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Impact of Routine Invasive Physiology at Time of Angiography in Patients With Multivessel Coronary Artery Disease on Reclassification of Revascularization Strategy

Results From the DEFINE REAL Study

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ABSTRACT

OBJECTIVES This study sought to prospectively assess the impact of routine invasive physiology at the time of angiography on reclassification of therapeutic management of multivessel disease (MVD) patients, and to assess how implementation of instantaneous wave-free ratio (iFR) alters the process.

BACKGROUND Routine invasive physiology in intermediate coronary lesions at the time of diagnostic angiography, primarily in patients with single-vessel disease and using fractional flow reserve (FFR), reclassifies coronary revascularization management in 26% to 44% of patients. The role of invasive physiology in patients with MVD is unclear.

METHODS In 18 centers, 484 patients undergoing diagnostic angiography disclosing MVD with lesions >40% by visual assessment were included. Investigators were asked to prospectively define their initial management strategy based on angiography and clinical information. Invasive physiology (FFR or iFR driven) was then performed and final strategy defined. Initial and final vessel, patient, procedural, and overall management were described. Reclassification was defined as the difference between initial and final strategy.

RESULTS The majority of patients were clinically stable (82.2%). Two- and 3-vessel disease was present in 73.3% and 26.7% of patients, respectively. Lesions investigated were "intermediate" with median percent stenosis, median FFR, and median iFR at 60% (interquartile range [IQR]: 50% to 70%), 0.84 (IQR: 0.78 to 0.90), and 0.92 (IQR: 0.85 to 0.96), respectively. Vessel management was reclassified by physiology in 30.0% (249 of 828) of vessels. Patient and overall management were reclassified in 26.9% (130 of 484) and 45.7% (211 of 484) of patients, respectively. Reclassification rates were high irrespective of initial management (optimal medical therapy, percutaneous coronary intervention, or coronary artery bypass grafting), and performance and results of pre-procedural noninvasive tests. Reclassification of overall management in particular increased with the number of vessels investigated (1 vessel: 37.3%; 2 vessels: 45.0%; 3 vessels: 66.7%; $p = 0.002$). Incorporating iFR in the decision process was associated with investigation of more vessels ($p = 0.04$) and higher reclassification ($p = 0.0001$).

CONCLUSIONS In patients with MVD and intermediate coronary lesions, invasive physiology at time of angiography reclassifies revascularization strategy in a large proportion of cases (26.9%) and investigation of more vessels is associated with higher reclassification rates. (J Am Coll Cardiol Intv 2018;11:354–65) © 2018 by the American College of Cardiology Foundation.

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Patients with coronary artery disease (CAD) may be assessed using angiographic or physiological methods to determine the appropriate revascularization strategy, with fractional flow reserve (FFR) serving as one of the primary physiological methods (1,2). It has been shown that patients whose vessels were interrogated by physiology experience superior outcomes (short and long term) following revascularization compared with patients whose vessels were interrogated by angiography alone (1,2). Several studies have suggested that routine use of FFR in intermediate lesions is associated with a high rate of reclassification in treatment strategy (up to 44%). These studies have also found that change toward a strategy that differed from the one that was recommended based on angiography is safe (3–6). However, those studies have consisted primarily (53% to 64%) of patients with single-vessel CAD (3,5,6). In addition in those studies, the few patients with multivessel CAD were often interrogated by FFR on 1 vessel only (3,5,6). Therefore, the value of invasive physiological assessment on reclassification of patients with multivessel disease (MVD) remains unclear.

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The instantaneous wave-free ratio (iFR) is a pressure-only invasive index of coronary stenosis severity that, unlike FFR, does not require the administration of an hyperemic drug such as adenosine (7). iFR has been validated in more than 3,000 patients across multiple centers (7–11), with numerous validation studies demonstrating a classification match of >90% between FFR and iFR (7–9). The ADVISE II (ADenosine Vasodilator Independent Stenosis Evaluation II) study demonstrated that when using the hybrid iFR-FFR approach the percentage of stenoses properly classified could be as high as 94.2% (12). Finally, it has recently been shown that coronary revascularization guided by iFR is noninferior to revascularization guided by FFR with respect to the risk of major adverse cardiac events at 1 year (13,14). Because iFR can be calculated without pharmacological provocation, it has the potential to allow interrogation of a greater number of vessels in a timely manner while minimizing the risk of side effects.

The objective of the DEFINE REAL (REal-life information for the utilization of instantaneous wave-free ratio™ (iFR®) in Assessing coronary stenosis relevance in the MultivesseL disease patient population) study was to prospectively assess in patients with angiographically defined (>40% stenosis) MVD: 1) the impact of routine invasive physiological assessment at the time of angiography on reclassification of revascularization strategy; 2) the proportion of lesions properly classified by iFR with respect to hemodynamic severity compared with FFR in MVD patients; 3) the effect of interrogation of additional coronary vessels on reclassification rates and procedural safety; 4) how implementation of iFR as part of the invasive physiological assessment alters the reclassification process; and 5) how pre-procedural noninvasive tests and their results impact the reclassification process.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

IQR = interquartile range

MVD = multivessel disease

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

METHODS

PATIENT POPULATION. The study protocol was approved by the ethics committee at each participating center, as applicable, and was conducted in accordance with the declaration of Helsinki. Patients were included in the study if they had MVD (i.e., coronary lesion[s] >40% diameter stenosis) by visual estimate in ≥2 major epicardial vessels or their branches by angiography, with an indication for

