Original Contribution

iFR/FFR/IVUS Discordance and Clinical Implications: Results From the Prospective Left Main Physiology Registry

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Abstract

OBJECTIVES: This study aimed to assess discordance between results of instantaneous wave-free ratio (iFR), fractional flow reserve (FFR), and intravascular ultrasound (IVUS) in intermediate left main coronary (LM) lesions, and its impact on clinical decision making and outcome.

METHODS: We enrolled 250 patients with a 40%-80% LM stenosis in a prospective, multicenter registry. These patients underwent both iFR and FFR measurements. Of these, 86 underwent IVUS and assessment of the minimal lumen area (MLA), with a 6 mm^2 cutoff for significance.

RESULTS: Isolated LM disease was recognized in 95 patients (38.0%), while 155 patients (62.0%) had both LM disease and downstream disease. In 53.2% of iFR+ and 56.7% of FFR+ LM lesions, the measurement was positive in only one daughter vessel. iFR/FFR discordance occurred in 25.0% of patients with isolated LM disease and 36.2% of patients with concomitant downstream disease (*P*=.049). In patients with isolated LM disease, discordance was significantly more common in the left anterior descending artery and younger age was an independent predictor of iFR-/FFR+ discordance. iFR/MLA and FFR/MLA discordance occurred in 37.0% and 29.4%, respectively. Within 1 year of follow-up, major cardiac adverse events (MACE) occurred in 8.5% and 9.7% (*P*=.763) of patients whose LM lesion was deferred or revascularized, respectively. Discordance was not an independent predictor of MACE.

CONCLUSIONS: Current methods of estimating LM lesion significance often yield discrepant findings, complicating therapeutic decision-making.

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Key words: fractional flow reserve, instantaneous wave-free ratio, intravascular ultrasound, plaque rupture

Introduction

More than 80% of the coronary flow to the left ventricle passes through the left main coronary artery (LM).[1] Plaque rupture in the LM often causes sudden death or results in large myocardial infarctions and cardiogenic shock with high mortality.[2] Patients with significant LM disease not revascularized by coronary artery bypass surgery (CABG) or percutaneous coronary intervention were found to have a poor prognosis.[3]

In patients with chronic coronary syndromes, revascularization is recommended for persistent invalidating ischemic symptoms and functionally significant lesions.[4] In patients with a LM stenosis, inappropriate deferral of revascularization may

impede symptom improvement and increase the risk of spontaneous, possibly fatal, adverse events, while inappropriate revascularization would unnecessarily expose patients to procedure-related risks and early bypass failure when CABG is chosen. [5]

The European Society of Cardiology (ESC) guidelines recommend using fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) to demonstrate functional significance of intermediate-grade coronary stenoses.[4] Randomized trials have shown that revascularization of functionally significant lesions improves outcomes while deferring non-significant lesions appears safe.[1] For the evaluation of intermediate LM lesions, which are notoriously difficult to assess angiographically, the ESC endorsed both FFR and iFR with a class I recommendation.[4] Intravascular ultrasound (IVUS) received a class IIa recommendation for this purpose.[4] In general, a minimal lumen area (MLA) of ≤/>6 mm^2 on IVUS is then used to decide on revascularization or deferral.[1,4,6]

The Prospective Left Main Physiology Registry (PHYNAL) registry was designed to assess prevalence and clinical importance of conflicting results of iFR, FFR, and IVUS in intermediate LM lesions.

Methods

Patient population. Between January 2019 and May 2021, 14 university and large community Belgian centers enrolled 250 consecutive patients with a LM lesion of intermediate severity, defined as a 40%-80% diameter stenosis on visual assessment of the angiogram. Patients with concomitant disease in the left anterior descending (LAD), circumflex (LCx), and/or right coronary artery were also included. The LM lesions had to be presumably stable. The study was approved by local ethics committees and all patients provided written informed consent.

Study procedure. The enrolled patients underwent both iFR and FFR measurements. IVUS use was at operator's discretion, but recommended if the stenosis was >50%, iFR 0.90 to 0.93, or FFR 0.80 to 0.85.

iFR and FFR were measured with the Verrata pressure wire and associated software (Philips). All operators received training on best practices and systematic approaches. This included use of a guiding catheter, upfront intracoronary administration of nitrates, pressure equalization in the aorta, and final verification of absence of significant drift. First, the iFR was measured in both LAD and LCx. Thereafter, FFR measurements were performed in both vessels during intravenous administration of adenosine. If the intermediate branch was larger than LCx, measurements in the former were considered LCx measurements. iFR and FFR were always measured distally in LAD and LCx where the vessels where approximately 2 mm in diameter. In cases of downstream disease in LAD and/or LCx, additional proximal iFR measurements were performed 5 mm distal to the LM carina in both LAD and LCx (iFR_{PROX}). In patients with an isolated LM lesion, the lesion was considered positive (significant) by iFR if the iFR was ≤0.89 in at least one daughter vessel and positive by FFR if the FFR was ≤0.80 in at least one daughter vessel. In patients with downstream disease, the LM lesion was considered positive by iFR if the iFR_{PROX} was ≤0.89 in at least one daughter vessel. In those patients, the FFR measurements were not used to decide upon significance of the LM lesion. iFR/FFR discordance was assessed in all patients using the distal iFR and FFR measurements only.

IVUS was performed with the Refinity rotational device (Philips) and automated pullbacks at 0.5 mm/sec. A LM lesion with an MLA ≤6 mm^2 was considered significant by IVUS. To analyze discordance between physiological and imaging parameters, the lowest iFR and FFR values were correlated with the MLA. For iFR, this analysis used the distal iFR value in patients with isolated LM disease and the iFR_{PROX} value in patients with concomitant downstream disease. For the comparison with FFR, only the patients with isolated LM disease were considered.

After each step in the LM lesion assessment, the preferred therapeutic strategy was noted. The final treatment was determined by the treating physician and the Heart Team considering all relevant patient characteristics and patient preference. All angiographic images and physiological measurements were analyzed by two experienced operators together (PK, MC). IVUS images were analyzed by the "UMONS Cœur" core laboratory.

