Journal of the Society for Cardiovascular Angiography & Interventions 3 (2024) 101288

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

Optical Coherence Tomography Measures Predicting Fractional Flow Reserve: The OMEF Study

Rocco Vergallo, MD, PhD[a,†], Marco Lombardi, MD[a,†], Tsunekazu Kakuta, MD, PhD[b], Tomasz Pawlowski, MD, PhD[c], Antonio Maria Leone, MD, PhD[a], Gennaro Sardella, MD, PhD[d], Pierfrancesco Agostoni, MD, PhD[e], Jonathan M. Hill, MD[f], Giovanni Luigi De Maria, MD, PhD[g], Adrian P. Banning, MD[g], Tomasz Roleder, MD, PhD[h], Anouar Belkacemi, MD, PhD[i], Carlo Trani, MD[a], Francesco Burzotta, MD, PhD[a,*]

[a] *Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica Sacro Cuore, Rome, Italy;* [b] *Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan;* [c] *Department of Cardiology, Central Hospital of Internal Affairs and Administration Ministry, Postgraduate Medical Education Centre, Warsaw, Poland;* [d] *Department of Cardiovascular Sciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy;* [e] *HartCentrum, Ziekenhuis Netwerk Antwerpen (ZNA) Middelheim, Antwerp, Belgium;* [f] *Royal Brompton Hospital, London, United Kingdom;* [g] *Oxford Heart Centre, John Radcliffe Hospital, Oxford University Hospitals, NHS Foundation Trust, Oxford, United Kingdom;* [h] *Department of Cardiology, Hospital Wroclaw, Wroclaw, Poland;* [i] *Department of Cardiology, AZ West, Veurne, Belgium*

ABSTRACT

Background: Optical coherence tomography (OCT) allows to carefully characterize coronary plaque morphology and lumen dimensions. We sought to evaluate the value of OCT in predicting fractional flow reserve (FFR).

Methods: We performed a multicenter, international, pooled analysis of individual patient-level data from published studies assessing FFR and OCT on the same vessel. Data from stable or unstable patients who underwent both FFR and OCT of the same coronary artery were collected through a dedicated database. Predefined OCT parameters were minimum lumen area (MLA), percentage area stenosis (%AS), and presence of thrombus or plaque rupture. Primary end point was FFR ≤0.80. Secondary outcome was the incidence of major adverse cardiac events in patients not undergoing revascularization based on negative FFR (>0.80).

Results: A total of 502 coronary lesions in 489 patients were included. A significant correlation was observed between OCT-MLA and FFR values (R = 0.525; *P* < .001), and between OCT-%AS and FFR values (R = –0.482; *P* < .001). In Receiver operating characteristic analysis, MLA <2.0 mm^2 showed a good discriminative power to predict an FFR ≤0.80 (AUC, 0.80), whereas %AS >73% showed a moderate discriminative power (AUC, 0.73). When considering proximal coronary segments, the best OCT cutoff values predicting an FFR ≤0.80 were MLA <3.1 mm^2 (AUC, 0.82), and %AS >61% (AUC, 0.84). In patients with a negative FFR not revascularized, the combination of lower MLA and higher %AS had a trend toward worse outcome (which was statistically significant in the analysis restricted to proximal vessels).

Conclusions: OCT lumen measures (MLA, %AS) may predict FFR, and different cutoffs are needed for proximal vessels.

Introduction

The decision-making process of patients with angiographically intermediate coronary lesions is clinically challenging and may benefit from adjunctive invasive techniques.

According to the current international guidelines, fractional flow reserve (FFR), an invasive functional assessment used to detect myocardial ischemia, represents the gold standard in guiding the decision to proceed or not with coronary revascularization.[1,2]

Abbreviations: %AS, area stenosis; DS, diameter stenosis; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LL, lesion length; MACE, major adverse cardiac events; MLA, minimum lumen area; OCT, optical coherence tomography; QCA, quantitative coronary angiography.

Keywords: fractional flow reserve; intermediate coronary lesions; optical coherence tomography.

* Corresponding author: francesco.burzotta@unicatt.it (F. Burzotta).

† Co-first authors.

https://doi.org/10.1016/j.jscai.2023.101288

Received 18 November 2023; Received in revised form 20 December 2023; Accepted 1 January 2024

Available online 9 February 2024

On the other hand, the use of intravascular imaging techniques is well-established for an optimized result of a percutaneous coronary intervention (PCI).[3-8] Optical coherence tomography (OCT) is a novel, high-resolution intracoronary imaging technique that has recently been shown to be of value in the management of patients with angiographically intermediate coronary lesions in a randomized study versus FFR.[9]

In fact, OCT allows to carefully characterize the coronary plaque morphology and lumen dimension. Such anatomic features may influence coronary blood flow, but the value of OCT in predicting FFR has not been established.

Thus, we designed and conducted a multicenter international study aiming: (1) to investigate the relation between OCT and FFR parameters in intermediate lesions and assess whether OCT parameters may predict FFR, and (2) to evaluate whether OCT parameters may predict clinical outcome of patients with intermediate lesions not undergoing revascularization based on negative FFR.

Methods

Study design

The OMEF (Optical Coherence Tomography Measures PrEdicting Fractional Flow Reserve) study was a multicenter, international, pooled analysis of individual patient data from 8 centers across Italy, Japan, the United Kingdom, Poland, and the Netherlands that agreed to share data of study populations collected in published studies (Supplemental Table S1).[10–17]

Patients with stable or unstable ischemic heart disease and angiographic evidence of at least 1 angiographically intermediate coronary lesion (defined as a visual diameter stenosis between 30% and 80%) who underwent both FFR and OCT assessment of the same coronary lesion in a previously published study were enrolled.

A typical case of a patient enrolled in the OMEF study is available in Supplemental Figure S1.

The outline of the study protocol and the full list of participating centers are available in the Supplemental Methods and Supplemental Table S1. The study was registered in 2018 on ClinicalTrials.gov under the identifier of NCT03573388.

Principal investigators were asked to complete a structured database by providing a series of key baseline clinical and angiographic data (such as percentage diameter stenosis [%DS] and lesion length [LL] by quantitative coronary angiography [QCA]), OCT and FFR parameters, and major adverse cardiovascular events at the follow-up. The full list of collected data is reported in Supplemental Methods. Anonymized data were provided by the principal investigators of previously published studies so that the specific study protocols and ethical details were reported in the individual publications.

