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Physiology-guided optimisation of percutaneous coronary intervention

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Submitted in fulfilment of the requirements for the degree of Doctor of Medicine (MD)

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Abstract

Aims

A fractional flow reserve (FFR) value ≥ 0.90 after percutaneous coronary intervention (PCI) is associated with a reduced risk of adverse cardiovascular events. TARGET-FFR was an investigator-initiated, single centre, randomised controlled trial to determine the feasibility and efficacy of a post-PCI FFR-guided optimisation strategy versus standard coronary angiography in achieving final post-PCI FFR values ≥ 0.90.

Methods and Results

After angiographically-guided PCI, patients were randomised 1:1 to receive a Physiology-guided Incremental Optimisation Strategy (PIOS) or a blinded coronary physiology assessment (control group). The primary outcome was the proportion of patients with a final post-PCI FFR ≥ 0.90. Final FFR ≤ 0.80 was a prioritised secondary outcome. 260 patients were randomised (131 to PIOS, 129 to control). 68.1% of patients had an initial post-PCI FFR < 0.90. In the PIOS group, 30.5% underwent further intervention (stent post-dilation and/or additional stenting). There was no significant difference in the primary endpoint of the proportion of patients with final post-PCI FFR ≥ 0.90 between groups (PIOS minus control 10%, 95% CI -1.84 to 21.91, p=0.099). The proportion of patients with a final FFR ≤ 0.80 was significantly reduced when compared to the angiography-guided control group (-11.2%, 95% CI -21.87 to -0.35, p=0.045).

Conclusion

Over two-thirds of patients had a physiologically suboptimal result after angiographically guided PCI. A post-PCI FFR-guided optimisation strategy did not significantly increase the proportion of patients with a final FFR ≥ 0.90 but did reduce the proportion of patients with a final FFR ≤ 0.80. Larger increases in FFR following PCI were associated with greater improvements in patient-reported angina and quality-of-life.

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Publications Arising from this Research

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Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

The experimental design of the TARGET-FFR trial was a collaboration between Professors Oldroyd, Berry and me with statistical input from Dr John McClure at the University of Glasgow. I conducted the research at the NHS Golden Jubilee National Hospital under the supervision of Professors Keith Oldroyd and Colin Berry. All percutaneous coronary intervention procedures were performed by interventional cardiologists at the Golden Jubilee National Hospital. To enhance the external validity of our randomised controlled trial, we utilised additional blinded observers and arranged independent analyses of the trial's outcome data. Blinded follow-up assessments were conducted by Golden Jubilee cardiology research nurses, primarily Robert McDade and Ruth McLaren. Blinded quantitative coronary angiography analysis was undertaken by Drs Matthaios Didagelos and Muhammad Aetesam-ur-Rahman. Additional processing of raw coronary physiology data was undertaken by Johan Svanerud at Coroventis Research AB, Uppsala, Sweden prior to an independent core-lab analysis of the study's coronary physiology outcomes by the team at CoreAalst, Aalst, Belgium. An independent Clinical Events Committee adjudicated clinical outcomes in the trial. Independent statistical analysis of trial data was performed by Dr Samuel Copt, University of Geneva. Figures contributed by Dr Takuya Mizukami are acknowledged in the text.

Damien Collison

Glasgow, September 2022

Abbreviations / Acronyms

ACS	Acute Coronary Syndrome
BMS	Bare Metal Stent
CCS	Canadian Cardiovascular Society
CFR	Coronary Flow Reserve
DES	Drug-Eluting Stent
dPR	diastolic Pressure Ratio
EQ-5D-5L	European Quality-of-Life–5 Dimensions–5 Level questionnaire
FFR	Fractional Flow Reserve
HTG	Hyperaemic Tran-stent Gradient
IC	Intracoronary
iFR_{sim}	simulated instantaneous wave-Free Ratio
IMR	Index of Microcirculatory Resistance
IMRc	corrected Index of Microcirculatory Resistance
IV	Intravenous
IVUS	Intravascular Ultrasound
NHPR	Non-Hyperaemic Pressure Ratio
LAD	Left Anterior Descending artery
LCx	Left Circumflex artery

LMS	Left Main Stem artery
MACE	Major Adverse Cardiovascular Events
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
Pd/Pa	Distal Coronary Pressure/Aortic Pressure
PIOS	Physiology-guided Incremental Optimisation Strategy
PPG	Pullback Pressure Gradient index
PROMs	Patient-Reported Outcome Measures
RCA	Right Coronary Artery
RFR	Resting Full-cycle Ratio
SAQ	Seattle Angina Questionnaire
STEMI	ST-segment Elevation Myocardial Infarction
TT_{hyp}	Hyperaemic Transit Time
TT_{rest}	Resting Transit Time
TVF	Target Vessel Failure

Chapter 1 Introduction

1.1 Introduction

Revascularisation decisions guided by hyperaemic or resting indices of myocardial blood flow lead to improved clinical outcomes following invasive management. Fractional Flow Reserve (FFR)-guided percutaneous coronary intervention (PCI) is recommended in practice guidelines based on long-term follow-up results of landmark trials.(1, 2) On the other hand, evidence for the clinical utility of post-PCI FFR is lacking and standard practice for adjudicating the success of a PCI procedure continues to be angiographic assessment alone. In the United Kingdom for example, despite the evidence base, FFR is still only utilized in approximately 10% of PCI procedures annually and post-PCI measurements likely represent a very small fraction of this usage.(3) The hypothesis that post-PCI FFR might be clinically useful is supported by prognostic studies with other adjunctive technologies, such as intravascular ultrasound.(4) This chapter summarizes the current evidence on the use of post-PCI coronary physiology in both stable angina and acute coronary syndromes and addresses the most common questions relating to the practice: what is an optimal post-PCI FFR value, why does it matter and what can be done to improve a physiologically sub-optimal result.

1.2 Establishing a threshold for post-PCI FFR – a historical perspective

In 1999, Bech et al published a retrospective analysis of 60 patients with single vessel disease who received balloon angioplasty alone. The 2-year event-free survival after plain balloon angioplasty in patients with both post-PCI FFR ≥ 0.90 and residual diameter stenosis ≤ 35% was excellent and comparable to the outcome observed after coronary stenting in patients with similar characteristics.(5) Early studies assessed post-PCI FFR as a measure of optimal stent deployment based on Intravascular Ultrasound (IVUS) criteria. From a study of 30 patients with coiled bare metal stents (BMS), Hanekamp et al reported that both IVUS and FFR had similar diagnostic value for the assessment of optimal

stent deployment. They concluded that coronary pressure measurement could be used as a less expensive and rapid alternative to IVUS for that purpose. These investigators suggested that a post-PCI FFR result of ≥ 0.94 most accurately predicted optimum stent deployment by IVUS.(6)

In 2001, Fearon et al reported on a series of 84 patients who received slotted-tube BMS. They concluded that an FFR < 0.96 after stent deployment, predicted a suboptimal result based on validated IVUS criteria. However, an FFR ≥ 0.96 did not reliably predict an optimal stent result.(7) The authors noted that significantly better diagnostic performance was achieved in a subgroup that received higher doses of intracoronary (IC) adenosine. This suggests that sub-maximal hyperaemia with low-dose IC adenosine may have led to an overestimation of FFR. In the same year, a smaller study of 14 patients with slotted-tube BMS employed intravenous (IV) adenosine infusions to achieve hyperaemia and reported that a post-PCI FFR > 0.94 predicted an optimal IVUS result while values < 0.91 correlated with sub-optimal stent deployment (0.91-0.94 representing a diagnostic grey zone).(8) These initial studies established that a post-PCI FFR result of ≥ 0.95 correlated with optimal bare metal stent (BMS) deployment by validated IVUS criteria but the technique still lacked any outcome data in its own right.

In 2002, Pijls et al reported that post-PCI FFR measured in 750 patients was a strong independent predictor of clinical outcome. The authors found that at 6 months, the lowest event rates occurred in patients with FFR ≥ 0.90 (4.9% for > 0.95 and 6.2% for 0.90-0.95 vs. 20.3% for < 0.90 and 29.5% for < 0.80).(9) The FFR thresholds of > 0.95 and > 0.90 were subsequently verified by 2 further registry studies of 119 and 586 patients respectively, which correlated post-PCI FFR with 6-month outcome data following implantation of BMS.(10, 11) In the era of drug-eluting stents (DES), several cohort studies and meta-analyses have identified lower post-PCI FFR thresholds to predict better clinical outcomes.(12-25) These values range from ≥ 0.82 to ≥ 0.92. A systematic review of 7470 patients reported that a post-PCI FFR ≥ 0.90 was associated with significantly lower risk of repeat PCI and Major Adverse Cardiovascular Events (MACE).(18) Table 1-1 provides a summary of studies which reported optimal threshold values of post-PCI FFR to predict clinical outcomes.

Table 1-1 - Studies evaluating post-PCI FFR result as a predictor of clinical outcomes

Study	Population	Sample Size	Stent Type	Follow-Up Duration	Outcome	Post-PCI FFR Cut-off	Result
Hoshino et al 2019(25)	Stable CAD	201	DES	24 (14-48) months	VOCE	< 0.86	VOCE-Free Survival rate lower in the < 0.86 group, log-rank p=0.002
Nishi et al 2019(24)	Stable CAD	572	DES (87%)	4 (1.6-5.6) years	MACE	≤ 0.84	35.2% [> 0.84] vs. 31.1% [≤ 0.84], p=0.45
Azzalini et al 2019(23)	Stable CAD (66%) ACS (23%)	65	DES (86%), DEB (8%), BVS (6%)	12 months	MACE	< 0.90	31.6% [< 0.90] vs. 9.1% [≥ 0.90], p=0.047
Hwang et al 2019(22)	Stable CAD & Non-Culprit ACS lesions (45.9%).	835	DES	24 months	TVF	≤ 0.84 [All] ≤ 0.82 [LAD] ≤0.88 [Non-LAD]	All: 8.3% [≤ 0.84] vs. 3.1% [> 0.84], adjusted HR 2.98 (CI 1.92-4.61), p< 0.001; LAD: 10.9% [≤ 0.82] vs. 2.9% [> 0.82], adjusted HR 4.47 (CI 2.83-7.08), p< 0.001; Non-LAD: 8.0% [≤ 0.88] vs. 1.9% [> 0.88], adjusted HR 18.20 (CI 4.31-76.76), p<0.001
Lee et al 2018(21)	Stable CAD	621	DES	24 months	TVF	< 0.84	9.1% [< 0.84] vs. 2.6% [≥ 0.84]; HR 3.367, CI 1.412-8.025; p=0.006

Piroth et al 2017(20)	Stable CAD & ACS (Patients from FAME 1 & 2 trials)	639 (838 lesions)	DES	24 months	VOCE	< 0.93	For FFR < 0.88 vs. > 0.92 HR 1.46 (1.02-2.08, p=0.037)
Li et al 2017(19)	Stable CAD	1476	DES	36 months	TVF	≤ 0.88 [All] ≤ 0.905 [LAD]	6.1% [> 0.88] vs. 12.3% [≤ 0.88], p=0.002
Rimac et al 2017(18)	Meta-analysis	7470	BMS/DES	Up to 30 months	MACE	< 0.90	OR 0.71 (CI 0.59-0.85, p=0.0003) [≥ 0.90]
Kasula et al 2016(17)	Stable CAD (62.5%) & ACS (32.1%)	579 (613 lesions)	DES (80% SIHD, 74% ACS)	2.6±1.3 years	MACE	≤ 0.91	ACS Patients: 30% [≤ 0.91] vs. 19% [> 0.91], p=0.03. Stable CAD 16%
Agarwal et al 2016(15)	Stable CAD & ACS (32%).	574 (664 lesions)	DES (79%)	31±16 months	MACE	≤ 0.86 [All]; ≤ 0.91 [Excluding CKD, DM, diffuse disease]	17% [≥ 0.86] vs. 23% [≤ 0.86], log-rank p=0.02
Doh et al 2015(14)	Stable CAD	107 (115 lesions)	DES	36 months	TVF	< 0.89	TVF-Free Survival 89.3% [≥ 0.89] vs. 61.1% [< 0.89], p=0.03
Reith et al 2015(13)	Stable CAD	66	DES (95.5%)	20 months	MACE	≤ 0.905	35.9% [≤ 0.905] vs. 5.3% [> 0.905]; p=0.01

Ito et al 2014(12)	Stable CAD	97	DES	17.8 (13.2-27.9) months	MACE	≤ 0.90	MACE-free survival rate lower in ≤ 0.90 group, log-rank p=0.02
Klauss et al 2005(10)	Stable CAD	119	BMS	6 months	MACE	< 0.95	OR 6.22 (CI 1.79-21.62) [< 0.95]
Rieber et al 2002(26)	Stable CAD	89	BMS	10.9±7.1 months	MACE	< 0.94	RR 3.50 (CI 1.29-9.52) [< 0.94]
Pijls et al 2002(9)	N/R	750	BMS	6 months	MACE	≤ 0.95	Crude OR 2.83 (CI 1.53-5.26) [≤ 0.95]

ACS=Acute Coronary Syndrome; BMS=Bare Metal Stent; CI=Confidence Interval; BVS=Bioresorbable Vascular Scaffold; CAD=Coronary Artery Disease; DES=Drug-Eluting Stent; FFR=Fractional Flow Reserve; HR=Hazard Ratio; ICI=Intracoronary Imaging; IVUS=Intravascular Ultrasound; LAD=Left Anterior Descending artery; MACE=Major Adverse Cardiovascular Events; N/R=Not Reported; OR=Odds Ratio; RR=Risk Ratio; TVF=Target Vessel Failure; VOCE=Vessel-Oriented Composite Endpoint

1.3 The relationship between post-PCI FFR and clinical outcomes

In a landmark meta-analysis of patient-level data, Johnson et al correlated the immediate post-PCI FFR results from 970 lesions in 966 patients with clinical outcomes out to 3 years and demonstrated a significant, inverse relationship between post-PCI FFR and subsequent clinical events.(27) Furthermore, they showed that the prognostic value of FFR differs between stented and de novo lesions with higher event rates after PCI at each level of FFR. They hypothesized that the mechanism for this inverse prognostic gradient (assuming optimal stent deployment) was residual diffuse disease, arguing that other potential mechanisms were unlikely – PCI had largely removed focal disease and the presence of microvascular dysfunction would usually increase FFR values and create a direct relationship between post-PCI FFR and outcomes (the opposite effect to that which was observed). From a study of 1,476 patients Li et al subsequently reported that, more specifically, the post-PCI FFR value had a strong correlation with the rate of target vessel failure (TVF).(19)

Piroth et al analysed the vessel-oriented composite endpoints (VOCE) at 2 years in a group of 639 patients who had post-PCI FFR measured in the FAME 1 and FAME 2 randomised controlled trials.(20) This cohort represented approximately two thirds of the patients who received PCI in these studies. From this retrospective analysis, the authors concluded that while a higher post-PCI FFR value is associated with a better vessel-related outcome, its predictive value is too low to use as a surrogate clinical end point.

