

# Prospective Randomized Comparison of Fractional Flow Reserve Versus Optical Coherence Tomography to Guide Revascularization of Intermediate Coronary Stenoses: One-Month Results

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**Background**—Fractional flow reserve (FFR) and optical coherence tomography (OCT) may help both in assessment and in percutaneous coronary intervention optimization of angiographically intermediate coronary lesions. We designed a prospective trial comparing the clinical and economic outcomes associated with FFR or OCT in angiographically intermediate coronary lesions.

**Methods and Results**—Three hundred fifty patients with angiographically intermediate coronary lesions ( $n=446$ ) were randomized to FFR or OCT guidance. In the FFR arm, percutaneous coronary intervention was performed if FFR was  $\leq 0.80$  aiming for a postprocedure FFR  $>0.90$ . In the OCT arm, percutaneous coronary intervention was performed if percentage of area stenosis was  $\geq 75\%$  or 50% to 75% with minimal lumen area  $<2.5 \text{ mm}^2$  or plaque ulceration. Costs, angina frequency, and major adverse cardiac events were assessed at 1 month and at 13 months. We present early data at 1 month consistent with a prespecified analysis of secondary end points. Patients randomized to FFR, as compared with OCT, were significantly more commonly managed with medical therapy alone (67.7% versus 41.1%;  $P<0.001$ ), required less contrast media ( $245\pm 137$  versus  $280\pm 129 \text{ mL}$ ;  $P=0.004$ ), and exhibited a lower occurrence of contrast-induced acute kidney injury (1.7% versus 8.6%;  $P=0.034$ ). At 1 month, in comparison to FFR, OCT was associated with increased total costs ( $2831\pm 1288$  versus  $4292\pm 3844$  euros/patient;  $P<0.001$ ) whereas occurrence of major adverse cardiac events or significant angina was similar.

**Conclusions**—In patients with angiographically intermediate coronary lesions, a functional guidance by FFR, as compared with OCT, increased the rate of patients treated with medical therapy alone. This translated into a significant reduction in administered contrast, contrast-induced acute kidney injury, and total costs at 1 month with FFR.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01824030. (*J Am Heart Assoc.* 2019;8:e012772. DOI: 10.1161/JAHA.119.012772.)

**Key Words:** fractional flow reserve • fractional flow reserve • optical coherence tomography • optical coherence tomography • personalized medicine

A large body of evidence supports the notion that percutaneous coronary revascularization driven by functional assessment of coronary stenoses is associated with a better clinical outcome as compared with angiography.<sup>1–4</sup> Nevertheless, percutaneous coronary intervention (PCI) optimization,

using fractional flow reserve (FFR), is much less established.<sup>5</sup> In contrast, the use of intracoronary imaging techniques, such as optical coherence tomography (OCT), has clearly demonstrated a favorable impact on PCI optimization,<sup>6–9</sup> whereas its role in choosing the lesions to treat is still debated.<sup>10,11</sup>

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## Clinical Perspective

### What Is New?

- In the present randomized study, we compared fractional flow reserve and optical coherence tomography in patients with angiographically intermediate coronary lesions, and we found that, 1 month after randomization, optical coherence tomography guidance in angiographically intermediate coronary lesions was associated with a significantly lower rate of patients treated with medical therapy alone and with a significant increase in contrast dose, rate of contrast-induced acute kidney injury, number of implanted stents, and costs in comparison with fractional flow reserve guidance.
- The higher number of optical coherence tomography–guided percutaneous coronary intervention, in comparison with fractional flow reserve guidance, did not affect clinical outcomes, at least at 1 month.

### What Are the Clinical Implications?

- These novel data are clinically relevant given that they provide new support for the use of fractional flow reserve in the decision-making process of patients with angiographically intermediate coronary lesions.
- The possible clinical impact of the higher number of percutaneous coronary interventions performed on the bases of optical coherence tomography has to be evaluated at longer-term follow-up.

Thus, we designed and conducted a prospective, randomized trial aimed at comparing the clinical and economic implications associated with the selection of FFR or OCT in the management of patients with angiographically intermediate coronary lesions (AICLs). In the present article, the results observed at 1 month are reported.

## Methods

### Study Design

The FORZA study (Fractional Flow Reserve versus Optical Coherence Tomography to Guide Revascularization of Intermediate Coronary Stenoses; ClinicalTrials.gov Identifier: NCT01824030; URL: <https://clinicaltrials.gov/ct2/show/NCT01824030>) is an open-label, single-center, prospective, randomized trial comparing the costs and rate of adverse clinical outcomes in patients with at least 1 AICL, randomized to an FFR versus OCT guidance. The rationale and details of the study design have been previously published.<sup>12</sup> In brief, consecutive patients with stable or stabilized ischemic heart disease and evidence of at least 1 AICL, defined as a coronary lesion with a visually estimated percentage diameter stenosis

