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Safety of Revascularization Deferral of Left Main Stenosis Based on Instantaneous Wave-Free Ratio Evaluation

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ABSTRACT

OBJECTIVES The aim of this study was to assess the long-term clinical outcomes of patients with left main coronary artery (LM) stenosis in whom treatment strategy was based on the instantaneous wave-free ratio (iFR).

BACKGROUND The overall safety of iFR to guide revascularization decision making in patients with stable coronary artery disease has been established. However, no study has examined the safety of deferral of revascularization of LM disease on the basis of iFR.

METHODS This multicenter observational study included 314 patients in whom LM stenosis was deferred (n = 163 [51.9%]) or revascularized (n = 151 [48.1%]) according to the iFR cutoff ≤0.89. The primary endpoint was a composite of all-cause death, nonfatal myocardial infarction, and ischemia-driven target lesion revascularization. The secondary endpoints were each individual component of the primary endpoint and also cardiac death.

RESULTS At a median follow-up period of 30 months, the primary endpoint occurred in 15 patients (9.2%) in the deferred group and 22 patients (14.6%) in the revascularized group (hazard ratio: 1.45; 95% confidence interval: 0.75 to 2.81; p = 0.26), indicating no evidence of a significant difference between the 2 groups. For the secondary endpoints, findings in the iFR-based deferral and revascularization groups were as follows: all-cause death, 3.7% versus 4.6%; cardiac death, 1.2% versus 2.0%; nonfatal myocardial infarction, 2.5% versus 5.3%; and target lesion revascularization, 4.3% versus 5.3% (p > 0.05 for all).

CONCLUSIONS Deferral of revascularization of LM stenosis on the basis of iFR appears to be safe, with similar long-term outcomes to those in patients in whom LM revascularization was performed according to iFR values.
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Fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) are the most commonly used intracoronary physiology indexes to determine revascularization strategy in patients with coronary artery disease. Both FFR and iFR use intracoronary pressure ratio to determine the hemodynamic significance of a coronary artery stenosis. Both indexes are supported by a large body of evidence with patient outcomes data (1-5) and have been incorporated into international treatment guidelines (6).

However, to date, patients with left main coronary artery (LM) disease have largely been excluded from all randomized clinical trials of physiology-guided revascularization (1-5). Although the clinical utility of

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

FFR = fractional flow reserve

HR = hazard ratio

iFR = instantaneous wave-free ratio

IQR = interquartile range

LAD = left anterior descending coronary artery

LCx = left circumflex coronary artery

LM = left main coronary artery

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

FFR measurement in patients with intermediate angiographic severity LM disease has been demonstrated by several small nonrandomized studies (7-9), dedicated studies on the safety of revascularization decision-making for LM disease on the basis of iFR are currently lacking. Some studies have shown that lesion location in the LM or the proximal left anterior descending coronary artery (LAD) might be associated with a higher discrepancy between iFR and FFR values and suggested caution in the use of resting intracoronary pressure indexes in this setting (10,11). Therefore, clarifying whether iFR, a nonhyperemic index of stenosis severity, can be used in decision making when a stenosis subtends a large myocardial territory is of key importance for its adoption (12).

The aim of this study was to assess the long-term clinical outcomes of patients in whom the decision to perform or defer revascularization in LM stenosis was based on iFR.

METHODS

STUDY POPULATION. The DEFINE-LM (Deferral of Coronary Revascularization Based on Instantaneous Wave-Free Ratio Evaluation for Left Main Coronary Artery Disease) registry is an international multicenter registry including all patients with stable angina and angiographically intermediate LM disease assessed using iFR between October 2012 and October 2018 at 10 cardiac centers in Europe, the United States, and Japan (Hammersmith Hospital, Hospital Clínico San Carlos, Mayo Clinic, Gifu Heart Center, Tsukuba Medical Center Hospital, Toda Central General Hospital, Tachikawa General Hospital, Fukuyama Cardiovascular Hospital, New Tokyo Hospital, and St. Marianna University School of Medicine Yokohama City Seibu Hospital). This registry was launched in November 2017, and data collection was performed both retrospectively and prospectively.

Inclusion criteria for this study were: 1) stable angina; 2) unprotected LM stenosis of 40% to 70% on visual angiographic assessment; and 3) iFR interrogation for LM stenosis. iFR was measured at the distal point of the LM segment either in the LAD or in the left circumflex coronary artery (LCx). If the bifurcation lesion involved an ostial LAD or LCx, it was also considered an LM segment. If iFR was measured in both the LAD and LCx in the case of a bifurcation lesion, the lower iFR value was used. When further downstream disease was present in the LAD or LCx, the wire was placed either in the nondiseased artery or proximal to the first angiographic stenosis. Revascularization options included both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Exclusion criteria were as follows: iFR interrogation performed <6 months before the end of the study, previous CABG or previous PCI for LM disease, severe valvular pathology, and any type of nonischemic cardiomyopathy. Patients in whom the operator decided the treatment strategy on factors other than the iFR values were also excluded. Essentially, we included consecutive cases with stable unprotected LM disease of intermediate angiographic severity in whom the treatment strategy was based on the current iFR cutoff. The study

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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flow diagram is shown in Figure 1. All patients provided written informed consent. This study was approved by the local ethics committee at each participating center and was conducted according to the principles of the Declaration of Helsinki.