1.4 Suboptimal post-PCI FFR results – the scope of the problem

Published values for overall mean or median final post-PCI FFR results vary between studies and range from 0.84 to 0.97.(6-11, 13-15, 17, 20-26, 28-52) A large meta-analysis reported a mean value of 0.90 ± 0.04.(18) What these average values do not reveal however, is the proportion of patients who are left with suboptimal final post-PCI FFR results. Again, where this is reported, results vary significantly with the proportion of patients achieving a final FFR ≥ 0.90 ranging widely from 21.3% up to 100%.(8, 9, 11-15, 23, 39, 48, 50, 52-55) Potentially, 4 out of 5 patients may have a sub-optimal post-PCI by physiological criteria. More concerning still is that the proportion of patients with an initial post-PCI FFR ≤ 0.80 has been reported as ranging from < 1% to 36.5%.(9, 13, 14, 17, 19, 21, 22, 24, 33, 36, 41, 44, 48, 50-52, 56) This indicates that, despite angiographically satisfactory results, as many as 1 in 3 patients may have a post-PCI FFR result that remains below the threshold for performing revascularisation in the first place. With up to 38% of patients still reporting angina 1 year after PCI procedures,(57) it seems plausible that persistently abnormal post-PCI FFR results may be associated with symptom recurrence. Table 1-2 provides a summary of studies which have reported the proportion of patients with optimal and/or persistently ischemic post-PCI FFR values. It also allows an overview of how the interplay of factors such as the proportion of LAD target arteries, the number of ACS patients included, stent length, intracoronary vs. intravenous adenosine use and the distal position of the pressure-wire transducer may all have had a bearing on the average final post-PCI FFR value reported in these studies.

Table 1-2 - Studies reporting proportions of optimal and/or persistently ≤ 0.80 post-PCI FFR results.

Study	Population	Sample Size	Proportion of LAD lesions	Stent Type	Stent Length (mm)	ICI Guidance	Adenosine Delivery / Dose	Position of Pressure Transducer	Pressure Wire Pullback	Mean/Median Final Post-PCI FFR	Post-PCI FFR ≥ 0.90	Post-PCI FFR ≤ 0.80
Uretsky et al 2020(52)	Stable CAD (59%) ACS-UA/NSTEMI (39%)	206 (230 vessels)	44.8%	DES (87%), BMS (5.2%), POBA (7.8%)	24.1±20	N/R	IV* or IC Bolus (100-200mcg)	"the distal artery" at a site with a diameter ≥ 2 mm	Y	0.86 (0.79 - 0.90)	21.3% (vessels) [23.5% (vessels) after optimisation]	36.5% (vessels) [30% (vessels) after further optimisation]
Ahn et al 2019(55)	Stable CAD (54.5%) UA (45.5%)	101	72.3%	N/R	28±14 [≤ 0.90 Group]; 27±12 [> 0.90 Group]	N/R	IV*	N/R	Y (22.8%)	0.86±0.05 [≤0.90 Group]; 0.95±0.03 [>0.90 Group]	54.5% (> 0.90) but vessels with serial stenoses or diffuse disease were excluded	N/R
Nishi et al 2019(24)	Stable CAD	572	62%	DES (87%)	26.2±11.6	N/R	IV*	"advanced to the distal two-thirds of the vessel"	N	0.87 (0.83 - 0.93)	N/R	11.4% (91% were LAD lesions)
Azzalini et al 2019(23)	Stable CAD (66%) ACS (23%)	65	75%	DES (86%), DEB (8%), BVS (6%)	37.9±25.4 [All]; 33.0±19.1 [< 0.90 Group]; 47.0±32.9 [≥ 0.90 Group]	IVUS or OCT in 6 patients (9%)	IV*	Navvus Microcatheter N/R	N/R	0.86±0.07	34%	N/R
Van Bommel et al 2019(50)	Stable CAD (45%) ACS-UA/NSTEMI (55%)	637 (794 lesions)	N/R	N/R	29±18	IVUS in 87/794 lesions (11%)	IV*	Navvus Microcatheter "approximately 20mm distal to the most distal stent edge"	Y	0.90±0.07	44% (patients); 50% (lesions)	11.5% (patients); 9.8% (lesions)

Hwang et al 2019(22)	Stable CAD & Non-Culprit ACS lesions (45.9%).	835	72.2%	DES	25.1 (18.2 - 32.1)	IVUS or OCT used in 479/835 (57.4%) of patients for stent optimisation	IV * (77.4%)	N/R	N	0.86 (0.82 - 0.91) [All]; 0.85 (0.81 - 0.89) [LAD]; 0.92 (0.85 - 0.96) [Non-LAD]		16.2%
Lee et al 2018(21)	Stable CAD	621	78.7%	DES	30.2±12.5	N/R	IV* (77.1%) or IC Bolus (0.5%)	"At the distal segment of a target vessel"	Y (Some post-PCI)	0.86 (0.82 - 0.90)	N/R	18.5%
Lee et al (2018)(48)	N/R	262 (291 lesions)	62.9%	N/R	N/R	OCT (100%)	N/R	N/R	N/R	0.89 (0.85 - 0.94)	48.1%	5.8%
Li et al 2017(19)	Stable CAD	1476	62.6%	DES	27±6.9	N/R	IV[y]	"10mm distal to the lesion or stent edge"	N/R	N/R	67.6% (> 0.88)	3.8%
Baranauskas et al 2016(41)	Stable CAD (71.6%) ACS (28.4%)	74	82.4%	DES	50.72±14.6	N/R	IV*	"sensor positioned at the beginning of the distal segment of the artery"	Y	0.88±0.06	28.4% (≥0.91)	10.8%
Ando et al 2016(39)	Stable CAD	190 (205 lesions)	72.7%	DES & BMS	N/R	N/R	IV[z]	"as distal in the artery as possible"	Y (only pre)	0.87±0.07	36.6% (lesions)	N/R
Agarwal et al (2016)(15)	Stable CAD & ACS (32%).	574 (664 lesions)	44.4%	DES (79%)	20.2±8.4	IVUS or OCT used in 13/137 lesions (9%) to assess a suboptimal initial post-PCI FFR	IV* or IC Bolus > 60mcg	"placed in the distal artery"	Y (some post-PCI)	0.89±0.06	34% (lesions >0.91) [43% (lesions >0.91) after further optimisation]	21% (lesions ≤0.81) [9% (lesions ≤0.81) after further optimisation]
Rai et al 2016(37)	Stable CAD	60	N/R	DES (71%) BMS (29%)	7.22	N/R	N/R	N/R	N/R	0.93±0.04	65% (≥ 0.92)	0

Kimura et al 2016(56)	Stable CAD (87.4%) & ACS	167	62.3%	DES	30.7±14.6	IVUS (100%)	IV* or IC Papaverine	"in the distal portions of the target vessel"	N/R	0.86±0.08 (LAD); 0.90±0.07 (RCA); 0.92±0.05 (LCx)	37.8% (≥ 0.91)	18.6% (87.1% were LAD lesions)
Doh et al 2015(14)	Stable CAD	107 (115 lesions)	75.7%	DES	30.7±14.5	IVUS (100%)	IV* or IC Bolus (40 mcg [RCA]; 80mcg [LAD])	N/R	N/R	0.92±0.04	75%	< 1%
Reith et al 2015(13)	Stable CAD	66	N/R	DES (95.5%)	15.27±5	OCT (100%)	IC Bolus 200mcg	"at least 20-30mm distal to the index lesion"	N/R	0.91±0.06	60.6% (>0.905)	3%
Murai et al 2015(36)	Stable CAD	98 (104 vessels)	55.8%	N/R	N/R	IVUS (100%)	IV[x]	"mean transducer distance from the guide tip was 9.7±2.0cm"	N/R	0.89±0.08	N/R	14.4% (vessels)
Ito et al 2014(12)	Stable CAD	97	55.7%	DES	20.2±9.4	IVUS (100%)	IV[jj]	N/R	Y	0.86±0.04 [MACE group]; 0.91±0.04 [No MACE group]	45.4%	N/R
Matsuo et al 2013(54)	Stable CAD	69	60.9%	DES (84%) BMS (16%)	42.2±23.03 [TLR]; 27.69±14.53 [No TLR]	IVUS (20%)	IC Papaverine 8mg (RCA); 12mg (LCA)	"as distal in the artery as possible"	Y	0.84±0.08 [TLR group]; 0.88±0.06 [No TLR]	39.1%	N/R
Kim et al 2012(33)	Stable CAD & Non-Culprit ACS Vessels	89	78.7%	DES	N/R	N/R	IV*	"distal to the most distal lesion"	Y	0.84±0.07	N/R	19.1%
Leesar et al 2011(58)	Stable CAD	66	36.4%	DES (57.6%) BMS (42.4%)	16±4.5 [≥0.96]; 16±5 [<0.96]	N/R	IC Bolus (42-54mcg)	"just to the distal and proximal edges of the stent"	Y	0.91±0.45 [<0.96 Group]; 0.97±0.41 [≥0.96 Group]	53% (≥ 0.96)	N/R

Nam et al 2011(53)	Stable CAD (31.25%) ACS (68.75%)	80	68.8%	DES	38±18 [≤0.90]; 28±13 [≥0.91]	N/R	IC Bolus 40mcg (RCA); 80-120mcg (LCA)	"> /= 10mm distal to stented segment"	No	0.86±0.04 [≤0.90 Group]; 0.94±0.03 [≥0.91 Group]	50% (≥ 0.91)	N/R
Samady et al 2009(11)	N/R	586	49% [≥ 0.90]; 64% [< 0.90]	BMS	17.5±7.5 [≥0.90]; 18.4±9.5 [<0.90]	N/R	IV[2] (31%) or IC Bolus (57%) ≥ 30mcg (RCA); ≥ 40mcg (LCA) or IC Papaverine (12%) 15mg (RCA); 20mg (LCA)	N/R	No	0.92±0.07 [All]; 0.95±0.05 [≥ 0.90 GROUP]; 0.84±07 [< 0.90 GROUP]	72%	N/R
Dupouy et al 2005(29)	Stable CAD & UA (60.2%)	98	N/R	BMS	16	N/R	IC Bolus 36mcg	N/R	No	0.97±0.05	73.5% (≥ 0.96)	N/R
Klauss et al 2005(10)	Stable CAD	119	39%	BMS	18±9	N/R	IC Bolus 30-150mcg	"> 30mm distal to stenosis"	No	0.94±0.06 [All]; 0.88±0.08 [MACE]; 0.95±0.05 [No MACE]	55% (≥ 0.95)	N/R
Stempfle et al 2005(59)	Stable CAD	30	37% (13/35 enrolled pts)	BMS	17±8	IVUS (100%)	IC Bolus 15-30mcg (RCA); 20-40mcg (LCA)	"< 10mm distal to the stenosis/stent implantation site to avoid the influence of diffuse atherosclerosis"	No	0.95±0.04	80% (≥ 0.94)	N/R

Pijls et al 2002(9)	N/R	750	52.2%	BMS	17.3±6.4	N/R	IV{ or IC Bolus ≥30mcg (RCA); ≥ 40mcg (LCA) or IC Papaverine 15mg (RCA); 20mg (LCA)	N/R	N/R	0.92±0.07 [All]; 0.88±0.07 [MACE]; 0.93±0.07 [NO MACE]	36% (≥ 0.96) 68% (≥ 0.91)	5.9%
Katritsis et al 2001(8)	Stable CAD	14	64.3%	BMS	N/R	IVUS (100%)	IV*	N/R	Y	0.94±0.02	85.7% (≥ 0.94) 100% (≥ 0.90)	0
Bech et al 1999(5)	Stable CAD	58	65.5%	POBA only	N/A	No	IV*	N/R	N/R	0.88±0.07	50%	N/R
Hanekamp et al 1999(6)	Stable CAD	30	33.3%	BMS	N/R	IVUS (100%)	IV*	N/R	Y	0.93±0.07	56.7% (≥ 0.94)	N/R

