Supplemental Material

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Table S1. Inclusion criteria/exclusion criteria in the TARGET FFR study

Inclusion criteria
Patients >18 years of age with coronary artery disease including stable angina and NSTEMI
Participants must be able to provide informed consent
Exclusion criteria
PCI in a coronary artery bypass graft
• PCI to an ISR lesion
• PCI to a target artery providing Rentrop grade 2 or 3 collateral blood supply to another vessel
• Inability to receive adenosine (eg, severe reactive airway disease, marked hypotension, or advanced atrioventricular block without pacemaker).
• Recent (within 1 week prior to cardiac catheterisation) STEMI in any arterial distribution (not specifically target lesion).
Severe cardiomyopathy (LVEF <30%)
• Renal insufficiency such that an additional 20 to 30 mL of contrast would, in the opinion of the operator, pose unwarranted risk to the patient.

ISR = in-stent restenosis; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-elevated myocardial infarction; PPG = pullback pressure gradient.

Table S2. Comparison of functional characteristics between focal and diffuse coronary artery disease (CAD)

Variables	Focal CAD	Diffuse CAD	P
N	**38**	**76**	
Physiological characteristics			
Pre PCI Pd/Pa, median [IQR]	0.87 [0.74, 0.95]	0.85 [0.79, 0.88]	0.21
Pre PCI CFR, median [IQR]	1.87 [1.40, 2.15]	2.25 [1.48, 2.71]	0.052
Pre PCI IMR, median [IQR]	24.5 [19.5, 33.9]	21.7 [16.6, 31.2]	0.36
Pre PCI FFR, median [IQR]	0.61±0.16	0.62±0.13	0.73
Final Post PCI Pd/Pa, median [IQR]	0.98 [0.95, 1.01]	0.91 [0.89, 0.93]	<0.001
Final Post PCI CFR, median [IQR]	3.64 [2.47, 5.51]	3.05 [2.10, 4.13]	0.004
Final Post PCI IMR, median [IQR]	14.4 [11.5, 19.2]	17.3 [13.0, 23.5]	0.052
Final Post PCI FFR, mean ± SD	0.90±0.07	0.83±0.07	<0.001
Normalised delta FFR (%), mean ± SD	72.0 ± 20.3	52.5 ± 19.2	<0.001
Final FFR ≤ 0.80 (%), n (%)	5 (13.2)	22 (28.9)	0.10
Final FFR ≥ 0.80 (%), n (%)	34 (89.5)	54 (71.1)	0.048
Final FFR ≥ 0.90 (%), n (%)	20 (52.6)	12 (15.8)	<0.001
PPG, median [IQR]	0.81 [0.78, 0.82]	0.58 [0.49, 0.66]	<0.001

Categorical variables are expressed as number and percentage. Continuous variables are indicated as median (interquartile range). CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance; Pa = aortic pressure; Pd = distal coronary pressure; PPG = pullback pressure gradient.

Normalised delta FFR was normalised by pre-PCI FFR ([final post-PCI FFR minus pre-PCI FFR divided by one minus pre-PCI FFR] by a factor of one hundred).

Table S3. Multivariate regression analyses of post-PCI FFR with pullback pressure gradient (PPG).

Variables	Multivariate analysis		
	Estimate	CI	P value
Age	-0.001	[-0.002, 0.001]	0.36
Gender (male)	-0.035	[-0.070, 0.000]	0.051
Renal failure	-0.003	[-0.080, 0.074]	0.93
Hypertension	0.005	[-0.020, 0.030]	0.69
Diabetes	-0.018	[-0.049, 0.014]	0.27
Pre-PCI FFR	0.175	[0.084, 0.266]	<0.001
PPG	0.24	[0.153, 0.328]	<0.001
PIOS	0.006	[-0.019, 0.031]	0.63

PCI = percutaneous coronary intervention; FFR = fractional flow reserve; PPG = pullback pressure gradient, PIOS = physiology-guided incremental optimisation strategy.

Table S4. Comparison of fractional characteristics between focal and diffuse CAD in patients with additional optimisation.

