JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 16, 2022

NEW RESEARCH PAPERS

CORONARY

FFR-Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care

The FFR REACT Trial

Tara Neleman, BSc, Laurens J.C. van Zandvoort, PhD, Maria N. Tovar Forero, MD, Kaneshka Masdjedi, MD, PhD, Jurgen M.R. Ligthart, RT, Karen T. Witberg, CCRN, Frederik T.W. Groenland, MD, Paul Cummins, CCRN, Mattie J. Lenzen, PhD, Eric Boersma, PhD, Rutger-Jan Nuis, MD, PhD, Wijnand K. den Dekker, MD, PhD, Roberto Diletti, MD, PhD, Jeroen Wilschut, MD, Felix Zijlstra, MD, PhD, Nicolas M. Van Mieghem, MD, PhD, Joost Daemen, MD, PhD

ABSTRACT

BACKGROUND Post-percutaneous coronary intervention (PCI) fractional flow reserve (FFR) <0.90 is common and has been related to impaired patient outcome.

OBJECTIVES The authors sought to evaluate if PCI optimization directed by intravascular ultrasound (IVUS) in patients with post-PCI FFR <0.90 could improve 1-year target vessel failure (TVF) rates.

METHODS In this single-center, randomized, double-blind trial, patients with a post-PCI FFR <0.90 at the time of angiographically successful PCI were randomized to IVUS-guided optimization or the standard of care (control arm). The primary endpoint was TVF (a composite of cardiac death, spontaneous target vessel myocardial infarction, and clinically driven target vessel revascularization) at 1 year.

RESULTS A total of 291 patients with post-PCI FFR <0.90 were randomized (IVUS-guided optimization arm: n = 145/152 vessels, control arm: n = 146/157 vessels). The mean post-PCI FFR was 0.84 ± 0.05. A total of 104 (68.4%) vessels in the IVUS-guided optimization arm underwent additional optimization including additional stenting (34.9%) or postdilatation only (33.6%), resulting in a mean increase in post-PCI FFR in these vessels from 0.82 ± 0.06 to 0.85 ± 0.05 ($P < 0.001$) and a post-PCI FFR ≥0.90 in 20% of the vessels. The 1-year TVF rate was comparable between the 2 study arms (IVUS-guided optimization arm: 4.2%, control arm: 4.8%; $P = 0.79$). There was a trend toward a lower incidence of clinically driven target vessel revascularization in the IVUS-guided optimization arm (0.7% vs. 4.2%, $P = 0.06$).

CONCLUSIONS IVUS-guided post-PCI FFR optimization significantly improved post-PCI FFR. Because of lower-than-expected event rates, post-PCI FFR optimization did not significantly lower TVF at the 1-year follow-up.

From the Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands.
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 Author Center.

Manuscript received March 6, 2022; revised manuscript received June 6, 2022, accepted June 14, 2022.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2022.06.018

ABBREVIATIONS AND ACRONYMS

CD-TVR = clinically driven target vessel revascularization

FFR = fractional flow reserve

IVUS = intravascular ultrasound

MACE = major adverse cardiac event(s)

MLA = minimal lumen area

MSA = minimal stent area

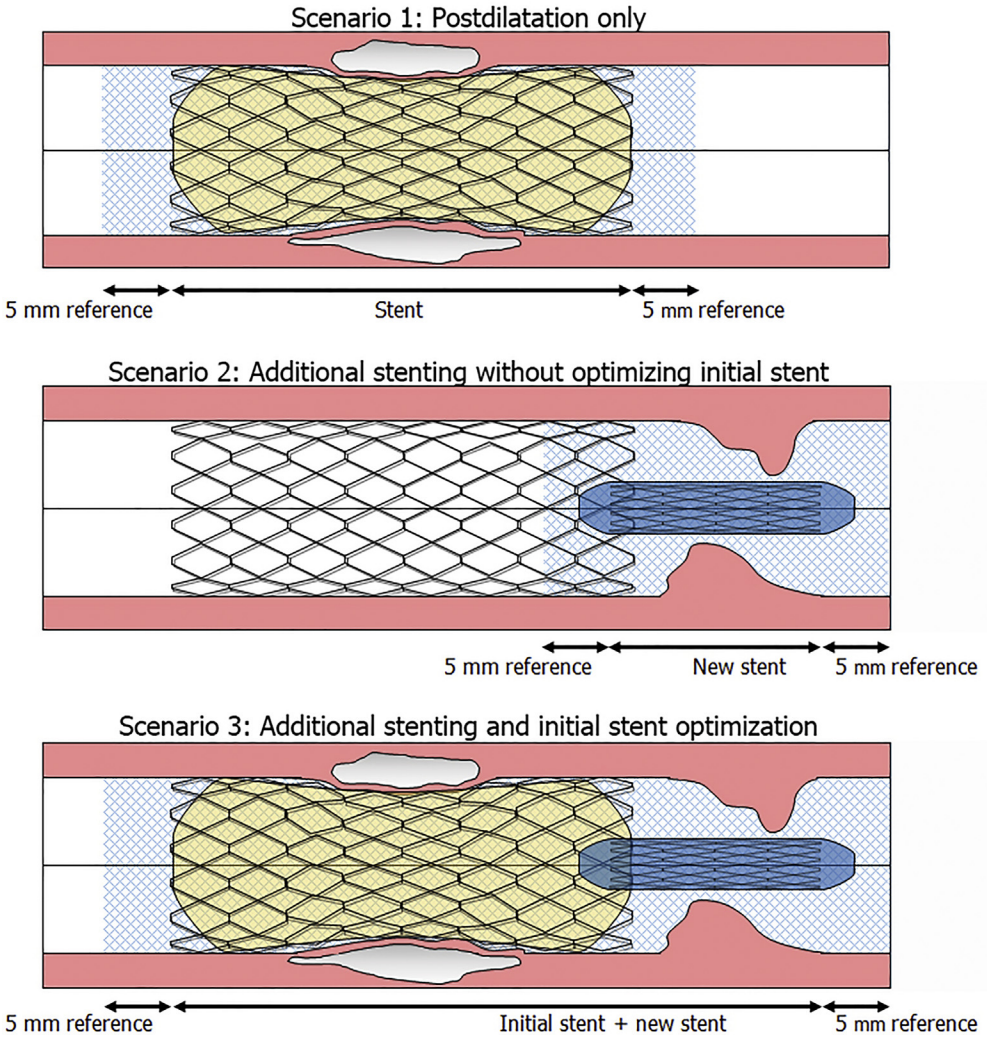
PCI = percutaneous coronary intervention

TVF = target vessel failure

Despite significant improvements in percutaneous coronary intervention (PCI) techniques over the past decades, 5-year target vessel failure (TVF) rates of up to 15% have been reported.[1-3] Pre-PCI physiological lesion assessment using fractional flow reserve (FFR) improves clinical outcome.[4,5] Moreover, higher rates of major adverse cardiac events (MACE) have been reported in patients with low post-PCI FFR values (threshold values ranging from ≤0.83 to ≤0.91).[6-11] Subsequent observational studies demonstrated that post-PCI FFR can be increased by additional stenting or postdilatation.[12-14] However, these studies were neither designed nor powered to detect whether post-PCI FFR optimization improves patient outcome, and additional treatment in these studies was often directed by the FFR pull back pattern, which merely serves as a surrogate of the true cause of the suboptimal FFR.[12-14] Conversely, intravascular ultrasound (IVUS) provides real-time anatomical assessment and could guide targeted post-PCI optimization.[15] The objective of the FFR