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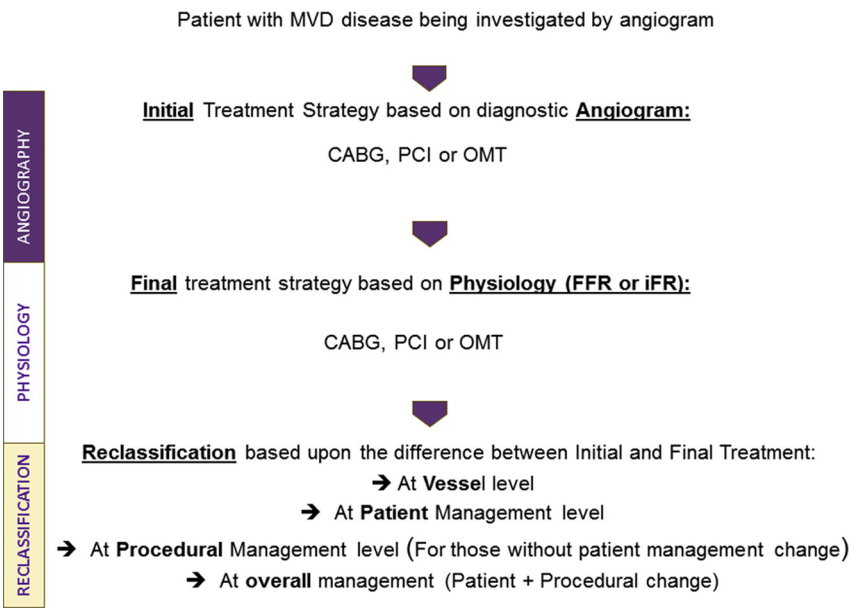
FIGURE 1 Representation of Study Protocol



Physicians were asked to prospectively define an initial treatment strategy based on results of angiography. After pressure wire assessment, a final treatment strategy was determined based on the physiological assessment. Reclassification of treatment strategy was defined as a discordance between the initial and final strategies and was measured in 4 different ways: 1) vessel management; 2) patient management; 3) procedural management; and 4) overall management. The combination of patient and procedural management reclassification defined the overall management change. CABG = coronary artery bypass grafting; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; MVD = multivessel disease; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

pressure wire assessment during the same procedure. Exclusion criteria included inability to sign informed consent as well as any contraindications for functional assessment as determined by the investigators. All enrolled patients provided written informed consent.

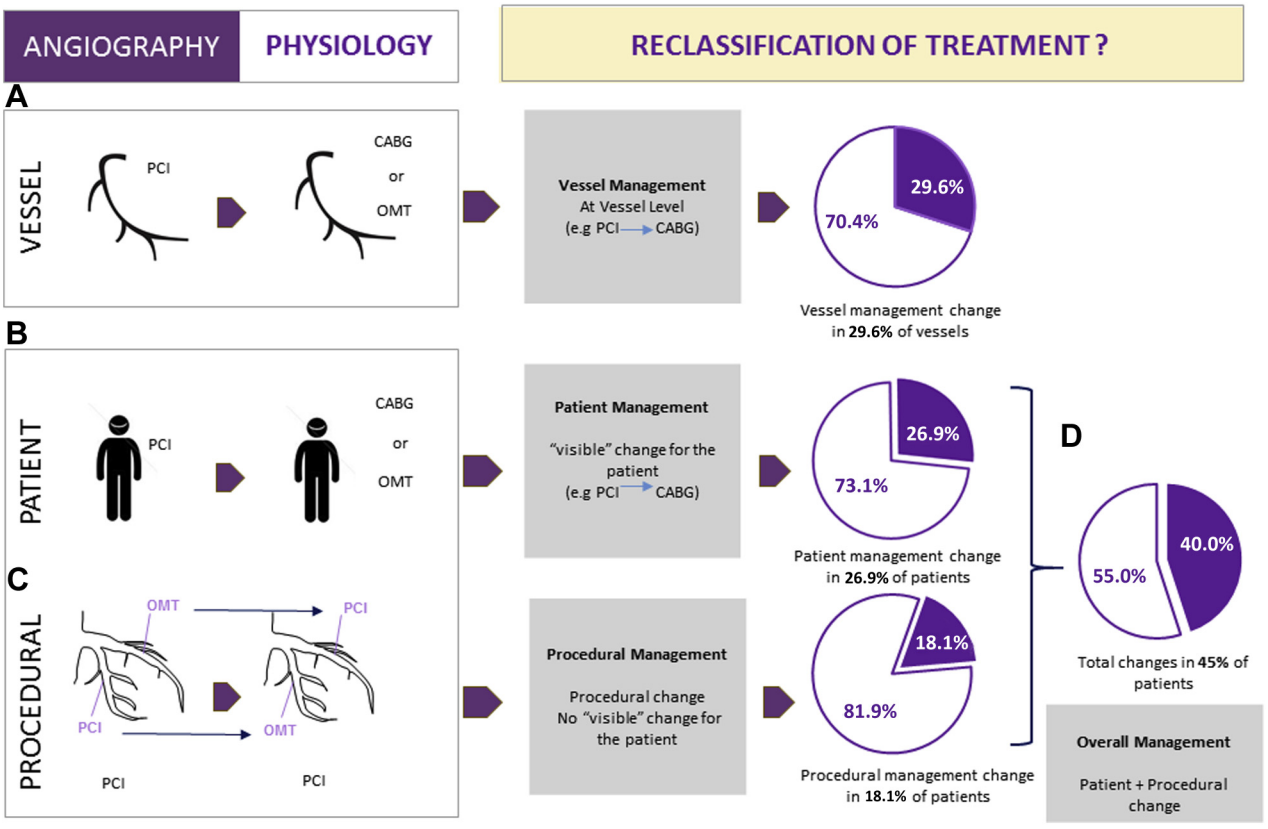
STUDY SITES. All sites recruiting patients were centers with expertise and experience in performing physiological measurements. Patients were screened and enrolled across 18 sites and 9 countries in Europe and the Middle East.

