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ORIGINAL RESEARCH

Incremental Prognostic Value of Myocardial Blood Flow Quantified With Stress Dynamic Computed Tomography Perfusion Imaging

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ABSTRACT

OBJECTIVES This study aimed to evaluate whether myocardial blood flow (MBF) quantified with dynamic computed tomography perfusion imaging (CTP) has an incremental prognostic value over coronary CT angiography (CTA) for major adverse cardiac events (MACEs) in patients with suspected coronary artery disease (CAD).

BACKGROUND The incremental prognostic value of CTP over CTA is unclear. The quantification of MBF with dynamic CTP may potentially enhance risk stratification.

METHODS A total of 332 patients (67% men; age: 67 ± 10 years) with suspected CAD who underwent CTA and dynamic CTP was analyzed. A MACE was defined as cardiac death, nonfatal myocardial infarction (MI), unstable angina, or hospitalization for congestive heart failure. A summed stress score (SSS) was calculated by adding scores of all myocardial segments according to normalized MBF values. Abnormal perfusion was defined as SSS ≥4. Obstructive CAD was defined as ≥50% stenosis in ≥1 vessel on CTA.

RESULTS During a median follow-up of 2.5 years, 19 patients had a MACE. Multivariate analysis showed that, when adjusted for obstructive CAD on CTA, abnormal perfusion was significantly associated with hazards for MACEs (hazard ratio [HR]: 5.7; 95% confidence interval [CI]: 1.9 to 16.9; p = 0.002), with a significant improvement in the prognostic value. Abnormal perfusion was an independent predictor even when adjusted for ≥70% stenosis in ≥1 vessel (HR: 5.4; 95% CI: 1.7 to 16.7; p = 0.003) or adjusted for ≥50% stenosis in ≥2 vessels (HR: 6.5; 95% CI: 2.2 to 18.9; p = 0.001). In the setting of obstructive CAD, annualized event rates showed a significant difference between the patients with and without abnormal perfusion for all events (12.2% vs. 1.5%; p = 0.002) and for cardiac death and nonfatal MI (4.2% vs. 0%; p = 0.015).

CONCLUSIONS MBF quantified with dynamic CTP has an incremental prognostic value over CTA. The addition of dynamic CTP to CTA allows improved risk stratification of patients with CTA-detected stenosis. (J Am Coll Cardiol Img 2019;12:1379–87) © 2019 by the American College of Cardiology Foundation.

Coronary computed tomography angiography (CTA) is a reliable and established noninvasive imaging tool for the diagnosis of coronary artery disease (CAD) (1). CTA coronary images are useful for evaluating the extent and severity of anatomical stenosis but are poor predictors of hemodynamically significant stenosis (2). Therefore, hemodynamic assessment of coronary

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CAD-RADS = Coronary Artery Disease-Reporting and Data System

CI = confidence interval

CTA = computed tomography angiography

CTP = computed tomography perfusion

FFR = fractional flow reserve

HR = hazard ratio

ICA = invasive coronary angiography

MACE = major adverse cardiac event

MBF = myocardial blood flow

MI = myocardial infarction

MPI = myocardial perfusion imaging

NRI = net reclassification improvement

ROC = receiver-operating curve

lesions is often required to select patients who would benefit from coronary revascularization. Inducible ischemia has been detected using several imaging techniques, including nuclear myocardial perfusion imaging (MPI), magnetic resonance MPI, and stress echocardiography. Dynamic computed tomography (CT) myocardial perfusion imaging (CTP) is a recently introduced imaging method that enables the quantification of myocardial blood flow (MBF). Several studies have shown that dynamic CTP has good diagnostic accuracy in identifying ischemia determined by different reference standards (3-6). The combination of CTA and dynamic CTP may provide a more comprehensive evaluation of patients with suspected CAD than CTA alone.

Previous studies have shown that anatomical information from CTA images have similar prognostic significance to that obtained using invasive coronary angiography (ICA) (7). Recently, a multicenter study by Chen et al. (8) compared a predictive value of CTA and/or CTP for major adverse cardiac events (MACEs) with that of ICA and/or nuclear MPI, and revealed a prognostic value of perfusion defects qualitatively determined by static CTP. However, the incremental prognostic value of CTP over CTA remained unclear. Furthermore, the quantification of MBF with dynamic CTP may potentially enhance risk stratification. Therefore, the purpose of the present study was to evaluate whether MBF quantified with dynamic CTP has an incremental prognostic value over CTA for MACEs in patients with suspected CAD.

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METHODS

STUDY POPULATION. A total of 625 consecutive patients who were referred for CTA and dynamic CTP for evaluation of CAD between March 2012 and February 2017 at our hospital were screened for this study. The inclusion criteria included: 1) age between 45 and 85 years; and 2) written informed consent for study participation. The exclusion criteria were as follows: 1) impaired renal function (estimated glomerular filtration rate <30 ml/min per 1.73 m^2 body surface area); 2) contraindication against an iodinated contrast or a stress agent; 3) previous coronary revascularization via coronary artery bypass grafting or percutaneous coronary intervention; 4) history of myocardial infarction (MI); 5) incomplete tests or severe artifacts due to motion or breathing; and 6) loss to follow-up. The study was approved by the institutional review board, and each patient gave written informed consent for participation in the study.

