Changes in post-PCI physiology based on anatomical vessel location: a DEFINE PCI substudy

Mitsuaki Matsumura[1], BS; Akiko Maehara[1,2], MD; Justin E. Davis[3], MD; Gautam Kumar[4], MD; Andrew Sharp[5], MD; Habib Samady[4], MD; Arnold H. Seto[6], MD; David Cohen[1,7], MD; Manesh R. Patel[8], MD; Ziad A. Ali[1,7], MD, DPhil; Gregg W. Stone[9], MD; Allen Jeremias[1,7]*, MD, MSc

1. Cardiovascular Research Foundation, New York, NY, USA; 2. Columbia University Irving Medical Center, New York, NY, USA; 3. Hammersmith Hospital, Imperial College NHS Trust, London, United Kingdom; 4. Emory University Hospital, Atlanta, GA, USA; 5. Royal Devon & Exeter NHS Foundation Trust, Exeter, United Kingdom; 6. Tibor Rubin VA Medical Center, Long Beach, CA, USA; 7. St. Francis Hospital, Roslyn, NY, USA; 8. Duke University Hospital, Durham, NC, USA; 9. Icahn School of Medicine at Mount Sinai, New York, NY, USA

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Abstract

Background: Anatomical vessel location affects post-percutaneous coronary intervention (PCI) physiology.
Aims: We aimed to compare the post-PCI instantaneous wave-free ratio (iFR) in left anterior descending (LAD) versus non-LAD vessels and to identify the factors associated with a suboptimal post-PCI iFR.
Methods: DEFINE PCI was a multicentre, prospective, observational study in which a blinded post-PCI iFR pullback was used to assess residual ischaemia following angiographically successful PCI.
Results: Pre- and post-PCI iFR recordings of 311 LAD and 195 non-LAD vessels were compared. Though pre-PCI iFR in the LAD vessels (median 0.82 [0.63, 0.86]) were higher compared with those in non-LAD vessels (median 0.72 [0.49, 0.84]; p<0.0001), post-PCI iFR were lower in the LAD vessels (median 0.92 [0.88, 0.94] vs 0.98 [0.95, 1.00]; p<0.0001). The prevalence of a suboptimal post-PCI iFR of <0.95 was higher in the LAD vessels (77.8% vs 22.6%; p<0.0001). While the overall frequency of residual physiological diffuse disease (31.4% vs 38.6%; p=0.26) and residual focal disease in the non-stented segment (49.6% vs 50.0%; p=0.99) were similar in both groups, residual focal disease within the stented segment was more common in LAD versus non-LAD vessels (53.7% vs 27.3%; p=0.0009). Improvement in iFR from pre- to post-PCI was associated with angina relief regardless of vessel location.
Conclusions: After angiographically successful PCI, post-PCI iFR is lower in the LAD compared with non-LAD vessels, resulting in a higher prevalence of suboptimal post-PCI iFR in LAD vessels. This difference is, in part, due to a greater frequency of a residual focal pressure gradient within the stented segment which may be amenable to more aggressive PCI.

Corresponding author: Department of Cardiology, St. Francis Hospital, 100 Port Washington Blvd #105, Roslyn, NY, 11576, USA. E-mail: allen.jeremias@chsli.org

Abbreviations

AF	angina frequency
BSA	body surface area
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
LAD	left anterior descending artery
LCx	left circumflex artery
PCI	percutaneous coronary intervention
RCA	right coronary artery
RVD	reference vessel diameter
SAQ	Seattle Angina Questionnaire

Introduction

The instantaneous wave-free ratio (iFR) has been validated as a useful diagnostic tool to assess the haemodynamic significance of a coronary artery lesion without pharmacological induction of hyperaemia[1,2], allowing a rapid assessment of lesion severity with clinical outcomes comparable to those of fractional flow reserve (FFR)[1-3]. Although the use of coronary physiology for lesion assessment prior to percutaneous coronary intervention (PCI) has been widely adopted and endorsed by clinical guidelines[4], it is not presently recommended for post-PCI assessment of the adequacy of revascularisation. Prior studies have shown that despite an angiographically successful procedure, many vessels continue to demonstrate suboptimal physiological results, with ~20% of FFR values in the ischaemic range[5,6]. Additionally, a suboptimal physiological post-PCI result has been associated with an increased risk of major adverse cardiovascular events[5-7]. Lesions located in the left anterior descending (LAD) coronary artery have been identified as a major predictor of a suboptimal post-PCI FFR result[7-9].

In the Physiologic Assessment of Coronary Stenosis Following PCI study (DEFINE PCI), 24.0% of 467 patients demonstrated residual ischaemia (iFR ≤0.89) after angiographically successful PCI, and in 81.6% this was attributable to focal lesions[10]. At 1-year follow-up, a post-PCI iFR ≥0.95 was associated with a significant reduction in cardiac death, spontaneous myocardial infarction (MI), or clinically driven target vessel revascularisation (TVR) compared with a post-PCI iFR <0.95[11]. Herein, we aim to evaluate post-PCI iFR in LAD versus non-LAD vessels, comparing the prevalence and predictors of post-PCI iFR, patterns of residual disease (focal vs diffuse), as well as angina and clinical outcomes at 1 year.

Methods

PATIENT POPULATION

The study design and protocol of DEFINE PCI have been published previously[10]. In brief, DEFINE PCI was a prospective, single-arm, blinded, multicentre study designed to assess the incidence and mechanisms of an abnormal iFR after angiographically successful PCI. A total of 28 sites from the USA and Europe participated in the study. The study protocol was approved by the institutional review board or ethics committee at each participating site. The original study was supported by funding from Philips/

Volcano; the current analysis was conducted independently by the Cardiovascular Research Foundation, New York, NY, USA.

STUDY PROCEDURES

A distal spot iFR assessment (Verrata and Verrata Plus guide wire [Philips/Volcano]) was performed in all vessels in which a lesion of at least 40% angiographic severity was identified and deemed suitable for PCI. The wire was positioned in the distal third of the vessel, at least 10 mm distal to the most distal stenosis (pre-PCI) or treated segment (post-PCI) with angiographic documentation. Patients with a pre-PCI iFR of ≤0.89 in at least 1 vessel were formally enrolled. An iFR pullback with interrogation of individual lesions was not allowed before PCI. PCI was performed according to the standard of care based on angiographic guidance. Intravascular imaging was allowed and used per operator discretion. Once PCI was successfully completed, a blinded post-PCI iFR measurement was taken in the distal vessel, and an iFR pullback was performed along the length of the vessel until the pressure sensor reached the tip of the guiding catheter at the coronary ostium under resting conditions to determine residual transstenotic pressure gradients. Bookmarks were inserted 5 mm distal and proximal to the implanted stent as well as at the coronary ostium for core laboratory analysis. A final drift check was performed and recorded with the pressure wire located in the coronary ostium.

CORE LABORATORY ANALYSIS

All pressure tracings and angiograms were sent to the physiology and angiographic core laboratories at the Cardiovascular Research Foundation (New York, NY, USA) for centralised independent review. All physiology tracings were reviewed on a Volcano s5 imaging system (Philips/Volcano), and all angiograms were analysed on QAngio XA 7.3.92.0 (Medis Medical Imaging). The physiology core laboratory assessed each individual tracing for quality based on prespecified criteria that included evaluation of the aortic and coronary pressure signals for waveform distortion or loss, aortic pressure ventricularisation, and arrhythmias, as previously outlined[12]. A range of 0.98-1.02 for mean wire pressure/aortic pressure in the coronary ostium was considered acceptable.

