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Validation of Minimal Luminal Area Measured by Intravascular Ultrasound for Assessment of Functionally Significant Coronary Stenosis

Comparison With Myocardial Perfusion Imaging

Jung-Min Ahn, MD,* Soo-Jin Kang, MD, PhD,* Gary S. Mintz, MD,‡
Jun-Hyok Oh, MD,* Won-Jang Kim, MD,* Jong-Young Lee, MD,*
Duk-Woo Park, MD, PhD,* Seung-Whan Lee, MD, PhD,*
Young-Hak Kim, MD, PhD,* Cheol Whan Lee, MD, PhD,*
Seong-Wook Park, MD, PhD,* Dae Hyuk Moon, MD, PhD,†
Seung-Jung Park, MD, PhD*

Seoul, Korea; and New York, New York

Objectives This study sought to evaluate the ability of minimal luminal area (MLA) measured by intravascular ultrasound (IVUS) to assess the functional significance of coronary artery disease.

Background The use of IVUS to determine the functional significance of coronary artery lesions remains a matter for debate.

Methods From our prospective IVUS imaging database, between July 2009 and April 2010, 170 coronary lesions in 150 patients who underwent stress myocardial single-photon emission computed tomography (SPECT) performed within 1 month of IVUS evaluation were identified and analyzed. MLA and other parameters were measured by IVUS and compared with the results of myocardial SPECT.

Results Overall, 45 lesions had positive SPECT, and 125 lesions had negative SPECT. The MLA of lesions with positive SPECT was smaller than the MLA of those with negative SPECT (1.7 $\pm$ 0.5 mm^2 vs. 2.3 $\pm$ 1.1 mm^2, $p < 0.001$). By logistic regression analysis, MLA (odds ratio: 3.1 by decrease of 1 mm^2, 95% confidence interval [CI]: 1.75 to 5.5, $p < 0.01$) was an independent predictor of the positive SPECT. Using receiver-operator characteristic curve analysis, the best cutoff value of MLA was $\leq$2.1 mm^2 with an 86.7% sensitivity, a 50.4% specificity, a 38.6% positive predictive value, and a 91.3% negative predictive value versus lesions with a positive SPECT (area under the curve: 0.690, 95% CI: 0.615 to 0.759, $p < 0.01$).

Conclusions The best cutoff value of MLA measured by IVUS to predict myocardial ischemia was 2.1 mm^2. The IVUS-measured MLA appeared to play a limited role in detecting functionally significant lesions assessed by myocardial SPECT. (J Am Coll Cardiol Intv 2011;4:665–71) © 2011 by the American College of Cardiology Foundation

From the *Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; †Department of Nuclear Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; and the ‡Cardiovascular Research Foundation, New York, New York. The authors have reported that they have no relationships to disclose. Drs. Kang and Ahn contributed equally to this paper.

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Current guidelines recommended noninvasive functional study before performing elective coronary intervention (1,2). Furthermore, a recently published, large randomized trial demonstrated the clinical benefit of coronary stenting based on invasive functional evaluation (3). Intravascular ultrasound (IVUS) has provided valuable information on cross-sectional coronary vascular structure with high spatial resolution and has played a key role in contemporary interventional cardiology (1). There have been attempts to determine the IVUS parameters corresponding to the functional significance of a coronary artery narrowing to integrate target lesion anatomy and physiology. Although several IVUS criteria have been suggested as an equivalent to physiological assessment (4–6), this approach remains controversial (7,8). Therefore, we sought to validate the ability of IVUS measurements, especially minimal luminal area (MLA), to assess the functional significance of coronary artery disease in comparison with the gold standard of myocardial perfusion imaging.

Abbreviations and Acronyms

CI = confidence interval
IVUS = intravascular ultrasound
MLA = minimal luminal area
NPV = negative predictive value
PPV = positive predictive value
QCA = quantitative coronary angiography
SPECT = single-photon emission computed tomography
Tl-201 = thallous chloride

Methods

Study population. From our prospective IVUS imaging database, between July 2009 and April 2010, 283 major epicardial coronary artery stenoses in 255 patients who underwent stress myocardial single-photon emission computed tomography (SPECT) within 1 month of IVUS evaluation were identified. Of these lesions, 2 or more stenoses in 1 coronary vessel (n = 14), bypass graft lesions (n = 18), left main coronary artery disease (n = 41), in-stent restenosis (n = 15), lesions with visible collateral development (n = 1), lesions corresponding to a fixed perfusion defect (n = 9), and undetermined vascular territory (n = 15) on SPECT imaging were excluded. Finally, 170 major epicardial coronary artery stenoses in 150 patients were included in the analysis. This study was approved by the institutional review boards, and all patients provided written informed consent.