ACS=Acute Coronary Syndrome; BMS=Bare Metal Stent; BVS=Bioresorbable Vascular Scaffold; CAD=Coronary Artery Disease; DES=Drug-Eluting Stent; FFR=Fractional Flow Reserve; IC=Intracoronary Bolus; ICI=Intracoronary Imaging; IV=Intravenous Infusion; IVUS=Intravascular Ultrasound; LAD=Left Anterior Descending artery; LCx=Left Circumflex artery; MACE=Major Adverse Cardiovascular Events; NSTEMI=Non-ST-segment-Elevation Myocardial Infarction; N/R=Not Reported; OCT=Optical Coherence Tomography; POBA=Balloon Angioplasty only; RCA=Right Coronary Artery; TLR=Target Lesion Revascularisation; UA=Unstable Angina

***= Intravenous infusion of adenosine at a rate of 140mcg/kg/min**

y= Intravenous infusion of either adenosine or ATP at a rate of 140-180mcg/kg/min

z= Intravenous infusion of ATP at a rate of 150mcg/kg/min

x= Intravenous infusion of ATP at a rate of 160mcg/kg/min

jj= Intravenous infusion of ATP at a rate of 180mcg/kg/min

{= Intravenous infusion of either adenosine or ATP at a rate of 140mcg/kg/min

1.5 Non-Hyperaemic Pressure Ratios (NHPRs) post-PCI

Non-hyperaemic pressure ratios, such as the Instantaneous wave-Free Ratio (iFR), have potential to be used as objective measures of improvement in coronary haemodynamics following PCI.(34) The DEFINE PCI study, which employed blinded post-PCI iFR assessments, reported residual ischemia (defined as an iFR < 0.90) in nearly 1 in 4 patients despite angiographically-successful stenting results. The authors concluded that the majority of these cases (81.6%) were due to inapparent focal lesions potentially amenable to treatment with additional PCI.(60) The original NHPR, the ratio of distal coronary to aortic pressure (Pd/Pa) is routinely available with all diagnostic guidewires. A retrospective analysis reported that a post-PCI Pd/Pa value ≤ 0.96 was an independent predictor of MACE at a median follow-up time of 30 months.(61)

Two additional resting physiology indices were subsequently developed which have diagnostic equivalence to iFR: the Diastolic Pressure Ratio (dPR) and the Resting Full-cycle Ratio (RFR)(62, 63). While an NHPR-guided PCI optimisation strategy might be more appealing to clinicians as it could facilitate multiple physiological assessments without the need to repeatedly induce hyperaemia, data on the prognostic value of post-PCI NHPR values are currently lacking and warrants further study.

1.6 Predictors of a suboptimal post-PCI FFR

Several clinical and procedural characteristics have been implicated as contributing factors to a sub-optimal post-PCI FFR result. Amongst 586 patients receiving BMS, Samady et al reported that patients with a stent diameter ≥ 3 mm and baseline FFR > 0.70 had a significant (77%) likelihood of achieving post-PCI FFR > 0.90.(11) The inference being that those with smaller stent diameters and lower baseline FFRs were more likely to have a sub-optimal post-PCI FFR. In 2009 Nam et al reported on a study of 80 patients undergoing PCI with DES in whom a target lesion within the left anterior descending artery (LAD) was the only significant predictor of post-PCI FFR ≤ 0.90.(53) Kimura et al reported that, in 167 patients undergoing PCI, an LAD lesion and lower baseline FFR value were significant predictors of not just a suboptimal result, but of a post-PCI FFR that remained ≤ 0.80.(56) Similar factors were identified in a cohort of 205 lesions by

Ando et al, concluding that lesions with an optimal post-PCI FFR were less frequently located in the LAD, had higher pre-PCI FFR values and a higher frequency of the “abrupt pressure drop pattern” on hyperaemic pressure wire pullback.(39)

Baranauskas et al reported that post-PCI FFR may be suboptimal in patients treated with long (≥ 30 mm) second- or newer-generation DES, and is particularly poor when the total stent length exceeds 50 mm. Among 74 patients, only 21 (28.4%) achieved a final post-PCI FFR > 0.90 (of which only 2 had a total stent length > 50mm). Of note, the majority of the 74 cases (82.4%) involved diffuse disease in the LAD which may have been an additional contributor to the suboptimal FFR results.(41) With the benefit of greater patient numbers, Agarwal et al identified univariate associations of clinical factors with an initial post-PCI FFR ≤ 0.80. In 664 lesions amongst 574 patients, they found that younger age, absence of regular oral nitrate use, inducing hyperaemia with IV rather than IC adenosine, diffuse disease (defined as diseased segment > 20 mm and diffuse downstream disease), coronary artery bypass graft, LAD disease, pre-PCI FFR (as a continuous variable), and stent length (sum of all stents deployed) were associated with an ischaemic FFR immediately post-PCI. A “persistently ischemic FFR”, defined as a final FFR ≤ 0.80 after further optimisation of the PCI, was reported in 63 (9.5%) arteries in this cohort. Multivariate analysis identified only age, presence of diffuse disease, LAD PCI, use of IV adenosine for inducing hyperaemia and pre-PCI FFR as significant associations with a final FFR ≤ 0.80.(44)

In 2017, Li et al reported the largest post-PCI FFR registry to date, consisting of data from 1,476 patients, and identified LAD lesions, longer stent length, and smaller stent diameter as 3 independent predictors of post-PCI FFR ≤ 0.88.(19) In an analysis of 639 patients from the FAME 1and FAME 2 trials, Piroth et al found that male sex, presence of diabetes mellitus and LAD lesion location were the only significant predictors of a lower post-PCI FFR value.(20)

Regarding sex differences in post-PCI FFR, an analysis of the prospective FFR SEARCH registry of 1165 lesions in 959 patients (695 men and 264 women) found that though there was no significant difference in absolute post-PCI FFR values

between sexes, a value ≤ 0.85 was more frequently observed in men than in women (24.9% vs. 15.2%, p=0.001).(64)

A target lesion within the LAD appears to be a consistent and robust predictor of a sub-optimal post-PCI FFR result. Li et al support the intuitive concept that this relates to the large territory of myocardium perfused by this artery, resulting in an impaired FFR for any residual stenosis in the vessel. Their analysis identified that, while a post-PCI FFR ≤ 0.88 predicted higher incidence of target vessel failure through 3-year clinical follow-up, when the lesion was located in the LAD a post-PCI FFR ≤ 0.905 was associated with clinical events.(19) Hwang et al suggested that different cut-off values of post-PCI FFR may need be applied according to target vessel. In their study of 835 patients, the distribution pattern of post-PCI FFR values was different between the LAD and non-LAD, and optimal cut-off values for predicting target vessel failure at 2 years were 0.82 and 0.88 in the LAD and non-LAD respectively.(22) Clinical predictors of suboptimal functional results from PCI are summarized in Table 1-3.

Table 1-3 - Predictors of suboptimal post-PCI FFR results

Predictor	Comment
LAD Lesion(19-21, 39, 44, 48, 52, 53, 56, 65, 66)	Post-PCI FFR is more likely to be suboptimal when the lesion is located in the LAD
Lower pre-PCI FFR(11, 39, 44, 52, 55, 56, 65, 66)	Pre-PCI FFR value ≤ 0.70 predicted post-PCI FFR < 0.90(11, 39)
Stent Length(19, 41, 44)	Long (30-49mm) & Ultra-long (> 50mm) stented segments in patients with diffuse CAD(41)
Stent Diameter(11, 19, 52)	Smaller stent diameter associated with post-PCI FFR ≤ 0.80(52)
Hyperaemic Trans-Stent Gradient (HTG)(52)	HTG > 0.04 predictive of post-PCI FFR ≤ 0.80
Higher Number of Stents(20)	Predictive of post-PCI FFR < 0.88
Presence of Diffuse Disease	Diffuse disease defined as: Diseased segment > 20mm with diffuse downstream disease(44); Angiographic stenosis > 30% DS and > 20mm in length(48); "Gradual FFR increase during pullback"(52)
IV Adenosine(44)	Use of IV adenosine (as opposed to IC adenosine) was predictive of post-PCI FFR ≤ 0.80
Male Sex(20)	Predictive of post-PCI FFR < 0.88
Diabetes(20)	Predictive of post-PCI FFR < 0.88
Previous PCI(52)	Predictive of post-PCI FFR ≤ 0.80
Lower pre-PCI IMR(65, 66)	
Age(55, 66)	Older age predictive of post-PCI FFR ≤ 0.90(55)
Lesion Diameter Stenosis(52, 66)	Lower % diameter stenosis predictive of post-PCI FFR ≤ 0.80(52)
Pre-PCI Syntax Score(21)	Higher pre-PCI syntax score was an independent predictor of post-PCI FFR < 0.84

CAD=Coronary Artery Disease; DS=Diameter Stenosis; FFR=Fractional Flow Reserve; IC=Intracoronary; IMR=Index of Microcirculatory Resistance; IV-Intravenous; LAD=Left Anterior Descending artery; PCI=Percutaneous Coronary Intervention

1.7 Mechanisms of suboptimal post-PCI FFR and the utility of the pressure wire pullback

A frequently identified limitation in the existing literature on post-PCI FFR is that pressure-wire pullbacks were not performed. A common factor is the use of intracoronary adenosine which, compared with a continuous intravenous infusion, cannot sustain maximal hyperaemia long enough to perform a detailed pullback recording. An assumption is often made that a suboptimal post-PCI FFR is the result of residual diffuse disease in the distal vessel, but this is not always the sole culprit and a detailed pressure wire pullback during hyperaemia is instrumental in delineating other potentially remediable factors.

Four principle mechanisms of a low FFR after PCI have been proposed by Tonino and Johnson.(67) The first occurs in the case of tandem or serial lesions in an artery whereby, after treating the more severe of 2 lesions, the improved coronary flow results in an increase in the pressure gradient across the remaining lesion. It has been suggested that post-PCI FFR in these cases should be mandatory as treating these unmasked lesions offers the largest further gains in FFR. The second, and assumed most common mechanism, is diffuse residual disease. If a pre-PCI pressure wire pullback curve does not contain a large, focal pressure gradient across the target lesion, it is likely that the residual gradient post-PCI reflects diffuse atherosclerosis. Third, the technical artefact of negative drift on the pressure wire of ≥ 0.03 units occurs in approximately 10% of cases which can render a spuriously low FFR result. It is recommended that every FFR measurement should be completed by returning the pressure sensor to the guide catheter to exclude significant pressure drift. Finally, as outlined above, suboptimal stent deployment can generate a residual gradient. This may be the result of a malapposed or under-expanded stent, partial geographic miss of the culprit lesion, inadequate lesion coverage (from and to un-diseased segments), an angiographically inapparent edge dissection or any combination of these factors.

Despite hyperaemic pullbacks being described in several studies, only a handful have reported which mechanisms contributing to suboptimal post-PCI FFR were identified. After pre-dilation but before stenting, Hanekamp et al identified “unexpected coronary disease” in 10% of their 30 patients. They employed

hyperaemic pullback measurements (in addition to IVUS) across the stented segment to inform the need for further sequential post-dilation of the stent.(6)

In a study of 98 patients who received a BMS to a single coronary artery lesion, Jensen et al reported that post-PCI hyperaemic pullback identified 58 patients (59%) with a diffuse pressure gradient distal to the stent (and consequently lower mean FFR than the group with no distal gradient 0.88±0.12 vs. 0.97±0.05).(68) Using IC adenosine boluses in their study of patients receiving a mixture of DES and BMS, Leesar et al performed a very focused pullback across the stented segment only and identified a hyperaemic trans-stent gradient (HTG) in 5 of the 34 patients (14.7%) who had an initial post-PCI FFR < 0.96.(58) Ito et al reported on a cohort of 97 patients who underwent optimal DES deployment as determined by IVUS and FFR guidance and concluded that the mechanism of a suboptimal post-PCI FFR in the 53 (54.6%) of their patients with a final FFR ≤ 0.90 was diffuse residual plaque as documented by IVUS.(12)