The blinded post-PCI iFR pullback was analysed for transstenotic pressure gradients, which were categorised according to their location (distal to the stent; in-stent including 5 mm proximal and distal margins; and proximal to the stent) and classified as focal lesions or diffuse disease. Transstenotic pressure gradients of ≥0.03 were categorised as focal lesions if their length was ≤15 mm and as diffuse disease if their length exceeded 15 mm. Focal lesions and diffuse disease could be present in the same vessel.

FOLLOW-UP ASSESSMENT

The 1-year outcomes included target vessel failure (TVF), a composite of target vessel MI, clinically driven TVR, or cardiac death. Each of these clinical events were adjudicated by an independent committee whose members were blinded to the angiographic and physiology data. The Seattle Angina Questionnaire (SAQ) Angina

Frequency (AF) scale was assessed at baseline and 12 months using standard questionnaires by trained personnel.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and frequencies and were compared with the chi-square test. Continuous variables are presented as means and standard deviations or medians with first and third quartiles and were compared using the Student's t-test or Wilcoxon signed-rank test based on the distribution. For post-iFR and follow-up SAQ-AF scores, least squares mean differences were compared between LAD versus non-LAD groups in an analysis of covariance (ANCOVA) model adjusted for baseline values. Multivariable linear regression models were used to evaluate 1) the association between the clinical and lesion-related characteristics and post-PCI iFR, and 2) the association between the change in iFR from pre- to post-PCI and change in SAQ-AF score from baseline to 1-year follow-up. Time-to-first event rates are shown as Kaplan-Meier estimates and were compared with the log-rank test. All probability values were 2-sided, and p-values<0.05 were considered to indicate statistical significance.

Results

PATIENT CHARACTERISTICS

Two vessels with a target lesion in the left main coronary artery were excluded from the present substudy. Among the remaining cases, 459 patients with 506 vessels with qualified pre- and post-PCI iFR were included. iFR was compared in 311 LAD and 195 non-LAD vessels (99 right coronary artery [RCA] and 96 left circumflex [LCx]). The prevalence of a proximal lesion location was similar between LAD versus non-LAD vessels (32.2% vs 31.8%). Baseline patient and angiographic procedural characteristics stratified by LAD versus non-LAD vessels are shown in **Table 1** and **Supplementary Table 1**. Compared with non-LAD vessels, the pre-PCI minimum lumen diameter was larger, the pre-PCI diameter stenosis was smaller, and there was greater lesion calcification in LAD vessels. Post-dilatation was performed more frequently in LAD vessels compared with non-LAD vessels.

PRE- AND POST-PCI PHYSIOLOGICAL ASSESSMENT

Pre-PCI iFR in the LAD vessels (median 0.82 [0.63, 0.86]) was higher compared with the non-LAD vessels (median 0.72 [0.49, 0.84]; p<0.0001) **(Table 2, Figure 1)**. Despite this, post-PCI iFR was lower in the LAD (median 0.92 [0.88, 0.94]) compared with the non-LAD vessels (median 0.98 [0.95, 1.00]; p<0.0001). Accordingly, ΔiFR (post-PCI iFR − pre-PCI iFR) was lower in the LAD vessels (median 0.09 [0.06, 0.28]) vs 0.26 [0.14, 0.51]; p<0.0001) **(Table 2**, **Figure 2)**. Almost half the patients undergoing LAD-PCI had a change in iFR of less than 0.10. Similarly, iFR gain ([Δ iFR/ pre-PCI iFR]*100) was lower in LAD compared with non-LAD vessels (median 11.5% [6.9, 45.0] vs 35.7% [16.7, 105.1]; p<0.0001).

Despite similar residual post-PCI angiographic diameter stenosis in both groups (median 19.9% [13.0, 32.3] vs 19.3% [12.2, 35.1]; p=0.75) **(Table 1)**, the prevalence of post-PCI iFR ≤0.89 (30.9% vs 6.7%; p<0.0001) and <0.95 (77.8% vs 22.6%; p<0.0001) were higher in LAD compared with non-LAD vessels **(Central illustration)**.

Table 1. Angiographic and procedural characteristics per vessel.

	All vessels (N=506)	LAD (N=311)	Non-LAD (N=195)	*p*-value
Bifurcation lesion	4.0 (20/505)	4.8 (15)	2.6 (5/194)	0.21
Calcification (moderate/severe)	38.2 (192/503)	43.4 (135)	29.7 (57/192)	0.002
Lesion length, mm	21.2 (13.8, 30.2)	21.9 (14.7, 31.5)	19.9 (12.5, 28.7)	0.051
Reference vessel diameter, mm	2.76 (2.45, 3.07)	2.73 (2.45, 3.01)	2.84 (2.45, 3.13)	0.09
Pre-PCI minimum lumen diameter, mm	0.86 (0.65, 1.12)	0.96 (0.72, 1.19)	0.74 (0.60, 0.96)	<0.0001
Pre-PCI DS, %	68.0 (59.5, 76.0)	64.2 (57.0, 65.6)	72.5 (65.6, 78.9)	<0.0001
Post-PCI worst DS in the target vessel, %	19.8 (12.7, 33.5)	19.9 (13.0, 32.3)	19.3 (12.2, 35.1)	0.75
Post-PCI worst DS ≥50%	7.1 (36/504)	7.4 (23/309)	6.7 (13)	0.74
Proximal	22.2 (8)	21.7 (5)	23.1 (3)	0.99
In-stent	5.6 (2)	4.3 (1)	7.7 (1)	0.99
Distal	72.2 (26)	73.9 (17)	69.2 (9)	0.99
Total stent length, mm	29 (20, 38)	30 (21, 38)	28 (18, 38)	0.07
Maximum device size, mm	3.0 (3.0, 3.5)	3.0 (3.0, 3.5)	3.0 (3.0, 3.5)	0.89
Maximum balloon pressure, atm	18 (16, 20)	17 (16, 20)	18 (16, 20)	0.25
Post-dilatation performed	59.0 (294/498)	63.8 (194/304)	51.5 (100/194)	0.007

Values are % (n), % (n/N), or median (first quartile, third quartile). DS: diameter stenosis; LAD: left anterior descending; PCI: percutaneous coronary intervention

PATTERNS OF RESIDUAL DISEASE

Among the 286 vessels with a suboptimal post-PCI iFR of <0.95, there was a larger translesion gradient in LAD compared with non-LAD vessels (median 0.10 [0.07, 0.13] vs 0.08 [0.06, 0.11]; p=0.056) (Table 2). However, the frequency of residual focal disease (68.6% vs 61.4%; p=0.26), and diffuse disease (31.4% vs 38.6%; p=0.26) were similar in both groups. While there was no difference between the groups in residual focal disease proximal to the stent (28.9% vs 36.4%; p=0.37), distal to the stent (30.2% vs 27.3%; p=0.64) or in the combined non-stented segment (49.6% vs 50.0%; p=0.99), the prevalence of residual focal disease within the stented segment was greater in LAD versus non-LAD vessels (53.7% vs 27.3%; p=0.0009) (Supplementary Figure 1).

FACTORS ASSOCIATED WITH POST-PCI IFR

By multivariable linear regression, the factors independently associated with a lower post-PCI iFR were different in LAD and non-LAD vessels. In the LAD vessels, a larger body surface area (BSA; p=0.03), older age (p=0.006), lower pre-PCI iFR (p=0.01), and a smaller reference vessel diameter (RVD; p=0.0002) were all associated with lower post-PCI iFR, whereas in non-LAD vessels, lesion calcification (p=0.03) and a smaller RVD (p=0.01) were the only predictors of lower post-PCI iFR (Table 3).