Myocardial perfusion imaging. Gated thallous chloride (Tl-201) SPECT images were acquired after adenosine stress testing (post-stress SPECT) and again 4 h after the injection of Tl-201 chloride (redistribution SPECT). Patients abstained from caffeine-containing foods, beverages, and drugs such as aminophylline and theophylline 24 h before the test. Adenosine was intravenously administered at a rate of 140 μg/kg/min for 6 min. Three minutes after the initiation of the adenosine infusion, a dose of Tl-201 (range 92.5 to 148 MBq, determined by the subject's body weight) was injected intravenously. Six min after adenosine infusion, post-stress myocardial perfusion images were acquired with a 2-head gamma camera (Ecam, Siemens, Germany) equipped with low-energy, all-purpose collimators (64 × 64 matrix, 32 projections over 180°, 8 frames per cardiac cycle, 50 s per projection). A zoom factor of 1.78 was used. The pixel size was 5.4 mm. Transaxial slices were reconstructed with a Butterworth filter (order 5; cutoff frequency 0.35). No attenuation or scatter correction was applied. Stress and rest tomographic images were displayed side by side in the short-axis, horizontal long-axis, and vertical long-axis reconstruction planes.

A 16-segment model was used in which myocardial segments were allocated to the territories of different coronary arteries as previously described (9,10). A vascular territory was classified as showing "no perfusion defect" if all segments in the territory had normal quantitative uptake. A vascular territory was considered as having a "perfusion defect" if quantitative tracer uptake in any segment within the vascular territory on the stress image was <75%. Each territory with a perfusion defect was further classified as "reversible" if any of the segments with a stress defect quantitatively improved tracer uptake at rest or "fixed" if segments with a stress defect showed no change or a further decrease in tracer uptake at rest. Accordingly, the result was considered positive when a "reversible perfusion defect" or negative when a "no perfusion defect" was allocated to the perfusion territory of the coronary artery of interest.

IVUS examination and measurement. IVUS imaging was performed after intracoronary administration of 0.2 mg nitroglycerin to prevent vessel spasm using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, Minnesota), consisting of a rotating 40-MHz transducer within a 3.2-F imaging sheath. The decision to perform IVUS was at the operator's discretion. Quantitative IVUS analysis was performed as previously described (11,12) in a core laboratory at the Asan Medical Center using computerized planimetry (EchoPlaque 2.7, Indec Systems, Mountain View, California). Quantitative measurement was done at the most severe stenotic lesion in each coronary vessel. MLA, plaque burden (external elastic membrane minus lumen divided by external elastic membrane), and external elastic membrane area and diameters were measured at the lesion site.

Angiographic analysis. Qualitative coronary angiography (QCA) measurements including percentage diameter stenosis, reference vessel diameter, and minimal luminal diameter were done using standard techniques with automated edge-detection algorithms (CASS-5, Pie-Medical, Maastricht, the Netherlands) in the angiographic analysis center of the Cardiovascular Research Foundation (Seoul, Korea) (13). Angiographic image acquisition was performed at target sites using ≥2 angiographic projections of the coronary narrowing.

Statistics analysis. Data were analyzed on a per-patient and per-lesion basis for the corresponding calculations. Contin-

Table 1. Demographic and Clinical Characteristics (n = 150)

Age, yrs	62.5 ± 9.8
Male/female	109/41
Hypertension	98 (65.3)
Hyperlipidemia	101 (67.3)
Diabetes	44 (29.3)
Smoking	33 (22.0)
Previous history of PCI	11 (7.3)
Number of diseased vessels	
1	74 (43.5)
2	65 (38.2)
3	31 (18.2)
Clinical manifestation	
Stable angina	133 (88.7)
Unstable angina	11 (7.3)
Acute myocardial infarction	6 (4.0)
Vessel investigated, n = 170	
Left anterior descending artery	111 (65.3)
Left circumflex artery	20 (11.8)
Right coronary artery	39 (22.9)