Variables	**Focal CAD**	**Diffuse CAD**	**P**
N	**1**	**18**	
Pre PCI			
Pre-PCI Pd/Pa, median [IQR]	0.83 [0.83, 0.83]	0.86 [0.82, 0.88]	0.86
Pre-PCI CFR, median [IQR]	2.00 [2.00, 2.00]	2.35 [1.57, 2.61]	0.63
Pre-PCI IMR, median [IQR]	20.6	26.5±7.39	NA
FFR Pre PCI, median [IQR]	0.61 [0.61, 0.61]	0.64 [0.56, 0.67]	0.72
PPG, mean ± SD	0.74	0.56±0.10	NA
Immediately after stenting			
Pd/Pa, median [IQR]	0.89 [0.89, 0.89]	0.90 [0.88, 0.91]	0.62
CFR, median [IQR]	2.06 [2.06, 2.06]	2.51 [2.05, 3.81]	0.47
IMR, median [IQR]	31.5 [31.5, 31.5]	22.4 [17.8, 27.1]	0.27
FFR, median, mean ± SD	0.80	0.76±0.09	NA
1st PIOS treatments			
Pd/Pa, median [IQR]	0.89 [0.89, 0.89]	0.90 [0.90, 0.92]	0.19
CFR, median [IQR]	3.59 [3.59, 3.59]	3.91 [3.17, 5.58]	0.45
IMR, mean ± SD	17.4	20.0±7.67	NA
FFR, mean ± SD	0.81	0.83±0.05	NA
2nd PIOS treatments			
Pd/Pa, median [IQR]	0.89 [0.89, 0.89]	0.91 [0.90, 0.92]	0.14
CFR, median [IQR]	3.59 [3.59, 3.59]	3.76 [2.69, 4.95]	0.59
IMR, mean ± SD	15.3±2.96	20.2±7.52	NA
FFR, mean ± SD	0.81	0.83±0.05	NA
Final coronary physiology			
Pd/Pa, median [IQR]	0.89 [0.89, 0.89]	0.91 [0.90, 0.92]	0.14
CFR, median [IQR]	3.59 [3.59, 3.59]	3.76 [2.69, 4.95]	0.59
IMR, mean ± SD	17.4	20.0±7.67	NA
FFR, mean ± SD	0.81	0.83±0.05	NA

Categorical variables are expressed as number and percentage. Continuous variables are indicated as median (interquartile range). CAD = coronary artery disease; CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance; Pa = aortic pressure; Pd = distal coronary pressure; PPG = pullback pressure gradient.

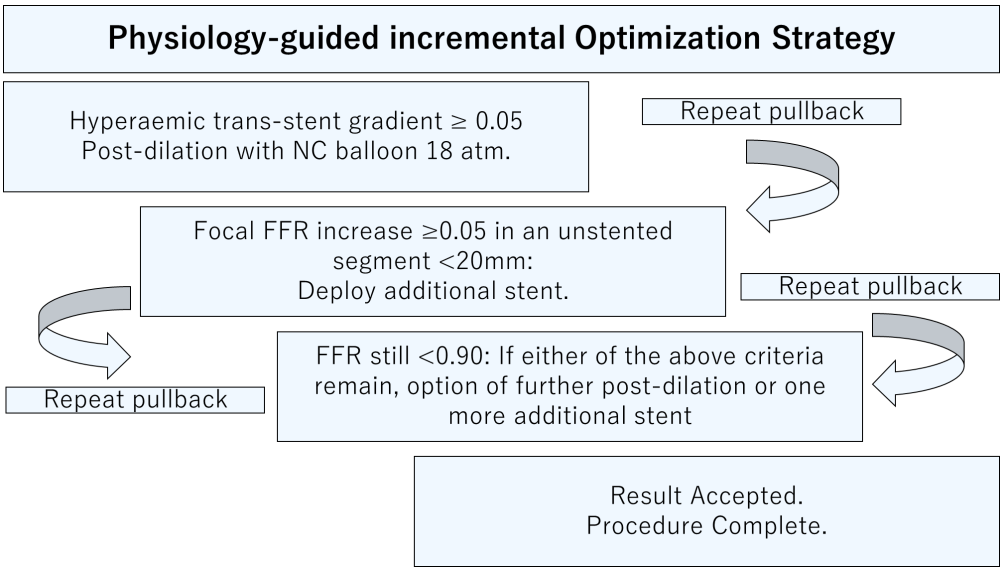

Figure S1. Physiology-guided incremental optimization strategy. FFR = fractional flow reserve; NC balloon = non-complainant balloon.

