**FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study**

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**Objectives**
The FIRST (Fractional Flow Reserve and Intravascular Ultrasound Relationship Study) aimed to determine the optimal minimum lumen area (MLA) by intravascular ultrasound (IVUS) that correlates with fractional flow reserve (FFR) and to assess the correlation between virtual histology IVUS and FFR for intermediate coronary lesions.

**Background**
FFR is considered the gold standard for assessing intermediate coronary lesions. Measurements of ≤0.8 are considered clinically significant and indicative of physiological ischemia.

**Methods**
The FIRST is a multicenter, prospective, international registry of patients with intermediate coronary lesions, defined as 40% to 80% stenosis by angiography. In total, 350 patients (367 lesions) were enrolled at 10 U.S. and European sites. Patients were followed through hospital discharge.

**Results**
Overall, an MLA < 3.07 mm² (64.0% sensitivity, 64.9% specificity, area under curve [AUC] = 0.65) was the best threshold value for identifying FFR < 0.8. The accuracy improved when reference vessel-specific analyses were performed. An MLA < 2.4 mm² (AUC = 0.66) was best for reference vessel diameters < 3.0 mm, an MLA < 2.7 mm² (AUC = 0.71) for reference vessel diameters of 3.0 to 3.5 mm; and an MLA < 3.6 mm² (AUC = 0.68) for reference vessel diameters > 3.5 mm. FFR correlated with plaque burden (r = −0.220, p < 0.001) but not with other plaque morphology.

**Conclusions**
Anatomic measurements by IVUS show a moderate correlation with the FFR values. The optimal cutoff for an MLA to FFR < 0.8 is vessel dependent. Plaque morphology characteristics do not correlate with FFR. The utility of IVUS MLA as an alternative to FFR to guide intervention in intermediate lesions may be limited in accuracy and should be tested clinically. (Fractional Flow Reserve and Intravascular Ultrasound Relationship Study [FIRST]; NCT01153555) (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation
ischemia has only been reported in retrospective analyses and is in question (5–8).

To date, available data regarding the relationship between anatomic IVUS parameters and functional FFR results have been from retrospective data analyses and are variable. Additionally, the optimal minimal lumen area (MLA) cutoff value by IVUS for FFR < 0.80 has not been well established (9–12). The traditional cutoff has been 4.0 mm² MLA; however, recent publications have deemed this cutoff to be too generous. Several studies reported different MLA cutoffs for different vessel diameters (9–12). However, these series were all retrospective, and the majority had small sample sizes and did not include correlation of plaque morphology or plaque burden with FFR. To date, the optimal cutoff for IVUS MLA to best correlate with FFR < 0.8 has yet to be determined, as is the question of whether IVUS MLA can be a reliable alternative to FFR in determining the functional status of intermediate lesions.

The FIRST (Fractional Flow Reserve and Intravascular Ultrasound Relationship Study) was designed to determine the correlation between FFR, IVUS, and virtual histology (VH) IVUS in a multinational, multicenter, prospective registry of a large patient cohort with intermediate coronary stenosis and to integrate the anatomic IVUS criteria and VH and plaque burden parameters that correlate with ischemic FFR.

Methods

Study design, population, and endpoints. The FIRST was designed as a multicenter, prospective registry of patients who underwent elective coronary angiography and had intermediate coronary stenosis defined as stenosis of 40% to 80% by visual estimation at 1 or more major epicardial coronary arteries. From July 2010 to December 2011, 350 patients (367 intermediate lesions) were assessed by QCA, IVUS gray scale, and VH IVUS, and FFR. Exclusions included patients with myocardial infarction within 72 h, saphenous vein graft lesions, with lesions in vessels with < 2.5-mm reference vessel diameter (RVD), or with > 1 lesion in the studied vessel. Written informed consent for all procedures was obtained from each patient. Additional clinical data regarding medical history, particularly cardiac risk factors and left ventricular function, were also collected.

QCA analysis. QCA analysis was performed by an independent technician blinded to the results of both IVUS and FFR. A computer-assisted, automatic contour detection technique (CAAS 5.9.2 Quantitative Coronary Angiography for Research, Pie Medical Imaging BV, Maastricht, the Netherlands) was used. The outer diameter of the contrast-filled catheter served as the calibration standard. After selection of the optimal projection displaying the most severe stenosis, the percentage of diameter stenosis at end-diastole, minimal lumen diameter, RVD, and lesion length were measured. Lesion length was calculated as the distance between the proximal and distal reference in the projection demonstrating the stenosis with the least foreshortening.