Values are mean ± SD or n (%).
PCI = percutaneous coronary intervention.

uous variables are presented as mean ± SD and were compared with Student *t* test. Categorical variables are presented as counts or percentages. Receiver-operator characteristic curve analyses were performed to assess the discriminate power of the IVUS and QCA parameters using MedCalc (MedCalc Software, Mariakerke, Belgium) to define sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals (CIs). The best cutoff values of IVUS and QCA parameters to determine positive SPECT were identified as the values with the highest sum of sensitivity and specificity. Furthermore, the kappa statistic was used to evaluate the agreement of functional significance between IVUS or QCA cutoff values and the results of myocardial SPECT. Multivariate logistic regression analysis was also performed to determine the independent predictors of positive SPECT. The IVUS and QCA parameters such as MLA, plaque burden, minimal lumen diameter, diameter stenosis, vessel size, and lesion length were entered into the multivariate model and backward stepping was used to determine the independent predictors. A p value <0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the study population were summarized in Table 1. Patient age was 62.5 ± 9.8 years. Approximately 30% of patients had diabetes mellitus. Stable angina was the most frequent indication for coronary angiogram. One-, two-, and three-vessel coronary artery disease was present in 43.5%, 38.2%, and 18.2% of study patients, respectively. The left anterior descending artery was the most frequently investigated vessel.

In total, 45 lesions had positive SPECT, and 125 lesions had negative SPECT. IVUS and QCA measurements are summarized in Table 2. Between lesions with positive versus negative SPECT, reference vessel diameter was almost identical. However, MLA and minimal luminal diameter were smaller in lesions with positive SPECT. In addition, diameter stenosis, vessel size, and plaque burden were larger. The lesion length tended to be longer in lesions with positive SPECT but did not reach the statistical significance.

Using receiver-operator characteristic curve analysis, the best cutoff value of IVUS MLA to predict positive SPECT was ≤ 2.1 mm^2, with an 86.7% sensitivity, a 50.4% specificity, a 38.6% PPV, and a 91.3% NPV in predicting the lesions with positive SPECT (Fig. 1). The kappa value was 0.27, indicating poor agreement between myocardial SPECT and IVUS-measured MLA at the best determined

Table 2. Angiographic and Intravascular Ultrasound Parameters

		Myocardial SPECT		
	All (n = 170)	Positive (n = 45)	Negative (n = 125)	p Value
QCA parameters				
Reference vessel diameter, mm	3.3 ± 0.6	3.3 ± 0.5	3.3 ± 0.6	0.892
Minimal luminal diameter, mm	1.5 ± 0.4	1.3 ± 0.4	1.5 ± 0.4	0.002
Percentage of diameter stenosis	55.3 ± 10.7	60.3 ± 10.6	53.5 ± 10.2	<0.001
Lesion length, mm	21.2 ± 11.1	23.7 ± 11.9	20.4 ± 10.8	0.091
IVUS parameters				
Minimal luminal area, mm^2	2.1 ± 1.0	1.7 ± 0.5	2.3 ± 1.1	<0.001
Lesion vessel area, mm^2	11.8 ± 4.4	12.9 ± 4.0	11.4 ± 4.4	0.059
Lesion vessel diameter, mm	3.8 ± 0.7	4.0 ± 0.7	3.8 ± 0.7	0.06
Plaque burden, %	79.8 ± 10.6	85.5 ± 6.9	77.7 ± 11.0	<0.001

Values are mean ± SD.
IVUS = intravascular ultrasound; QCA = quantitative coronary angiography.