Study endpoints. This registry was designed with two primary aims. First, to examine the occurrence of discordance in iFR/FFR, iFR/MLA, and FFR/MLA results. Second, to determine the percentage of *major adverse cardiac events (MACE),* defined as a composite of death, nonfatal myocardial infarction (MI), and unplanned target lesion (LM) revascularization

(TLR) at 1-, 2-, and 5-years follow-up. It was pre-specified to assess the outcomes of patients whose LM lesion was deferred based on a negative iFR. The study design and flowchart are presented in the supplemental appendix (**Figure S1**).

Statistical analysis. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 27 (IBM Corp). Continuous variables are presented as mean ± standard deviation (SD) or as median with interquartile range. The Shapiro-Wilk test was used to test normality. Categorical variables are presented as counts and percentages. Continuous variables were compared using Student's t or Mann-Whitney U-tests, and categorical variables using $\chi 2$ or Fisher's exact tests, as appropriate. A logistic regression model was used for multivariate analysis to detect influencing factors on iFR/FFR discordance. Correlations between iFR/FFR and iFR/MLA were assessed using the Pearson test. A two-tailed $P<.05$ was considered statistically significant for all tests.

Results

Clinical features and patient demographics are presented in **Table 1.** Both iFR and FFR were measured in 250 patients, and 86 (34.4%) of these patients also underwent IVUS. **Table 2** summarizes the results from the assessments by angiography, physiology, and IVUS.

TABLE 1. PATIENT CLINICAL CHARACTERISTICS AND DEMOGRAPHICS.

	Overall n = 250	Isolated LM Disease n = 95(38.0%)	LM and Downstream Disease n = 155(62.0%)	*P*-Value
CLINICAL CHARACTERISTICS				
Age, years	68.3±10.3	68.7±10.3	68.0±10.4	.542
Male	203(81.5)	75(79.8)	128(82.6)	.582
BMI, kg/m²	27.1±4.4	27.4±4.2	26.9±4.5	.453
Current smoker	59(23.6)	23(24.2)	36(23.2)	.840
Ex-smoker	92(36.8)	35(36.8)	57(36.8)	.924
Hypertension	171(68.4)	65(68.4)	106(68.4)	.996
Hypercholesterolemia	216(86.4)	82(87.2)	134(86.5)	.860
Diabetes	63(25.2)	26(27.4)	37(23.9)	.536
Previous MI	63(25.2)	23(24.2)	40(25.8)	.895
Previous PCI	106(42.4)	34(35.8)	72(46.5)	.098
Atrial fibrillation	47(18.9)	19(20.2)	28(18.1)	.675
Heart failure	31(12.4)	10(10.5)	21(13.7)	.459
Peripheral artery disease	38(15.4)	15(16.0)	23(15.0)	.845
Previous TIA/stroke	22(8.8)	7(7.4)	15(9.7)	.522
Chronic kidney disease*	43(17.2)	15(15.8)	28(18.1)	.644
LVEF	n=218	n=79	n=139	.839
> 60%	130(59.6)	45(56.9)	85(61.1)	
50%–60%	42(19.3)	19(24.0)	23(16.5)	
35%–50%	36(16.5)	13(16.5)	23(16.5)	
< 35%	10(4.6)	2(2.5)	8(5.7)	

Table 1, *continued*

Table 1. Patient clinical characteristics and demographics.

	Overall n = 250	Isolated LM Disease n = 95(38.0%)	LM and Downstream Disease n = 155(62.0%)	*P*-Value
Presentation				
Asymptomatic	56(22.6)	17(17.9)	39(25.2)	.210
Stable angina	89(35.6)	36(37.9)	53(34.1)	.512
CCS class ≥ 2	83(33.2)	30(31.6)	53(34.1)	.515
ACS	28(11.2)	15(15.8)	13(8.4)	.075
Silent ischemia	37(15.0)	10(10.8)	27(17.5)	.148
Atypical chest pain	27(10.8)	11(11.6)	16(10.3)	.756
Arrhythmia	49(19.7)	24(25.5)	25(16.1)	.070
Dyspnea	116(46.4)	45 (47.4)	71 (45.8)	.636
NYHA class ≥ 2	104(41.6)	39(41.1)	65(41.9)	.686
Noninvasive evidence of ischemia	139(55.6)	52(54.7)	87(56.1)	.830
On ECG	99(39.6)	35(36.8)	64(41.3)	.485
On imaging	73(29.2)	32(33.6)	41(26.4)	.222

Values are n(%); *glomerular filtration <60 mL/min
ACS = acute coronary syndrome; BMI = body mass index; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; LM = left main coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

As assessed by iFR, 24.8% (62/250) of the LM lesions were considered significant: 29.5% (28/95) of the patients with isolated LM disease and 21.9% (34/155) of the patients with downstream disease. As assessed by FFR, 31.6% (30/95) of the patients with isolated LM disease were considered significant.

The significance of the LM lesion as suggested by the physiological measurement often depended on the daughter branch in which the measurement was taken (**Figure 1**). In 53.2% of iFR-positive and 56.7% of FFR-positive LM lesions, the value was positive in only one daughter vessel. In those patients, that vessel was the LAD in 63.6% and 88.2% of cases, respectively.

iFR/FFR discordance. In **Figure 2,** we present the occurrence of iFR/FFR discordance per patient and vessel. In patients with isolated LM disease, the lowest iFR and FFR values showed a moderate correlation (Pearson r=0.553, *P*<.001), represented in **Figure 3**. In those patients, discordance was more frequent in LAD compared with LCx (16.8% vs 14.3%, *P* =.003). In a multivariate analysis, younger age was an independent predictor of iFR-/FFR+ discordance (*P* =.005).

iFR/MLA and FFR/MLA discordance. The lowest iFR and MLA were poorly related (r=0.040, *P*=.063). iFR/MLA discordance occurred in 37.0% of patients (44.1% of patients with isolated LM disease). Minimal FFR and MLA were also poorly related in patients with isolated LM disease. Discordant values were found in 29.4%. The discordance between physiological parameters and MLA in patients with isolated disease is illustrated in **Figure 3.** No parameter emerged as an independent predictor of this type of discordance.

Table 2. Results from angiography, physiology, and imaging.

