic CAOD and hidden cardiac or aortic causes of stroke in stroke patients may help to reduce the risks of cardiovascular events and recurrent strokes. However, it remains unknown whether evaluation using MDCT in stroke patients affects long-term outcomes. Therefore, we investigated whether long-term cardio-cerebrovascular outcomes differ between patients who underwent MDCT during the acute stage of stroke and those who did not.

MATERIALS AND METHODS

Study design and population

This was a retrospective study of a prospective cohort of ischemic stroke patients designed to evaluate the usefulness of MDCT. This cohort included consecutive patients with acute cerebral infarction or transient ischemic attack within 7 days after symptom onset who were admitted to the neurology department of the Severance Stroke Center, Yonsei University in Seoul, Korea. Upon admission, all patients were thoroughly evaluated to determine demographic data, medical history, clinical manifestations, and vascular risk factors.[14] All patients underwent brain CT and/or magnetic resonance imaging with cerebral angiographic studies, standard blood tests, and 12-lead electrocardiography. Most patients were admitted to a stroke unit and were monitored continuously with electrocardiography during their stay (average 4.9 days). Holter monitoring was also performed if a cardiac embolism was suspected on the basis of infarction pattern, patient age, or previous cardiac history. Transesophageal echocardiography was a part of the routine examination, unless it could not be performed due to either the patient's condition or failure to obtain informed consent.

For determination of the presence of asymptomatic CAOD in stroke patients, since July 2006, MDCT was consecutively performed when a patient had at least one of the following: 1) presence of atherosclerosis in an intracranial or extracranial cerebral artery; 2) presence of ≥2 risk factors for CAOD, such as hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and central obesity; and 3) old age (males >45 years, females >55 years).[12] MDCT was not performed if patients had 1) known CAOD; 2) high pulse rates that were not controlled with beta-blockers at the time of MDCT; 3) poor cooperation; 4) impaired renal function; or 5) failure to obtain informed consent. When significant (≥50%) stenosis of the coronary artery was observed on MDCT, the patients were routinely referred to cardiologists at our cardiovascular center. CAOD was then managed at the discretion of the cardiologists and neurologists, which included percutaneous coronary intervention with stent (PCI) and coronary artery bypass graft (CABG). This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System. Informed consent was waived due to the retrospective nature of the study.

Clinical variables

We collected data on vascular risk factors for coronary heart disease, such as hypertension, diabetes mellitus, hyperlipidemia, and current smoking. The presence of valvular heart disease, atrial fibrillation, congestive heart failure, previous ischemic or hemorrhagic stroke, peripheral arterial occlusive diseases, metabolic syndrome, underlying malignancy (cancer diagnosed within 6 months prior to the index stroke, ongoing treatment for cancer, or recurrent or metastatic cancer), chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), and prior medication before the index stroke were also investigated. Initial stroke severity was determined based on the National Institute of Health Stroke Scale (NIHSS). Cerebral atherosclerosis was defined as having at least ≥1 stenoocclusive lesion of >50% based on the North American Symptomatic Carotid Endarterectomy Trial (for extracranial arteries)[15] or on the Warfarin vs. Aspirin for Symptomatic Intracranial Disease method (for intracranial arteries).[16] Framingham risk scores were calculated for each patient. Data on lipid profiles were also obtained.

Outcome data

Outcomes measured in this study were death and first occurrence of cardiovascular events or recurrent ischemic stroke. We obtained data for vascular events and death (date and causes of death) by review of the medical records and face-to-face or telephone interviews carried out by the stroke research nurse and stroke specialists. For mortality data, the date and cause of death were also identified using data from the Korean National Statistical Office. These mortality data are known to be reliable because they are collected based on a unique 13-digit identification code assigned to subjects at birth and on the death certificate. The causes of death are coded according to the International Classification of Disease, 10th Revision (ICD-10). Cardiovascular events were defined as nonfatal or fatal myocardial infarction (ICD-10 code I20-21), chronic ischemic heart disease (I25), sudden cardiac death (R96), death due to ventricular fibrillation (I49), or congestive heart failure (I50). The ICD-10 code used for coding fatal or nonfatal ischemic stroke was I63. The date of censoring was December 31, 2012.