SAQ-AF SCORES AT ONE-YEAR FOLLOW-UP

As shown in Supplementary Table 2, SAQ-AF scores at baseline and at 1 year were similar in patients with LAD and non-LAD disease. Compared with patients with an iFR gain <median after LAD-PCI, patients with an iFR gain ≥median had a higher mean SAQ-AF score at 1 year (97.2±8.0 vs 91.7±15.7; p=0.0002) and greater improvement in mean SAQ-AF score (26.9±21.0 vs 16.9±25.7; p=0.0006), although the SAQ-AF scores at baseline were similar. By multivariable linear regression, lower baseline SAQ-AF scores (p<0.0001) and greater ΔiFR (p=0.007), but not target lesion location in LAD (p=0.74), were associated with greater improvement of SAQ-AF scores from baseline to 1 year (Table 4).

CLINICAL OUTCOMES

The 1-year incidence of target vessel failure (TVF) and its components were similar in patients with LAD target vessel disease and non-LAD target vessel disease (Supplementary Table 3, Figure 3).

Discussion

As shown in the **Central illustration**, the main findings of this substudy from the multicentre, prospective DEFINE PCI registry are as follows: compared with PCI in non-LAD vessels, PCI in LAD vessels showed 1) lower absolute post-PCI iFR; 2) greater residual focal pressure gradient within the treated segment; 3) different clinical and anatomical factors predicting post-PCI iFR, though smaller RVD was associated with lower post-PCI iFR both in LAD and non-LAD vessels; and 4) improvement in iFR from pre- to post-PCI was associated with an improvement of angina, regardless of vessel location.

Table 2. Physiology findings per vessel.

	All vessels (N=506)	LAD (N=311)	Non-LAD (N=195)	p-value
Pre-PCI iFR	0.79 (0.55, 0.86)	0.82 (0.63, 0.86)	0.72 (0.49, 0.84)	<0.0001
Post-PCI iFR	0.94 (0.90, 0.97)	0.92 (0.88, 0.94)	0.98 (0.95, 1.00)	<0.0001
LSM±SE - ANCOVA model*	-	0.90±0.005	0.98±0.007	<0.0001
Post-PCI iFR <0.95	56.6 (286)	77.8 (242)	22.6 (44)	<0.0001
Post-PCI iFR ≤0.89	21.5 (109)	30.9 (96)	6.7 (13)	<0.0001
Δ iFR (post-iFR–pre-iFR)	0.15 (0.07, 0.39)	0.09 (0.06, 0.28)	0.26 (0.14, 0.51)	<0.0001
LSM±SE - ANCOVA model	-	0.22±0.005	0.29±0.007	<0.0001
Percentage Δ iFR, %	18.8 (8.6, 72.8)	11.5 (6.9, 45.0)	35.7 (16.7, 105.1)	<0.0001
Post-PCI iFR pullback assessment in 286 vessels with post-PCI iFR <0.95				
	All vessels (N=286)	LAD (N=242)	Non-LAD (N=44)	p-value
iFR gradient from distal to aorta	0.09 (0.07, 0.13)	0.10 (0.07, 0.13)	0.08 (0.06, 0.11)	0.056
Diffuse lesion	32.5 (93)	31.4 (76)	38.6 (17)	0.26
Any focal lesion	67.5 (193)	68.6 (166)	61.4 (27)	0.26
Any focal lesion proximal to the stent	30.1 (86)	28.9 (70)	36.4 (16)	0.37
Any focal lesion in-stent	49.7 (142)	53.7 (130)	27.3 (12)	0.0009
Any focal lesion distal to the stent	29.7 (85)	30.2 (73)	27.3 (12)	0.64

Values are % (n) or median (first quartile, third quartile). *Least squares mean (LSM) difference tested between groups in an analysis of covariance model (ANCOVA) adjusted for baseline values. iFR: instantaneous wave-free ratio; LAD: left anterior descending; PCI: percutaneous coronary intervention; SE: standard error
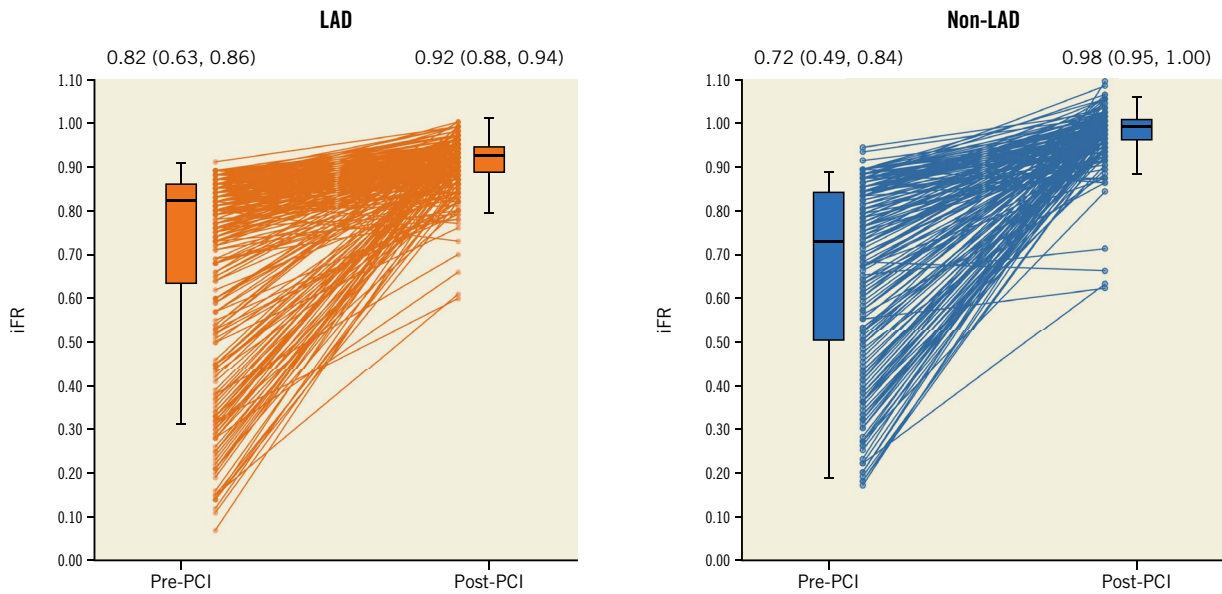
Figure 1. *Comparison of individual pre- and post-PCI iFR in LAD versus non-LAD vessels. Median (first quartile, third quartile) pre-PCI and post-PCI iFR were 0.82 (0.63, 0.86) and 0.92 (0.88, 0.94) in LAD vessels and 0.72 (0.49, 0.84) and 0.98 (0.95, 1.00) in non-LAD vessels, respectively. Pre- to post-PCI iFR gain was less in LAD versus non-LAD vessels. iFR: instantaneous wave-free ratio; LAD: left anterior descending artery; PCI: percutaneous coronary intervention*

