Combination of Anatomical and Functional Evaluations Improves the Prediction of Cardiac Event in Coronary Artery Bypass Patients

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Combination of Anatomical and Functional Evaluations Improves the Prediction of Cardiac Event in Coronary Artery Bypass Patients

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Abstract

Objective: To study the usefulness of combined risk stratification of coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) in patients with previous coronary-artery-bypass grafting (CABG).

Design: retrospective, observational, single center

Setting and Patients: 204 patients (84.3% male, mean age 68.7±7.6) undergoing CTA and MPI.

Main outcome measures: CTA defined the number of unprotected coronary territories (UCT) (0, 1, 2, or 3) by evaluating grafts, distal runoffs, and nongrafted vessels. Using the cut-off value with receiver-operating characteristics analysis, all patients were divided into 4 groups: Group A (UCT = 0, summed stress score [SSS] < 4), Group B (UCT ≥ 1, SSS < 4), Group C (UCT = 0, SSS ≥ 4), and Group D (UCT ≥ 1, SSS ≥ 4).

Results: Cardiac events, as a composite endpoint including cardiac death, nonfatal myocardial infarction, unstable angina requiring revascularization, and heart-failure hospitalization were observed in 27 patients for a median follow-up of 27.5 months. The annual event rates were 1.1%, 2.0%, 5.7%, and 12.9% of patients in Group A, B, C, and D, respectively (Log Rank P-value < 0.0001). Adding UCT or SSS to a model with significant clinical factors including left ventricular ejection fraction, time since CABG, and Euro SCORE Ⅱ improved the prediction of events, while adding both UCT and SSS to the model improved it greatly with increasing C-index, net reclassification improvement and integrated discrimination improvement.

Conclusions: The combination of anatomical and functional evaluations non-invasively enhances the predictive accuracy of cardiac events in CABG patients.

Article summary

1) Article Focus

- To study the prognosis and predictors of previous coronary-artery-bypass grafting (CABG) patients.
- Both coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) are useful for the risk stratification with previous CABG patients.
- It is usefulness to combine risk stratification of coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) in patients with previous CABG.

2) Key Messages

- UCT defined by CTA, SSS by MPI, Left ventricular ejection fraction, time since CABG, and Euro SCORE Ⅱ were independent predictors.
- Each CTA and MPI reflected the prognosis of CABG patients.
- The combination of anatomical (CTA) and functional (MPI) evaluations non-invasively enhances the predictive accuracy of cardiac events in CABG patients. The advantages of each imaging examination complement the limitations of the other.

3) Strengths and Limitations

- A limited number of patients in a single center were enrolled and were observed retrospectively.
- In a large number and prospective study, the usefulness and cost-effectiveness of combined evaluation will be studied further.
- We did not perform invasive coronary angiography in all studied patients. (The diagnosis of unprotected coronary territory based on CTA may contain some false-positives and/or false-negatives.)

【Introduction】

Coronary computed tomography angiography (CTA) is a useful tool not only for the detection of obstructive coronary artery disease [1-3], but also for the risk stratification of patients with coronary artery disease [4-5]. Some studies using CTA have shown good diagnostic performance for the

detection of significant stenosis in grafts, with accuracy improved by the newer generation of CT scanners [6-9]. Recently, Chow et al. and Small et al. demonstrated that CTA was of prognostic value in patients with previous coronary-artery-bypass grafting (CABG) [10-11]. On the other hand, CTA has some limitations in the evaluation of distal runoffs, metal clip artifacts, and native coronary segments of nongrafted vessels, particularly due to the high prevalence of severe calcification in previous CABG patients [6, 8].

Myocardial perfusion imaging (MPI) has been also useful for the risk stratification of patients with previous CABG [12-14]. MPI is regarded as the gold standard for the risk stratification of such patients [15], despite some limitations. Patients after CABG have a high prevalence of perfusion defects because of old myocardial infarction or ischemic areas resulting from coronary side branch occlusion, and so there is a low positive predictive value for prognostic evaluation.

In previous studies, Schuijf et al. showed that MPI and CTA provided different and complementary information on patients with suspected CAD [16]. Werkhoven et al. concluded that combined anatomical and functional assessment might allow improved risk stratification [17]. The purpose of the present study was to assess the prognosis of CABG patients by CTA and MPI, and to determine the efficacy of such combined anatomical and functional assessment.

【Methods】

We studied 211 patients with a history of CABG. From January 2006 to October 2011, they underwent both CTA and MPI within 3 months of each other, and their clinical endpoints were followed. Exclusion criteria were: 1) complicating congenital heart disease; 2) after valve surgery or left ventricular (LV) aneurysm resection; 3) known allergy to iodinated contrast agents; 4) severe renal insufficiency not requiring hemodialysis (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2). To determine the preoperative risk assessment of these patients, we used a logistic European System for Cardiac Operative Risk Evaluation risk model (EuroSCORE Ⅱ) [18]. The study was approved by the Institutional Review Board and the ethics committee of Fujita Health University.

Coronary Computed Tomography Angiography

In the first 27 patients, 64-slice CT (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) was used with a collimation of 64 × 0.5mm, rotation speed of 350, 375, 400msec, and retrospective triggering electrocardiogram (ECG). For the contrast enhanced scan, a total amount of 80 to 90 mL of contrast medium with an injection flow rate of 4 mL/second was injected, followed by a 40-mL saline bolus chase. Volumetric data were reconstructed with segmented reconstruction [9]. In the remaining 184 patients, 320-slice CT (Aquilion One Toshiba Medical Systems, Otawara, Japan) was used with a collimation of 320 × 0.5mm, rotation speed of 350, 375, 400msec, and prospective triggering ECG. A bolus of 1.1 mL/kg contrast medium was injected over 18 s, followed by a 20-mL

saline bolus chase. Volumetric data were reconstructed with half or segmented reconstruction [19]. All scans were performed during a single breath-hold. Isosorbide dinitrate spray was provided immediately before CTA. The effective radiation dose was 12.7 ± 9.1 mSv (9.8 ± 3.7 mSv in 320-slice CT and 32.6 ± 10.4 mSv in 64-slice CT). After acquisition of the reconstructed volumetric data, images were transferred to a workstation (ZIOSTATION System 1000, Amin/ZIO, Tokyo, Japan). On CT images, coronary arteries were divided into 15 segments based on the recommendations of the American Heart Association [20]. All native coronary arteries and bypass grafts were evaluated by two experienced observers (SM and HI) unaware of the clinical history and MPI findings of the patients. Atherosclerotic lesions and stenoses were classified visually as mild (< 50% luminal diameter), moderate (50% to 69%), or severe (≥70%). Significant stenoses were defined as left main trunk ≥50% diameter stenosis, other native vessel stenosis ≥70%, or graft stenosis ≥70%. Native coronary segments (including stented segments) and grafts, that were not assessable because of severe calcification and motion artifacts, were regarded as severe stenoses. Patients were categorized according to the number (0, 1, 2, or 3) of unprotected coronary territories (UCT) [10].

Stress-rest myocardial perfusion imaging:

In all patients, stress-rest MPI using thallium (Tl)-201 was performed with adenosine stress [21]. Data were acquired with a dual headed SPECT gamma camera (ADAC, VERTEX-plus EPIC, USA)

followed by reconstruction into long- and short-axis projections perpendicular to the heart axis; data were presented in polar map format and a 17-segment model was used in which myocardial segments were allocated to the territories of the different coronary arteries [22]. Tl-201 uptake was graded subjectively in three orthogonal planes (short axis, horizontal long axis, vertical long axis) divided into 17 segments on a five-point scale (4 = absent uptake; 3 = severely, 2 = moderately, 1 = mildly decreased uptake; 0 = normal uptake, respectively) on the post stress and delayed images displayed side by side by the consensus of two experienced observers (MS and HK) unaware of the clinical history and CTA findings of the patients [19]. The segmental perfusion scores during stress and rest were added together to calculate the summed stress score (SSS).

Patient follow-up:

Patient follow-up data were gathered by observers blinded to the baseline CTA and MPI results using clinical visits or standardized telephone interviews. Cardiac events (cardiac death, nonfatal myocardial infarction, unstable angina requiring revascularization, and admission to a hospital due to heart failure) were regarded as clinical end points. Deaths were considered cardiac when the primary cause of death was related to myocardial ischemia/infarction, heart failure or arrhythmia, and when a noncardiac cause of death could not be identified. Nonfatal myocardial infarction was defined as myocardial ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper normal limits). Unstable angina was defined as acute chest pain with or without the presence of ECG

abnormalities, and negative cardiac enzyme levels [23-24]. Patients undergoing elective revascularization within 3 months after CTA or MPI (early elective revascularization) were excluded after enrollment.

Statistical analysis:

All data were presented as the mean ± SD for continuous variables and frequency (percentage) for categorical variables. The mean values for the two groups were compared with chi-square tests for categorical and Wilcoxon sum rank test for continuous variables. All analyses were performed with JMP Version 10, (SAS Institute Inc., Cary, NC, USA) and a p-value of < 0.05 was considered as statistically significant.

The prognosis of CABG patients was assessed in univariate and multivariate models based on UCT, SSS, and their combination. Receiver-operating characteristics (ROC) analysis was performed to determine cutoff values of UCT and SSS for cardiac events. Risk adjusted analyses were performed with Cox proportional hazard models to determine the independent prognostic value of UCT, SSS, and their combination by controlling for other predictors. Cumulative event rates were estimated with the Kaplan-Meier method and were compared with the log-rank test.

The increased discriminative value after addition of UCT and/or SSS to the established clinical risk factors was estimated using the C-index for ROC curve, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under an ROC

curve between individual predicted probabilities and incidence of events, and is compared between in a baseline model consisting of established clinical risk factors with $p<0.05$ by univariate Cox analysis, and in an enriched model with UCT and/or SSS [25]. The NRI indicates relatively how many patients show a decrease in their predicted probabilities for events, while the IDI represents the average decrease in predicted probabilities for events after adding UCT and/or SSS into the baseline model, respectively [26].

【Results】

Clinical characteristics:

In total, 204 patients (84.3% male, mean age 68.7±7.6 years) were enrolled after excluding 7 patients: 4 undergoing early elective revascularization within 3 months after imaging examination, and 3 lost to follow-up. The mean follow-up period was 30.3±17.6 months (median; 27.5 months). In Table 1, baseline characteristics are listed in detail. At follow-up, cardiac events were observed in 27 patients (13.2%) with an annualized event rate of 5.2% (3 patients with cardiac death, 9 patients with non-fatal infarction, 3 patients with unstable angina requiring revascularization, and 12 patients with heart failure). In the univariate Cox analysis, LVEF determined by cardiac ultrasound [Hazard Ratio (HR): 0.936; 95% Confidence Interval (CI): 0.905 to 0.968; p = 0.0002], time since CABG (HR: 1.01; 95% CI: 1.00-1.02; p=0.0008), and EuroSCORE Ⅱ (HR: 1.29; 95% CI: 1.02-1.57; p=0.038)

were significant predictors of cardiac events.