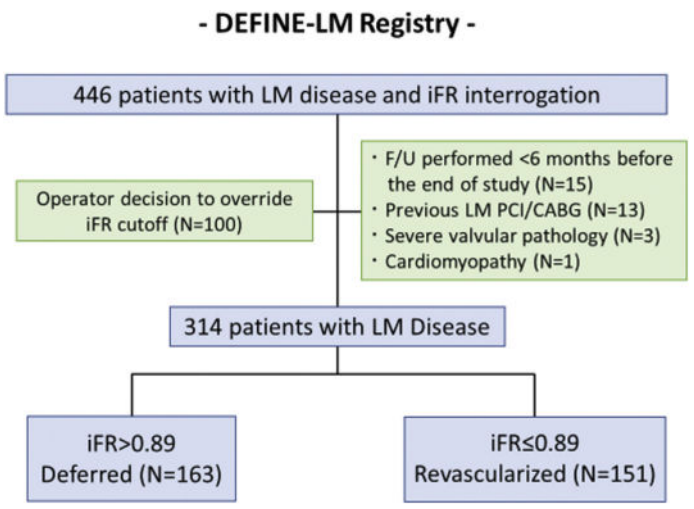
STUDY ENDPOINTS. The pre-defined primary endpoint was the rate of major adverse cardiac events (MACE) over follow-up. MACE were defined as a composite of all-cause death, nonfatal myocardial infarction (MI), and ischemia-driven target lesion revascularization (TLR) of LM disease. Secondary endpoints were individual components of the primary endpoint, and cardiac death. Any death was considered of cardiovascular origin unless an unequivocal noncardiovascular cause was established. MI included spontaneous ST-segment elevation MI or non-ST-segment elevation MI and periprocedural MI. TLR was recorded as a MACE when it was not the index procedure and was not identified at the time of the index procedure as a staged procedure to occur within 60 days. Any other revascularization that was not associated with LM stenosis was not considered to be TLR in this study. Patients were followed up for clinical visits at each participating center. When needed, patients or their general practitioners or family doctors were contacted for additional confirmatory clinical information.

STATISTICAL ANALYSIS. Categorical data are expressed as numbers and percentages. Continuous variables are expressed as mean ± SD or as median (interquartile range [IQR]) as appropriate. Continuous variables were compared using Student's *t*-test or the Mann-Whitney *U* test and categorical variables using chi-square or Fisher exact tests, as appropriate. The dependent variable in the analysis was time to initial event during follow-up. Kaplan-Meier curves for MACE-free survival were constructed and compared between the 2 groups using the log-rank test, while relative differences were summarized using hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox regression models. Variables that could potentially predict MACE were analyzed using univariate and multivariate Cox regression analyses. All probability values were 2-sided, and p values <0.05 were considered to indicate statistical significance. All the statistical analysis was performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

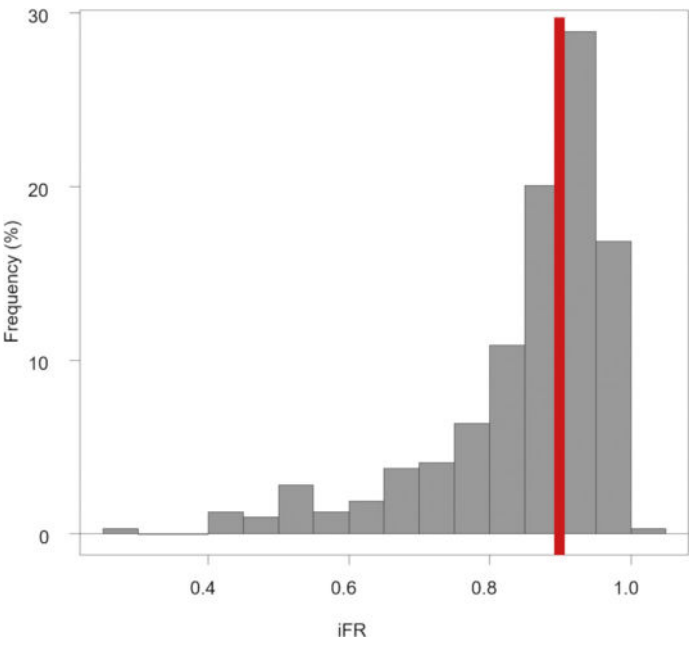
STUDY POPULATION. A total of 314 patients were included for analysis (Figure 1). The mean age was

FIGURE 1 Study Flow



Consecutive cases with de novo stable left main coronary artery (LM) disease of intermediate angiographic severity in whom the treatment strategy was based on the current instantaneous wave-free ratio (iFR) cutoff were included. CABG = coronary artery bypass grafting; DEFINE-LM = Deferral of Coronary Revascularization Based on Instantaneous Wave-Free Ratio Evaluation for Left Main Coronary Artery Disease; F/U = follow-up; PCI = percutaneous coronary intervention.