	Overall n = 250	Isolated LM Disease n = 95 (38.0%)	LM and Downstream Disease n = 155 (62.0%)	*P*-Value
ANATOMY				
LM Lesion Type				
Ostial	91(36.4)	39(41.1)	52(33.5)	.231
Shaft	55(22.0)	18(18.9)	37(23.9)	.362
Distal bifurcation	117(46.8)	37(38.9)	80(51.6)	.051
Distal trifurcation	43(17.2)	20(21.1)	23(14.8)	.242
LM DS, visual,%	50.5±9.9	51.1±11.0	49.6±9.7	.245
LM DS, QCA, %	50.1±10.3	51.2±10.5	50.0±9.5	.335
≥ 50%	139(55.6)	53(55.8)	86(55.5)	.962
≥ 70%	8(3.2)	5(5.3)	3(1.9)	.161
SYNTAX score	18(11)	15(10)	21(13)	<.001
Bystander disease				
RCA	71(28.4)	22(23.2)	49(31.6)	.150
RCA CTO	18(7.2)	6(6.3)	12(7.7)	.672
Right dominance	250(100)	85(89.5)	144(92.9	.343
Left dominance		5(5.3)	5(3.2)	.425
Codominance		5(5.3)	6(3.9)	.602
PHYSIOLOGY				
iFR performed	250(100)			
LAD	250(100)			
iFR proximal			0.94±0.06	
iFR distal		0.91±0.07	0.83±0.11	<.001
LCx	241(96.4)			
iFR proximal			0.95±0.06	
iFR distal		0.94±0.08	0.91±0.11	.022
FFR performed	250(100)			
LAD	250(100)	0.84±0.08	0.75±0.11	<.001
LCx	231(92.4)	0.89±0.09	0.85±0.09	.008
IMAGING				
IVUS performed	86(34.4)			
MLA, mm^2	6.1±2.6	6.2±2.3	5.9±2.2	.480

Values are n(%), mean±SD or median(IQR)
CTO = chronic total occlusion; DS = diameter stenosis; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main coronary artery; MLA = minimal lumen area; QCA = quantitative coronary angiography; RCA = right coronary artery; SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery

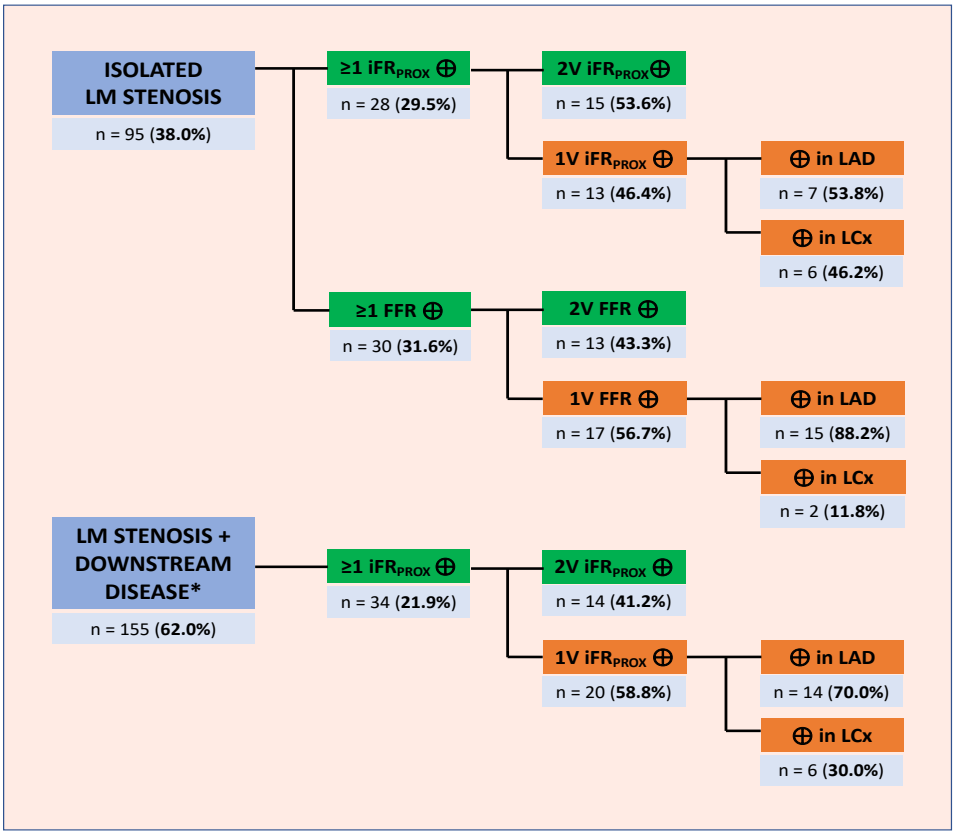

Figure 1. Impact of a LM stenosis on the daughter vessels. The impact of a LM stenosis on the daughter vessels is shown for patients with isolated LM disease and patients with LM disease and downstream disease.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main coronary artery; iFR$_{PROX}$ = iFR measured 5 mm distal to LM carina; V = daughter vessel

*not applicable for FFR as FFR is influenced by downstream disease

Figure 2. Occurrence of iFR/FFR discordance per patient and per vessel. The occurrence of iFR/FFR discordance is presented per patient and per vessel for each situation: isolated LM disease and LM disease with downstream disease. Discordance was assessed at distal level. iFR and FFR values were available for both daughter vessels in 92 patients with isolated LM disease* and 149 patients with LM disease and downstream disease†.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main coronary artery