In patients with FFR >0.80 not undergoing myocardial revascularization, the occurrence of cardiac death (any death not clearly attributed to noncardiac causes), (spontaneous) myocardial infarction (MI), surgical or percutaneous coronary revascularization of the target lesion (PCI or coronary bypass graft [CABG]) after the procedure and during the longest available clinical follow-up was reported. Major adverse cardiovascular events (MACE) comprised cardiac death, MI, and target-lesion revascularization.

Coronary lesion assessment

Quantitative coronary angiography. Quantitative coronary angiography was performed offline using validated softwares on a single, selected 2D end-diastolic image frame.

Vessel diameters were calculated as absolute values (mm). The vessel contours were automatically determined and, in case of incorrect automated analysis, manual correction was applied. The reference vessel diameter was based on the computer estimation of the original arterial dimensions at the stenosis site. The following angiographic parameters were obtained: minimum lumen diameter (mm), proximal and distal reference diameter (mm), %DS, and LL (mm).

Fractional flow reserve. A guiding catheter was placed at the coronary ostium. After intracoronary administration of nitroglycerin, a 0.014-inch pressure monitoring guidewire (type chosen by the operator according to local practice and/or study protocol) was advanced beyond the angiographically intermediate coronary lesion under radioscopic examination. Then, FFR was defined as the lowest ratio of distal coronary pressure divided by aortic pressure after achievement of hyperemia using intracoronary or endovenous adenosine according to local practice at each center.[18]

FFR >0.80 was defined as "negative FFR." According to the clinical practice of participating centers, myocardial revascularization was not performed in the presence of negative FFR.

OCT. OCT images were acquired (after intracoronary administration of nitroglycerin) at the site of the same angiographically intermediate coronary lesion with commercially available systems (as reported in the individual studies) after the OCT catheter was advanced to the distal end of the target lesion. The entire length of the region of interest was scanned, collecting the following measures: minimum luminal area (MLA, defined as the cross-sectional area at the smallest luminal area level), proximal reference luminal area (RLA) (defined as the cross-section at the frame with largest lumen within 10 mm proximal to MLA and before any major side branch), distal RLA (defined as the cross-section at the frame with largest lumen within 10 mm distal to MLA and before any major side branch), and mean RLA (defined as [proximal RLA + distal RLA]/2). On the basis of these parameters, percentage of area stenosis (%AS) was calculated using the following formula: ([mean RLA–MLA]/mean RLA) × 100. Plaque rupture (also called ulceration) was defined as a recess in the plaque beginning at the luminal-intimal border. Plaque thrombus included both red thrombus (intraluminal mass with high backscatter and high attenuation) and white thrombus (intraluminal mass with high backscatter and low attenuation).

The quantitative and qualitative parameters were in accordance with the indications of the consensus document from the International Working Group for intravascular OCT (IWG-IVOCT) standardization and validation.[19]

Study end points

The main aim of the study was to evaluate the impact of OCT measures (MLA, %AS, and presence of plaque thrombus or rupture) in predicting FFR. The primary end point was positive FFR (≤0.80). The secondary aim of the study was to evaluate the impact of OCT measures (MLA, %AS, and presence of plaque thrombus or rupture) in predicting the outcome of patients not undergoing revascularization based on negative FFR (>0.80). Accordingly, the secondary end point of the study was MACE occurring during the longest available follow-up in patients who did not undergo revascularization.

Statistical analysis

Categorical variables were expressed as counts (percentages), and compared using the chi-square or Fisher exact test. After assessing data distribution using the Kolmogorov-Smirnov test, continuous variables were expressed as mean ± SD or median (IQR), and compared using the independent samples *t* test or the Mann-Whitney *U* test. Lesion-based comparisons were carried out using generalized estimating equations to consider potential cluster effects of multiple lesions in a single patient. Univariate Cox regression analysis was performed to evaluate the correlation of OCT parameters and FFR. Receiver operating characteristic (ROC) curve analysis was performed to assess the OCT-defined MLA and %AS values best predicting an FFR ≤0.80 or FFR ≤0.75. Optimal cutoffs were identified with the Youden index (J) statistics method. Survival curves, determined with Kaplan-Meier methods, were compared by means of the log-rank test. All tests were 2-sided. A *P* value <.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM Corp) and MedCalc version 20.218 (MedCalc Software Ltd).

Results

A total of 502 intermediate coronary lesions in 489 patients were included in the study. Baseline clinical characteristics of the study population are summarized in Table 1. The mean age of patients was 65 years, the clinical presentation was stable angina in about 90% of the cases. The majority of patients were male (75.3%), the cardiovascular risk factors were highly prevalent, and 30.7% of patients were diabetic; 27% of patients included had a history of prior MI and about one-half of them had undergone a prior PCI. The median follow-up was 5.3 years (IQR, 1.7-8.2).

QCA and OCT parameters of intermediate lesions stratified according to the FFR values (≤0.80 or >0.80) are reported in Table 2.

In the QCA, LL and %DS were significantly greater in intermediate lesions with positive FFR (≤0.80) than in those with negative FFR (>0.80), whereas minimum lumen diameter and mean reference diameter were significantly smaller (all *P* < .001).

In OCT, MLA was significantly smaller in intermediate lesions with positive FFR (≤0.80) than in those with normal FFR (>0.80), while LL and %AS were significantly greater (all *P* < .001). No statistically significant differences were observed in the prevalence of OCT-detected ulceration and thrombus between the 2 groups of intermediate lesions (Table 2).

Impact of OCT measures to predict FFR

Linear regression analysis showed a significant correlation between OCT-defined MLA and FFR values (R = 0.525; *P* < .001), as well as a significant inverse correlation between OCT-defined %AS and FFR values (R = –0.482; *P* < .001) (Figure 1A, B).

No significant differences were observed in the prevalence of OCT-detected rupture/thrombus between intermediate lesions with positive or negative FFR, irrespective of the FFR cutoff value used (ie, 0.80 or 0.75) (Figure 1C, D).

Detailed univariate logistic regression analyses of OCT parameters, and clinical and procedural factors for prediction of FFR ≤0.80 are reported in Table 3 and Supplemental Table S2. Similar results were found when assessing the OCT parameters for prediction of FFR ≤0.75 (Supplemental Table S3).