Statistical analysis

Continuous variables are expressed as mean±standard deviation, and categorical data are expressed as number (percentage). The chi-square test or Student's t-test was used to compare groups for categorical variables and continuous data, as appropriate. A Kaplan-Meier estimate of survival was used to compare the differences in rates of cardiovascular events or recurrent ischemic stroke between the MDCT (+) group and the MDCT (-) group. Differences were determined by the log-rank test. To identify independent factors for the events, multiple Cox regression analysis was used.

Further, to reduce the potential effects of selection bias and confounding factors in this retrospective cohort study, we estimated propensity scores for each of the entire patients enrolled in this study to match the patients who had undergone MDCT to those who had not. This was computed for each patient with a logistic regression model, including variables of age, sex, hypertension, diabetes, hypercholesterolemia, current smoking status, valvular heart diseases, atrial fibrillation, congestive heart failure, previous ischemic or hemorrhagic stroke, peripheral arterial occlusive diseases, metabolic syndrome, underlying malignancy, chronic kidney disease, prior antiplatelet/anticoagulant/statin use, initial stroke severity, concomitant cerebral atherosclerosis, and lipid profiles. Each patient was then assigned an estimated propensity score, which was the predicted probability of undergoing MDCT on the basis of patient's observed baseline characteristics. Then, we divided the cohort into five strata defined by quintiles of estimated propensity scores. Cox proportional hazards models were employed separately within each stratum to compare the overall survival of patients undergoing MDCT with that of patients not undergoing MDCT. The five hazard ratios (HR) estimated from each stratum were combined into an overall HR for the whole cohort.

We also used Cox models for adjusting differences between the groups in other ways. First, regression adjustment was performed with inclusion of the propensity score as a linear predictor in the model. Second, the inverse probability of treatment weighting was used. We used Cox regression analysis to adjust the inverse probability of treatment weighting, as well as baseline characteristics. Finally, propensity score matching was conducted between paired patients who underwent MDCT and those who did not undergo MDCT. After matching, the baseline characteristics were compared with McNemar's test and the paired t-test. Clustered Cox regression analysis was also performed. All calculated p-values were two-sided, and $p<0.05$ was considered to be statistically significant. Statistical analyses were performed using the Windows IBM SPSS software package (version 20, IBM Corp., Armonk, NY, USA) and SAS (version 9.2, SAS Inc., Cary, NC, USA).

RESULTS

Study population

A total of 4381 consecutive patients were registered between July 2006 and December 2012. This comparative analysis was designed to investigate the usefulness of MDCT among patients who had no previous history of CAOD. Consequently, of the 4381 patients, we first excluded 938 patients who had a history of CAOD (myocardial infarction, angiographically confirmed CAOD, unstable angina, PCI, or CABG) or who underwent coronary angiographic evaluation within 1 year prior to the index stroke. We further excluded 160 patients who did not have any of the inclusion criteria for screening of asymptomatic CAOD with MDCT. Patients with unavailable data on initial NIHSS scores (n=19), estimated glomerular filtration rate (n=20), or incomplete lipid profiles (n=100) and those who died of acute index stroke within 7 days of symptom onset (n=27) were also excluded. Finally, 3117 patients were included in this study. Among them, 1842 patients underwent MDCT and 1275 patients did not undergo MDCT (Fig. 1). In the MDCT (-) group (n=1275), the reasons for not performing MDCT could be determined as follows: medical reasons (52.5%, 669/1275), such as poor cooperation or general condition (34.0%), renal or contrast agent-related factors (10.0%), and rapid heart rate (8.5%); and nonmedical reasons (47.5%, 606/1275), including a failure to obtain informed consent or no specific documented reasons.