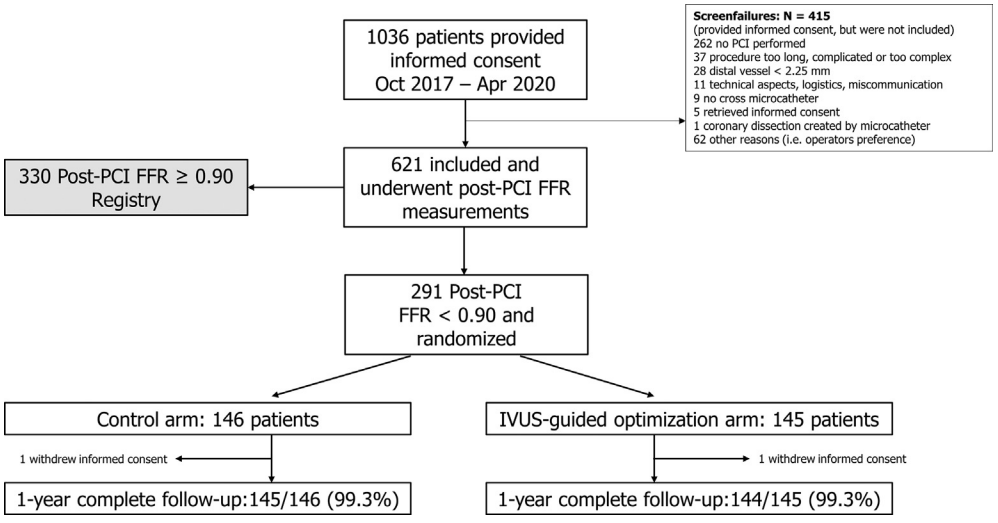
SEE PAGE 1608

FIGURE 1 Visual Overview of the 3 Optimization Scenarios



The **blue areas** indicate which luminal areas were compared preoptimization and postoptimization.

FIGURE 2 Study Flowchart



FFR = fractional flow reserve; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

REACT trial was to assess whether IVUS-guided optimization of post-PCI FFR <0.90 reduces the rate of TVF at 1-year follow-up compared with the standard of care.

METHODS

The FFR REACT study is an investigator-initiated, single-center, double-blind, parallel-arm trial that randomized patients with a post-PCI FFR <0.90 in a 1:1 ratio to IVUS-guided PCI optimization or the standard of care (the control arm [ie, the end of the procedure]) between October 31, 2017, and April 22, 2020. Patients with a post-PCI FFR ≥0.90 were enrolled in a dedicated registry. The study was approved by the local ethics committee (MEC-2017-489) and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients provided informed consent before all study procedures. The study is registered at the Netherlands Trial Register (NL6523).

STUDY POPULATION. Adult patients presenting with (un)stable angina or non-ST-segment elevation myocardial infarction who underwent angiographically successful PCI with stenting were eligible. The exclusion criteria were as follows: 1) ST-segment elevation myocardial infarction <72 hours; 2) target vessel distal reference diameter <2.25 mm; 3) cardiogenic shock or severe hemodynamic instability; 4) PCI without stenting; 5) inability to perform post-procedure FFR; and 6) medical illnesses that preclude protocol compliance or are associated with limited life expectancy (<1 year).

STUDY PROCEDURES. All patients underwent PCI according to routine clinical practice with the use of preprocedural coronary physiology or intravascular imaging left at the operator's discretion. After angiographic confirmation of successful PCI, defined as residual stenosis <30% by visual estimation in the presence of Thrombolysis In Myocardial Infarction flow grade 3, post-PCI distal coronary pressure to aortic pressure ratio and FFR measurements were obtained using a dedicated microcatheter (Navvus, ACIST Medical Systems, Inc). Measurements started at least 20 mm distal to the distal stent edge. Distal coronary pressure to aortic pressure ratio and FFR values were recorded at 4 locations: the distal coronary artery, the distal and proximal stent edge, and the coronary ostium. Maximal hyperemia was achieved by an intravenous infusion of adenosine at a rate of 140 μg/kg/min through an antecubital vein. In case drift exceeded 0.02, measurements were repeated.

Patients with a distal post-PCI FFR <0.90 were randomized. Randomization to the control arm determined the end of the procedure (standard of care). In the IVUS-guided optimization arm, IVUS was performed by an automated pull back (Kodama HD-IVUS catheter, ACIST Medical Systems, Inc) at 24 frames/mm starting from the same location as the tip of the microcatheter. Pull backs were analyzed online. A dedicated stepwise optimization

TABLE 1 Baseline Characteristics

	IVUS-Guided Optimization Arm (n = 145)	Control Arm (n = 146)	Total (N = 291)	*P* Value
Age, y	66 (60-72)	67 (57-74)	66 (58-73)	0.54
Male	123 (84.8)	112 (76.7)	235 (80.8)	0.079
Hypertension	101 (69.7)	107 (73.3)	208 (71.5)	0.49
Hypercholesterolemia	100 (69.0)	89 (61.0)	189 (64.9)	0.15
Diabetes	37 (25.5)	26 (17.8)	63 (21.6)	0.11
Diet only	5 (13.5)	0 (0.0)	5 (7.9)	0.071
Oral medication	18 (48.6)	16 (61.5)	34 (54.0)	0.31
Insulin use	14 (37.8)	10 (38.5)	24 (38.1)	0.96
Smoking history	73 (50.3)	74 (50.7)	147 (50.5)	0.95
Prior stroke	17 (11.7)	9 (6.2)	26 (8.9)	0.096
Peripheral arterial disease	13 (9.0)	16 (11.0)	29 (10.0)	0.57
Prior PCI	47 (32.4)	45 (30.8)	92 (31.6)	0.77
Prior CABG	7 (4.8)	5 (3.4)	12 (4.1)	0.55
Prior myocardial infarction	36 (24.8)	32 (21.9)	68 (23.4)	0.56
Indication for PCI				0.10
Stable angina	89 (61.4)	72 (49.3)	161 (55.3)	
Unstable angina	17 (11.7)	26 (17.8)	43 (14.8)	
NSTEMI	39 (26.9)	48 (32.9)	87 (29.9)	
Atrial fibrillation	24 (16.6)	21 (14.4)	45 (15.5)	0.61
eGFR, mL/min	84 (71-94)	84 (64-94)	84 (68-94)	0.19
LVEF				0.086
Good (>50%)	95/133 (71.4)	101/134 (75.4)	196/267 (73.4)	
Moderate (30%-49%)	27/133 (20.3)	30/134 (22.4)	57/267 (21.3)	
Poor (<30%)	11/133 (8.3)	3/134 (2.2)	14/267 (5.2)	

Values are median (IQR), n (%), or n/N (%).

CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

protocol was developed to standardize optimization (Supplemental Table 1).[16] In case of post-PCI optimization, both physiological assessment and IVUS imaging were repeated. Pressure wave form tracings and IVUS pull backs were stored for off-line analysis in a dedicated local database.

Routine laboratory sampling including cardiac biomarkers was performed before discharge or earlier in case of signs or symptoms of ischemia. Patients were discharged on guideline-recommended medical therapy.