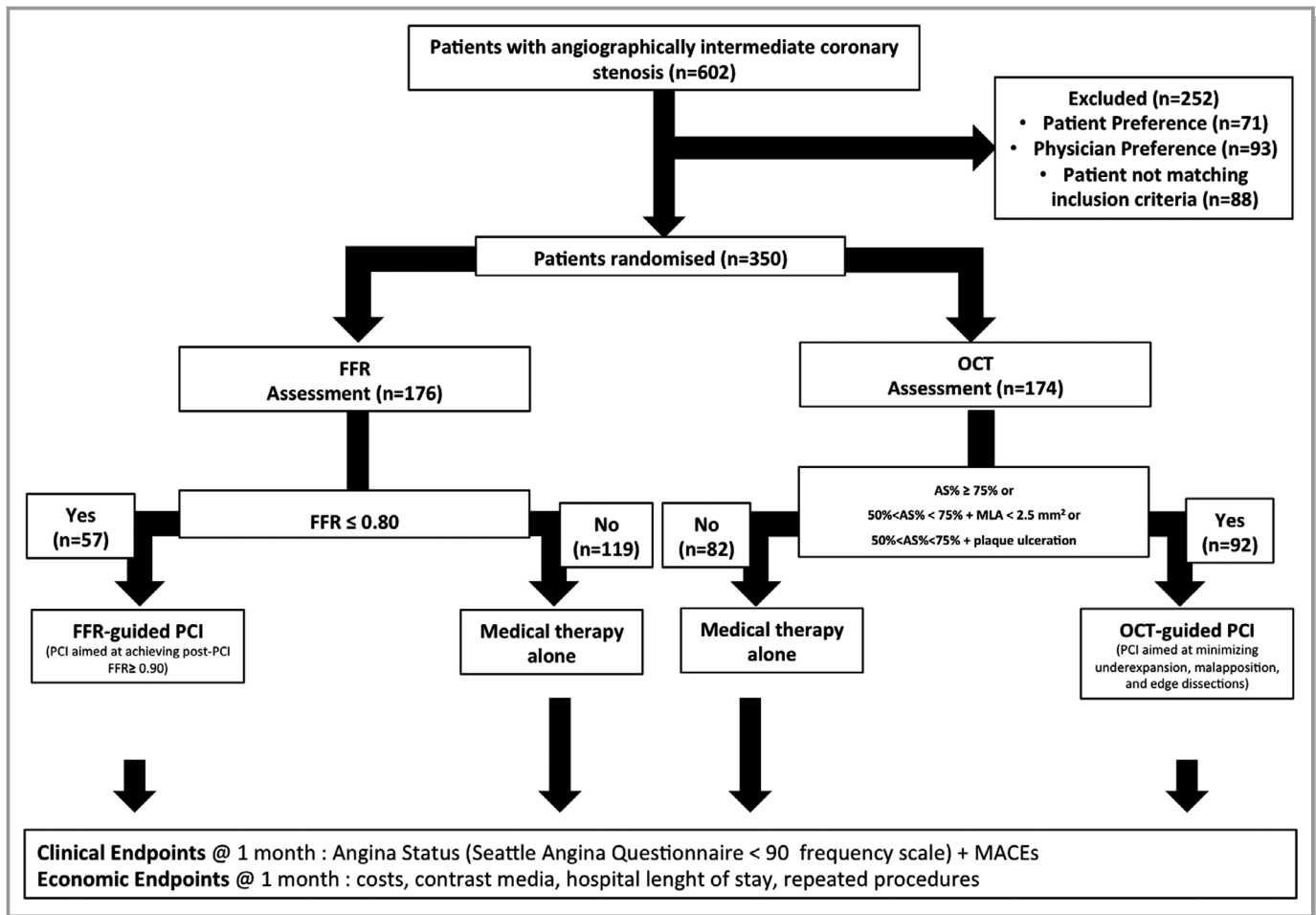
ranging from between 30% and 80%, have been prospectively enrolled and randomized to FFR guidance or OCT guidance at a ratio of 1:1. Specific inclusion and exclusion criteria were previously reported.<sup>12</sup> The study flow chart is shown in Figure 1. The study was approved by the ethics committee of our institution (internal code: 6261/13), and all patients signed a dedicated informed consent form. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Procedure Description

After placement of a guiding catheter at the coronary ostium, FFR or OCT assessments have been performed according to randomization as described previously.<sup>12</sup> Randomization was based on a computer-generated random series of numbers and took place through the opening of an envelope in which the treatment arm was reported. Both the operator and the patient were unblinded to the technique used.

In the FFR arm, a 0.014-inch pressure-monitoring guidewire (Pressure Wire Certus or Aeris; Abbott Vascular, Abbott Park, IL) was advanced beyond the AICL under radioscopic examination to calculate the lowest ratio of distal coronary pressure (Pd) divided by aortic pressure (Pa) after achievement of hyperemia using adenosine. When the FFR value was  $>0.80$ , PCI was deferred. On the contrary, an FFR value  $\leq 0.80$  was considered abnormal and, in this case, PCI was performed with the aim of achieving a poststenting FFR  $\geq 0.90$ . If poststenting FFR was  $<0.90$  a further postdilation of the stent could be performed, and if FFR remained at  $<0.90$ , a pullback of the wire to identify another possible pressure drop and/or a subsequent stent implantation at least 5 mm from the stent was performed according to the physician's preference.<sup>13</sup> The final achievement of an FFR  $\geq 0.90$  was defined as an "optimal FFR result."

In the OCT arm, OCT images were acquired at the site of AICL with commercially available systems (C7 System; LightLab Imaging Inc/St Jude Medical, Westford, MA; and after its availability, Optis System; Abbott Vascular) after the OCT catheter (C7 Dragonfly; LightLab Imaging Inc/St Jude Medical; and Dragonfly Optis; Abbott Vascular) was advanced to the distal end of the target lesion. The entire length of the region of interest was scanned collecting the following measures: minimal lumen area (MLA; defined as cross-section area at the smallest lumen area level), proximal reference lumen area (defined as cross-section at the frame with largest lumen within 10 mm proximal to MLA and before any major side branch), distal reference lumen area (defined as cross-section at the frame with largest lumen within 10 mm distal to MLA and before any major side branch), and mean reference lumen area (defined as  $[\text{proximal reference lumen area} + \text{distal reference lumen area}] / 2$ ). On the basis of these parameters, percentage of area stenosis was calculated using