IVUS analysis. IVUS/VH IVUS studies were performed using the Volcano Corporate Eagle Eye Platinum IVUS catheter (San Diego, California), which incorporates a phased array immobile set of crystals arranged circularly around the catheter and was activated sequentially at 20 MHz. All IVUS/VH images were recorded after the administration of 150 to 200 µg intracoronary nitroglycerin. The transducer was pulled back from the distal coronary artery through the target stenosis and to the proximal portion at 0.5 or 1.0 mm/s. Images were recorded on DVDs for analysis by an independent core laboratory. Quantitative analysis of the IVUS gray-scale images was performed by a skilled interpreter using computerized planimetry with Volcano Imaging Software 3.0.422 (Volcano Corporation), and the VH IVUS images were analyzed using Echoplaque 4.0.17 (INDEC Systems, Inc., Mountain View, California). Lumen cross sections were measured at the most stenotic site with the smallest lumen. Data were analyzed on various IVUS parameters including, but not limited to, the minimal lumen diameter, MLA, lesion length, area stenosis, and elastic membrane area. The area stenosis was calculated as the reference lumen area minus the MLA divided by reference lumen area. Gray-scale IVUS and VH IVUS data were collected to define plaque composition, including the percentage of necrotic core, dense calcium, and plaque-type presence. The definition of thin cap fibroatheroma (TCFA) was a confluent necrotic core > 10% of the total plaque, no evidence of fibrotic plaque in direct contact with the lumen, with dense calcium > 5% and plaque burden > 40%.

FFR analysis. To assess FFR, a 0.014-inch pressure guide wire (Volcano Corporation or Radi Medical System, Uppsala, Sweden) was deployed. Distal pressure was measured immediately distal to the distal edge of the stenosis during a period of maximum hyperemia induced by intravenous adenosine (140 µg/kg/min for the right coronary artery and 180 µg/kg/min for the left coronary artery). Aortic pressure was measured through the guiding catheter (6 or 7 French). FFR was calculated as the ratio of the coronary pressure distal to the lesion measured by the pressure wire to the mean aortic pressure measured by the guiding catheter.

Based on the results of these 3 methods, the analyses correlated the IVUS and QCA parameters with FFR.
Continuous variables are expressed as mean ± SD or n (%). Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). Results. Percutaneous coronary intervention (PCI) was not mandatory and was left to the operator’s discretion.

**Statistical analysis.** Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). Continuous variables are expressed as mean ± SD and categorical variables as frequency and percentage. The relationship and variability between FFR and IVUS or QCA parameters were analyzed by Pearson correlation analysis to define correlation coefficients between FFR and IVUS or QCA index of lesion severity. Area stenosis was calculated by comparing the distal and proximal lumen areas with that of the lesion MLA. Logistic regression and receive-operating characteristic (ROC) curve analyses were performed to establish the value of IVUS indexes most predictive of FFR <0.8. Specifically, the optimal cutoff values were calculated as the minimal distance from point (0,1) to the ROC curve. Multivariable analysis was performed to identify independent correlates of FFR <0.8 with logistic regression.

**Results**

A total of 367 intermediate coronary lesions were analyzed in 350 patients. The baseline clinical characteristics and lesion-specific characteristics are presented in Tables 1 and 2. The mean age of the patients was 61.4 ± 10.9 years; 260 (74.3%) patients were male. Of the 367 lesions, 210 (57.2%) were located in the left anterior descending artery territory. In 100 (27.2%) stenoses, FFR was <0.8.

The relationship of FFR with the IVUS parameter of MLA was compared graphically in a scatterplot detailed in Figures 1A through 1D. There was a moderate correlation between FFR and MLA overall, with variable correlation given to the RVD. For the lesions located in the lower right quadrant of Figure 1A (lesions with FFR <0.8 and MLA >3.07), 67.7% of lesions (21/31) underwent PCI. For the 10 lesions that did not undergo PCI, the median MLA was 4.45 mm² with a median FFR of 0.77. The breakdown by RVD demonstrated an improvement in correlation between MLA and FFR with the increase in vessel diameter. The weakest correlation was for RVDs of 2.5 to 3.0 mm (r = 0.22, p = 0.003) with a gradual increase in correlation with 3.0 to 3.5 mm and slightly more with >3.5-mm vessels (r = 0.27, p = 0.01 and r = 0.34, p = 0.007, respectively). There was a difference in correlation between lesions with a thin-capped fibroatheroma (TCFA) or calcified TCFA (CaTCFA) versus none (r = 0.25, p = 0.01 and r = 0.32, p < 0.0001). Interestingly, there was a stronger correlation between MLA and FFR in those lesions without the presence of a TCFA or CaTCFA. This analysis is limited,
however, because the resolution for the VH-IVUS may not account for the identification of TCFA <200 μm.

