# Predictive value of plaque characteristics assessed by coronary computed tomography angiography and optical coherence tomography for identification of lesions causing ischemia

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# Predictive value of plaque characteristics assessed by coronary computed tomography angiography and optical coherence tomography for identification of lesions causing ischemia

Directed by Professor Jung-Sun Kim

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ABSTRACT

**Predictive value of plaque characteristics assessed by coronary computed tomography angiography and optical coherence tomography for identification of lesions causing ischemia**

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(Directed by Professor Jung-Sun Kim)

**Background and Aim:** In patients with intermediate coronary stenosis, the functional assessment with fractional flow reserve (FFR) and the anatomical assessment with optical coherence tomography (OCT) have been widely used in clinical practice. In addition, coronary computed tomography angiography (CTA) is commonly used non-invasive imaging technique for evaluating suspected coronary artery disease before being referred for coronary angiography. This study sought to investigate the association between FFR and plaque characteristics assessed by coronary CTA and OCT in patients with intermediate coronary stenosis.

**Methods:** Based on the prospective multicenter registry, a total of 159 patients including 339 coronary lesions with intermediate stenosis were included. All patients underwent coronary CTA before being referred for coronary angiography and both FFR measurement and OCT examination were performed during angiography. The stenotic lesion with FFR $\leq$0.80 was considered diagnostic of lesion causing ischemia. The predictive value of plaque characteristics assessed by coronary CTA and OCT for identifying lesions causing ischemia was analyzed.

**Results:** Plaque characteristics on coronary CTA and OCT were different between the lesions causing ischemia versus not causing ischemia. On multivariate analysis, quantitative degree of stenosis on coronary CTA and OCT were independent predictors for the lesions causing ischemia, and OCT had a trend for higher predictive value than that of coronary CTA. In addition, qualitative characteristics including low attenuation plaque on coronary CTA and thrombus, intimal vasculature, and plaque rupture on OCT were also independent predictors for the lesions causing ischemia. Increasing number of these qualitative characteristics offered incremental improvement in predicting the lesions causing ischemia.

**Conclusion:** The results from this study suggest that comprehensive anatomical evaluation of coronary stenosis may be able to provide additional supportive information for predicting the lesions causing ischemia.

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Key words: coronary plaque, coronary computed tomography angiography, optical coherence tomography, fractional flow reserve

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## I. INTRODUCTION

Decision to recommend coronary revascularization in patients with chest pain and intermediate stenosis noted on coronary angiography is challenging.[1, 2] Therefore, a firm evidence that the stenotic lesion is the reason for the chest pain is usually required in patient with intermediate stenosis.[1, 2] There have been two important concept in terms of providing the evidence for the intermediate stenotic lesion needing revascularization; functional assessment with fractional flow reserve (FFR) measurement or anatomical assessment with intravascular imaging techniques.[1-4] FFR measurement using pressure-wire can provide functional information by detecting inducible myocardial ischemia and has been considered as the gold standard for functional assessment of coronary stenosis causing ischemia based on the previous studies which demonstrated the benefit of FFR-guided percutaneous coronary intervention (PCI) compared to angiography-guided PCI.[3, 5] On the other hand, intravascular imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) with higher resolution than IVUS, are widely used adjunctive methods which can provide detailed anatomical information based on the quantitative and qualitative assessment for the stenotic lesions.[4, 6, 7] Based on these anatomical information, intravascular imaging-guided PCI has been associated improved procedural or clinical outcomes compared to angiography-guided PCI.[8-10] Although the underlying rationale of FFR and intravascular imaging techniques are distinct, both are widely used methods during coronary angiography in order to help make appropriate decisions regarding coronary revascularization.[1, 2, 11] Besides, a randomized single-center trial demonstrated that in patients with intermediate coronary stenosis, OCT-guidance was associated with lower occurrence of composite cardiovascular events or significant angina, while FFR-guidance was associated with higher rate of medical treatment and lower costs.[12] Thus, the functional and anatomical assessment of coronary stenosis should be complementary rather than competitive. However, the association between FFR and plaque characteristics using OCT have not been clearly noted. In addition, in current clinical practice, coronary computed tomography angiography (CTA) is commonly used non-invasive imaging technique for evaluating suspected coronary artery disease before being referred for coronary angiography.[13] Thus, the aim of this study was to evaluate the predictive value of plaque characteristics assessed by coronary CTA and OCT for identification of lesions causing ischemia assessed by FFR, based on the prospective multicenter registry.

## II. MATERIALS AND METHODS

### 1. Subjects and study design

The Integrated Coronary Multicenter Imaging Registry is a collaboration between four medical institutions in South Korea, created to investigate the clinical impact of anatomical information from coronary CTA and OCT, and functional information from FFR in patients with intermediate coronary stenosis (ClinicalTrials.gov, Identifier: NCT03298282). The study was approved by the institutional review board of each participating center and followed the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. In brief, among patients who underwent coronary CTA for evaluation of chest pain before being referred for coronary angiography, a total of 180 patients who received both FFR measurement and OCT examination during angiography for evaluating intermediate stenosis (40–70%) in any coronary artery were enrolled between November 2017 and June 2019 (the full inclusion and exclusion criteria are provided in **Table 1**). Of these, 21 patients were excluded due to poor image quality of coronary CTA or OCT (n=9) and insufficient data regarding coronary CTA, OCT, or FFR (n=12). Consequently, a total of 159 patients including 339 coronary lesions with intermediate stenosis that had complete analyzable imaging data from coronary CTA and OCT, and FFR values were included in this study.