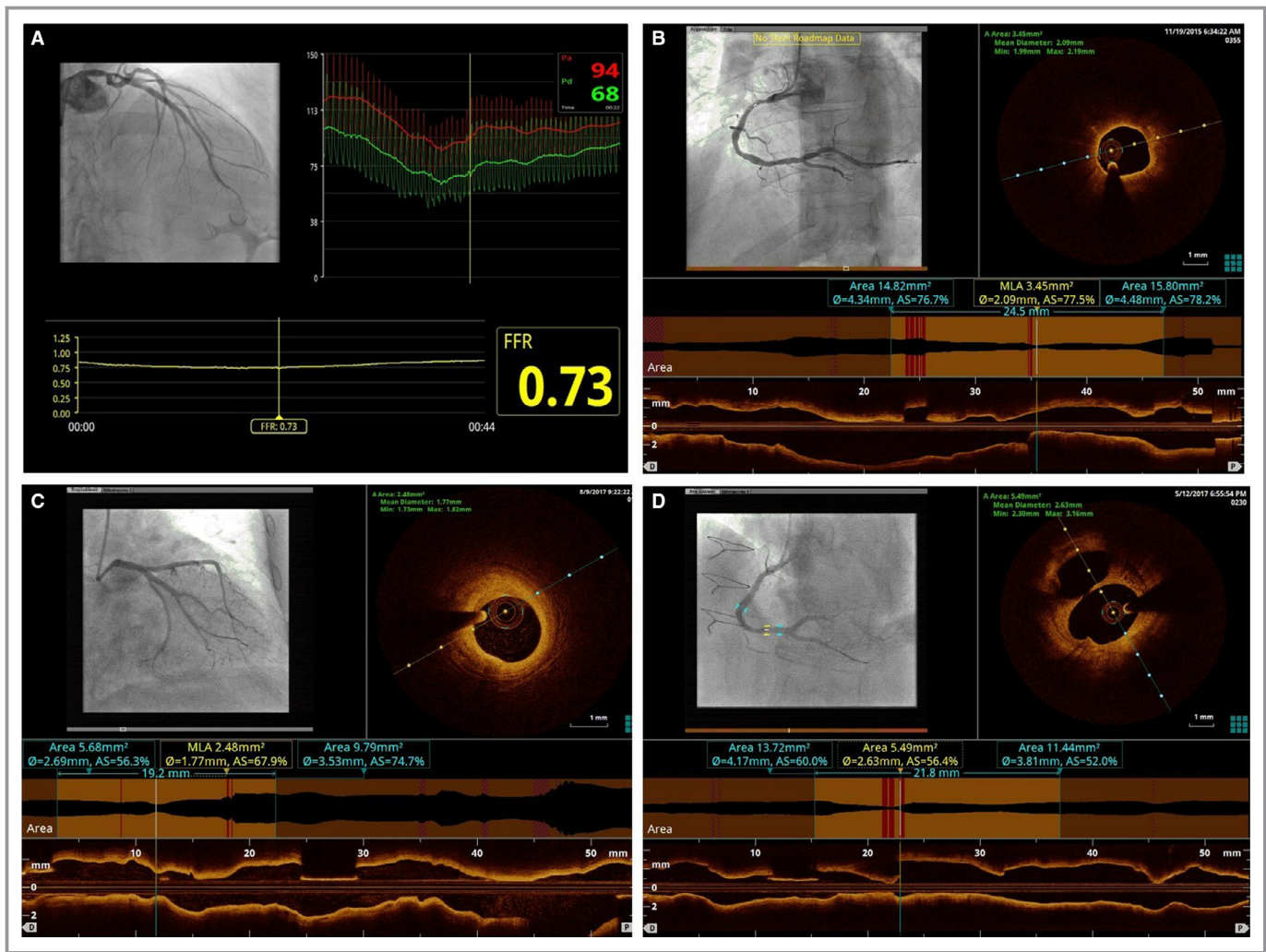
**Figure 1.** Study flow chart. AS indicates area stenosis; FFR, fractional flow reserve; MACEs, major adverse cardiovascular events; MLA, minimal lumen area; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

the following formula:  $(\text{mean reference lumen area} - \text{MLA}) / \text{mean reference lumen area} \times 100$ . PCI was performed when at least 1 of the following criteria was present: (1) percentage of area stenosis  $\geq 75\%$ ; (2) percentage of area stenosis from 50% to 75% with  $\text{MLA} < 2.5 \text{ mm}^2$ ; and (3) percentage of area stenosis from 50% to 75% and plaque ulceration. Plaque ulceration (or rupture) was defined as a recess in the plaque beginning at the luminal-intimal border.<sup>14</sup> Notably, the described criteria were not used in the past and were developed specifically for the present study.<sup>12</sup> The FORZA criteria are summarized in Figure 2. In OCT patients undergoing PCI, OCT was also used to optimize PCI results. Further interventions, following stent implantation, were performed in the presence of major stent malapposition, underexpansion, and major edge dissection. Absence of any of the above-mentioned abnormalities was defined an “optimal OCT result.” All OCT images were evaluated during the procedure by the operator in charge, who decided whether to perform PCI or optimize PCI according to the above-mentioned criteria.

### Study End Points

Each enrolled patient completed a Seattle Angina Questionnaire (SAQ) before FFR or OCT evaluation and at 1- and 13-month follow-up. The SAQ consists of a questionnaire of 11 questions grouped into 5 main scales measuring clinically important dimensions of coronary artery disease (physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception) and is scored by assigning each response an ordinal value, beginning with 1 for the response implying lowest level of functioning, and summing across items within each of the 5 scales. Scale scores are then transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100.<sup>15</sup> For the present study, because of the evidence of overlaps between the 5 assessment scales, we focused on the angina frequency scale and a cut-off value of 90 in this scale was used to define “significant residual angina.”

The combined clinical end point of significant residual angina ( $< 90$  score at SAQ angina frequency scale) plus major



**Figure 2.** FORZA criteria for revascularization. A, FFR  $\leq 0.80$ ; (B) AS  $\geq 75\%$ ; (C) AS from 50% to 75% with MLA  $< 2.5 \text{ mm}^2$ ; and (D) AS from 50% to 75% and plaque ulceration. AS indicates area stenosis; FFR, fractional flow reserve; MLA, minimal lumen area.

adverse cardiovascular events (MACE), defined as the occurrence of death, spontaneous myocardial infarction (MI), and target vessel revascularization at 13 months represented the predefined primary end point of the study.<sup>12</sup> Prevalence of the individual components of the primary combined end point at 1 and 13 months was considered secondary end points.