PATIENT DEFINITION AND RECORDING OF BASELINE CHARACTERISTICS. Diabetes mellitus was defined according to usual definitions. Left ventricular ejection fraction was assessed using echocardiography or angiography. Clinical instability was defined as the occurrence, <7 days before inclusion, of an acute coronary syndrome (ACS), defined according to current recommendations (15,16). All other patients were considered stable. Performance and results of noninvasive tests designed to detect myocardial ischemia or CAD were recorded before angiography. These tests included either global tests (stress electrocardiography) or localization tests (stress echocardiography, stress single-photon emission computed tomography, stress magnetic resonance imaging, and computed tomography).

ANGIOGRAPHIC ASSESSMENT AND ANALYSIS. Coronary angiography was performed in accordance with hospital standard practice. Qualitative (American College of Cardiology/American Heart Association) and quantitative (proximal, distal, % diameter stenosis by visual estimate) descriptions of vessels assessed by physiology were performed before performing the physiological measurement.

PRESSURE WIRE ASSESSMENT SCHEME AND ANALYSIS. Coronary pressure wire assessment was performed according to local standard practice and prospectively collected in an electronic Case Report Form. Although functional assessment of all vessels with intermediate lesions was recommended, it was left to the operator's discretion to decide how many vessels should be interrogated to achieve an appropriate therapeutic decision. For the investigation of each vessel, FFR or iFR could be used at the investigator's discretion. For FFR it was recommended to use either intracoronary bolus or intravenous infusion of adenosine as previously described (3,5). At

FIGURE 2 Reclassification of Vessel, Patient, Procedural, and Overall Management in Patients With Multivessel Coronary Artery Disease



Changes of procedural management are those occurring at **(A)** the vessel level in patients in whom the patient management was not changed. Distinction between **(B)** reclassification of patient management and **(C)** reclassification of procedural management: treatment strategy was PCI before physiology and remained PCI after physiology, but PCI was performed in a different vessel (from the left circumflex artery to the left anterior descending artery). This case is described as not reclassified for patient management (a PCI was performed as initially planned) **(C)** but reclassified for procedural management (PCI was done in a different vessel than initially planned) **(C)**. **(D)** Changes of overall management (45%) are combining changes of **(B)** patient management (26.9%) and **(C)** procedural management (18.1%). Abbreviations as in Figure 1.

each vessel, iFR could be performed as an add-on of the FFR measurement or as the main method of evaluation. Patients in whom iFR was used as the main method in at least 50% of vessels were classified as having undergone an iFR-driven approach. All others were considered to have undergone an FFR-driven approach. More details are provided in Online Table 1 and the Online Appendix.

REVASCULARIZATION STRATEGY AND RECLASSIFICATION. Before performing pressure wire assessment, investigators were asked to prospectively define and collect an initial treatment based on results of angiography and available clinical information before performing pressure wire assessment. Once physiology data were available, the investigators defined the final treatment. The following treatment options were available for selection in an electronic Case Report Form: optimal medical therapy (OMT) alone, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (Figure 1). Physicians recorded as well which vessel required either OMT, PCI, or coronary artery bypass grafting.

Reclassification of treatment strategy was defined as a discordance between the a priori and final strategies and was measured in 4 different ways (Figures 1 and 2): 1) vessel management; 2) patient management; 3) procedural management; and 4) overall management (Figures 1 and 2). More details are provided in Online Table 1 and the Online Appendix.

SAFETY ANALYSIS AND MONITORING. Periprocedural events including mortality were documented. Monitoring was conducted both on site and remotely,

TABLE 1 Baseline Characteristics According to the Methods of Investigation and Patient Management Change by Physiology