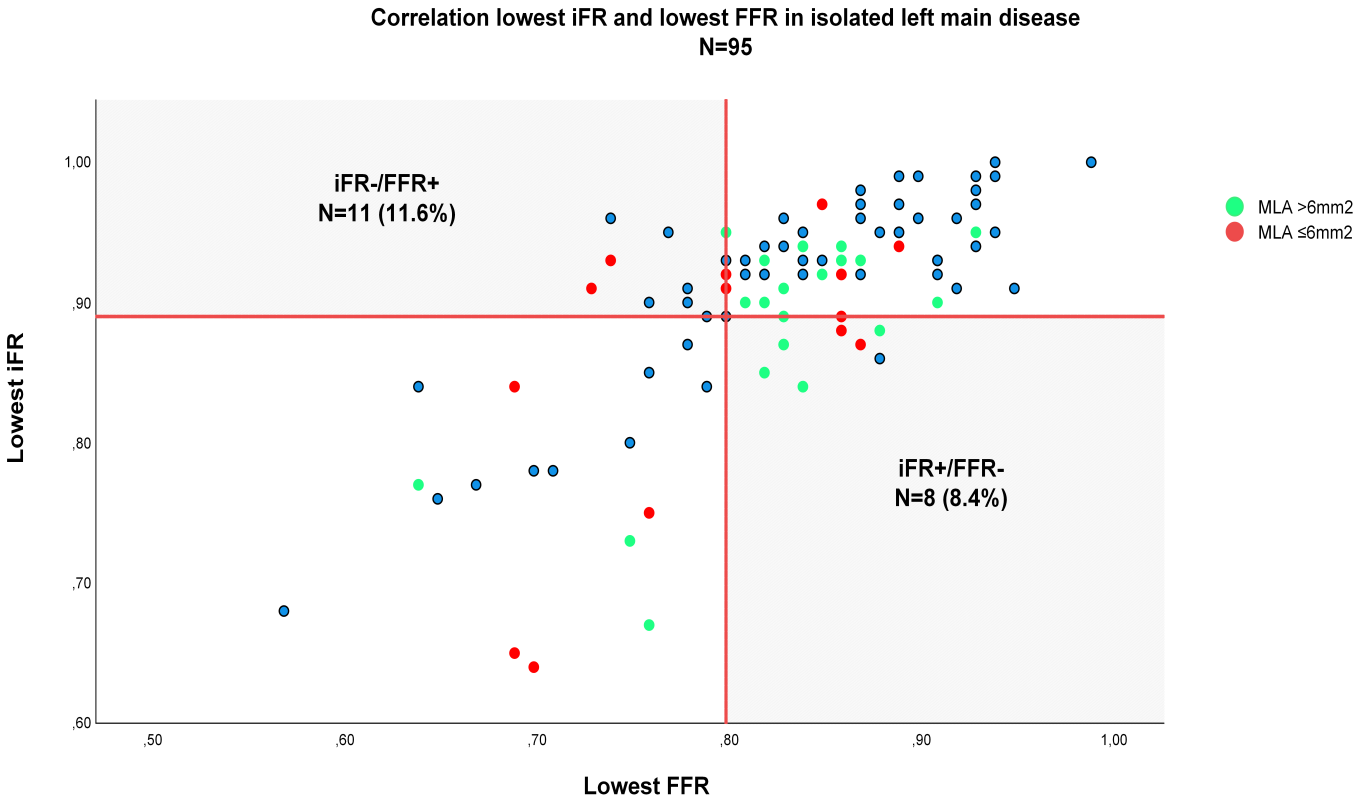

Figure 3. Relationship between the lowest iFR_{LM}, the lowest FFR and the MLA.
The relationship between the lowest iFR and FFR is shown in a scatter plot for the patients with isolated LM disease (Pearson correlation coefficient r = 0.553; *P* <.001). For the patients who have also undergone IVUS, the relationship with the MLA is shown: red dots represent patients with an MLA ≤6 mm^2, while patients with an MLA >6 mm^2 are shown as green dots, and patients in whom IVUS was not performed are shown as blue dots. iFRLM = instantaneous wave-free ratio, left main; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; LM = left main coronary artery; MLA = minimal lumen area