ROC analysis was conducted to identify MLA by IVUS with the best discriminatory value for identifying FFR <0.8. Overall, an MLA <3.07 mm² (64.0% sensitivity, 64.9% specificity, area under curve [AUC] = 0.65) was the best threshold value for identifying FFR <0.8. For the reference vessel breakdown, an MLA <2.4 mm² (AUC = 0.66) was the best threshold value in lesions with RVDs <3.0 mm, an MLA <2.7 mm² (AUC = 0.71) in lesions with RVDs of 3.0 to 3.5 mm, and an MLA <3.6 mm² (AUC = 0.68) in lesions with RVDs >3.5 mm (Fig. 2).

Given the optimal cutoff values for MLA to FFR >0.8, the false-positive rate in the overall population was 25.7%. The rate was 24.0% for the vessels <3.0 mm and slightly better for vessels 3.0 to 3.5 mm and >3.5 mm given their cutoff values of 18.5% and 22.6%, respectively. The false-negative rate, given the same cutoff values, was 9.6% for the overall population of lesions and ranged from 9.7% to 10.9% for the RVD breakdown. ROC analysis was also performed for TCFA or CaTCFA and no TCFA or CaTCFA with (AUC = 0.62 and 0.65, respectively).

The VH IVUS findings by FFR are shown in Table 3. The mean overall plaque burden was 68.7 ± 11.2% and was the only VH IVUS variable that correlated with FFR <0.8. Plaque burden was higher in FFR <0.8 than in FFR ≥0.8 with values of 72.1 ± 8.7 versus 67.4 ± 11.7, p < 0.001.

Of the 367 intermediate stenoses in this registry, 37.1% underwent PCI with a mean MLA of 3.01 mm² and FFR of 0.78. For lesions that did not undergo PCI, the mean MLA was 3.91 mm² and the FFR was 0.88 (Figs. 3A and B). For lesions undergoing PCI, there was a total of 55 (45%) lesions that had an FFR of ≥0.8, of which only 20 lesions with an MLA >3.067 mm², and only a further 7 (5.7%) b lesions also had an MLA >4 mm². For the lesions that did not undergo PCI, 19 lesions had an FFR <0.8, whereas only 8 had an MLA <4 mm² and 6 had an MLA <3.067 mm².

Multivariable logistic regression analysis demonstrated MLA by IVUS, diameter stenosis by QCA, and left anterior descending coronary artery lesions (compared with right coronary artery lesions) as being the strongest independent correlates for an FFR value <0.8 (Table 4).

**Discussion**

The FIRST is the first prospective, multinational, multicenter registry to examine the correlation of anatomic IVUS...
and VH IVUS criteria with physiological FFR values to determine the significance of intermediate coronary lesions. The main finding of the study suggests that the correlation is modest and varied depending on the vessel size, with increasing correlations in larger vessel diameters. Additionally, the optimal cutoff value for an MLA correlated with an FFR of \( \leq 0.8 \) also varies with vessel diameter and increases with RVD; the accuracy of these cutoff values increase with vessel diameter. This registry also evaluated VH IVUS parameters in correlation with FFR and identified only plaque burden as having any correlation with the FFR value. Lesions without CaTCFA or TCFA had better correlation with FFR compared with lesions with CaTCFA or TCFA. Although angiography has failed to detect functionally significant intermediate lesions, FFR is considered the gold standard for detecting the physiological significance of intermediate lesions based on numerous clinical trials (3,13).

Currently, FFR is used in routine clinical practice as a diagnostic test to determine whether intervention should be performed in those lesions. Over the years, the use of IVUS has been established to assess lesion and plaque morphology and has been proven to optimize stent implantation with the potential to reduce the rates of subacute stent thrombosis (14–16). The attempt to use the anatomic findings to

![Figure 2](image1)

**Figure 2** Diagnostic Accuracy of IVUS MLA in the Prediction of Functionally Significant Stenosis Overall and by RVD

Diagnostic accuracy of intravascular ultrasound (IVUS) MLA in the prediction of functionally significant stenosis overall and by RVD. Diagnostic sensitivity, specificity, positive predictive value (ppv), and negative predictive value (npv) of IVUS MLA in the prediction of functionally significant stenosis overall and by RVD breakdown of \(< 3.0 \text{ mm}, 3.0 \text{ to } 3.5 \text{ mm}, \text{ and } > 3.5 \text{ mm.}