IMAGE ACQUISITION. All patients were scanned using a second-generation, dual-source CT scanner (n = 202; Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) or a third-generation, dual-source CT scanner (n = 130; Somatom Force; Siemens Healthcare). Patients were instructed to avoid caffeine drinks for at least 24 h before undergoing a stress test.

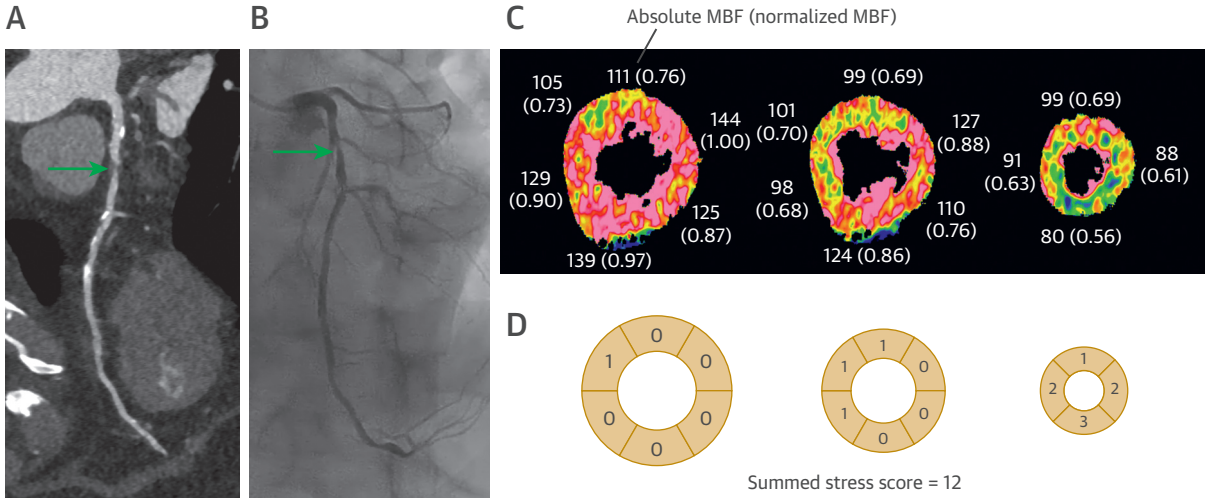
During the administration of 20 mg of adenosine triphosphate at 160 μg/kg/min for >3 min (9,10), scan acquisition of dynamic CTP was initiated by injecting 40 ml of contrast medium with an iodine concentration of 370 mg/ml at a flow rate of 5 ml/s. Dynamic data sets were acquired for 30 s via an electrocardiographically-triggered axial scan mode, repeated at 2 alternating table positions to obtain a Z-axis coverage of 73 or 102 mm (11). Tube voltage was set at 70 or 80 kV, and tube current was determined using an automatic exposure control system with a quality reference of 350 mA per rotation at 120 kV (12,13). After completing data acquisition, adenosine triphosphate administration was stopped. Electrocardiography, blood pressure, and arterial oxygen saturation were monitored and recorded throughout the procedure.

After dynamic stress CTP, standard prospective CTA was performed at rest using the following scan parameters: 2 × 100-kV tube voltage or 80 kV and 0.28-s gantry rotation time, with injection of 0.84 ml/kg of contrast medium over 12 s. Tube current was determined using the angular modulation technique.

IMAGE ANALYSIS. The analysis of dynamic CTP images was performed using commercially available perfusion software (Syngo VPCT body, Siemens Healthcare). MBF was estimated using a dedicated parametric deconvolution technique, based on a 2-compartment model of the intravascular and extravascular spaces (14). The maximum slope of time attenuation curves fitted for every voxel was used to generate a MBF map of 3 mm thickness and 1 mm increments.

Polygonal regions of interest that measured 1 to 2 cm^2 were placed within each of the 16 myocardial segments (according to the American Heart Association), excluding an apical segment, in the short-axis view on the MBF map, at a minimal distance of 1 mm from the endocardial and epicardial borders to avoid contamination. A normalized MBF value was

FIGURE 1 A Case in a Patient With Abnormal Perfusion



Images in a 72-year-old man with multiple risk of coronary artery disease (CAD) are shown. Severe stenosis was found in the proximal left anterior descending artery (LAD) on **(A)** computed tomography angiography (CTA) and **(B)** invasive coronary angiography (ICA). No significant stenosis was present in the right coronary artery or the left circumflex artery. Color-coded myocardial blood flow (MBF) maps in short axis showed reduced perfusion in the left anterior descending vascular territory **(C)**, and summed stress score (SSS) was calculated to be 12 by adding scores of all segments **(D)**.

calculated as a MBF value in each segment divided by the highest MBF value within the 16 segments on a MBF map. A summed stress score (SSS) was calculated by adding scores of all segments using a 5-point scale based on normalized MBF values: 0 = normal (>0.75), 1 = mildly abnormal (≤0.75, >0.675), 2 = moderately abnormal (≤0.675, >0.60), 3 = severely abnormal (≤0.60), or 4 = absent. This division was suggested by the fact that, in patients without ≥50% stenosis on CTA, the lowest MBF value divided by the highest MBF value within all segments was 0.750 ± 0.075. Abnormal perfusion per patient was defined as SSS ≥4. An example of SSS in a patient with abnormal perfusion is shown in Figure 1. Global MBF was defined as a mean value of MBFs in all segments.