In ROC analysis, an OCT-MLA of <2.0 mm^2 showed a good discriminative power to predict an FFR ≤0.80 (AUC, 0.80; sensitivity, 77%; specificity, 68%), and an OCT %AS of 73% (AUC, 0.73; sensitivity, 66%; specificity, 69%) showed a moderate discriminative power (Figure 2A, B).

ROC curves comparison showed a significantly higher performance of OCT parameters vs %DS (AUC, 0.67; %DS vs MLA *P* < .0001; and %DS vs %AS, *P* = .01, respectively) and a significant difference between %AS alone and the combination of MLA and %AS (Supplemental Figures S2 and S3 and Supplemental Table S4).

Based on sensitivity, we did additional analyses considering only patients with chronic coronary syndrome and previous MI that confirmed the good discriminative abilities of the aforementioned cutoffs. On the other hand, it showed lower MLA and higher %AS cutoffs for the right coronary artery and the left circumflex artery (Supplemental Table S5). ROC analysis for OCT parameters predicting an FFR ≤0.75 is reported in Supplemental Figure S4.

When considering proximal coronary segments only, the best OCT cutoff values predicting an FFR ≤0.80 were MLA <3.1 mm^2 (AUC, 0.82; sensitivity, 83%; specificity, 76%), and %AS >61% (AUC, 0.84; sensitivity, 72%; specificity, 85%) (Figure 3A, B).

ROC curves comparison for proximal segments showed no difference between MLA and %AS, also when combined (Supplemental Figure S5 and Supplemental Table S4).

Impact of OCT measures to predict outcome in those with FFR-negative lesions who did not undergo revascularization

Among 105 patients with intermediate lesions who had not undergone revascularization based on negative FFR, 11 (10.5%) experienced a MACE during the follow-up, including 4 deaths (3.8%), 2 MI (1.8%), and 7 (6.7%) target vessel PCI, with no target vessel CABG.

Patients with an OCT-MLA <2.0 mm^2 showed a higher incidence of MACE at follow-up compared with those with an OCT-MLA ≥2.0 mm^2, although this difference did not reach a statistical significance (16.7% vs 9.2%, respectively; log-rank *P* value = .139).

Table 1. Baseline clinical characteristics.

	N = 489
Age, y	65.2 ± 10.4
Male sex	368 (75.3)
Hypertension	322 (65.8)
Dyslipidemia	279 (57.1)
Diabetes mellitus	150 (30.7)
Current smoking	121 (24.7)
Family history	40 (8.2)
Clinical presentation	
Acute coronary syndrome	55 (11.2)
Chronic coronary syndrome	434 (88.8)
Previous myocardial infarction	132 (27.0)
Previous percutaneous coronary interventions	234 (47.9)
Previous coronary artery by-pass surgery	8 (1.6)

Data are expressed as counts (percentages) or mean ± SD.

Table 2. QCA and OCT findings in angiographically intermediate coronary lesions with positive or negative FFR.

	FFR ≤0.80 (289 lesions)	FFR >0.80 (213 lesions)	*P* value
Lesion location			
LAD	199 (68.9)	112 (52.6)	
LCx	32 (11.1)	40 (18.8)	.001
RCA	58 (20.1)	61 (28.6)	
QCA parameters			
Lesion length, mm	15.2 ± 8.8	12.5 ± 6.0	<.001
MLD, mm	1.08 ± 0.37	1.47 ± 0.46	<.001
Mean RD, mm	2.65 ± 0.62	3.05 ± 0.73	<.001
%DS	58.7 ± 12.4	51.0 ± 12.5	<.001
OCT parameters			
Lesion length, mm	15.0 ± 6.6	12.7 ± 6.2	<.001
MLA, mm^2	1.55 ± 0.85	2.91 ± 1.64	<.001
%AS	75.5 ± 11.7	60.8 ± 20.4	<.001
Ulceration	31 (11.6)	23 (10.8)	.805
Thrombus	13 (4.5)	10 (4.7)	.917

Data are expressed as count (%) or mean ± SD.
%AS, percentage area stenosis; %DS, percentage diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending; LCx, left circumflex; MLA, minimum lumen area; MLD, minimum lumen diameter; OCT, optical coherence tomography; QCA, quantitative coronary angiography; RCA, right coronary artery; RD, reference diameter.

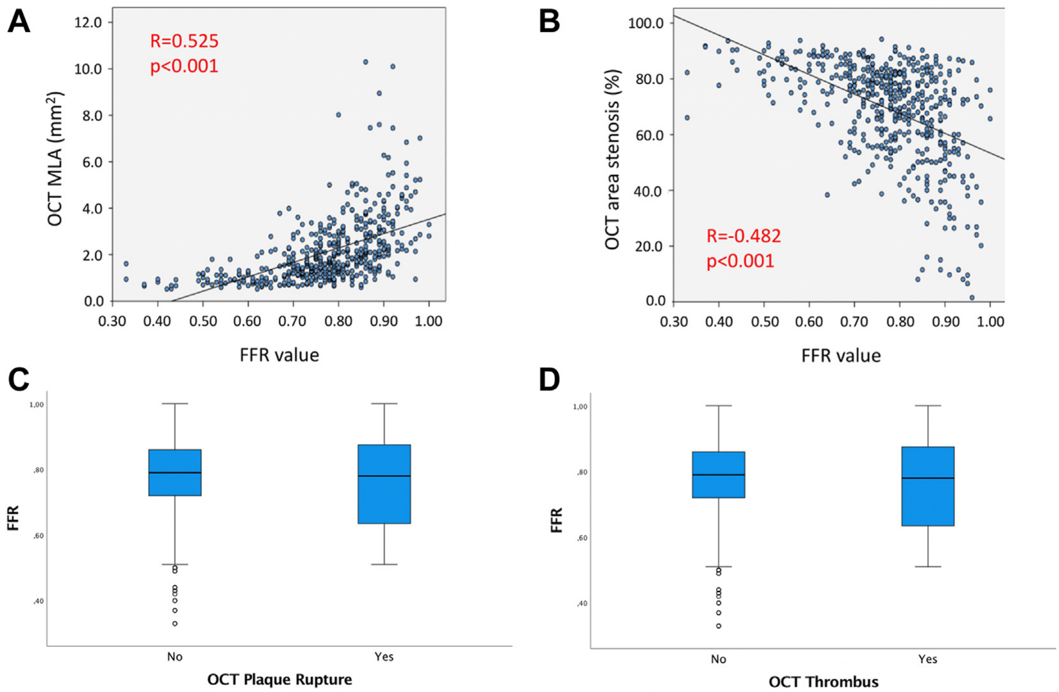


Figure 1.
Correlation between fractional flow reserve (FFR) values and OCT-derived minimum lumen area (MLA). (**A**) linear regression analysis, (**B**) % area stenosis (linear regression analysis), (**C**) plaque rupture, (**D**) thrombus. OCT, optical coherence tomography.