<table>
<thead>
<tr>
<th>VH IVUS Variable</th>
<th>Overall (N = 343)</th>
<th>FFR &lt;0.8 (n = 92)</th>
<th>FFR ≥0.8 (n = 251)</th>
<th>r* Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque burden, %</td>
<td>68.7 ± 11.2</td>
<td>72.1 ± 8.7</td>
<td>67.4 ± 11.7</td>
<td>-0.220</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plaque area, mm</td>
<td>8.8 ± 3.8</td>
<td>8.8 ± 3.7</td>
<td>8.8 ± 3.9</td>
<td>0.028</td>
<td>0.903</td>
</tr>
<tr>
<td>Necrotic core tissue, %</td>
<td>21.7 ± 9.3</td>
<td>21.9 ± 7.9</td>
<td>21.7 ± 9.9</td>
<td>-0.037</td>
<td>0.809</td>
</tr>
<tr>
<td>Necrotic core tissue, mm²</td>
<td>1.4 ± 0.6</td>
<td>1.4 ± 0.9</td>
<td>1.4 ± 1.0</td>
<td>0.002</td>
<td>0.676</td>
</tr>
<tr>
<td>Fibrofatty tissue, %</td>
<td>13.1 ± 9.3</td>
<td>13.3 ± 8.1</td>
<td>13.0 ± 9.7</td>
<td>0.006</td>
<td>0.787</td>
</tr>
<tr>
<td>Fibrofatty tissue, mm²</td>
<td>0.9 ± 0.9</td>
<td>0.9 ± 0.8</td>
<td>0.9 ± 0.9</td>
<td>-0.015</td>
<td>0.861</td>
</tr>
<tr>
<td>Fibrous tissue, %</td>
<td>52.5 ± 15.6</td>
<td>54.3 ± 12.6</td>
<td>51.8 ± 16.5</td>
<td>-0.020</td>
<td>0.205</td>
</tr>
<tr>
<td>Fibrous tissue, mm²</td>
<td>3.2 ± 2.0</td>
<td>3.3 ± 1.8</td>
<td>3.2 ± 2.0</td>
<td>0.011</td>
<td>0.723</td>
</tr>
<tr>
<td>Dense calcium, %</td>
<td>11.1 ± 10.7</td>
<td>10.5 ± 8.1</td>
<td>11.4 ± 11.5</td>
<td>-0.008</td>
<td>0.469</td>
</tr>
<tr>
<td>Dense calcium, mm²</td>
<td>0.7 ± 0.7</td>
<td>0.7 ± 0.7</td>
<td>0.7 ± 0.7</td>
<td>0.013</td>
<td>0.992</td>
</tr>
</tbody>
</table>

*r* value of correlation with FFR.

VH, virtual histology; FFR, fractional flow reserve.
determine the functional significance of intermediate lesions was first reported in 1999, and an MLA of <4 mm² was suggested as the cutoff threshold for intervention (7).

Over the past 2 years, numerous publications have challenged the use of IVUS MLA criteria to identify those intermediate lesions that are ischemic. Recent retrospective analyses of patients who underwent both IVUS and FFR for these intermediate lesions have suggested a weak correlation between the 2 modalities, with an IVUS MLA cutoff ranging from 2.5 mm² to 3.6 mm² for an FFR <0.8. Vessel size and lesion location, which affect the amount of myocardium subjected to ischemia, were also taken into consideration. As a result, different cutoffs for IVUS MLA were suggested for large vessels, such as an unprotected left main or proximal left anterior descending coronary artery, and small vessels, such as distal lesions involving small areas of myocardium.

Previous publications by Ben-Dor et al. (10,11), Kang et al. (12), and Koo et al. (13) reported different accuracies of and correlation with FFR for these vessel size/location–dependent cutoff values for IVUS MLA. However, these studies were retrospective with relatively small patient cohorts. These studies did not take into account the potential impact of plaque morphology. Additionally, these studies did not include either IVUS or QCA core laboratories, and there were various protocols for administering adenosine to induce hyperemia, both intracoronary and peripheral. The FIRST was designed to overcome these limitations by incorporating a unified methodology for IVUS and FFR. Both QCA and IVUS/VH analyses were performed by independent core laboratories. In the FIRST, the cutoff for the entire cohort was <0.8 and 3.07 mm² for the IVUS MLA with a sensitivity of 64.0% and specificity of 64.9%. The correlation and accuracy increased in larger vessel sizes. However, this cutoff varied from 2.7 mm² for vessels 2.5 to 3.0 to 3.2 mm in diameter up to 3.7 mm² for vessels >3.5 mm in diameter. Therefore, we propose the use of different cutoffs of IVUS MLA based on the measured RVD.