CTA, MPI Findings and Analysis with the Combination of UCT and SSS

The UCT and SSS were significant predictors for cardiac events (HR: 2.52; 95% CI: 1.59 to 3.96; p=0.0001 and HR: 1.08; 95% CI: 1.05 to 1.12; p < 0.0001, respectively). To maximize the predictive power of UCT and SSS, cut-off levels were determined as 1 for UCT [area under curve (AUC) = 0.71] and 4 for SSS (AUC = 0.76), respectively. Cumulative incidence rates for cardiac events are demonstrated in Figure 1A and 1B (log rank p-value = 0.0054 and < 0.0001, respectively). After adjustment for LVEF, time since CABG and EuroSCORE Ⅱ, patients with UCT ≥ 1 had 2.34-fold higher risk of cardiac events (95% CI 1.01 to 5.89, p = 0.0465). Similarly, patients with SSS ≥ 4 had 3.36-fold higher risk of cardiac events (95% CI 1.18 to 12.12, p = 0.0217) (Table 2a).

Based on the CTA and MPI findings, we divided all patients into 4 groups: Group A (UCT = 0, SSS <4), Group B (UCT; ≥1, SSS <4), Group C (UCT = 0, SSS ≥4), and Group D (UCT; ≥1, SSS ≥4). The annual event rates of cardiac events were 1.1%, 2.0%, 5.7%, and 12.9% of patients in group A, B, C and D, respectively. Cardiac event curves are demonstrated in Figure 1C (log rank p-value < 0.0001). After adjustment for LVEF, time since CABG, and EuroSCORE Ⅱ, patients with UCT ≥ 1 and SSS ≥ 4 had 6.84-fold (95% CI 1.83 to 44.50, p = 0.0026) higher risk for cardiac events compared to those with UCT = 0 and SSS < 4 (Table 2b).

Discrimination of Each Predicting Models for Cardiac Events (Table 3)

Addition of UCT alone, SSS alone, and both UCT and SSS to a baseline model with clinical risk factors consisting of LVEF, time since CABG, and EuroSCORE II significantly improved both the NRI and IDI. However, C-index was significantly greater only in the model with both UCT and SSS compared to the baseline model (0.834 vs. 0.768, p=0.045). In addition, the NRI and IDI significantly increased in the model containing both UCT and SSS even if compared to the model containing UCT alone or SSS alone.

【Discussion】

We focused on the prognosis of CABG patients assessed by CTA and MPI, and the usefulness of this combination. The patients without unprotected territories on CTA and without perfusion defects on MPI have a good prognosis. The prognosis of patients with abnormal CTA (UCT; ≥1) and MPI (SSS ≥ 4) is significantly poorer than that of patients with normal CTA and MPI. Each examination has incremental prognostic value, and the combination of anatomical and functional evaluation facilitates non-invasive assessment of the prognosis of CABG patients. This improvement was indicated to be statistically significant by the increase in the NRI and IDI.

Several reports have shown the utility of MPI with assessment of the prognosis in CABG patients

[12-14], but there are some limitations.

First, many CABG patients have some abnormal findings on MPI, because of a history of prior myocardial infarctions, and others have ischemic territories with side branch occlusion even if the major coronary trees are protected. Actually in the present study, 48.5% of the enrolled patients had an abnormal MPI finding (SSS ≥ 4). To identify the patients with a poor prognosis strictly among those with MPI abnormalities, the evaluation of unprotected coronary territories on CTA was useful. The event rates were 33.3% in the abnormal CTA patients (Group D), in contrast to 12.5% in the normal CTA patients (Group C).

Importantly, MPI does not clarify the anatomy of grafts or native coronary arteries, even when high risk patients are identified. On the other hand, CTA provides information on grafts and unprotected native coronary arteries non-invasively, and in this way contributes to devising the most appropriate therapeutic strategy.

Several studies have also demonstrated the diagnostic accuracy of CTA in CABG patients [6-9], and two recent studies reported the prognostic value of CTA in CABG patients [10-11]. They concluded that assessment with CTA is of prognostic value in CABG patients, despite some limitations.

First, some difficulties remain regarding the diagnostic accuracy [7-9]. Indeed the diagnostic accuracy of graft segments is good, but CABG patients have a high prevalence of severe calcifications and stented segments in the native coronary arteries, leading to some overestimation of stenosis of the distal runoff segments of the protected coronary arteries, and unprotected native coronary arteries

including stented segments. Actually in our study, unassessable native coronary or graft segments were regarded as severe stenosis, likely resulting in some overestimation of the number of unprotected coronary territories. In other words, some CTA findings in Group B patients (abnormal CTA and normal MPI) may be false positives. In a prior study, Chow et al. excluded cases with > 5 unassessable segments. Actually, it is of use to add MPI in the assessment of patients with poor CTA images [10].

Second, patients with normal CTA may experience any kind of cardiac event. Some patients with major branches protected have an ischemic or infarcted area due to prior myocardial infarction or side branch occlusion, and so the at risk area might cause fatal arrhythmia and heart failure in them even if the risk of ungrafted coronary events or graft failure is very low. The present study demonstrates that the prognosis of patients with normal CTA and abnormal MPI (Group C) is poorer (event-free rate; 87.5%) than that of those with normal CTA and MPI (Group A: 97.3).

Finally, prior CTA studies lacked some necessary data [10-11]. Small et al. and Chow et al. did not obtain data of the time since CABG [10-11] or the variety of graft types [10]. In prior prognostic studies of MPI or CAG, time since CABG and the variety of grafts were identified as important predictors [12-14]. When the prognosis of CABG patients is discussed, information on the time since CABG and the variety of grafts is indispensible.

Limitations:

This study has some limitations. First, a limited number of patients in a single center were enrolled and were observed retrospectively. Second, we did not perform invasive coronary angiography in all studied patients. The diagnosis of unprotected coronary territory based on CTA may contain some false-positives and/or false-negatives.

【Conclusions】

Our results indicate that the combination of MPI and CTA is useful for the risk stratification of patients with previous CABG. The advantages of each imaging examination complement the limitations of the other. The combination of anatomical and functional evaluations enhances assessment of the prognosis of CABG patients non-invasively.

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There is no additional data available.

【Authors' contribution】

Hideki Kawai and Masayoshi Sarai evaluated myocardial perfusion imaging (MPI). Sadako

Motoyama and Hajime Ito evaluated CT imaging. Kayoko Takada and Junichi Ishii did MPI exam. Hiroto Harigaya and Hirofumi Anno did CT exam. Hiroshi Takahashi and Shuji Hashimoto gave me some advices about statistics. Yasushi Takagi and Motomi Ando are CABG operators and attending doctors for most patients. Toyoaki Murohara, and Yukio Ozaki conducted this study.

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Figure legends

Figure 1. Cardiac event curves according to (A) UCT, (B) SSS, (C) each group

UCT: unprotected coronary territory, SSS: summed stress score

Table 1. Patient Characteristics

	All (n=204)	Cardiac Events (n=27)	No Events (n=177)	p Value
Age (years)	68.7±7.6	70.0±7.7	68.5±7.6	0.46
Gender (male)	172 (84.3%)	21 (77.8%)	151 (85.3%)	0.527
Diabetes	106 (52.0%)	17 (63.0%)	89 (50.3%)	0.234
Dyslipidemia	116 (56.9%)	18 (66.7%)	98 (55.4%)	0.214
Hypertension	172 (84.3%)	24 (88.9%)	148 (83.6%)	0.673
Hemodialysis	9 (4.4%)	2 (7.4%)	7 (4.0%)	0.229
Current Smoker	39 (19.1%)	5 (18.5%)	34 (19.2%)	0.905
LVEF (%)	52.1±9.9	44.9±11.5	53.2±9.3	0.0002
Time since CABG (months)	25.3±51.2	55.8±66.7	20.7±47.0	0.0008
OMI	34 (16.7%)	8 (29.6%)	26 (14.7%)	0.08
Post PCI	23 (11.3%)	5 (18.5%)	18 (10.2%)	0.319
Using ITA	191 (93.6%)	23 (85.2%)	168 (94.9%)	0.089
EuroSCORE II	1.90±1.32	2.43±1.69	1.81±1.24	0.038

LVEF: left ventricular ejection fraction by ultrasonic cardiography, CABG: coronary aorta bypass graft, OMI: old myocardial infarction, PCI: percutaneous coronary intervention, ITA: internal thoracic artery

Table 2a. CTA, MPI Findings: Univariable and Multivariate Analysis for Cardiac Events

	Cardiac Events (n=27)	No Events (n=177)	Annual Event Rate, %	Unadjusted Hazards Ratio (95%CI)	P value	Adjusted Hazards Ratio (95%CI)	P value
UCT= 0	8 (6.5%)	115 (93.5%)	2.82	1		1	
UCT ≥ 1	19 (23.5%)	62 (76.5%)	8.27	3.07 (1.38-7.49)	0.0054	2.34# (1.01-5.89)	0.0465
SSS < 4	4 (3.8%)	101 (96.2%)	1.44	1		1	
SSS ≥ 4	23 (23.2%)	76 (76.8%)	9.67	6.73 (2.59-22.96)	<0.0001	3.36& (1.18-12.12)	0.0217

UCT: unprotected coronary territory, SSS: summed stress score, # Hazards ratio was adjusted for LVEF, time since CABG, EuroSCORE Ⅱ, and SSS, & Hazards ratio was adjusted for LVEF, time since CABG, EuroSCORE Ⅱ, and UCT

Table 2b. Combination of UCT and SSS: (Univariable and Multivariate Analysis for Cardiac Events)

Group	UCT	SSS	No of patients	No of patients with Cardiac Events (%)	Annual Event Rate (%)	Unadjusted hazards ratio (95%CI)	P value	Adjusted hazards ratio$ (95%CI)	P value
A	0	<4	75	2(2.7)	1.1	1		1	
B	≥1	<4	30	2(6.7)	2.0	1.93 (0.23-16.16)	0.515	1.76 (0.21-15.11)	0.579
C	0	≥4	48	6(13.0)	5.7	5.15 (1.19-35.17)	0.0279	2.73 (0.55-19.93)	0.225
D	≥1	≥4	51	17(33.0)	12.9	11.9 (3.40-75.19)	<0.0001	6.84 (1.83-44.5)	0.0026

