

Plaque Volume and Morphology are Associated with Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography

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Aim: Coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}) accurately diagnoses ischemic lesions of intermediate stenosis severity. However, significant determinants of FFR_{CT} have not been fully evaluated.

Methods: This was a sub-analysis of the Treatment of Alogliptin on Coronary Atherosclerosis Evaluated by Computed Tomography-Based Fractional Flow Reserve trial. Thirty-nine diabetic patients (117 vessels) with intermediate coronary artery stenosis [percent diameter stenosis (%DS) <70%] in whom FFR_{CT} was measured were included in this study. CCTA-defined, vessel-based volumetric and morphological characteristics of plaques were examined to determine their ability to predict FFR_{CT}.

Results: Patient-based, multivariate linear regression analysis showed that hemoglobinA1c, triglycerides, and the estimated glomerular filtration rate were significant independent factors associated with FFR_{CT}. Vessel-based, univariate linear regression analysis showed that the total atheroma volume ($r = -0.233$, $p = 0.01$) and the percentage atheroma volume (PAV) ($r = -0.284$, $p = 0.002$) as well as %DS ($r = -0.316$, $p = 0.006$) were significant determinants of FFR_{CT}. Among the plaque components, significant negative correlations were observed between FFR_{CT} and low- ($r = -0.248$, $p = 0.007$) or intermediate-attenuation plaque volume ($r = -0.186$, $p = 0.045$), whereas calcified plaque volume was not associated with FFR_{CT}. In the left anterior descending coronary artery (LAD), the plaque volume of each component was associated with FFR_{CT}.

Conclusions: Plaque volume, PAV, and %DS were significant determinants of FFR_{CT}. Plaque morphology, particularly in LAD, was associated with FFR_{CT} in diabetic patients with intermediate coronary artery stenosis.

Key words: Coronary atherosclerosis, Coronary computed tomography angiography, Fractional flow reserve, Plaque volume, Morphology

Introduction

The use of coronary computed tomography angiography (CCTA) for noninvasive anatomical detection or exclusion of coronary artery disease (CAD) is increasing¹. However, stenosis severity, evaluated using CCTA, overestimates the severity of atherosclerotic obstructions² and does not correlate with functional ischemia assessed by invasive fractional flow

reserve (FFR)³. CCTA-derived fractional flow reserve (FFR_{CT}) analysis was recently developed^{4, 5}. FFR_{CT} accurately diagnoses ischemic lesions of intermediate stenosis severity⁵⁻⁷.

Many previous studies have reported that an intravascular ultrasound (IVUS)-derived minimal lumen area (MLA) is useful in predicting the functional significance of invasive FFR^{8, 9}. However, CCTA MLA is less able than IVUS MLA to detect

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significant ischemia defined as an FFR of ≤ 0.80 ; thus, stenosis severity or MLA of CCTA had lower diagnostic performance for assessing ischemia¹⁰). Compared with these parameters, the percentage atheroma volume (PAV) determined by CCTA improves the accuracy of determination of lesion-specific hemodynamic significance by invasive FFR¹¹). However, these reports were based on invasive FFR. In other words, significant determinants of FFR_{CT} have not been fully evaluated.

Aim

The purpose of the present study was to evaluate significant determinants of FFR_{CT}.

Methods

Study Design

This study was a sub-analysis of the Treatment of Alogliptin on Coronary Atherosclerosis Evaluated by Computed Tomography-Based Fractional Flow Reserve (TRACT) trial. TRACT was a prospective, multicenter, observational trial to evaluate the effects of 48-week alogliptin treatment on coronary atherosclerosis using CCTA in patients with type 2 diabetes. Details of the study design have been reported previously¹²). Briefly, patients with type 2 diabetes who were suspected of having CAD and underwent CCTA examination were screened and had intermediate coronary artery stenosis [percent diameter stenosis (%DS) $< 70\%$], as evaluated by CCTA, were included in the TRACT trial. Inclusion and exclusion criteria have been described previously¹²). In total, 51 patients were enrolled in the TRACT trial, but one patient was lost to follow-up. Therefore, quantitative analysis of CCTA images was performed on 143 vessels from 50 patients. The FFR value could not be measured in 11 patients because of poor CCTA image quality¹³). Therefore, we evaluated the significant determinants of FFR_{CT} in 117 vessels from 39 patients using CCTA examination at baseline.