		Methods of Investigation			Reclassification of Patient Management by Physiology		
	Total (N = 484)	FFR Driven (n = 324)	iFR Driven (n = 160)	p Value	No Change (n = 354)	Change (n = 130)	p Value
Male	387 (80.0)	255 (78.7)	132 (82.5)	0.67	286 (80.8)	101 (77.7)	0.45
Age, yrs							
Mean ± SD	66.66 ± 10.68	66.83 ± 10.26	66.32 ± 11.45	0.89	65.92 ± 11.01	68.68 ± 9.46	0.01
Median (range)	68 (30–91)	67 (38–91)	68.5 (30–89)		67 (30–90)	70 (38–91)	
Diabetes	129 (26.7)	89 (27.5)	40 (25.0)	0.80	93 (26.3)	36 (27.7)	0.75
Insulin dependent	44 (34.1)	28 (31.5)	16 (40.0)	0.68	32 (34.4)	12 (33.3)	0.91
Previous MI	174 (36.0)	112 (34.6)	62 (38.8)	0.69	127 (35.9)	47 (36.2)	0.96
LVEF							
Low	24 (5.0)	18 (5.6)	6 (3.8)	0.69	16 (4.5)	8 (6.2)	0.03
Intermediate	70 (14.5)	48 (14.8)	22 (13.8)		42 (11.9)	28 (21.5)	
Normal	304 (62.8)	191 (59.0)	113 (70.6)		227 (64.1)	77 (59.2)	
Clinical presentation							
ACS	86 (17.8)	47 (14.5)	39 (24.4)	0.22	66 (18.6)	20 (15.4)	0.41
STEMI	14 (16.3)	7 (14.9)	7 (17.9)	0.90	14 (21.2)	0 (0.0)	0.08
NSTEMI	44 (51.1)	26 (55.3)	18 (46.2)		32 (48.5)	12 (60)	
Without troponin elevation	28 (32.6)	14 (29.8)	14 (35.9)		20 (30.3)	8 (40.0)	
Stable	398 (82.2)	277 (85.5)	121 (75.6)		288 (81.4)	110 (84.6)	
Noninvasive tests performed*	166 (41.7)	114 (41.2)	52 (43.0)	0.89	118 (41.0)	48 (43.6)	0.63
Stress ECG	78 (47.0)	48 (42.1)	30 (57.7)	<0.001	54 (45.8)	24 (50.0)	0.18
Stress echocardiography	33 (19.9)	16 (14.0)	17 (32.7)		21 (17.8)	12 (25.0)	
Stress MRI	3 (1.8)	2 (1.8)	1 (1.9)		1 (0.8)	2 (4.2)	
CT scan	12 (7.2)	11 (9.6)	1 (1.9)		11 (9.3)	1 (2.1)	
Stress SPECT	42 (25.3)	28 (24.6)	4 (7.7)		32 (27.1)	10 (23.8)	
No stress test performed	232 (58.3)	163 (58.8)	69 (57.0)		170 (59.0)	62 (56.4)	
Stress test result							
Negative	26 (15.7)	22 (19.3)	4 (7.7)	0.43	18 (15.3)	8 (16.7)	0.82
Positive	140 (84.3)	92 (80.7)	48 (92.3)		100 (84.8)	40 (83.3)	
Major vessels with significant lesions > 40% DS							
2 VD	355 (73.3)	242 (74.7)	113 (70.6)	0.67	261 (73.7)	94 (72.3)	0.75
Is LM one of the vessels: yes	27 (7.6)	21 (8.7)	6 (5.3)	0.64	18 (6.9)	9 (9.6)	0.40
Is LM one of the vessels: no	328 (92.4)	221 (91.3)	107 (94.7)		243 (93.1)	85 (90.4)	
3 VD	129 (26.7)	82 (25.3)	47 (29.4)		93 (26.3)	36 (27.7)	
Is LM one of the vessels: yes	17 (13.2)	12 (14.6)	5 (10.6)	0.76	12 (12.9)	5 (13.9)	
Is LM one of the vessels: no	112 (86.8)	70 (85.4)	42 (89.4)		81 (87.1)	31 (86.1)	0.88
Vessels interrogated/patient	1.710 ± 0.607	1.640 ± 0.611	1.870 ± 0.562	0.045	1.670 ± 0.607	1.830 ± 0.586	0.01
1 vessel interrogated	177 (36.6)	140 (43.2)	37 (23.1)	0.17	142 (40.1)	35 (26.9)	0.02
2 vessels interrogated	268 (55.4)	161 (49.7)	107 (66.9)		186 (52.6)	82 (63.1)	
3 vessels interrogated	39 (8.1)	23 (7.1)	16 (10.0)		26 (7.3)	13 (10.0)	
Method of investigation							
iFR driven	160 (33.1)	NA	NA	NA	110 (68.8)	50 (31.2)	0.13
FFR driven	324 (66.9)	NA	NA		244 (75.3)	80 (24.7)	

Values are n (%) unless otherwise indicated. *Two patients had more than 1 noninvasive stress test performed.

ACS = acute coronary syndrome(s); CT = computed tomography; DS = diameter stenosis; ECG = electrocardiography; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LM = left main artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; NA = not available; NSTEMI = non-ST-segment elevation myocardial infarction; SPECT = single-photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction; VD = vessel disease.

using a risk-based approach including the review of critical variables. Data verification was conducted in at least 10% of cases in each center. Monitoring included protocol compliance, as well as quality and accuracy of electronic Case Report Form completion. Informed consent and all reported safety endpoints were checked in all patients.

OBJECTIVES. The main objective was to prospectively asses in patients with MVD defined angiographically: 1) the impact of invasive physiology on reclassification of the treatment strategy compared with the strategy that would have been implemented based on the combination of angiographic and clinical information alone; and 2) the proportions of

TABLE 2 Lesion Characteristics According to Reclassification of Treatment Decision by Physiology at Vessel Level

			Impact of Invasive Physiology on Treatment Decision at Vessel Level		
		Total (N = 828)	No Change (n = 581)	Change (n = 247)	p Value
Lesion	Single	636 (76.8)	443 (76.2)	193 (78.1)	0.34
	More than 1	116 (14.0)	79 (13.6)	37 (15.0)	
	Diffuse	75 (9.1)	58 (10.0)	17 (6.9)	
Lesion location	Proximal	359 (43.4)	249 (42.9)	110 (44.5)	0.43
	Mid	368 (44.4)	265 (45.6)	103 (41.7)	
	Distal	99 (12.0)	65 (11.2)	34 (13.8)	
Lesion type	A	279 (33.7)	194 (33.4)	85 (34.4)	0.009
	B1	336 (40.6)	241 (41.5)	95 (38.5)	
	B2	115 (13.9)	67 (11.5)	48 (19.4)	
	C	87 (10.5)	69 (11.9)	18 (7.3)	
Vessel territory	LAD	388 (46.9)	266 (45.8)	122 (49.4)	0.71
	LCX	250 (30.2)	182 (31.3)	68 (27.5)	
	RCA	164 (19.8)	115 (19.8)	49 (19.8)	
	LM	25 (3.0)	17 (2.9)	8 (3.2)	
% DS	n	828	580	246	
	Mean ± SD	61.1 ± 13.3	60.7 ± 14.1	61.9 ± 11.0	0.24
	Median (IQR)	60.0 (50.0–70.0)	60.0 (50.0–70.0)	60.0 (50.0–70.0)	
iFR value	n	790 (95.4)	555 (95.5)	235 (95.1)	
	Mean ± SD	0.88 ± 0.12	0.88 ± 0.13	0.89 ± 0.10	0.29
	Median (IQR)	0.92 (0.85–0.96)	0.92 (0.84–0.96)	0.92 (0.85–0.96)	
iFR value (if FFR reported)	n	564 (68.1)	399 (68.7)	165 (66.8)	
	Mean ± SD	0.90 ± 0.09	0.91 ± 0.08	0.89 ± 0.09	0.06
	Median (IQR)	0.92 (0.86–0.96)	0.92 (0.87–0.96)	0.91 (0.86–0.96)	
iFR negative/positive (if FFR reported)	n	564 (68.1)	399 (68.7)	165 (66.8)	
	Negative	375 (66.5)	270 (67.7)	105 (63.6)	0.35
	Positive	189 (33.5)	129 (32.3)	60 (36.4)	
FFR value	n	600 (72.5)	424 (73.0)	176 (71.3)	
	Mean ± SD	0.84 ± 0.08	0.84 ± 0.08	0.83 ± 0.09	0.18
	Median (IQR)	0.84 (0.78–0.90)	0.85 (0.78–0.91)	0.83 (0.77–0.89)	
FFR value (if iFR reported)	n	564 (68.1)	399 (68.7)	165 (66.8)	
	Mean ± SD	0.84 ± 0.08	0.84 ± 0.08	0.83 ± 0.08	0.10
	Median (IQR)	0.84 (0.78–0.90)	0.85 (0.78–0.91)	0.83 (0.77–0.88)	
FFR negative/positive (if iFR reported)	n	564 (68.1)	399 (68.7)	165 (66.8)	
	Negative	373 (66.1)	276 (69.2)	97 (58.8)	0.06
	Positive	191 (33.9)	123 (30.8)	68 (41.2)	