OFF-LINE FFR AND IVUS ANALYSIS. All FFR tracings and IVUS pull backs were assessed off-line in a blinded fashion by the Erasmus University Medical Center academic core laboratory. Quantitative IVUS parameters were obtained by manual lumen, stent, and vessel contouring every 0.5 mm using dedicated software (QCU-CMS, version 4.69, Leiden University Medical Centre, LKEB, Division of Image Processing). Qualitative IVUS parameters were scored according to predefined protocol definitions (Supplemental Table 1).[16] Additional post hoc-defined analyses included evaluation of the optimal stent implantation criteria as suggested by the ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial as well as dedicated optimization segment analyses to enable direct comparisons between pre- and post-optimization for areas target to optimization procedures.[17] We considered 3 different optimization scenarios (Figure 1): scenario 1, "postdilatation only" in which the region of interest included the stented segment + 5-mm reference segments distal and proximal; scenario 2, "additional stenting without optimization of the initial stent," which included the newly placed stent + 5-mm reference segments distal and proximal; and scenario 3, "additional stenting in combination with initial stent optimization," which included both stents + 5-mm reference segments distal and proximal.

RANDOMIZATION AND BLINDING PROCEDURES. Randomization (block size varying from 4-6) was performed online in a 1:1 fashion by a web-based application (ALEA, Formvision). Patients were randomized after the first post-PCI FFR value <0.90; in case of a second vessel with post-PCI FFR <0.90, the vessel was allocated to the same treatment arm as the first vessel.

Patients, physicians involved in patient care, study personnel performing follow-up calls and visits, and the independent clinical event committee were blinded to post-PCI FFR values and group allocation. Per protocol, operators were uninvolved in the study follow-up and analysis.

CLINICAL FOLLOW-UP. Patients were followed up via telephone at 6, 24, and 36 months and by outpatient clinic visit at 12 months. Source documentation was retrieved from local electronic patient records, referring hospitals, and general practitioners.

ENDPOINTS, DEFINITIONS, AND ADJUDICATION. The primary study endpoint was TVF at 1 year, defined as a composite of cardiac death, spontaneous target vessel myocardial infarction, and clinically driven target vessel revascularization (CD-TVR). Target vessel was defined as the vessel subject to study-specific interventions. The secondary endpoints and their definitions are listed in Supplemental Table 2. Patient-reported outcomes were adjudicated by an independent clinical event committee according to predefined definitions.[16]

SAMPLE SIZE CALCULATION. The FFR REACT trial was powered to detect a drop in the 1-year TVF rate from 19% to 7.5% after IVUS-guided PCI optimization in patients with post-PCI FFR <0.90 (2-sided $\alpha = 0.05$,

TABLE 2 Characteristics of Vessels Subject to Study Interventions (Prerandomization)

	IVUS-Guided Optimization Arm (n = 152)	Control Arm (n = 157)	Total (N = 309)	*P* Value
Target vessel				0.45
Left anterior descending artery	109 (71.7)	120 (76.4)	229 (74.1)	
Left circumflex artery	16 (10.5)	14 (8.9)	30 (9.7)	
Isolated left main artery	2 (1.3)	1 (0.6)	3 (1.0)	
Right coronary artery	25 (16.4)	21 (13.4)	46 (14.9)	
Saphenous venous graft	0 (0.0)	1 (0.6)	1 (0.3)	
Predilatation	104 (68.4)	108 (68.8)	212 (68.6)	0.92
Predilatation NC balloon	38 (25.0)	44 (28.0)	82 (26.5)	0.52
Postdilatation	108 (71.1)	108 (68.8)	216 (69.9)	0.67
Postdilatation NC balloon	85 (55.9)	96 (61.1)	181 (58.6)	0.35
>1 stent implanted	64 (42.1)	48 (30.6)	112 (36.2)	0.036
Median stent diameter, mm	3.00 (2.88-3.50)	3.00 (3.00-3.50)	3.00 (3.00-3.50)	0.33
Total stent length, mm	31 (18-50)	27 (18-40)	30 (18-47)	0.045
Lesion type B2/C	128 (84.2)	109 (69.4)	237 (76.7)	0.002
Bifurcation 2-stent strategy	13 (8.6)	9 (5.7)	22 (7.1)	0.52
Aorta-ostial lesion	13 (8.6)	19 (12.1)	32 (10.4)	0.31
In-stent restenosis	12 (7.9)	12 (7.6)	24 (7.8)	0.93
Heavy calcification	74 (48.7)	57 (36.3)	131 (42.4)	0.19
CTO	16 (10.5)	8 (5.1)	24 (7.8)	0.081
FFR guidance	33 (21.7)	39 (24.8)	72 (23.3)	0.52
Intravascular imaging guidance	35 (23.0)	25 (15.9)	60 (19.4)	0.22
Preprocedural quantitative coronary angiography	163 lesions in 152 vessels	166 lesions in 157 vessels	329 lesions in 309 vessels	
Diameter stenosis, %	60 (49-75)	57 (46-71)	59 (48-73)	0.18
Reference diameter, mm	2.44 (2.14-2.85)	2.48 (2.14-2.85)	2.48 (2.14-2.85)	0.58
Lesion length, mm	22 (15-39)	21 (14-30)	22 (15-33)	0.061
Minimal lumen diameter, mm	0.96 (0.59 - 1.23)	1.08 (0.71 - 1.33)	1.00 (0.66 - 1.27)	0.060
Post-PCI physiology				
Pd/Pa, distal	0.94 ± 0.04 0.94 (0.91-0.96)	0.94 ± 0.03 0.94 (0.92-0.96)	0.94 ± 0.04 0.94 (0.92-0.96)	0.65
FFR, distal	0.83 ± 0.05 0.84 (0.80-0.87)	0.84 ± 0.04 0.85 (0.81-0.88)	0.84 ± 0.05 0.85 (0.81-0.87)	0.096
FFR ≤0.80	40 (26.3)	31 (19.7)	71 (23.0)	0.24
FFR gradient over stent	0.05 ± 0.04 0.05 (0.02-0.07)	0.04 ± 0.03 0.04 (0.02-0.06)	0.05 ± 0.03 0.04 (0.02-0.06)	0.43

Values are n (%), median (IQR), or mean ± SD.

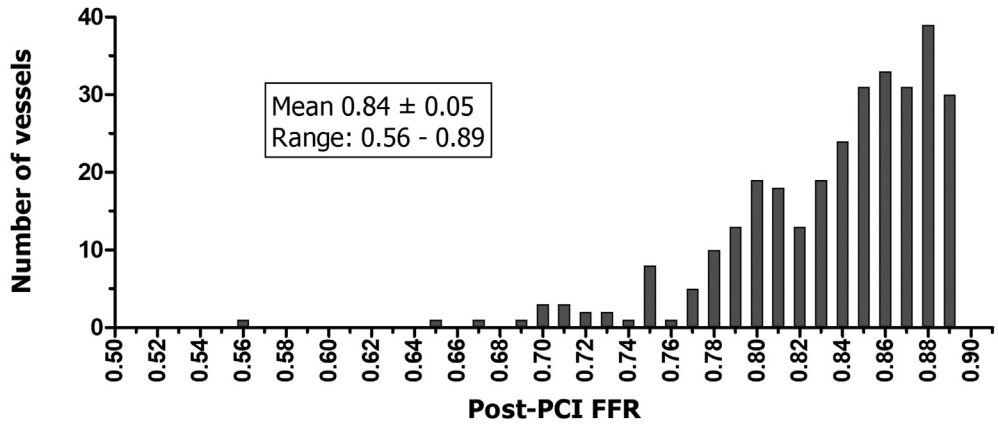
CTO = chronic total occlusion; FFR = fractional flow reserve; NC = noncompliant; Pd/Pa = distal coronary pressure to aortic pressure ratio; other abbreviations as in Table 1.