The TRACT trial was conducted in accordance with the Declaration of Helsinki and had the approval of the institutional ethical committees of the three participating institutions. The TRACT trial has been registered with the University Hospital Medical Information Network (UMIN; UMIN ID: 000015381). Written informed consent was obtained from each patient enrolled in the study.

Examination Using CCTA and Image Acquisition

The CCTA examination details were described previously¹²). Each center performed CCTA examina-

tions in accordance with the Society of Cardiovascular Computed Tomography (SCCT) guidelines on the performance of CCTA using a variety of different CT scanner platforms¹⁴). CCTA was performed using 64-detector-row CT scans. Sublingual nitrates were administered to all patients before scanning. If necessary, beta-blockers were orally or intravenously administered, targeting a heart rate of < 60 beats per minute. During acquisition, 80–100 mL of contrast material was injected intravenously, followed by a saline flush. Helical or axial scan data were obtained with retrospective or prospective electrocardiographic gating, respectively. Image acquisition was prescribed to include the coronary arteries, left ventricle, and proximal ascending aorta.

CCTA Core Laboratory Analysis

CCTA images recorded in DVD format were transmitted to the core laboratory (HeartFlow, Redwood City, CA, USA) for computational analysis of FFR_{CT}, which was performed in a blinded manner. FFR_{CT} was calculated after semi-automated segmentation of the coronary arteries and left ventricular mass⁴). Briefly, we conducted three-dimensional blood flow simulations in the coronary vasculature via proprietary software with quantitative image quality analysis, image segmentation, and physiological modeling using computational fluid dynamics. Coronary blood flow and pressure were calculated under conditions simulating maximal hyperemia. FFR_{CT} was displayed at each point in the coronary tree > 2.0 mm in vessel diameter. The lowest FFR_{CT} values in the major epicardial arteries [left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA)] were registered.

Quantitative analyses of the coronary artery were performed at another independent core laboratory (Cardiocore Japan, Tokyo, Japan) in accordance with the SCCT guidelines on CCTA interpretation¹⁴). Details of the core laboratory analyses were reported previously¹²). Briefly, quantitative atheroma analyses were performed by independent, experienced observers who were blinded to the FFR_{CT} and clinical data. All reconstructed datasets were transferred to an offline workstation for quantitative coronary atheroma volume analysis using a dedicated software with a semi-automated three-dimensional contour detection algorithm (QAngioCT version 2.1 RC4; MEDISTM, Leiden, the Netherlands)¹⁵). The reconstructed image was set at a window width of 740 and level of 220 for the quantitative coronary artery assessment. All three coronary vessels measuring > 2.0 mm in diameter were analyzed (QAngioCT, vs. 2.1 RC4, MEDISTM) according to an American Heart Association 17-seg-

Table 1. Baseline characteristics of the subjects

Age (years)	71 ± 9
Males	21 (54)
Body mass index (kg/m ²)	24.7 ± 3.4
Hypertension	33 (85)
Dyslipidemia	24 (62)
Smoking	8 (21)
Statin	17 (44)
Ezetimibe	5 (13)
Antiplatelet	8 (21)
ACE inhibitor or ARB	17 (44)
Beta-blocker	8 (21)
Hypoglycemic medications	
DPP-4 inhibitor	21 (54)
Sulfonylurea	11 (28)
Biguanide	10 (26)
α-Glucosidase inhibitor	4 (10)
Glinide	2 (5)
Thiazolidine	1 (3)
Insulin	0 (0)

Data are expressed as mean ± SD or *n* (%).

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DPP-4, dipeptidyl peptidase-4.

ment model. Only the major coronary vessels were considered for analysis (segments 1, 2, 3, 6, 7, 8, 11, 13, and 15). Automated luminal and vessel border detection was manually corrected when necessary. We defined quantitative atheroma volume indices as follows: total atheroma volume (TAV) = (total vessel volume – total lumen volume), PAV = (TAV/total vessel volume) × 100. All plaques were characterized based on Hounsfield units (HU) into low-attenuation (< 30 HU), intermediate-attenuation (30–150 HU), and calcified plaque (> 150 HU)¹⁶, and the volume of each component was measured.