The ILUMIEN 1 trial suggested that with the guidance of intracoronary imaging, post-PCI FFR gains of approximately 0.05 might be obtained through further stent optimisation (both in-stent post-dilation and additional stent implantation).(35) Tanaka et al performed IVUS and hyperaemic pressure wire pullback in 60 arteries post-PCI and identified a HTG of ≥ 0.05 in 11 (18.3%) of cases. Of these, 4 were caused by insufficient stent expansion (incomplete apposition and asymmetric dilation) and 5 were due to issues with the stent edge (dissection and/or incomplete coverage of coronary plaques). Ten arteries (16.6%) had an initial post-PCI FFR < 0.80 and of these, the main residual pressure gradient occurred within the stented segment in 5 lesions (50%), and outside the stented segment in the other 5 lesions.(45) Lee et al performed post-PCI FFR pullbacks in 291 arteries and reported that 31% (19% proximal, 12% distal to implanted stent) had residual focal lesions, defined as an abrupt pressure step-up ≥ 0.05, that could potentially have been corrected by additional PCI.(48) Wolfrum et al undertook OCT assessment of 21 arteries with suboptimal post-PCI FFR (< 0.90). Thirteen arteries (62%) were reported to have a suboptimal stent result based on protocol-defined OCT criteria: stent malapposition was observed in 7, stent under-expansion in 6, incomplete lesion coverage in 5, distal stent edge dissection in 2 and tissue protrusion in 1. The remaining 8 arteries (38%) with FFR < 0.90 had angiographic/OCT evidence of diffuse distal disease with no

significant pressure step-up during pressure wire pullback and did not fulfil the criteria for a sub-optimal stent result.(69) Van Zandvoort et al assessed 100 arteries with post-PCI FFR ≤ 0.85 (mean 0.79 ± 0.05) using high-definition IVUS. They identified significant untreated focal proximal lesions in 29% and focal distal lesions in 30%. Stent under-expansion was identified in 74% while malapposition defined by the MUSIC criteria was identified in 23%.(70)

1.8 Can the use of intravascular imaging improve the final post-PCI FFR value?

Though there are numerous reports of the correlation between sub-optimal post-PCI FFR and sub-optimal stent deployment by intravascular imaging criteria(6-8, 13, 45, 59, 69, 70), no study to date has directly compared the impact of IVUS- versus angiography-guided PCI on the post-PCI FFR result. Observational data from a number of non-randomised Japanese studies in which IVUS was routinely used before and after PCI have reported final post-PCI FFR values within the same range reported from cohorts where no adjunctive intracoronary imaging techniques were employed.(12, 14, 32, 36, 38, 43, 45, 47, 56)

In the prospective, non-randomised ILUMIEN 1 study which assessed the impact of OCT during PCI on physician decision-making in 467 lesions (84% of which had post-PCI FFR performed), no significant difference was found in the final post-PCI FFR between optimisation groups regardless of whether the OCT findings were acted upon by the operator or not.(35) Conversely, the DOCTORS study randomised 240 patients with NSTEMI to either OCT- or angiography-guided PCI and found that higher post-PCI FFR values were obtained in the OCT arm (0.94 ± 0.04 vs. 0.92 ± 0.05, p=0.005).(42) A prospective study of 35 patients reported that implementation of an OCT-guided PCI optimisation protocol may reveal potentially treatable causes, allowing optimisation of the post-PCI functional result.(69)

1.9 How often can the initial post-PCI FFR be further optimised?

One of the reasons clinicians do not routinely perform post PCI FFR is that there are currently limited data available to determine how often it is possible to improve an angiographically acceptable but physiologically sub-optimal result. Leesar et al increased the proportion of their patients achieving a final FFR ≥ 0.96 from 48% to 53% by performing additional high-pressure post-dilation of the stented segment. A non-compliant balloon with an inflated diameter 0.5 mm greater than stent diameter was deployed in the 5 patients with FFR < 0.96 who were found to have a hyperaemic trans-stent gradient (HTG). While only a modest increase (3 of the 5 patients had their final FFR increased to > 0.96), as noted previously, this study utilised intra-coronary adenosine and only assessed for HTG so the authors were not in a position to identify (and therefore treat) additional unmasked lesions beyond the focused pullback assessment of the stented segment.(58)

In the largest assessment to date of the capacity for further optimisation of the post-PCI FFR result, Agarwal et al reported that 137 of the 664 lesions (20.6%) in their patient cohort underwent additional intervention based on a suboptimal initial post-PCI FFR result. Overall, 58 (42%) of the lesions received further post-dilation of the implanted stent with a bigger balloon size (median balloon to stent diameter difference: +0.25 mm [IQR: 0.25–0.5 mm]) and higher pressure and duration of inflation (median: 19 atm [IQR: 15–23 atm]; +23 seconds [IQR: 15–34]). These subsequent interventions led to an improvement in FFR in this subgroup from an initial mean value of 0.78 ± 0.07 to 0.87 ± 0.05. Overall, sub-optimal initial post-PCI FFR prompting subsequent intervention led to an increase in lesions with final FFR > 0.91 from 34% to 43% (≥ 0.86 from 60% to 74%) and decreased persistently ischemic lesions (≤ 0.81) from 21% to 9%.(15) In a cohort of 13 patients who fulfilled both functional and OCT-defined criteria for suboptimal stent results, Wolfrum et al increased the mean post-PCI FFR from 0.80 ± 0.02 to 0.88 ± 0.01 through a combination of additional stent post-dilation (46%), additional stenting (39%) or a combination of both strategies (15%). Larger increases in FFR were observed in the 7 patients who received additional stents.(69) Most recently, Uretsky et al reported on a prospective registry of 206 patients in which 36.5% of arteries had an initial post-PCI FFR ≤ 0.80. Additional

PCI optimisation measures, guided by post-PCI FFR pullback recordings, were attempted in just over one-third of these arteries (12.6% of the entire study cohort), and successfully reduced the overall proportion of patients with a final post-PCI FFR ≤ 0.80 from 36.5% to 30%. The improvement in the proportion of arteries with a final FFR > 0.90 as a result of these optimisation efforts was more modest, only increasing from 21.3% to 23.5%.(52)

1.10 Post-PCI Coronary Flow Reserve (CFR) and Index of Microcirculatory Resistance (IMR)

In 2002, Nishida et al published a retrospective analysis of 448 participants receiving bare metal stents in the DESTINI study and concluded that a final coronary flow velocity reserve of < 2.0 after stent implantation was an independent predictor of the need for target lesion revascularisation at 12 months.(71) Overall, 126 patients (28% of this cohort) had a final CFR < 2.0 post-PCI as measured by a Doppler-tipped guidewire. Conversely, in a subsequent study of 220 patients with stable CAD (92% receiving DES) in whom significant peri-procedural myocardial infarctions were excluded, Matsuda et al found that low pre-PCI CFR, not post-PCI physiological indices, was an independent predictor of adverse events at a median follow-up time of 2 years. The authors reported that FFR increased in all arteries post-PCI, but CFR increased in only 158 (71.8%) and actually decreased in 62 (28.2%). A post-PCI CFR increase was associated with low pre-PCI FFR, low pre-PCI CFR, high pre-PCI IMR and increased post-PCI hyperaemic coronary flow. Discordant change (where FFR increased but CFR decreased) was associated with higher pre-PCI CFR, lower pre-PCI IMR and no significant post-PCI hyperaemic coronary flow increase (as measured by mean hyperaemic transit time using the bolus thermodilution method).(40) Usui et al reported that FFR/CFR concordance or discordance influenced coronary physiological indices after elective PCI for lesions with an ischaemic FFR. Compared with territories showing an ischaemic FFR (≤ 0.80) and preserved CFR (≥ 2.0), FFR/CFR concordantly abnormal territories showed a favourable impact on shortening of hyperaemic mean transit time and CFR improvement after elective PCI. The authors found that lower pre-PCI CFR (≤ 2.26) was an independent predictor of MACE at a median follow-up of 26.5 months, whereas neither pre- nor post-PCI FFR was predictive in their cohort.(46)

IMR values after successful PCI are widely distributed, with increased microcirculatory resistance frequently noted. Murai et al postulated that microvascular dysfunction (represented by raised IMR) may lead to an increased (overestimated) FFR value, possibly due to a reduction of coronary flow after successful elective stenting.(36) In a subsequent publication reporting on 71 patients who underwent PCI for stable angina, the same authors demonstrated that high pre-PCI IMR values could decrease after stenting, and that this decrease was significantly associated with increased coronary flow after PCI (as defined by decreased mean hyperaemic transit time). The authors proposed that using a pre-PCI IMR threshold value (IMR > 16.8 in their study) to predict the increase or decrease in the IMR after PCI may help to indicate which arteries stand to benefit from an increase in coronary flow following PCI.(38) This initial report was later followed by a larger Receiver Operating Characteristic (ROC) curve analysis of 182 arteries in 174 patients undergoing PCI for stable CAD (in whom periprocedural MIs were again excluded) which suggested that the optimal pre-PCI IMR and pre-PCI FFR cut-off values to predict an increase in hyperaemic coronary flow post-PCI were > 12.7 and < 0.73 respectively.(43)

Combined FFR and IMR assessment may be of particular help in identifying which patients within the FFR grey zone are most likely to benefit from PCI. Niida et al investigated the differences in coronary flow improvement between territories with low-FFR (< 0.75) and grey-zone FFR (0.75–0.80) by comparing serial changes in physiological indices including mean hyperaemic transit time, CFR and IMR between these two groups. Compared to low-FFR territories, grey-zone FFR territories showed significantly lower prevalence of transit time shortening, CFR improvement, and decrease in IMR. Worsening of physiological indices after PCI was not uncommon in grey-zone FFR territories. Multivariate analysis showed that pre-PCI IMR predicted improved coronary flow profile in both groups (> 16.3 [grey-zone], > 16.8 [low FFR]), whereas pre-PCI FFR ≤ 0.64 predicted increased coronary flow indices in low-FFR territories.(49) Table 4 summarises the studies which have evaluated the prognostic value of post-PCI IMR.

Table 1-4 - Clinical studies evaluating the prognostic value of post-PCI IMR

Study	Population	Post-PCI IMR Cut-off	Outcomes	Follow-up Duration	Comment
Nishi, 2019(24)	572 patients with stable CAD	≥ 25	Cumulative MACE rate was significantly higher in the high IMR group (n=66/148) compared with the low IMR group (n=128/424; HR, 1.56; 95% CI, 1.16–2.105; P=0.001). High IMR post-PCI was an independent predictor of MACE.	4 (1.6–5.6) years	MACE: All-cause mortality, any MI, target vessel revascularisation.
Murai, 2018(47)	83 patients undergoing PCI in NSTE-ACS culprit vessels within 48 hours of admission	> 15.4	Post-PCI IMR was the only independent predictor of MACE (Hazard ratio 1.033, 95% confidence interval 1.013–1.052, P=0.001). MACE-free survival was significantly worse in patients with high post-PCI IMR (x^2 7.12; P=0.008).	20.7 (10.8–47.2) months	MACE: Death, MI, clinically-driven target or non-target revascularisation and congestive heart failure requiring hospitalization

CAD=Coronary Artery Disease; HR=Hazard Ratio; IMR=Index of Microcirculatory Resistance; MACE=Major Adverse Cardiac Events; MI=Myocardial Infarction; NSTE-ACS= Non-ST-segment-Elevation Acute Coronary Syndrome; PCI=Percutaneous Coronary Intervention

1.11 Post-PCI coronary physiology in Acute Coronary Syndromes

Tamita et al performed a small, prospective study of post-PCI IVUS and FFR measurements in 48 patients (33 undergoing primary PCI for STEMI within 12 hours of onset and 15 undergoing elective PCI for stable CAD). Post-PCI FFR was significantly higher in STEMI patients than stable angina patients (0.95 ± 0.04 vs. 0.90 ± 0.04; P=0.002) although there were no significant differences in IVUS parameters between the groups. FFR was also shown to be higher in patients with TIMI 2 flow grade than in those with TIMI 3 (i.e., higher FFR where slower flow was evident on angiography). The authors concluded that in patients with STEMI, the marked microvascular dysfunction renders FFR unreliable for post-PCI assessment.(28) The concept that the presence of microvascular dysfunction could limit the degree of maximal hyperaemia (thereby potentially overestimating FFR) has sparked much debate about the utility (and reliability) of FFR in identifying functionally significant lesions in acute coronary syndrome (ACS) culprit arteries. Are all ACS subtypes equally affected by microvascular dysfunction though? A study by Layland et al comparing pre-PCI coronary physiology (FFR, CFR, IMR) in 140 patients with STEMI, NSTEMI and stable angina concluded that the vasodilatory capacity of the coronary microcirculation (as measured by the Resistive Reserve Ratio) is preserved in selected patients with NSTEMI and that baseline levels of microvascular injury were similar in both stable angina and NSTEMI groups.(72) Can this finding then also be extrapolated to post-PCI FFR in the setting of non-ST segment elevation acute coronary syndromes (NSTE-ACS)?

Kasula et al retrospectively compared the pre- and post-PCI FFR values of 202 lesions in 189 ACS patients (35% NSTEMI, 65% Unstable Angina) with 411 lesions in 390 stable ischemic heart disease (SIHD) patients and found that though mean pre-PCI FFR was lower in the ACS cohort (0.62 vs. 0.65) there was no significant difference in the final post-PCI FFR values between the groups.(17) Final post-PCI FFR was identified as an independent predictor of MACE among patients with ACS and a final FFR cut-off of ≤ 0.91 was identified as having the best predictive accuracy for MACE in this cohort. Patients with ACS who achieved final post-PCI

FFR > 0.91 had similar outcomes at 2.4 ± 1.5 years compared with patients with SIHD.

Conversely, in another sub-analysis from the FFR SEARCH registry of 959 patients (285 with stable angina, 352 NSTEMI and 322 STEMI), van Bommel et al reported small but significant differences in mean post-PCI between these groups (0.93 ± 0.06 [STEMI]; 0.90 ± 0.06 [NSTEMI]; 0.89 ± 007 [SA] but there was no significant difference in MACE at 30 days.(73)

Murai et al measured coronary physiology indices post-PCI in the culprit arteries of 83 patients with NSTE-ACS (NSTEMI and Unstable Angina) who underwent stenting within the first 48 hours of their index hospital admission.(47) After a median follow-up period of 20.7 months, the patients with MACE had higher post-PCI IMR and lower post-PCI CFR than those without MACE (IMR: 27.2 vs. 16.3; P=0.001, CFR: 1.82 vs. 2.55; P=0.04), whereas post-PCI FFR was not significantly different, regardless of the occurrence of MACE. Although CFR as a continuous variable was not a significant predictor for prognosis on the univariate analysis, it remained as a weak but significant predictor when considered as a dichotomous variable with a cut-off value of 2.0 post-PCI.