β = 0.80, and allocation ratio 1:1). The assumed 1-year TVF rate in both arms was based on the incidence of MACE (heterogeneous definitions used; post-PCI FFR <0.90: 21.4% vs ≥0.90: 5%) in a recent meta-analysis and extrapolated to the incidence of MACE in our center (overall: 10%, estimated MACE in post-PCI FFR <0.90: 19%).[18] The required sample size (n = 272) was enlarged to 290 patients to account for possible technical failures, loss to follow-up, and unsuitable FFR or IVUS acquisition.

STATISTICAL ANALYSIS. We applied the Shapiro-Wilk test to evaluate the normality of the variables under investigation. Continuous variables with a normal and non-normal distribution are presented as mean ± SD and median (IQR), respectively. Continuous variables related to coronary physiology are reported in both ways to facilitate direct comparisons with prior literature. Categoric variables are displayed as counts (percentages). Differences in patient-level variables were assessed using standard statistical tests, and differences in lesion-level variables were assessed using (generalized) linear mixed models with random intercepts to adjust for clustering of vessels within patients.

In time-to-event analyses, patients were censored at the 1-year follow-up (365 days), the moment of last contact, or the day of the event of interest, whichever occurred first. For the primary study endpoint (TVF) analysis, the first occurring event was counted. Event probabilities were derived from the Kaplan-Meier

FIGURE 3 Frequency Distribution of Post-PCI FFR Values Before Randomization



Abbreviations as in Figure 2.

function, and the log-rank test was applied to test for differences in event probabilities between the 2 study arms. Univariate HRs with corresponding 95% CIs were derived from Cox proportional hazard regression models. A sensitivity analysis was performed on the primary endpoint to take into account competing risks by noncardiovascular mortality.[19]

All analyses were performed on the intention-to-treat population. A 2-sided P value <0.05 was considered to be significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp) and R software, version 4.1.0, (R Core Team 2021, packages: survival, cmprsk, glme, nlme).

RESULTS

PATIENT SCREENING AND INCLUSION. A total of 621 patients with angiographically successful PCI underwent post-PCI FFR measurements (mean post-PCI FFR 0.90 ± 0.07 in 720 vessels), 291 of whom had a post-PCI FFR value <0.90 and were subsequently randomized (Figure 2). A total of 145 patients were assigned to the IVUS-guided optimization arm, and 146 patients were allocated to the control arm.

BASELINE AND PROCEDURAL CHARACTERISTICS. The median age was 66 years (IQR: 58-73 years), 80.8% of patients were male, and diabetes was present in 21.6% of the patients. The clinical presentation was stable angina in 55.3% of the patients (Table 1).

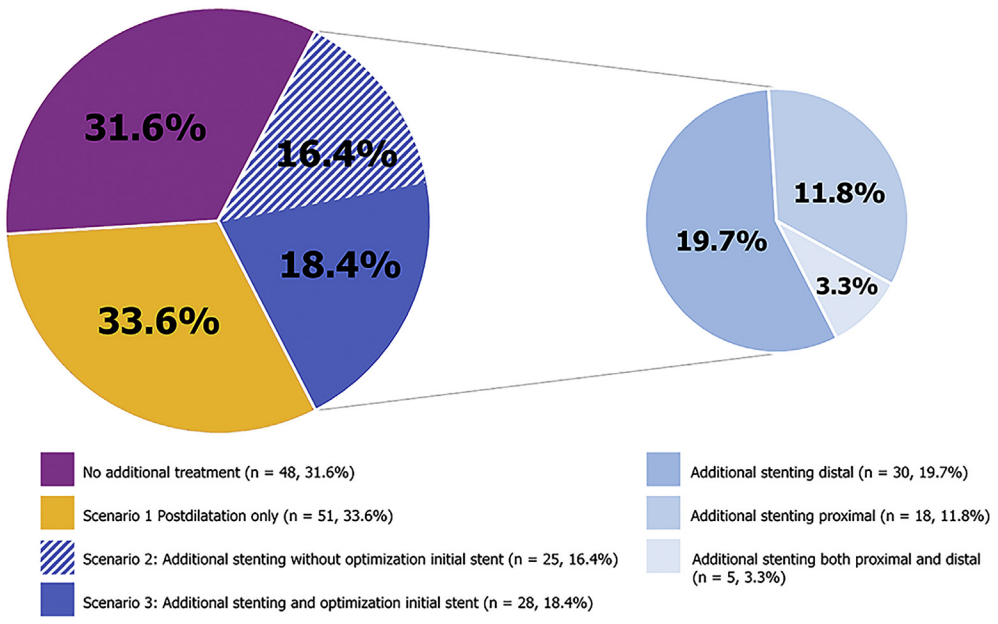
In the 291 randomized patients, 309 vessels had a post-PCI FFR <0.90 (IVUS-guided optimization arm: n = 145, 152 vessels; control arm: n = 146, 157 vessels) (Table 2). Most vessels were left anterior descending arteries (74.1%). Lesion type B2/C was more frequent in the IVUS-guided optimization arm compared with the control arm (84.2% vs 69.4%, respectively; $P = 0.002$), resulting in more stents and longer total stent lengths (≥1 stent implanted in 42.1% vs 30.6%; $P = 0.036$ and 31 mm [IQR: 18-50 mm] vs 27 mm [IQR: 18-40 mm], $P = 0.045$, respectively).

BASELINE POST-PCI FFR AND IVUS DATA (PREOPTIMIZATION). The overall mean post-PCI FFR was 0.84 ± 0.05; the mean post-PCI FFR was 0.83 ± 0.05 in the IVUS-guided optimization arm and 0.84 ± 0.04 in the control arm (Figure 3, Table 2). The mean cross-stent gradient was 0.05 ± 0.03. A total of 71 vessels (23.0%) had a post-PCI FFR ≤0.80.

In the IVUS-guided optimization arm, stent underexpansion was present in 62.2% of vessels, whereas residual focal lesions either proximal or distal to the stented segment were found in 14.7% and 16.1% of vessels, respectively. Only 9.1% of the vessels met all 3 optimal stenting criteria. The mean minimal lumen area (MLA) and minimal stent area (MSA) were 3.15 ± 1.27 mm^2 and 4.92 ± 1.81 mm^2, respectively. Detailed IVUS pull back data are presented in Supplemental Table 3.