Rate of patients treated with medical therapy alone in the 2 different arms (FFR versus OCT) was also calculated. In addition, radioscopic time (minute), amount of contrast medium (mL), rate of contrast-induced acute kidney injury (CI-AKI), postprocedural release of markers of myonecrosis, rate of periprocedural (type 4a) MI, and global costs associated with the 2 different strategies were prospectively evaluated as further secondary end points at 1- and 13-month follow-up.

Iomeprol (Iomeron; Bracco Imaging, Milan, Italy) was the only contrast medium used in the present study. CI-AKI was defined according to the Acute Kidney Injury Network (AKIN) if

at least 1 of 3 conditions was met: (1) an absolute increase in serum creatinine levels by  $\geq 0.3 \text{ mg/dL}$  from baseline; (2) a relative increase in serum creatinine by  $\geq 50\%$  from baseline; or (3) a urine output reduced to  $\leq 0.5 \text{ mL/kg}$  per hour for at least 6 hours.<sup>16</sup> Type 4a MI was defined according to the third universal definition of MI.<sup>17</sup> Global costs comprised the consumables (regular wires, pressure wires, OCT catheters, balloon dilatation catheters, stents, antiplatelet therapy, adenosine, and contrast media), the cost of every day of hospitalizations post-PCI, and of any possible unplanned procedure or rehospitalization related to the index procedure. Personnel and laboratory time costs of the index procedure have not been included because they were assumed to be similar between the 2 strategies. Costs of consumables were provided by the hospital's pharmacy, and, in the case of change over time, a mean of costs noticed during the enrollment time was used. They were the following: drug eluting stent 600 euros, balloon catheters 95 euros, pressure



wire 940 euros, workhorse coronary wire 85 euros, iomeprol 0.24 euros/mL, OCT catheter 1600 euros, and adenosine 16 euros/vial. Every day of hospitalization in cardiology ward after procedure was computed as 500 euros. In the present article, we present early data concerning angina, clinical outcomes, and costs at 1-month follow-up, according to a prespecified analysis of secondary end points. Results of the primary end point of the study and of the secondary end points at 13 months will be presented later after follow-up completion of all the enrolled population.

## Sample-Size Calculation for Clinical Outcome and Statistical Analysis

The FFR-guided approach has been proven superior to the angio-guided approach by reducing the occurrence of MACE in the long term without affecting on the rate of angina. Thus, the FORZA trial was aimed to test whether OCT guidance may help toward improving the clinical management of patients with ischemic heart disease and inconclusive results at coronary angiography. Sample-size calculation was based on the clinical outcome at 13 months (a time point chosen assuming that most of patients had completed their 12-month double antiplatelet therapy 1 month before).<sup>18</sup> The primary end point was the combination of significant residual angina (<90 score at SAQ angina frequency scale) and MACE at 13 months, and all the assumptions have been previously reported. Indeed, we assumed to have a 5% rate of MACE in the FFR guidance group, in line with the rate observed in a previous study of patients with intermediate lesions treated on the basis of FFR.<sup>19</sup> Thus, combined with the 20% of patients suffering persistent angina at follow-up in the FFR guidance group, 25% of patients were expected to have reached the secondary end point at 13 months in the FFR guidance group. Given that we expected a significant reduction in angina, but not in MACE occurrence, in the OCT patients, we assumed a 50% reduction (exclusively attributed to angina relief) of the secondary end point in this group. As a consequence, a total number of at least 304 patients have been calculated necessary to satisfy the primary end-point requirements, with an alpha error of 5% and a beta error of 20%. Of note, this sample size was also deemed adequate for the prespecified analysis of the secondary clinical and economical end points at 1 month that are the focus of the present article.<sup>12</sup>

Categorical variables were expressed as percentages and analyzed by Fisher's exact test. Continuous variables (including clinical and economical end points) are expressed as mean±SD and/or median [interquartile range] and compared using the paired and unpaired *t* tests or the nonparametric Wilcoxon and Mann–Whitney U tests, as appropriate, after having tested normality using the Kolmogorov–Smirnov test.

Lesion-based analyses were carried out using generalized estimating equations in order to take into account potential cluster effects of the presence of multiple lesions in a single patient. A multivariate Cox regression analysis including potential confounding factors (ie, demographic and clinical findings) was carried out for the primary end point. Differences were considered significant with  $P<0.05$ . Missing values were not counted, and all analysis were based only on valid values and performed by intention to treat using GraphPad Prism (version 5.0; GraphPad Software Inc., San Diego, CA) and SPSS software (v.21.0; SPSS, Inc., Chicago, IL).

## Results

### Baseline Characteristics of the Study Population

From March 2013 to May 2018, a total of 350 patients were randomized to FFR (225 lesions evaluated in 176 patients) or OCT (221 lesions evaluated in 174 patients). The characteristics of the patients and lesions enrolled in the 2 study arms are reported in Tables 1 and 2. The vast majority of enrolled patients had stable ischemic heart disease (79.0% in FFR group versus 82.2% in OCT group;  $P=0.5$ ) with a preserved left ventricular ejection fraction ( $60\pm 8\%$  in FFR group versus  $56\pm 9\%$  in OCT group;  $P=0.74$ ). The 2 groups were well balanced for all clinical and angiographic characteristics, except for a significantly higher prevalence of previous MI and a lower prevalence of left anterior location for target lesion in patients randomized to OCT as compared with those randomized to FFR (Tables 1 and 2). Notably, the 2 groups had a similar value of frequency of angina at SAQ ( $83\pm 21\%$  in FFR group versus  $83\pm 24\%$  in OCT group;  $P=0.78$ ; Table 1). Roughly half of the population was constituted by patients with multivessel disease (52% in FFR group versus 48% in OCT group;  $P=0.45$ ), and in  $\approx 40\%$  of patients, more than 1 lesion was assessed by FFR or OCT (45% in FFR group versus 40% in OCT group;  $P=0.25$ ; Table 2).