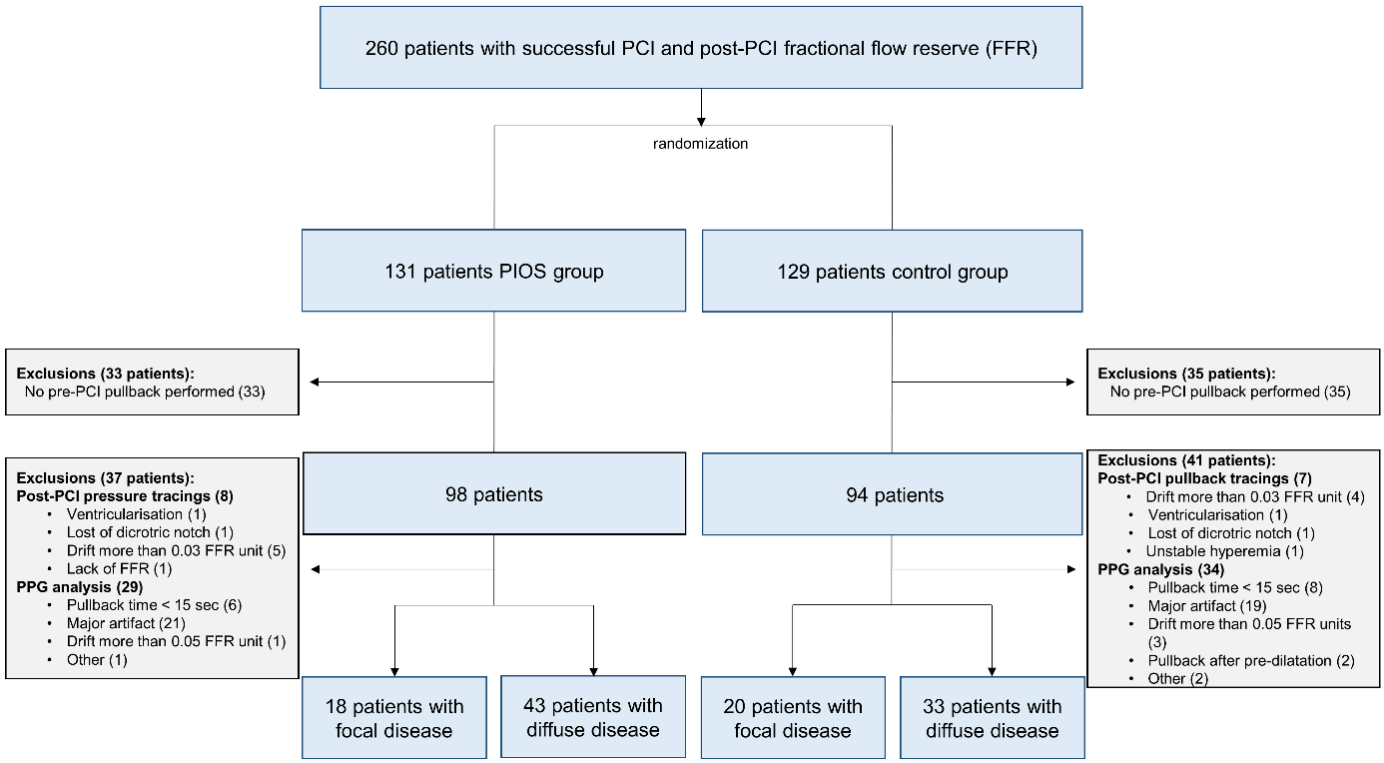

Figure S2. Study flowchart. Focal is defined as PPG ≥ 0.74 and diffuse as PPG < 0.74. FFR = fractional flow reserve; PCI = percutaneous coronary intervention; PIOS = physiology-guided incremental optimisation strategy; PPG = pullback pressure gradient;

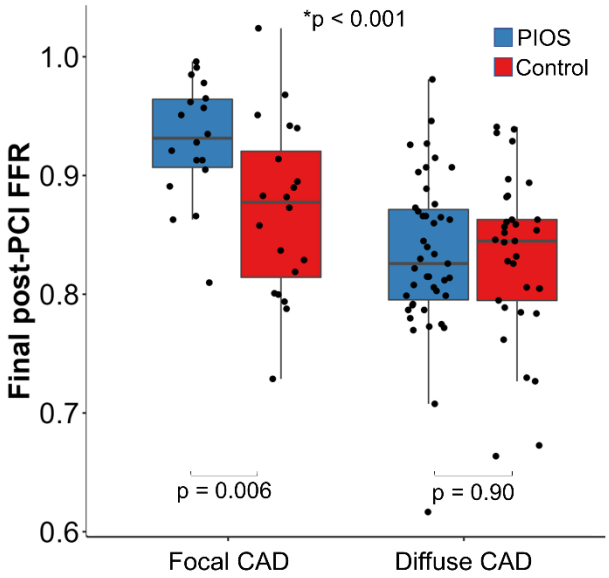

Figure S3. Final post-PCI fractional flow reserve (FFR) stratified by randomization arm and PPG defined focal or diffuse disease.