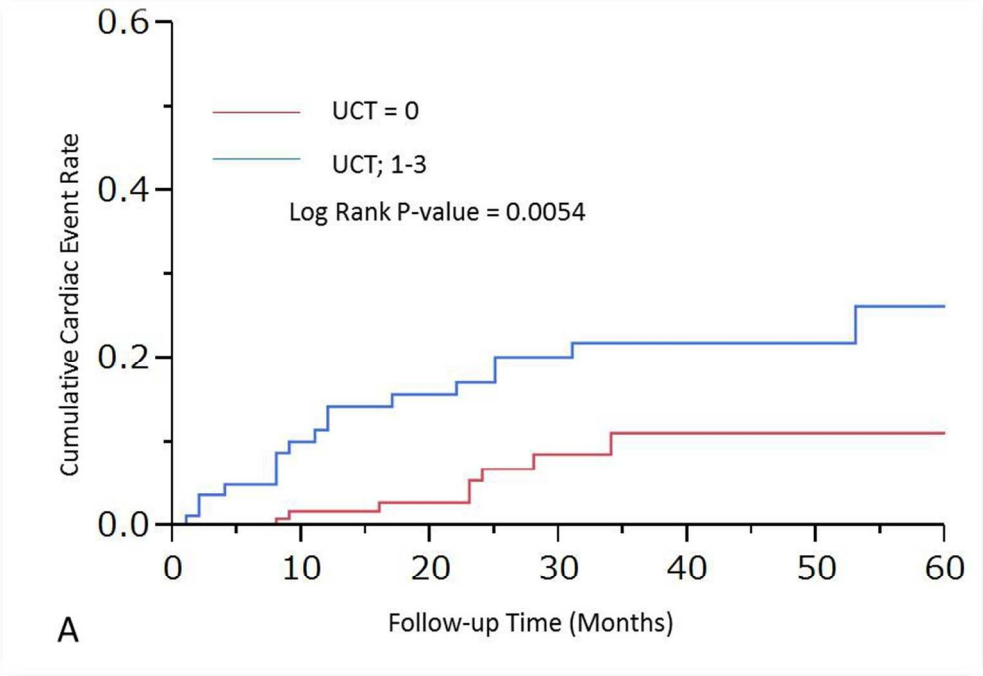
$ Hazards ratio was adjusted for LVEF, time since CABG, and EuroSCORE II

Table 3. Discrimination of Each Predicting Models for Cardiac Events

	Discrimination					
Risk Factors and Imaging Findings	C Index (95%CI)	p Value	NRI	p Value	IDI	p Value
Clinical risk factors#	0.768 (0.655-0.880)	Reference	Reference		Reference	
Clinical risk factors# plus UCT	0.811 (0.718-0.905)	0.1049	0.707	0.0003*	0.0369	0.0235
Clinical risk factors# plus SSS	0.807 (0.701-0.912)	0.1156	0.731	0.0002*	0.0421	0.0005
Clinical risk factors# plus UCT and SSS	0.834 (0.742-0.927)	0.0454*	0.649	0.0008*	0.0701	0.0006
Clinical risk factors# plus UCT		Reference	Reference		Reference	
Clinical risk factors# plus UCT and SSS		0.1989	0.707	0.0003*	0.0281	0.039
Clinical risk factors# plus SSS		Reference	Reference		Reference	
Clinical risk factors# plus UCT and SSS		0.1486	0.645	0.0009*	0.0333	0.0009

UCT: unprotected coronary territory, SSS: summed stress score, NRI: Net Reclassification Improvement, IDI: Integrated Discrimination Improvement

#Clinical risk factors comprise LVEF, time since CABG, and EuroSCORE Ⅱ



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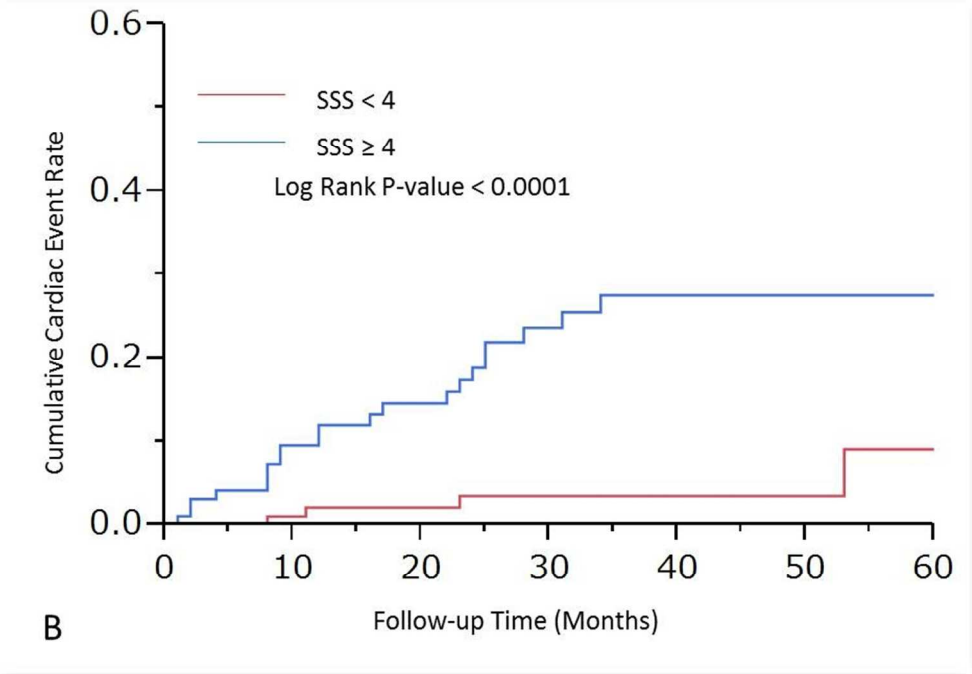

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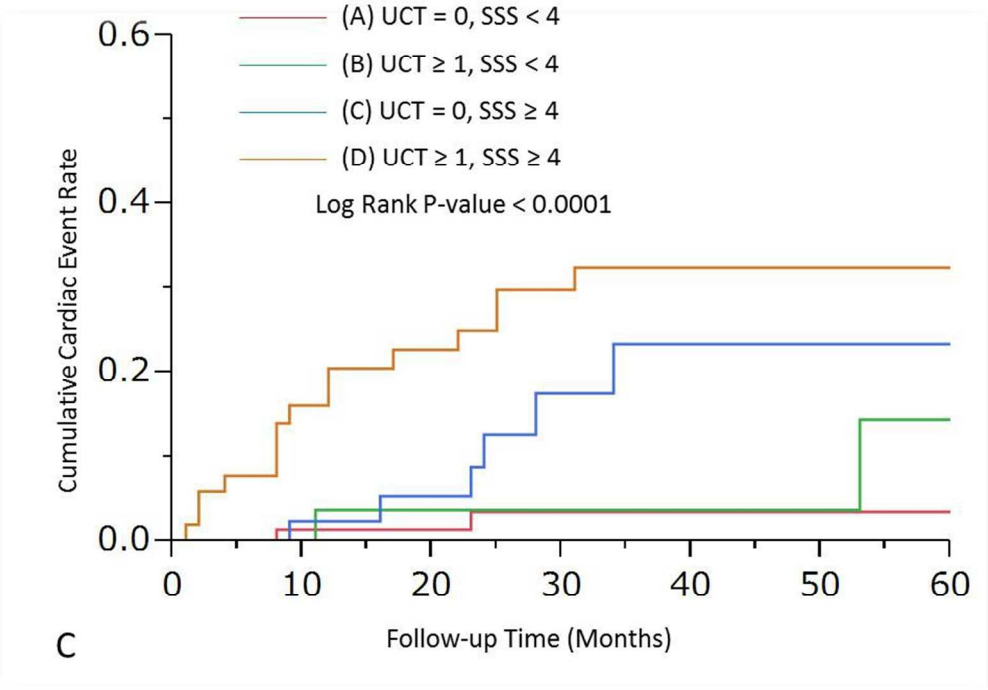

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Combination of Anatomical and Functional Evaluations Improves the Prediction of Cardiac Event in Coronary Artery Bypass Patients

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Combination of Anatomical and Functional Evaluations Improves the Prediction of Cardiac Event in Coronary Artery Bypass Patients

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myocardial perfusion imaging

Study approval: The study was approved by the Institutional Review Board and the ethics committee of Fujita Health University.

Patient consent: We got all patients' consent.

Abstract

Objective: To study the usefulness of combined risk stratification of coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) in patients with previous coronary-artery-bypass grafting (CABG).

Design: retrospective, observational, single center

Setting and Patients: 204 patients (84.3% male, mean age 68.7±7.6) undergoing CTA and MPI.

Main outcome measures: CTA defined unprotected coronary territories (UCT) (0, 1, 2, or 3) by evaluating the number of significant stenoses which were defined as left main trunk ≥50% diameter

stenosis, other native vessel stenosis ≥70%, or graft stenosis ≥70%. Using the cut-off value with receiver-operating characteristics analysis, all patients were divided into 4 groups: Group A (UCT = 0, summed stress score [SSS] < 4), Group B (UCT ≥ 1, SSS < 4), Group C (UCT = 0, SSS ≥ 4), and Group D (UCT ≥ 1, SSS ≥ 4).

Results: Cardiac events, as a composite endpoint including cardiac death, nonfatal myocardial infarction, unstable angina requiring revascularization, and heart-failure hospitalization were observed in 27 patients for a median follow-up of 27.5 months. The annual event rates were 1.1%, 2.0%, 5.7%, and 12.9% of patients in Group A, B, C, and D, respectively (Log Rank P-value < 0.0001). Adding UCT or SSS to a model with significant clinical factors including left ventricular ejection fraction, time since CABG, and Euro SCORE Ⅱ improved the prediction of events, while adding both UCT and SSS to the model improved it greatly with increasing C-index, net reclassification improvement and integrated discrimination improvement.

Conclusions: The combination of anatomical and functional evaluations non-invasively enhances the predictive accuracy of cardiac events in CABG patients.

Article summary

1) Article Focus

- To study the prognosis and predictors of previous coronary-artery-bypass grafting (CABG) patients.

- Both coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) are useful for the risk stratification with previous CABG patients.
- It is usefulness to combine risk stratification of coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) in patients with previous CABG.

2) Key Messages

- UCT defined by CTA, SSS by MPI, Left ventricular ejection fraction, time since CABG, and Euro SCORE Ⅱ were independent predictors.
- Each CTA and MPI reflected the prognosis of CABG patients.
- The combination of anatomical (CTA) and functional (MPI) evaluations non-invasively enhances the predictive accuracy of cardiac events in CABG patients. The advantages of each imaging examination complement the limitations of the other.