Interestingly, plaque morphology did not correlate with FFR values and most likely will not contribute to determining the level of ischemia generated by the lesion. Plaque burden was greater in patients with an FFR <0.80; however, this was expected and can be explained by its contribution to the decrease in lumen diameter and smaller IVUS MLA.

Given the modest correlation of IVUS MLA with FFR and the variability in cutoffs, the key question is whether IVUS-derived indexes should be used to guide intervention versus deferral of intermediate lesions. If anatomically feasible, IVUS could be used to guide the decision pathway regarding the need for PCI of intermediate lesions, in addition to lesion assessment, stent and selection optimization, and stent deployment. The FIRST and previous publications, however, suggest that the accuracy in detecting functional intermediate lesions with IVUS MLA is not optimal and is only ~70%.

FFR also has accuracy issues, especially in patients with ischemia and myocardial dysfunction (17,18). Given the limitations of both modalities, the operator should use these tools only to support his or her clinical judgment. As seen in the FIRST and in previous studies, it is rare to find FFR <0.8 with an MLA >4.0 mm². In the case of stable patients with false-negative FFR, medical therapy will most likely be adequate. The use of IVUS MLA would likely be associated with more false-positive outcomes than FFR and would overestimate the severity of the lesions, which could result in increased stent use that would be avoided if the lesion were assessed by FFR. A study comparing FFR with IVUS based on an IVUS MLA cutoff of 4.0 mm² performed in 167 patients with 1-year follow-up had similar and favorable outcomes irrespective of the guiding strategy; however, the FFR-guided lesion assessment reduced the need for revascularization for many lesions compared with the IVUS-guided strategy (19).

Therefore, we suggest that if a study design like that of FAME is performed based on IVUS rather than FFR, it is possible that the results will be the same as published for FAME (14), despite some increase in revascularization when determined by the IVUS criteria. To address the question of which assessment is most appropriate, a large randomized clinical trial comparing the assessment based on IVUS criteria with FFR is warranted. Until such a study is conducted, physicians should primarily use their clinical judgment and FFR because FFR is the most accurate tool to detect ischemia. However, adequate IVUS–MLA cutoff values should be considered as an alternative to FFR in addition to the role of IVUS.

**Study limitations.** In the FIRST, the decision for PCI was at the discretion of the investigator and was not dictated by protocol. Given that there were relatively few lesions with an FFR <0.8 and an MLA <4.0 mm² that did not undergo PCI, as well as even fewer lesions with an FFR >0.8 and an MLA >4.0 mm² that underwent PCI, it is clear that the investigators did not exclusively use either tool as a guide for interventional necessity. Therefore, the FIRST is limited with respect to the impact of correlation between the 2 modalities on clinical outcome.

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**Table 4 Correlates of Fractional Flow Reserve (FFR) <0.8: Multivariable Logistic Regression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS MLA, mm²</td>
<td>0.72</td>
<td>0.52–0.98</td>
<td>0.039</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>1.03</td>
<td>0.99–1.06</td>
<td>0.110</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>1.05</td>
<td>1.01–1.09</td>
<td>0.028</td>
</tr>
<tr>
<td>Left anterior descending lesions (vs. RCA)</td>
<td>3.19</td>
<td>1.44–7.05</td>
<td>0.004</td>
</tr>
<tr>
<td>Left circumflex lesions (vs. RCA)</td>
<td>0.37</td>
<td>0.11–1.31</td>
<td>0.124</td>
</tr>
</tbody>
</table>

IVUS, intravascular ultrasound; MLA, minimum lumen area; RCA, right coronary artery.
Conclusions

Anatomic measurements of intermediate coronary lesions obtained by IVUS show a moderate correlation with FFR measurements. The correlation between MLA cutoff and FFR values is vessel size dependent and better correlates in larger diameter vessels. Different MLA cutoffs should be used for different vessel sizes. Plaque composition assessed by VH IVUS does not correlate with FFR for the detection of ischemia in intermediate lesions defined as 40% to 80%. The utility of IVUS MLA as an alternative to FFR to guide intervention in intermediate lesions may be limited in accuracy and should be confirmed clinically.

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REFERENCES


Key Words: fractional flow reserve • intermediate coronary lesion • intravascular ultrasound • minimal lumen area.