FIGURE 2 Distribution of iFR



Frequency histograms reveals unimodal data distributions of instantaneous wave-free ratio (iFR) values in the investigated vessels. The **solid red line** indicates the median value.

TABLE 1 Patient Characteristics

	Deferred Group (n = 163)	Revascularized Group (n = 151)	p Value
Age, yrs	69.3 ± 10.3	67.1 ± 10.2	0.053
Male	124 (76.1)	125 (82.8)	0.14
Hypertension	121 (74.2)	111 (73.5)	0.88
Dyslipidemia	118 (72.4)	107 (70.9)	0.76
Diabetes mellitus	51 (31.3)	68 (45.0)	0.012
Renal insufficiency*	32 (19.6)	38 (25.2)	0.24
Current smoker	70 (42.9)	44 (29.1)	0.011
Family history of CAD	36 (22.1)	19 (12.6)	0.027
Previous MI	50 (30.7)	43 (28.5)	0.67

Values are mean ± SD or n (%). *Renal insufficiency was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2.

CAD = coronary artery disease; MI = myocardial infarction.

TABLE 2 Vessel and Lesion Characteristics

	Deferred Group (n = 163)	Treated Group (n = 151)	p Value
Left main lesion type			0.032
Ostial	40 (24.5)	43 (28.5)	
Mid	21 (12.9)	39 (28.5)	
Distal	122 (74.8)	128 (84.8)	
Other diseased vessels			
Number of diseased vessels			<0.001
0	50 (30.7)	13 (8.6)	
1	64 (39.3)	38 (25.2)	
2	34 (20.9)	62 (41.1)	
3	15 (9.2)	38 (25.2)	
LAD	69 (42.3)	121 (80.1)	<0.001
LCx	44 (27.0)	77 (51.0)	<0.001
RCA	64 (39.3)	78 (51.7)	0.028
With CTO	20 (12.3)	19 (12.6)	0.93
SYNTAX score	15.3 ± 8.7	22.6 ± 8.4	<0.001
Quantitative coronary angiography			
Diameter stenosis, %	43.1 ± 11.9	49.2 ± 13.5	<0.001
Minimum luminal diameter, mm	2.32 ± 0.64	1.86 ± 0.63	<0.001
Reference diameter, mm	4.09 ± 0.88	3.69 ± 0.71	<0.001
Lesion length, mm	10.0 ± 5.3	14.0 ± 8.1	<0.001
Physiological stenosis severity			
iFR	0.94 (0.92-0.96)	0.82 (0.70-0.86)	<0.001
Use of intracoronary imaging			
Intravascular ultrasound	35 (21.5)	96 (63.6)	<0.001

Values are n (%) or mean ± SD.

CTO = chronic total occlusion; iFR = instantaneous wave-free ratio; LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

68.3 ± 10.3 years (79.3% men). The mean SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score was 18.7 ± 9.3, and the mean percentage diameter stenosis was 46.0 ± 13.0%. On average, LM stenoses were of intermediate hemodynamic significance, with a unimodal distribution of iFR values (median iFR 0.90; IQR: 0.82 to 0.94) (Figure 2). According to physiological assessment, LM revascularization was deferred in 163 patients (51.9%). In the remaining 151 patients (48.1%), LM revascularization was performed either percutaneously (n = 85 [56.3%]) or surgically (n = 66 [43.7%]).

BASELINE CHARACTERISTICS. Full descriptions of the baseline characteristics are provided in Table 1. Compared with the deferred revascularization group, the frequency of diabetes mellitus was significantly higher in the revascularized group (31.3% vs. 45.0%; p = 0.012). Conversely, the deferred group included a higher proportion of current smokers (42.9% vs. 29.1%; p = 0.011) and patients with family histories of coronary artery disease (22.1% vs. 12.6%; p = 0.027).

LESION CHARACTERISTICS. In the revascularized group, lesion complexity and stenosis severity were significantly greater than those in the deferred group. Specifically, in the revascularized group, there was a higher frequency of LM bifurcation involvement and multivessel disease, which resulted in a significantly higher SYNTAX score (15.3 ± 8.7 vs. 22.6 ± 8.4; p < 0.001). Angiographic stenosis severity was also greater in the revascularized group (mean diameter stenosis 43.1 ± 11.9% vs. 49.2 ± 13.5%; p < 0.001). The full descriptions of vessel and lesion characteristics are shown in Table 2. Figure 3 shows the relationship between angiographic LM stenosis severity and physiological significance according to the iFR cutoff.