3) Strengths and Limitations

- A limited number of patients in a single center were enrolled and were observed retrospectively.
- In a large number and prospective study, the usefulness and cost-effectiveness of combined evaluation will be studied further.
- We did not perform invasive coronary angiography in all studied patients. (The diagnosis of

unprotected coronary territory based on CTA may contain some false-positives and/or false-negatives.)

【Introduction】

Coronary computed tomography angiography (CTA) is a useful tool not only for the detection of obstructive coronary artery disease [1-3], but also for the risk stratification of patients with coronary artery disease [4-5]. Some studies using CTA have shown good diagnostic performance for the detection of significant stenosis in grafts, with accuracy improved by the newer generation of CT scanners [6-9]. Recently, Chow et al. and Small et al. demonstrated that CTA was of prognostic value in patients with previous coronary-artery-bypass grafting (CABG) [10-11]. On the other hand, CTA has some limitations in the evaluation of distal runoffs, metal clip artifacts, and native coronary segments of nongrafted vessels, particularly due to the high prevalence of severe calcification in previous CABG patients [6, 8].

Myocardial perfusion imaging (MPI) has been also useful for the risk stratification of patients with

previous CABG [12-14]. MPI is regarded as the gold standard for the risk stratification of such patients [15], despite some limitations. Patients after CABG have a high prevalence of perfusion defects because of old myocardial infarction or ischemic areas resulting from coronary side branch occlusion, and so there is a low positive predictive value for prognostic evaluation.

In previous studies, Schuijf et al. showed that MPI and CTA provided different and complementary information on patients with suspected CAD [16]. Werkhoven et al. concluded that combined anatomical and functional assessment might allow improved risk stratification [17]. The purpose of the present study was to assess the prognosis of CABG patients by CTA and MPI, and to determine the efficacy of such combined anatomical and functional assessment.

【Methods】

We studied 211 patients with a history of CABG. From January 2006 to October 2011, they underwent both CTA and MPI within 3 months of each other, and their clinical endpoints were followed. Exclusion criteria were: 1) complicating congenital heart disease; 2) after valve surgery or left ventricular (LV) aneurysm resection; 3) known allergy to iodinated contrast agents; 4) severe renal insufficiency not requiring hemodialysis (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2). To determine the preoperative risk assessment of these patients, we used a logistic European System for Cardiac Operative Risk Evaluation risk model (EuroSCORE Ⅱ) [18]. The study

was approved by the Institutional Review Board and the ethics committee of Fujita Health University.

Coronary Computed Tomography Angiography

In the first 27 patients, 64-slice CT (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) was used with a collimation of 64 × 0.5mm, rotation speed of 350, 375, 400msec, and retrospective gating electrocardiogram (ECG). For the contrast enhanced scan, a total amount of 80 to 90 mL of contrast medium with an injection flow rate of 4 mL/second was injected, followed by a 40-mL saline bolus chase. Volumetric data were reconstructed with segmented reconstruction [9]. In the remaining 184 patients, 320-slice CT (Aquilion One Toshiba Medical Systems, Otawara, Japan) was used with a collimation of 320 × 0.5mm, rotation speed of 350, 375, 400msec, and prospective triggering ECG. A bolus of 1.1 mL/kg contrast medium was injected over 18 s, followed by a 20-mL saline bolus chase. Volumetric data were reconstructed with half or segmented reconstruction [19]. All scans were performed during a single breath-hold. Isosorbide dinitrate spray 1.25mg was provided immediately before CTA. The effective radiation dose was 12.7 ± 9.1 mSv (9.8 ± 3.7 mSv in 320-slice CT and 32.6 ± 10.4 mSv in 64-slice CT). After acquisition of the reconstructed volumetric data, images were transferred to a workstation (ZIOSTATION System 1000, Amin/ZIO, Tokyo, Japan). On CT images, coronary arteries were divided into 15 segments based on the recommendations of the American Heart Association [20]. All native coronary arteries and bypass

grafts were evaluated by two experienced observers (SM and HI) unaware of the clinical history and MPI findings of the patients. Atherosclerotic lesions and stenoses were classified visually as mild (< 50% luminal diameter), moderate (50% to 69%), or severe (≥70%). Significant stenoses were defined as left main trunk ≥50% diameter stenosis, other native vessel stenosis ≥70%, or graft stenosis ≥70%. Native coronary segments (including stented segments) and grafts, that were not assessable because of severe calcification and motion artifacts, were regarded as severe stenoses. Patients were categorized according to the number (0, 1, 2, or 3) of unprotected coronary territories (UCT) [10]. Each patient had 3 coronary territories, corresponding to each major epicardial artery (left anterior descending artery, circumflex artery or artery supplying the posterior descending artery [right coronary artery or circumflex artery]) and their corresponding branches (diagonal and marginal arteries). A coronary territory was deemed unprotected if: 1) an ungrafted native coronary artery had a significant stenosis; 2) a significant stenosis in the native artery was distal to the graft insertion; or 3) a native artery and its graft both had significant stenoses.

Stress-rest myocardial perfusion imaging

In all patients, stress-rest MPI using thallium (Tl) -201 was performed with adenosine stress [21]. Early single photon emission tomography (SPECT) was performed 10 min after the adenosine stress

test; late SPECT was performed 4 h thereafter. SPECT images were acquired using a dual-headed SPECT gamma camera (ADAC VERTEX-plus; EPIC, USA). Tomographic reconstruction was performed using a standard filtered back-projection technique with a ramp filter to produce a transaxial tomogram. No scatter or attenuation correction was applied. From these transaxial tomograms, the long axis of the left ventricle was identified, and oblique-angled tomograms were generated (i.e., vertical long-axis, short-axis, and horizontal long-axis tomograms) [22]. Tl-201 uptake was graded subjectively in three orthogonal planes (short axis, horizontal long axis, vertical long axis) divided into 17 segments on a five-point scale (4 = absent uptake; 3 = severely, 2 = moderately, 1 = mildly decreased uptake; 0 = normal uptake, respectively) on the post stress and delayed images displayed side by side by the consensus of two experienced observers (MS and HK) unaware of the clinical history and CTA findings of the patients [19]. The segmental perfusion scores during stress and rest were added together to calculate the summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS).

Patient follow-up:

Patient follow-up data were gathered by observers blinded to the baseline CTA and MPI results using clinical visits or standardized telephone interviews. Cardiac events (cardiac death, nonfatal myocardial infarction, unstable angina requiring revascularization, and admission to a hospital due to heart failure) were regarded as clinical end points. Deaths were considered cardiac when the primary

cause of death was related to myocardial ischemia/infarction, heart failure or arrhythmia, and when a noncardiac cause of death could not be identified. Nonfatal myocardial infarction was defined as myocardial ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper normal limits). Unstable angina was defined as acute chest pain with or without the presence of ECG abnormalities, and negative cardiac enzyme levels [23-24]. Patients undergoing elective revascularization within 3 months after CTA or MPI (early elective revascularization) were excluded after enrollment.

Statistical analysis:

All data were presented as the mean ± SD for continuous variables and frequency (percentage) for categorical variables. The mean values for the two groups were compared with chi-square tests for categorical and Wilcoxon sum rank test for continuous variables. All analyses were performed with JMP Version 10, (SAS Institute Inc., Cary, NC, USA) and a p-value of < 0.05 was considered as statistically significant.

The prognosis of CABG patients was assessed in univariate and multivariate models based on UCT, SSS, and their combination. Receiver-operating characteristics (ROC) analysis was performed to determine cutoff values of UCT and SSS for cardiac events. Risk adjusted analyses were performed with Cox proportional hazard models to determine the independent prognostic value of UCT, SSS, and their combination by controlling for other predictors. Cumulative event rates were estimated

with the Kaplan-Meier method and were compared with the log-rank test.

The increased discriminative value after addition of UCT and/or SSS to the established clinical risk factors was estimated using the C-index for ROC curve, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under an ROC curve between individual predicted probabilities and incidence of events, and is compared between in a baseline model consisting of established clinical risk factors with $p<0.05$ by univariate Cox analysis, and in an enriched model with UCT and/or SSS [25]. The NRI indicates relatively how many patients show a decrease in their predicted probabilities for events, while the IDI represents the average decrease in predicted probabilities for events after adding UCT and/or SSS into the baseline model, respectively [26].

【Results】

Clinical characteristics:

In total, 204 patients (84.3% male, mean age 68.7±7.6 years) were enrolled after excluding 7 patients: 4 undergoing early elective revascularization within 3 months after imaging examination, and 3 lost to follow-up. The mean follow-up period was 30.3±17.6 months (median; 27.5 months). Four patients who underwent early revascularization were excluded because we could not study their natural histories after examination. In Table 1, baseline characteristics are listed in detail. At

follow-up, cardiac events were observed in 27 patients (13.2%) with an annualized event rate of 5.2% (3 patients with cardiac death, 9 patients with non-fatal infarction, 3 patients with unstable angina requiring revascularization, and 12 patients with heart failure). In the univariate Cox analysis, LVEF determined by cardiac ultrasound [Hazard Ratio (HR): 0.936; 95% Confidence Interval (CI): 0.905 to 0.968; p = 0.0002], time since CABG (HR: 1.01; 95% CI: 1.00-1.02; p=0.0008), and EuroSCORE Ⅱ (HR: 1.29; 95% CI: 1.02-1.57; p=0.038) were significant predictors of cardiac events.

CTA, MPI Findings and Analysis with the Combination of UCT and SSS

Mean UCT was 0.51±0.72, and % uninterpretable segments on CTA were 0.4%, 7.37%, and 3.61% in grafts, LMT, and other coronary artery segments, respectively. Mean SSS, SRS, and SDS were 7.03±8.65, 5.21±7.70, and 1.82±3.23, respectively. Mean % fixed defects was 10.3%.

The UCT and SSS were significant predictors for cardiac events (HR: 2.52; 95% CI: 1.59 to 3.96; p=0.0001 and HR: 1.08; 95% CI: 1.05 to 1.12; p < 0.0001, respectively). To maximize the predictive power of UCT and SSS, cut-off levels were determined as 1 for UCT [area under curve (AUC) = 0.71] and 4 for SSS (AUC = 0.76), respectively. Cumulative incidence rates for cardiac events are demonstrated in Figure 1A and 1B (log rank p-value = 0.0054 and < 0.0001, respectively). After adjustment for LVEF, time since CABG and EuroSCORE Ⅱ, patients with UCT ≥ 1 had 2.34-fold higher risk of cardiac events (95% CI 1.01 to 5.89, p = 0.0465). Similarly, patients with SSS ≥ 4 had

3.36-fold higher risk of cardiac events (95% CI 1.18 to 12.12, p = 0.0217) (Table 2a).