When combining both MLA <2.0 mm^2 and %AS >73%, patients with those OCT findings had a significantly increased occurrence of MACE at follow-up (37.5% vs 8.2%, respectively; log-rank *P* value <.001) (Figure 4A).

Among 47 patients with intermediate lesions located in the proximal coronary segments not undergoing revascularization based on a negative FFR, the combination of MLA <3.1 mm^2 and %AS >61% showed a significantly higher risk of MACE at the follow-up (33.3% vs 9.8%, respectively; log-rank *P* value = .04) (Figure 4B).

Discussion

The decision-making process of patients with angiographically intermediate coronary lesions is clinically challenging and may benefit from adjunctive invasive techniques. FFR represents the gold standard but OCT is a novel, promising, high-resolution coronary imaging technique.

The OMEF study represents the first multicenter study including almost 500 patients performing a coregistration of FFR and OCT with an available long-term follow-up (median time 5.3 years).

In the present pooled analysis of OCT and FFR data obtained in the same vessels, we found that: (1) easy-to-assess OCT lumen measures (MLA, %AS) predict FFR; and (2) proximal lesion location might change the OCT thresholds for positive FFR prediction (Central Illustration).

Table 3. Univariate logistic regression analysis of OCT parameters for prediction of FFR ≤0.80.

	Prediction of FFR ≤0.80		
	Odds ratio	95% CI	*P* value
MLA, mm^2	0.34	0.27-0.43	<.001
Lesion length, mm	1.06	1.03-1.10	<.001
%AS	1.06	1.05-1.08	<.001
Plaque rupture	1.08	0.61-1.91	.805
Thrombus	0.96	0.41-2.22	.917

%AS, area stenosis; FFR, fractional flow reserve; MLA, minimum lumen area; OCT, optical coherence tomography.

Moreover, the combination of OCT lumen measures (reduced MLA and higher %AS) was associated with a trend toward worse outcomes in conservatively managed patients with negative FFR.

These data shed new light on the potential of OCT to predict the functional impact of coronary lesions.

An accurate evaluation of coronary lesions is of foremost importance in guiding the management of patients with coronary artery disease. So far, according to the international guidelines, in absence of noninvasive functional studies, the evaluation of angiographically intermediate coronary lesions via FFR (or alternatively, the instantaneous wave-free ratio) is mainly dedicated to decision-making regarding coronary revascularization.[1,2]

The OCT imaging technique is generally used to characterize the coronary plaque morphology and to guide the optimization of PCI.[8,19] The simultaneous use of both modalities might be expected to achieve better clinical outcomes. However, there are limitations to conducting both tests because of time, cost, and lack of evidence. Recently, in a randomized clinical trial, the OCT has been proven to be a valuable option for evaluating the decision to revascularize intermediate lesions.[9]

Hence, we assumed that OCT may therefore provide additional insights into the functional significance evaluation of intermediate coronary lesions.

In the present study we found that, in patients with intermediate lesions (both stable and unstable), specific cutoff MLA and %AS OCT-derived were able to discriminate intermediate lesions with a positive FFR from those with a negative one, with a good predictive value. An OCT-MLA <2.0 mm^2 showed a good predictive value for the identification of intermediate lesions with an abnormal FFR (AUC, 0.80), as well as an OCT %AS >73% (AUC, 0.73) showed a moderate prediction power. In the past decade, diverse intravascular ultrasound (IVUS) studies have tried to find measurements able to predict the functional significance of angiographically intermediate coronary lesions. In the FIRST study[20] (Fractional Flow Reserve and Intravascular Ultrasound

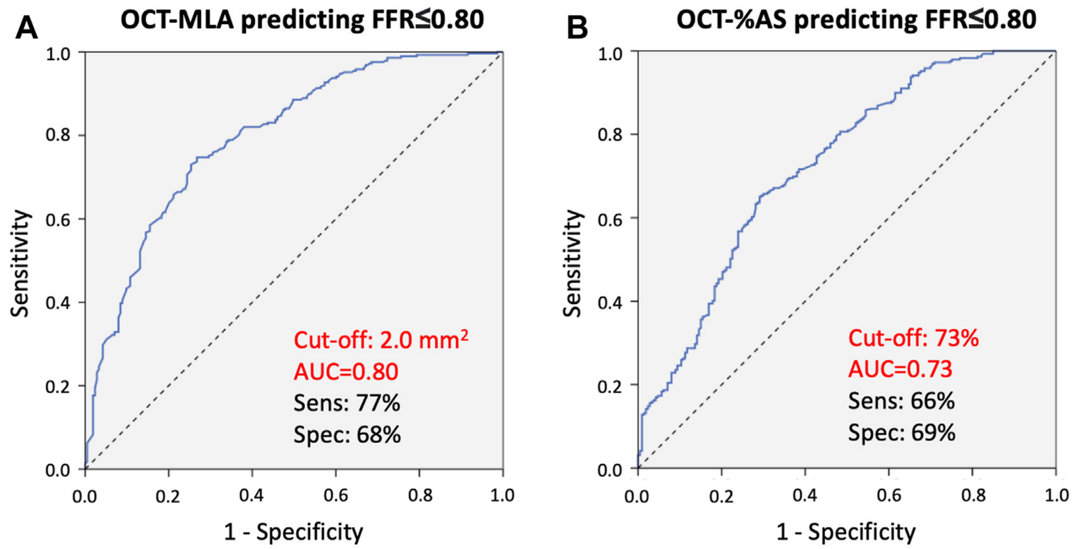


Figure 2.
Receiver operating characteristic analysis for optical coherence tomography (OCT) parameters predicting fractional flow reserve (FFR) ≤0.80. (**A**) Minimum lumen area (MLA), (**B**) % area stenosis (AS). AUC, area under the curve; Sens, sensitivity; Spec, specificity.