Values are n (%) unless otherwise indicated.

IQR = interquartile range; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; other abbreviations as in Table 1.

lesions properly classified by iFR with respect to hemodynamic severity compared with FFR (with cutoff ≤0.80) in patients with MVD.

Additional objectives were to assess: 1) how the interrogation of more vessels by invasive physiology in patients with MVD influences the reclassification process and the safety of the procedure; 2) how the use of an FFR-driven approach or an iFR-driven approach in patients with MVD influences the reclassification process and the safety of the procedure; and 3) how pre-procedural noninvasive tests and their results influence the reclassification process.

STATISTICAL ANALYSES. It was estimated that reclassification of treatment strategy by invasive physiology in patients with MVD would be at least 20%, which is in the lower range of reclassification previously reported in the general population (3-5). At least 450 subjects were required to allow a point estimate of reclassification of 25% and a confidence interval of 21% to 29%.

All data are presented as mean ± SD (normally distributed data) or median and interquartile range (non-normally distributed data) for continuous variables. Categorical variables are presented as numbers

(percentage). Groups and subgroups were compared with Student *t* tests or Wilcoxon rank sum tests for continuous variables and with chi-square tests or Fisher exact tests for categorical variables. To describe the change of strategy, logistic regression analyses in which change of treatment strategy was the ordinal dependent variable were performed; p values ≤0.05 were considered statistically significant. No adjustments on the alpha level were made. Data were analyzed with SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

CLINICAL CHARACTERISTICS OF THE STUDY POPULATION. The study population included 484 patients, of which 398 (82.2%) were clinically stable and 86 (17.8%) underwent coronary angiography and routine FFR evaluation in the context of an ACS (**Table 1**). Diabetes mellitus was present in 129 (26.7%) patients, and 174 (36.0%) patients reported history of previous myocardial infarction. In 41.7% of the stable patients, a noninvasive test was performed. Among ACS patients, 16.3% had recent ST-segment elevation myocardial infarction, 51.1% had non-ST-segment elevation myocardial infarction, and 32.6% had unstable angina without troponin elevation.

ANGIOGRAPHIC AND INVASIVE PHYSIOLOGY CHARACTERISTICS. Two-vessel and 3-vessel angiographically defined CAD was observed in 73.3% and 26.7% of patients, respectively, making an average number of 2.29 diseased vessels per patient (**Table 1**). Of this population, 9.1% had left main disease.

Of the 1,097 vessels interrogated by angiography, 828 (75.5%) were also interrogated by invasive physiology (1.71 vessels investigated per patient). Lesions were located proximally in 43.4% of cases. The most frequently interrogated vessel was the LAD (46.9%). Interrogated lesions were typically intermediate by visual estimate with a median percent stenosis of 60% (interquartile range [IQR]: 50% to 70%) (**Table 2**).

In 564 vessels both FFR and iFR were recorded; in 228 vessels iFR only was recorded and in 36 vessels FFR only was assessed (Online Figure 1A).

When FFR was measured, adenosine was administrated mostly intracoronary (76%) with a majority of high-dosage bolus (≥100 μg in 90% of cases). Intravenous adenosine was used in 24% of cases (140 μg/kg/min in 85% and >140 μg/kg/min in 15% of cases).

Median FFR (0.84 [IQR: 0.78 to 0.90]) and median iFR (0.92 [IQR: 0.85 to 0.96]) were typical of intermediate lesions (**Table 2**, Online Figure 1B). In the 564 vessels in which both FFR and iFR were measured, FFR was positive in 33.3% of cases, whereas iFR was positive in 33.5% of cases (**Table 2**). Agreement between iFR and FFR was observed in 92% of cases (Online Figure 1C).

PROCEDURAL SAFETY AND TIME. No patients died.