Based on the CTA and MPI findings, we divided all patients into 4 groups: Group A (UCT = 0, SSS <4), Group B (UCT; ≥1, SSS <4), Group C (UCT = 0, SSS ≥4), and Group D (UCT; ≥1, SSS ≥4). The annual event rates of cardiac events were 1.1%, 2.0%, 5.7%, and 12.9% of patients in group A, B, C and D, respectively. Cardiac event curves are demonstrated in Figure 1C (log rank p-value < 0.0001). After adjustment for LVEF, time since CABG, and EuroSCORE Ⅱ, patients with UCT ≥ 1 and SSS ≥ 4 had 6.84-fold (95% CI 1.83 to 44.50, p = 0.0026) higher risk for cardiac events compared to those with UCT = 0 and SSS < 4 (Table 2b).

Discrimination of Each Predicting Models for Cardiac Events (Table 3)

Addition of UCT alone, SSS alone, and both UCT and SSS to a baseline model with clinical risk factors consisting of LVEF, time since CABG, and EuroSCORE II significantly improved both the NRI and IDI. However, C-index was significantly greater only in the model with both UCT and SSS compared to the baseline model (0.834 vs. 0.768, p=0.045). In addition, the NRI and IDI significantly increased in the model containing both UCT and SSS even if compared to the model containing UCT alone or SSS alone.

【Discussion】

We focused on the prognosis of CABG patients assessed by CTA and MPI, and the usefulness of this combination. The patients without unprotected territories on CTA and without perfusion defects on MPI have a good prognosis. The prognosis of patients with abnormal CTA (UCT; ≥1) and MPI (SSS ≥ 4) is significantly poorer than that of patients with normal CTA and MPI. Each examination has incremental prognostic value, and the combination of anatomical and functional evaluation facilitates non-invasive assessment of the prognosis of CABG patients. This improvement was indicated to be statistically significant by the increase in the NRI and IDI.

Several reports have shown the utility of MPI with assessment of the prognosis in CABG patients [12-14], but there are some limitations.

First, many CABG patients have some abnormal findings on MPI, because of a history of prior myocardial infarctions, and others have ischemic territories with side branch occlusion even if the major coronary trees are protected. Actually in the present study, 48.5% of the enrolled patients had an abnormal MPI finding (SSS ≥ 4). To identify the patients with a poor prognosis strictly among those with MPI abnormalities, the evaluation of unprotected coronary territories on CTA was useful. The event rates were 33.3% in the abnormal CTA patients (Group D), in contrast to 12.5% in the normal CTA patients (Group C).

Importantly, MPI does not clarify the anatomy of grafts or native coronary arteries, even when high risk patients are identified. On the other hand, CTA provides information on grafts and unprotected

native coronary arteries non-invasively, and in this way contributes to devising the most appropriate therapeutic strategy.

Several studies have also demonstrated the diagnostic accuracy of CTA in CABG patients [6-9], and two recent studies reported the prognostic value of CTA in CABG patients [10-11]. They concluded that assessment with CTA is of prognostic value in CABG patients, despite some limitations.

First, some difficulties remain regarding the diagnostic accuracy [7-9]. Indeed the diagnostic accuracy of graft segments is good, but CABG patients have a high prevalence of severe calcifications and stented segments in the native coronary arteries, leading to some overestimation of stenosis of the distal runoff segments of the protected coronary arteries, and unprotected native coronary arteries including stented segments. Actually in our study, unassessable native coronary or graft segments were regarded as severe stenosis, likely resulting in some overestimation of the number of unprotected coronary territories. In other words, some CTA findings in Group B patients (abnormal CTA and normal MPI) may be false positives. In a prior study, Chow et al. excluded cases with > 5 unassessable segments. Actually, it is of use to add MPI in the assessment of patients with poor CTA images [10].

Second, patients with normal CTA may experience any kind of cardiac event. Some patients with major branches protected have an ischemic or infarcted area due to prior myocardial infarction or side branch occlusion, and so the at risk area might cause fatal arrhythmia and heart failure in them even if the risk of ungrafted coronary events or graft failure is very low. The present study

demonstrates that the prognosis of patients with normal CTA and abnormal MPI (Group C) is poorer (event-free rate; 87.5%) than that of those with normal CTA and MPI (Group A: 97.3).

Finally, prior CTA studies lacked some necessary data [10-11]. Small et al. and Chow et al. did not obtain data of the time since CABG [10-11] or the variety of graft types [10]. In prior prognostic studies of MPI or CAG, time since CABG and the variety of grafts were identified as important predictors [12-14]. When the prognosis of CABG patients is discussed, information on the time since CABG and the variety of grafts is indispensible.

Limitations:

This study has some limitations. First, a limited number of patients in a single center were enrolled and were observed retrospectively. Additionally, small number of hard events including cardiac death and nonfatal myocardial infarction was observed during follow-up. Second, we did not perform invasive coronary angiography in all studied patients. The diagnosis of unprotected coronary territory based on CTA may contain some false-positives and/or false-negatives. Last, due to the lack of data regarding the medical therapy when cardiac events were occurred, we could not discuss the appropriateness of medical therapy which may have influenced results.

【Conclusions】

Our results indicate that the combination of MPI and CTA is useful for the risk stratification of patients with previous CABG. The advantages of each imaging examination complement the limitations of the other. The combination of anatomical and functional evaluations enhances assessment of the prognosis of CABG patients non-invasively.

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There is no additional data available.

【Authors' contribution】

Hideki Kawai and Masayoshi Sarai evaluated myocardial perfusion imaging (MPI). Sadako Motoyama and Hajime Ito evaluated CT imaging. Kayoko Takada and Junichi Ishii did MPI exam. Hiroto Harigaya and Hirofumi Anno did CT exam. Hiroshi Takahashi and Shuji Hashimoto gave me some advices about statistics. Yasushi Takagi and Motomi Ando are CABG operators and attending doctors for most patients. Toyoaki Murohara, and Yukio Ozaki conducted this study.

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Competing interests: no

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Figure legends

Figure 1. Cardiac event curves according to (A) UCT, (B) SSS, (C) each group

UCT: unprotected coronary territory, SSS: summed stress score

Table 1. Patient Characteristics

	All (n=204)	Cardiac Events (n=27)	No Events (n=177)	p Value
Age (years)	68.7±7.6	70.0±7.7	68.5±7.6	0.46
Gender (male)	172 (84.3%)	21 (77.8%)	151 (85.3%)	0.527
Diabetes	106 (52.0%)	17 (63.0%)	89 (50.3%)	0.234
Dyslipidemia	116 (56.9%)	18 (66.7%)	98 (55.4%)	0.214
Hypertension	172 (84.3%)	24 (88.9%)	148 (83.6%)	0.673
Hemodialysis	9 (4.4%)	2 (7.4%)	7 (4.0%)	0.229
Current Smoker	39 (19.1%)	5 (18.5%)	34 (19.2%)	0.905
LVEF (%)	52.1±9.9	44.9±11.5	53.2±9.3	0.0002
Time since CABG (months)	25.3±51.2	55.8±66.7	20.7±47.0	0.0008
Prior MI	34 (16.7%)	8 (29.6%)	26 (14.7%)	0.08
Post PCI	23 (11.3%)	5 (18.5%)	18 (10.2%)	0.319
Prior HF	17 (8.3%)	3 (11.1%)	14 (7.9%)	0.539

Using ITA	191 (93.6%)	23 (85.2%)	168 (94.9%)	0.089
EuroSCORE Ⅱ	1.90±1.32	2.43±1.69	1.81±1.24	0.038

LVEF: left ventricular ejection fraction by ultrasonic cardiography, CABG: coronary aorta bypass graft, MI: myocardial infarction, PCI: percutaneous coronary intervention, HF: heart failure, ITA: internal thoracic artery

Table 2a. CTA, MPI Findings: Univariable and Multivariate Analysis for Cardiac Events

	Cardiac Events (n=27)	No Events (n=177)	Annual Event Rate, %	Unadjusted Hazards Ratio (95%CI)	P value	Adjusted Hazards Ratio (95%CI)	P value
UCT= 0	8 (6.5%)	115 (93.5%)	2.82	1		1	
UCT ≥ 1	19 (23.5%)	62 (76.5%)	8.27	3.07 (1.38-7.49)	0.0054	2.34# (1.01-5.89)	0.0465
SSS < 4	4 (3.8%)	101 (96.2%)	1.44	1		1	
SSS ≥ 4	23 (23.2%)	76 (76.8%)	9.67	6.73 (2.59-22.96)	<0.0001	3.36& (1.18-12.12)	0.0217

UCT: unprotected coronary territory, SSS: summed stress score, # Hazards ratio was adjusted for LVEF, time since CABG, EuroSCORE Ⅱ, and SSS, & Hazards ratio was adjusted for LVEF, time since CABG, EuroSCORE Ⅱ, and UCT. Eight events in patients with UCT=0 included 3 nonfatal MI and 5 HF, 19 events in

UCT≥1 included 3 cardiac death, 6 nonfatal MI, 3 late revascularization, and 7 heart failure. Four events in patients with SSS<4 included 3 nonfatal MI and 1 late revascularization, 23 events in SSS≥4 included 3 cardiac death, 6 nonfatal MI, 2 late revascularization, and 12 heart failure.

Table 2b. Combination of UCT and SSS: (Univariable and Multivariate Analysis for Cardiac Events)

Group	UCT	SSS	No of patients	No of patients with Cardiac Events (%)	Annual Event Rate (%)	Unadjusted hazards ratio (95%CI)	P value	Adjusted hazards ratio$ (95%CI)	P value
A	0	<4	75	2(2.7)	1.1	1		1	
B	≥1	<4	30	2(6.7)	2.0	1.93 (0.23-16.16)	0.515	1.76 (0.21-15.11)	0.579
C	0	≥4	48	6(13.0)	5.7	5.15 (1.19-35.17)	0.0279	2.73 (0.55-19.93)	0.225
D	≥1	≥4	51	17(33.0)	12.9	11.9 (3.40-75.19)	<0.0001	6.84 (1.83-44.5)	0.0026

$ Hazards ratio was adjusted for LVEF, time since CABG, and EuroSCORE II

Table 3. Discrimination of Each Predicting Models for Cardiac Events

	Discrimination					
Risk Factors and Imaging Findings	C Index (95%CI)	p Value	NRI	p Value	IDI	p Value
Clinical risk factors#	0.768 (0.655-0.880)	Reference	Reference		Reference	
Clinical risk factors# plus UCT	0.811 (0.718-0.905)	0.1049	0.707	0.0003*	0.0369	0.0235
Clinical risk factors# plus SSS	0.807 (0.701-0.912)	0.1156	0.731	0.0002*	0.0421	0.0005

Clinical risk factors# plus UCT and SSS	0.834 (0.742-0.927)	0.0454*	0.649	0.0008*	0.0701	0.0006
Clinical risk factors# plus UCT		Reference	Reference		Reference	
Clinical risk factors# plus UCT and SSS		0.1989	0.707	0.0003*	0.0281	0.039
Clinical risk factors# plus SSS		Reference	Reference		Reference	
Clinical risk factors# plus UCT and SSS		0.1486	0.645	0.0009*	0.0333	0.0009

UCT: unprotected coronary territory, SSS: summed stress score, NRI: Net Reclassification Improvement, IDI: Integrated Discrimination Improvement

#Clinical risk factors comprise LVEF, time since CABG, and EuroSCORE II

Combination of Anatomical and Functional Evaluations Improves the Prediction of Cardiac Event in Coronary Artery Bypass Patients

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myocardial perfusion imaging

Study approval: The study was approved by the Institutional Review Board and the ethics committee of Fujita Health University.