CTA images were visually evaluated by at least 2 observers, including a radiologist with 10 years of experience in CTA, in a joint reading. Coronary segments with a reference diameter ≥1.5 mm were assessed for the detection of stenosis. Severity of CAD on CTA was ranked by the Coronary Artery Disease-Reporting and Data System (CAD-RADS): 0 (0%), 1 (1% to 24%), 2 (25% to 49%), 3 (50% to 69%), 4A (70% to 99% in 1 to 2 vessels), 4B (70% to 99% in 3 vessels or ≥50% left main), or 5 (100%). Obstructive CAD was defined as ≥50% stenosis in ≥1 vessel (CAD-RADS ≥3).

FOLLOW-UP. Follow-up information was gathered through a review of hospital records or telephone interviews. Recorded MACEs consisted of cardiac death, nonfatal MI, unstable angina, and hospitalization for congestive heart failure. Hard events included cardiac death and nonfatal MI. Cardiac death was defined as death caused by acute MI, ventricular arrhythmias, or congestive heart failure. Nonfatal MI was defined as prolonged angina accompanied by new electrocardiographic abnormalities and increased cardiac biomarkers. Unstable angina was defined as new-onset, worsening, or angina at rest that required hospital admission. Congestive heart failure was defined as the emergence of appropriate symptoms (cough, shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, and reduced exercise tolerance) associated with either new radiological findings consistent with congestive heart failure or the development of physical signs, including pulmonary rales, S_3 gallop sound, and weight gain.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or as the median, and were assessed using the Student's *t*- or Mann-Whitney U tests, as appropriate. Categorical variables are expressed as frequency (percentage) and were compared using Fisher's exact test.

The influence of CTP, CTA, and clinical predictors on MACEs was determined using Cox regression analysis, and the results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Univariate analysis of baseline clinical characteristics, CTA, and dynamic CTP was performed to identify potential predictors. To determine independent predictors of MACEs, multivariate analysis was performed using stepwise forward selection for variables, with $p < 0.05$ in the univariate analysis. The incremental value of CTP over CTA was assessed by calculating the global chi-square test. Kaplan-Meier curves were used to estimate cumulative event rates for CTP, CTA, and combined CTA and CTP. Differences between time-to-event curves were compared using the log-rank test. Annualized event rates were calculated by dividing the 4-year Kaplan-Meier event rates by 4. Patients who underwent early (within 60 days after CT) revascularization were censored from follow-up thereafter. Receiver-operating characteristic (ROC) curves were built for CTA, and combined CTA and dynamic CTP based on a logistic regression model. The Delong test was used to compare the areas under the curve. Net reclassification improvement (NRI) was calculated, and categorical and continuous NRI and integrated discrimination improvement were estimated. A 2-sided p value of 0.05 was considered statistically significant. All analyses were performed using the SPSS statistical package (version 23.0, IBM, Armonk, New York) and the R statistical package (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS, RADIATION DOSE, AND HEMODYNAMIC RESPONSE DURING ADENOSINE TRIPHOSPHATE STRESS. A total of 585 patients met the inclusion criteria. Of these, we excluded 253 patients who had contraindications against iodinated contrast agents (n = 2) or a stress agent (n = 2), previous coronary revascularization via coronary artery bypass graft (n = 43) or percutaneous coronary intervention (n = 143), history of MI (n = 31), incomplete tests (n = 2), or severe artifacts due to motion or breathing (n = 10). Incomplete tests were attributable to complications of a contrast agent (n = 1) or a stress agent (n = 1). An additional 20 patients were lost to follow-up. The study population consisted of the remaining 332 patients with suspected CAD.

Baseline patient characteristics are presented in Table 1. Mean age of the population was 67 ± 10 years, and male patients accounted for 67% of the population. Most patients (61%) presented with chest pain or dyspnea.

The dose–length products for CTA and CTP were 185 ± 113 mGy·cm and 322 ± 117 mGy·cm, respectively, and the effective dose for the 2 techniques was 2.60 ± 1.59 mSv and 4.52 ± 1.68 mSv, respectively, using a conversion coefficient of 0.014. Heart rate significantly increased from 66 ± 25 beats/min at baseline to 78 ± 29 beats/min during stress ($p < 0.001$). Systolic blood pressure significantly decreased from 136 ± 52 mm Hg at baseline to 120 ± 46 mm Hg during stress ($p < 0.001$), whereas diastolic blood pressure significantly declined from 71 ± 27 mm Hg to 59 ± 22 mm Hg ($p < 0.001$).