Laboratory Data

Hemoglobin A1c (HbA1c) levels were measured using high-performance liquid chromatography (Adams A1c HA-8160; Arkray Inc., Kyoto, Japan), whereas plasma glucose (PG) levels were measured using the glucose oxidation method (chemical reagent and Glucose AUTO and STAT GA-1160 analyzer; Arkray Inc.). Serum levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, triglycerides (TG), and high-density lipoprotein (HDL) cholesterol were measured using standard enzymatic methods (AU2700; Beckman Coulter, CA, USA) and commercially available kits (Kyowa Medex, Tokyo, Japan). Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured at a central clinical laboratory (SRL, Inc., Tokyo, Japan). The estimated glo-

Table 2. Risk factor control at the time of the CCTA examination

Total cholesterol (mg/dL)	199 ± 30
LDL cholesterol (mg/dL)	120 ± 31
Triglycerides (mg/dL)	146 (36–442)
HDL cholesterol (mg/dL)	63 ± 15
hs-CRP (ng/mL)	683 (65–8970)
PG (mg/dL)	140 ± 46
HbA1c (%)	7.1 ± 0.8
SBP (mmHg)	139 ± 19
DBP (mmHg)	83 ± 13
HR (beats/min)	63 ± 10
eGFR (mL/min/1.73m ²)	65 ± 12

Data are expressed as mean ± SD or median (range).

CCTA, coronary computed tomography angiography; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PG, plasma glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate.

merular filtration rate (eGFR) was calculated as follows: eGFR (mL/min/1.73 m²) = 194 × serum creatinine (mg/dL)^{-1.094} × Age (years)^{-0.287} (× 0.739 for female subjects)¹⁷.

Statistical Analysis

The statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, NC, USA). The results are expressed as mean ± standard deviation or median (range). Univariate linear regression analysis was performed to assess the factors associated with FFR_{CT}. Statistically significant variables on univariate analysis were entered into multivariate models. Statistical significance was set at *p* < 0.05.

Results

The subjects' baseline characteristics are shown in **Table 1**. Twenty-one patients (54%) were men, and the mean patient age was 71 years. Seventeen patients (44%) were treated with statins at the time of the CCTA examination. The risk factor control at the time of the CCTA examination is shown in **Table 2**. Mean levels of TC, LDL cholesterol, HDL cholesterol, and eGFR were 199 ± 30 mg/dL, 120 ± 31 mg/dL, 63 ± 15 mg/dL, and 65 ± 12 mL/min/1.73 m², respectively. Median TG and hs-CRP levels were 146 mg/dL and 683 ng/mL, respectively. Mean PG and HbA1c levels were 140 mg/dL and 7.1%, respectively.

A case example illustrating quantitative plaque analysis and FFR_{CT} is shown in **Fig. 1**. A 62-year-old man with history of diabetes presented with atypical chest pain on effort. The CCTA images showed intermediate stenosis in the three coronary arteries. FFR_{CT}