1.12 Limitations of the current evidence base

Much of the current evidence on post-PCI FFR derives from retrospective, observational data. The lack of randomisation or control groups allows for potential selection bias. FFR is predominantly performed to assess intermediate coronary lesions and it could be speculated that post-PCI FFR measurements, where available, were preferentially performed in cases with a good angiographic result following PCI. As such, this cohort may not be representative of a real-world population where severe or diffuse CAD is more prevalent.

Many of the earlier studies assessing post-PCI FFR used relatively small bolus doses of intracoronary adenosine to induce hyperaemia and some authors subsequently acknowledged that this method may not have achieved maximal hyperaemia, thereby potentially overestimating the final FFR results. This is a confounding factor that higher IC bolus doses or use of an IV adenosine infusion might have overcome. A further limitation of the frequent use of IC adenosine

boluses in these studies is the inability to perform detailed hyperaemic pressure wire pullback assessments of the target arteries due to the relatively short period of stable maximal hyperaemia. As a result, the potential causes of suboptimal post-PCI FFR results (suboptimal stent deployment, unmasking of additional lesions, diffuse disease etc.) could not be categorised and quantified in these studies. It is frequently unclear (or unreported) as to whether patients with suboptimal initial post-PCI FFR underwent further optimisation, what this entailed and in what proportion of patients these efforts achieved an improvement in the final FFR result.

1.13 Rationale for the TARGET-FFR clinical trial

Post-PCI FFR is associated with clinical outcomes—the higher the post-PCI FFR result, the greater the freedom from vessel-related adverse events. While suggested thresholds for an optimal result vary, the largest metanalysis to date identified that a post-PCI value of ≥ 0.90 was associated with significantly lower risk of repeat revascularisation and MACE. As many as two in three patients may fall below this target, however, and post-PCI physiology assessment is likely to identify a significant proportion who would benefit from further optimisation measures. This has even greater relevance for the estimated 20% of patients whose FFR remains below the clinical revascularisation threshold (FFR ≤ 0.80) following PCI despite angiographically satisfactory results. Additional assessment of CFR and IMR after stenting can identify patients with significant microvascular dysfunction who may be at greater risk of adverse events. Nevertheless, post-PCI coronary physiology assessments are rarely performed in clinical practice. Potential barriers may be the assumptions that: 1) the incidence of suboptimal FFR results post-PCI is low; 2) where this occurs, it is primarily related to residual diffuse disease in the vessel and, accordingly, 3) there is limited scope to improve the FFR result through further intervention.

Registry data indicate it is possible to improve on many suboptimal initial post-PCI FFR results and these efforts are likely best informed by performing systematic pressure wire pullback assessments in the target vessel. Given the association with long-term clinical outcomes, there was a clear need for randomised controlled trials to identify the extent and impact of physiologically

suboptimal results post-PCI in clinical practice, systematically categorise the remediable mechanisms for this and establish which PCI optimisation strategies can successfully increase the proportion of patients with functionally optimal revascularisation results. With these aims in mind, the Trial of Angiography versus pressure-Ratio-Guided Enhancement Techniques - Fractional Flow Reserve (TARGET-FFR) was designed to assess the efficacy of a post-PCI Physiology-guided Incremental Optimisation Strategy (PIOS) versus standard angiographic guidance in achieving final post-PCI FFR values ≥ 0.90.

Chapter 2 Methods

2.1 Study design & organisation

TARGET-FFR was a prospective, single-centre, randomised, controlled, parallel group, blinded, clinical trial conducted at the Golden Jubilee National Hospital in Glasgow, United Kingdom. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guideline and the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013). The West of Scotland Research Ethics Committee 3 gave a favourable opinion on 18/08/2017 (reference 17/WS/0153). TARGET-FFR was an investigator-initiated trial supported by endowment funds at the Golden Jubilee National Hospital (NHS National Waiting Times Centre Board). The trial was sponsored and monitored by the NHS National Waiting Times Centre. Coronary physiology data were adjudicated and validated by a core laboratory (CoreAalst BV, Aalst, Belgium) blinded to treatment group assignment. Clinical endpoints were adjudicated by an independent Clinical Events Committee. The study is registered on ClinicalTrials.gov (Identifier: NCT03259815).

2.2 Hypothesis & power calculation

There were no prior randomised clinical trials of post-PCI FFR optimisation strategies. In a registry of 664 vessels from 574 patients, 20.6% (137/664) underwent additional intervention based on either a post-PCI FFR ≤ 0.80 or an otherwise “unsatisfactory” value as determined by the operator (87/137 (63.5%) had post-PCI FFR ≤ 0.80). Prior to these additional optimisation measures, the mean initial post-PCI FFR value was 0.87 ± 0.08. Optimisation increased the final overall proportion of patients with FFR > 0.91 by 9%.(15) We hypothesised that a systematic approach to measuring FFR post-PCI to detect the subgroup of patients with an FFR < 0.90 and facilitate additional intervention with a Physiology-guided Optimisation Strategy (PIOS), could increase the proportion of patients with a final FFR ≥ 0.90 by 20%. We believed a change of this magnitude would be clinically relevant. On this basis, a sample size of 130 patients per group was required to have 90% power to detect a 20% difference between

groups at the 5% significance level. Patients with stable angina or NSTEMI attending the Golden Jubilee National Hospital for diagnostic coronary angiography proceed to PCI during the same procedure in approximately 40% of cases. Therefore, it was estimated that approximately 650 patients would need to be enrolled in the study in order to randomise 260 following standard-of-care PCI.

2.3 Study participants

Patients eligible for the trial were over 18 years of age and undergoing PCI for either stable angina, medically-stabilised non-ST-segment elevation myocardial infarction (NSTEMI), or staged completion of non-culprit vessel revascularisation following either NSTEMI or ST-segment elevation myocardial infarction (STEMI). Since the primary objective was focused on PCI optimisation, the target population was unrestricted and patients with either stable or acute coronary syndromes were included. Table 2-1 contains a full list of the study's inclusion and exclusion criteria. Patients were invited to participate prior to undergoing coronary angiography and were enrolled only after providing written informed consent.

2.4 Randomisation and masking

Randomisation and electronic Case Report Form (eCRF) services were provided through a secure (ISO 27001 & 9001 compliant) web-based platform which is compliant with GCP regulations, Annex 11 and 21 CFR Part 11 (Castor EDC, Amsterdam, Netherlands). Patients proceeding to PCI had an invasive coronary physiology assessment prior to intervention. Once the operator declared the PCI procedure to be complete, patients meeting all inclusion and exclusion criteria were eligible for randomisation. This was performed in the catheterisation laboratory using a 1:1 variable block (2, 4, 6) randomisation method generated from within the study's eCRF platform. The timing of the randomisation before post-PCI FFR measurement was intended to limit bias and prevent selection of patients for randomisation when FFR was already known. An operator-blinded, post-PCI, invasive coronary physiology assessment was then performed. The coronary physiology data were obscured and the digital interface was visible only

to the researcher who advised on measurement quality. This concluded the procedure for all patients in the control group and those in the PIOS intervention group with FFR ≥ 0.90. In patients randomised to the PIOS group with post-PCI FFR < 0.90, operators reviewed the measurements and planned additional intervention based on the findings of the FFR pullback assessment. Following these additional optimisation measures, physiology assessment was repeated and the procedure was completed. Final coronary physiology results were not disclosed to patients.

Table 2-1 – Study Inclusion / Exclusion Criteria

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 (e.g., 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

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ISR=In-Stent Restenosis; LVEF=Left Ventricular Ejection Fraction; NSTEMI=Non-ST segment Myocardial Infarction; PCI=Percutaneous Coronary Intervention; STEMI=ST-segment Elevation Myocardial Infarction

2.5 Study procedures

2.5.1 Percutaneous coronary intervention

In line with contemporary standards of care, treatment decisions during percutaneous coronary intervention (including the use of adjunctive intracoronary imaging) and the definition of an angiographically acceptable PCI result were left entirely at the interventional cardiologist's discretion. All procedures were performed using drug-eluting stents.

2.5.2 Coronary physiology measurements

Coronary physiology measurements were acquired using the PressureWire X Guidewire (Abbott Laboratories, Illinois, U.S.A.) and analysed in real-time using dedicated software (CoroFlow v3.0, Coroventis Research AB, Uppsala, Sweden). Following administration of a 200 mcg bolus of intracoronary nitrate to the study artery, the pressure wire sensor was positioned at the tip of the guide catheter and equalised with the aortic pressure. The pressure wire was then advanced into the study artery until the sensor (located 30mm proximal to the wire tip) was positioned as far distally as practical, but always within the distal third of the vessel. Effectively, operators were encouraged to match the position a standard angioplasty wire would usually occupy in the artery to allow for a more accurate approximation of the myocardial FFR value which can be overestimated with more proximal sensor positions.

The following non-hyperaemic (resting) pressure ratios measured: Pd/Pa - the ratio of resting distal coronary pressure (Pd) to aortic pressure (Pa) over a full cardiac cycle, averaged over three consecutive beats; diastolic pressure ratio (dPR) - the Pd/Pa ratio of the averaged Pa and Pd values measured during the entire diastolic period of 5 consecutive cardiac cycles; resting full-cycle ratio (RFR) - the lowest Pd/Pa ratio over an entire cardiac cycle averaged over 5 consecutive cycles. An analogue of the instantaneous wave-Free Ratio (iwFR/iFR) was also retrospectively derived using standard mathematical methods (CoroLab, Coroventis Research AB, Uppsala, Sweden). This simulated iFR (iFR_{sim}) was calculated from the average Pd/Pa from 20% into diastole until 30 milliseconds before the end of diastole over five consecutive heartbeats.

Similar formulae for diastolic indices have previously been shown to be numerically identical to iFR with correlation and AUC values ≥ 0.99.(62) Clinical revascularisation and proposed optimal thresholds for the individual NHPRs were selected based on previously published data.(61-63, 74, 75)

After resting measurements were obtained, coronary hyperaemia was induced by infusion of adenosine into an antecubital vein at a rate of 140 mcg/kg/min. Fractional Flow Reserve (FFR), the mean distal coronary artery pressure divided by mean aortic pressure during maximal hyperaemia, was then recorded.

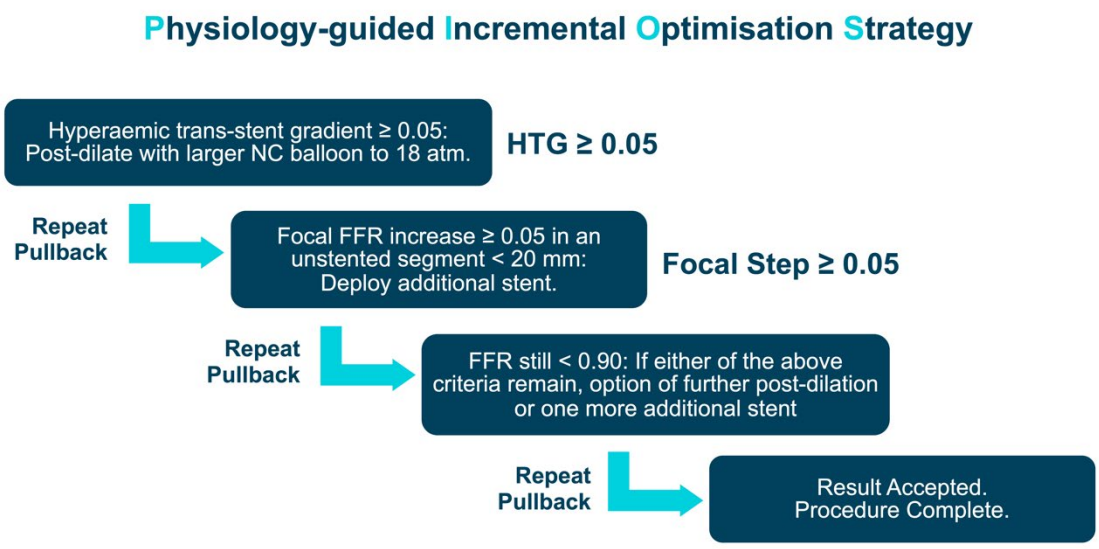
Microvascular function was simultaneously assessed during the hyperaemic phase. Using a thermodilution technique, coronary flow reserve (CFR - the ratio of resting to hyperaemic coronary flow) and the index of microcirculatory resistance (IMR - the product of mean hyperaemic distal coronary pressure and mean hyperaemic transit time) were calculated as previously described.(76-79)

Finally, a hyperaemic pressure wire pullback assessment was performed and the sensor returned to the tip of the guide catheter to assess for pressure drift. If there was drift of > 0.03 units, repeat measurements were requested. Using the CoroFlow software, the research cardiologist annotated the hyperaemic pullback recording to co-register the anatomical landmarks during fluoroscopy-guided pullback of the pressure wire (distal and proximal stent edges, the position of relevant side branches and the tip of the guiding catheter, etc.). On post-PCI pullback recordings this allowed calculation of the hyperaemic trans-stent gradient (HTG) and localisation of residual pressure gradients proximal or distal to the stented segment.