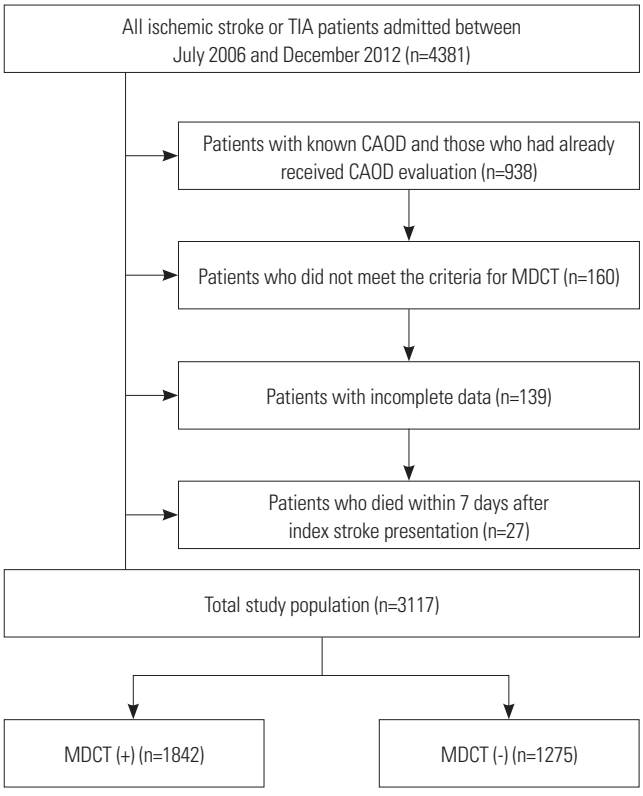

Fig. 1. Patient selection for this study. TIA, transient ischemic attack; CAOD, coronary artery occlusive disease; MDCT, multi-detector coronary computed tomography.

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Baseline characteristics of the MDCT (+) and MDCT (-) groups

The mean age of the 3117 ischemic stroke patients enrolled in this study was 65.7±12.0 years, and 60.5% of patients were men (n=1886). On the basis of Framingham risk scores, 28.6% of patients were classified into a low risk group (10-year risk <10%), 33.2% into a moderate risk group (10–20%), and 38.2% into a high risk group (>20%). In the MDCT (+) group (1842 patients), asymptomatic CAOD was detected in 1237 patients (67.2%): minimal CAOD in 725 (39.4%), 1-vessel disease in 301 (16.3%), 2-vessel disease in 149 (8.1%), and 3-vessel disease in 62 (3.4%).

Compared to patients of the MDCT (+) group, those of the MDCT (-) group were more likely to be older, female, and nonsmokers and to have hypertension, valvular heart disease, atrial fibrillation, congestive heart failure, previous ischemic stroke, peripheral arterial occlusive diseases, underlying malignancy, chronic kidney disease, prior anticoagulant treatment, more severe stroke, concomitant cerebral atherosclerosis, and relatively low triglyceride, low density lipoprotein, or high density lipoprotein levels (Table 1). In terms of medication at discharge, statins were more frequently prescribed in the MDCT (+) group (n=1773, 96.3%) than in the MDCT (-) group (n=1148, 90.0%) (p<0.001). There were similar trends in prescribing antithrombotics [n=1810 (98.3%) in MDCT (+) vs. n=1202 (94.3%) in MDCT (-), p<0.001] or beta-blockers [n=631 (34.3%) in MDCT (+) vs. n=287 (22.5%) in MDCT (-), p<0.001].

Cardiovascular and cerebrovascular outcomes

Outcomes in the original population

During a follow-up of 38.0±24.8 months (range: 0–85.9 months), 486 patients (15.6%) died. Recurrent stroke developed in 297 patients (9.5%) [fatal stroke in 106 (3.4%) and nonfatal stroke in 191 (6.1%)] and cardiovascular events in 60 patients (1.9%) [fatal myocardial infarction or sudden cardiac death in 27 (0.9%), nonfatal myocardial infarction in 29 (0.9%), and con-

Table 1. Comparison of Baseline Characteristics between the MDCT (+) and MDCT (-) Groups