### Diagnostic Performance of FFR Versus OCT

OCT guidance was associated with a significantly lower number of lesions and patients treated with medical therapy alone than FFR guidance: 109 of 221 lesions (49%) in 82 of 174 patients (41%) for OCT versus 159 of 225 lesions (71%) in 119 of 176 patients (68%;  $P<0.001$ ) for FFR (Table 3; Figure 3). Prevalence of the different OCT features can be found in Table 3. Of note, in 2 cases, OCT catheter was unable to cross the lesions, and, in another case, despite randomization to OCT, FFR was performed showing a value  $\leq 0.80$ .

**Table 1.** Patients Clinical Characteristics

	All Patients (n=350)	FFR (n=176)	OCT (n=174)	P Value
Age, y	68±9	68±10	69±9	0.5
Male sex	261 (74.6%)	126 (71.6%)	135 (77.6%)	0.22
BMI	27±4	27±10	27±5	0.74
Risk factors				
Diabetes mellitus	124 (35.4%)	61 (34.7%)	63 (36.2%)	0.82
Hypertension	299 (85.4%)	148 (84.1%)	151 (86.8%)	0.54
Dyslipidemia	250 (71.4%)	120 (68.2%)	130 (84.7%)	0.19
Smoking	136 (38.9%)	70 (39.8%)	66 (37.9%)	0.74
CKD	62 (17.7%)	32 (18.2%)	30 (17.2%)	0.90
Previous history				
Previous PCI	149 (42.6%)	73 (41.5%)	76 (43.7%)	0.74
Previous CABG	9 (2.6%)	4 (2.3%)	5 (2.9%)	0.75
Previous MI	85 (24.3%)	33 (18.8%)	52 (29.9%)	0.02
Clinical presentation				
Stable ischemic heart disease	282 (80.6%)	139 (79%)	143 (82.2)	0.5
ACS	68 (19.4%)	37 (21%)	31 (17.8%)	0.68
Unstable angina	40 (58.8%)	23 (62.2%)	17 (54.8%)	0.40
NSTEMI	25 (36.8%)	13 (35.1%)	12 (38.7%)	1
STEMI	3 (4.4%)	1 (2.7%)	2 (6.5%)	0.62
LVEF, %	57±8	60±8	56±9	0.74
Seattle Angina Questionnaire	83±21	83±21	83±23	0.78
Therapy at discharge				
Aspirin	329 (94%)	166 (94.3%)	163 (93.6%)	0.83
P2Y12 inhibitors	248 (70.8%)	115 (65.3%)	133 (76.4%)	0.02
Beta blockers	281 (80.2%)	137 (77.8%)	144 (82.7%)	0.28
Calcium-channel blockers	111 (31.7%)	56 (31.8%)	55 (31.6%)	1
ACE inhibitors/ARB	279 (79.7%)	147 (83.5%)	132 (75.8%)	0.48
Statin	313 (89.4%)	152 (86.3%)	161 (92.5%)	0.08
Nitrates	44 (12.5%)	25 (14.2%)	19 (10.9%)	0.42
Ranolazine	55 (15.7%)	31 (17.6%)	24 (13.7%)	0.38
Diuretics	121 (34.5%)	64 (36.3%)	57 (32.7%)	0.50
Oral anticoagulant	68 (19.4%)	32 (18.1%)	36 (20.6%)	0.59

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndromes; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction.

## Procedural Findings

Despite significant OCT findings, PCI was not performed in a patient with 2 significant lesions for an unexpected gastrointestinal bleeding. Consequently, PCI was performed on 66 lesions in 57 patients in the FFR group and on 110 lesions in 91 patients in the OCT group. OCT was associated with significantly higher consumption of contrast media

(280±129 mL) in comparison with FFR (245±137 mL;  $P=0.004$ ), rise in postprocedural creatinine blood levels (from  $0.97\pm0.34$  to  $1.03\pm0.40$  in the FFR group versus from  $1.02\pm0.51$  to  $1.11\pm0.72$  in the OCT group;  $P=0.04$ ), and rate of CI-AKI (3 cases [1.7%] in the FFR group versus 15 [8.6%] in the OCT group;  $P=0.034$ ). No patient required hemodialysis. Radioscopic time and dose area product were numerically, but not significantly, higher in the OCT than in the FFR group

**Table 2.** Lesion Characteristics

	FFR	OCT	P Value
Multivessel disease	92 (52.3%)	83 (47.7%)	0.45
Studied lesions	225	221	1
Single lesion studied	123 (54.7%)	133 (60.2%)	0.25
>1 lesion studied	102 (45.3%)	88 (39.8%)	
Target lesion			
LAD	150 (66.7%)	134 (60.6%)	0.02
LCX	37 (16.4%)	27 (12.2%)	
RCA	38 (16.9%)	60 (27.1%)	
Angiographic diameter stenosis, %	51±8	52±8	0.19
Baseline findings according to technique of randomization			
Resting Pd/Pa	0.93±0.04	N/A	
FFR	0.85±0.06	N/A	
MLA, mm <sup>2</sup>	N/A	3.09±1.57	
AS, %	N/A	63±12	

AS indicates area stenosis; FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; MLA, minimal lumen area; N/A, not applicable; OCT, optical coherence tomography; RCA, right coronary artery.