TABLE 1 Baseline Patient Characteristics (N = 332)

Male	221 (67)
Age (yrs)	67 ± 10
Coronary risk factors	
Hypertension	225 (68)
Dyslipidemia	162 (49)
Diabetes	98 (30)
Current smoker	48 (14)
Family history of CAD	52 (16)
Body mass index >25	112 (34)
Echocardiography	
LVEF <50%	20 (6)
Abnormal wall motion	50 (15)
Symptom	
Typical	34 (10)
Atypical	76 (23)
Nonanginal	57 (17)
Dyspnea	37 (11)

Values are n (%) or mean ± SD.
CAD = coronary artery disease; LVEF = left ventricular ejection fraction.

IMAGING RESULTS. The results of CTA and dynamic CTP are given in Table 2. CAD-RADS scores of 0, 1 to 2,

TABLE 2 Imaging Results (N = 332)

Coronary CT angiography	
CAD-RADS 0	87 (26)
CAD-RADS 1-2	127 (38)
CAD-RADS 3	50 (15)
CAD-RADS 4A	48 (14)
CAD-RADS 4B	9 (3)
CAD-RADS 5	11 (3)
Obstructive CAD	118 (36)
1-vessel disease	48 (14)
Multivessel disease	70 (21)
Dynamic CT perfusion	
Global MBF value (ml/100 ml/min)	120 ± 40
Lowest MBF value (ml/100 ml/min)	102 ± 37
SSS ≥4*	94 (28)
SSS ≥8	44 (12)
SSS ≥12	21 (6)

Values are n (%) or mean ± SD. *Perfusion abnormality was defined as a summed stress score (SSS) ≥4 in this study.
CAD-RADS = Coronary Artery Disease-Reporting and Data System; CT = coronary tomography; MBF = myocardial blood flow; other abbreviation as in Table 1.

TABLE 3 Univariate Predictors of MACEs

	HR (95% CI)	p Value
Male	0.6 (0.3–1.5)	0.313
Age >70 yrs	2.1 (0.8–5.2)	0.113
Coronary risk factors		
Hypertension	1.2 (0.4–3.4)	0.681
Dyslipidemia	0.9 (0.4–2.2)	0.800
Diabetes	1.9 (0.8–4.7)	0.178
Current smoker	1.0 (0.3–3.6)	0.951
Family history of CAD	0.2 (0.0–1.8)	0.169
Body mass index >25 kg/m^2	0.1 (0.1–1.2)	0.091
Echocardiography		
LVEF <50%	3.2 (0.9–11.1)	0.063
Abnormal wall motion	1.7 (0.6–5.0)	0.366
Coronary CT angiography		
Obstructive CAD	6.3 (2.3–17.5)	<0.001
CAD-RADS ≥4A	7.2 (2.9–17.9)	<0.001
Multivessel disease	5.5 (2.2–13.6)	<0.001
Dynamic CT perfusion		
SSS ≥4	8.9 (3.2–24.9)	<0.001
SSS ≥8	6.0 (2.4–14.8)	<0.001

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; other abbreviations as in Tables 1 and 2.

TABLE 4 Multivariate Analysis

	Model 1		Model 2		Model 3	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Abnormal perfusion	5.7 (1.9–16.9)	0.002	5.4 (1.7–16.7)	0.003	6.5 (2.2–18.9)	0.001
Coronary CT angiography						
Obstructive CAD	3.3 (1.1–9.9)	0.030				
CAD-RADS ≥4A			3.4 (1.2–9.2)	0.018		
Multivessel disease					3.1 (1.2–8.0)	0.017

Abbreviations as in Table 2 and 3.

3, 4A, 4B, or 5 was observed in 87 (26%), 127 (38%), 50 (15%), 48 (14%), 9 (3%), or 11 (3%) of 332 patients, respectively. Obstructive CAD was detected in 118 (36%) patients. Single-vessel disease (≥50% stenosis in 1 vessel) and multivessel disease (≥50% stenosis in ≥2 vessels) were detected in 48 (14%) and 70 (21%) patients, respectively.

The global MBF values and lowest MBF values were 120 ± 40 ml/100 ml/min and 102 ± 37 ml/100 ml/min, respectively. Abnormal perfusion, defined as SSS ≥4, was observed in 94 (28%) patients. SSS ≥8 and ≥12 were detected in 44 (12%) and 21 (6%) patients, respectively.

OUTCOMES. The median follow-up was 2.5 years. Twenty-two patients underwent early revascularization and were censored at the time of revascularization. Nineteen patients had MACEs: cardiac death (n = 2), nonfatal MI (n = 3), unstable angina (n = 7), and hospitalizations for congestive heart failure (n = 7). Noncardiac death was observed in 4 patients.