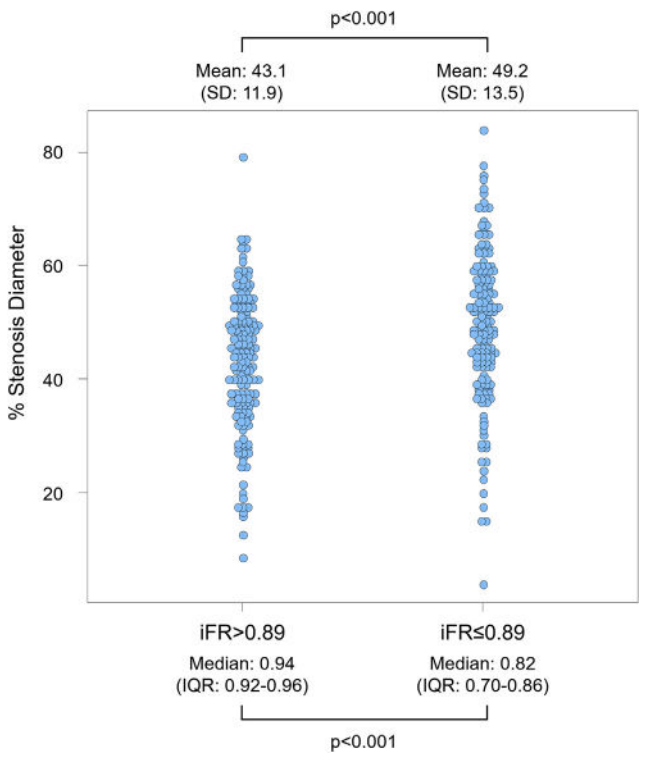
PRIMARY AND SECONDARY ENDPOINTS. The median follow-up period was 30 months (IQR: 17 to 44 months). For the primary endpoint, MACE occurred in 15 patients (9.2%) in the deferred group and 22 patients (14.6%) in the revascularized group. Kaplan-Meier event-free survival estimates at 4 years demonstrated no significant difference between the 2 groups (HR: 1.45; 95% CI: 0.75 to 2.81; p = 0.26) (Figure 4). For the secondary endpoints, findings in the iFR-based deferred and revascularized groups were as follows: all-cause death, 3.7% versus 4.6% (HR: 1.06; 95% CI: 0.36 to 3.17; p = 0.91); cardiac death, 1.2% versus 2.0% (HR: 1.31; 95% CI: 0.22 to 7.88; p = 0.77); nonfatal MI, 2.5% versus 5.3% (HR: 1.96; 95% CI: 0.59 to 6.54; p = 0.27); and TLR, 4.3% versus 5.3% (HR: 1.11; 95% CI: 0.40 to 3.06; p = 0.84) (Figure 5).

In the deferred group, 6 patients died during follow-up, of which 2 cases were considered to be cardiac death. There were 4 nonfatal MIs (all spontaneous) and 7 instances of TLR (4 CABG and 3 PCI). Two nonfatal MIs required urgent PCI for LM stenosis, and the remaining 5 TLRs were performed because of recurrent angina. In the revascularized group, 7 patients died during follow-up, of which 3 deaths were considered to be cardiac. There were 8 nonfatal MIs, 2 of which were periprocedural MI following CABG and 6 of which were due to the acute occlusion of saphenous vein grafts to either the LCx or the right coronary artery. Stent thrombosis was not observed. TLR was observed in 8 patients with LM stenosis, consisting of 2 patients who underwent PCI in the native LM stenosis because of an occluded left internal mammary artery graft to the LAD and 6 patients who underwent additional PCI for LM in-stent restenosis. One patient died 1 year after percutaneous TLR for LM in-stent restenosis. There were no differences in the rates of MACE between PCI and CABG during follow-up (11 of 85 [12.9%] vs. 11 of 66 [16.7%]; HR: 1.23; 95% CI: 0.53 to 2.86; $p = 0.63$) despite older age (69.8 ± 10.3 years vs. 63.6 ± 8.9 years; $p < 0.001$) and lower iFR value (0.78 [IQR: 0.67 to 0.85] vs. 0.84 [IQR: 0.76 to 0.87]; $p = 0.014$) in the PCI group with similar SYNTAX score (22.6 ± 9.4 vs. 22.5 ± 7.1; $p = 0.91$) and other patient and lesion characteristics ($p > 0.05$ for all). The causes of noncardiac death in each group are summarized in Supplemental Table 1.

REVASCULARIZATION FOR NON-LM DISEASE. In the deferred group, 6 patients (3.7%) underwent revascularization for non-LM disease during follow-up, which consisted of 3 LCx and 3 right coronary artery lesions (5 for de novo lesions and 1 for in-stent restenosis). In the revascularized group, 19 patients (12.6%) underwent non-LM revascularization, which consisted of 2 LAD, 6 LCx, and 11 right coronary artery lesions (11 for de novo lesions, 4 for in-stent restenosis, and 4 for bypass graft occlusion). The rates of non-LM revascularization between 2 groups during follow-up were significantly different (HR: 3.22; 95% CI: 1.28 to 8.07; $p = 0.013$).