Relationship Study), the authors found that the best threshold value for identifying FFR <0.80 was an MLA<3.07 mm^2 (64.0% sensitivity, 64.9% specificity, AUC = 0.65) at the IVUS. On the other hand, Kang et al[21] demonstrated that IVUS-derived MLA ≥2.4 mm^2 may be a useful cutoff in order to exclude a positive FFR, but poor specificity limits its value for physiological assessment of lesions with MLA <2.4 mm^2. Such a wide variation in IVUS estimations might be related to many factors including race, supplied territory, vessel size, and lumen estimation precision. OCT has a completely different resolution power translating into more accurate lumen dimension assessment.[22] In this regard, the optimal cutoff value of MLA for positive FFR prediction we found was similar to the finding of a previous meta-analysis,[23] where a median OCT-MLA of 1.96 mm^2 (1.85-1.98) was derived from 5 OCT studies. Since significant MLA is expected to change with vessel size and subtended myocardium, we also assessed %AS and proximal lesion location. Interestingly, the combination of MLA and %AS generated very promising AUC while different cutoffs for these parameters were found in the analyses restricted to proximal lesions, higher MLA and lower %AS being associated with positive FFR. In particular, the combination of MLA <3.1 mm^2 and %AS >61% allowed an increasing predictive value for proximal coronary segments (AUC, 0.85). These signals suggest that a comprehensive assessment of vessel geometry might generate an accurate prediction of FFR.

In this regard, recently a machine learning approach using intravascular OCT to predict FFR was developed by Cha et al[24] showing the potential of OCT-based machine learning-FFR. Additionally, computational methods for deriving the FFR values from OCT have demonstrated a good correlation with the invasive FFR,[25-27] even in the absence of statistically significant differences compared to the angiography-based physiological indices.[25,26]

Despite these intriguing results, there are still some challenges to address before the widespread use of these indices in the cath-lab

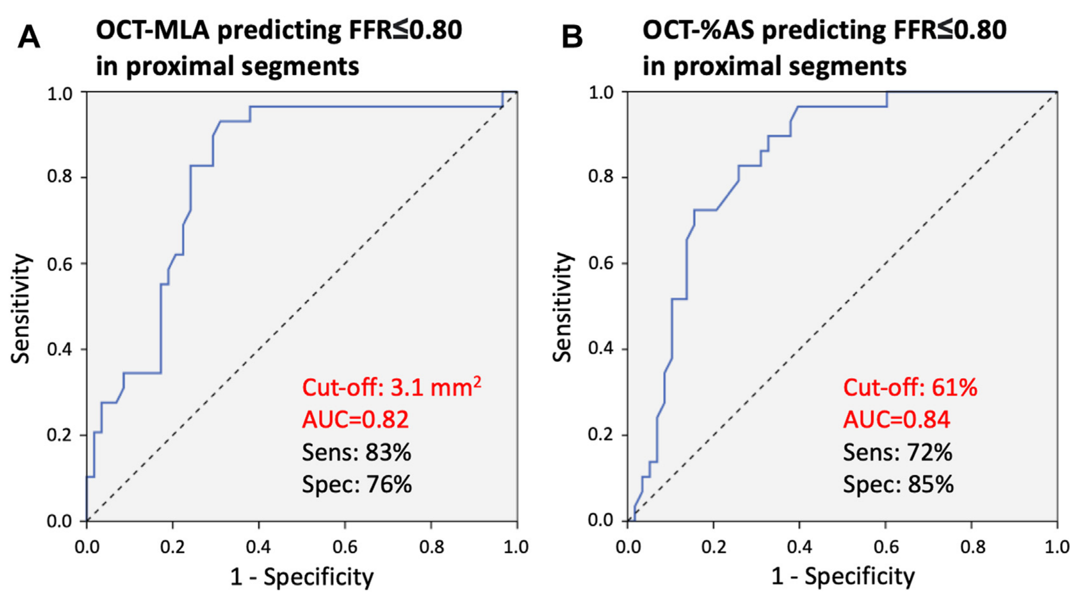


Figure 3.
ROC analysis for optical coherence tomography (OCT) parameters predicting fractional flow reserve (FFR) ≤0.80 in proximal segments. (**A**) Minimum lumen area (MLA), (**B**) % area stenosis (AS). AUC, area under the curve; Sens, sensitivity; Spec, specificity.