IMPAIRED POST-PCI PHYSIOLOGY IN LAD COMPARED WITH NON-LAD VESSELS

Lesion location in the LAD was a predictor of a lower post-PCI iFR[10]. This finding in DEFINE PCI is consistent with prior studies demonstrating that LAD lesion location is an independent predictor of an abnormal post-PCI FFR[7-9]. In the current study, though pre-PCI iFR in LAD vessels was higher compared with those in non-LAD vessels, lower post-PCI iFR in LAD compared with non-LAD vessels was observed. Specifically, iFR pullback analysis

demonstrated that iFR focal lesions within the stented segment were more frequent in LAD compared with non-LAD vessels, whereas no significant differences were observed outside the treated segment or in the prevalence of diffuse disease. Of note, the lesion and stent length were similar between the 2 groups, indicating that worse PCI results may, in part, be responsible for the overall smaller iFR improvement in the LAD group. This is an important finding since suboptimal PCI is potentially modifiable with additional stent optimisation[13]. A recently published paper demonstrated that segmental
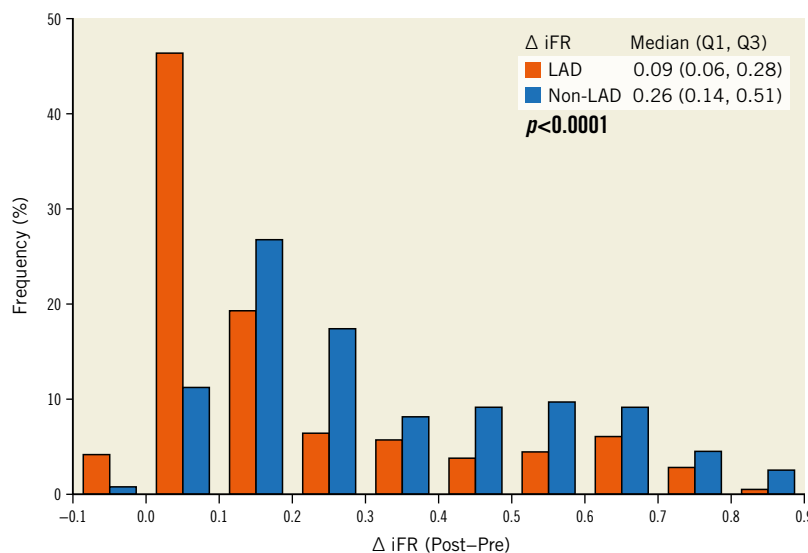
Figure 2. *Distribution of iFR gain in LAD versus non-LAD vessels. iFR gain (defined as post-PCI iFR minus pre-PCI iFR) was significantly less in LAD vessels compared with non-LAD vessels. iFR: instantaneous wave-free ratio; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; Q: quartile*

CENTRAL **ILLUSTRATION** Comparison of physiological assessment in the LAD versus non-LAD vessels.
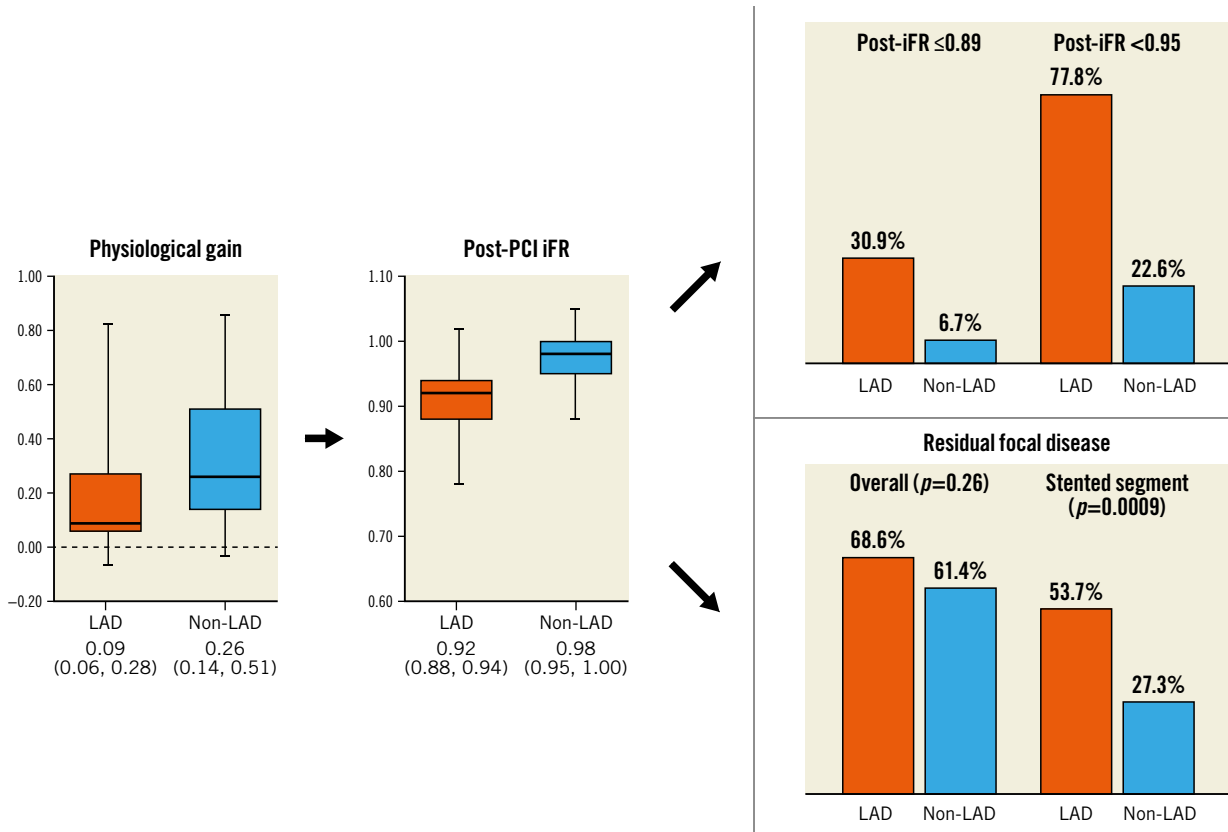
iFR: instantaneous wave-free ratio; LAD: left anterior descending; PCI: percutaneous coronary intervention

Table 3. Patient or pre-PCI lesion characteristics associated with post-PCI iFR by multivariable linear regression.

Dependent variable Post-PCI iFR per 0.01	All vessels (N=506)		LAD (N=311)		Non-LAD (N=195)	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Age, per 10 years	−0.40 (−0.97, 0.16)	0.16	−0.84 (−1.43, −0.24)	0.006	−0.04 (−0.98, 0.90)	0.93
Body surface area, m²	−2.53 (−4.96, −0.09)	0.04	−2.54 (−4.88, −0.19)	0.03	−1.56 (−6.28, 3.16)	0.52
Diabetes mellitus	−0.41 (−1.70, 0.88)	0.53	−0.17 (−1.43, 1.08)	0.79	−1.26 (−3.18, 0.66)	0.20
Pre-PCI RVD, mm	3.47 (2.02, 1.91)	<0.0001	2.95 (1.41, 4.49)	0.0002	2.65 (0.63, 4.67)	0.01
Lesion length, mm	0.01 (−0.03, 0.04)	0.75	0.02 (−0.02, 0.06)	0.35	0.01 (−0.04, 0.05)	0.68
Calcification (moderate/ severe)	−2.16 (−3.32, -1.01)	0.0002	−0.59 (−1.72, 0.54)	0.30	−2.44 (−4.68, −0.20)	0.03
Pre-PCI iFR	1.07 (−1.99, 4.13)	0.49	4.62 (1.05, 8.18)	0.01	1.24 (−3.14, 5.62)	0.58

CI: confidence interval; iFR: instantaneous wave-free ratio; LAD: left anterior descending; PCI: percutaneous coronary intervention; RVD: reference vessel diameter

Table 4. Factors associated with absolute change of SAQ-AF score from baseline to 1-year follow-up in multivariate linear regression model.