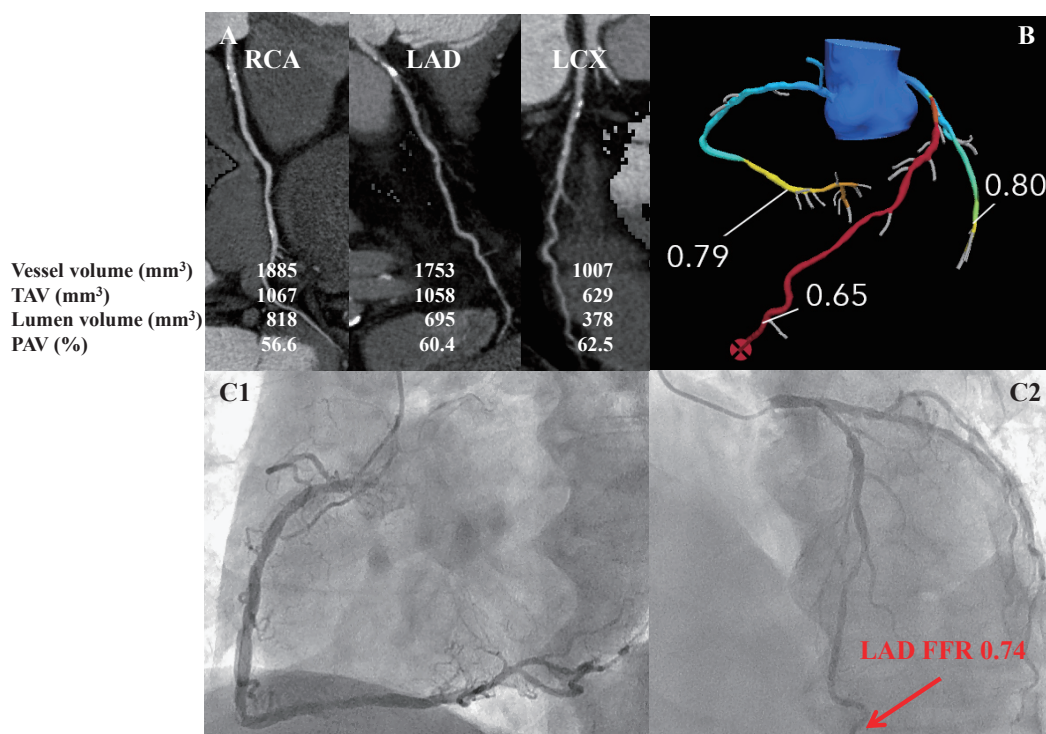


Fig. 1. A case example

(A) CCTA (curved multiplanar reconstructions) images. (B) FFR_{CT} values of the three coronary arteries. (C) Invasive coronary angiograms.

A 62-year-old man with history of diabetes presented with atypical chest pain on effort. The CCTA images and invasive coronary angiograms demonstrated intermediate stenosis in the three coronary arteries. FFR_{CT} values in RCA, LAD, and LCX were 0.79, 0.65, and 0.80, respectively. An invasive FFR value of LAD was 0.74.

CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; TAV, total atheroma volume; PAV, percentage atheroma volume; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

values in RCA, LAD, and LCX were 0.79, 0.65, and 0.80, respectively. An invasive FFR value of LAD was 0.74.

Vessel-based quantitative and qualitative analyses of coronary atherosclerosis in the whole three coronary arteries are shown in **Table 3**. FFR_{CT}, %DS, vessel volume, TAV, lumen volume, and PAV per-vessel were 0.86 ± 0.09, 41.9% ± 10.4%, 1267.2 ± 728.7 mm³, 658.5 ± 390.5 mm³, 608.7 ± 405.9 mm³, and 52.9% ± 10.9%, respectively. Overall, 93 vessels (79%) were negative for ischemia (FFR_{CT} > 0.80), whereas 24 (21%) were positive (FFR_{CT} ≤ 0.8). Patient-based univariate linear regression analyses showed that HbA1c ($r = -0.276, p = 0.003$), TG ($r = 0.280, p = 0.002$), and eGFR ($r = -0.305, p = 0.001$) were associated with FFR_{CT} (**Table 4**). Multivariate linear regression analyses showed that HbA1c ($\beta = -0.296, p = 0.0009$), TG ($\beta = 0.281, p = 0.002$), and eGFR ($\beta = -0.180, p = 0.04$) were significant independent factors associated with FFR_{CT} (**Table 4**). Vessel-based univariate linear regression analysis showed that TAV ($r = -0.233, p = 0.01$), PAV ($r = -0.284, p = 0.002$), and %DS ($r = -$

Table 3. Vessel based quantitative and qualitative analyses of the three coronary arteries

FFR _{CT}	0.86 ± 0.09
FFR _{CT} > 0.8	93 (79)
FFR _{CT} ≤ 0.8	24 (21)
Percent diameter stenosis (%)	41.9 ± 10.4
Vessel volume (mm ³)	1267.2 ± 728.7
TAV (mm ³)	658.5 ± 390.5
Lumen volume (mm ³)	608.7 ± 405.9
PAV (%)	52.9 ± 10.9
Plaque characteristics	
Absolute value	
Low-attenuation (mm ³)	93.0 ± 84.1
Intermediate-attenuation (mm ³)	317.1 ± 194.3
Calcified (mm ³)	234.4 ± 218.4
Relative value	
Low-attenuation (%)	13.7 ± 10.0
Intermediate-attenuation (%)	50.6 ± 13.8
Calcified (%)	35.8 ± 19.2

Data are expressed as mean ± SD or *n* (%).