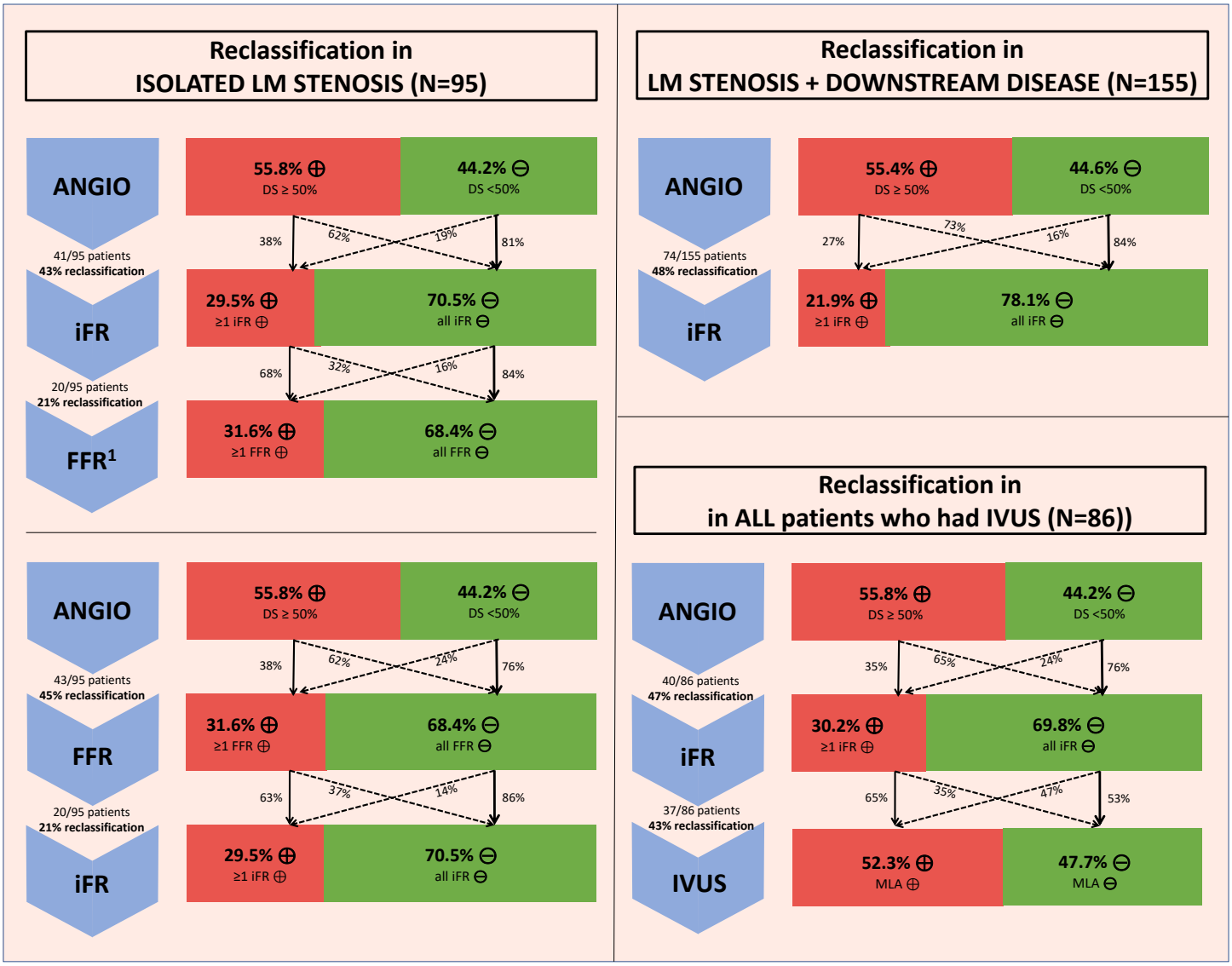

Figure 4. Patient reclassification according to the assessment method.
Depending on the tool one uses to assess the significance of an intermediate LM, the lesion is often classified differently.

Δ = reclassification percentage; angio = coronary angiogram; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio at distal level in patients with isolated disease and at 5 mm distal to the LM carina in patients with downstream disease; LM = left main coronary artery; IVUS = intravascular ultrasound

Impact on strategy. Figure 4 shows how adding iFR, FFR, or IVUS to angiography reclassified LM significance. **Figure 5** shows how the treatment strategy changed based on physiological assessments and how the patient was ultimately treated. The decision to defer revascularization of the LM disease was consistent with the iFR in 91.5% of patients, while the decision to revascularize was consistent with the iFR in 64.4% of patients. The reasons why the iFR was overruled are stated in the online supplement. No intervention for LM disease was performed in 177 (70.8%) patients.

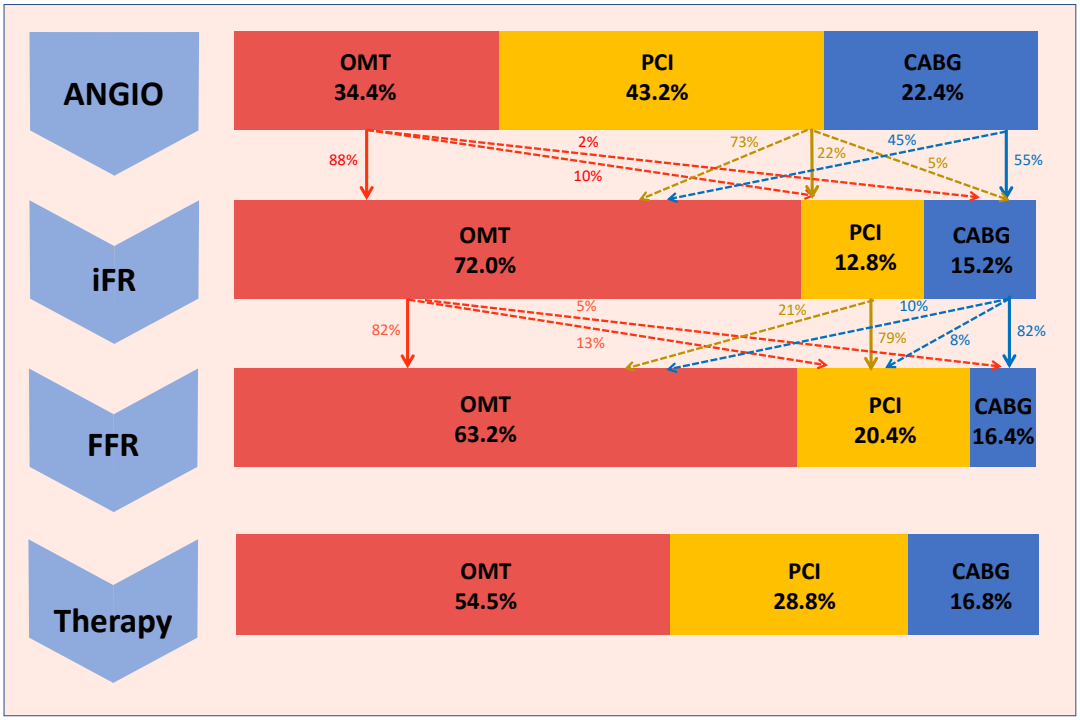

Figure 5. Treatment plan in LM disease with or without downstream disease. The treatment strategy for the LM lesion is displayed as communicated by the operator during the procedure and as ultimately executed.

Angio = coronary angiogram; CABG = coronary artery bypass grafting; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LM = left main coronary artery; OMT = optimal medical therapy