	Regression coefficient (95%CI)	p-value
Δ iFR (pre-iFR–post-iFR)	7.86 (2.15, 13.58)	0.007
LAD versus non-LAD	−0.48 (−3.32, 2.36)	0.74
Baseline SAQ-AF score	−0.87 (−0.93, −0.81)	<0.0001

AF: angina frequency; CI: confidence interval; iFR: instantaneous wave-free ratio; LAD: left anterior descending artery; SAQ: Seattle Angina Questionnaire

non-hyperaemic pressure ratios (distal coronary pressure-to-aortic pressure ratio and diastolic pressure ratio gradients) had moderate ability to identify intravascular ultrasound-detected focal residual lesions and stent underexpansion[14]. Whether PCI guidance with iFR pullback and stent optimisation leads to improved clinical outcomes is currently being tested in the large-scale randomised Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting (DEFINE GPS) trial (ClinicalTrials.gov: NCT04451044).

### DIFFUSE ATHEROSCLEROSIS IN THE LAD COMPARED WITH NON-LAD VESSELS

Smaller angiographic RVD was an independent predictor of lower post-PCI iFR in both LAD and non-LAD vessels, and RVD tended to be smaller in the LAD compared with non-LAD vessels (2.73 mm vs 2.84 mm). Smaller RVD in the LAD may indicate diffuse atherosclerosis, although no statistical difference was observed when compared with non-LAD vessels. Prior intravascular ultrasound studies have shown that angiographically "normal" segments are rarely normal[15], and plaque burden is greater in LAD compared with non-LAD vessels[16]. Coronary artery calcification has also been shown to be greater in LAD compared with non-LAD vessels in patients with mild to moderate levels of overall coronary artery calcium[17]. Warisawa et al reported that an iFR-derived diffuse pattern was more frequent in LAD compared with non-LAD vessels (53.8% in 520 LAD vessels vs 18.5% in 151 non-LAD vessels)[18]. A similar trend was observed using the hyperaemic pullback pressure gradient[19]. These factors may all contribute to smaller minimum stent areas in LAD lesions, potentially explaining the higher prevalence of residual in-stent pressure gradients in the LAD.

PRESSURE LOSS IN THE LAD ANATOMY INDEPENDENT OF STENOSIS

Vessel curvature, the presence of branches, and vessel tapering affect pressure loss even in relatively normal coronary arteries[20,21]. In addition, compared with the ground truth, wire-based invasive physiology measurements in the supine position may reveal lower values in the LAD and higher values in the LCx because of hydrostatic pressure[22]. Using computed tomography, a prior study showed that the mid- to distal LAD is located higher than

the ostium of the left main coronary artery, and the LCx is located lower than the ostium. Thus, compared with the position of the ostium, where equalisation between the aortic pressure and pressure sensor on the wire is performed, the hydrostatic pressure is negative in the mid- to distal LAD (i.e., invasive physiology measurements may reveal lower numbers than the ground truth) and positive in the LCx (i.e., invasive physiology measurements may reveal higher values than the ground truth). Fukunaga et al reported that in 26 angiographically normal LAD vessels, FFR values gradually decreased from proximal to distal, measuring 0.85±0.06 at 12 cm distal to the ostium. In 6 swine with normal coronary arteries, the FFR was 0.95±0.01 at 10 cm distal to the ostium in the LAD, compared with a value of 1.0 at 10 cm distal to the ostium in all RCA and LCx arteries[23]. Finally, the larger myocardial mass that is typically subtended by the LAD may lead to a greater pressure loss and consequently smaller post-PCI physiological gain[24]. Kang et al showed that a larger BSA or greater left ventricular mass were independently associated with lower FFR values after adjustment for intravascular ultrasound minimum lumen area[25]. In this study, the RVD among the different vessels was similar, with the LAD being the longest vessel. Consequently, the normalised arterial volume to left ventricular mass ratio is much smaller in the LAD than in the other arteries.

Ultimately, a combination of more advanced disease, worse acute PCI results with larger in-stent pressure gradients, greater subtended myocardium, and the LAD anatomy itself may explain the lesser iFR gain from pre- to post-PCI in LAD compared with non-LAD vessels. In this regard, Hwang et al reported that the cut-off value of post-PCI FFR to predict TVF was different for LAD (≤0.82) and non-LAD vessels (≤0.88)[8].
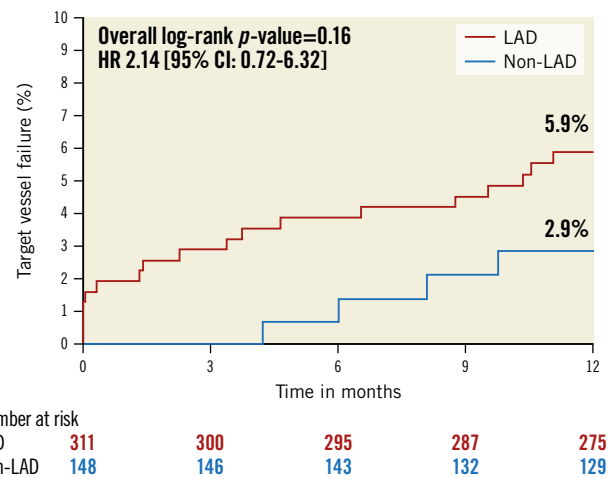
Figure 3. *One-year target vessel failure between LAD versus non-LAD vessels. Patient-level Kaplan-Meier curves for target vessel failure. There was no significant difference in clinical events at 1 year between LAD versus non-LAD target vessels. CI: confidence interval; HR: hazard ratio; LAD: left anterior descending artery*

CORRELATION BETWEEN IMPROVEMENT IN SAQ-AF SCORE AND LESION LOCATION

There is a strong correlation between invasive physiology measurements and stress echocardiography-detected ischaemia, as well as with the efficacy of PCI in reducing ischaemia and angina frequency[26]. Symptomatic patients with ischaemia treated with revascularisation are more likely to be free from angina at follow-up compared with patients managed with medical therapy only[27], especially those with greater degrees of ischaemia as assessed by stress echocardiography or with invasive physiology[26,28]. In the present study, greater improvements of iFR were associated with greater reductions in angina, independent of the target vessel location. Similarly, larger relative improvements in FFR have been associated with a reduced burden of patient-reported angina at 3-month follow-up[29].

Limitations

First, the present analysis only included patients with pre- and post-PCI iFR measurements and excluded left main lesions, therefore, some degree of selection bias cannot be excluded. The current study included only patients with abnormal pre-PCI iFR. Prior studies have shown that a reverse mismatch (angiographically mild stenosis, but physiologically significant) occurs more frequently in the LAD compared with non-LAD[30]. Given that the current study included only patients with abnormal pre-PCI iFR assessment, lesion severity was greater in non-LAD vessels. Second, intravascular imaging was only performed in a small proportion of patients and was not made available to the core laboratory. As such, we cannot correlate the physiology findings with the severity of residual atherosclerosis. Third, the optimal post-PCI iFR target value of 0.95 was identified *post hoc* and requires prospective validation before being adopted into clinical practice. Finally, there were a relatively small number of clinical events at 1 year, limiting our ability to determine differences in vessel-based angina-related and clinical outcomes.