POST-PCI OPTIMIZATION. A total of 104 of 152 (68.4%) vessels in patients randomized to the IVUS-guided optimization arm underwent additional treatment (Figure 4). In 51 vessels (33.6%), additional postdilatation of the initially implanted stent was performed (optimization scenario 1). A total of 53 vessels (34.9%) received additional stents; 25

FIGURE 4 Additional Treatment After Randomization to the IVUS-Guided Optimization Arm



IVUS = intravascular ultrasound. Abbreviations as in Figure 2.

vessels (16.4%) received additional stents without optimization of the initial stent (optimization scenario 2), and 28 vessels (18.4%) also received optimization of the initial stent (optimization scenario 3). Vessels that received PCI optimization had lower post-PCI FFR values, smaller MSAs, and more often had residual focal disease as assessed by IVUS compared with vessels in which no further optimization was performed (Supplemental Table 3). Of the 45 nonoptimized vessels in which successful IVUS pull backs were performed, significant focal residual disease being either relevant edge dissections or residual focal lesions proximal or distal to the stent and relevant underexpansion (according to the ULTIMATE criteria) were present in 16 vessels (35.6%), suggesting missed opportunities for optimization. In the remaining cases, no residual focal treatable disease was found. Three patients underwent PCI optimization after low post-PCI FFR despite allocation to the control arm.

TABLE 3 Physiology Results Preoptimization and Postoptimization

	Preoptimization	Postoptimization	*P* Value
FFR distal	0.82 ± 0.06 0.84 (0.79-0.86)	0.85 ± 0.05 0.86 (0.82-0.89)	<0.001
Scenario 1 "postdilatation only"[a] (n = 49)	0.84 ± 0.04 0.85 (0.81-0.86)	0.86 ± 0.06 0.86 (0.82-0.89)	0.006
Scenario 2 "additional stenting without optimization of the initial stent"[a] (n = 24)	0.79 ± 0.07 0.80 (0.76-0.85)	0.85 ± 0.05 0.86 (0.82-0.89)	<0.001
Scenario 3 "additional stenting in combination with initial stent optimization"[a] (n = 27)	0.81 ± 0.06 0.82 (0.79-0.87)	0.85 ± 0.05 0.87 (0.81-0.89)	0.003
Pd/Pa distal	0.93 ± 0.04 0.93 (0.91-0.96)	0.95 ± 0.04 0.94 (0.92-0.97)	<0.001
FFR ≥0.90	0 (0)	20 (20)	<0.001
FFR ≤0.80	31 (31.0)	17 (17.0)	0.014
FFR gradient over stent	0.05 ± 0.04 0.05 (0.02-0.07)	0.03 ± 0.03 0.03 (0.01-0.05)	<0.001

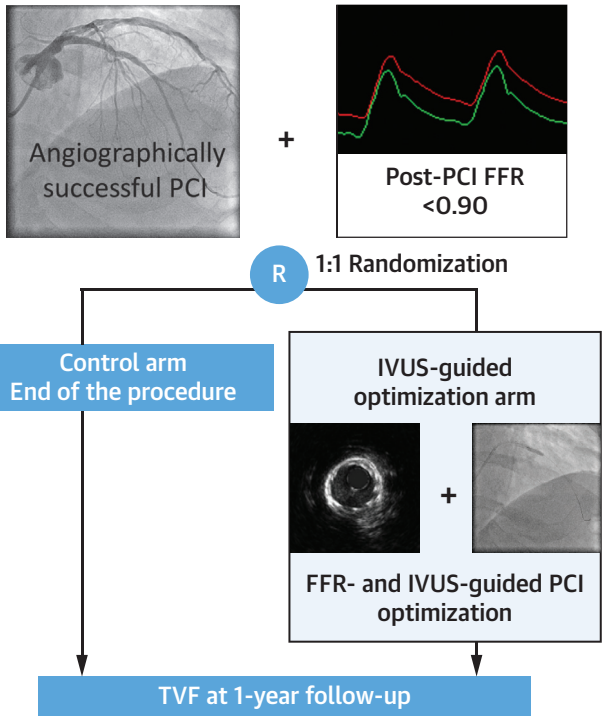
Values are displayed as mean ± SD, median (IQR), or n (%). [a]Additional stenting (scenario 2 and 3 combined) resulted in significantly higher increases in post-PCI FFR compared with postdilatation alone (scenario 1) ($P = 0.011$). Optimized in 104 vessels; paired data available in 100 vessels.

Abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION The FFR REACT Trial

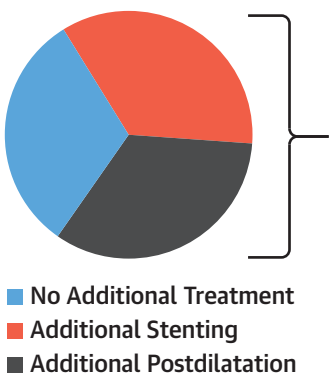
FFR-Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care: The FFR REACT Trial (N = 291)

A Study Design of the FFR REACT Trial

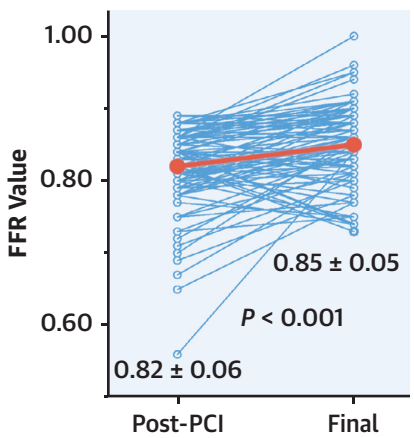


B Results of Additional Treatment in the IVUS-Guided Optimization Arm

Optimization in 68.4% of Vessels



FFR and IVUS Optimization Results



Minimal lumen area
3.40 ± 1.43 mm² to 4.25 ± 1.90 mm²
P < 0.001

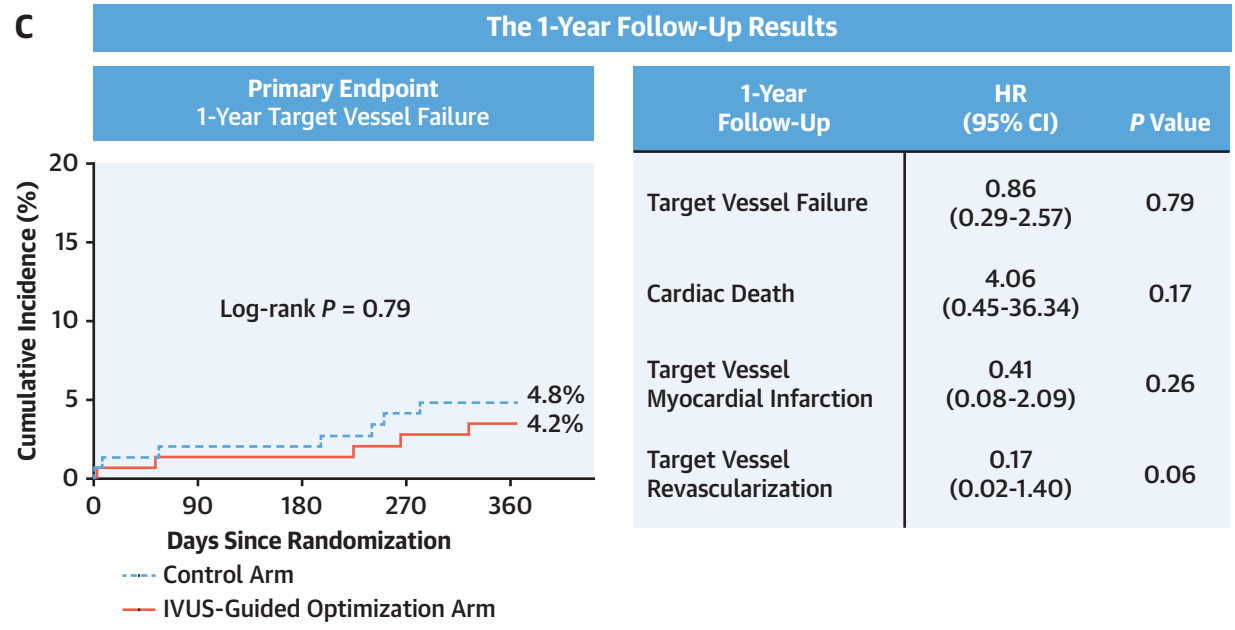
Minimal stent area
4.46 ± 1.50 mm² to 4.98 ± 1.50 mm²
P < 0.001

Neleman T, et al. J Am Coll Cardiol Intv. 2022;15(16):1595-1607.