(Table 3). A significantly lower number of balloons and stents per patient was used in those randomized to FFR guidance than in those randomized to OCT guidance ( $0.74\pm 1.48$  balloons and  $0.33\pm 0.57$  stents per patient versus  $1.45\pm 1.85$  and  $0.64\pm 0.70$  in the OCT group; both  $P<0.001$ ; Table 3). When limiting to those patients treated with PCI, costs remained lower in the FFR group in comparison with the OCT group, with a little increase in the number of balloon and stents per patient (data not shown). A future specific subanalysis about this topic will help understanding better the effect of OCT and FFR on equipment utilization once the decision has been made to proceed with an intervention. No difference was found in the rate of procedural complications (2 minor vascular complications in the FFR group versus 1 minor stroke and 2 minor vascular complications in the OCT group) and in the rate of type 4a MI (3 cases [1.7%] in the FFR group versus 4 [2.3%] in the OCT group;  $P=0.72$ ; Table 3).

### PCI Optimization

OCT was used more frequently than FFR after PCI (76% versus 61%;  $P=0.017$ ; Table 4). In the remaining cases, post-PCI assessment by FFR or OCT was not performed for technical reasons or operator's preference. Moreover, an "optimal" result was significantly more frequent in OCT-guided than in FFR-guided PCI (65% versus 47%;  $P=0.001$ ). In the FFR arm, 13 of the remaining cases, despite associated with an FFR  $<0.90$ , were deemed acceptable by the operator. The latter 8 cases underwent FFR-guided optimization consisting in 8 cases of further stent postdilatation and in 2 cases of an additional

stenting. On the contrary, in the OCT arm, a suboptimal result was followed in all cases but 1 by an OCT-guided PCI optimization that consisted in 26 cases of stent postdilatation and in 7 cases of an additional stenting. In summary, the rate of PCI optimization was numerically higher with OCT, but was not significantly different between the 2 groups ( $P=0.09$ ; Table 4).

### Clinical and Economic Assessment at 1-Month Follow-up

Therapy at discharge was similar in both groups, except for an increased prevalence of P2Y12 inhibitor prescription in the OCT group attributed to the higher rate of PCI (Table 1). The combined clinical end point of significant residual angina and/or MACE at 1 month was not significantly different between FFR and OCT (7.3% versus 8.0%;  $P=0.84$ ; Table 5; Figure 3), even after adjustment for potential confounding (Table S1). Specifically, we observed only 1 MACE at 1 month: a noncardiac death for respiratory failure 13 days after the procedure in a patient randomized to FFR. Notably, this patient underwent coronary angiography before death and implanted stents were patent. Consequently, this death was adjudicated as attributed to respiratory failure in a patient with myositis. Regarding symptoms, both groups improved equally in the value of SAQ angina frequency scale (from  $82.8\pm 21.0$  to  $97.7\pm 8.6$  in FFR,  $P<0.001$  and from  $83.4\pm 23.8$  to  $97.1\pm 10.1$  in OCT,  $P<0.001$ ; delta SAQ in FFR  $14.7\pm 20.0$  versus delta SAQ in OCT  $13.0\pm 22.5$ ,  $P=0.45$ ). More important, the prevalence of persisting significant angina, as defined in the primary end point ( $<90$  in frequency

**Table 3.** Overall Procedural Results

	FFR 176 Patients 225 Lesions	OCT 174 Patients 221 Lesions	P Value
Patients treated with medical therapy alone	119 (67.7%)	82 (41.1%)	<0.0001
Lesions treated with medical therapy alone	159 (71.0%)	109 (49.3%)	0.061
Significant lesions			
FFR $\leq$ 0.80	66 (29.0%)	N/A	
Positive OCT for FORZA criteria	N/A	112 (50.7%)	
AS% $\geq$ 75%	N/A	35 (31.2%)	
AS% 50%–75%+MLA $<$ 2.5 mm <sup>2</sup>	N/A	63 (56.2%)	
AS% 50%–75%+plaque ulceration	N/A	11 (9.8%)	
Other*	N/A	3 (2.7%)	
Radioscopic time, min	17.2 $\pm$ 11.4	20.1 $\pm$ 22.6	0.14
DAP, mGy $\times$ cm <sup>2</sup>	20 819 $\pm$ 26 172	23 799 $\pm$ 29 179	0.32
Contrast media, mL	245 $\pm$ 137	280 $\pm$ 129	0.004
Delta creatinine, mg/dL	0.02 $\pm$ 0.18	0.08 $\pm$ 0.25	0.04
CI-AKI	3 (1.7%)	15 (8.6%)	0.034
Procedural complication	0 major 2 minor (1.1%)	1 major 2 minor (1.7%)	0.68
Type IVa MI ( $<$ 3x)	3 (1.7%)	4 (2.3%)	0.72
Post-PCI troponin T, ng/mL	0.25 $\pm$ 0.82	0.45 $\pm$ 1.82	0.11
No. of balloons per patient	0.74 $\pm$ 1.48	1.45 $\pm$ 1.85	<0.0001
No. of stents per patient	0.33 $\pm$ 0.57	0.64 $\pm$ 0.70	<0.0001

AS indicates area stenosis; CI-AKI, contrast-induced acute kidney injury; DAP, dose area product; FFR, fractional flow reserve; FORZA, Fractional Flow Reserve versus Optical Coherence Tomography to Guide Revascularization of Intermediate Coronary Stenoses; MI, myocardial infarction; MLA, minimal lumen area; NA, not applicable; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

\*In 2 cases, the OCT was unable to cross the lesions and, in another case, despite randomization to OCT, FFR was performed with an  $\leq$ 0.80 value.

scale of SAQ), was similar in FFR and OCT (6.8% versus 8.0%;  $P=0.69$ ; Table 5).

Use of OCT was associated with a trend toward longer hospital stay (2.8 $\pm$ 2.1 versus 3.8 $\pm$ 7.3 days;  $P=0.078$ ) and a significantly higher procedural cost (1416 $\pm$ 585 versus 2367 $\pm$ 714 euros;  $P<0.001$ ) in comparison with FFR. This was also maintained when analysis was restricted to those cases in which PCI was performed (2109 $\pm$ 577 euros in FFR versus 2929 $\pm$ 540 euros in OCT;  $P<0.001$ ) and when analysis was performed on a per-lesion basis (1145 $\pm$ 654 versus 1941 $\pm$ 773 euros;  $P<0.001$ ). Consequently, at 1-month follow-up, total costs per patient were significantly lower in the FFR group than in the OCT group (2831 $\pm$ 1288 versus 4292 $\pm$ 3844 euros;  $P<0.001$ ; Figure 3).