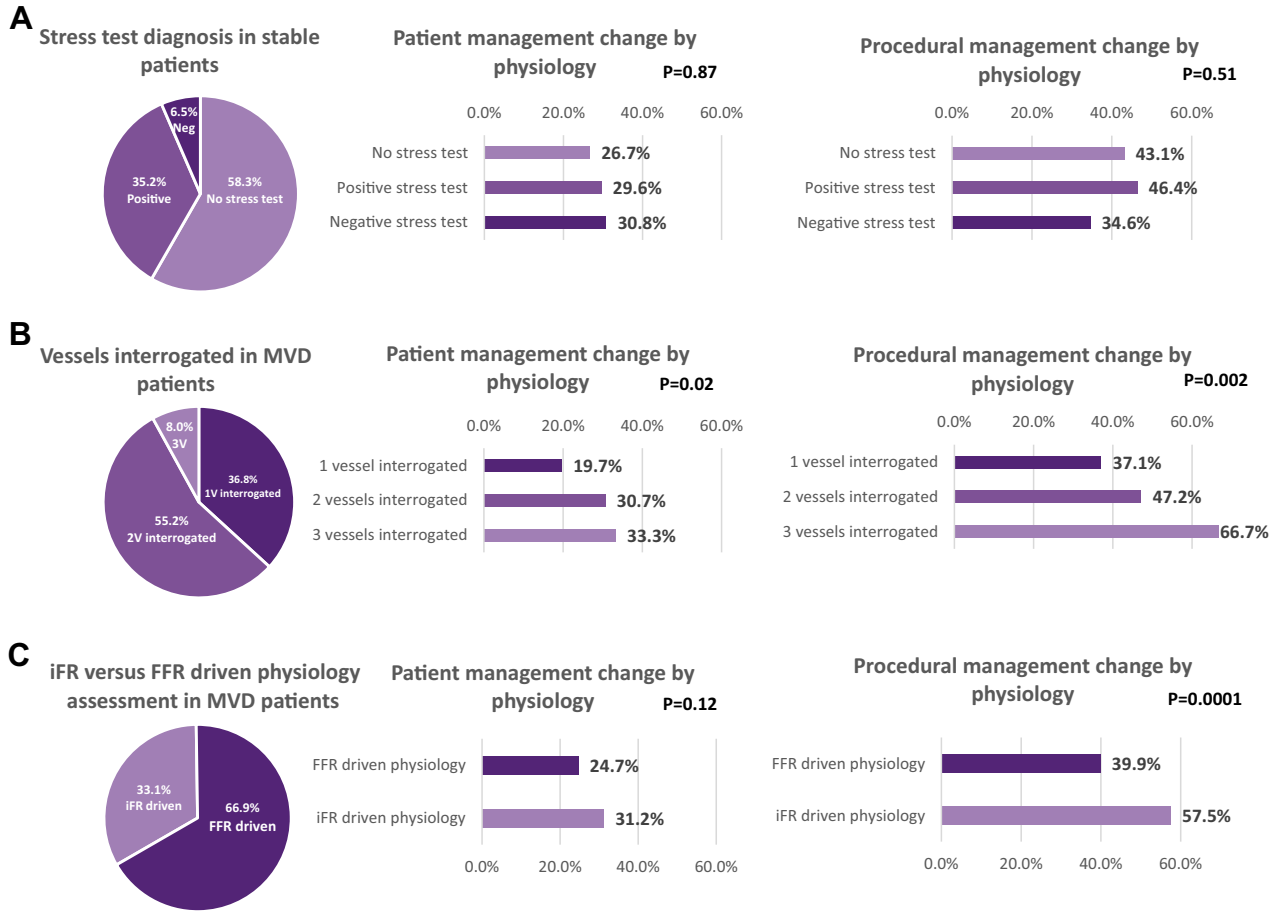
The average time needed for physiological evaluation in patients to investigate 1 vessel was 10 min 49 s ± 9 min 50 s. The average additional time needed to investigate 2 vessels was 4 min 43 s, while the average additional time needed to investigate 3 vessels was 8 min 13 s.

RECLASSIFICATION OF TREATMENT STRATEGY IN MVD PATIENTS. Vessel management. At the vessel level, treatment strategy was reclassified in 29.6% of vessels, which represents 247 of the 828 vessels that were interrogated by invasive physiology (**Figure 2A**, Online Figure 2A). The reclassification in treatment strategy was 43.8% in vessels initially designated to undergo PCI, 37.5% in vessels initially designated to undergo surgery, and 17.6% in vessels initially designated to OMT (Online Figure 2A). The reclassification process was associated with an increase in the proportion of vessels requiring OMT (52.2% to 61.8%), and surgery (4.8% to 5.7%), with a concomitant decrease in the proportion of vessels referred to PCI (43.0% to 32.5%) (Online Figure 2A). Overall, after reclassification, the majority of vessels evaluated by physiology were treated medically (2 of 3).

Patient management. At the patient level, the overall treatment strategy was reclassified in 26.9% of patients (**Figure 2B**, Online Figure 2B). The rate of reclassification in treatment strategy differed as follows, based on initial patient treatment strategy: PCI (27.3%), surgery (19.4%), and OMT (27.6%). The overall reclassification process was associated with an increase (8.0%) in the proportion of patients referred to OMT (28.6% to 36.6%), a slight increase (1.3%) in the proportion of patients referred to surgery (6.2% to 7.5%), and a concomitant decrease (9.3%) in the proportion of patients referred to PCI (65.2% to 55.9%) (Online Figure 2B). Overall, after reclassification, and in contrast to the observation made at the level of vessel management, the majority of patients (2 of 3) underwent revascularization.

Procedural and overall management. In the previous patient management approach, patients belonging to the PCI group before and after physiology, but with PCI performed in a different vessel, were not considered reclassified. Procedural management was defined to overcome this limitation (see Methods and Online Appendix). With this definition, one-third of patients initially considered for PCI and remaining in the PCI group after invasive physiology could be identified has having a change in procedural management for at

FIGURE 3 Reclassification by Invasive Physiology in 3 Major Subgroups of MVD Patients



Reclassification of patient management **(left)** and overall management **(right)** according to the results of **(A)** pre-procedural noninvasive tests, **(B)** the number of vessels interrogated, and **(C)** the use of an iFR- or a FFR-driven approach. Abbreviations as in Figure 1.

least 1 vessel (**Figure 2C**, Online Figure 2B). This translated into a higher figure of overall management reclassification compared with patient management (45.0% instead of 26.9%) (**Figure 2D**).