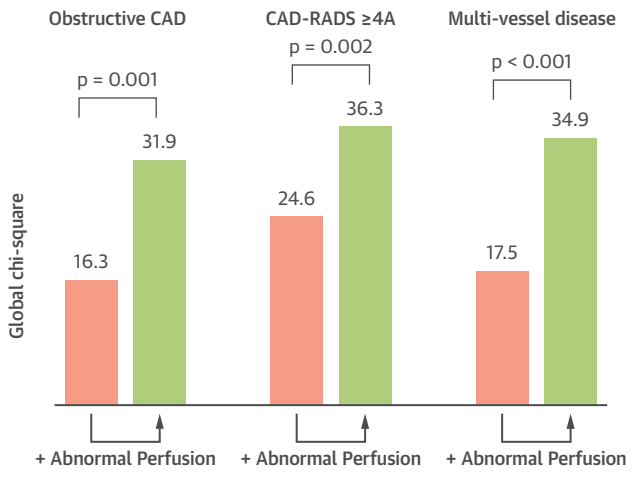
UNIVARIATE AND MULTIVARIATE ANALYSES. Univariate predictors for MACEs are listed in Table 3. Clinical predictors and findings of echocardiography did not reach statistical significance. Obstructive CAD (HR: 6.3; 95% CI: 2.3 to 17.5; p < 0.001), CAD-RADS score ≥4A (HR: 7.2; 95% CI: 2.9 to 17.9; p < 0.001), and multivessel disease (HR: 5.5; 95% CI: 2.2 to 13.6; p < 0.001) were significant predictors of MACEs. SSS ≥4 was the strongest predictor of events (HR: 8.9; 95% CI: 3.2 to 24.9; p < 0.001). SSS ≥8 was significantly associated with risk of events (HR: 6.0; 95% CI: 2.4 to 14.8; p < 0.001).

Multivariate models were created to evaluate whether MBF quantified with dynamic CTP was an independent predictor (Table 4). When adjusted for obstructive CAD on CTA, abnormal perfusion had a significant association with hazards for MACEs (HR: 5.7; 95% CI: 1.9 to 16.9; p = 0.002). In this model, obstructive CAD was also an independent predictor (HR: 3.3; 95% CI: 1.1 to 9.9; p = 0.030). Even when adjusted for CAD-RADS ≥4A, abnormal perfusion remained an independent predictor (HR: 5.4; 95% CI: 1.7 to 16.7; p = 0.003). CAD-RADS ≥4A was also an independent predictor in this model (HR: 3.4; 95% CI: 1.2 to 9.2; p = 0.018). Furthermore, when adjusted for multivessel disease, abnormal perfusion remained an independent predictor (HR: 6.5; 95% CI: 2.2 to 18.9; p = 0.001), and multivessel disease was also an independent predictor (HR: 3.1; 95% CI: 1.2 to 8.0; p = 0.017).

To assess the incremental prognostic value of dynamic CTP, global chi-square scores were calculated (Figure 2). The addition of abnormal perfusion to obstructive CAD (global chi-square: 16.3) significantly increased the global chi-square score (31.9; p = 0.001). Adding abnormal perfusion to the CAD-RADS score ≥4A (global chi-square score: 24.6) resulted in a significantly increased global chi-square score (36.3; p = 0.002). When abnormal perfusion was added to multivessel disease, the global chi-square score significantly increased from 17.5 to 34.9 (p < 0.001).

EVENT RATE. Kaplan-Meier curves by SSS with dynamic CTP (Figure 3) showed that annualized event rates for all events were 0.7% for SSS ≤3, 5.3% for SSS 4 to 7, and 10.7% for SSS ≥8 (p < 0.001) (Figure 3A). Annualized event rates for hard events were 0% for SSS ≤3, 1.9% for SSS 4 to 7, and 3.3% for SSS ≥8 (p < 0.001) (Figure 3B). Kaplan-Meier curves by absolute MBF (lowest MBF) demonstrated that annualized event rates were 3.2%, 3.4%, and 0.3% for MBFs of ≤80, 80 to 120, and >120 for all events, respectively (p = 0.059), and 1.0%, 0.7%, and 0% for MBFs

FIGURE 2 Incremental Prognostic Value of Dynamic CTP Over CTA



This illustration shows the incremental prognostic value of dynamic computed tomography perfusion (CTP) when added **(A)** to obstructive coronary artery disease (CAD), **(B)** to Coronary Artery Disease–Reporting and Data System (CAD-RADS) ≥4A, or **(C)** to multi-vessel disease.

of ≤80, 80 to 120, and >120 for hard events, respectively (p = 0.294) (Supplemental Figure 1).