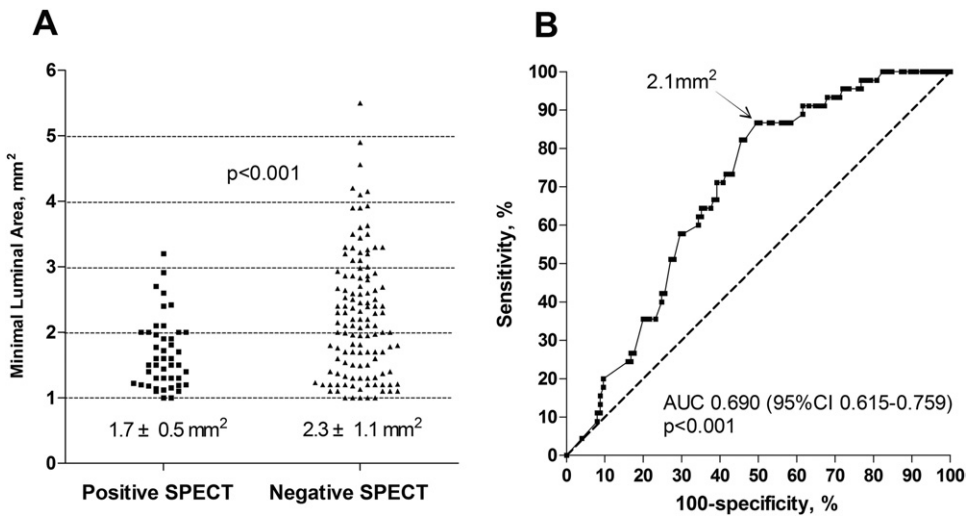

Figure 1. SPECT Versus IVUS Measured MLA in All Lesions

Scatterplot **(A)** and receiver-operator characteristic curve **(B)** of single-photon emission computed tomography (SPECT) versus intravascular ultrasound (IVUS)-measured minimal luminal area (MLA) in all lesions. AUC = area under the curve; CI = confidence interval.

cutoff value. Diagnostic performance of other IVUS and QCA parameters to detect a functionally significant coronary stenosis assessed by myocardial SPECT are summarized in Table 3.

When the receiver-operator characteristic curve analysis was repeated in 73 lesions with single-vessel disease, the area under the curve was 0.740 (95% CI: 0.625 to 0.834, $p < 0.001$); and the best cutoff value was ≤ 2.1 mm^2 with sensitivity of 91.6%, specificity of 64.0%, PPV of 55.0%, and NPV of 94.1%. By contrast, in 96 lesions with multivessel disease, the area under the curve was 0.657 (95% CI: 0.554 to 0.751, $p = 0.014$); and the best cutoff value was ≤ 1.6 mm^2 with sensitivity of 66.7%, specificity of 69.3%, PPV of 37.8%, and NPV of 88.1%.

In addition, a subanalysis was performed according to reference vessel diameter. In 121 lesions of reference vessel diameter >3 mm, the best cutoff value of IVUS-measured MLA was ≤ 2.1 mm^2. However, in 49 lesions of reference vessel diameter ≤ 3 mm, IVUS-measured MLA lost its discriminatory power to predict an abnormal myocardial SPECT (area under the curve: 0.586, $p = 0.942$). A further subanalysis is summarized in Table 4.

By multivariate logistic regression analysis, the independent determinant of positive SPECT among the IVUS and QCA parameters was an IVUS-measured MLA (odds ratio: 3.1 by decrease of 1 mm^2, 95% CI: 1.75 to 5.5, $p < 0.01$).

Discussion

Decisions regarding coronary intervention should be based on objective evidence of functional significance of coronary artery narrowing. Even in the drug-eluting stent era, every coronary intervention carries the risk of procedural-associated complications, late stent thrombosis, and restenosis (14). Fur-

Table 3. Diagnostic Performance of IVUS and QCA Parameters to Detect a Functionally Significant Stenosis Evaluated by Myocardial SPECT

	AUC*	p Value	BCV	Sensitivity	Specificity	PPV	NPV	Kappa
QCA parameters								
MLD, mm	0.670 (0.594–0.740)	<0.001	≤1.26	57.8 (42.2, 72.3)	76.8 (68.4, 83.9)	47.3 (33.5, 61.3)	83.5 (75.4, 89.7)	0.32
DS, %	0.692 (0.617–0.761)	<0.001	>58.2	62.2 (46.5, 76.2)	70.4 (61.6, 78.2)	43.1 (30.8, 56.0)	83.8 (75.3, 90.3)	0.28
LL, mm	0.582 (0.504–0.658)	0.12	>26.2	43.2 (28.3, 59.0)	79.2 (71.0, 85.9)	42.2 (27.5, 58.0)	79.8 (71.7, 86.5)	0.21
IVUS parameters								
MLA, mm^2	0.690 (0.615–0.759)	<0.001	≤2.1	86.7 (73.2, 94.9)	50.4 (41.3, 59.5)	38.6 (29.1, 48.8)	91.3 (81.9, 96.8)	0.27
PB, %	0.730 (0.656–0.795)	<0.001	>83.4	73.3 (58.1, 85.4)	64.8 (55.8, 73.1)	42.9 (31.6, 54.7)	87.1 (78.5, 93.2)	0.31

*95% confidence interval.