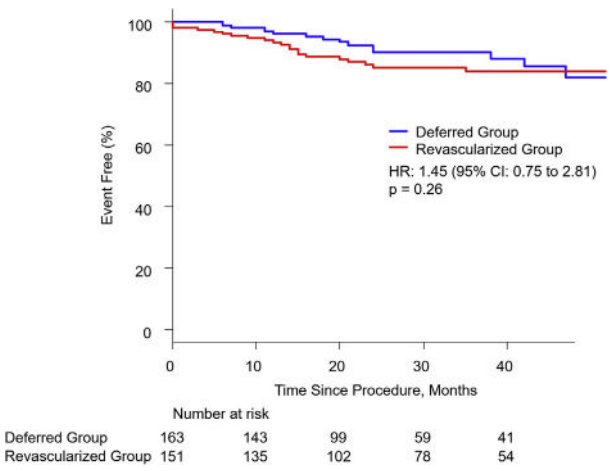
PREDICTIVE FACTORS FOR MACE. To investigate potential predictors of MACE, we assessed all patient and lesion characteristics as well as performance of revascularization between patients with MACE ($n = 37$) and those without ($n = 277$). Older age ($p = 0.0088$), current smoking ($p = 0.041$), the presence of chronic total occlusion ($p = 0.042$), and shorter lesion length ($p = 0.032$) were significantly predictive of MACE in univariate analysis. However,

FIGURE 3 Relationship Between Angiographic and Functional Severity of LM Stenosis



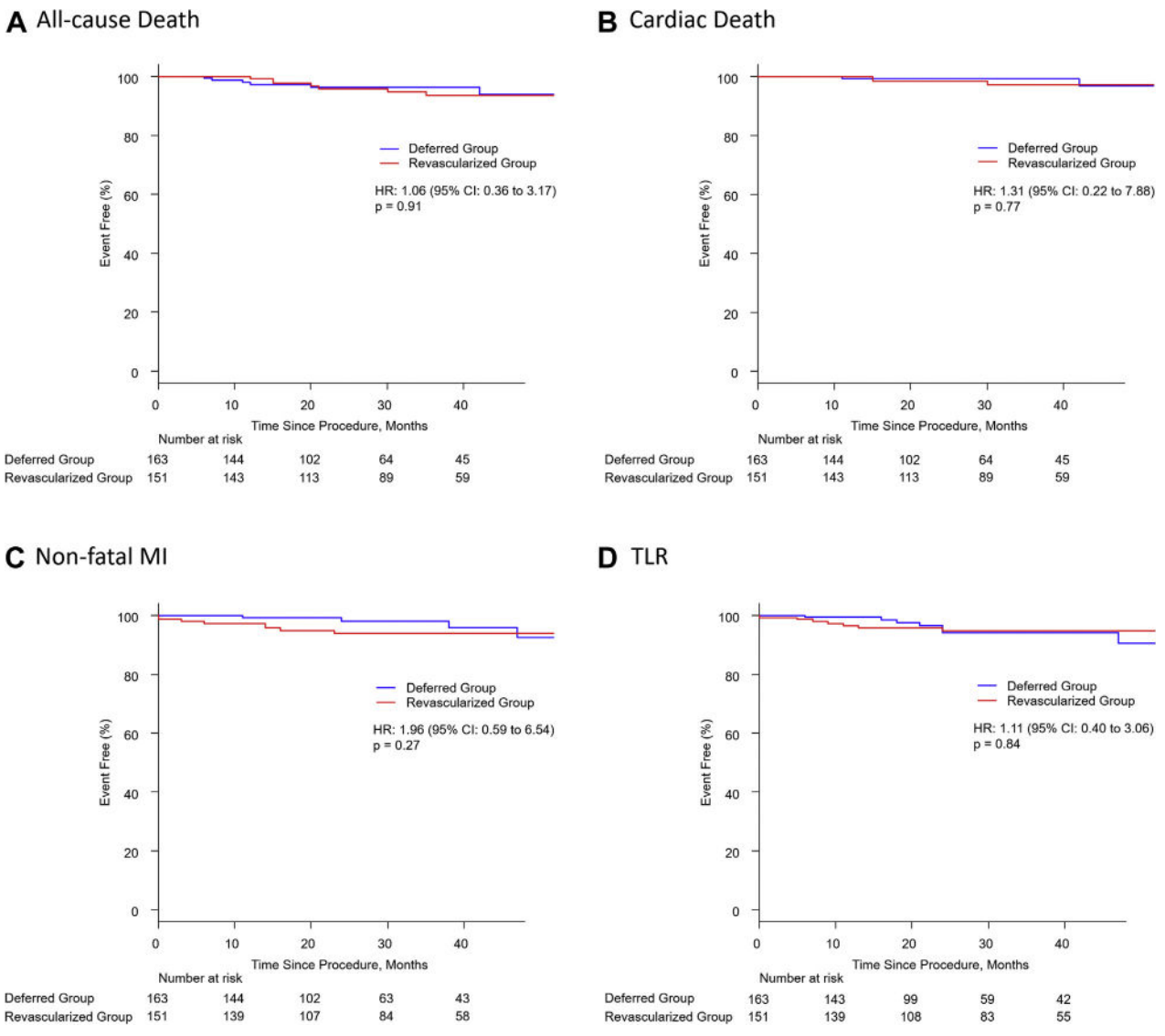
The degree of angiographic stenosis severity was widely distributed in both groups. IQR = interquartile range; other abbreviations as in Figure 1.