AS = aortic stenosis; CAD = coronary artery disease; FFR = fractional flow reserve; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

Continued on the next page

CENTRAL ILLUSTRATION Continued



1-Year Follow-Up	HR (95% CI)	*P* Value
Target Vessel Failure	0.86 (0.29-2.57)	0.79
Cardiac Death	4.06 (0.45-36.34)	0.17
Target Vessel Myocardial Infarction	0.41 (0.08-2.09)	0.26
Target Vessel Revascularization	0.17 (0.02-1.40)	0.06

Neleman T, et al. J Am Coll Cardiol Intv. 2022;15(16):1595-1607.

POSTOPTIMIZATION FFR AND IVUS FINDINGS. The mean post-PCI FFR in these vessels increased from 0.82 ± 0.06 to 0.85 ± 0.05 after additional treatment (Δ0.03 ± 0.06, $P < 0.001$; **Table 3, Central Illustration**). After optimization, 20 of 100 (20.0%) vessels ended with a final post-PCI FFR ≥0.90 ($P < 0.001$). Post-PCI FFR ≤0.80 decreased from 31 vessels (31%) preoptimization to 17 vessels (17%) after optimization ($P = 0.014$). The final FFR increased significantly in all 3 optimization scenarios, but larger increases were found in cases in which additional stents were implanted ($P = 0.011$) (**Table 3**). The mean post-PCI FFR in the total IVUS-guided optimization arm (including both optimized and nonoptimized patients) improved to 0.85 ± 0.05, which was significantly higher than the post-PCI FFR in the control arm (0.84 ± 0.04) ($P = 0.012$) (Supplemental Figure 1).

MLA in the target segment of optimization increased from 3.40 ± 1.43 mm^2 to 4.25 ± 1.90 mm^2 ($P < 0.001$) (Supplemental S4). The implantation of additional stents resulted in a higher increase in the luminal area compared with scenarios in which no additional stents were implanted (scenario 2 and scenario 3 vs scenario 1: both $P < 0.05$). IVUS-guided optimization led to a significant decrease in the number of proximal and distal residual lesions (15.1% to 4.7%, $P = 0.004$, and 19.8% to 10.5%, $P = 0.021$, respectively) as well as diffuse disease (14.0% to 3.5%, $P = 0.004$). Finally, the proportion of patients meeting all 3 optimal stenting criteria increased from 8.1% to 19.8% ($P = 0.006$).

PROCEDURAL SAFETY DATA. The procedural time, contrast usage, and fluoroscopy time were significantly higher in patients randomized to the IVUS-guided optimization arm (**Table 4**). There were no differences in the incidence of periprocedural complications between both study arms. Optimization procedure-related complications were restricted to a single case of Ellis type II perforation after additional postdilatation, which recovered after 2 minutes of balloon inflation. All other periprocedural complications were considered unrelated to the study or optimization procedures (Supplemental Table 4). Periprocedural myocardial infarction, according to the Society for Cardiac Angiography and Intervention definition, occurred in 8 patients (5.5%) in the IVUS-guided optimization arm and 4 patients (2.7%) in the control arm ($P = 0.23$) and did not differ between patients who were optimized (5/103 [4.9%]) versus patients who did not receive optimization (3/42 [7.1%], $P = 0.69$).

CLINICAL FOLLOW-UP ENDPOINTS. The 1-year follow-up was completed in 99.3% of patients. Six patients (4.2%) in the IVUS-guided optimization arm and 7 patients (4.8%) in the control arm experienced TVF at 1 year follow-up ($P = 0.79$; HR: 0.86;

TABLE 4 Procedural Characteristics and Complications (Patient Level)

	IVUS-Guided Optimization Arm (n = 145)	Control Arm (n = 146)	Total (N = 291)	*P* Value
Procedural characteristics				
Procedural time, min	96 (78-118)	73 (57-95)	84 (68-109)	<0.001
Contrast usage, mL	140 (100-170)	113 (89-150)	125 (100-160)	0.003
Fluoroscopy time, min	18.3 (13.2-25.5)	15.4 (8.9-22.1)	17.1 (11.6-24.2)	0.002
Periprocedural complications				
No reflow/slow reflow	0 (0.0)	1 (0.7)	1 (0.3)	1.00
Side branch occlusion	0 (0.0)	3 (2.1)	3 (1.0)	0.25
Vessel perforation	4 (2.8)	1 (0.7)	5 (1.7)	0.21
Coronary dissection	2 (1.4)	4 (2.7)	6 (2.1)	0.68
Procedural death	1 (0.7)	0 (0.0)	1 (0.3)	0.50
Adenosine complications	0 (0.0)	1 (0.7)	1 (0.3)	1.00
Postprocedural complications				
Periprocedural myocardial infarction	8 (5.5)	4 (2.7)	12 (4.1)	0.23
Periprocedural stroke	0 (0.0)	1 (0.7)	1 (0.3)	1.00
Acute kidney injury	1 (0.7)	2 (1.4)	3 (1.0)	1.00

Values are median (IQR) or n (%).
IVUS = intravascular ultrasound.

95% CI: 0.29-2.57) (**Table 5, Central Illustration**). In the IVUS-guided optimization arm, 6 patients died (4 deaths attributed to cardiac cause), whereas 2 patients died in the control arm (1 cardiac death) ($P = 0.15$; HR: 3.05; 95% CI: 0.62-15.10 for all-cause mortality; $P = 0.17$; HR: 4.06; 95% CI: 0.45-36.34 for cardiac death). A detailed report on cardiac deaths is provided in Supplemental Table 5. There was a trend toward a lower rate of CD-TVR in the IVUS-guided optimization arm (1 [0.7%] vs 6 [4.2%] CD-TVR events; $P = 0.06$; HR: 0.17; 95% CI: 0.02-1.40). One patient (0.7%) in the control arm experienced a definite subacute stent thrombosis at day 8 after the study procedure. A description of all TVF events is provided in Supplemental Table 6.

A sensitivity analysis on TVF taking into account competing risks by noncardiovascular mortality did not alter the results (subdistribution HR: 0.86; 95% CI: 0.29-2.55; $P = 0.79$). Finally, no TVF occurred in patients with a final post-PCI FFR ≥0.90 after optimization.