Conclusions

In a large cohort of patients undergoing angiographically successful PCI, post-PCI iFR values were lower in LAD vessels compared with non-LAD vessels. Larger residual in-stent pressure gradients were observed in LAD vessels, the treatment of which may result in improved acute physiological gain and clinical outcomes; this hypothesis is currently being tested in the pivotal DEFINE GPS trial.

Impact on daily practice

The current study demonstrates that LAD vessels have a smaller improvement of iFR from pre-PCI to post-PCI with a greater frequency of residual focal pressure gradients within the stented segment compared with non-LAD vessels; this directly contributes to a lower absolute post-PCI iFR and higher prevalence of post-PCI iFR ≤0.89 and <0.95. The clinical and anatomical factors associated with lower post-PCI iFR were different between LAD and non-LAD vessels.

Conflict of interest statement

M. Matsumura is a consultant for Terumo and Boston Scientific. A. Maehara is a consultant for Boston Scientific; receives honoraria from Nipro and Boston Scientific; and is on the advisory board of SpectraWave. J. Davies has patents pertaining to the iFR technology; and is a consultant for Philips. A. Sharp is a consultant for Philips, Medtronic, Boston Scientific, Recor Medical, and Penumbra; and receives honoraria from Medtronic, Boston Scientific, Philips, ReCor Medical, and Penumbra. H. Samady is on the advisory board of Philips; co-founder and equity holder in Covanos; and a holder of four patents in the computational physiology space. A. Seto receives research grants from Philips; and is part of the leadership of SCAI. D. Cohen receives institutional grant support from Philips; is a consultant for Abbott, Edwards Lifesciences, and HeartBeam; and is on the advisory board of Medtronic. M. Patel receives research grants from Philips; and is a consultant for Bayer, Janssen, and Novartis. Z.A. Ali receives institutional grant support from Abbott, Abiomed, Acist, Amgen, Boston Scientific, Cathworks, Canon, Conavi, HeartFlow, Inari, Medtronic Inc, National Institute of Health, Nipro, Opsens Medical, Medis, Philips, Shockwave Medical, Siemens, Spectrawave, and Teleflex; is a consultant for Abiomed, AstraZeneca, Boston Scientific, Cathworks, OpSens, Philips, and Shockwave Medical; receives a honoraria from Abiomed, AstraZeneca, Boston Scientific, Cathworks, OpSens, Philips, and Shockwave Medical; and has equity/options from Elucid, Lifelink, SpectraWave, Shockwave Medical, and VitalConnect. G.W. Stone has received institutional grant support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Philips, Biosense-Webster, Shockwave Medical, Vascular Dynamics, Pulnovo, and V-Wave; is a consultant for Abbott, Daiichi Sankyo, Ablative Solutions, CorFlow, Cardiomech, Robocath, Miracor, Vectorious, Apollo Therapeutics, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Elucid Bio, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, Oxitope, Cardiac Success, and HighLife; received honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, Amgen, and Boehringer Ingelheim; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter. A. Jeremias receives institutional grant support from Philips; is a consultant for Philips, Abbott Vascular, ACIST Medical, Shockwave Medical, and Cathworks; and is on the advisory board of Philips. The other authors have no conflicts of interest to declare.

References

1. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Härle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P,

Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med.* 2017;376:1824-34.

2. Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Kåregren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Fröbert O; iFR-SWEDE-HEART Investigators. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med.* 2017;376:1813-23.

3. Hwang D, Jeon KH, Lee JM, Park J, Kim CH, Tong Y, Zhang J, Bang JI, Suh M, Paeng JC, Na SH, Cheon GJ, Cook CM, Davies JE, Koo BK. Diagnostic Performance of Resting and Hyperemic Invasive Physiological Indices to Define Myocardial Ischemia: Validation With ¹³N-Ammonia Positron Emission Tomography. *JACC Cardiovasc Interv.* 2017;10:751-60.

4. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Bryne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention.* 2019;14:1435-534.

5. 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. *JACC Cardiovasc Interv.* 2016;9:1022-31.

6. Lee JM, Hwang D, Choi, KH, Rhee TM, Park J, Kim HY, Jung HW, Hwang JW, Lee HJ, Jang HJ, Kim SH, Song YB, Cho YK, Nam CW, Hahn JY, Shin ES, Kawase Y, Matsuo A, Tanaka N, Doh JH, Koo BK, Matsuo H. Prognostic Implications of Relative Increase and Final Fractional Flow Reserve in Patients With Stent Implantation. *JACC Cardiovasc Interv.* 2018;11:2099-109.

7. Samady H, McDaniel M, Veledar E, Bruyne BD, Pijls NH, Fearon WF, Vaccarino V. Baseline fractional flow reserve and stent diameter predict optimal post-stent fractional flow reserve and major adverse cardiac events after bare-metal stent deployment. *JACC Cardiovasc Interv.* 2009;2:357-63.

8. Hwang D, Lee JM, Lee HJ, Kim SH, Nam CW, Hahn JY, Shin ES, Matsuo A, Tanaka N, Matsuo H, Lee SY, Doh JH, Koo BK. Influence of target vessel on prognostic relevance of fractional flow reserve after coronary stenting. *EuroIntervention.* 2019;15:457-64.

9. Agarwal SK, Kasula S, Almomani A, Hacioglu Y, Ahmed Z, Uretsky B, Hakeem A. Clinical and angiographic predictors of persistently ischemic fractional flow reserve after percutaneous revascularization. *Am Heart J.* 2017;184:10-16.

10. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, Talwar S, Marques K, Shammas NW, Gruberg L, Seto A, Samady H, Sharp A, Ali ZA, Mintz GS, Patel M, Stone GW. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI study. *JACC Cardiovasc Interv.* 2019;12:1991-2001.

11. Patel MR, Jeremias A, Maehara A, Matsumura M, Zhang Z, Schneider J, Tang K, Talwar S, Marques K, Shammas NW, Gruberg L, Seto A, Samady H, Sharp ASP, Ali ZA, Mintz G, Davies J, Stone GW. 1-Year Outcomes of Blinded Physiological Assessment of Residual Ischemia After Successful PCI: DEFINE PCI Trial. *JACC Cardiovasc Interv.* 2022;15:52-61.

12. Matsumura M, Johnson NP, Fearon WF, Mintz GS, Stone GW, Oldroyd K, De Bruyne B, Pijls NHJ, Maehara A, Jeremias A. Accuracy of Fractional Flow Reserve Measurements in Clinical Practice: Observations From a Core Laboratory Analysis. *JACC Cardiovasc Interv.* 2017;10:1392-401.

13. Neleman T, van Zandvoort LJC, Tovar Forero MN, Masdjedi K, Ligthart JMR, Witberg KT, Groenland FTW, Cummins P, Lenzen MJ, Boersma E, Nuis RJ, den Dekker WK, Diletti R, Wilschut J, Zijlstra F, Van Mieghem NM, Daemen J. FFR-Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care: The FFR REACT Trial. *JACC Cardiovasc Interv.* 2022;15:1595-607.

14. Neleman T, Scoccia A, Groenland FTW, Ziedses des Plantes AC, van Zandvoort LJC, Ligthart JMR, Witberg KT, Lenzen MJ, Boersma E, Nuis RJ, den Dekker WK, Diletti R, Wilschut J, Zijlstra F, Van Mieghem NM, Daemen J. Validation of Segmental Post-PCI Physiological Gradients With IVUS-Detected Focal Lesions and Stent Underexpansion. *JACC Cardiovasc Interv.* 2023;16:1763-73.

15. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, Chuang YC, Bucher TA, Sokolowicz LE, Leon MB. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. *J Am Coll Cardiol.* 1995;25:1479-85.

16. Zheng B, Mintz GS, McPherson JA, De Bruyne B, Farhat NZ, Marso SP, Serruys PW, Stone GW, Maehara A. Predictors of Plaque Rupture Within Nonculprit

17. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Nagamachi K, Samukawa M. Distribution of coronary atherosclerosis in patients with coronary artery disease. *Heart Vessels.* 2010;25:14-8.

18. Warisawa T, Cook CM, Seligman H, Howard JP, Ahmad Y, Rajkumar C, Doi S, Nakayama M, Tanigaki T, Omori H, Nakajima A, Yamanaka F, Goto S, Yakuta Y, Karube K, Uetani T, Kikuta Y, Shiono Y, Kawase Y, Nishina H, Nakamura S, Escaned J, Akashi YJ, Matsuo H, Davies JE. Per-Vessel Level Analysis of Fractional Flow Reserve and Instantaneous Wave-Free Ratio Discordance - Insights From the AJIP Registry. *Circ J.* 2020;84:1034-8.

19. Collet C, Sonck J, Vandeloo B, Mizukami T, Roosens B, Lochy S, Argacha JF, Schoors D, Colaiori I, Di Gioia G, Kodeboina M, Suzuki H, Van 't Veer M, Bartunek J, Barbato E, Cosyns B, De Bruyne B. Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis. *J Am Coll Cardiol.* 2019;74:1772-84.

20. Li Y, Gutierrez-Chico JL, Holm NR, Yang W, Hebsgaard L, Christiansen EH, Maeng M, Lassen J, Yan F, Reiber JH, Tu S. Impact of Side Branch Modeling on Computation of Endothelial Shear Stress in Coronary Artery Disease: Coronary Tree Reconstruction by Fusion of 3D Angiography and OCT. *J Am Coll Cardiol.* 2015;66:125-35.

21. Gould KL, Kelley KO, Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. *Circulation.* 1982;66:930-7.

22. Harle T, Luz M, Meyer S, Kronberg K, Nickau B, Escaned J, Davis J, Elsasser A. Effect of Coronary Anatomy and Hydrostatic Pressure on Intracoronary Indices of Stenosis Severity. *JACC Cardiovasc Interv.* 2017;10:764-73.

23. Fukunaga M, Fujii K, Mintz GS, Kawasaki D, Nakata T, Miki K, Imanaka T, Tamaru H, Shibuya M, Masuyama T. Distribution of pressure gradients along the left anterior descending artery in patients with angiographically normal arteries. *Catheter Cardiovasc Interv.* 2020;96:E67-74.

24. Ide S, Sumitsuji S, Yamaguchi O, Sakata Y. Cardiac computed tomography-derived myocardial mass at risk using the Voronoi-based segmentation algorithm: A histological validation study. *J Cardiovasc Comput Tomogr.* 2017;11:179-82.

25. Kang SJ, Ahn JM, Han S, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Mintz GS, Park SJ. Sex differences in the visual-functional mismatch between coronary angiography or intravascular ultrasound versus fractional flow reserve. *JACC Cardiovasc Interv.* 2013;6:562-8.

26. Al-Lamee RK, Shun-Shin MJ, Howard JP, Nowbar AN, Rajkumar C, Thompson D, Sen S, Nijjer S, Petraco R, Davis J, Keeble T, Tang K, Malik I, Bual N, Cook C, Ahmad Y, Seligman H, Sharp ASP, Gerber R, Talwar S, Assomull R, Cole G, Keenan NG, Kanaganayagam G, Sehmi J, Wensel R, Harrell FE Jr, Mayet J, Thom SA, Davies JE, Francis DP. Dobutamine Stress Echocardiography Ischemia as a Predictor of the Placebo-Controlled Efficacy of Percutaneous Coronary Intervention in Stable Coronary Artery Disease: The Stress Echocardiography-Stratified Analysis of ORBITA. *Circulation.* 2019;140:1971-80.

27. Spertus JA, Jones PG, Maron DJ, O'Brien SM, Reynolds HR, Rosenberg Y, Stone GW, Harrell FE Jr, Boden WE, Weintraub WS, Baloch K, Mavromatis K, Diaz A, Gosselin G, Newman JD, Mavromichalis S, Alexander KP, Cohen DJ, Bangalore S, Hochman JS, Mark DB; ISCHEMIA Research Group. Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease. *N Engl J Med.* 2020;382:1408-19.

28. Al-Lamee R, Howard JP, Shun-Shin MJ, Thompson D, Dehbi HM, Sen S, Nijjer S, Petraco R, Davies J, Keeble T, Tang K, Malik IS, Cook C, Ahmad Y, Sharp ASP, Gerber R, Baker C, Kaprielian R, Talwar S, Assomull R, Cole G, Keenan NG, Kanaganayagam G, Sehmi J, Wensel R, Harrell FE, Mayet J, Thom SA, Davies JE, Francis DP. Fractional Flow Reserve and Instantaneous Wave-Free Ratio as Predictors of the Placebo-Controlled Response to Percutaneous Coronary Intervention in Stable Single-Vessel Coronary Artery Disease. *Circulation.* 2018;138:1780-92

29. Collison D, Didagelos M, Aetesam-Ur-Rahman M, Copt S, McDade R, McCartney P, Ford TJ, McClure J, Lindsay M, Shaukat A, Rocchiccioli P, Brogan R, Watkins S, McEntegart M, Good R, Robertson K, O'Boyle P, Davie A, Khan A, Hood S, Eteiba H, Berry C, Oldroyd KG. Post-stenting fractional flow reserve vs coronary angiography for optimisation of percutaneous coronary intervention (TARGET-FFR). *Eur Heart J.* 2021;42:4656-68.

30. Park SJ, Kang SJ, Ahn JM, Shim EB, Kim YT, Yun SC, Song H, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv.* 2012;5:1029-36.

Supplementary data

Supplementary Table 1. Baseline patient characteristics.
Supplementary Table 2. One-year angina status.
Supplementary Table 3. One-year clinical events in patients with LAD and non-LAD target vessels.

Supplementary Figure 1. Representative images.

The supplementary data are published online at:
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Supplementary data

Supplementary Table 1. Baseline patient characteristics.

	All patients (N=459)	Patients with LAD target vessel (N=311)	Patients without LAD target vessel (N=148)	P Value
Age, years	66.5 ± 9.9	66.7 ± 9.7	66.1 ± 10.4	0.54
Male	76.0 (349)	76.2 (237)	75.7 (112)	0.90
Body surface area, m^2	2.03 ± 0.26	2.03 ± 0.26	2.03 ± 0.25	0.86
Body mass index, kg/m^2	30.8 ± 9.0	30.9 ± 10.0	30.5 ± 6.2	0.94
Diabetes mellitus	33.1 (152)	32.5 (101)	34.5 (51)	0.67
Current smoker	15.9 (7)	15.8 (49)	16.2 (24)	0.90
Hyperlipidemia	69.3 (318)	66.6 (207)	75.0 (111)	0.07
Hypertension	76.3 (350)	73.6 (229)	81.8 (121)	0.06
Prior PCI	44.2 (203)	42.8 (133)	47.3 (70)	0.37
Prior myocardial infarction	27.2 (125)	24.8 (77)	32.4 (48)	0.08
Left ventricular ejection fraction*, %	56.5 ± 8.7	56.1 ± 8.4	57.1 ± 9.3	0.42
Clinical presentation				
Stable angina	41.6 (191)	43.4 (135)	37.8 (56)	0.26
Silent ischemia	5.4 (25)	5.8 (18)	4.7 (7)	0.64
Unstable angina	31.4 (144)	30.2 (94)	33.8 (50)	0.44
NSTEMI	17.0 (78)	15.8 (49)	19.6 (29)	0.31
Recent STEMI (>7 days)	4.6 (21)	4.8 (15)	4.1 (6)	0.71

Values are mean±standard deviation or % (n). *Available in only 315 patients. LAD: left anterior descending; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

Supplementary Table 2. One-year angina status.