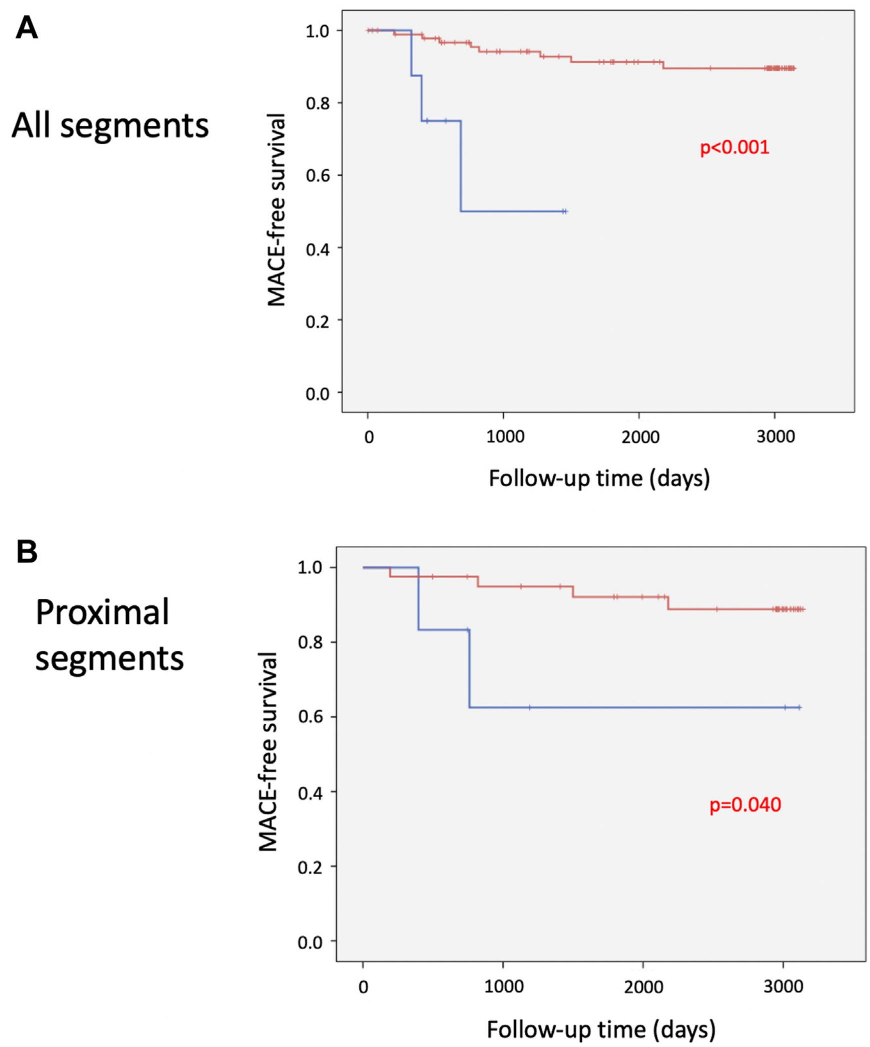


Figure 4.
Event-free from major adverse cardiac events (MACE) survival curve in patients with fractional flow reserve (FFR) >0.80 who had not undergone revascularization stratified according to the combination of OCT-MLA and OCT. (**A**) % area stenosis cutoff values in all segments and in (**B**) proximal segments. MLA, minimum lumen area; OCT, optical coherence tomography.

environment. Firstly, additional validation is required in more distinct coronary lesions and patient cohorts. Secondly, the computational time remains relatively high and is performed offline, currently limiting its everyday use.

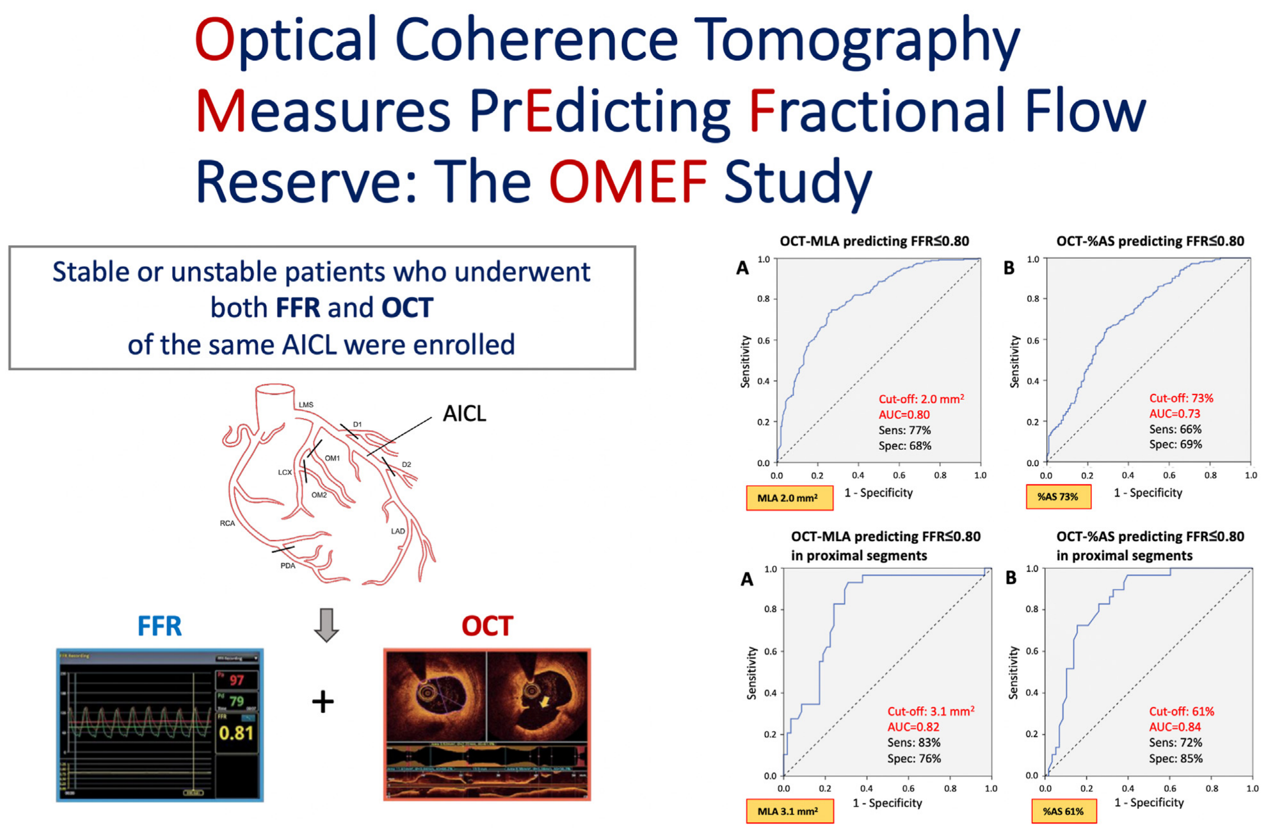
Generally, the integration of morphological information obtained from OCT with physiological data assessed through invasive FFR has the potential to expand the role of OCT in decision-making for the management of intermediate coronary stenosis. This approach could prove beneficial and cost effective, especially in coronary procedures where an OCT catheter was already employed for other purposes, such as the evaluation of ambiguous lesions or OCT-guided PCI for a calcific lesion.

Regarding the association with clinical events, a (small) group of patients included in the OMEF study was not revascularized due to negative FFR and offered the possibility to evaluate the possible value of OCT lumen assessment. Interestingly, patients with MLA <2.0 mm^2 and %AS >73% had a significantly increased occurrence of MACE at follow-up. Similarly, among 47 patients with proximal angiographically intermediate coronary lesions who had not undergone coronary revascularization, the combination of MLA <3.1 mm^2 and %AS >61% showed a significantly higher risk of MACE at the follow-up. These findings should be recognized as hypothesis generating rather than hypothesis-testing, given that the assessment of clinical outcomes was underpowered and not adjusted for multiple comparisons.