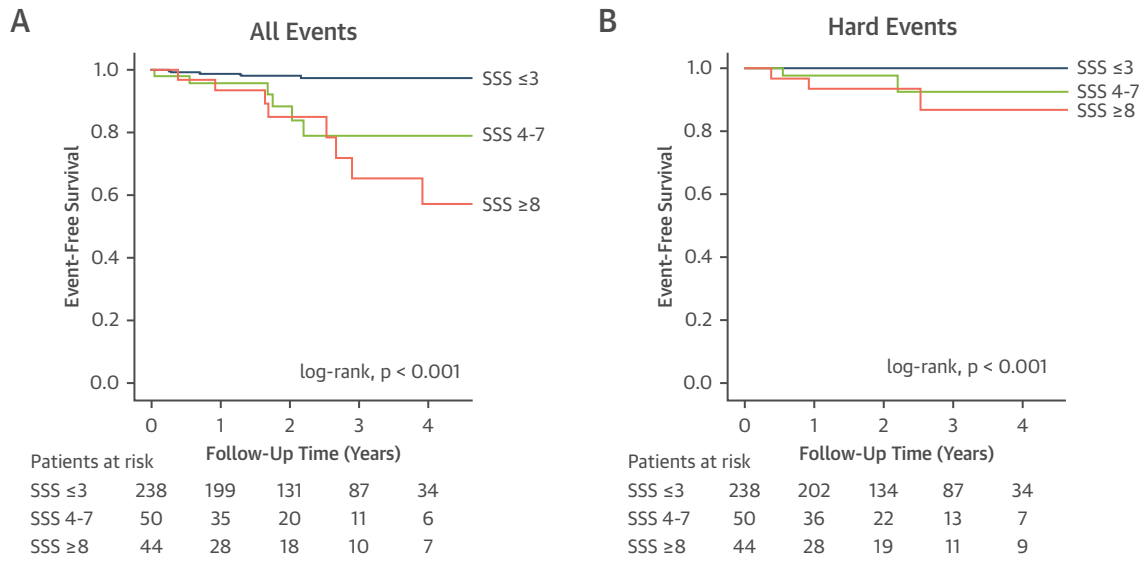
Kaplan-Meier curves by CTA (**Figure 4**) revealed that the annualized event rates for all events were 0.7%, 2.7%, and 10.0% in patients with CAD-RADS scores of ≤2, 3, and ≥4A, respectively (p < 0.001) (**Figure 4A**), and annualized event rates for hard events were 0%, 1.5%, and 2.6% in each patient group, respectively (p < 0.001) (**Figure 4B**).

Figure 5 shows Kaplan-Meier curves in patients with and without abnormal perfusion among the patients who had obstructive CAD. In the setting of obstructive CAD, patients with abnormal perfusion had significantly higher annualized event rates than those without abnormal perfusion for all events (12.2% vs. 1.5%; p = 0.002) (**Figure 5A**) and for hard events (4.2% vs. 0%; p = 0.015) (**Figure 5B**). Annualized event rates for MACEs were not significantly different between patients with obstructive CAD but without abnormal perfusion and patients with abnormal perfusion but not obstructive CAD (1.5% vs. 2.1%; p = 0.596) (Supplemental Figure 2).

ROC CURVE ANALYSIS AND NRI. ROC curve analysis showed that CAD-RADS plus SSS had better discriminative ability for MACEs than CAD-RADS did alone (area under the curve: 0.876 vs. 0.770; p = 0.016) (Supplemental Figure 3). The sensitivity, specificity, positive predictive value, and negative predictive value were 74%, 72%, 15%, and 98% for CAD-RADS and 95%, 74%, 19%, and 99% for CAD-RADS plus SSS, respectively.

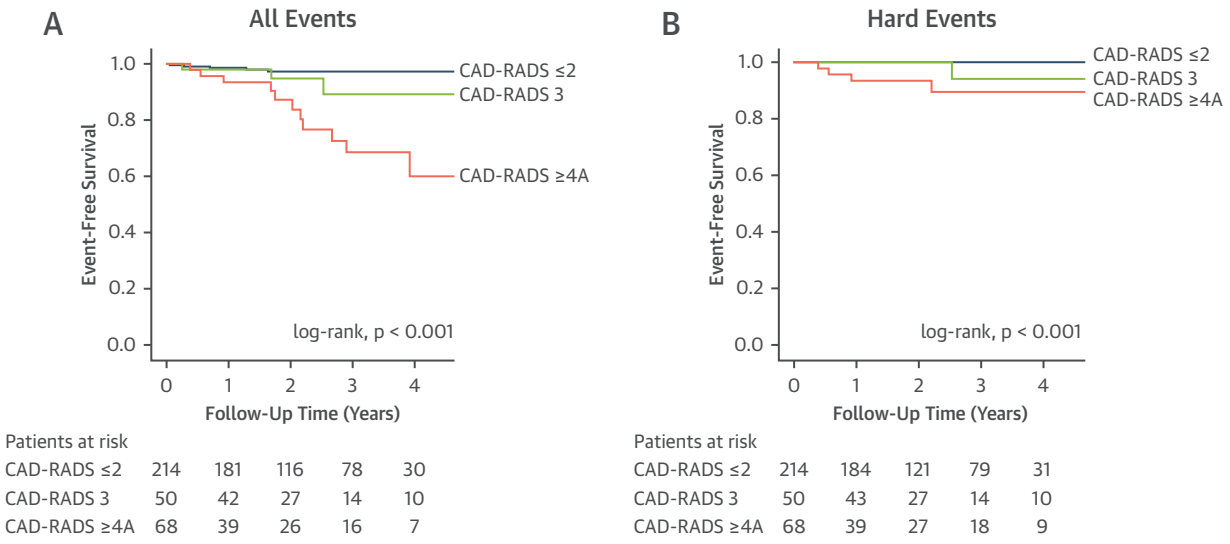
Adding SSS to CAD-RADS resulted in improvement in risk reclassification for MACEs (Supplemental Table 1). Risk improvement in annual risk categories of ≤1%, 1% to 3%, and >3% was 0.192 for nonevent cases and 0.157 for event cases; therefore, categorical