TREATMENT RECLASSIFICATION: IMPACT OF PREVIOUS NONINVASIVE TESTS. Among stable patients, 42% had a previous noninvasive test performed (Online Table 2A). These patients with a previous test had reclassification rates of the same magnitude as patients without a previous test (Online Table 2A, **Figure 3A**). Reclassification rates were not different when comparing patients with a global test (stress electrocardiography) with those with a localization test (stress echocardiography, stress magnetic resonance imaging, stress single-photon emission computed tomography, or computed tomography scan).

More specifically, among the 3 groups (no test, negative test, positive test), no difference in reclassification of patient management strategy (26.7%, 28.6%, 30.8%, respectively; $p = 0.87$) nor in overall management reclassification (43.1%, 46.4%, and 34.6%, respectively; $p = 0.51$) was observed. Between patients with a global test and those with a localization test, no difference in reclassification of patient management strategy (30.8% vs. 27.3%; $p = 0.62$) or in overall management reclassification (47.4% vs. 42.0%; $p = 0.49$) was observed.

TREATMENT RECLASSIFICATION: IMPACT OF THE NUMBER OF VESSELS INVESTIGATED. Reclassification of treatment strategy was higher with increased number of interrogated vessels (Online Table 2B, **Figure 3B**). Patient management was reclassified in 19.7% of

patients when invasive physiology was performed in 1 vessel, 30.7% of patients when performed in 2 vessels, and 33.3% of patients when performed in 3 vessels ($p = 0.02$) (**Figure 3B**). Similarly, overall management was reclassified in 37.3% of patients when invasive physiology was performed in 1 vessel, 47.0% of patients when performed in 2 vessels, and 66.7% of patients when performed in 3 vessels ($p = 0.002$) (**Figure 3B**).

TREATMENT RECLASSIFICATION IN PATIENTS WITH ACS. In ACS ($n = 86$), reclassification of patient management (23.3% vs. 27.6%; $p = 0.41$) and of overall management (51.1% vs. 43.7%; $p = 0.23$) were not different than in non-ACS patients ($n = 398$).

IMPLEMENTATION OF iFR AS PART OF THE INVASIVE PHYSIOLOGY PROCEDURE. Implementation of iFR as part of the procedure (iFR-driven procedures: see Online Appendix for definition) was conducted in 160 (33.1%) patients, including 12 (2.5%) patients in whom iFR was used as the main method in 50% of vessels (**Table 1,** Online Figure 1A). iFR-driven procedures were associated with less adverse symptoms (more details in the Online Appendix and Online Table 3). They were also associated with the interrogation of more vessels ($p = 0.04$), a trend for a higher patient management reclassification ($p = 0.12$) (Online Table 2C, **Figure 3C**), and a higher overall management reclassification rate ($p = 0.0001$) (Online Table 2C, **Figure 3C**; more details in the Online Appendix and Online Table 2C).

DISCUSSION

The DEFINE REAL study is the first to report on the impact of routine invasive physiology performed at the time of angiography on reclassification of treatment strategy in patients with multivessel CAD. This is also the first study to describe the use of iFR in this setting. DEFINE REAL discloses 4 key findings: 1) reclassification of treatment strategy by invasive physiology is high in this population, ranging from 26.9% to 45.0% depending on the definition; 2) reclassification rates are independent of the pre-angiography performance of noninvasive testing and results; 3) interrogation of more vessels is associated with an increased rate of reclassification without any increase in the rate of major periprocedural safety events (although there was an increase in the rate of minor safety events); and 4) incorporating iFR as part of the process is associated with the investigation of more vessels, which in turn leads to a higher reclassification rate and a decrease in the occurrence of minor safety events.

RECLASSIFICATION IN MVD: THE PRESENT STUDY VERSUS PREVIOUS STUDIES. Using invasive physiology at the time of angiography to reclassify coronary revascularization strategy has been investigated in a number of previous studies that demonstrated a reclassification rate ranging from 26% to 44% of patients (3-6). However, because they focused mainly on patients with single-vessel CAD, the impact of this approach in patients with MVD remained unclear. The DEFINE REAL study, by including only patients with MVD, is filling this gap.

The DEFINE REAL study also extends to the MVD population the previous observation of R3F (Registre Français de la FFR) and POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease) studies that reclassification of treatment by invasive physiology occurs at the same high rate (>25%) irrespective of whether a noninvasive test has been performed before angiography, and also whether this noninvasive test was positive (3,5). Because the add-on diagnostic value of noninvasive tests has been challenged (17) and because, as reported many times in large nationwide cohorts, noninvasive tests are performed in only 50% of patients referred for elective coronary angiography (18,19), this reinforces the concept of using invasive physiology at the time of angiography as a one-stop shop aiming to a shorten the decision process to the patient's benefit and to reduce the additional costs related to the performance of pre- or post-procedural noninvasive tests (20,21).

Another key contribution of the DEFINE REAL study is to help elucidate an important misconception about FFR. As the results of the DEFER study conducted in a very peculiar population of patients referred for PCI only (22), most interventionalists believe that an extensive use of FFR will unequivocally lead to a drastic reduction in PCI procedures. Interestingly, separate and pooled analysis of the 2,193 patients of R3F, RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain) and POST-IT studies, in which FFR was used in a broader population (including not only those considered for PCI, but also those for medical treatment or surgery) demonstrates that a routine use of FFR is overall neutral on the number of patients indicated to PCI (21). The present study, showing that a broad use of invasive physiology in MVD patients is associated with a very marginal decrease in the number of lesions and patients referred to revascularization (−9.6% and −8.0%, respectively), is highly consistent with these previous observations and extends them to the MVD patients.