FFR, fractional flow reserve; TAV, total atheroma volume; PAV, percentage atheroma volume.

Table 4. Univariate and multivariate linear regression analyses for predictors of FFR_{CT} (per-patient analysis)

	Univariate		Multivariate	
	<i>r</i>	<i>p</i> value	β	<i>p</i> value
Age	-0.084	0.31		
Sex	-0.154	0.1		
BMI	0.079	0.39		
Smoking	-0.123	0.19		
Statin use	0.121	0.2		
Total cholesterol	0.100	0.3		
LDL cholesterol	0.114	0.22		
Triglycerides	0.280	0.002	0.281	0.002
HDL cholesterol	-0.040	0.67		
hs-CRP	-0.176	0.07		
PG	-0.063	0.5		
HbA1c	-0.276	0.003	-0.296	0.0009
eGFR	-0.305	0.001	-0.180	0.04

Male sex, smoking, and statin use were assigned a value of 1. Female sex, and the absence of smoking and statin use were assigned a value of 0. FFR, fractional flow reserve; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PG, plasma glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate.

Table 5. Univariate linear regression analysis for predictors of FFR_{CT} (per-vessel analysis)

	Whole coronary arteries		LAD		Non-LAD	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
Percent diameter stenosis	-0.316	0.006	-0.235	0.16	-0.294	0.009
Vessel volume	-0.099	0.29	-0.395	0.02	-0.093	0.42
TAV	-0.233	0.01	-0.568	0.0002	-0.198	0.08
Low-attenuation	-0.248	0.007	-0.430	0.007	-0.171	0.13
Intermediate-attenuation	-0.186	0.045	-0.473	0.003	-0.178	0.12
Calcified	-0.124	0.18	-0.354	0.03	-0.116	0.31
Lumen volume	0.046	0.62	-0.082	0.63	0.021	0.86
PAV	-0.284	0.002	-0.309	0.06	-0.254	0.02

FFR, fractional flow reserve; LAD, left anterior descending coronary artery; TAV, total atheroma volume; PAV, percentage atheroma volume.

0.316, *p*=0.006) were significant determinants of FFR_{CT} (Table 5). Among the plaque components, significant negative correlations were observed between FFR_{CT} and low- (*r* = -0.248, *p*=0.007) or intermediate-attenuation plaque volume (*r* = -0.186, *p*=0.045), whereas calcified plaque volume was not associated with FFR_{CT} (Table 5). In LAD, the plaque volume of each component was associated with FFR_{CT} (low-attenuation plaque volume: *r* = -0.430, *p*=0.007; intermediate-attenuation plaque volume: *r* = -0.473, *p*=0.003; calcified plaque volume: *r* = -0.354, *p*=0.03) (Table 5).

Discussion

The present study's major findings are as follows: (1) greater atheroma volume, PAV, and %DS were associated with a low FFR_{CT}; (2) plaque morphology, particularly in LAD, was a significant determinant of FFR_{CT}; and (3) a significant negative correlation was observed between HbA1c and FFR_{CT}.

FFR is a useful tool for detecting lesion-specific myocardial ischemia and assessing the functional significance of CAD¹⁸. Many previous studies have reported that MLA evaluated by IVUS is useful for predicting the functional significance of invasive FFR^{8,9}. However, a recent study reported that the optimal cut-

off for an MLA to FFR of ≤ 0.80 was vessel dependent¹⁹). However, the diagnostic performance of CCTA MLA is lower than that of IVUS MLA for detecting significant ischemia, defined as an FFR of ≤ 0.80 ¹⁰). Compared with stenosis severity or MLA, PAV by CCTA improves the determination of lesion-specific hemodynamic significance by invasive FFR¹¹). Recently, Doris *et al.* reported that the total plaque volume, quantified on a per-vessel basis, predicted an abnormal FFR_{CT}, suggesting that an abnormal FFR_{CT} may reflect diffuse coronary atherosclerosis²⁰). Consistent with above reports, we found a significant negative correlation between FFR_{CT} and vessel-based TAV or PAV. Thus, plaque volume and its ratio to the vessel are significant determinants of FFR_{CT}.