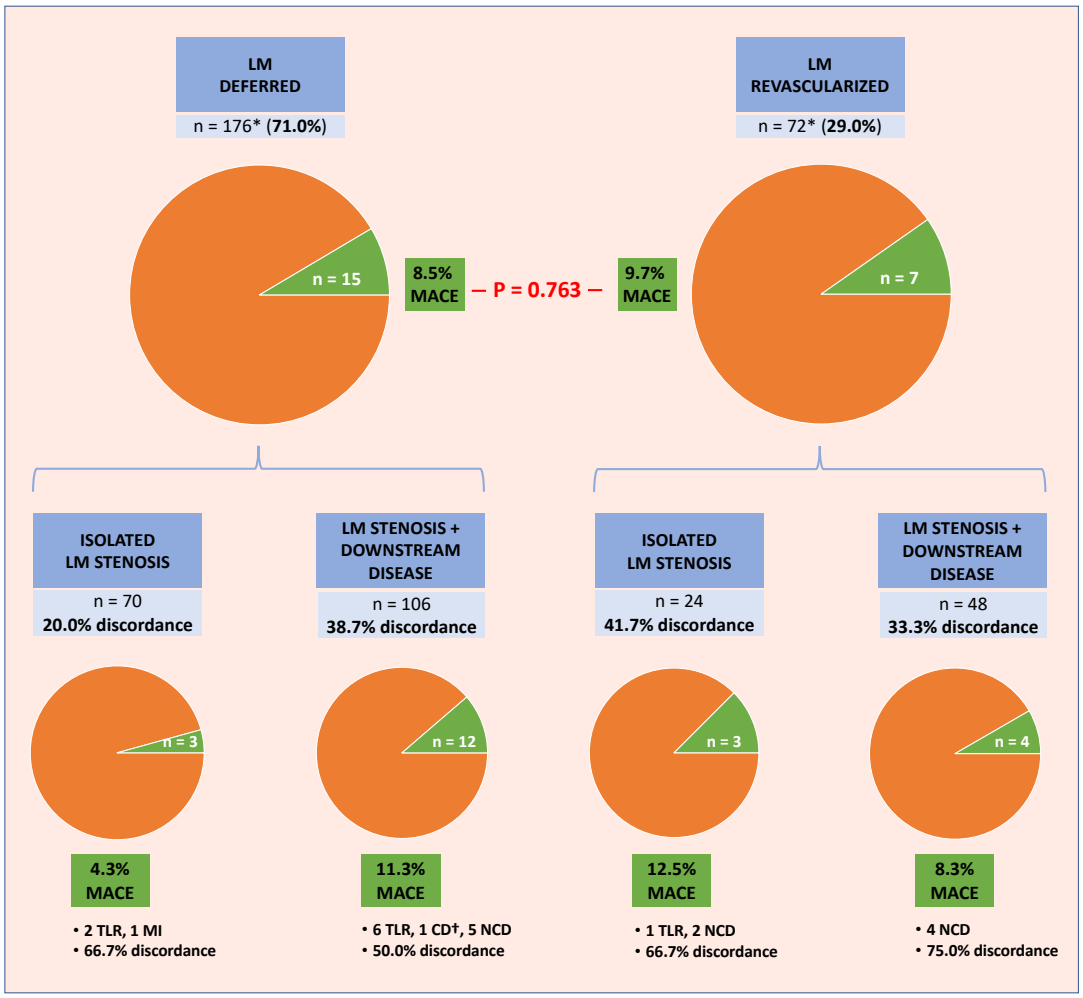

Figure 6. One-year clinical outcomes. The MACE rates are presented for patients whose LM lesion was deferred and for patients whose LM lesion was revascularized. MACE were a composite of all-cause death, nonfatal MI, or TLR. All-cause death cases were further categorized as CD and NCD. Discordance refers to iFR/FFR discordance.
*The outcome was unknown in 1 deferred patient and 1 revascularized patient as they were lost to follow-up. †The one CD that occurred was not related to a coronary event (known cardiomyopathy and ventricular arrythmia).

CD = cardiac death; LM = left main coronary artery; MACE = major adverse cardiac events; NCD = non-cardiac death; TLR = target lesion

One-year clinical outcomes. Patients whose LM lesion was deferred had similar one-year MACE rates compared with revascularized patients (**Figure 6**). However, 12 of the 22 events (54.5%) were deaths that could not be associated with a coronary event. Of the remaining 10 events, all of which occurred in deferred patients, 9 were TLRs, including 6 in patients with iFR/FFR discordance. Only 2 TLRs were performed for acute coronary syndrome (1 unstable angina, 1 MI). The presence of iFR/FFR/MLA discordance was not an independent predictor of MACE.

Discussion

In the PHYNAL study, intermediate-grade LM lesions were assessed using both the guideline-recommended physiological indices, iFR and FFR, and IVUS in selected patients. Three key findings emerged from this systematic approach.

1. Discordance is common and impacts clinical decision-making.

When taking measurements in both LAD and LCx into account, iFR/FFR discordance occurred in 25.0% of patients with isolated LM disease and significantly more frequently (36.2%) when downstream disease was present. Previously, discordance, has been reported in approximately 20% of non-LM lesions and explained by differences in hyperemic coronary flow velocity.[1,7,8] It was later found to be more common in proximal LAD and LM lesions (predominantly iFR-/FFR+ discordance) and this was attributed to higher hyperemic flows and pressure gradients (lower FFR values) across lesions supplying more myocardium.[9,10] Subsequently, 3 observational studies focused on LM lesions. The first series included 80 patients and found iFR/FFR discordance in 18.7% of cases.[11] Only 10.0% of patients had measurements in both LAD and LCx. It was not reported how many patients had downstream disease and how pressure measurements were taken and interpreted in such cases. The iLITRO-EPIC07 prospective registry enrolled 300 patients with a 25%-60% LM diameter stenosis.[12] Severe lesions in LAD or LCx had to be treated with PCI before and patients with an indication for CABG, regardless of LM lesion significance, were excluded. More than 85% of patients underwent pressure measurements in both LAD and LCx. Discordance occurred in 20.3% of patients when measurements were performed in the LAD, compared with 13.6% when performed in the LCx. In PHYNAL, LM lesions with a 40%-80% diameter stenosis were enrolled. To reflect the challenges of real-life decision-making, patients with concomitant downstream disease were deliberately allowed. 96% of the patients had iFR and FFR measurements in both LAD and LCx. We also found that discordance was more frequent in LAD than in LCx: 16.8% and 14.3%, respectively (*P*=.003) in isolated LM disease and 23.0% and 18.2%, respectively (*P* -value non significant) in LM disease with additional downstream disease. Younger age was associated with iFR-/FFR+ discordance in patients with isolated LM disease, a finding probably related to preserved microvascular function in younger patients.[13]

We also found that MLAs measured with IVUS poorly correlated with iFR and FFR results. Discordance with a binary 6 mm^2 MLA cut-off occurred in more than 30% of cases, a finding comparable to recent series in which IVUS was performed systematically.[12,14]

The use of iFR or FFR assessments is known to alter initial angiogram-based treatment decisions in non-LM lesions by up to 40% and 48%, respectively, usually in favor of medical therapy.[15,16] Also in our study, iFR, FFR, and IVUS reclassified more than 40% of angiographic intermediate LM lesions from significant to non-significant and vice versa, resulting in a change in treatment plan.

2. Physiological assessment of LM lesions requires assessment of both daughter vessels and attention to downstream disease.