DISCUSSION

Low post-PCI FFR values have been consistently linked to an increase in the number of future cardiovascular events.[6-11] Whether PCI optimization would result in improved outcome remains a subject of debate. The FFR REACT trial is the first dedicated randomized controlled study designed to prospectively address this question. Our findings can be summarized as follows: 1) IVUS-guided PCI optimization was safe and significantly improved post-PCI FFR and the MLA in the target segment of optimization; and 2) IVUS evaluation in patients with a post-PCI FFR <0.90 triggered further optimization efforts in two-thirds of cases but did not significantly reduce the risk of 1-year TVF compared with the standard of care.

After contemporary angiographically successful PCI, we found that post-PCI FFR remained <0.90 in 46.9% of patients, a finding that concurs with recently published data.[8,20] The mean post-PCI FFR in the randomized cohort was 0.84 ± 0.05, and 23% of the vessels were left with a post-PCI FFR ≤0.80. In patients randomized to the IVUS-guided optimization arm, IVUS assessment demonstrated residual disease that remained unrecognized on coronary angiography in up to 80% of cases, which is in line with a previous report from the FFR-SEARCH (Fractional Flow Reserve Stent Evaluated at Rotterdam Cardiology Hospital) IVUS study.[15] Moreover, we were able to demonstrate that optimal stenting criteria were achieved in merely 9.1% of vessels with a post-PCI FFR <0.90, a finding that was mainly driven by a high prevalence of residual edge disease (reference segment plaque burden >50% in 84.6%).

Subsequent post-PCI optimization was attempted in 68.4% of the cases, comprising a cohort that was characterized by lower FFR values, more pronounced residual disease, and smaller MSAs compared with vessels in which no additional optimization was performed. The rate of additional optimization maneuvers (68.4%) in FFR REACT was substantially higher compared with previous studies in which additional interventions were mainly guided by FFR pull back patterns.[12,14] The latter suggests that IVUS compared with FFR is a more potent tool to identify residual disease in vessels with low post-PCI FFR values.

In vessels that were optimized, we found a moderate, albeit statistically significant, increase in post-PCI FFR with the most pronounced increases in post-PCI FFR in cases in which additional stents were placed. The subsequent increase in post-PCI FFR of 0.03 was less pronounced compared with previous studies reporting improvements in FFR ranging from 0.06 to 0.10.[12,14] The latter discrepancy could be explained by the fact that in these studies additional interventions were undertaken less frequently (ranging from 34.5%-43.0% of vessels with suboptimal post-PCI FFR according to varying definitions vs 68.4% of vessels in FFR REACT) and restricted to vessels with lower post-PCI FFR values (mean post-PCI FFR values before optimization ranging from

0.71-0.78 vs 0.82 in FFR REACT) in which the potential yield of optimizing FFR is eminent.[12-14]

Despite the higher percentage of procedural optimization in the present study compared with previous studies, 1 out of 3 vessels did not undergo optimization despite the fact that residual treatable focal disease was present in 35.6% (16/45) of cases, findings that went unrecognized even in the course of a dedicated study. The latter supports the need for adequate imaging training, sufficient time to assess imaging findings and proper guidelines for procedural optimization along with advancements in automated pull back analyses.

In the present study, we were able to demonstrate for the first time the effect of IVUS-guided PCI optimization on the final MSA and MLA within the target segment of optimization. We found that the most significant improvement on the final MLA and the subsequent final FFR was achieved in cases in which additional stents were placed, whereas the effect of postdilatation alone was restricted to a marginal 0.52 ± 0.57 mm^2 difference in MSA.

IVUS-guided optimization appeared to be safe with no significant increased risk of periprocedural complications. However, optimization did come at the cost of a significantly increased procedural time, radiation dose, and contrast usage, along with a numerical higher incidence of periprocedural myocardial infarction. At the 1-year follow-up, we were not able to find a significant decrease in the risk of TVF after IVUS-guided post-PCI optimization. In order to better appreciate this principal finding, several issues need to be mentioned. First, despite higher residual luminal areas in the segment of optimization as determined by IVUS, the subsequent mean increase in post-PCI FFR in vessels receiving optimization was limited (0.03 ± 0.06) and should be put into perspective of the subsequent absolute difference in the final post-PCI FFR between the 2 complete study arms that appeared marginal (IVUS-guided optimization arm: 0.85 ± 0.05, control arm: 0.84 ± 0.04) (Supplemental Figure 1). More specifically, we found that post-PCI FFR values ≥0.90 can only be achieved in a minority of vessels with post-PCI FFR <0.90 (20% in our study), a finding in line with recent results of the TARGET FFR (Trial of Angiography vs. Pressure-Ratio-Guided Enhancement Techniques-Fractional Flow Reserve) study (7.5%).[14] Likewise, the majority of vessels in the IVUS-guided optimization arm still failed to meet the optimal stenting criteria, leaving them at a known 3-fold increased risk of TVF.[17]

Second, the rate of TVF in the IVUS-guided optimization arm was mainly driven by a nonsignificant surplus of cardiovascular deaths (4/6 events), of which only 1 cardiac death may have been related to the index procedure (cardiac death case 1, sudden death 3 days post-PCI, possible subacute stent thrombosis). The other cardiac deaths were very unlikely to be related to the study procedures and seemed to be coincidental in light of the small study size (Supplemental Table 5).

TABLE 5 Event Rates at the 1-Year Follow-Up

	IVUS-Guided Optimization Arm (n = 145)	Control Arm (n = 146)	*P* Value Log-Rank Test	HR (95%CI)
Target vessel failure	6 (4.2)	7 (4.8)	0.79	0.86 (0.29-2.57)
Cardiac death	4 (2.8)	1 (0.7)	0.17	4.06 (0.45-36.34)
TVMI	2 (1.4)	5 (3.4)	0.26	0.41 (0.08-2.09)
Clinically driven TVR	1 (0.7)	6 (4.2)	0.06	0.17 (0.02-1.40)
All-cause mortality	6 (4.2)	2 (1.4)	0.15	3.05 (0.62-15.10)
Any myocardial infarction (spontaneous) type 1, 2, 3, 4b	4 (2.8)	7 (4.8)	0.37	0.58 (0.17-1.97)
Any revascularization	7 (4.9)	11 (7.6)	0.35	0.64 (0.25-1.65)
MACE	12 (8.3)	15 (10.3)	0.56	0.80 (0.37-1.71)
Stroke	1 (0.7)	3 (2.1)	0.32	0.33 (0.04-3.21)
Definite stent thrombosis	0	1 (0.7)	0.32	No convergence

Values are n (%). Percentages are cumulative incidences derived from the Kaplan-Meier function.

MACE = major adverse cardiovascular event(s); TVMI = target vessel myocardial infarction; TVR = target vessel revascularization.