**Table 1. Inclusion and exclusion criteria for Integrated Coronary Multicenter Imaging Registry**

| |
|---|
| **Inclusion criteria** |
| 1. Patients who underwent coronary CTA for chest pain |
| 2. Age 20-80 years |
| 3. Intermediate diameter stenosis (40–70%) on coronary angiography at de novo lesions in the proximal to middle portion of any coronary artery which requires pressure wire-based FFR measurement or OCT examination |
| **Exclusion criteria** |
| 1. Requirement for inotropics for hemodynamic instability |
| 2. Severe left ventricular dysfunction (ejection fraction <30%) |
| 3. Severe valvular dysfunction |
| 4. Declined kidney dysfunction (serum creatinine >2.0 mg/dL) |
| 5. Contraindication to adenosine or contrast |
| 6. Expected survival less than 12 months |
| 7. Inability to follow the patient over the period of 2 years after enrollment, as assessed by the investigator |

8. Inability to understand or read the informed consent

**Abbreviation:** CTA, computed tomography angiography; FFR, fractional flow reserve; OCT, optical coherence tomography.

2. Image acquisition

All patients underwent coronary CTA before coronary angiography. Performance of coronary CTA and acquisition of images (64- or higher detector row scanners with prospective or retrospective electrocardiographic gating) were in accordance with the Society of Cardiovascular Computed Tomography guidelines.[14] OCT imaging was performed using a frequency-domain OCT system (C7-XR OCT imaging system, LightLab Imaging Inc., St. Jude Medical, MN, USA). Cross-sectional OCT images were generated at a rotational speed of 100 frames/s while the fiber probe was withdrawn at 20 mm/s within the stationary imaging sheath.

3. Image analysis

Coronary CTA analysis was performed at Yonsei University CONNECT-AI Research Center (Seoul, South Korea), while OCT and quantitative coronary angiography (QCA) analyses were performed at an independent core laboratory of Cardiovascular Research Center (Seoul, South Korea). All analyses were performed by experienced analysts who were blinded to the patient and procedure data.

Coronary CTA analysis was performed using semi-automated image analysis software (QAngio CT RE, Medis Medical Imaging Systems, Leiden, the Netherlands). In addition to quantitative analysis of target lesions including minimal lumen area, diameter stenosis, and plaque burden, qualitative analysis of plaque characteristics was performed. Low attenuation plaque was defined as plaque with average density ≤30 HU from 3 random region-of-interest measurement with approximately 0.5 to 1.0 $mm^2$ in noncalcified low attenuation portion of the plaque.[15] Remodeling index was calculated using the following formula: maximal lesion vessel diameter/proximal reference vessel diameter. Positive remodeling was defined as remodeling index ≥1.1.[15] Spotty calcification was defined as calcifications with average density >130 HU, diameter <3 mm in any direction, length of the calcium <1.5 x the vessel diameter, and width less than two-thirds of the vessel diameter.[15] Napkin-ring sign was defined as presence of ring-like attenuation pattern with peripheral high attenuation tissue surrounding a central lower attenuation portion.[15] The representative images of plaque characteristics on coronary CTA is presented in **Fig. 1**.