2.5.3 Physiology-guided Incremental Optimisation Strategy (PIOS)

Patients randomised to the PIOS group with post-PCI FFR < 0.90 had their coronary physiology findings disclosed to the operator. Based on the clinical interpretation of the FFR changes (pressure loss) in the treated artery post-PCI, the operator then followed the PIOS algorithm to optimise the final PCI result (Figure 2-1). If the residual pressure gradient reflected diffuse atherosclerosis with no focal step-changes in pressure gradient, the result was accepted and no optimisation attempted.

Figure 2-1 - Physiology-guided Incremental Optimisation Strategy (PIOS)



FFR=Fractional Flow Reserve; HTG=Hyperaemic Trans-stent Gradient; NC=Non-compliant

2.6 Patient-Reported Outcomes Measures (PROMs)

All patients completed questionnaires on anginal symptoms (Seattle Angina Questionnaire: SAQ-7) and health-related quality-of-life (European Quality-of-Life–5 Dimension–5 Level: EQ-5D-5L) at baseline and were contacted to repeat the assessments 3 months after their procedure. The questionnaires were administered by telephone or mail by a research nurse blinded to the randomised group allocation and the physiology results.

SAQ scores range from 0 to 100 with higher scores indicating better health status. The EQ-5D-5L comprises 2 components: a descriptive profile and a single-index visual analogue scale (VAS). The descriptive profile assesses 5 dimensions of general health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with a 5-level scale. Higher scores indicate more severe limitation within that dimension. When the descriptive system profile is linked to a ‘value set’, a single summary index value for health status is derived with scores that range from 0 to 1 (1 representing perfect health and 0 representing the poorest health). A value set provides values (weights) for each health state description according to the preferences of the general population of a country/region. The VAS records the patient’s personal perspective of their current health status on a vertical rating scale with scores ranging from 0 to 100, higher scores representing better quality-of-life.

2.7 Physiology core lab analysis

Due to nature of the trial, clinical decisions pertaining to revascularisation and optimisation measures were undertaken in real-time on the basis of the on-site coronary physiology measurements. For the purposes of the primary and relevant secondary endpoints, coronary physiology data underwent post-hoc adjudication by an independent core laboratory (CoreAalst BV, Aalst, Belgium). Analyses were performed following internal standard operational procedures using CoroFlow version 3.5 software (Coroventis research, Uppsala, Sweden). Each individual tracing was assessed for quality based on pre-specified criteria. Each tracing received a binary decision regarding adequate quality for inclusion and FFR was calculated independently for each tracing Aortic pressure tracings were visually

adjudicated based on the quality of the aortic pressure waveform defined by the following criteria:

1) Presence of dicrotic notch
2) Absence of ventricularisation
3) Absence of pressure curve distortion
4) Absence of arrhythmia
5) Stability of hyperaemia

Fractional flow reserve (FFR) was defined as the lowest value during steady state hyperaemia. Drift was evaluated when available and reported as a continuous variable. FFR measurements with drift greater than 0.03 FFR units were excluded.

Temperature/pressure tracings were adjudicated based on completeness of measurement and morphology of the temperature waveform. In addition, stability of the intracoronary pressure tracing (Pd) was also assessed as this influences IMR calculation. Temperature tracings were quantitively evaluated to extract the following parameters:

1) Maximal temperature reduction (MinTemp): mean of maximal temperature reduction of three saline injections
2) Temperature decrease time (TDT): Time from the beginning of the temperature reduction to nadir temperature.
3) Transit recovery time (TRT): duration (seconds) from the nadir of the hyperaemic thermodilution curve in the distal sensor to 20% from baseline temperature.

Tracings (i.e., temperature and accompanying pressure tracings) were visually adjudicated and considered adequate for analysis based on the following criteria:

1) Absence of major coronary pressure waveform artefact (defined as cyclic oscillation of the pressure curve with change in Pd more than 10mmHg)
2) Presence of Pa curve
3) Complete set of injections

For the IMR calculation, the Pd was selected at the level of the lowest fractional flow reserve (FFR). Higher than expected variability in Tmn identified by the Coroflow software was recorded but this was not considered a reason for exclusion of the measurement.

2.8 Study endpoints

The primary endpoint of the study was the proportion of patients with a final post-PCI FFR result ≥ 0.90. Secondary endpoints were: proportion of patients with final FFR ≤ 0.80 (the guideline-directed threshold for revascularisation) ; change from baseline SAQ-7 scores at 3 months; change from baseline EQ-5D-5L scores at 3 months; rate of target vessel failure and its components (cardiac death, myocardial infarction, stent thrombosis, unplanned rehospitalisation with target vessel revascularisation) at 1 year; proportion with final post-PCI dPR ≥ 0.90; proportion with final post-PCI RFR ≥ 0.90; proportion with final post-PCI CFR ≥ 2.0; proportion with final post-PCI IMR > 25; proportion with final post-PCI IMRc > 25; absolute and relative change in FFR (pre-to-final); absolute and relative change in dPR (pre-to-final); absolute and relative change in RFR (pre-to-final); absolute and relative change in CFR (pre-to-final); absolute and relative change in resting transit time (pre-to-final); absolute and relative change in hyperaemic transit time (pre-to-final); absolute and relative change in IMR (pre-to-final); absolute and relative change in IMRc (pre-to-final).

Safety analyses included: procedure duration, fluoroscopy dose; contrast material dose; adenosine dose; incidence of the following procedural complications - coronary artery dissection, side branch occlusion, no flow/slow flow, haematoma > 5cm, and Type 4a myocardial infarction.

Clinical outcomes at one-year post-PCI were assessed by electronic health record linkage and endpoints were defined according to the Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document and the Fourth Universal Definition of Myocardial Infarction.(80, 81) The trial's endpoint definitions are summarised in Table 2-1.

Table 2-1 - Clinical Endpoint Definitions

Endpoint	Definition
Death	The cause of death will be adjudicated as being due to cardiovascular causes, non-cardiovascular causes, or undetermined causes. • Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction (MI), heart failure or cardiogenic shock, stroke, other cardiovascular causes, or bleeding • Non-cardiovascular death is defined as any death with known cause not of cardiac or vascular causes • Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. For this trial all deaths of undetermined cause will be included in the cardiovascular category
Myocardial Infarction	In this trial myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction (2018)(81)
Stroke	The rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral haemorrhage with no apparent non-vascular cause (e.g., trauma, tumour, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, haemorrhagic, or unknown. Four criteria must be fulfilled to diagnosis stroke: 1. Rapid onset of a focal/global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia/aphasia, hemianopia, amaurosis fugax, other new neurological sign(s)/symptom(s) consistent with stroke; and 2. Duration of a focal/global neurological deficit ≥ 24 hours or < 24 hours if any of the following conditions exist: **i.** At least one of the following therapeutic interventions: a. Pharmacologic (i.e., thrombolytic drug administration)

	b. Non-pharmacologic (i.e., neuro-interventional procedure such as intracranial angioplasty) **ii.** Available brain imaging clearly documents a new haemorrhage or infarct **iii.** The neurological deficit results in death 3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies. 4. Confirmation of the diagnosis by a specialist and at least one of the following: **i.** Brain imaging procedure (at least one of the following): a. CT scan b. MRI scan c. Cerebral vessel angiography **ii.** Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial haemorrhage)
Target Vessel Revascularisation	The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. Target vessel revascularisation is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion. Revascularisation will be considered ischaemia-driven if the diameter stenosis of the revascularised coronary segment is ≥ 50% by Quantitative Coronary Angiography (QCA) and any of the following criteria for ischemia are met: **i.** A positive functional study corresponding to the area served by the target lesion; or **ii.** Ischaemic ECG changes at rest in a distribution consistent with the target vessel; or **iii.** Typical ischaemic symptoms referable to the target lesion; or

	iv. IVUS of the target lesion with a minimal lumen area (MLA) of ≤ 4 mm^2 for non-left main lesions or ≤ 6 mm^2 for left main lesions. If the lesions are de novo (i.e., not re-stenotic), the plaque burden must also be ≥ 60%; or **v.** FFR of the target lesion ≤ 0.80 A target lesion revascularisation for a diameter stenosis < 50% might also be considered ischaemia-driven by the Clinical Events Committee if there was a markedly positive functional study or ECG changes corresponding to the area served by the target lesion.
Stent Thrombosis	*Definite Stent Thrombosis* Angiographic confirmation of stent thrombosis The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent or in a side branch originating from the stented segment and the presence of at least 1 of the following criteria: • Acute onset of ischaemic symptoms at rest • New electrocardiographic changes suggestive of acute ischaemia • Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction) Or Pathological confirmation of stent thrombosis • Evidence of recent thrombus within the stent determined at autopsy • Examination of tissue retrieved following thrombectomy (visual/histology) *Probable Stent Thrombosis* Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.‡

	Silent Stent Thrombosis The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis. *Timing of Stent Thrombosis (duration after stent implantation)* Acute: 0§–24 hours Subacute: > 24 hours–30 days Late: 30 days–1 year Very late: > 1 year Early stent thrombosis is 0 to 30 days (acute plus subacute stent thrombosis). †Occlusive thrombus: Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow within or proximal to a stent segment. Non-occlusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolisation of intraluminal material downstream. ‡When the stented segment is in the left circumflex coronary artery or in the presence of pre-existing electrocardiographic abnormalities (eg, left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee adjudication is based on review of all available evidence). §Defined as the moment the patient is undraped and taken off the catheterisation table.

2.9 Statistical analysis

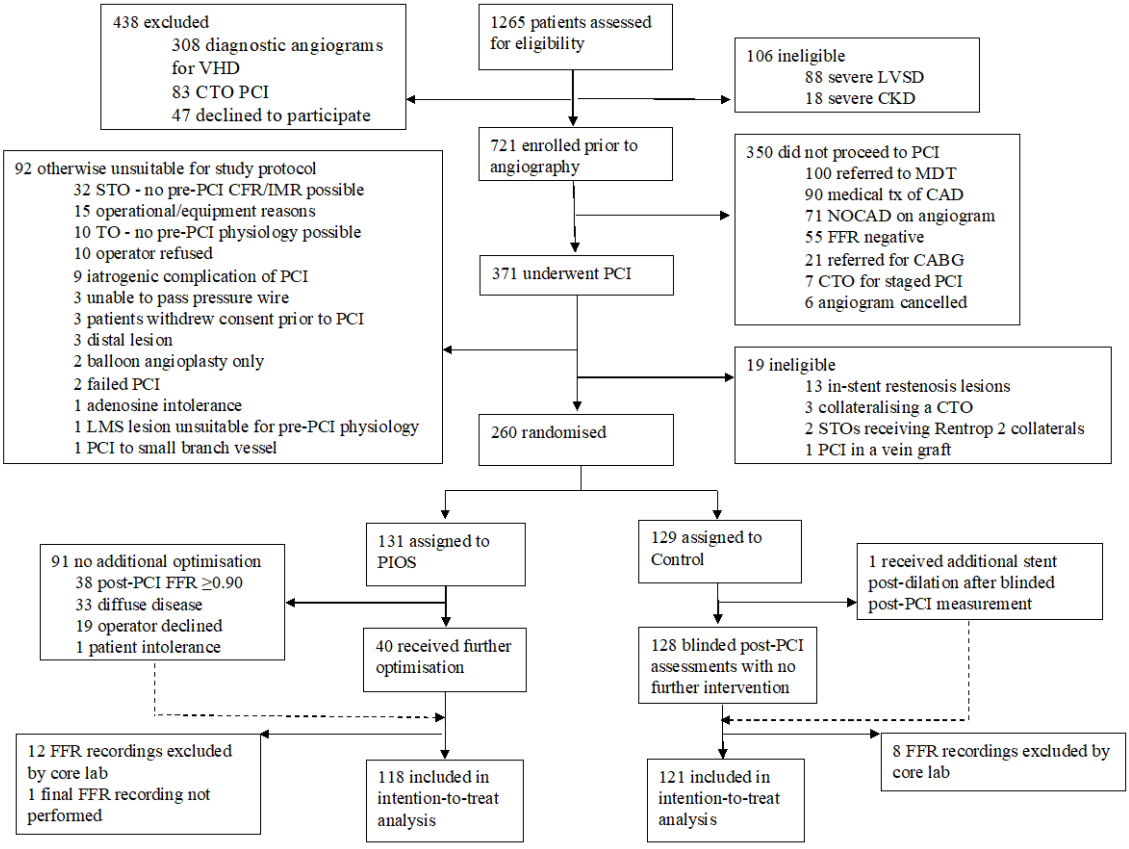
Continuous variables are presented as mean ± standard deviation, and categorical data as counts and percentages. A 2-sample t-test was used to compare patient-level characteristics with continuous variables. Categorical variables were compared using a chi-square test without continuity correction. Whenever appropriate, a Fisher exact test was used instead. 95% confidence intervals for between-group differences were calculated using the Wald method without continuity correction. Comparison of pre- and post-PCI values were performed using an ANCOVA model on the parameter's percent change adjusted for treatment group and baseline value. Correlation between variables was assessed using Pearson's correlation coefficient. All tests were two-sided and a p-value of < 0.05 was considered significant.