FIGURE 4 Major Adverse Cardiac Events in iFR-Guided LM-Treated Patients



Kaplan-Meier event-free curves showing major adverse cardiac events in the 2 groups. There was no difference between the deferred and revascularized groups. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

FIGURE 5 **Kaplan-Meier Curves for Secondary Endpoints**



Kaplan-Meier event-free curves showing **(A)** all-cause death, **(B)** cardiac death, **(C)** nonfatal myocardial infarction (MI), and **(D)** target lesion revascularization (TLR). There were no differences between the 2 groups.

multivariate analysis revealed that only older age was a significant predictor of MACE (Table 3).

In the deferred group (n = 163), we assessed all patient and lesion characteristics as potential predictors of MACE between cases with MACE (n = 15) and those without (n = 148). Univariate analysis revealed that the presence of chronic total occlusion was the sole significant predictor of MACE (HR: 4.11; 95% CI: 1.26 to 13.4; p = 0.019) (Table 4). Numerically, chronic total occlusion was present in 4 of 15 patients (26.7%) with MACE and 16 of 148 patients (10.8%) without.

OUTCOMES IN NON-iFR-BASED PATIENTS. Regarding the patients in whom decision making was not based on the iFR cutoff, revascularization was deferred in 74 patients (74.0%) despite iFR ≤0.89, while 26 patients (26.0%) underwent revascularization (14 PCI and 12 CABG) despite iFR >0.89 (Supplemental Figure 1). Patient and lesion characteristics were not significantly different from those of iFR-based patients who were included for main analysis of this study (Supplemental Table 2). The factors that were prioritized over the iFR cutoff are shown in Supplemental Table 3 and consisted largely of findings on

TABLE 3 Multivariate Predictors of Major Cardiac Adverse Events

	Hazard Ratio	95% Confidence Interval	p Value
Older age	1.05	1.01-1.09	0.012
Current smoking	1.91	0.95-3.80	0.067
Presence of CTO	1.75	0.75-4.04	0.19
Shorter lesion length	0.94	0.88-1.00	0.058

For continuous variables, hazard ratios are per 1 unit. For nominal variables, hazard ratios are with the presence of the factors.
CTO = chronic total occlusion.

noninvasive testing, FFR, and intravascular ultrasound. Clinical events during follow-up compared with those among iFR-based patients are summarized in Supplemental Table 4, showing numerically higher events rates for all components. The rate of MACE during follow-up in the revascularized group (despite iFR >0.89) was numerically lower than that in the deferred group (despite iFR ≤0.89) (5 of 26 [19.2%] vs. 21 of 74 [28.4%]). However, the difference was not statistically significant (HR: 0.76; 95% CI: 0.28 to 2.02; p = 0.57).

TABLE 4 Univariate Predictors of Major Cardiac Adverse Events in the Deferred Group

	Hazard Ratio	95% Confidence Interval	p Value
Age	1.05	1.00-1.11	0.062
Male	0.94	0.30-2.97	0.92
Hypertension	0.58	0.21-1.64	0.31
Dyslipidemia	0.67	0.24-1.88	0.45
Diabetes mellitus	0.40	0.11-1.43	0.16
Renal insufficiency*	0.77	0.17-3.4	0.73
Current smoker	1.93	0.70-5.36	0.20
Family history of CAD	0.79	0.18-3.53	0.76
Previous MI	1.57	0.56-4.43	0.39
Distal LM disease	1.24	0.35-4.44	0.74
Number of additional diseased vessels (0-3)	1.19	0.69-2.04	0.54
Isolated LM disease	0.86	0.31-2.38	0.77
Diseased LAD	1.08	0.38-3.04	0.89
Diseased LCx	1.14	0.36-3.58	0.83
Diseased RCA	1.54	0.55-4.26	0.41
CTO	4.11	1.26-13.4	0.019
SYNTAX score	1.04	0.98-1.09	0.18
% diameter stenosis	1.03	0.98-1.07	0.24
Lesion length	0.91	0.80-1.03	0.14
iFR value	1.02	0.85-1.23	0.83

For continuous variables, hazard ratios are per 1 unit. For nominal variables, hazard ratios are with the presence of the factors. *Renal insufficiency was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2.
LM = left main coronary artery; other abbreviations as in Tables 1 and 2.