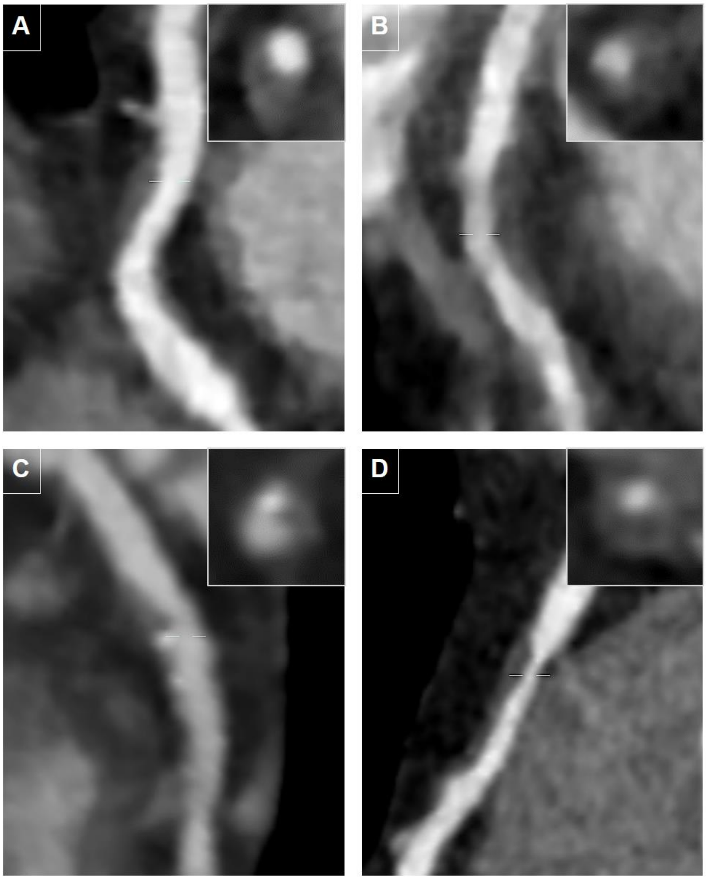

**Figure 1. Plaque characteristics assessed by coronary computed tomography angiography**

**Note:** (A) Low attenuation plaque, (B) positive remodeling, (C) spotty calcification, and (D) napkin-ring sign

OCT analysis was performed using certified software (QIvus, Medis Medical Imaging Systems, Leiden, the Netherlands). Cross-sectional OCT images were analyzed at interval of 1 mm. The reference lumen area was defined as the region within the same segment as the lesion with the largest lumen. These reference area was proximal or distal to the stenotic area (usually within 10 mm of the stenosis, without major intervening branches). The minimal lumen area was identified at the segment with the smallest lumen area. Area stenosis was calculated using the following formula: [(mean reference lumen area – minimal lumen area)/mean reference lumen area] x 100%. For qualitative analysis, plaque morphology was analyzed at the site of minimal lumen area in at least three consecutive frames and classified into fibrous, fibrocalcific, or lipid plaque.[16-18] Fibrous plaque was defined as plaque that had high backscattering and a relatively homogenous signal.[16-18] Fibrocalcific plaque was defined as plaque that contained fibrous tissue with calcium which appeared as a signal-poor or heterogeneous region with a sharply delineated border and lipid plaque was defined as plaque that had diffusely bordered signal-poor region overlain by signal rich band.[16-18] In lipid plaque, lipid arc was measured at every 1 mm interval throughout the entire length of each lesion and the average value was used and lipid length on longitudinal view was also measured.[16-18] Among lipid plaques, thin-cap fibroatheroma was defined as lipid-pool covered by fibrous cap in which the minimal thickness of fibrous cap was ≤65 μm and lipid arc >90°.[16-18] Thrombus was defined as mass attached to the luminal surface or floating within the lumen.[19] Intimal vasculature was defined as the presence of small, signal-poor regions with vesicular or tubular shape within the intima without a connection to the vessel lumen which can usually be followed in continuous frames and cholesterol crystal was defined as the presence of thin, linear and back scattering regions of high intensity.[16-18] Macrophage accumulation was defined as the signal-rich, distinct, or confluent punctate regions that exceeded the intensity of background speckle noise.[16-18] Plaque rupture was identified as the presence of fibrous cap discontinuity with a clear cavity formed inside the plaque and plaque erosion was identified by the presence of attached thrombus overlying an intact fibrous cap, or luminal surface irregularity at the lesion in the absence of thrombus, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus.[20] **Fig. 2** shows the representative images of plaque characteristics on OCT.

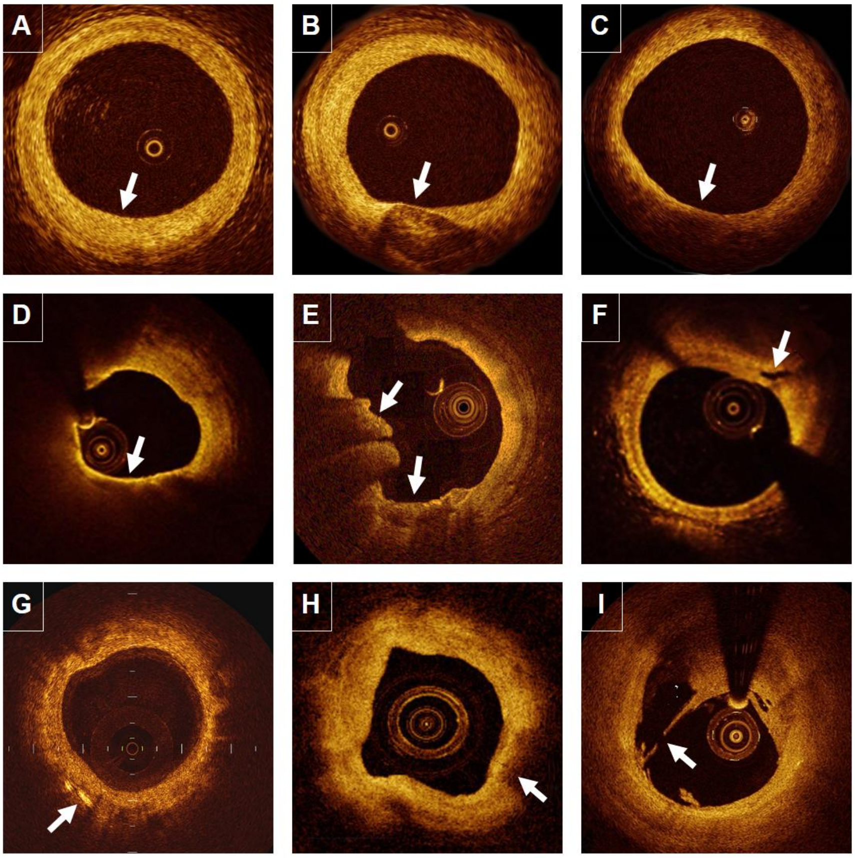

**Figure 2. Plaque characteristics assessed by optical coherence tomography**
**Note:** (A) Fibrous plaque, (B) fibrocalcific plaque, (C) lipid plaque, (D) thin-cap fibroatheroma, (E) thrombus, (F) intimal vasculature, (G) cholesterol crystal, (H) macrophage accumulation, and (I) plaque rupture

QCA analysis was performed using an off-line quantitative coronary angiographic system (CAAS, Pie Medical Instruments, Maastricht, the Netherlands). Minimal lumen diameter was measured from diastolic frames in a single, matched view showing the smallest lumen diameter, using the guiding catheter for magnification calibration.

4. FFR measurement

FFR measurement was performed using a 0.014-inch pressure guide wire (St. Jude Medical, MN, USA). Followed by the equalizing process, the pressure guide wire was positioned distal to the target lesion. Hyperemia was induced by intravenous adenosine administered at 140 μg/kg/min via an antecubital vein. FFR was calculated using the following formula: mean hyperemic distal coronary pressure/mean aortic pressure. The stenotic lesion with FFR ≤0.80 was considered diagnostic of lesion causing ischemia.

5. Statistical analyses

Continuous variables were reported as mean±standard deviation or median (interquartile range) and compared using Student's t-tests or Mann–Whitney test. Categorical variables were reported as numbers (percentages) and compared using $\chi 2$ tests or Fisher's exact tests. To determine the influence of plaque characteristics assessed by coronary CTA or OCT on predicting lesions causing ischemia (FFR ≤0.80), univariate and multivariate logistic regression analyses were performed. The variables with $P<0.001$ in univariate analysis were included in the multivariate analysis model. Correlations between variables have been expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Analysis of receiver operating characteristics (ROC) was used to determine the performance (sensitivity and specificity) of diameter stenosis on coronary CTA and area stenosis on OCT and for predicting the lesions causing ischemia and to determine an optimal cutoff value. The comparison between ROC curves was performed using DeLong's test. Incremental predictive value of qualitative characteristics on coronary CTA and OCT regarding the lesions causing ischemia was assessed by Global chi-square analyses using logistic regression and a likelihood ratio test. All tests were two-sided, and $P<0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS, version 25.0 (IBM Corporation, Chicago, IL, USA) and R 3.5.3 software (R foundations for Statistical Computing, Vienna, Austria).