Chapter 3 Results – FFR-guided optimisation

3.1 Patient & procedural characteristics

Between 22/02/2018 and 22/11/2019, 1265 patients attending for coronary angiography and/or PCI were assessed for eligibility (Figure 3-1). Of these, 721 were enrolled in the trial before their procedures. Following percutaneous coronary intervention, 260 patients were randomised to either the PIOS intervention group or the control group (blinded physiology assessment). Clinical and procedural characteristics at baseline were evenly distributed between the randomised groups (Tables 3-1 and 3-2).

Figure 3-1 – Trial profile



CABG=Coronary Artery Bypass Graft surgery; CAD=Coronary Artery Disease; CFR=Coronary Flow Reserve; CKD= Chronic Kidney Disease; CTO=Chronic Total Occlusion; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; LMS= Left Main Stem; LVSD=Left Ventricular Systolic Dysfunction; MDT=Multi-Disciplinary Team meeting; NOCAD=No Obstructive Coronary Artery Disease; PCI=Percutaneous Coronary Intervention; PIOS=Physiology-guided Incremental Optimisation Strategy; STO=Sub-Total Occlusion; TO=Total Occlusion; VHD=Valvular Heart Disease.

Table 3-1 – Baseline patient characteristics

	Total (n=260)	PIOS (n=131)	Control (n=129)	P value
Male	226 (86.9%)	117 (89.3%)	109 (84.5%)	0.25
Age	59 (12)	58 (12)	60 (13)	0.17
BMI	29.1 (5.7)	28.9 (6)	29.4 (5.3)	0.34
Hypertension	116 (44.6%)	58 (44.3%)	58 (45%)	0.91
Hypercholesterolaemia	146 (56.2%)	72 (55%)	74 (57.4%)	0.70
Diabetes	49 (18.8%)	24 (18.3%)	25 (19.4%)	0.83
OHAs	42 (85.7%)	21 (87.5%)	21 (84%)	1.00
Insulin	5 (10.2%)	3 (12.5%)	2 (8%)	0.67
Atrial Fibrillation	19 (7.3%)	10 (7.6%)	9 (7%)	0.84
OAC	13 (68.4%)	6 (60%)	7 (77.8%)	0.63
Previous TIA/Stroke	17 (6.5%)	8 (6.1%)	9 (7%)	0.78
CKD*	5 (1.9%)	3 (2.3%)	2 (1.6%)	1.00
Family History of CAD	172 (66.2%)	88 (67.2%)	84 (65.1%)	0.73
History of Smoking	183 (70.4%)	92 (70.2%)	91 (70.5%)	0.96
Type of Smoker				0.44
Current	50 (27.3%)	28 (30.4%)	22 (24.2%)	
Within Past Year	41 (22.4%)	22 (23.9%)	19 (20.9%)	
Ex-Smoker > 1 year	92 (50.3%)	42 (45.7%)	50 (54.9%)	
Thyroid Dysfunction	20 (7.7%)	9 (6.9%)	11 (8.5%)	0.62
Heart Failure	63 (24.2%)	35 (26.7%)	28 (21.7%)	0.35
HFrEF	62 (98.4%)	35 (100%)	27 (96.4%)	0.44
HFrEF Severity				0.21
Mild	43 (69.4%)	22 (62.9%)	21 (77.8%)	
Moderate	19 (30.6%)	13 (37.1%)	6 (22.2%)	
NYHA Class				0.42
Class I	44 (69.8%)	23 (65.7%)	21 (75%)	
Class II	19 (30.2%)	12 (34.3%)	7 (25%)	
Previous MI	95 (36.5%)	50 (38.2%)	45 (34.9%)	0.58
Previous PCI	100 (38.5%)	54 (41.2%)	46 (35.7%)	0.36
Previous CABG	1 (0.4%)	1 (0.8%)	0	1.00
Valvular Heart Disease†	8 (3.1%)	2 (1.5%)	6 (4.7%)	0.17
Aortic Stenosis	6 (2.3%)	1 (0.8%)	5 (3.9%)	0.12
Mitral Regurgitation	2 (0.8%)	1 (0.8%)	1 (0.8%)	1.00
Angina	215 (82.7%)	107 (81.7%)	108 (83.7%)	0.66
CCS Class				0.98
Class I	58 (27%)	28 (26.2%)	30 (27.8%)	
Class II	101 (47%)	51 (47.7%)	50 (46.3%)	
Class III	55 (25.6%)	27 (25.2%)	28 (25.9%)	
Class IV	1 (0.5%)	1 (0.9%)	0	
Cardiac Medications				
Single APT	253 (97.3%)	128 (97.7%)	125 (96.9%)	0.72
Dual APT	185 (71.2%)	97 (74.1%)	88 (68.2%)	0.30
OAC	16 (6.2%)	8 (6.1%)	8 (6.2%)	0.98
Statin	250 (96.2%)	127 (96.9%)	123 (95.3%)	0.54
Beta Blocker	237 (91.2%)	121 (92.4%)	116 (89.9%)	0.49
CCB	52 (20%)	22 (16.8%)	30 (23.3%)	0.19
ACEI	175 (67.3%)	91 (69.5%)	84 (65.1%)	0.46

ARB	23 (8.9%)	11 (8.4%)	12 (9.3%)	0.80
Diuretic	30 (11.5%)	13 (9.9%)	17 (13.2%)	0.41
GTN Spray Use	123 (47.3%)	61(46.6%)	62 (48.1%)	0.81
Frequency GTN Use				0.73
Daily	30 (24.4%)	13 (21.3%)	17 (27.4%)	
Weekly	67 (54.55)	34 (55.7%)	32 (51.6%)	
Monthly	27 (22%)	14 (23%)	13 (21%)	
Oral Nitrate	69 (26.5%)	26 (19.8%)	43 (33.3%)	0.01
Nicorandil	22 (8.5%)	14 (10.7%)	8 (6.2%)	0.19
Ivabradine	5 (1.9%)	3 (2.3%)	2 (1.6%)	1.00
Number of Anti-Anginal Meds				0.65
0	9 (3.5%)	4 (3.1%)	5 (3.9%)	
1	99 (38.1%)	55 (42%)	44 (34.1%)	
2	114 (43.8%)	55 (42%)	59 (45.7%)	
3	31 (11.9%)	13 (9.9%)	18 (14%)	
4	7 (2.7%)	4 (3.1%)	3 (2.3%)	

***= All 5 patients had Stage 3a CKD (eGFR 45-59): Mild-moderate renal impairment.**

†= Degree of valve disease was either mild or moderate.

Values are n (%), median (IQR), or mean ± SD. ACEI=Angiotensin Converting Enzyme Inhibitor; APT=Antiplatelet Therapy; ARB=Angiotensin II-Receptor Blocker; BMI=Body Mass Index; CABG= Coronary Artery Bypass Grafting; CAD=Coronary Artery Disease; CCB=Calcium Channel Blocker; CCS=Canadian Cardiovascular Society; CKD=Chronic Kidney Disease; eGFR=estimated Glomerular Filtration Rate; GTN=Glyceryl Trinitrate; HFrEF=Heart Failure with Reduced Ejection Fraction; MI=Myocardial Infarction; OAC=Oral Anticoagulant; OHAs=Oral Hypoglycaemic Agents; PCI=Percutaneous Coronary Intervention; PIOS=Physiology-guided Incremental Optimisation Strategy.

Table 3-2 – Procedural characteristics

	Total (n=260)	PIOS (n=131)	Control (n=129)	P value
Indication				
Stable Angina	72 (27.7%)	32 (24.4%)	40 (31%)	0.24
ACS-NSTEMI	101 (38.8%)	50 (38.2%)	51 (39.5%)	0.82
Days Post MI	21 (17)	20 (19)	23 (15)	0.06
ACS-Unstable Angina	3 (1.2%)	2 (1.5%)	1 (0.8%)	1.00
Staged PCI/Completion Revascularisation	84 (32.3%)	47 (35.9%)	37 (28.7%)	0.22
Stable Angina	16 (19%)	8 (17%)	8 (21.6%)	0.98
Post-NSTEMI	22 (26.2%)	10 (21.3%)	12 (32.4%)	0.63
Days Since MI	67 (44)	64 (33)	80 (58)	0.67
Post-STEMI	46 (54.8%)	29 (61.7%)	17 (45.9%)	0.06
Days Since MI	69±29	70±31	66±28	0.64
Multivessel PCI (%)	28 (10.8%)	17 (13%)	11 (8.5%)	0.25
Target Vessel				
LAD	149 (57.3%)	75 (57.3%)	74 (57.4%)	0.98
RCA	67 (25.8%)	28 (21.4%)	39 (30.2%)	0.10
LCx	33 (12.7%)	20 (15.3%)	13 (10.1%)	0.21
OM	10 (3.8%)	8 (6.1%)	2 (1.6%)	0.10
Diagonal	1 (0.4%)	0	1 (0.8%)	0.50
QCA diameter stenosis (%)	65.7±15.1	65.85±14.78	65.60±15.51	0.89
QCA area stenosis (%)	85.8±12.4	85.73±12.86	85.80±11.92	0.96
QCA lesion length (mm)	12.2±5.9	11.96±5.50	12.36±6.37	0.59
Clinically instigated pressure wire	91 (35%)	43 (32.8%)	48 (37.2%)	0.46
PCI performed on pressure wire	64 (24.6%)	32 (24.4%)	32 (24.8%)	0.94
Pre-dilation of lesion	260 (100%)	131 (100%)	129 (100%)	NS
Rotational atherectomy	7 (2.7%)	2 (1.5%)	5 (3.9%)	0.24
Intravascular imaging	42 (16.2%)	17 (13%)	25 (19.4%)	0.16
Intravascular imaging modality				0.07
IVUS	34 (81%)	16 (94.1%)	18 (72%)	
OCT	8 (19%)	1 (5.9%)	7 (28%)	
Target lesion stent diameter (mm)	3.23±0.43	3.21±0.43	3.25±0.43	0.45
Target lesion stent length (mm)	31±10	31±10	31±10	0.94
More than one stent deployed	79 (30.4%)	35 (26.7%)	44 (34.1%)	0.20
Total stent number in target artery (n)	1.4±0.7	1.5±0.7	1.4±0.6	0.49
Total stent length in target artery (mm)	41±20	42±21	41±19	0.67
Post-dilation of stent	255 (98.1%)	130 (99.2%)	125 (96.9%)	0.17
Post-dilation balloon diameter (mm)	3.75±0.58	3.72±0.58	3.79±0.58	0.33
Post-dilation pressure (atm)	17±3	17±3	17±2	0.74
Diameter difference post-dilation balloon to stent	0.5±0.4	0.5±0.4	0.5±0.4	0.63

Values are n (%), median (IQR), or mean ± SD. ACS=Acute Coronary Syndrome; IVUS=Intravascular Ultrasound; LAD=Left Anterior Descending; LCx=Left Circumflex; MI=Myocardial Infarction; NS=Non-Significant; NSTEMI=Non-ST-segment-Elevation Myocardial Infarction; OCT=Optical Coherence Tomography; OM=Obtuse Marginal; PCI=Percutaneous Coronary Intervention; PIOS=Physiology-guided Incremental Optimisation Strategy; RCA=Right Coronary Artery; STEMI=ST-segment-Elevation Myocardial Infarction; QCA=Quantitative Coronary Angiography. [Adapted from Collison et al, Eur Heart J. 2021;42(45):4656-68.]

Intracoronary imaging (ICI) was utilised during the initial PCI in 16.2% (42/260) of patients. There was no significant difference in initial post-PCI FFR between those with ICI-guided PCI (0.83±0.09) and those guided by angiography alone (0.85±0.09, difference -0.02, 95% CI -0.05 to 0.01, p=0.26).