## Discussion

FFR and OCT may offer valuable help both in the decision-making process of severity of AICL and in PCI optimization. In

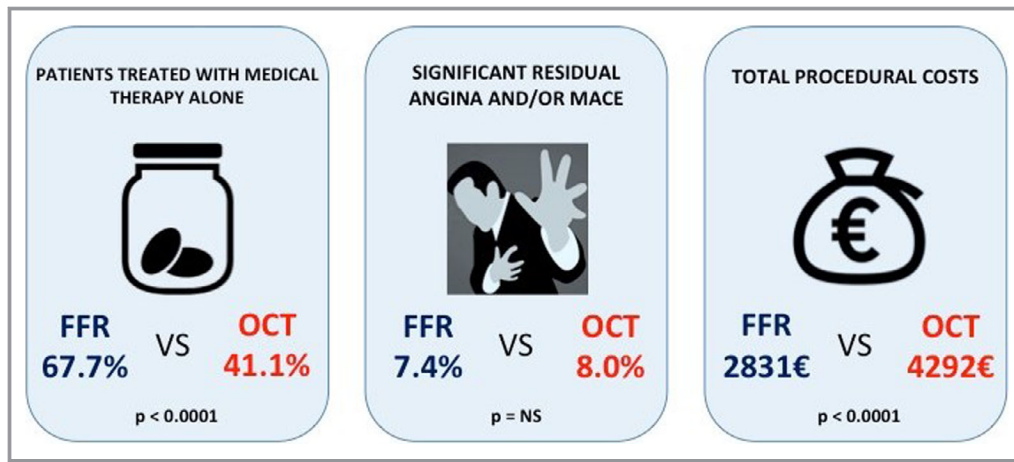
the present randomized study, we compared these 2 techniques in patients with AICL, and we found that:

1. OCT guidance in AICL was associated with a significantly lower probability of a treatment consisting of a medical therapy alone and with a significant increase in contrast dose, rate of CI-AKI, number of implanted stents, and costs in comparison with FFR guidance.
2. The higher number of OCT-guided PCI, in comparison with FFR guidance, did not affect clinical outcomes, at least at 1 month.

These novel data are clinically relevant given that they provide new support for the use of FFR in the decision-making process of patients with AICL. The possible clinical impact of the higher number of PCIs performed on the bases of OCT has to be evaluated at longer-term follow-up.

Current guidelines confer a class IA recommendation to FFR as the preferred tool to assess hemodynamic significance of coronary stenosis.<sup>18,20</sup> Nevertheless, FFR is still underused.<sup>21</sup>





**Figure 3.** One-month clinical and economic impact of FFR vs OCT in the management of angiographically intermediate coronary stenosis. FFR indicates fractional flow reserve; MACE, major adverse cardiovascular events; OCT, optical coherence tomography.

Regarding OCT, the identification of specific “imperfections” (that are undetectable by angiography, diagnosed better than by intravascular ultrasound, and that can be fixed by appropriate interventions) has been found to have clinical implications.<sup>22</sup> Yet, despite the outstanding correlation with histopathological findings, the role of OCT in defining lesions to be treated is, so far, undefined. Ideally, the combination of FFR for stenosis assessment and OCT for PCI optimization might be the perfect approach. However, for cost constraints, the choice of one technique or the other in the real world is often left to the operator’s discretion or logistical reasons. Thus, we decided to compare the performances of the 2 techniques both before and after PCI.

Use of FFR has been demonstrated as consistently superior to angiography in guiding PCI. More specifically, FFR-guided PCI can reduce recurrence of MACEs by reducing both the number of treated lesions and the costs in comparison with angiography-guided PCI.<sup>3,4</sup> Given that the ability of angiography to accurately assess severity of coronary lesions is affected by several imaging pitfalls,<sup>23</sup> the use of intravascular imaging, in particular using

intravascular ultrasound, has been advocated to guide operators in the choice of lesions to be treated, but the choice of an anatomical cut-off value for treating or deferring PCI remains unsettled.<sup>24</sup> The present study confirms that FFR guidance is associated with a significantly higher number of conservatively treated lesions even in comparison with the most accurate intravascular imaging technique. In fact, we found that, among AICL, OCT was still associated with 50% probability of PCI versus 30% using FFR. In addition, although the large increase in the rate of PCI was accompanied by an increase in amount of contrast medium, rate of CI-AKI, use of consumables, and, more generally, in costs, this was not followed by a difference in the improvement of symptoms, at least at 1-month follow-up. During planning of the present study, we hypothesized that a predicted increase in the rate of PCI could favorably affect the rate of angina. In practice, despite that the observed rate of PCI in the OCT arm was what we predicted in the trial design, we found a similarly low rate of significant angina (<10%) in both groups. It is worth mentioning, however, that the current analysis is underpowered to identify differences in the rate of angina at 1-month

**Table 4.** Technical Characteristics in Lesions That Underwent FFR-Guided or OCT-Guided PCI

	FFR-Guided PCI	OCT-Guided PCI	P Value
No. of lesions	66	112	
Poststenting assessment according to protocol	40 (60.6%)	85 (75.9%)	0.004
Poststenting assessment showing optimal result achievement	19 (47.5%)	55 (64.7%)	0.001
PCI optimization	8 (20%)	29 (34.1%)	0.09
By further balloon dilation	8 (20%)	26 (30.6%)	
By additional stent implantation	2 (5%)	7 (8.2%)	

FFR indicates fractional flow reserve; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