There was a significant difference in final post-PCI FFR between the focal PIOS, diffuse PIOS, focal control, and diffuse control groups. (0.93±0.05 focal PIOS vs 0.87±0.07 focal controls vs 0.83±0.07 diffuse PIOS vs 0.83±0.07 diffuse controls; p-value<0.001)
The left side panel shows focal disease stratified by randomized arm (PIOS in blue and controls in red). In patients with focal CAD, there was a significant difference in final post-PCI FFR between randomization arms. The right side panel shows diffuse disease (PIOS in blue and controls in red) with no significant difference in final post-PCI FFR between randomization arms. Focal CAD defined as PPG ≥ 0.74. *Focal CAD PIOS vs. Diffuse CAD PIOS vs. Focal CAD Controls vs. Diffuse CAD Controls group.
CAD = coronary artery disease; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; PIOS = physiology-guided incremental optimisation strategy;

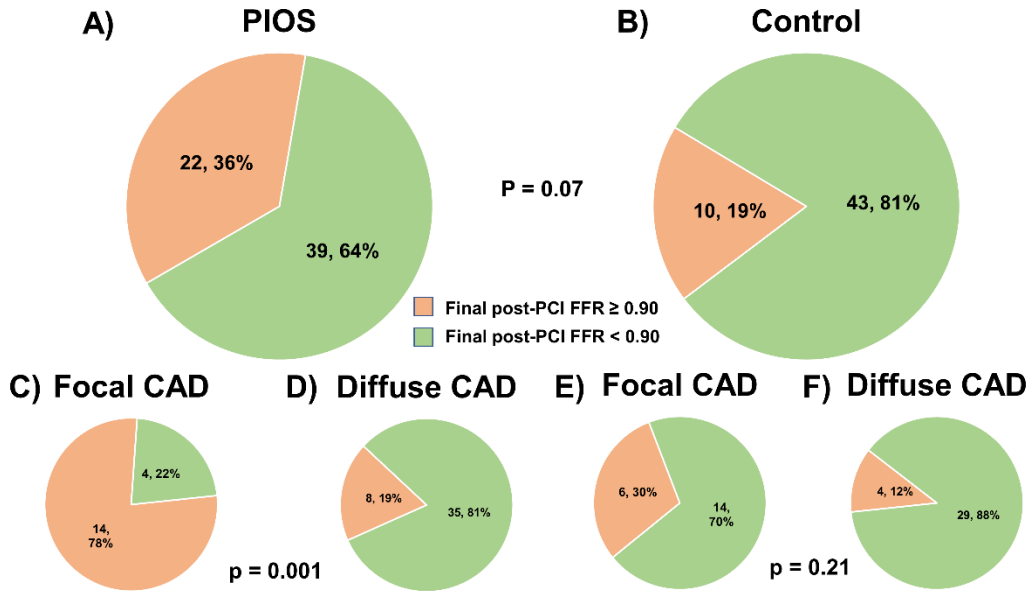

Figure S4. The rate of optimal final post-PCI FFR (≥0.90) stratified by randomization arm and focal or diffuse coronary artery disease. Panel A showed the proportion of patients achieving final post-PCI FFR ≥0.90 in PIOS group. Panel B showed the proportion of patients achieving final post-PCI FFR ≥0.90 in control group. Panel C showed the proportion of patients achieving final post-PCI FFR ≥0.90 in focal PIOS group. Panel D showed the proportion of patients achieving final post-PCI FFR ≥0.90 in diffuse PIOS group. Panel E showed the proportion of patients achieving final post-PCI FFR ≥0.90 in focal control group. Panel F showed the proportion of patients achieving final post-PCI FFR ≥0.90 in diffuse control group. CAD = coronary artery disease; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; PIOS = physiology-guided incremental optimisation strategy.