## III. RESULTS

### 1. Study population and baseline characteristics

The baseline characteristics of the study population included in this study are presented in **Table 2**. There were no complications during any of the procedures. The mean age was 63.2±8.8 years, 118 patients (74.2%) were male, and mean body mass index was 25.2±2.9 kg/$m^2$. Eight eight patients (55.3%) had history of hypertension, 47 patients (29.6%) had diabetes mellitus, 62 patients (39.0%) had dyslipidemia, and 36 patients (22.6%) were current smokers. One hundred patients (62.9%) presented with clinical presentation of stable coronary artery disease, while 59 patients (37.1%) presented with acute coronary syndrome. Among 339 target lesions, 149 lesions (93.7%) were left anterior descending artery, 83 lesions (52.2%) were left circumflex artery, and 107 lesions (67.3%) were right coronary artery.

**Table 2. Baseline characteristics of the study population**

| | **Total (N=159)** |
|---|---|
| Age, years | 63.2 (8.8) |
| Male sex | 118 (74.2) |

| | |
|---|---|
| Height, cm | 165.7 (8.0) |
| Weight, kg | 69.2 (10.3) |
| Body mass index, kg/m$^2$ | 25.2 (2.9) |
| Hypertension | 88 (55.3) |
| Diabetes mellitus | 47 (29.6) |
| Dyslipidemia | 62 (39.0) |
| Current smoker | 36 (22.6) |
| Previous myocardial infarction | 1 (0.6) |
| Previous percutaneous coronary intervention | 3 (1.9) |
| Previous stroke | 3 (1.9) |
| Family history of coronary artery disease | 8 (5.0) |
| Clinical presentation | |
| Stable coronary artery disease | 100 (62.9) |
| Acute coronary syndrome | 59 (37.1) |
| Number of target lesion | 339 |
| Left anterior descending artery | 149 (93.7) |
| Left circumflex artery | 83 (52.2) |
| Right coronary artery | 107 (67.3) |

**Note:** Data are mean (SD) or number (%).

The median value of FFR was 0.89 (interquartile range, 0.80–0.96) and lesion causing ischemia (FFR ≤0.80) was observed in 88 lesions (26.0%). The median value of FFR in the lesions causing ischemia was 0.73 (interquartile range, 0.63–0.77), whereas it was 0.94 (interquartile range, 0.87–0.97) in the lesions not causing ischemia (P<0.001). Coronary angiographic findings are presented in **Table 3**. The lesions causing ischemia had smaller reference vessel diameter (3.0 versus 3.1 mm; P=0.005) and minimal lumen diameter (1.1 versus 2.0 mm; P<0.001) compared to the lesions not causing ischemia. Conversely, the lesions causing ischemia had higher diameter stenosis (63.5 versus 36.2%; P<0.001) and longer lesion length (26.1 versus 17.2 mm; P<0.001).

**Table 3. Angiographic characteristics of the target lesions according to FFR**

| | FFR >0.8 (N=251) | FFR ≤0.8 (N=88) | P-value |
|---|---|---|---|
| **Quantitative coronary angiography data** | | | |
| Reference vessel diameter, mm | 3.1 (0.6) | 3.0 (0.5) | 0.005 |
| Minimal lumen diameter, mm | 2.0 (0.7) | 1.1 (0.4) | <0.001 |
| Diameter stenosis, % | 36.2 (14.1) | 63.5 (13.7) | <0.001 |
| Lesion length, mm | 17.2 (8.1) | 26.1 (13.1) | <0.001 |

**Note:** Data are mean (SD) or number (%). **Abbreviation:** FFR, fractional flow reserve

2. Plaque characteristics assessed by coronary CTA and OCT according to FFR

Quantitative as well as qualitative analyses based on coronary CTA and OCT are presented in **Table 4**. Based on coronary CTA, the lesions causing ischemia had smaller minimal lumen area compared to those not causing ischemia (1.8 versus 3.4 $mm^2$; P<0.001). On the other hand, the lesions causing ischemia had larger diameter stenosis (50.5 versus 32.8%; P<0.001) and plaque burden (71.8 versus 51.8%; P<0.001). In the qualitative analysis, the lesions causing ischemia had higher proportion of low attenuation plaque (29.5 versus 9.6%; P<0.001), whereas positive remodeling, spotty calcification, and napkin ring sign were not different between the lesions causing ischemia versus not causing ischemia.

Based on OCT, the lesions causing ischemia had smaller proximal reference lumen area (7.9 versus 9.2 $mm^2$; P=0.005), distal reference lumen area (5.5 versus 7.7 $mm^2$; P<0.001), and minimal lumen area (1.7 versus 4.0 $mm^2$; P<0.001) compared to those not causing ischemia. Conversely, the lesions causing ischemia had higher area stenosis (87.0 versus 74.9%; P<0.001) and longer lesion length (28.9 versus 22.7 mm; P<0.001). In the qualitative analysis, the lesions causing ischemia had lower proportion of fibrous plaque (19.3 versus 33.1%; P=0.022). On the other hand, the lesions causing ischemia had higher proportion of thrombus (14.8 versus 1.6%; P<0.001), intimal vasculature (42.0 versus 22.3%;

P=0.001), cholesterol crystal (50.0 versus 37.1%; P=0.045), macrophage accumulation (17.0 versus 7.6%; P=0.019), plaque rupture (25.0 versus 8.0%; P<0.001), and plaque erosion (13.6 versus 5.2%; P=0.018).