More than half of patients with a positive LM iFR or FFR had positive measurements in only one vessel (usually LAD). Thus, measuring in all major daughter vessels is important to avoid missing significant LM disease. Knowing that the physiological findings are only significant in one branch may also be particularly important when the patient is sent for surgery, as the bypass graft may fail on a branch in which the flow is not significantly impeded.[5,17]

LM disease often involves the distal bifurcation and may extend to daughter vessels, affecting perfusion differently in each vessel.[1] Other factors may also play a role. The greater the mass of the perfused myocardium subtended by a stenosis, the more likely the stenosis will be functionally significant.[18] Because the LAD perfuses a greater mass of myocardium than the LCx, the same LM lesion may lower iFR and FFR more in LAD than in LCx. The distal segments of LAD and LCx, where the distal pressure measurements were performed in this study, are also exposed to different hydrostatic pressures.[19] In a supine

patient, when the pressure wire sensor is placed in the distal LAD, it is located several centimeters higher than the coronary ostium, while it is located several centimeters lower than the ostium when the sensor is placed in distal LCx. This may result in measured pressures and iFR and FFR values that are lower in the distal LAD and higher in the distal LCx.[19,20]

Three out of 5 patients with LM disease also had downstream disease, which is consistent with real clinical practice but challenging for physiological assessments.[1] Downstream disease could potentially reduce flow, and especially hyperemic flow across a LM lesion, thereby decreasing the hyperemic pressure gradient across the LM lesion and increasing the FFR value.[1] iFR is measured at rest when flow is kept constant due to autoregulation and expected to be less affected by lesion interaction than FFR, provided the lesions are not so critical that the autoregulatory reserve is already depleted at rest.[1] iFR is therefore put forward as a technique to assess serial lesions individually.[21] Whether using an iFR value just distal to the LM lesion (iFR_{PROX} in our study) in a case with downstream disease is sufficient to assess the significance of the LM lesion and safe to guide treatment remains to be proven. Our finding that iFR/FFR discordance at the distal level was significantly more frequent in the presence of downstream disease and evidence indicating that the significance of individual lesions in serial disease may still be underestimated with FFR, but also with iFR, call for additional outcome data.[22]

3. Short-term clinical outcomes

Observational data suggest that FFR and iFR can guide the decision to revascularize or defer LM lesions, although evidence for this is limited to 6 studies with FFR in 525 patients (of which only one used the 0.80 cut-off) and one partial retrospective study with iFR in 314 patients.[23,24] In PHYNAL, the decision to defer the LM lesion was largely consistent with the iFR assessment and the 1-year outcomes of patients whose LM lesion was deferred were comparable to the outcomes of the revascularized patients.

Patients with concordant iFR and FFR positive LM lesions are likely to benefit from revascularization, while patients with concordant negative findings are unlikely to, although negative physiological findings alone are not sufficient to predict an event-free outcome.[1] For LM lesions with discordant iFR/FFR results, the prognosis with or without revascularization is less clear. The prognosis was not worse in patients with deferred iFR/FFR discordant non-LM lesions in one study.[25] In our study, cardiac events in the deferred group were uncommon. Six out of 9 TLRs occurred in patients with iFR/FFR discordance, but only 2 presented with an ACS. Awaiting further outcome data, one should closely monitor patients with a deferred LM lesion, especially if discordant physiological findings are obtained. In those patients, one might consider performing IVUS and deferring the LM lesion only when the MLA is above 6 mm^2, as data from the LITRO and iLITRO-EPIC07 study then suggest acceptable outcomes.[12,26]

Study limitations. First, selection bias was likely present, as some operators may have been reluctant to invasively interrogate some intermediate LM lesions, especially in the presence of noninvasive evidence of ischemia, a fragile appearance, or significant bystander disease that favors surgery anyway. Overestimation of diameter stenosis by angiography may have resulted in inclusion of milder lesions.

Second, because of the material costs and lower estimated risk-benefit ratio in cases with highly abnormal or highly reassuring physiological findings, IVUS was performed only for lesion evaluation in patients with more borderline disease. This may explain the higher rates of discordance compared to physiological findings.

Third, patients with angiographically isolated LM disease may have had significant downstream disease that was not diagnosed because systematic iFR/FFR or IVUS pullback was not mandatory.

Fourth, iFRs at 5 mm from the LM carina may have been affected by disease and related flow disturbances at that level.

Finally, enrollment slowed down in some centers. As this was mainly attributable to local COVID-19 measures and/or change in provider of physiological hardware, we assume this did not affect our results.

Conclusions

In the PHYNAL study we found that current methods of estimating significance of LM lesions often yield contradictory findings, making the therapeutic decision-making challenging. Our study does not indicate a poor outcome in patients whose LM lesion is deferred, regardless of discordant physiological findings. Nevertheless, as available outcome data are still limited and physiology as a predictor of events is imperfect, patients with a deferred LM lesion require optimal medical treatment and careful follow-up.