DISCUSSION

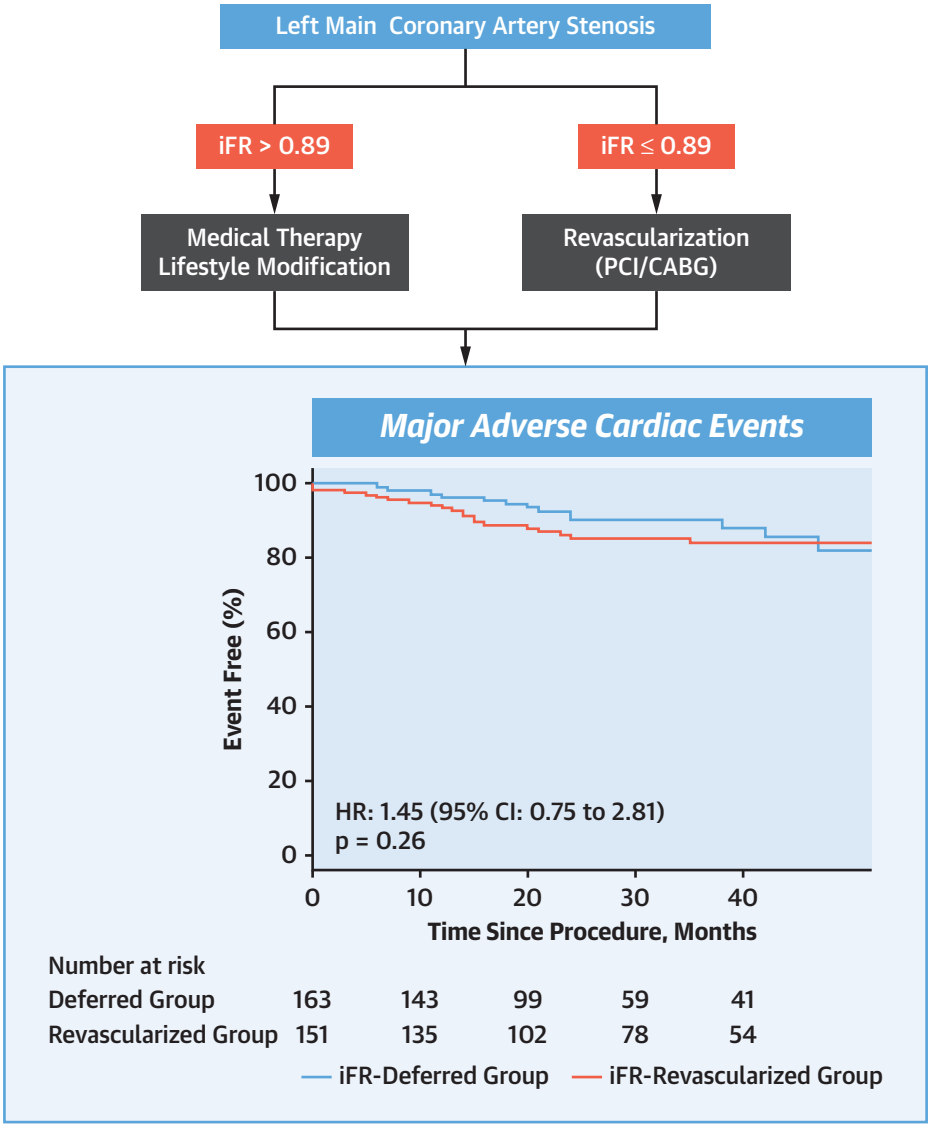
This is the first study to document the long-term clinical outcomes of patients with LM disease in whom the decision to perform or defer revascularization was based on iFR measurement (**Central Illustration**). Our main findings are as follows. First, the long-term clinical outcomes of patients with LM stenosis in whom revascularization was deferred on the basis of an iFR value >0.89 were favorable, with a low event rate (MACE rate 9.2% at a median of 30 months). Second, these outcomes were similar to those of patients in whom LM revascularization was performed on the basis of an iFR value ≤0.89 (HR: 1.45; 95% CI: 0.75 to 2.81; p = 0.26).

DEFERRAL OF LM REVASCULARIZATION ON THE BASIS OF INVASIVE PHYSIOLOGY. Major randomized clinical trials assessing the utility of invasive coronary physiology have not reported clinical outcomes for LM disease, with either FFR or iFR (1-5). However, several nonrandomized cohort studies have suggested the safety of LM revascularization decision making using hyperemic FFR (7-9). Specifically, these observational studies showed no significant differences in MACE-free survival between the FFR-deferred and FFR-revascularized groups. Several meta-analyses also supported the use of FFR in LM disease (13,14). Those studies constitute the supporting evidence for the current use of invasive physiology in assessing LM stenosis.

Following a similar design to the aforementioned studies, in the present study, we demonstrated the safety of revascularization decision making for LM disease on the basis of iFR. Kaplan-Meier analysis showed MACE-free survival rates at 4 years of 90.8% in the deferred group (n = 163) and 85.4% in the revascularized group (n = 151) (p = 0.26). These favorable clinical outcomes are consistent with previous FFR-based studies with numerically similar results (7-9,13,14). Unfortunately, however, as in the previous FFR-based studies, the deferred group did not show significantly better outcomes than the revascularized group despite low SYNTAX scores. The reason for this result is still unclear. Potentially, in addition to the relatively older age in the deferred group, we hypothesized that patients with LM stenosis, considering a disease entity, have remarkably high cardiovascular event risks.

iFR-GUIDED LM REVASCULARIZATION. In the largest pooled meta-analysis of FFR-guided LM

CENTRAL ILLUSTRATION **MACE in Patients With LM Stenosis: Kaplan-Meier Curves**



Warisawa, T. et al. J Am Coll Cardiol Intv. 2020;■(■):■–■.