**Table 5.** Clinical and Economical End Points

	FFR 176 Patients 225 Lesions	OCT 174 Patients 221 Lesions	P Value
Primary end point at 1-month FU	13 (7.4%)	14 (8%)	0.84
MACE	1 (0.6%)	0 (0%)	1
SAQ frequency <90	12 (6.8%)	14 (8.0%)	0.69
SAQ angina frequency score at baseline	82.8±21.0	83.4±23.8	0.78
SAQ angina frequency score at 1-month FU	97.7±8.6*	97.1±10.1*	0.76
Delta SAQ frequency	14.7±20.0	13.0±22.5	0.45
Length of stay after procedure (days/patient)	2.82±2.10	3.85±7.31	0.07
Procedural costs (euros/patient)	1416±585	2367±714	<0.0001
Procedural costs for PCI (euros/patient)	2109±577	2929±540	<0.0001
Procedural costs (euros/lesion)	1145±654	1941±773	<0.0001
Total costs (euros/patient)	2831±1288	4292±3844	<0.0001

FFR indicates fractional flow reserve; FU, follow-up; MACE, major adverse cardiovascular events; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire.

\* $P<0.001$  vs SAQ frequency at baseline.

follow-up given that this study was powered to assess differences at 13-month follow-up. One-month data are therefore hereby presented, in accord with the study protocol, and must be viewed overall as prespecified secondary end points.

Regarding PCI optimization, OCT and FFR were associated with a remarkably different impact on the procedure. Optimization based on OCT was undertaken in the presence of: major stent strut malapposition (defined as a distance between the strut and vessel wall of  $>350$  or  $<350$   $\mu\text{m}$ ), but  $>200$   $\mu\text{m}$  for a length  $>600$   $\mu\text{m}$  (appreciable in  $>3$  contiguous frames at a pull-back speed of 20 mm/s), major stent underexpansion (defined as: in-stent minimal cross-section area of  $<75\%$  of the reference lumen area), and major edge dissection (defined as dissection  $>600$   $\mu\text{m}$  [appreciable in  $>3$  contiguous frames at a pull-back speed of 20 mm/s]). Despite these criteria differing from the ILUMIEN criteria (minimum stent area  $>90\%$ ),<sup>25</sup> it must be acknowledged that, at the time of the study, these represented the most extensively validated criteria in the literature and are stated in the study protocol.<sup>26</sup>

Indeed, despite protocol recommendation for systematic use after stenting, FFR was significantly less performed as compared with OCT. This was attributed to technical problems (mostly lack of signal after disconnection and reconnection, significant drift, or damage of the pressure wire when PCI was performed using the pressure wire itself as a guidewire) or inability or unwillingness of the operator after an angiographically successful PCI. Another important finding is related with the achievement of an immediate “optimal result” more

frequently in OCT than in FFR-guided PCI, probably suggesting that OCT lesion evaluation before PCI may facilitate, in the setting of expert OCT operators, the specific PCI planning.<sup>27</sup> The issue of appropriate device selection on the bases of OCT pre-PCI results has been extensively discussed and has currently been standardized in the design of contemporary OCT-guidance trials.<sup>28</sup> Regarding FFR, several studies, summarized in the meta-analysis of Johnson et al,<sup>29</sup> suggest that the best prognosis is associated with a post-PCI FFR value of at least 0.90. Accordingly, the 3V-FFR study showed that the lower the sum of FFR in all major branches, the worst the prognosis even after a successful PCI.<sup>30</sup> However, the 0.90 cut-off value takes into account not only the treated segment of the artery, but also the disease below and above the stent. This means that the definition of a suboptimal result could be a little broader and even irrespective of a technically perfect result on the treated lesion. Accordingly, in our study, although a suboptimal result was obtained in half of the lesions, in the majority of cases the operator interpreted the low FFR value as a consequence of the concomitant disease and not attributable to stented lesion, thus refraining from further action.

### Limitations

The FORZA trial is a single-center, relatively small, randomized clinical trial that cannot draw conclusions about hard clinical end points; nevertheless, the quite elevated rate of enrollment (approximately 1.5 patients/week) and the homogenous and practical approach in assessment and PCI optimization make

the results transferable to the everyday clinical scenario. In this regard, the possible limitation represented by the use of unconventional OCT criteria has to be acknowledged in light of the lack of clear data at the time of design of the trial. However, it is worth noting that, after initiation of the study, these criteria were validated in comparison with FFR in a retrospective cohort of patients assessed with both FFR and OCT.<sup>31</sup> Finally, despite trial design recommended reassessment by FFR or OCT after PCI, the rate of FFR or OCT guidance in optimization was suboptimal. This could have played a limited role in the immediate procedural results, but we cannot exclude an effect in the final clinical results at 13-month follow-up. In any case, this highlights the need for technical refinements for both FFR and OCT technologies that can facilitate the use of these quite expensive tools to every setting.

## Conclusions

The present study demonstrates that a functional guidance using FFR is associated with a significantly higher percentage of lesions treated with medial therapy alone in comparison with a morphological guidance by OCT. This is associated with a lower rate of AKI, shorter hospitalizations, and an overall significant early cost reduction with FFR.

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Multivariate Cox regression analysis.**

	<b>HR</b>	<b>CI 95%</b>	<b>P Value</b>
Age >65 years	0.64	0.27–1.49	0.299
Male sex	0.65	0.24–1.77	0.403
Diabetes	0.82	0.33–2.01	0.660
Hypertension	0.52	0.21–1.30	0.159
Dyslipidemia	1.21	0.49–2.99	0.684
Smoking	0.79	0.34–1.81	0.575
CKD	1.57	0.51–4.84	0.428
Previous MI	0.58	0.21–1.63	0.303
Stable Ischemic Heart Disease	0.59	0.25–1.43	0.246
Aspirin	1.78	0.23–13.71	0.579
P2Y12 inhibitors	0.94	0.40–2.19	0.879
Statin	0.70	0.21–2.32	0.563
FFR group	0.86	0.40–1.87	0.707

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; MI, myocardial infarction; FFR, fractional flow reserve.