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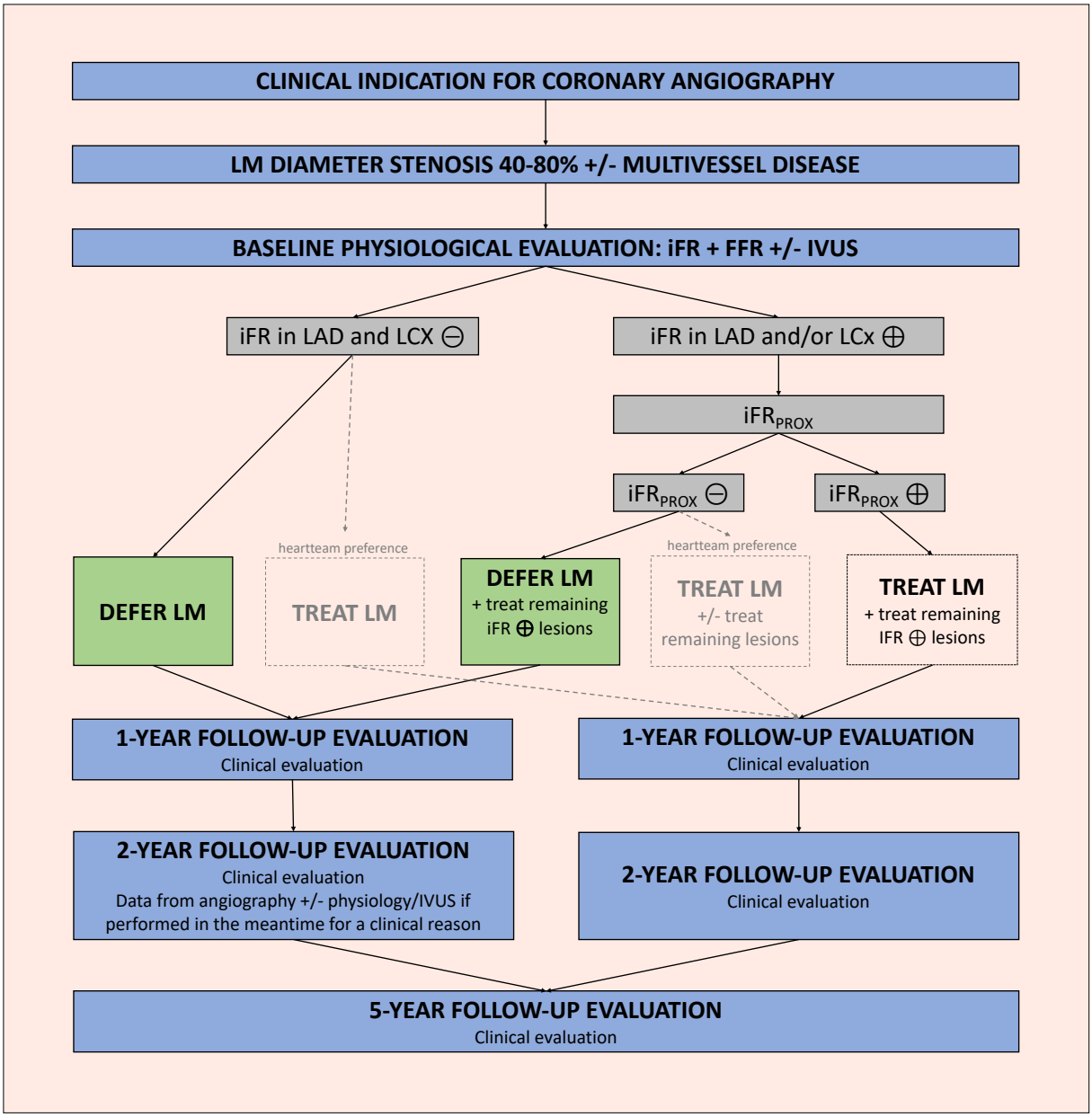
SUPPLEMENTAL APPENDIX

Study outline

1. Study flowchart

Supplemental Figure S1. Study flowchart.



Design of the ongoing Prospective Left Main Physiology Registry (PHYNAL) registry.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; iFR$_{PROX}$ = iFR measured 5 mm distal to LM carina; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main coronary artery; V = daughter vessel

Enrollment continued until 200 patients are enrolled whose left main coronary artery (LM) treatment is being deferred. This was decided in view of an estimated number of fifty control angiographies within two years after enrollment in order to collect sufficient paired data to estimate the evolution of the angiographic and physiological parameters.

2. Subject selection

SUPPLEMENTAL TABLE 1. STUDY INCLUSION AND EXCLUSION CRITERIA

	Inclusion criteria	Exclusion criteria
General	• > 18 year old patient • patient is willing to comply with all protocol-required follow-up evaluation	• patient participates or intends to participate in another investigational clinical trial that may cause non-compliance with the protocol or confound data interpretation
Clinical	• stable disease or stabilized ACS	• STEMI • NSTEMI with hemodynamic instability • navigation of the LM lesion by a coronary wire is expected to behold a significant complication risk
Angiographical	• LM diameter stenosis 40%-80% on visual assessment of the coronary angiogram with or without additional coronary lesions	• Angiographical arguments for lesion instability • Previous LM stenting • Previous CABG on LCA

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; LCA = left coronary artery; LM = left main coronary artery; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI =ST-elevation myocardial infarction

3. Observations

Primary observations

1. Percentage of LM lesions considered hemodynamically insignificant by instantaneous wave-free ratio (iFR) >0.89 but significant by fractional flow reserve (FFR) ≤0.80 or minimal lumen area (MLA) ≤6.0 mm^2 as assessed by intravascular ultrasound (IVUS).

- Percentage of reclassification between significant and insignificant depending on the assessment technique used
- Percentage change of therapeutic plan, when the operator is asked to indicate his plan based on angiography, then based on iFR, FFR, and IVUS.

2. Safety endpoint. Percentage of major adverse cardiac events (MACE), defined as a composite of death, nonfatal myocardial infarction (MI), and unplanned target lesion (LM) revascularization (TLR) at 1,2, and 5-year follow-up. Percentage of MACE in the patient subpopulation where LM treatment was deferred based on iFR.

Secondary observations

Outcome related. Lesion progression at follow-up compared to baseline. If repeat coronary angiography is performed during follow-up, the evolution of the available physiological or imaging parameters can be studied: eg, evolution of iFR and FFR, plaque burden, and MLA.

Operator-indicated reasons why the revascularization strategy deviated from that suggested by the iFR result

In the deferred group, the decision to defer was consistent with the iFR in 162/177 patients (91.5%). In the remaining 15 patients the strategy was overruled for the following reasons:

- comorbidity impairing patient prognosis (n=2),
- borderline iFR+ and FFR+ and operator preference (n=4),
- iFR+/FFR- discordance and operator preference (n=1),
- iFR+/FFR- discordance with MLA > 6 mm^2 and operator preference (n=3),
- iFR 0.89 in one daughter branch only (n=4),
- FFR 0.90 in one daughter branch and MLA > 6 mm^2 (n=1).

In the revascularized group, the decision to revascularize was consistent with the iFR in 47/73 patients (64.4%). In the remaining 26 patients the strategy was overruled for the following reasons:

- concomitant multivessel disease (syntax score) (n=7),
- concomitant LAD disease (n=13),
- concomitant downstream disease and valvular disease (n=1),
- repetitive LM spasm and proven ischemia (n=1),
- iFR-/FFR+ discordance and operator preference (n=3),
- iFR-/FFR+ discordance and MLA < 6 mm^2 (n=1)