Patient consent: We got all patients' consent.

Abstract

Objective: To study the usefulness of combined risk stratification of coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) in patients with previous coronary-artery-bypass grafting (CABG).

Design: retrospective, observational, single center

Setting and Patients: 204 patients (84.3% male, mean age 68.7±7.6) undergoing CTA and MPI.

Main outcome measures: CTA defined unprotected coronary territories (UCT) (0, 1, 2, or 3) by evaluating the number of significant stenoses which were defined as left main trunk ≥50% diameter

stenosis, other native vessel stenosis ≥70%, or graft stenosis ≥70%. Using the cut-off value with receiver-operating characteristics analysis, all patients were divided into 4 groups: Group A (UCT = 0, summed stress score [SSS] < 4), Group B (UCT ≥ 1, SSS < 4), Group C (UCT = 0, SSS ≥ 4), and Group D (UCT ≥ 1, SSS ≥ 4).

Results: Cardiac events, as a composite endpoint including cardiac death, nonfatal myocardial infarction, unstable angina requiring revascularization, and heart-failure hospitalization were observed in 27 patients for a median follow-up of 27.5 months. The annual event rates were 1.1%, 2.0%, 5.7%, and 12.9% of patients in Group A, B, C, and D, respectively (Log Rank P-value < 0.0001). Adding UCT or SSS to a model with significant clinical factors including left ventricular ejection fraction, time since CABG, and Euro SCORE Ⅱ improved the prediction of events, while adding both UCT and SSS to the model improved it greatly with increasing C-index, net reclassification improvement and integrated discrimination improvement.

Conclusions: The combination of anatomical and functional evaluations non-invasively enhances the predictive accuracy of cardiac events in CABG patients.

Article summary

1) Article Focus

- To study the prognosis and predictors of previous coronary-artery-bypass grafting (CABG) patients.

- Both coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) are useful for the risk stratification with previous CABG patients.
- It is usefulness to combine risk stratification of coronary computed tomography angiography (CTA) and myocardial perfusion imaging (MPI) in patients with previous CABG.

2) Key Messages

- UCT defined by CTA, SSS by MPI, Left ventricular ejection fraction, time since CABG, and Euro SCORE Ⅱ were independent predictors.
- Each CTA and MPI reflected the prognosis of CABG patients.
- The combination of anatomical (CTA) and functional (MPI) evaluations non-invasively enhances the predictive accuracy of cardiac events in CABG patients. The advantages of each imaging examination complement the limitations of the other.

3) Strengths and Limitations

- A limited number of patients in a single center were enrolled and were observed retrospectively.
- In a large number and prospective study, the usefulness and cost-effectiveness of combined evaluation will be studied further.
- We did not perform invasive coronary angiography in all studied patients. (The diagnosis of

unprotected coronary territory based on CTA may contain some false-positives and/or false-negatives.)

【Introduction】

Coronary computed tomography angiography (CTA) is a useful tool not only for the detection of obstructive coronary artery disease [1-3], but also for the risk stratification of patients with coronary artery disease [4-5]. Some studies using CTA have shown good diagnostic performance for the detection of significant stenosis in grafts, with accuracy improved by the newer generation of CT scanners [6-9]. Recently, Chow et al. and Small et al. demonstrated that CTA was of prognostic value in patients with previous coronary-artery-bypass grafting (CABG) [10-11]. On the other hand, CTA has some limitations in the evaluation of distal runoffs, metal clip artifacts, and native coronary segments of nongrafted vessels, particularly due to the high prevalence of severe calcification in previous CABG patients [6, 8].

Myocardial perfusion imaging (MPI) has been also useful for the risk stratification of patients with

previous CABG [12-14]. MPI is regarded as the gold standard for the risk stratification of such patients [15], despite some limitations. Patients after CABG have a high prevalence of perfusion defects because of old myocardial infarction or ischemic areas resulting from coronary side branch occlusion, and so there is a low positive predictive value for prognostic evaluation.

In previous studies, Schuijf et al. showed that MPI and CTA provided different and complementary information on patients with suspected CAD [16]. Werkhoven et al. concluded that combined anatomical and functional assessment might allow improved risk stratification [17]. The purpose of the present study was to assess the prognosis of CABG patients by CTA and MPI, and to determine the efficacy of such combined anatomical and functional assessment.

【Methods】

We studied 211 patients with a history of CABG. From January 2006 to October 2011, they underwent both CTA and MPI within 3 months of each other, and their clinical endpoints were followed. Exclusion criteria were: 1) complicating congenital heart disease; 2) after valve surgery or left ventricular (LV) aneurysm resection; 3) known allergy to iodinated contrast agents; 4) severe renal insufficiency not requiring hemodialysis (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2). To determine the preoperative risk assessment of these patients, we used a logistic European System for Cardiac Operative Risk Evaluation risk model (EuroSCORE Ⅱ) [18]. The study

was approved by the Institutional Review Board and the ethics committee of Fujita Health University.

Coronary Computed Tomography Angiography

In the first 27 patients, 64-slice CT (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) was used with a collimation of 64 × 0.5mm, rotation speed of 350, 375, 400msec, and retrospective gating electrocardiogram (ECG). For the contrast enhanced scan, a total amount of 80 to 90 mL of contrast medium with an injection flow rate of 4 mL/second was injected, followed by a 40-mL saline bolus chase. Volumetric data were reconstructed with segmented reconstruction [9]. In the remaining 184 patients, 320-slice CT (Aquilion One Toshiba Medical Systems, Otawara, Japan) was used with a collimation of 320 × 0.5mm, rotation speed of 350, 375, 400msec, and prospective triggering ECG. A bolus of 1.1 mL/kg contrast medium was injected over 18 s, followed by a 20-mL saline bolus chase. Volumetric data were reconstructed with half or segmented reconstruction [19]. All scans were performed during a single breath-hold. Isosorbide dinitrate spray 1.25mg was provided immediately before CTA. The effective radiation dose was 12.7 ± 9.1 mSv (9.8 ± 3.7 mSv in 320-slice CT and 32.6 ± 10.4 mSv in 64-slice CT). After acquisition of the reconstructed volumetric data, images were transferred to a workstation (ZIOSTATION System 1000, Amin/ZIO, Tokyo, Japan). On CT images, coronary arteries were divided into 15 segments based on the recommendations of the American Heart Association [20]. All native coronary arteries and bypass

grafts were evaluated by two experienced observers (SM and HI) unaware of the clinical history and MPI findings of the patients. Atherosclerotic lesions and stenoses were classified visually as mild (< 50% luminal diameter), moderate (50% to 69%), or severe (≥70%). Significant stenoses were defined as left main trunk ≥50% diameter stenosis, other native vessel stenosis ≥70%, or graft stenosis ≥70%. Native coronary segments (including stented segments) and grafts, that were not assessable because of severe calcification and motion artifacts, were regarded as severe stenoses. Patients were categorized according to the number (0, 1, 2, or 3) of unprotected coronary territories (UCT) [10]. Each patient had 3 coronary territories, corresponding to each major epicardial artery (left anterior descending artery, circumflex artery or artery supplying the posterior descending artery [right coronary artery or circumflex artery]) and their corresponding branches (diagonal and marginal arteries). A coronary territory was deemed unprotected if: 1) an ungrafted native coronary artery had a significant stenosis; 2) a significant stenosis in the native artery was distal to the graft insertion; or 3) a native artery and its graft both had significant stenoses.

Stress-rest myocardial perfusion imaging

In all patients, stress-rest MPI using thallium (Tl) -201 was performed with adenosine stress [21]. Early single photon emission tomography (SPECT) was performed 10 min after the adenosine stress

test; late SPECT was performed 4 h thereafter. SPECT images were acquired using a dual-headed SPECT gamma camera (ADAC VERTEX-plus; EPIC, USA). Tomographic reconstruction was performed using a standard filtered back-projection technique with a ramp filter to produce a transaxial tomogram. No scatter or attenuation correction was applied. From these transaxial tomograms, the long axis of the left ventricle was identified, and oblique-angled tomograms were generated (i.e., vertical long-axis, short-axis, and horizontal long-axis tomograms) [22]. Tl-201 uptake was graded subjectively in three orthogonal planes (short axis, horizontal long axis, vertical long axis) divided into 17 segments on a five-point scale (4 = absent uptake; 3 = severely, 2 = moderately, 1 = mildly decreased uptake; 0 = normal uptake, respectively) on the post stress and delayed images displayed side by side by the consensus of two experienced observers (MS and HK) unaware of the clinical history and CTA findings of the patients [19]. The segmental perfusion scores during stress and rest were added together to calculate the summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS).

Patient follow-up:

Patient follow-up data were gathered by observers blinded to the baseline CTA and MPI results using clinical visits or standardized telephone interviews. Cardiac events (cardiac death, nonfatal myocardial infarction, unstable angina requiring revascularization, and admission to a hospital due to heart failure) were regarded as clinical end points. Deaths were considered cardiac when the primary

cause of death was related to myocardial ischemia/infarction, heart failure or arrhythmia, and when a noncardiac cause of death could not be identified. Nonfatal myocardial infarction was defined as myocardial ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper normal limits). Unstable angina was defined as acute chest pain with or without the presence of ECG abnormalities, and negative cardiac enzyme levels [23-24]. Patients undergoing elective revascularization within 3 months after CTA or MPI (early elective revascularization) were excluded after enrollment.

Statistical analysis:

All data were presented as the mean ± SD for continuous variables and frequency (percentage) for categorical variables. The mean values for the two groups were compared with chi-square tests for categorical and Wilcoxon sum rank test for continuous variables. All analyses were performed with JMP Version 10, (SAS Institute Inc., Cary, NC, USA) and a p-value of < 0.05 was considered as statistically significant.