Variable	Before matching (n=3117)			After matching (n=1616)		
	MDCT (+) (n=1842)	MDCT (-) (n=1275)	*p* value	MDCT (+) (n=808)	MDCT (-) (n=808)	*p* value
Age	64.0±11.1	68.1±12.8	<0.001	65.0±11.3	65.8±12.9	0.109
Male sex	1176 (63.8)	710 (55.7)	<0.001	483 (59.8)	479 (59.3)	0.872
Hypertension	1350 (73.3)	1000 (78.4)	0.001	620 (76.7)	623 (77.1)	0.903
Diabetes	565 (30.7)	430 (33.7)	0.072	254 (31.4)	265 (32.8)	0.586
Hypercholesterolemia	174 (9.4)	98 (7.7)	0.087	67 (8.3)	68 (8.4)	>0.999
Current smoker	505 (27.4)	237 (18.6)	<0.001	192 (23.8)	179 (22.2)	0.449
Valvular heart disease	66 (3.6)	88 (6.9)	<0.001	38 (4.7)	42 (5.2)	0.724
Atrial fibrillation	245 (13.3)	375 (29.4)	<0.001	155 (19.2)	148 (18.3)	0.664
Congestive heart failure	34 (1.8)	70 (5.5)	<0.001	17 (2.1)	18 (2.2)	>0.999
Previous ischemic stroke	235 (12.8)	246 (19.3)	<0.001	110 (13.6)	128 (15.8)	0.217
Previous intracranial hemorrhage	59 (3.2)	47 (3.7)	0.464	25 (3.1)	24 (3.0)	>0.999
Peripheral arterial occlusive disease	88 (4.8)	83 (6.5)	0.037	34 (4.2)	45 (5.6)	0.235
Metabolic syndrome	741 (40.2)	481 (37.7)	0.159	295 (36.5)	310 (38.4)	0.477
Malignancy	181 (9.8)	157 (12.3)	0.028	94 (11.6)	95 (11.8)	>0.999
Chronic kidney disease	29 (1.6)	78 (6.1)	<0.001	18 (2.2)	13 (1.6)	0.442
Prior medication						
Antiplatelet	535 (29.0)	375 (29.4)	0.825	223 (27.6)	229 (28.3)	0.786
Anticoagulant	71 (3.9)	114 (8.9)	<0.001	49 (6.1)	45 (5.6)	0.738
Statin	253 (13.7)	192 (15.1)	0.299	115 (14.2)	117 (14.5)	0.944
Initial NIHSS			<0.001			0.212
0–5	1478 (80.2)	704 (55.2)		576 (71.3)	585 (72.4)	
6–19	350 (19.0)	440 (34.5)		221 (27.4)	216 (26.7)	
≥20	14 (0.8)	131 (10.3)		11 (1.4)	7 (0.9)	
Concomitant cerebral atherosclerosis	1011 (54.9)	846 (66.4)	<0.001	470 (58.2)	486 (60.1)	0.424
Total cholesterol >6.2 mmol/L	154 (8.4)	99 (7.8)	0.549	67 (8.3)	68 (8.4)	>0.999
Triglyceride >3.9 mmol/L	467 (25.4)	266 (20.9)	0.004	186 (23.0)	183 (22.6)	0.907
High density lipoprotein <1.3 mmol/L	1435 (77.9)	926 (72.6)	0.001	611 (75.6)	612 (75.7)	>0.999
Low density lipoprotein >2.6 mmol/L	1121 (60.9)	723 (56.7)	0.02	471 (58.3)	472 (58.4)	>0.999

MDCT, multi-detector coronary computed tomography; NIHSS, National Institutes of Health Stroke Scale.
Values are represented as numbers (%) or mean±SD.

gestive heart failure in 4 (0.1%)]. The frequency of receiving revascularization therapy was statistically different between the two groups (p<0.001) in that 96 patients (5.2%) received PCI (n=87) or CABG (n=9) in the MDCT (+) group, while 13 patients (1.0%) received PCI (n=9) or CABG (n=4) in the MDCT (-) group, during follow-up. The occurrence of cardiovascular events was not associated with the Framingham risk score stratification (p=0.400).