**Table 4. Coronary computed tomography angiographic and optical coherence tomographic characteristics of the target lesions according to FFR**

| | **FFR >0.8 (N=251)** | **FFR ≤0.8 (N=88)** | **P-value** |
|---|---|---|---|
| **Coronary CTA data** | | | |
| Minimal lumen area, $mm^2$ | 3.4 (2.1) | 1.8 (1.0) | <0.001 |
| Diameter stenosis, % | 32.8 (14.3) | 50.5 (13.2) | <0.001 |
| Plaque burden, % | 51.8 (18.7) | 71.8 (16.5) | <0.001 |
| Low attenuation plaque | 24 (9.6) | 26 (29.5) | <0.001 |
| Positive remodeling | 159 (63.3) | 58 (65.9) | 0.763 |
| Spotty calcification | 17 (6.8) | 8 (9.1) | 0.632 |
| Napkin-ring sign | 2 (0.8) | 2 (2.3) | 0.277 |
| **OCT data** | | | |
| Proximal reference lumen area, $mm^2$ | 9.2 (3.6) | 7.9 (3.5) | 0.005 |
| Distal reference lumen area, $mm^2$ | 7.7 (3.5) | 5.5 (2.8) | <0.001 |
| Minimal lumen area, $mm^2$ | 4.0 (2.5) | 1.7 (1.0) | <0.001 |
| Area stenosis, % | 74.9 (9.9) | 87.0 (5.9) | <0.001 |
| Lesion length, mm | 22.7 (12.4) | 28.9 (11.3) | <0.001 |
| Plaque morphology | | | |
| Fibrous plaque | 83 (33.1) | 17 (19.3) | 0.022 |
| Fibrocalcific plaque | 140 (55.8) | 57 (64.8) | 0.178 |
| Lipid plaque | 61 (24.3) | 29 (33.0) | 0.150 |
| Lipid arc, ° | 136.1 (35.2) | 141.0 (43.0) | 0.632 |
| Longitudinal length of lipid, mm | 5.5 (4.5) | 4.7 (2.5) | 0.350 |
| Thin-cap fibroatheroma | 23 (9.2) | 8 (9.1) | 0.984 |
| Thrombus | 4 (1.6) | 13 (14.8) | <0.001 |
| Intimal vasculature | 56 (22.3) | 37 (42.0) | 0.001 |

| | | | |
|---|---|---|---|
| Cholesterol crystal | 93 (37.1) | 44 (50.0) | 0.045 |
| Macrophage accumulation | 19 (7.6) | 15 (17.0) | 0.019 |
| Plaque rupture | 20 (8.0) | 22 (25.0) | <0.001 |
| Plaque erosion | 13 (5.2) | 12 (13.6) | 0.018 |

**Note:** Data are mean (SD) or number (%). **Abbreviation:** CTA, computed tomography angiography; FFR, fractional flow reserve; OCT, optical coherence tomography.

3. Predicting the lesions causing ischemia by plaque characteristics

Univariate and multivariate analyses for predicting the lesions causing ischemia are presented in **Table 5** and **Table 6**. On multivariate analysis, independent predictors for the lesions causing ischemia were coronary CTA-based diameter stenosis (OR 1.08; 95% CI 1.03-1.13; P=0.002) and low attenuation plaque (OR 2.78; 95% CI 1.06-7.30; P=0.038) and OCT-based area stenosis (OR 1.13; 95% CI 1.02-1.25; P=0.018), thrombus (OR 5.13; 95% CI 1.06-24.74; P=0.042), intimal vasculature (OR 2.57; 95% CI 1.23-8.58; P=0.012), and plaque rupture (OR 3.25; 95% CI 1.23-8.58; P=0.017).

**Table 5. Univariate analysis for predicting the lesions causing ischemia**

| | **Odd ratio (95% CI)** | **P-value** |
|---|---|---|
| **Coronary CTA data** | | |
| Minimal lumen area | 0.45 (0.35-0.58) | <0.001 |
| Diameter stenosis | 1.09 (1.07-1.12) | <0.001 |
| Plaque burden | 1.07 (1.05-1.08) | <0.001 |
| Low attenuation plaque | 3.97 (2.13-7.39) | <0.001 |
| Positive remodeling | 1.12 (0.67-1.86) | 0.667 |
| Spotty calcification | 1.38 (0.57-3.31) | 0.476 |
| Napkin-ring sign | 2.90 (0.40-20.87) | 0.291 |
| **OCT data** | | |
| Proximal reference lumen area | 0.89 (0.83-0.97) | 0.006 |

| | | |
|---|---|---|
| Distal reference lumen area | 0.79 (0.72-0.87) | <0.001 |
| Minimal lumen area | 0.33 (0.24-0.45) | <0.001 |
| Lesion length | 1.04 (1.02-1.06) | <0.001 |
| Area stenosis | 1.25 (1.18-1.32) | <0.001 |
| Plaque morphology | | |
| Fibrous plaque | 0.49 (0.27-0.88) | 0.016 |
| Fibrocalcific plaque | 1.46 (0.88-2.41) | 0.142 |
| Lipid plaque | 1.53 (0.90-2.60) | 0.115 |
| Lipid arc | 1.00 (0.99-1.02) | 0.626 |
| Longitudinal length of lipid | 0.94 (0.80-1.10) | 0.438 |
| Thin-cap fibroatheroma | 0.99 (0.42-2.31) | 0.984 |
| Thrombus | 10.70 (3.39-33.81) | <0.001 |
| Intimal vasculature | 2.53 (1.51-4.24) | <0.001 |
| Cholesterol crystal | 1.70 (1.04-2.77) | 0.034 |
| Macrophage accumulation | 2.51 (1.21-5.19) | 0.013 |
| Plaque rupture | 3.85 (1.98-7.48) | <0.001 |
| Plaque erosion | 2.89 (1.27-6.60) | 0.012 |