The prognosis of CABG patients was assessed in univariate and multivariate models based on UCT, SSS, and their combination. Receiver-operating characteristics (ROC) analysis was performed to determine cutoff values of UCT and SSS for cardiac events. Risk adjusted analyses were performed with Cox proportional hazard models to determine the independent prognostic value of UCT, SSS, and their combination by controlling for other predictors. Cumulative event rates were estimated

with the Kaplan-Meier method and were compared with the log-rank test.

The increased discriminative value after addition of UCT and/or SSS to the established clinical risk factors was estimated using the C-index for ROC curve, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under an ROC curve between individual predicted probabilities and incidence of events, and is compared between in a baseline model consisting of established clinical risk factors with $p<0.05$ by univariate Cox analysis, and in an enriched model with UCT and/or SSS [25]. The NRI indicates relatively how many patients show a decrease in their predicted probabilities for events, while the IDI represents the average decrease in predicted probabilities for events after adding UCT and/or SSS into the baseline model, respectively [26].

【Results】

Clinical characteristics:

In total, 204 patients (84.3% male, mean age 68.7±7.6 years) were enrolled after excluding 7 patients: 4 undergoing early elective revascularization within 3 months after imaging examination, and 3 lost to follow-up. The mean follow-up period was 30.3±17.6 months (median; 27.5 months). Four patients who underwent early revascularization were excluded because we could not study their natural histories after examination. In Table 1, baseline characteristics are listed in detail. At

follow-up, cardiac events were observed in 27 patients (13.2%) with an annualized event rate of 5.2% (3 patients with cardiac death, 9 patients with non-fatal infarction, 3 patients with unstable angina requiring revascularization, and 12 patients with heart failure). In the univariate Cox analysis, LVEF determined by cardiac ultrasound [Hazard Ratio (HR): 0.936; 95% Confidence Interval (CI): 0.905 to 0.968; p = 0.0002], time since CABG (HR: 1.01; 95% CI: 1.00-1.02; p=0.0008), and EuroSCORE Ⅱ (HR: 1.29; 95% CI: 1.02-1.57; p=0.038) were significant predictors of cardiac events.

CTA, MPI Findings and Analysis with the Combination of UCT and SSS

Mean UCT was 0.51±0.72, and % uninterpretable segments on CTA were 0.4%, 7.37%, and 3.61% in grafts, LMT, and other coronary artery segments, respectively. Mean SSS, SRS, and SDS were 7.03±8.65, 5.21±7.70, and 1.82±3.23, respectively. Mean % fixed defects was 10.3%.

The UCT and SSS were significant predictors for cardiac events (HR: 2.52; 95% CI: 1.59 to 3.96; p=0.0001 and HR: 1.08; 95% CI: 1.05 to 1.12; p < 0.0001, respectively). To maximize the predictive power of UCT and SSS, cut-off levels were determined as 1 for UCT [area under curve (AUC) = 0.71] and 4 for SSS (AUC = 0.76), respectively. Cumulative incidence rates for cardiac events are demonstrated in Figure 1A and 1B (log rank p-value = 0.0054 and < 0.0001, respectively). After adjustment for LVEF, time since CABG and EuroSCORE Ⅱ, patients with UCT ≥ 1 had 2.34-fold higher risk of cardiac events (95% CI 1.01 to 5.89, p = 0.0465). Similarly, patients with SSS ≥ 4 had

3.36-fold higher risk of cardiac events (95% CI 1.18 to 12.12, p = 0.0217) (Table 2a).

Based on the CTA and MPI findings, we divided all patients into 4 groups: Group A (UCT = 0, SSS <4), Group B (UCT; ≥1, SSS <4), Group C (UCT = 0, SSS ≥4), and Group D (UCT; ≥1, SSS ≥4). The annual event rates of cardiac events were 1.1%, 2.0%, 5.7%, and 12.9% of patients in group A, B, C and D, respectively. Cardiac event curves are demonstrated in Figure 1C (log rank p-value < 0.0001). After adjustment for LVEF, time since CABG, and EuroSCORE Ⅱ, patients with UCT ≥ 1 and SSS ≥ 4 had 6.84-fold (95% CI 1.83 to 44.50, p = 0.0026) higher risk for cardiac events compared to those with UCT = 0 and SSS < 4 (Table 2b).

Discrimination of Each Predicting Models for Cardiac Events (Table 3)

Addition of UCT alone, SSS alone, and both UCT and SSS to a baseline model with clinical risk factors consisting of LVEF, time since CABG, and EuroSCORE II significantly improved both the NRI and IDI. However, C-index was significantly greater only in the model with both UCT and SSS compared to the baseline model (0.834 vs. 0.768, p=0.045). In addition, the NRI and IDI significantly increased in the model containing both UCT and SSS even if compared to the model containing UCT alone or SSS alone.

【Discussion】

We focused on the prognosis of CABG patients assessed by CTA and MPI, and the usefulness of this combination. The patients without unprotected territories on CTA and without perfusion defects on MPI have a good prognosis. The prognosis of patients with abnormal CTA (UCT; ≥1) and MPI (SSS ≥ 4) is significantly poorer than that of patients with normal CTA and MPI. Each examination has incremental prognostic value, and the combination of anatomical and functional evaluation facilitates non-invasive assessment of the prognosis of CABG patients. This improvement was indicated to be statistically significant by the increase in the NRI and IDI.

Several reports have shown the utility of MPI with assessment of the prognosis in CABG patients [12-14], but there are some limitations.

First, many CABG patients have some abnormal findings on MPI, because of a history of prior myocardial infarctions, and others have ischemic territories with side branch occlusion even if the major coronary trees are protected. Actually in the present study, 48.5% of the enrolled patients had an abnormal MPI finding (SSS ≥ 4). To identify the patients with a poor prognosis strictly among those with MPI abnormalities, the evaluation of unprotected coronary territories on CTA was useful. The event rates were 33.3% in the abnormal CTA patients (Group D), in contrast to 12.5% in the normal CTA patients (Group C).

Importantly, MPI does not clarify the anatomy of grafts or native coronary arteries, even when high risk patients are identified. On the other hand, CTA provides information on grafts and unprotected

native coronary arteries non-invasively, and in this way contributes to devising the most appropriate therapeutic strategy.

Several studies have also demonstrated the diagnostic accuracy of CTA in CABG patients [6-9], and two recent studies reported the prognostic value of CTA in CABG patients [10-11]. They concluded that assessment with CTA is of prognostic value in CABG patients, despite some limitations.

First, some difficulties remain regarding the diagnostic accuracy [7-9]. Indeed the diagnostic accuracy of graft segments is good, but CABG patients have a high prevalence of severe calcifications and stented segments in the native coronary arteries, leading to some overestimation of stenosis of the distal runoff segments of the protected coronary arteries, and unprotected native coronary arteries including stented segments. Actually in our study, unassessable native coronary or graft segments were regarded as severe stenosis, likely resulting in some overestimation of the number of unprotected coronary territories. In other words, some CTA findings in Group B patients (abnormal CTA and normal MPI) may be false positives. In a prior study, Chow et al. excluded cases with > 5 unassessable segments. Actually, it is of use to add MPI in the assessment of patients with poor CTA images [10].

Second, patients with normal CTA may experience any kind of cardiac event. Some patients with major branches protected have an ischemic or infarcted area due to prior myocardial infarction or side branch occlusion, and so the at risk area might cause fatal arrhythmia and heart failure in them even if the risk of ungrafted coronary events or graft failure is very low. The present study

demonstrates that the prognosis of patients with normal CTA and abnormal MPI (Group C) is poorer (event-free rate; 87.5%) than that of those with normal CTA and MPI (Group A: 97.3).

Finally, prior CTA studies lacked some necessary data [10-11]. Small et al. and Chow et al. did not obtain data of the time since CABG [10-11] or the variety of graft types [10]. In prior prognostic studies of MPI or CAG, time since CABG and the variety of grafts were identified as important predictors [12-14]. When the prognosis of CABG patients is discussed, information on the time since CABG and the variety of grafts is indispensible.

Limitations:

This study has some limitations. First, a limited number of patients in a single center were enrolled and were observed retrospectively. Additionally, small number of hard events including cardiac death and nonfatal myocardial infarction was observed during follow-up. Second, we did not perform invasive coronary angiography in all studied patients. The diagnosis of unprotected coronary territory based on CTA may contain some false-positives and/or false-negatives. Last, due to the lack of data regarding the medical therapy when cardiac events were occurred, we could not discuss the appropriateness of medical therapy which may have influenced results.

【Conclusions】

Our results indicate that the combination of MPI and CTA is useful for the risk stratification of patients with previous CABG. The advantages of each imaging examination complement the limitations of the other. The combination of anatomical and functional evaluations enhances assessment of the prognosis of CABG patients non-invasively.

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There is no additional data available.

【Authors' contribution】

Hideki Kawai and Masayoshi Sarai evaluated myocardial perfusion imaging (MPI). Sadako Motoyama and Hajime Ito evaluated CT imaging. Kayoko Takada and Junichi Ishii did MPI exam. Hiroto Harigaya and Hirofumi Anno did CT exam. Hiroshi Takahashi and Shuji Hashimoto gave me some advices about statistics. Yasushi Takagi and Motomi Ando are CABG operators and attending doctors for most patients. Toyoaki Murohara, and Yukio Ozaki conducted this study.