Third, despite randomization, we noticed slight imbalances in several baseline variables: a less favorable risk profile was observed in the IVUS-guided optimization arm including (nonsignificantly) lower post-PCI FFR values, more complex lesion characteristics (heavy calcifications, chronic total occlusion, and bifurcations), and longer lesions requiring longer (and multiple) implanted stents. Nevertheless, in line with substantial evidence on the superiority of IVUS compared with angiography-guided PCI, we found a promising trend toward lower CD-TVR rates (P = 0.06) in the IVUS-guided optimization arm supporting the relevance of longer-term outcome data of our study.[17,21]

In summary, based on the 1-year data of the FFR REACT trial, we cannot provide a definite answer regarding the potential net clinical benefit of IVUS-guided post-PCI in patients with post-PCI FFR <0.90. Larger-scale trials are required to investigate whether post-PCI FFR (and IVUS-guided) optimization techniques may affect TVF and whether the benefits of such interventions outweigh the potential risks and disadvantages in terms of procedural time, radiation dose, contrast usage, and a potential higher incidence of procedural complications.[22] One of the trials that might provide further insights in these discussions is the DEFINE GPS (Distal Evaluation of Functional

Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting; NCT04451044), which is currently enrolling up to 3,200 patients to investigate whether physiology-guided PCI (using preinstantaneous and post-instantaneous wave-free ratio) and optimization improves patient outcome compared with angiographically-guided PCI.

STUDY LIMITATIONS. The main limitation of the FFR REACT trial is the power, which, in retrospect, proved unrealistic. The large difference between the observed and expected event rates might be explained by the differential definitions of MACE used in the specific meta-analysis as well as the inclusion of older studies including patients treated with bare metal and first-generation drug-eluting stents, which may have increased event rates in the data used to power the present study.[18] Therefore, the FFR REACT trial could not demonstrate that additional IVUS imaging, and subsequently optimization procedures, could provide significant benefit in patients with post-PCI FFR <0.90. Ongoing follow-up (until 3 years) will lead to higher event rates and might therefore shed more light on this issue (with increased power). Also, post-PCI physiology measurements were performed using a microcatheter, which is known to result in a slight underestimation of FFR values (mean difference = −0.02) and therefore a consequent overestimation of lesion severity.[23]

CONCLUSIONS

Although this trial was underpowered (caused by lower-than-expected event rates), an IVUS-guided optimization strategy in response to post-PCI FFR <0.90 did not affect the 1-year TVF rate compared with the standard of care. There was evidence of improved physiological outcome and increased luminal areas but that did not translate into discerned clinical benefit.

ACKNOWLEDGMENTS The authors thank Dr Jouke Dijkstra for providing dedicated IVUS analysis software (QCU-CMS, Leiden University Medical Centre, LKEB, Division of Image Processing, version 4.69).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Erasmus Medical Center received institutional research support from ACIST Medical Systems, Inc. Dr Diletti has received institutional research grant support from ACIST Medical Systems, Inc. Dr Van Mieghem has received institutional research grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, Daiichi-Sankyo, PulseCath BV, and Abiomed. Dr Daemen has received institutional grant/research support from AstraZeneca, Abbott Vascular, Boston Scientific, ACIST Medical Systems, Inc, Medtronic, Pie Medical, and ReCor medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Joost Daemen, Department of Cardiology, Room Rg-628, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail: j.daemen@erasmusmc.nl. Twitter: CathlabNews@erasmusmc.nl.

PERSPECTIVES

WHAT IS KNOWN? Post-PCI FFR values <0.90 are frequently encountered in routine practice and are related to an increased rate of major adverse cardiac events. Suboptimal post-PCI FFR values can be improved by additional interventions, but it remains unknown whether this optimization impacts patient outcome.

WHAT IS NEW? In patients with post-PCI FFR <0.90, IVUS evaluation prompted optimization efforts in 68.4% of patients, leading to a small, though significant, increase in post-PCI FFR and minimal lumen and stent areas. IVUS-guided PCI optimization was not able to decrease the rate of target vessel failure at 1-year follow-up caused by lower-than-expected event rates, although a trend towards lower target vessel revascularization rates was observed.

WHAT IS NEXT? Ongoing follow-up of the FFR REACT trial and dedicated physiology optimization trials (DEFINE-GPS: NCT04451044) will provide further insights on the effect of optimization of patients with suboptimal post-PCI physiology.

REFERENCES

1. Piccolo R, Bonaa KH, Efthimiou O, et al. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet*. 2019;393:2503-2510.

2. Konigstein M, Madhavan MV, Ben-Yehuda O, et al. Incidence and predictors of target lesion failure in patients undergoing contemporary DES implantation-individual patient data pooled analysis from 6 randomized controlled trials. *Am Heart J*. 2019;213:105-111.

3. Madhavan MV, Redfors B, Ali ZA, et al. Long-term outcomes after revascularization for stable ischemic heart disease: an individual patient-level pooled analysis of 19 randomized coronary stent trials. *Circ Cardiovasc Interv*. 2020;13:e008565.

4. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. 2010;56:177–184.

5. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.

6. Li SJ, Ge Z, Kan J, et al. Cutoff value and long-term prediction of clinical events by FFR measured immediately after implantation of a drug-eluting stent in patients with coronary artery disease: 1- to 3-year results from the DKCRUSH VII Registry Study. *J Am Coll Cardiol Intv*. 2017;10:986–995.

7. Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation*. 2002;105:2950–2954.

8. Diletti R, Masdjedi K, Daemen J, et al. Impact of poststenting fractional flow reserve on long-term clinical outcomes: the FFR-SEARCH study. *Circ Cardiovasc Interv*. 2021;14:e009681.

9. Piroth Z, Toth GG, Tonino PAL, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. *Circ Cardiovasc Interv*. 2017;10(8):e005233.

10. Lee JM, Hwang D, Choi KH, et al. Prognostic implications of relative increase and final fractional flow reserve in patients with stent implantation. *J Am Coll Cardiol Intv*. 2018;11:2099–2109.

11. Hwang D, Lee JM, Lee HJ, et al. Influence of target vessel on prognostic relevance of fractional flow reserve after coronary stenting. *EuroIntervention*. 2019;15:457–464.

12. Uretsky BF, Agarwal SK, Vallurupalli S, et al. Prospective evaluation of the strategy of functionally optimized coronary intervention. *J Am Heart Assoc*. 2020;9:e015073.

13. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. *J Am Coll Cardiol Intv*. 2016;9:1022–1031.

14. Collison D, Didagelos M, Aetesam-ur-Rahman M, et al. Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR). *Eur Heart J*. 2021;42(45):4656–4668.

15. van Zandvoort LJC, Masdjedi K, Witberg K, et al. Explanation of postprocedural fractional flow reserve below 0.85. *Circ Cardiovasc Interv*. 2019;12:e007030.

16. van Zandvoort LJC, Masdjedi K, Tovar Forero MN, et al. Fractional flow reserve guided percutaneous coronary intervention optimization directed by high-definition intravascular ultrasound versus standard of care: rationale and study design of the prospective randomized FFR-REACT trial. *Am Heart J*. 2019;213:66–72.

17. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72:3126–3137.

18. Wolfrum M, Fahrni G, de Maria GL, et al. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2016;16:177.

19. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.

20. Rimac G, Fearon WF, De Bruyne B, et al. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: a systematic review and meta-analysis. *Am Heart J*. 2017;183:1–9.

21. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. *Circ Cardiovasc Interv*. 2016;9:e003700.

22. Johnson NP, Collet C. Can FFR after stenting help reduce target vessel failure? *J Am Coll Cardiol Intv*. 2021;14:1901–1903.

23. Fearon WF, Chambers JW, Seto AH, et al. ACIST-FFR Study (Assessment of Catheter-Based Interrogation and Standard Techniques for Fractional Flow Reserve Measurement). *Circ Cardiovasc Interv*. 2017;10:e005905.

KEY WORDS fractional flow reserve, intravascular ultrasound, patient outcome

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