FIGURE 3 Kaplan-Meier Curves by Dynamic CTP



Kaplan-Meier curves in patients with SSS ≤ 3, 4-7, or ≥8 **(A)** for all events and **(B)** for hard events are shown. Abbreviations as in **Figure 1 and 2**.

FIGURE 4 Kaplan-Meier Curves by CTA



Patients at risk

CAD-RADS ≤2	214	181	116	78	30
CAD-RADS 3	50	42	27	14	10
CAD-RADS ≥4A	68	39	26	16	7

Patients at risk

CAD-RADS ≤2	214	184	121	79	31
CAD-RADS 3	50	43	27	14	10
CAD-RADS ≥4A	68	39	27	18	9

Kaplan-Meier curves according to coronary status by CTA based on CAD-RADS **(A)** for all events and **(B)** for hard events are shown. Abbreviations as in Figure 1 and 2.

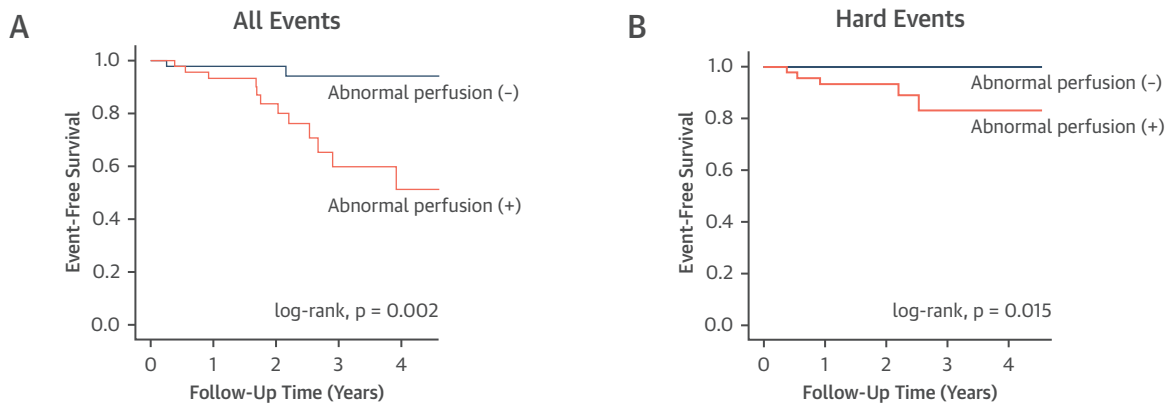
NRI was 0.349 (p = 0.003). Continuous NRI and integrated discrimination improvement were 0.514 (p = 0.028) and 0.196 (p = 0.011), respectively.

DISCUSSION

To our knowledge, this is the first study to evaluate the incremental prognostic value of MBF quantified with dynamic CTP in patients with suspected CAD. The main findings of our study were that dynamic CTP had an incremental prognostic value over CTA and that abnormal perfusion was associated with worse prognosis among those who had obstructive CAD.

RISK STRATIFICATION WITH CTA AND STATIC CTP. A few studies have reported the prognostic

FIGURE 5 Kaplan-Meier Curves for Abnormal Perfusion Among Patients With Obstructive CAD



Patients at risk

Abnormal perfusion (-)	55	43	30	20	11
Abnormal perfusion (+)	63	38	23	10	6

Patients at risk

Abnormal perfusion (-)	55	44	30	20	11
Abnormal perfusion (+)	63	38	24	12	8

Kaplan-Meier curves in patients with and without abnormal perfusion in the setting of obstructive CAD **(A)** for all events and **(B)** for hard events are shown. Abbreviations as in Figure 1.

value of static CTP. Linde et al. (15) showed that in 240 patients with acute onset chest pain but who had normal electrocardiograms and troponin levels, static CTP was useful for predicting mid-term (median follow-up: 19 months) clinical outcome independently of the pre-test probability of obstructive CAD. A prospective multicenter international study by Chen et al. (8) demonstrated that the combination of CTA and static CTP yielded a similar prediction of 2-year event-free survival to that obtained by ICA and single-photon emission computed tomography MPI among a cohort of 379 patients with suspected or known CAD. However, the 2 studies did not investigate an independent and incremental prognostic value of static CTP over CTA.