AUC = area under the curve; BCV = best cutoff value; DS = diameter stenosis; LL = lesion length; MLA = minimal luminal area; MLD = minimal luminal diameter; NPV = negative predictive value; PB = plaque burden; PPV = positive predictive value; SPECT = single-photon emission computed tomography; other abbreviations as in Table 2.

Table 4. Diagnostic Performance of IVUS Measured MLA to Detect a Functionally Significant Stenosis Evaluated by Myocardial SPECT According to the Important Subgroups

	AUC*	p Value	BCV	Sensitivity	Specificity	PPV	NPV	Kappa
RVD								
>3 mm (n = 121)	0.729 (0.641–0.806)	<0.001	≤2.1	87.8 (71.8, 96.6)	56.8 (45.8, 67.3)	43.3 (31.1, 56.1)	92.6 (82.1, 97.9)	0.338
≤3 mm (n = 49)	0.586 (0.436–0.724)	0.942	≤2.0	83.3 (51.6, 97.9)	40.5 (24.8, 57.9)	31.2 (16.1, 50.0)	88.2 (62.6, 96.6)	0.153
Lesion length								
>26.2 mm (n = 45)	0.683 (0.528–0.814)	0.025	≤1.96	84.2 (60.4, 96.6)	50.0 (29.9, 70.1)	55.2 (35.3, 73.9)	81.2 (53.3, 96.2)	0.319
≤26.2 mm (n = 125)	0.676 (0.586–0.757)	<0.001	≤2.0	80.8 (60.6, 93.4)	57.6 (47.2, 67.5)	33.3 (21.9, 46.5)	91.9 (82.1, 97.4)	0.251
Vascular extent								
SVD (n = 74)	0.740 (0.625–0.835)	<0.001	≤2.1	91.7 (73.0, 99.0)	64.0 (49.2, 77.1)	55.0 (38.5, 70.7)	94.1 (80.3, 99.3)	0.474
MVD (n = 96)	0.657 (0.554–0.751)	0.014	≤1.6	66.7 (43.0, 85.4)	69.3 (57.6, 79.5)	37.8 (22.3, 55.5)	88.1 (77.1, 95.1)	0.283
Lesion location								
LAD (n = 111)	0.703 (0.608–0.786)	<0.001	≤2.1	90.3 (74.2, 98.0)	52.5 (41.0, 63.8)	42.4 (30.2, 55.3)	93.3 (81.7, 98.6)	0.318
Non-LAD (n = 59)	0.669 (0.534–0.786)	0.040	≤1.5	64.3 (35.1, 87.2)	73.3 (58.1, 85.4)	42.9 (21.8, 66.0)	86.8 (71.9, 95.6)	0.321

*95% confidence interval.
LAD = left anterior descending coronary artery; MVD = multivessel disease; RVD = relative vessel diameter; SVD = single vessel disease; other abbreviations as in Tables 2 and 3.

thermore, noninvasive or invasive functional studies triage patients who benefit most from coronary intervention (15,16). Therefore, current guidelines highlight the functional evaluation of a target coronary lesion before elective intervention (2). However, noninvasive functional study is not always performed before coronary intervention (17). In addition, an intraprocedural invasive functional study increases time and cost. Therefore, to identify the functional threshold of IVUS measurements that predict ischemia would be of value, especially in patients undergoing IVUS-guided stent implantation.

The current study comparing IVUS-measured MLA with the results of myocardial SPECT showed that the best cutoff value was an MLA ≤2.1 mm^2 to discriminate functionally significant coronary artery disease. Several previous studies demonstrated a correlation between anatomic data obtained from IVUS and functional severity assessed by myocardial perfusion SPECT, coronary flow reserve, and fractional flow reserve (4–6,18). Most of these reports suggested that the optimal threshold of MLA was <4 mm^2 to detect a functionally significant coronary artery narrowing. However, MLA of 4 mm^2 theoretically yields <50% diameter stenosis in the usually treated coronary vessel with diameters ranged between 2 and 4 mm. Therefore, it might not have a critical effect on blood flow (7,19). In addition, previous studies enrolled coronary lesions with relatively mild stenoses and larger vessel diameters that likely increased the MLA cutoff value to 4.0 mm^2. In the current study, evaluated lesions were enrolled from a "real-world" prospective IVUS cohort and, therefore, had a smaller MLA cutoff than other previous studies (4–6,18).