This figure outlines the study design and the primary endpoint in patients with LM stenosis in whom treatment strategy was determined based on the iFR cutoff value. Major adverse cardiac events (MACE) were defined as the composite of all-cause death, nonfatal MI, and TLR. The **blue line** denotes the deferred arm, and the **red line** denotes the revascularized arm. The iFR-guided deferral showed similar clinical outcomes to those who were revascularized according to the ischemic iFR values (hazard ratio: 1.45; 95% confidence interval: 0.75 to 2.81; p = 0.26). Abbreviations as in Figure 1.

stenosis revascularization studies (n = 308 in the deferred group vs. n = 217 in the revascularized group), the vast majority of patients underwent CABG as revascularization options (94.0% [204 of 217]), in which the rate of MACE at 26.5 months was 14.2% (13). In the present study, the rate of MACE in the revascularized group was 14.6% at 30 months, numerically similar to those in the previous reports. Of note, more than half of the patients underwent PCI as their mode of revascularization (56.3% [85 of 151]) in our study, which showed similar outcomes to those who underwent CABG (MACE in 12.9% vs. 16.7%; HR: 1.23; 95% CI: 0.53 to 2.86; p = 0.63) despite higher risks. Accordingly, our analysis provides new insight into

the safety of contemporary physiology-guided PCI for LM stenosis.

In the PCI group, all procedures were performed using new-generation drug-eluting stents under intracoronary imaging guidance, in addition to using coronary physiology for revascularization decision making. The SYNTAX II study demonstrated that the state-of-the-art PCI, guided by intracoronary physiology and optimized with intracoronary imaging, improved clinical outcomes significantly over a decade (15) and also suggested that contemporary PCI could provide similar outcomes to CABG in complex disease (16). Thus, the present study, though a nonrandomized study with a limited number, further indicated that iFR-guided revascularization, either with PCI or CABG, resulted in similar and favorable long-term outcomes in patients with complex LM disease. However, to elucidate the safety of iFR-guided PCI compared with iFR-guided CABG, prospective randomized data are needed.

IMPACT OF USE OF INTRACORONARY IMAGING. As shown in **Table 3**, intracoronary ultrasound was used in more than 20% of patients in the deferred group, which might have contributed to revascularization decision making. Previous studies demonstrated a good correlation between FFR and intracoronary ultrasound (17) and indicated that intracoronary ultrasound can be safely used to defer revascularization of intermediate coronary lesions as well as FFR (18). However, the correlation between iFR and intracoronary ultrasound remains unclear.

STUDY LIMITATIONS. First, because of the nonrandomized nature of this study, a potential for selection bias of iFR measurement for LM stenosis must be considered. This was, however, an all-comers registry for stable LM disease. The value of such a registry-based approach is that it reflects the patient population in real-world clinical practice. Additionally, its clinical value is emphasized by the fact that previous randomized trials regarding iFR excluded LM disease patients (4,5).

Second, we acknowledge that the design of this registry itself is one of the major limitations of this study. We included only LM stenoses with iFR interrogation. There were no comparator arms, such as angiography-guided or intracoronary imaging-guided treatment strategies. We could not clarify the safety of iFR use in more objective way in this setting.

Third, the sample size was relatively small. Consideration should be given to the facts regarding penetration rate of the resting index: iFR is a relatively new index, its noninferiority to FFR with a cutoff value of 0.89 was demonstrated in 2017, and it was incorporated into international treatment guidelines in 2018. These caused the difference of time in iFR introduction at each participating center, which might have resulted in the relatively small size of this study despite consecutive case enrollment at 10 centers in 6 years. This might include a potential selection bias for enrollment of patients. The relatively small number of patients included might have affected statistical significance or nonsignificance. Further studies should validate the present results and warrant the safety of iFR for decision making in LM revascularization using randomized controlled designs or larger registry studies with propensity score matching.

Fourth, although our analysis suggests the presence of a chronic total occlusion as a predictive factor of MACE in the deferred group, detailed exploration of this finding is difficult because of the small sample size. However, support for the validity of this finding is provided by a previous study that demonstrated that the presence of an untreated chronic total occlusion predicted worse outcomes in patients with LM disease (19).

Finally, other several limitations should be acknowledged. Clinical events were recorded and reported by each participating center without an independent clinical events committee to adjudicate events. We could not provide details of medical therapy and risk factor control over the follow-up period in the deferred group. Furthermore, quantitative coronary angiographic analysis was not performed at an independent core laboratory.

CONCLUSIONS

The present study demonstrated that long-term clinical outcomes in patients with LM stenosis in whom revascularization was deferred on the basis of iFR >0.89 were favorable and similar to those of patients in whom LM revascularization was performed on the basis of iFR ≤0.89. iFR-guided deferral appears to be as safe as iFR-guided revascularization. Clinical use of a nonhyperemic intracoronary pressure index is feasible in patients with LM disease.

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PERSPECTIVES

WHAT IS KNOWN? The overall safety of iFR to guide revascularization decision making in patients with stable coronary artery disease has been established except for LM stenosis.

WHAT IS NEW? The iFR, a nonhyperemic intracoronary index, can be safely used for making revascularization decisions on a LM stenosis that has largest subtended myocardial territory.

WHAT IS NEXT? Further studies should validate the present results and warrant the safety of resting intracoronary index for decision making in LM intervention in randomized controlled designs.

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KEY WORDS coronary physiology, left main coronary artery disease, registry-based study, resting intracoronary index

APPENDIX For supplemental tables and a figure, please see the online version of this paper.