In the present study, we also tried to assess the possible role of OCT high-risk features on FFR. In doing this, we focused on plaque rupture and thrombus since these 2 features were assessed in the different study protocols that were combined in the OMEF database. Yet, the vast majority of patients were stable and, consequently, the number of lesions presenting rupture or thrombus was very low. Furthermore, other OCT markers of plaque risk like thin-cap fibroatheroma and macrophage infiltration were not evaluated in our study. Of note, in the CLIMA study, these features were recently found to significantly predict outcomes of proximal lesions located in the left anterior descending artery.[28] Similarly, in the COMBINE OCT-FFR trial,[29] among diabetic patients with more than 1 FFR-negative lesion, thin-cap fibroatheroma positive patients represented 25% of the population and were associated with a 5-fold higher rate of MACE despite the absence of ischemia.

Limitations

Our study has several limitations.



Central Illustration.
In the OMEF study, stable or unstable patients with angiographically intermediate coronary lesions who underwent both fractional flow reserve (FFR) and optical coherence tomography (OCT) of the same coronary artery were included. In receiver operating characteristic (ROC) analysis, minimum lumen area (MLA) <2.0 mm^2 and % area stenosis (AS) >73% showed a good discriminative power to predict an FFR ≤0.80 (AUC 0.80 and 0.73, respectively). When considering proximal coronary segments only, the best OCT cutoff values predicting an FFR ≤0.80 were MLA <3.1 mm^2 (AUC, 0.82), and %AS >61% (AUC, 0.84).

First, this was a retrospective study and therefore subject to potential selection bias. Second, the ischemic threshold for FFR that defines "significant ischemia" prompting the decision toward coronary revascularization is either ≤0.75 or ≤0.80; hence some have defined the range 0.75 to 0.80 as a "gray zone."[30] In this setting, we also performed a sensitivity analysis using the 2 different FFR cutoffs which did not report any statistically significant differences among the 2 groups.

Third, since we also included in the analysis patients with a previous CABG of another coronary lesion this could be acknowledged as a limitation for the possibility of an altered blood flow altering FFR measures. However, we did additional sensitivity analyses that did not report any influence of a previous CABG on the overall results.

Fourth, as proximal stenosis corresponds to a higher myocardial territory, we found that a different cutoff value for the MLA and %AS could derive a better prediction value compared to the overall analysis. Thus data from proximal lesions analysis and clinical outcome have to be considered as hypothesis generating only since they come from a retrospective study with a small sample size.

Fifth, the analysis of clinical events was performed only with the subgroup of patients with nonhemodynamically significant coronary stenoses (ie, >0.80 FFR), which includes a small number of patients and events. These findings should be considered with caution since the assessment of clinical events was underpowered, and additional studies on this topic should be performed.

Additionally, another limitation of the OMEF study was the lack of blinding of OCT analysis to the FFR values of the same intermediate coronary lesion.

Although qualitative analysis of the coronary lesions portends significant information related to clinical outcomes (such as thin-cap fibroatheroma, and macrophage infiltration) we did not perform sensitivity analysis regarding these parameters. Further studies will be required in order to account for these important features.

Finally, another important limitation of the OMEF study was the lack of complete data regarding the patients' medication.

Conclusions

The observations collected in the present collaborative study suggest that easy-to-assess OCT lumen parameters have significant correlation with FFR values and have the potential to help stratify risk of patients with negative FFR. Appropriately designed prospective studies are warranted to determine FFR prediction from OCT images and the possible clinical impact of OCT guidance in patients with negative FFR.

Acknowledgments

The authors wish to thank Emanuele Soraci who helped in the first phases of the study that represented his cardiology fellowship final thesis.

Declaration of competing interest

Rocco Vergallo received speaker fees from Abbott Vascular and Terumo. Tomasz Pawlowski received speaker fees from Abbott Vascular and Philips IGT. Antonio Maria Leone is an advisor for Abbott Vascular and Bracco Imaging and has received speaking honoraria from Abbott Vascular, Medtronic, and Abiomed in the past. Jonathan Hill received speaker fees, honoraria, and consulting fees from Abbott Vascular, Abiomed, Boston Scientific, and Shockwave Medical; and holds equity in Shockwave Medical. Giovanni Luigi De Maria received speaker fees from

Abbott Vascular, consultancy fees from Miracor Medical SA, and research grants from Abbott Vascular, Philips, Medtronic, Terumo, Opsens, and Miracor Medical SA. Carlo Trani and Francesco Burzotta received speakers' fees from Abbott Vascular, Abiomed, Medtronic, and Terumo. The other authors have no conflict of interest to disclose in relation to the present manuscript.

Funding sources

The study has been partially supported by Abbott with an unrestricted grant. The company has been not involved in the study conduction nor in results interpretation.

Ethics approval and patient consent

The OMEF study was conducted in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT03573388). Specific study protocols, ethical details and patient consents were reported in the individual publications.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.101288.