RISK STRATIFICATION WITH CTA AND DYNAMIC CTP. There have been only limited data on the prognostic value of dynamic CTP. A retrospective study by Meinel et al. (16) indicated that, during a median follow-up of 12 months in 144 patients (including 51 patients with known CAD), those who had perfusion defects assessed visually on CTP images were at an increased risk of MACEs (HR: 2.50; 95% CI: 1.34 to 4.65; $p = 0.004$). However, visual analysis as used in that study often requires expertise in the reading of CTP images. Another study by Meinel et al. (17) showed that in the same study population, global quantification of MBF obtained with dynamic CTP was an independent predictor of MACEs compared with clinical risk factors and assessment of stenosis at CTA. However, in the latter study, when early revascularizations were excluded from MACEs, Kaplan-Meier curves analysis showed no significant difference in event-free survival between the patients with and without low global MBF. Furthermore, these 2 studies by Meinel et al. (17) did not perform additional statistical analysis to investigate an incremental prognostic value of dynamic CTP over CTA.

FRACTIONAL FLOW RESERVED CALCULATED BY CTA DATA. Noninvasive fractional flow reserve (FFR) calculated using CTA (FFR_{CT}) data is an emerging imaging tool that can be used to determine the hemodynamic significance of stenosis without stress agents (18). Data on the prognostic value of FFR_{CT} are limited. Douglas et al. (19) revealed that in symptomatic patients referred for ICA, care guided by FFR_{CT} was associated with equivalent clinical outcomes compared with usual care over a 1-year follow-up.

Dynamic CTP has several potential advantages over FFR_{CT}. The evaluation of ischemia on CTP images is not influenced by coronary calcification, whereas heavy coronary calcification may affect the hemodynamic assessment of stenosis with FFR_{CT}. Furthermore, FFR_{CT} may be hampered by higher testing costs in the absence of on-site application.

CLINICAL IMPLICATIONS. Our results implied that MBF quantified with dynamic CTP could stratify patients with suspected CAD for future cardiac events. More importantly, the addition of dynamic CTP to CTA improved risk stratification in patients with CTA-detected stenosis. Abnormal perfusion was associated with higher event rates for MACEs in those who had obstructive CAD. Consequently, the addition of dynamic CTP to CTA enabled a more appropriate selection of patients with CAD who were at a higher risk of events.

According to the Kaplan-Meier curve analysis for absolute MBF, the absence of reduced perfusion was associated with good prognosis for MACEs. Moderately reduced perfusion was associated with similar adverse outcomes as those of severely reduced perfusion, which suggested that moderately reduced perfusion in absolute MBF was no less important for assessing risk of cardiac events than that of severely reduced perfusion.

STUDY LIMITATIONS. First, this was a single-center study, and second, this was a retrospective study; clinical decisions and test orders were not managed through a standardized protocol. Third, although the total radiation dose (7.1 mSv) applied in this study was relatively small, combining CTP with CTA inevitably increased the ionizing radiation dose, as well as the contrast medium volume, compared with CTA alone. Fourth, in the present study, a composite endpoint that included heart failure was used. In studies related to the prognostic value of MPI or CTA plus MPI, it is not uncommon to include heart failure as an MACE (8,20,21), because heart failure is frequently associated with ischemic heart disease. Fifth, all CTA and dynamic CTP images in this study were obtained using dual-source CT. Further research is necessary to evaluate whether the same results as our study could be obtained using other types of CT scanners, such as 320-row detector CT, which has different properties (e.g. temporal resolution, Z-axis coverage, and sampling rate) in acquisition of dynamic CTP data from dual-source CT. Sixth, our study population was restricted to patients with suspected CAD because known CAD could have a substantial impact on the occurrence of cardiac events (8). Furthermore, in a study population with a high prevalence of infarction, CTP at rest or with

delayed enhancement imaging was desired for evaluating the influence of infarction on MBF. Further studies are needed to investigate the prognostic usefulness of dynamic CTP in patients with known CAD (e.g., patients with stents).

CONCLUSIONS

In patients with suspected CAD, MBF quantified with dynamic CTP is an independent predictor of MACEs and has an incremental prognostic value over CTA. Abnormal perfusion was associated with worse prognosis among those who had obstructive CAD. The addition of dynamic CTP to CTA allows improved risk stratification of patients with CTA-detected stenosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Abnormal perfusion identified with dynamic CTP was strongly associated with risk of major adverse cardiac events. Dynamic CTP had an incremental prognostic value over CTA. In the setting of obstructive CAD, higher event rates were observed in patients with abnormal perfusion.

TRANSLATIONAL OUTLOOK: Dynamic CTP allows improved risk stratification of patients with CTA-detected stenosis. In the workup of patients with suspected CAD, the addition of dynamic CTP to CTA enables a more appropriate selection of patients with CAD who are at a higher risk of events.

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KEY WORDS coronary artery disease, coronary CT angiography, dynamic CT perfusion

APPENDIX For supplemental figures and a table, please see the online version of this paper.