**Abbreviation:** CI, confidence interval; CTA, computed tomography angiography; OCT, optical coherence tomography.

**Table 6. Multivariate analysis for predicting the lesions causing ischemia**

| | **Odd ratio (95% CI)** | **P-value** |
|---|---|---|
| **Coronary CTA data** | | |
| Minimal lumen area | 1.34 (0.84-2.12) | 0.219 |
| Diameter stenosis | 1.08 (1.03-1.13) | 0.002 |
| Plaque burden | 1.00 (0.97-1.04) | 0.985 |
| Low attenuation plaque | 2.78 (1.06-7.30) | 0.038 |
| **OCT data** | | |
| Distal reference lumen area | 0.93 (0.78-1.11) | 0.392 |
| Minimal lumen area | 0.64 (0.34-1.21) | 0.167 |
| Lesion length | 1.00 (0.97-1.04) | 0.909 |

| | | |
|---|---|---|
| Area stenosis | 1.13 (1.02-1.25) | 0.018 |
| Thrombus | 5.13 (1.06-24.74) | 0.042 |
| Intimal vasculature | 2.57 (1.23-5.38) | 0.012 |
| Plaque rupture | 3.25 (1.23-8.58) | 0.017 |

**Note:** Only variables with P-value <0.001 in the univariate analysis (Table 5) are presented. **Abbreviation:** CI, confidence interval; CTA, computed tomography angiography; OCT, optical coherence tomography

4. Impact of quantitative characteristics for predicting the lesions causing ischemia

The predictability of lesions causing ischemia using coronary CTA-based diameter stenosis and OCT-based area stenosis are presented in **Figure 3**. The area under the ROC curve for lesions causing ischemia according to coronary CTA-based diameter stenosis with cutoff value of 43% was 0.82 (P<0.001); values for sensitivity and specificity were 77.3% and 78.1%, respectively. The area under the ROC curve for lesions causing ischemia according to OCT-based area stenosis with cutoff value of 84% was 0.87 (P<0.001); values for sensitivity and specificity were 78.4% and 83.3%, respectively. Although not significant, OCT-based area stenosis presented a trend toward higher area under the curve compared to coronary CTA-based diameter stenosis (difference 0.05; P=0.093).

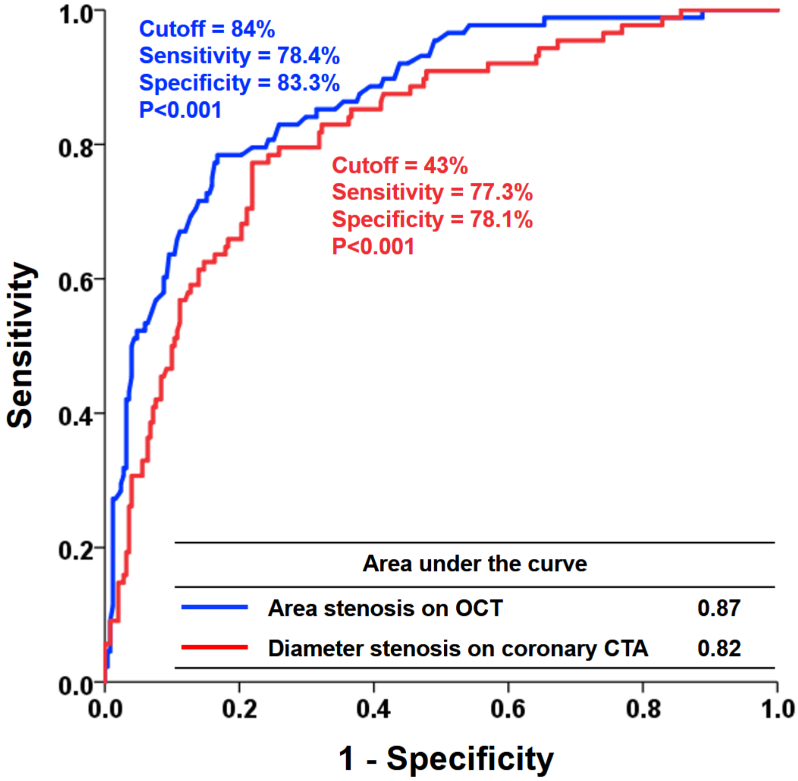


**Figure 3. Prediction of the lesions causing ischemia according to diameter stenosis on coronary computed tomography angiography and area stenosis on optical coherence tomography**

**Note:** Receiver operating characteristics curves with cutoff values for predicting the lesions causing ischemia according to diameter stenosis on coronary computed tomography angiography (CTA) and area stenosis on optical coherence tomography (OCT).

5. Impact of qualitative characteristics for predicting the lesions causing ischemia

Incremental risk prediction of qualitative plaque characteristics on coronary CTA and OCT regarding the lesions causing ischemia is presented in **Figure 4**. A model using only OCT-based thrombus (which had highest value of OR in multivariate analysis) gave a global chi-square value of 20.1. The addition of OCT-based plaque rupture improved the power of predicting the lesions causing ischemia of the model (global chi-square 31.5; P<0.001). The power of model was additionally improved by further addition of coronary CTA-based low attenuation plaque (global chi-square 49.7; P<0.001) and OCT-based intimal vasculature (global chi-square 62.2; P<0.001).