Compared to patients in the MDCT (+) group, those in the MDCT (-) more frequently experienced death (27.9% vs. 7.1%, p<0.001), cardiovascular events (3.5% vs. 0.8%, p<0.001), and recurrent stroke (13.3% vs. 6.9%, p<0.001). Kaplan-Meier curves showed that the MDCT (-) group had higher risks of death, cardiovascular events, and recurrent ischemic stroke than the MDCT (+) group (Fig. 2). The mean annual risk of death, cardiovascular events, or recurrent ischemic stroke was higher in the MDCT (-) group than in the MDCT (+) group (9.34% vs. 2.47% for death, 1.20% vs. 0.29% for cardiovascular events, and 4.70% vs. 2.56% for recurrent ischemic stroke). After adjusting for all demographic and clinical characteristics in multivariate Cox proportional hazard models, there were significantly higher risks of death, cardiovascular events, and recurrent stroke in the MDCT (-) group than in the MDCT (+) group (Table 2).

Outcomes in the propensity score-matched population

Propensity score matching resulted in well-balanced matching between the MDCT (+) group and the MDCT (-) group. All characteristics of the two groups were well balanced with those of the unmatched cohort (Table 1). The baseline characteristics in the five strata adjusted for propensity scores are shown in Supplementary Table 1 (only online).

Kaplan-Meier curves showed that the MDCT (-) group was in higher risk of death and cardiovascular events (Fig. 3). All of the five propensity score-adjusted models consistently demonstrated that the MDCT (-) group was at a higher risk of death and cardiovascular events (Table 2). In stratified analysis based on the propensity score, the difference in the risk of death and cardiovascular events between the MDCT (-) group and the MDCT (+) group was remarkably significant among patients with high propensity scores. The MDCT (-) group seemed to also have a higher risk of recurrent stroke in most propensity score-adjusted models than did the MDCT (+) group. However, the increased risk of recurrent stroke was weaker than that of cardiovascular events. For example, in the MDCT (-) group, the HR for cardiovascular events in stratified analyses based on propensity scores was 2.692 [confidence interval (CI) 1.450–4.997, p=0.002], while that for recurrent stroke was 1.419 (95% CI 1.108–1.816, p=0.005) (Table 2). The results of 1:1 propensity matching analysis showed the MDCT (-) was related with death (HR 2.783, 95% CI 1.987–3.897, p<0.001) or cardiovascular events (HR 3.2, 95% CI 1.172–8.735, p=0.023), but not with the recurrent stroke (HR 1.173, 95% CI 0.810–1.698, p=0.398).

In addition, we performed comparative analyses using the data of the MDCT (+) group (n=1842) and 606 patients of MDCT (-) subgroup who had not undergone MDCT due to nonmedical reasons (Supplementary Table 2, only online). Kaplan-Meier curves and Cox proportional hazards models showed patients in the MDCT (-) subgroup had significantly higher risks of all predetermined outcomes (Supplementary Fig. 1, Supplementary Table 3, only online). Propensity score analyses showed that compared with the MDCT (+) group, MDCT (-) group was higher risk of death and tended to be higher risk of cardiovascular events or recurrent stroke (Supplementary Fig. 2, Supplementary Table 3, only online).

DISCUSSION

In this study, we found that the risks of death, cardiovascular events, and recurrent stroke were higher in stroke patients who were not evaluated using MDCT during admission than in those who were evaluated. However, evaluation using MDCT was not randomized; consequently, many baseline character-