	All patients (N=459)	Patients with LAD target vessel (N=311)	Patients without LAD target vessel (N=148)	P Value
SAQ-AF at baseline, Mean ±SD	73.2±22.9	72.5±23.7	74.6±20.9	0.37
SAQ-AF at 1-year, Mean ±SD	94.3±13.4	93.9±13.4	95.2±13.5	0.38
LSM ± SE - ANCOVA model*	-	93.9±0.8	95.1±1.2	0.41
Δ SAQ-AF (1-year minus baseline), Mean ±SD	21.1±23.9	20.9±24.4	21.6±22.9	0.78
LSM ± SE - ANCOVA model	-	20.8±0.8	21.9±1.2	0.41
Δ SAQ-AF ⩾10	67.5 (264)	67.2 (180)	68.3 (84)	0.82
Δ SAQ-AF ⩾10 in patients with baseline SAQ-AF ⩽60	92.7 (127/137)	92.2 (83/90)	93.6 (44/47)	1.00
	Patients with LAD target vessel (N=311)	Patients with LAD target vessel and ΔiFR ≥median (n=122)	Patients with LAD target vessel and ΔiFR <median (n=189)	
SAQ-AF at baseline, Mean ±SD	72.5±23.7	70.6±21.1	73.7±25.3	0.24
SAQ-AF at 1-year, Mean ±SD	93.9±13.4	97.2±8.0	91.7±15.7	0.0002
LSM ± SE - ANCOVA model	-	97.6±1.2	91.4±1.0	0.0002
Δ SAQ-AF (1-year minus baseline), Mean ±SD	20.9±24.4	26.9±21.0	16.9±25.7	0.0006
LSM ± SE - ANCOVA model	-	24.6±1.2	18.5±1.0	0.0002
Δ SAQ-AF ⩾10	67.2 (180)	81.3 (87)	57.8 (93)	<0.0001
Δ SAQ-AF ⩾10 in patients with baseline SAQ-AF ⩽60	92.2 (83/90)	100 (39/39)	86.3 (44/51)	0.02

One-year SAQ available 392 patients in total (LAD: 268 patients, Non-LAD: 124 patients); one-year SAQ-AF available 268 patients in total (LAD target vessel and Δ iFR ⩾ median: 107 patients, LAD target vessel and Δ iFR < median: 161 patients). AF: angina frequency; SAQ: Seattle angina questionnaire; SD: standard deviation; other abbreviations as in Tables 1, 2 and 4.

Supplementary Table 3. One-year clinical events in patients with LAD and non-LAD target vessels.

	All patients (N=459)	Patients with LAD target vessel (N=311)	Patients without LAD target vessel (N=148)	Hazard ratio (95%CI)	P Value
Target vessel failure	4.9 (22)	5.9 (18)	2.9 (4)	2.14 (0.72, 6.32)	0.16
Cardiac death	0.2 (1)	0.0 (0)	0.7 (1)	-	0.14
Target vessel myocardial infarction	1.8 (8)	2.6 (8)	0.0 (0)	-	0.051
Clinically-driven TVR	2.9 (13)	3.3 (10)	2.1 (3)	1.55 (0.43, 5.62)	0.50

Data is shown as Kaplan-Meier estimate (number of events). TVR: target vessel revascularization. Other abbreviations are in Table 1.
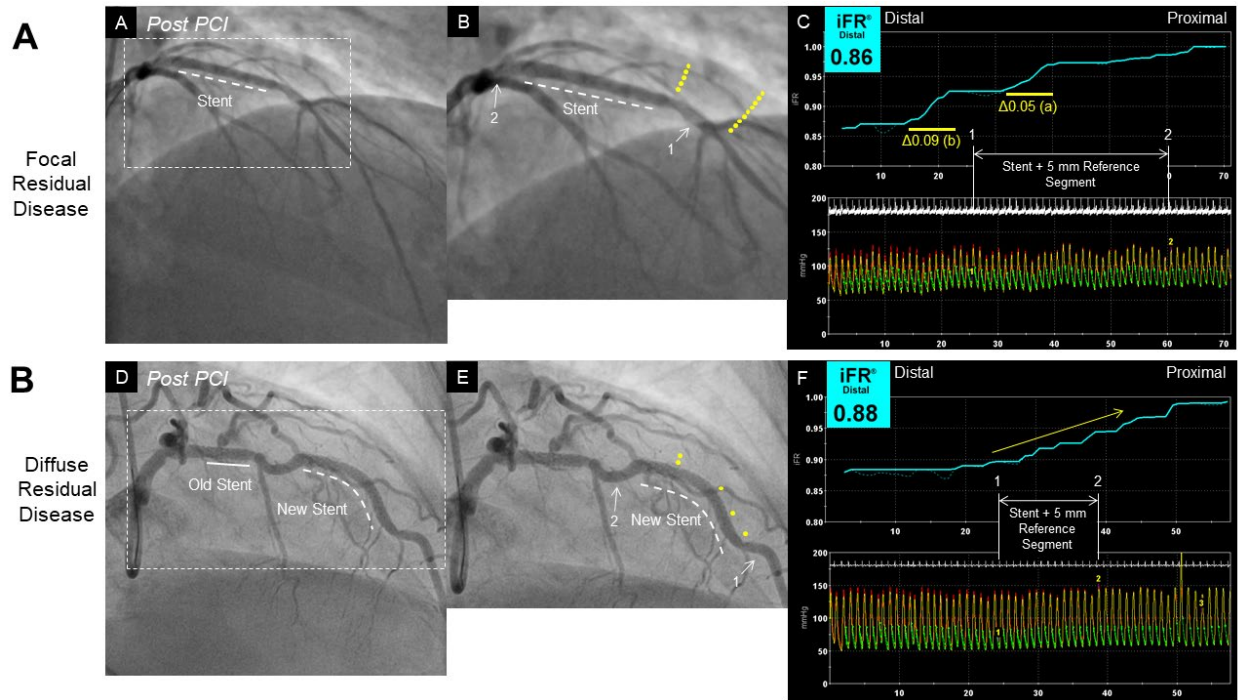
Supplementary Figure 1. Representative images.

(Top, A) After angiographically successful stent implantation of the proximal left anterior descending coronary artery (LAD) (A, B), the post-PCI iFR was 0.86 which remained lower than the ischemic threshold of 0.90. An iFR pullback (C) demonstrated 2 focal step-ups at distal (Δ0.09 [b]) and stent (Δ0.05 [a]) segments (1 yellow dot = 0.01 units of iFR pressure loss).

(Bottom, B) Despite angiographically successful stent implantation in the mid LAD (D,E), the post PCI iFR was 0.88. An iFR pullback (F) demonstrated diffuse disease within the stent and proximal segments without a focal step-up.