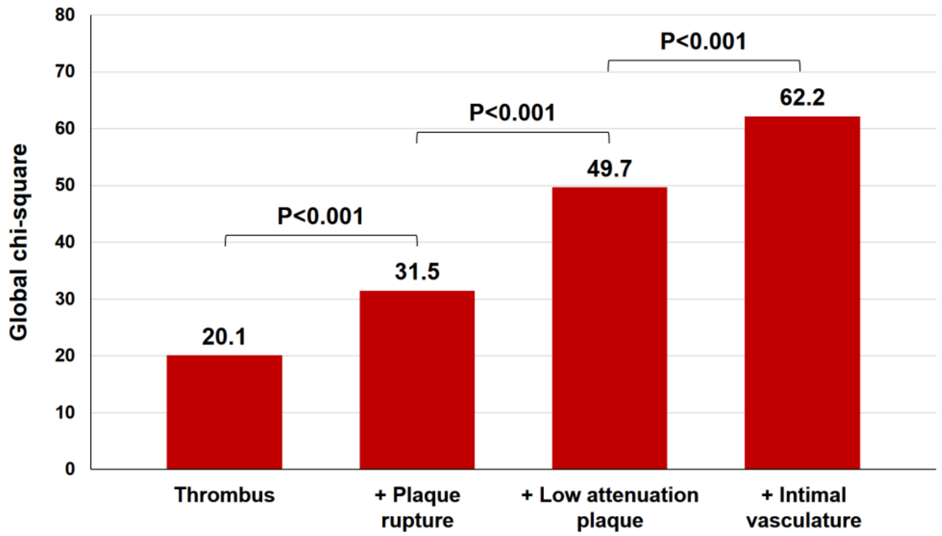


**Figure 4. Incremental predictive value of qualitative characteristics on coronary computed tomography angiography and optical coherence tomography regarding the lesions causing ischemia**

**Note:** Global chi-square values demonstrating incremental risk prediction of qualitative characteristics on coronary computed tomography angiography (CTA) and optical coherence tomography (OCT) regarding the lesions causing ischemia. The addition of plaque rupture (OCT), low attenuation plaque (coronary CTA), intimal vasculature (OCT) resulted in significant incremental improvement in the predictive value beyond thrombus alone (OCT). Thrombus had highest value of odds ratio in multivariate analysis (Table 6).

## IV. DISCUSSION

In this study, predictive value of plaque characteristics assessed by coronary CTA and OCT for identifying the lesions causing ischemia assessed by FFR was investigated and the main findings were as follows: 1) not only quantitative characteristics but also qualitative characteristics on coronary CTA and OCT were different between the lesions causing ischemia versus not causing ischemia; 2) quantitative degree of stenosis on coronary CTA and OCT, as well as qualitative characteristics including low attenuation plaque on coronary CTA and thrombus, intimal vasculature, and plaque rupture on OCT were independent predictors for the lesions causing ischemia; 3) quantitative degree of stenosis on OCT had a trend for higher predictive value for the lesions causing ischemia compared to that of coronary CTA; and 4) increasing number of aforementioned qualitative plaque characteristics provided incremental improvement in predicting the lesions causing ischemia.

Guidelines for the management of coronary artery disease support the use of functional assessment to guide revascularization in patients with intermediate stenosis.[1, 2] While physicians generally prefer using FFR in making decisions for coronary revascularization, intravascular coronary imaging techniques are preferred in the planning of PCI which includes making decisions for the proper size and length of stent as well as the need for adjuvant post-dilation after stent implantation.[7, 11, 21] In addition, OCT with higher resolution than IVUS can provide additional detailed anatomical information for the stenotic lesions such as plaque morphology, thrombus, intimal vasculature, and plaque rupture which have been associated with poor clinical outcomes.[16-20] Therefore, interest as well as demand for evidences regarding the association between FFR-based functional information and OCT-based anatomical information have been growing, since these two methods are difficult to be performed during single procedure.[22, 23] Furthermore, coronary CTA is widely used in clinical practice for evaluating suspected coronary artery disease before being referred for coronary angiography.[13] Therefore, the Integrated Coronary Multicenter Imaging Registry was generated to evaluate the clinical impact of these three methods; FFR, coronary CTA, and OCT, especially in those with intermediate coronary stenosis that require additional confirmation to proceed revascularization procedure.

Association between FFR and anatomical information from coronary CTA was shown in previous studies.[15, 24] Based on the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) study, Lee et al. demonstrated that presence of high-risk plaque characteristics on coronary CTA was associated with lower FFR values.[15] To be specific, minimal lumen area $<4$ $mm^2$, plaque burden $\geq 70\%$, low attenuation plaque, positive remodeling, napkin-ring sign, and spotty calcification were defined as the components of high-risk plaque characteristics on coronary CTA, and the proportion of lesions with $\geq 3$ high-risk plaque characteristics was significantly increased according to the decrease in FFR values.[15] Nakazato et al. also demonstrated that plaque burden and positive remodeling noted on coronary CTA were independent predictors for for the lesions causing ischemia.[24] Similarly, the association between FFR and anatomical information from OCT was also suggested. Based on the Yonsei OCT registry, Lee et al. showed that minimum lumen area and area stenosis on OCT were independent predictors for the lesions causing ischemia.[25] However, different from current study's population, these studies did not focus on the patients with intermediate stenosis, therefore, some of the patients might have not required additional functional or anatomical evaluation for the stenotic lesions.[15, 24, 25] Furthermore, there have been no studies which aggregated the anatomical analysis based on both coronary CTA and OCT, and functional analysis based on FFR for evaluating intermediate stenosis. In current study which focused on intermediate coronary stenosis, not only quantitative degree of stenosis on coronary CTA and OCT, but also qualitative characteristics including low attenuation plaque on coronary CTA and thrombus, intimal vasculature, and plaque rupture on OCT were independent predictors for the lesions causing ischemia.