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Figure legends

Figure 1. Cardiac event curves according to (A) UCT, (B) SSS, (C) each group

UCT: unprotected coronary territory, SSS: summed stress score

Table 1. Patient Characteristics

	All (n=204)	Cardiac Events (n=27)	No Events (n=177)	p Value
Age (years)	68.7±7.6	70.0±7.7	68.5±7.6	0.46
Gender (male)	172 (84.3%)	21 (77.8%)	151 (85.3%)	0.527
Diabetes	106 (52.0%)	17 (63.0%)	89 (50.3%)	0.234
Dyslipidemia	116 (56.9%)	18 (66.7%)	98 (55.4%)	0.214
Hypertension	172 (84.3%)	24 (88.9%)	148 (83.6%)	0.673
Hemodialysis	9 (4.4%)	2 (7.4%)	7 (4.0%)	0.229
Current Smoker	39 (19.1%)	5 (18.5%)	34 (19.2%)	0.905
LVEF (%)	52.1±9.9	44.9±11.5	53.2±9.3	0.0002
Time since CABG (months)	25.3±51.2	55.8±66.7	20.7±47.0	0.0008
Prior MI	34 (16.7%)	8 (29.6%)	26 (14.7%)	0.08
Post PCI	23 (11.3%)	5 (18.5%)	18 (10.2%)	0.319
Prior HF	17 (8.3%)	3 (11.1%)	14 (7.9%)	0.539

Using ITA	191 (93.6%)	23 (85.2%)	168 (94.9%)	0.089
EuroSCORE Ⅱ	1.90±1.32	2.43±1.69	1.81±1.24	0.038

LVEF: left ventricular ejection fraction by ultrasonic cardiography, CABG: coronary aorta bypass graft, MI: myocardial infarction, PCI: percutaneous coronary intervention, HF: heart failure, ITA: internal thoracic artery

Table 2a. CTA, MPI Findings: Univariable and Multivariate Analysis for Cardiac Events

	Cardiac Events (n=27)	No Events (n=177)	Annual Event Rate, %	Unadjusted Hazards Ratio (95%CI)	P value	Adjusted Hazards Ratio (95%CI)	P value
UCT= 0	8 (6.5%)	115 (93.5%)	2.82	1		1	
UCT ≥ 1	19 (23.5%)	62 (76.5%)	8.27	3.07 (1.38-7.49)	0.0054	2.34# (1.01-5.89)	0.0465
SSS < 4	4 (3.8%)	101 (96.2%)	1.44	1		1	
SSS ≥ 4	23 (23.2%)	76 (76.8%)	9.67	6.73 (2.59-22.96)	<0.0001	3.36& (1.18-12.12)	0.0217

UCT: unprotected coronary territory, SSS: summed stress score, # Hazards ratio was adjusted for LVEF, time since CABG, EuroSCORE Ⅱ, and SSS, & Hazards ratio was adjusted for LVEF, time since CABG, EuroSCORE Ⅱ, and UCT. Eight events in patients with UCT=0 included 3 nonfatal MI and 5 HF, 19 events in

UCT≥1 included 3 cardiac death, 6 nonfatal MI, 3 late revascularization, and 7 heart failure. Four events in patients with SSS<4 included 3 nonfatal MI and 1 late revascularization, 23 events in SSS≥4 included 3 cardiac death, 6 nonfatal MI, 2 late revascularization, and 12 heart failure.

Table 2b. Combination of UCT and SSS: (Univariable and Multivariate Analysis for Cardiac Events)

Group	UCT	SSS	No of patients	No of patients with Cardiac Events (%)	Annual Event Rate (%)	Unadjusted hazards ratio (95%CI)	P value	Adjusted hazards ratio$ (95%CI)	P value
A	0	<4	75	2(2.7)	1.1	1		1	
B	≥1	<4	30	2(6.7)	2.0	1.93 (0.23-16.16)	0.515	1.76 (0.21-15.11)	0.579
C	0	≥4	48	6(13.0)	5.7	5.15 (1.19-35.17)	0.0279	2.73 (0.55-19.93)	0.225
D	≥1	≥4	51	17(33.0)	12.9	11.9 (3.40-75.19)	<0.0001	6.84 (1.83-44.5)	0.0026

$ Hazards ratio was adjusted for LVEF, time since CABG, and EuroSCORE II

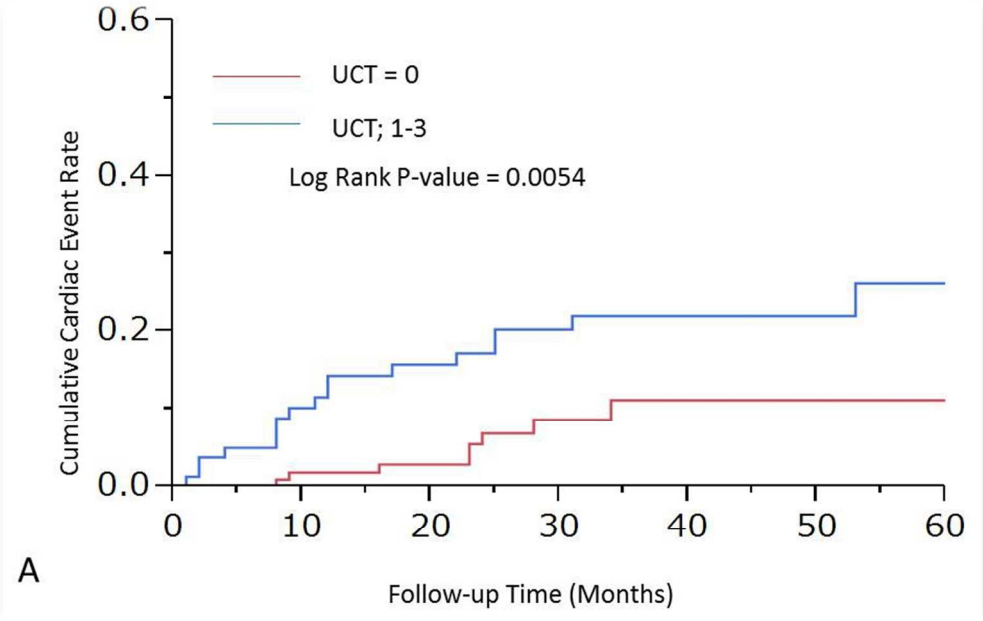
Table 3. Discrimination of Each Predicting Models for Cardiac Events

	Discrimination					
Risk Factors and Imaging Findings	C Index (95%CI)	p Value	NRI	p Value	IDI	p Value
Clinical risk factors#	0.768 (0.655-0.880)	Reference	Reference		Reference	
Clinical risk factors# plus UCT	0.811 (0.718-0.905)	0.1049	0.707	0.0003*	0.0369	0.0235
Clinical risk factors# plus SSS	0.807 (0.701-0.912)	0.1156	0.731	0.0002*	0.0421	0.0005

Clinical risk factors# plus UCT and SSS	0.834 (0.742-0.927)	0.0454*	0.649	0.0008*	0.0701	0.0006
Clinical risk factors# plus UCT		Reference	Reference		Reference	
Clinical risk factors# plus UCT and SSS		0.1989	0.707	0.0003*	0.0281	0.039
Clinical risk factors# plus SSS		Reference	Reference		Reference	
Clinical risk factors# plus UCT and SSS		0.1486	0.645	0.0009*	0.0333	0.0009

UCT: unprotected coronary territory, SSS: summed stress score, NRI: Net Reclassification Improvement, IDI: Integrated Discrimination Improvement

#Clinical risk factors comprise LVEF, time since CABG, and EuroSCORE II



No. at Risk:							
UCT = 0	123	107	82	47	28	15	5
UCT; 1-3	81	65	58	47	35	20	7

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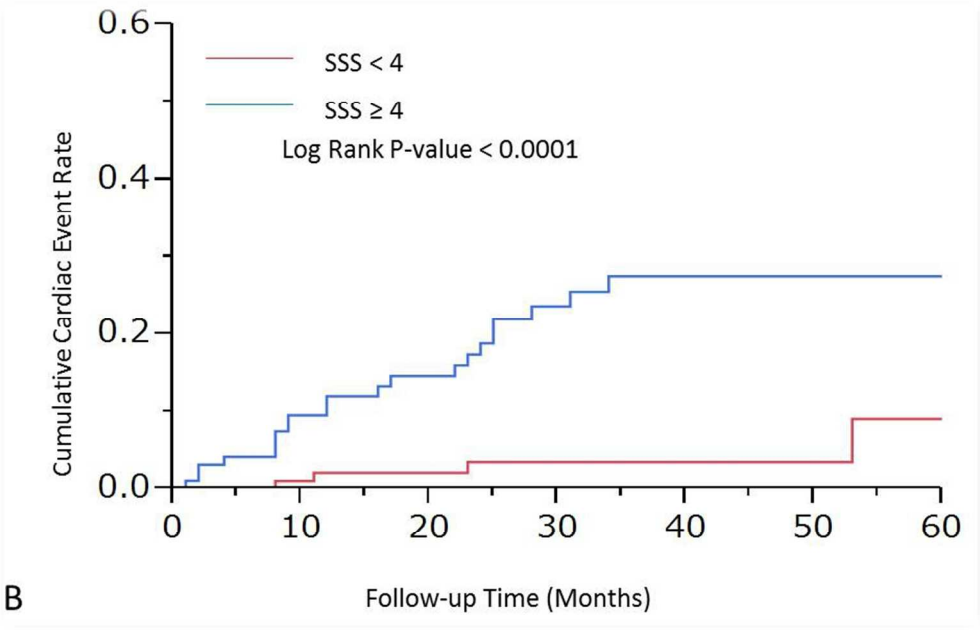

No. at Risk:							
SSS < 4	105	94	77	52	32	20	5
SSS ≥ 4	99	78	63	42	31	15	7

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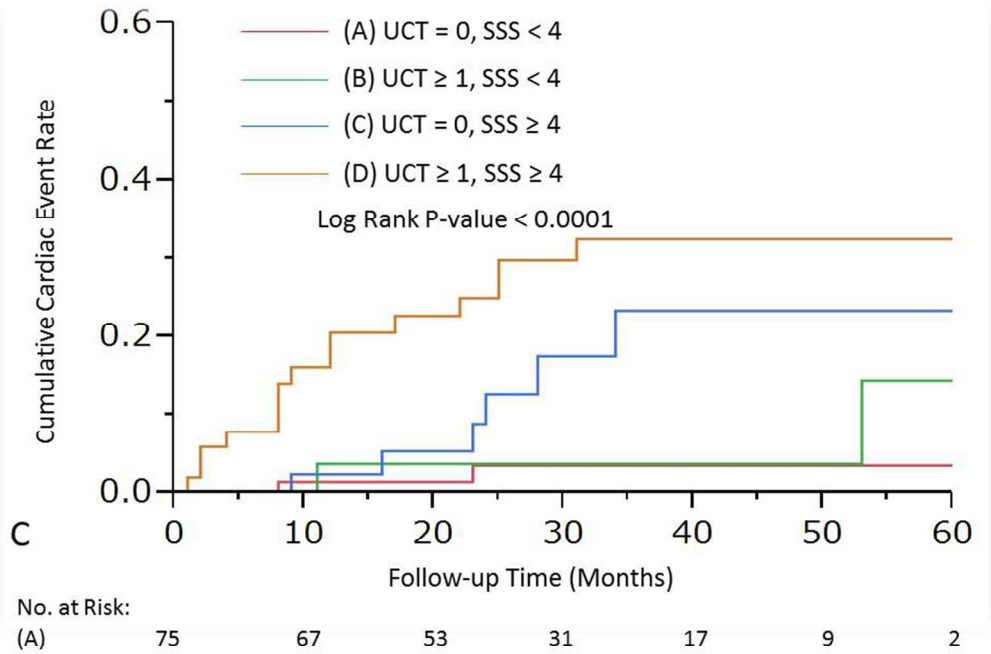

No. at Risk:

(A)	75	67	53	31	17	9	2
(B)	30	27	24	21	15	11	3
(C)	48	40	29	16	11	6	3
(D)	51	38	34	26	20	9	4

254x190mm (96 x 96 DPI)