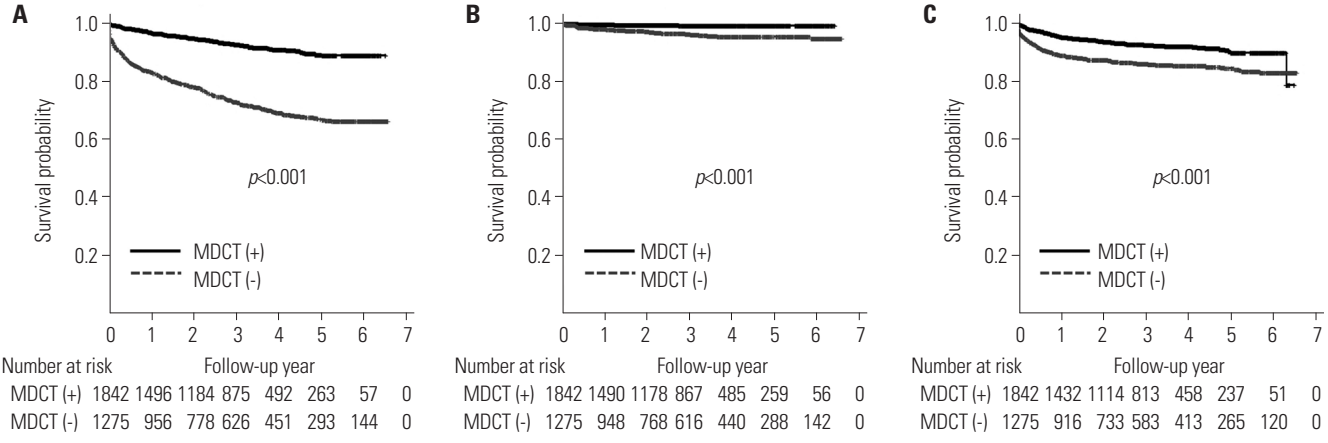

Fig. 2. Kaplan-Meier survival curves for (A) death (B) cardiovascular events, and (C) recurrent stroke according to the performance of MDCT in the entire population. MDCT, multi-detector coronary computed tomography.

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istics differed between the MDCT (+) group and the MDCT (-) group. Therefore, we compared outcomes in a propensity score-matched population. Comparison using various models in this propensity score-matched population also showed significant differences in the risk of death, cardiovascular events, and recurrent stroke between two groups. In particular, the high

Table 2. Impact of Not Performing MDCT on Hazard Ratios for Cardiovascular Events and Recurrent Stroke

Event	Sample size, no.	Hazard ratio (95% CI)	*p* value
Death			
Unadjusted model	1275 and 1842	4.038 (3.302–4.937)	<0.001
Multivariable-adjusted model*	1275 and 1842	2.248 (1.808–2.795)	<0.001
Propensity score-adjusted model†			
Stratification	1275 and 1842	2.410 (1.950–2.980)	<0.001
Within-propensity score quintile			
1 (kowest propensity)	149 and 474	0.845 (0.170–4.214)	0.838
2	162 and 462	2.347 (1.304–4.225)	0.004
3	198 and 425	1.736 (1.092–2.760)	0.020
4	303 and 321	2.731 (1.834–4.068)	<0.001
5 (high propensity)	463 and 160	2.888 (1.960–4.257)	<0.001
Regression adjustment	1275 and 1842	2.307 (1.858–2.866)	<0.001
Weighting (stabilized IPTW)	1275 and 1842	2.491 (2.090–2.970)	<0.001
Matching 1:1	808 and 808	2.783 (1.987–3.897)	<0.001
Cardiovascular events			
Unadjusted model	1275 and 1842	4.476 (2.493–8.034)	<0.001
Multivariable-adjusted model*	1275 and 1842	2.896 (1.551–5.408)	<0.001
Propensity score-adjusted model†			
Stratification	1275 and 1842	2.692 (1.450–4.997)	0.002
Within-propensity score quintile			
1 (lowest propensity)	149 and 474	-‡	-
2	162 and 462	1.932 (0.431–8.662)	0.389
3	198 and 425	1.075 (0.197–5.867)	0.934
4	303 and 321	2.523 (0.777–8.195)	0.124
5 (high propensity)	463 and 160	3.740 (1.137–12.304)	0.030
Regression adjustment	1275 and 1842	2.908 (1.556–5.437)	0.001
Weighting (stabilized IPTW)	1275 and 1842	3.462 (2.024–5.921)	<0.001
Matching 1:1	808 and 808	3.200 (1.172–8.735)	0.023
Recurrent stroke			
Unadjusted model	1275 and 1842	1.962 (1.558–2.470)	<0.001
Multivariable-adjusted model*	1275 and 1842	1.278 (0.993–1.645)	0.0527
Propensity score-adjusted model†			
Stratification	1275 and 1842	1.419 (1.108–1.816)	0.005
Within-propensity score quintile			
1 (lowest propensity)	149 and 474	0.528 (0.177–1.576)	0.253
2	162 and 462	1.868 (0.984–3.546)	0.056
3	198 and 425	1.248 (0.738–2.110)	0.408
4	303 and 321	1.233 (0.776–1.959)	0.375
5 (high propensity)	463 and 160	2.091 (1.227–3.565)	0.007
Regression adjustment	1275 and 1842	1.288 (1.000–1.0659)	0.050
Weighting (stabilized IPTW)	1275 and 1842	1.527 (1.235–1.889)	<0.001
Matching 1:1 (paired)	808 and 808	1.173 (0.810–1.698)	0.398