In current study, quantitative degree of stenosis on OCT had a trend for higher predictive value for the lesions causing ischemia compared to that of coronary CTA. Similar findings were noted in the previous study based on the Integrated Coronary Multicenter Imaging Registry.[23] Computational FFR values were estimated using coronary CTA and OCT images, and correlation between FFR and OCT-based computation FFR were numerically higher than that between FFR and coronary CTA-based computational FFR (r=0.705 versus 0.682).[23] This may be explained by the higher resolution of OCT (10–20 μm) than coronary CTA (600 um).[6, 22, 26] However, recent development in CTA hardware and reconstruction techniques have enabled coronary CTA with ultra-high-resolution and this may narrow the gap between coronary CTA and OCT.[27]

In terms of qualitative analysis, previous studies were insufficient to show the incremental improvement in predicting the lesions causing ischemia by the increasing number of qualitative plaque characteristics on coronary CTA or OCT. According to Nakazato et al., addition of any atherosclerotic plaque characteristics (positive remodeling, low attenuation plaque, and spotty calcification) beyond coronary CTA stenosis and computation FFR, provided incremental risk prediction of the lesions causing ischemia.[24] However, when assessing atherosclerotic plaque characteristics separately, the addition of low attenuation plaque or spotty calcification beyond positive remodeling failed to provide incremental improvement.[24] For the OCT-based qualitative analysis, while the quantitative degree of stenosis on OCT were independent predictors for for the lesions causing ischemia, qualitative characteristics of plaque assessed by OCT failed to independently predict the lesions causing ischemia, and therefore, incremental risk prediction of qualitative plaque characteristics on OCT were not evaluated.[25] To our knowledge, this is the first study to demonstrate the incremental improvement in predicting the lesions causing ischemia by the increasing number of qualitative plaque characteristics using both coronary CTA and OCT. However, qualitative analysis takes more time and effort than quantitative analysis in real world clinical practice. In this regard, machine-learning based algorithm for assessing qualitative plaque characteristics on coronary CTA and OCT may be promising to adopt current study findings into real world clinical practice.[28-30]

This study has several limitations. First, as a retrospective analysis using prospectively enrolled registry database, it has the inherent limitations of the current study design. Second, our study population included those with intermediate coronary stenosis, therefore, selection bias should be considered when interpreting the current study findings. Third, although we have shown the association between FFR and plaque characteristics assessed by OCT and coronary CTA, its impact regarding clinical endpoints such as cardiovascular death or myocardial infarction has not been analyzed. The Integrated Coronary Multicenter Imaging Registry is planned for clinical follow-up up to 10 years and further analysis is expected. Thus, current study should be regarded as a proof-of-concept study and requires further prospective investigations.

## V. CONCLUSION

In conclusion, we demonstrated that both the quantitative and qualitative plaque characteristics assessed by coronary CTA and OCT are closely related to functional assessment of coronary stenosis by FFR. The results from this study suggest that comprehensive anatomical evaluation of coronary stenosis may be able to provide additional supportive information for predicting the lesions causing ischemia.

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ABSTRACT (IN KOREAN)

## 관상동맥 CT 조영술과 광간섭 단층촬영 영상에서 발견되는 플라크 특성을 이용한 허혈성 병변의 예측도 평가

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**배경 및 목적**: 중등도의 관상동맥 폐쇄 병변이 있는 환자들에게 있어 분획혈류예비력 (fractional flow reserve: FFR)을 이용한 기능적 평가 및 광간섭 단층촬영 (optical coherence tomography: OCT)을 이용한 해부학적 평가가 현재 임상에서 광범위하게 사용되고 있다. 또한, 관상동맥 질환이 의심되는 환자들에 있어 관상동맥 조영술 전에 비침습적 검사인 관상동맥 CT 조영술이 널리 사용되고 있다. 본 연구에서는 중등도의 관상동맥 폐쇄 병변이 있는 환자들에게 있어 FFR과 관상동맥 CT 조영술 및 OCT에서 발견되는 플라크 특성 사이의 연관성을 알아보고자 하였다.

**방법**: 본 연구는 전향적, 다기관 레지스트리를 기반으로 하여 총 159명 환자에서 339개의 중등도의 관상동맥 폐쇄 병변을 그 대상으로 하였다. 모든 환자들은 관상동맥 조영술 전에 관상동맥 CT 조영술을 시행하였고, 조영술 시에는 FFR 측정과 OCT 검사를 모두 시행하였다. FFR 값이 0.8이하인 경우를 허혈성 병변으로 정의하였다. 관상동맥 CT 조영술과 OCT에서 발견되는 플라크 특성이 허혈성 병변을 예측하는데 있어 가지는 예측도를 평가하였다.

**결과**: 허혈성 병변과 비허혈성 병변 여부에 따라 관상동맥 CT 조영술과 OCT에서 발견되는 플라크 특성이 서로 상이하였다. 다변량 분석에서 관상동맥 CT 조영술 및 OCT의 양적인 폐쇄 정도가 허혈성 병변을 예측하는데 있어 독립적인 예측인자로서 작용하였으며, OCT가 관상동맥 CT 조영술에 비하여 보다 높은 예측도의 경향성을 보였다. 이와 더불어, 관상동맥 CT 조영술에서의 낮은 감쇠 계수를 가지는 플라크 및 OCT에서의 혈전, 내막 혈관, 그리고 플라크 파열을 포함하는 질적인 특성 또한 허혈성 병변을 예측하는데 있어 독립적인 예측인자로서 작용하였다. 이러한 질적인 특성의 숫자가 증가할수록 허혈성 병변에 대한 예측도가 상승하는 소견을 보였다.

**결론**: 본 연구의 결과를 통해서 관상동맥 폐쇄 병변에 대한 광범위한 해부학적인 평가가 허혈성 병변을 예측하는데 있어서 추가적인 정보를 제공할 수 있음을 확인하였다.

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핵심 되는 말: 관상동맥 플라크, 관상동맥 CT 조영술, 광간섭 단층촬영, 분획혈류예비력