References

1. Writing Committee Members, Lawton JS, Tamis-Holland JE, et al. ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79(2):e21–e129.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165. https://doi.org/10.1093/eurheartj/ehy394
3. Wijns W, Shite J, Jones MR, et al. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. *Eur Heart J*. 2015;36(47):3346–3355. https://doi.org/10.1093/eurheartj/ehv367
4. Maehara A, Ben-Yehuda O, Ali Z, et al. Comparison of stent expansion guided by optical coherence tomography versus intravascular ultrasound: the ILUMIEN II study (observational study of optical coherence tomography [OCT] in patients undergoing fractional flow reserve [FFR] and percutaneous coronary intervention). *JACC Cardiovasc Intv*. 2015;8(13):1704–1714. https://doi.org/10.1016/j.jcin.2015.07.024
5. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet*. 2016;388(10060):2618–2628. https://doi.org/10.1016/S0140-6736(16)31922-5
6. Meneveau N, Souteyrand G, Motreff P, et al. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome: results of the multicenter, randomized DOCTORS study (does optical coherence tomography optimize results of stenting). *Circulation*. 2016;134(13):906–917. https://doi.org/10.1161/CIRCULATIONAHA.116.024393
7. Jones DA, Rathod KS, Koganti S, et al. Angiography alone versus angiography plus optical coherence tomography to guide percutaneous coronary intervention: outcomes from the Pan-London PCI Cohort. *JACC Cardiovasc Intv*. 2018;11(14):1313–1321. https://doi.org/10.1016/j.jcin.2018.01.274
8. Burzotta F, Trani C. Intracoronary imaging. *Circ Cardiovasc Interv*. 2018;11(11):e007461. https://doi.org/10.1161/CIRCINTERVENTIONS.118.007461
9. Burzotta F, Leone AM, Aurigemma C, et al. Fractional flow reserve or optical coherence tomography to guide management of angiographically intermediate coronary stenosis: a single-center trial. *JACC Cardiovasc Intv*. 2020;13(1):49–58. https://doi.org/10.1016/j.jcin.2019.09.034
10. Pawlowski T, Prati F, Kulawik T, Ficarra E, Bil J, Gil R. Optical coherence tomography criteria for defining functional severity of intermediate lesions: a comparative study with FFR. *Int J Cardiovasc Imaging*. 2013;29(8):1685–1691. https://doi.org/10.1007/s10554-013-0283-x
11. Biały D, Wawrzyńska M, Arkowski J, et al. Multimodality imaging of intermediate lesions: data from fractional flow reserve, optical coherence tomography, near-infrared spectroscopy-intravascular ultrasound. *Cardiol J*. 2018;25(2):196–202. https://doi.org/10.5603/CJ.a2017.0082
12. Burzotta F, Nerla R, Hill J, et al. Correlation between frequency-domain optical coherence tomography and fractional flow reserve in angiographically-intermediate coronary lesions. *Int J Cardiol*. 2018;253:55–60. https://doi.org/10.1016/j.ijcard.2017.10.011
13. Wolfrum M, De Maria GL, Benenati S, et al. What are the causes of a suboptimal FFR after coronary stent deployment? Insights from a consecutive series using OCT imaging. *EuroIntervention*. 2018;14(12):e1324–e1331. https://doi.org/10.4244/EIJ-D-18-00071
14. Paraggio L, Burzotta F, Aurigemma C, et al. Trends and outcomes of optical coherence tomography use: 877 patients single-center experience. *Cardiovasc Revasc Med*. 2019;20(4):303–310. https://doi.org/10.1016/j.carrev.2018.12.017
15. D'Ascenzo F, Iannaccone M, De Filippo O, et al. Optical coherence tomography compared with fractional flow reserve guided approach in acute coronary syndromes: a propensity matched analysis. *Int J Cardiol*. 2017;244:54–58. https://doi.org/10.1016/j.ijcard.2017.05.108
16. Usui E, Yonetsu T, Kanaji Y, et al. Optical coherence tomography-defined plaque vulnerability in relation to functional stenosis severity and microvascular dysfunction. *JACC Cardiovasc Intv*. 2018;11(20):2058–2068. https://doi.org/10.1016/j.jcin.2018.07.012
17. Belkacemi A, Stella PR, Ali DS, et al. Diagnostic accuracy of optical coherence tomography parameters in predicting in-stent hemodynamic severe coronary lesions: validation against fractional flow reserve. *Int J Cardiol*. 2013;168(4):4209–4213. https://doi.org/10.1016/j.ijcard.2013.07.178
18. Leone AM, Porto I, De Caterina AR, et al. Maximal hyperemia in the assessment of fractional flow reserve: intracoronary adenosine versus intracoronary sodium nitroprusside versus intravenous adenosine: the NASCI (*Nitroprussiato versus Adenosina* nelle Stenosi Coronariche Intermedie) study. *JACC Cardiovasc Intv*. 2012;5(4):402–408. https://doi.org/10.1016/j.jcin.2011.12.014
19. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol*. 2012;59(12):1058–1072. https://doi.org/10.1016/j.jacc.2011.09.079
20. Waksman R, Legutko J, Singh J, et al. FIRST: fractional flow reserve and intravascular ultrasound relationship study. *J Am Coll Cardiol*. 2013;61(9):917–923. https://doi.org/10.1016/j.jacc.2012.12.012
21. Kang SJ, Lee JY, Ahn JM, et al. Validation of intravascular ultrasound-derived parameters with fractional flow reserve for assessment of coronary stenosis severity. *Circ Cardiovasc Interv*. 2011;4(1):65–71. https://doi.org/10.1161/CIRCINTERVENTIONS.110.959148
22. Kubo T, Akasaka T, Shite J, et al. OCT compared with IVUS in a coronary lesion assessment: the OPUS-CLASS study. *JACC Cardiovasc Imaging*. 2013;6(10):1095–1104. https://doi.org/10.1016/j.jcmg.2013.04.014
23. D'Ascenzo F, Barbero U, Cerrato E, et al. Accuracy of intravascular ultrasound and optical coherence tomography in identifying functionally significant coronary stenosis according to vessel diameter: A meta-analysis of 2,581 patients and 2,807 lesions. *Am Heart J*. 2015;169(5):663–673. https://doi.org/10.1016/j.ahj.2015.01.013
24. Cha JJ, Son TD, Ha J, et al. Optical coherence tomography-based machine learning for predicting fractional flow reserve in intermediate coronary stenosis: a feasibility study. *Sci Rep*. 2020;10(1), 20421. https://doi.org/10.1038/s41598-020-77507-y
25. Yu W, Huang J, Jia D, et al. Diagnostic accuracy of intracoronary optical coherence tomography-derived fractional flow reserve for assessment of coronary stenosis severity. *EuroIntervention*. 2019;15(2):189–197. https://doi.org/10.4244/EIJ-D-19-00182
26. Xu T, Yu W, Ding D, et al. Diagnostic performance of intracoronary optical coherence tomography-modulated quantitative flow ratio for assessing coronary stenosis. *J Soc Cardiovasc Angiogr Interv*. 2023;2(5):101043.
27. Ha J, Kim JS, Lim J, et al. Assessing computational fractional flow reserve from optical coherence tomography in patients with intermediate coronary stenosis in the left anterior descending artery. *Circ Cardiovasc Interv*. 2016;9(8):e003613. https://doi.org/10.1161/CIRCINTERVENTIONS.116.003613
28. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J*. 2020;41(3):383–391. https://doi.org/10.1093/eurheartj/ehz520
29. Kedhi E, Berta B, Roleder T, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the Combine OCT-FFR trial. *Eur Heart J*. 2021;42(45):4671–4679. https://doi.org/10.1093/eurheartj/ehab433
30. Agarwal SK, Kasula S, Edupuganti MM, et al. Clinical decision-making for the hemodynamic "gray zone" (FFR 0.75-0.80) and long-term outcomes. *J Invasive Cardiol*. 2017;29(11):371–376.