MDCT, multi-detector coronary computed tomography; CI, confidence interval; IPTW, inverse probability of treatment weighting.
*This model was adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, current smoking status, valvular heart diseases, atrial fibrillation, congestive heart failure, previous ischemic or hemorrhagic stroke, peripheral arterial occlusive diseases, metabolic syndrome, underlying malignancy, chronic kidney disease, prior antiplatelet/anticoagulant/statin use, initial stroke severity, and lipid profiles, †The propensity of undergoing MDCT was estimated using a multivariate logistic regression model, which included age, sex, hypertension, diabetes, hypercholesterolemia, current smoking status, valvular heart diseases, atrial fibrillation, congestive heart failure, previous ischemic or hemorrhagic stroke, peripheral arterial occlusive diseases, metabolic syndrome, underlying malignancy, chronic kidney disease, prior antiplatelet/anticoagulant/statin use, initial stroke severity, and lipid profiles, ‡This could not be estimated because of no event in MDCT (+) group.

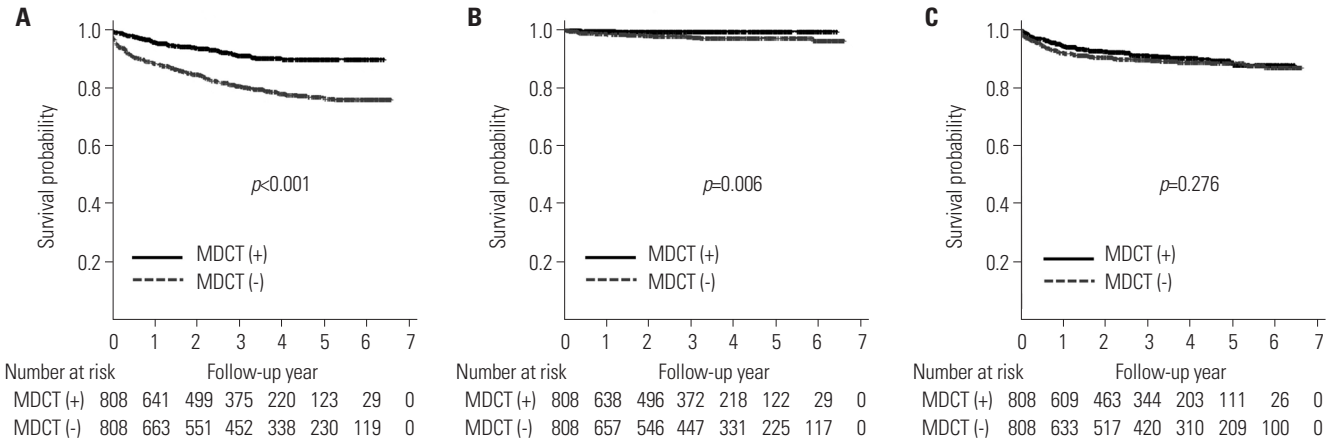

Fig. 3. Kaplan-Meier survival curves for (A) death (B) cardiovascular events, and (C) recurrent stroke according to the performance of MDCT in the propensity score-matched population. MDCT, multi-detector coronary computed tomography.

strata group (the highest propensity) more frequently suffered from death, cardiovascular events, and recurrent strokes.