ROLE OF INTERROGATION OF MORE VESSELS. This study is unique in its attempt to expand the use of physiological methods to interrogate multiple vessels in the same patient. The mean number of investigated vessels per patient (1.71) was much higher than in the previous R3F and POST-IT studies (1.3 to 1.4) (3,5,20,21) or the recent DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and IFR SWEDEHEART (Instantaneous Wave-Free Ratio versus Fractional Flow Reserve A multicenter, prospective, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry [SWEDEHEART] platform) studies (1.2 to 1.5) (13,14). Our results also clearly indicate that a higher reclassification rate was observed with increased number of interrogated vessels. The increase in number of vessels interrogated was accompanied by a modest increase in time expenditure and an increase in the rate of minor safety events, with no concomitant increase in the rate of major periprocedural safety events.

IMPLEMENTATION OF iFR AS PART OF THE INVASIVE PHYSIOLOGY PROCEDURE. The present study was designed to investigate how iFR was implemented as part of the invasive physiology process in patients with MVD. As such it was not a head-to-head comparison of the restricted use of iFR versus the restricted use of FFR. Agreement on classification of lesions between iFR and FFR was high (92%) and similar to previously reported studies (12). On average, an iFR-driven approach was associated with fewer side effects, in particular when patients were interrogated in 2 vessels ($p = 0.02$). An iFR-driven approach was also associated with interrogation of more vessels ($p = 0.04$) and a higher rate of reclassification of patient and procedural management than a FFR-driven approach ($p = 0.12$ and 0.0001). These observations demonstrate some of the theoretical advantages of incorporating iFR as part of the invasive physiology approach (i.e., because it does not require a hyperemic agent, the risk of minor side effects is decreased, enabling physicians to explore more vessels and therefore identify more opportunities for changes in revascularization strategy).

STUDY LIMITATIONS. First, the DEFINE REAL study is a prospective observational study; as such, its size was powered to detect a change in management and does not, therefore, take into account long-term clinical outcome. The specific issue of the impact of invasive physiology on clinical outcome in patients with MVD will be investigated in subsequent studies, in particular the SYNTAX II (A Trial to Evaluate a New Strategy in the Functional Assessment of 3-vessel Disease Using the SYNTAX II Score in Patients Treated With PCI) study (NCT02015832). Second, coronary angiography and invasive physiology were evaluated at each site without a central reading, and this could have induced some heterogeneity in reported angiographic and physiological values among participating centers. This issue was minimized by including centers well trained in both techniques, while the absence of heterogeneity was verified. In that aspect, the present study is in line with all previous studies investigating reclassification by invasive physiology (3–6) or the recent DEFINE-FLAIR and IFR SWEDEHEART studies, investigating physiology-based decision, which did not incorporate a core lab analysis (13,14). Third, the same investigator was performing the initial and final treatment decision, allowing potential bias when estimating reclassification rates. However, previous studies using 1 investigator only (3,5,6) or more than 1 investigator (4,23) reported very consistent rates of reclassification, thus suggesting that bias, if existing, is minimal. Last, although focusing on patients with MVD, the present study included mostly patients with intermediate lesions as illustrated by median FFR and iFR values of 0.84 and 0.92, respectively. Therefore, the results cannot be extrapolated to patients with angiographically severe MVD and tight lesions, as those included in the recently presented FUTURE (Functional Testing Underlying Coronary Revascularisation) study and in whom invasive physiology was reported to have little impact on reclassification of the revascularization decision (8% treatment change) and no clinical benefit (85% of the total population was reported at 1-year follow-up with no difference between groups) (24).

CONCLUSIONS

The DEFINE REAL study demonstrates that in patients with MVD who are scheduled to coronary angiography, routine invasive physiological assessment of vessels with intermediate lesions is associated with a very high rate of reclassification of the treatment strategy (26.9% up to 45%, depending on the definition). It extends to the MVD population the previous observation made in the general population (R3F, RIPCORD, and POST-IT studies) (3–5) and confirms that the ultimate effect of routine invasive physiological interrogation of vessels with

intermediate lesions at the time of angiography is to identify the optimal revascularization method for a particular patient, rather than decreasing the number of patients referred to revascularization (20,21). It further demonstrates that interrogation of additional vessels in conjunction with routine use of iFR can play an important role in determining the optimal method of revascularization while keeping the procedure safe. This is important additional information to the recent DEFINE-FLAIR and IFR SWEDEHEART randomized studies (13,14). Results of ongoing SYNTAX II study, focusing on long-term clinical outcome, should further clarify the role of invasive physiology in optimization of revascularization strategy in MVD patients.

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PERSPECTIVES

WHAT IS KNOWN? Routine invasive physiology at the time of diagnostic angiography reclassifies the coronary revascularization strategy in >25% of cases. Less is known about how coronary physiology reclassifies treatment strategy in MVD patients and the impact of implementing simplified pressure wire assessment such as iFR.

WHAT IS NEW? In patients with angiography-defined MVD, routine invasive physiology including FFR and iFR is associated with high a rate of reclassification of revascularization strategy (26% to 45%). Interrogation of more vessels is associated with an increased rate of reclassification (up to 67% in 3 vessels) without any increase in the rate of major periprocedural safety events. Integration of iFR is associated with the investigation of more vessels, which in turn leads to a higher reclassification rate.

WHAT IS NEXT? Randomized studies including long-term clinical outcome data are required to confirm that a refined decision tailored by physiology is a better and safer approach for revascularization strategy in MVD patients with intermediate coronary lesions.

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KEY WORDS coronary stenosis, iFR, FFR, MVD, physiological assessment

APPENDIX For an expanded Methods and Results sections as well as supplemental tables and figures, please see the online version of this paper.