Another important result of this study was that plaque morphology, particularly in LAD, was associated with FFR_{CT}. The prognostic outcome has traditionally been linked to the morphological features of high-risk plaques that are vulnerable to rupture. Therefore, it is important to address whether plaque morphology can influence FFR value. There are some discrepancies in the influence of plaque morphology on the FFR value. In the Fractional Flow Reserve and Intravascular Ultrasound Relationship Study, the plaque morphology, as measured by virtual histology (VH)-IVUS at the MLA site, did not correlate with the invasive FFR value¹⁹). Brown *et al.* also reported no relationship between the invasive FFR value and the VH-IVUS derived plaque composition²¹). However, Sakurai *et al.* reported that lipid plaque volume, evaluated using integrated backscatter IVUS, was significantly correlated with invasive FFR value²²). Hüseyinova *et al.* also reported that invasive FFR value negatively correlated with the necrotic core volume or presence of thin-cap fibroatheroma (TCFA) evaluated using VH-IVUS²³). Furthermore, the presence of optical coherence tomography-derived TCFA and reduced fibrous cap thickness was associated with lower FFR values²⁴). Recent studies also reported that the low-attenuation plaque volume, evaluated by CCTA, was an independent predictor of the invasive FFR value^{25, 26}). Furthermore, Doris *et al.* reported that the non-calcified plaque volume and the low-density, non-calcified plaque volume were stronger predictors of abnormal FFR_{CT} than calcified plaque volume²⁰). Consistent with these reports, low- and intermediate-attenuation plaque volumes were negatively and significantly correlated with FFR_{CT}, whereas the calcified plaque volume was not associated with FFR_{CT} in the whole three coronary arteries. Furthermore, although the plaque volume of each component was associated with FFR_{CT} in LAD, the correlation coefficients were stronger in low- and intermediate-

attenuation plaque volumes than in the calcified plaque volume. Thus, the presence of vulnerable plaque contributes to the dissociation of morphological findings from the hemodynamic consequence²⁶).

Diabetes mellitus is a major risk factor for CAD, and hyperglycemia is related to the progression of atherosclerosis²⁷). Recently, Kitabata *et al.* reported that diabetes and hypertension were independent predictors of abnormal FFR_{CT}²⁸). Consistent with this report, we found a significant negative correlation between HbA1c and FFR_{CT}. Thus, poor glycemic control is associated with the progression of diffuse coronary atherosclerosis and leads to decreased FFR_{CT}. We could not clearly explain the mechanisms associating FFR_{CT} with TG or eGFR. We speculate that vessel remodeling and plaque morphology under these conditions may affect FFR_{CT} value because a decreased eGFR is associated with expanding vessel remodeling and plaque morphology²⁹).

This study had several limitations. First, this was a post hoc sub-analysis of the non-randomized TRACT trial. Second, TRACT trial specifically included diabetic patients with intermediate coronary artery stenosis. Non-diabetic patients and those who required percutaneous coronary intervention were excluded. Furthermore, 93 vessels (79%) were negative for ischemia (FFR_{CT} >0.8). Therefore, the results of this study could not be generalized to all subjects and all vessels. Third, the remodeling index was not included in the analysis because FFR_{CT} was obtained from the far distal site of the coronary artery to evaluate whole vessel ischemia. Finally, this study was limited by its relatively small number of patients. Further studies with larger sample sizes are necessary to confirm our conclusions.

Conclusions

Plaque volume, PAV, and %DS were significant determinants of FFR_{CT}. Plaque morphology, particularly in LAD, was associated with FFR_{CT} in diabetic patients with intermediate coronary artery stenosis.

Declaration of Conflict of Interest

None.

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