Diagnosis of asymptomatic, but significant CAOD, using MDCT could change a treatment strategy. Likely, physicians and patients might be more motivated to manage modifiable risk factors for cardiovascular disease and to stick to treatment with medication if they recognized the presence of asymptomatic CAOD. When it comes to revascularization therapy, there has been no strong evidence of the usefulness of routine PCI for reducing cardiovascular events in patients with stable CAOD.[17,18] However, because the severity of silent CAOD was a strong predictor of future cardiovascular events in stroke patients, despite the use of the best medical treatment based on guidelines[1,18] and revascularization therapy, including CABG and PCI, may be helpful for specific group of patients, such as those with ≥50% stenosis of the left main coronary artery,[17,19] some patients in the MDCT (+) of our study might have benefitted from revascularization therapy.

Many of the patients who did not undergo MDCT in this study might have had significant CAOD that was undiagnosed on discharge. Indeed, about 18–33% of stroke patients have been reported to have asymptomatic but significant CAOD.[5,6,11] In this study, significant CAOD was detected in 28% of patients who underwent MDCT. Thus, patients with significant CAOD that was not diagnosed before discharge might have had a greater risk of cardiovascular events during follow-up.

Notably, in the MDCT (-) group, the annual risk was 4.2 times greater for cardiovascular events and 1.8 times greater for recurrent stroke than it was in the MDCT (+) group. This suggests that the effects of using MDCT were greater for reducing cardiovascular events than for reducing recurrent stroke. MDCT is also useful in diagnosing the causes of stroke, such as aortic plaques, intracardiac thrombi, and patent foramen ovale. Although the exact diagnosis of stroke mechanisms is helpful for better stroke prevention,[20] many of the etiologies, which were detected on MDCT, might have been also detected by echocardiographic studies that were a part of standard stroke evaluation in our center.[21,22] As a result, the treatment strategy for the secondary prevention of stroke might have not been changed in most cases of our population even though cardiac or aortic causes of stroke were detected by MDCT. However, asymptomatic CAOD could not have been diagnosed if patients were not evaluated using MDCT. These might be partly responsible for the different risks for cardiovascular events and recurrent stroke in the MDCT (-) group in the present study.

The present study does not address which patients are appropriate candidates for coronary evaluation. However, a scientific statement by the American Heart Association/American Stroke Association in 2003 recommended routine noninvasive testing for coronary heart disease in high risk groups, including stroke patients with cerebral atherosclerosis or a Framingham risk score of ≥20%.[23] Previous MDCT-based studies suggest that asymptomatic CAOD is common in stroke patients with multiple vascular risk factors and atherosclerosis of the cervicocephalic arteries.[11,12] The present study provides supportive evidence for the necessity of coronary evaluation in acute stroke patients. MDCT has some drawbacks, such as contrast agent-related side effects, radiation-related adverse effects, and the need for the patient's cooperation to hold their breath for a while. However, this test has an advantage for stroke patients. In contrast to a treadmill test, MDCT can be performed in patients with the level of disability seen in many stroke patients.[7] In addition, many cardiac and aortic causes of stroke can be diagnosed by MDCT, as described above. Therefore, this test can be useful especially in patients for whom transesophageal echocardiography cannot be performed.[13,24] Defining high-risk patients for future cardiovascular events that could benefit from cardiac evaluation using MDCT is required.

This study has merit in that it was performed in a large sample of stroke patients with a long-term follow-up. However, this study also has several limitations. First, evaluation using MDCT was not randomized. Although a previous report showed that asymptomatic CAOD is common regardless of the stroke mechanism[6] and we balanced the baseline characteristics of

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patients using various propensity score matching models, there might still be other confounders of outcomes, such as socioeconomic status. Second, adherence to medication during follow-up was not thoroughly checked. Third, although all cardiologists managed patients with CAOD based on the same guidelines, management, including revascularization therapy, was not controlled. Fourth, this study was performed in a single university hospital in one Asian country. However, the presence of vascular risk factors and occurrence of vascular events (cardiovascular or cerebrovascular) can differ between different ethnicities.[25] Therefore, these limitations should be considered in the interpretation of the results of the present study.

The present study showed that stroke patients who were not evaluated using MDCT during admission had increased risks of future death, cardiovascular events, or recurrent stroke. However, the overall cardiovascular events were lower in this study population. Therefore, further studies focusing on the selection of high-risk patients for future cardiovascular events or randomized clinical trials are needed to clearly demonstrate the clinical usefulness of MDCT.

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