The PPV of the current IVUS MLA criteria was too low for clinical decision making. In addition, the agreement of the result between IVUS MLA criteria and myocardial SPECT was poor, considering the kappa statistic of 0.27. A low PPV was also consistently observed in the other anatomical QCA or IVUS parameters that were measured in the current study. Although IVUS MLA is an important factor to determine the coronary blood flow, other anatomical factors measured by QCA or IVUS also act as the resistance to the flow. Therefore, a single parameter such as IVUS MLA may have limitations for predicting the result of myocardial SPECT.

In coronary vessels of reference vessel diameter <3 mm in the current study, IVUS-measured MLA lost its predictive power to discriminate the results of myocardial SPECT. This finding was consistent with a previous report comparing IVUS MLA and fractional flow reserve in vessels with a diameter of <2.8 mm (20).

In the current study, the IVUS MLA cutoff value had a >90% NPV. Therefore, IVUS criteria may be useful in the deferral of coronary intervention because it showed a high NPV for functional significance. A previous study evaluated 300 patients with 357 de novo intermediate native coronary lesions and confirmed the clinical usefulness of IVUS when intervention was deferred based on MLA >4 mm^2, with event rate of 4.4% and target lesion revascularization rate of 2.8% during a mean follow-up of 13 months (21). A similar strategy to defer treatment according to the MLA was also reported in the setting of left main coronary artery disease with favorable clinical outcomes (22).

Theoretically, the lesion length of coronary stenosis is another important physiological factor to determine the resistance to the coronary blood flow (18,23). However, in the current study, the influence of lesion length on the result of myocardial SPECT was less obvious. In addition, separate analysis for the IVUS-measured MLA according the lesion length cutoff value of 26.2 mm found no significant change of best cutoff value for the IVUS-measured MLA. Relatively longer lesion distribution of the current study may attenuate the impact of lesion length. In addition,

considering the diffuse nature of human coronary atherosclerosis (24), QCA lesion length could not reflect the true physiological or anatomic lesion length. This might be another contributing factor for the lack of lesion length impact on myocardial perfusion.

Study limitations. First, myocardial SPECT served as a gold standard, but it also has its own limitations to detect functional significance of coronary artery disease, particularly in the setting of multivessel disease (25). Indeed, the number of patients with multivessel disease accounted for 56% of the current study population. However, inclusion and exclusion of the lesions in the setting of multivessel disease had no impact on the overall cutoff value of IVUS MLA. By contrast, IVUS MLA cutoff value in the setting of multivessel disease decreased, which might be partly because of the lower sensitivity of myocardial SPECT to detect significant coronary stenosis in the presence of multivessel diseases. Second, although all the myocardial SPECT were analyzed by an independent, experienced nuclear physician, the region allocation between IVUS and myocardial SPECT was performed under the information of actual coronary distribution gathered by coronary angiography. As outlined previously, the lesions with undetermined territory were excluded in analysis. Third, to reduce the confounding in assessment of the relationship between IVUS-measured lesion anatomy and the result of myocardial SPECT, in-stent restenosis lesions, multiple stenotic lesions, and lesions with collateral vessels or fixed perfusion defect on myocardial SPECT were excluded. Fourth, the current cohort accounted for just 15% of IVUS-evaluated lesions during the study period. Finally, as all patients enrolled in the analysis were Asians, small body and vessel size may cause smaller MLA cutoff values than other previous studies in Western populations.

Conclusions

In the current study, we suggested a measured lesion MLA of 2.1 mm^2 as a practical IVUS criteria corresponding to functionally significant coronary artery disease. However, the low PPV limits its role in clinical decision making. Therefore, complementary functional studies are necessary for the accurate evaluation of functional significance of target lesions in real-world practice settings before or during coronary intervention.

Reprint requests and correspondence: Dr. Seung-Jung Park, Department of Cardiology, University of Ulsan College of Medicine, Heart Institute, Asan Medical Center, 86 Asanbyeongwon-gil, Songpa-gu, Seoul 138–736, Korea. E-mail: sjpark@amc.seoul.kr.

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