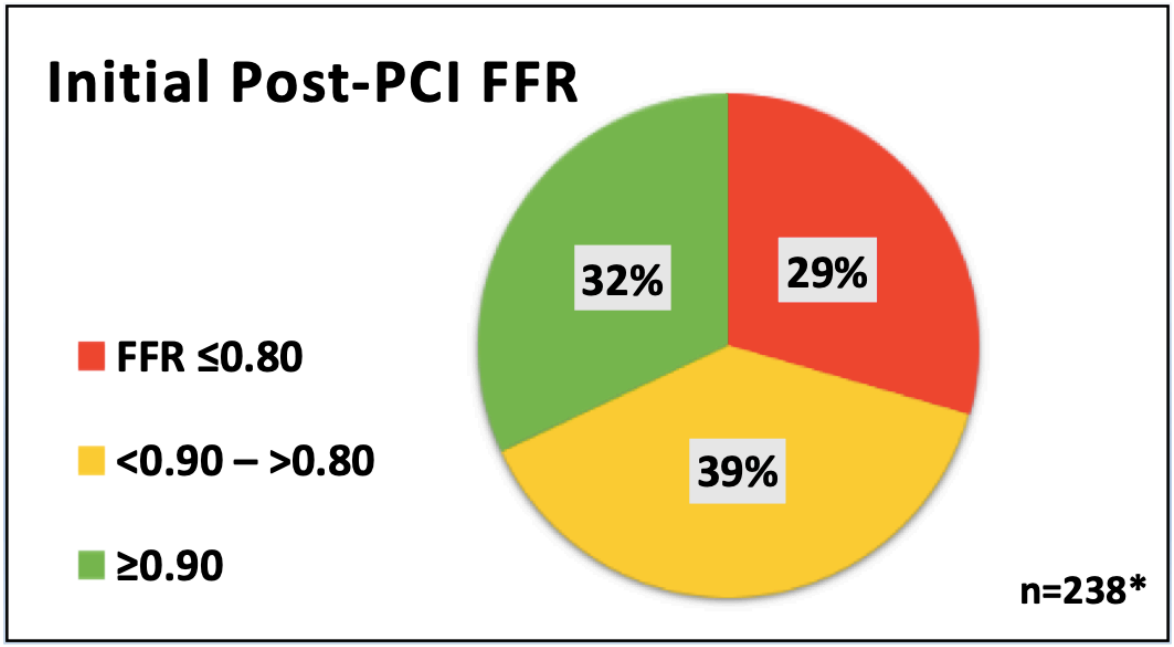
3.2 Coronary physiology results

The mean initial post-PCI FFR for the overall population was 0.85±0.09 and the distribution across the ≥ 0.90 and ≤ 0.80 thresholds is presented in Figure 3-2. Figure 3-3 outlines the patterns of residual disease identified on the initial post-PCI FFR pullback assessments. Overall, 30.5% (40/131) of patients randomised to the PIOS group received further intervention (Figure 3-4). The LAD was the target vessel in 85% (34/40) of these patients. There were no significant differences in physiology indices between randomised groups with respect to final mean FFR values or the absolute and relative changes from pre-PCI to final post-PCI phases (Table 3-3). 34/117 (29.1%) in the PIOS group had an initial post-PCI FFR ≤ 0.80, improving to 22/118 (18.6%) following additional FFR-guided optimisation. The proportion of vessels with post-PCI FFR ≥ 0.90 in the PIOS group was 42/117 (35.9%) initially, increasing to 45/118 (38.1%) following additional PCI.

3.3 Primary and secondary endpoints

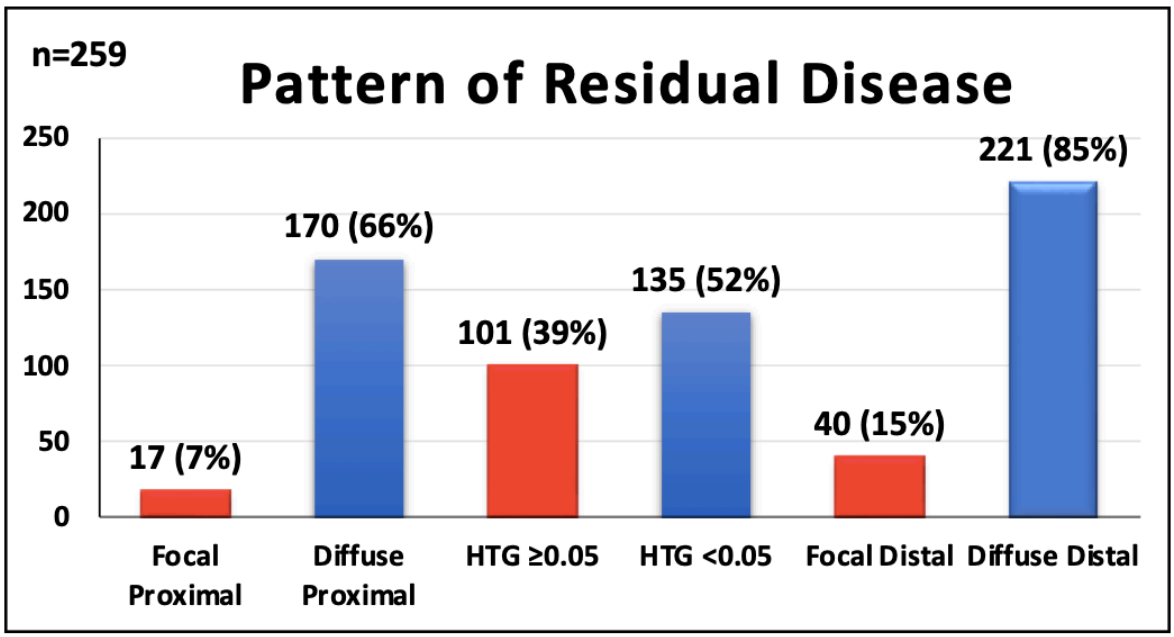
The primary and secondary endpoint results are presented in Table 3-4. There was no significant difference between groups with respect to the primary endpoint of the proportion of patients with final post-PCI FFR ≥ 0.90 (PIOS minus control 10%, 95% CI -1.84 to 21.91, p=0.099). The proportion of patients with final FFR ≤ 0.80 was significantly lower in the PIOS group (PIOS minus control -11.2%, 95% CI -21.87 to -0.35, p=0.045).

Figure 3-2 – Distribution of initial post-PCI FFR



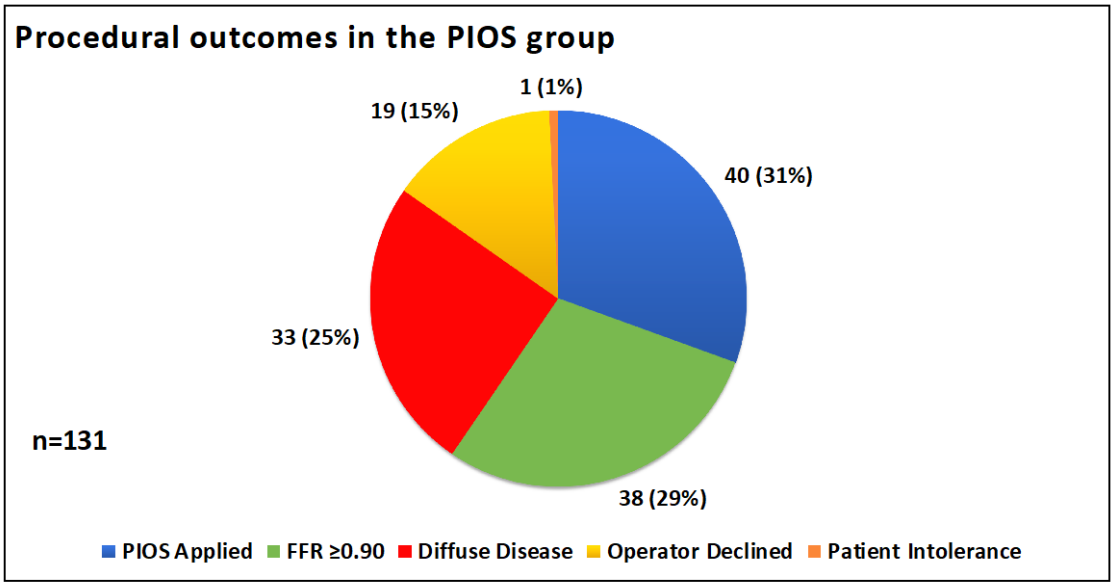
Post-percutaneous coronary intervention fractional flow reserve results following standard-of-care stenting. *238/260 patients (92%) with core lab-adjudicated post-PCI FFR results available for analysis. [Adapted from Collison et al, Eur Heart J. 2021;42(45):4656-68.]

Figure 3-3 – Patterns of residual disease on initial FFR pullback assessments



Summary findings of 259 initial post-percutaneous coronary intervention fractional flow reserve pullback assessments (pre-randomisation) demonstrating the patterns of residual disease in the study vessels. Protocol-defined targets for additional optimisation measures are shown in red bars. Multiple findings may have co-existed within individual vessels. Focal disease was defined as an abrupt pressure drop ≥ 0.05 FFR units on pullback. [Adapted from Collison et al, Eur Heart J. 2021;42(45):4656-68.]

Figure 3-4 - Procedural outcomes in the PIOS group



Following an initial post-PCI FFR assessment, 29% of patients had an FFR ≥ 0.90 and did not require optimisation. Of the remaining 93 patients with FFR < 0.90, 33 had diffuse residual patterns which did not meet the protocol-defined criteria for further intervention. Targets for additional intervention were identified in 60 patients. Operators attempted functional optimisation in 40 of these patients. The remaining 20 cases in which optimisation attempts were not undertaken are discussed in the Appendix. FFR=Fractional Flow Reserve; PIOS=Physiologically-guided Incremental Optimisation Strategy. [Adapted from Collison et al, Eur Heart J. 2021;42(45):4656-68.]

Table 3-3 - Coronary physiology characteristics

		Total (260)				PIOS (131)				Control (129)				P value
Index	Stage	N (%)	Value	Absolute Change	Relative Change (%)	N (%)	Value	Absolute Change	Relative Change (%)	N (%)	Value	Absolute Change	Relative Change (%)	
Pd/Pa	Pre	242 (93)	0.76±0.18			126 (96)	0.78±0.16			116 (90)	0.73±0.19			
	Final	246 (95)	0.94±0.05	0.18±0.18	35±55	122 (93)	0.94±0.05	0.15±0.16	27±49	124 (96)	0.94±0.06	0.21±0.19	43±60	0.98
dPR	Pre	242 (93)	0.70±0.21			126 (96)	0.73±0.20			116 (90)	0.67±0.22			
	Final	246 (95)	0.92±0.06	0.22±0.20	54±86	122 (93)	0.93±0.06	0.19±0.19	41±66	124 (96)	0.92±0.07	0.25±0.22	67±101	0.68
RFR	Pre	242 (93)	0.68±0.23			126 (96)	0.71±0.21			116 (90)	0.64±0.24			
	Final	246 (95)	0.92±0.06	0.24±0.22	71±132	122 (93)	0.92±0.06	0.21±0.20	51±89	124 (96)	0.91±0.07	0.28±0.23	93±163	0.38
TT_{rest}	Pre	240 (92)	1.12±0.45			121 (92)	1.12±0.43			119 (92)	1.12±0.47			
	Final	255 (98)	0.93±0.42	-0.20±0.45	-10±43	127 (97)	0.94±0.43	-0.21±0.40	-13±41	128 (99)	0.92±0.42	-0.19±0.50	-8±44	0.37
TT_{hyp}	Pre	236 (91)	0.67±0.38			122 (93)	0.66±0.36			114 (88)	0.69±0.41			
	Final	255 (98)	0.32±0.20	-0.36±0.39	-41±44	125 (95)	0.33±0.20	-0.34±0.36	-40±46	127 (98)	0.33±0.20	-0.38±0.42	-42±42	0.90
CFR	Pre	233 (90)	1.9±0.9			120 (92)	2.0±0.8			113 (88)	1.9±1.0			
	Final	252 (97)	3.4±1.9	1.5±1.8	99±127	125 (95)	3.4±1.8	1.3±1.7	84±111	127 (98)	3.4±2.0	1.6±1.9	114±140	0.12
IMR	Pre	223 (86)	28±12			117 (89)	28±12			106 (82)	27±12			
	Final	248 (95)	22±16	-7±15	-14±66	122 (93)	22±16	-7±16	-14±74	126 (98)	21±16	-7±15	-15±57	0.68
IMRc	Pre	223 (86)	21±10			117 (89)	22±11			106 (82)	19±10			
	Final	248 (95)	21±16	0±14	14±120	122 (93)	22±16	-1±15	12±106	126 (98)	20±16	0±14	16±133	0.81
FFR	Pre	236 (91)	0.59±0.14			126 (96)	0.60±0.14			110 (85)	0.57±0.15			
	Final	239 (92)	0.86±0.08	0.27±0.15	56±45	118 (90)	0.86±0.08	0.25±0.15	50±40	121 (94)	0.85±0.08	0.29±0.15	63±50	0.93

Values are n (%) or mean ± SD. Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; dPR=diastolic pressure ratio; RFR=Resting Full-cycle Ratio; TT_{rest}=mean resting transit time; TT_{hyp}=mean hyperaemic transit time; CFR=Coronary Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; FFR=Fractional Flow Reserve; PIOS=Physiology-guided Incremental Optimisation Strategy

Table 3-4 - Primary and secondary endpoints

	PIOS	Control	p value
Primary endpoint			
Final FFR ≥ 0.90 (%)			
Patients analysed (n)	118	121	
Proportion ≥ 0.90 (%)	38.1	28.1	
Difference between groups (95% CI)	10 [-1.84 - 21.91]		0.099
Secondary endpoints			
Final FFR ≤ 0.80 (%)			
Patients analysed (n)	118	121	
Proportion ≤ 0.80 (%)	18.6	29.8	
Difference between groups (95% CI)	-11.2 [-21.87 - -0.35]		**0.045**
Final dPR ≥ 0.90 (%)			
Patients analysed (n)	122	126	
Proportion ≥ 0.90 (%)	63.9	65.1	
Difference between groups (95% CI)	-1.2 [-13.1 – 10.8]		0.85
Final RFR ≥ 0.90 (%)			
Patients analysed (n)	122	126	
Proportion ≥ 0.90 (%)	59	60.3	
Difference between groups (95% CI)	-1.3 [-13.5 – 13.9]		0.83
Final CFR ≥ 2.0 (%)			
Patients analysed (n)	125	127	
Proportion ≥ 2.0 (%)	78.4	78	
Difference between groups (95% CI)	0.4 [-9.8 – 10.7]		0.93
Final IMR ≥ 25			
Patients analysed (n)	122	126	
Proportion ≥ 25 (%)	26.2	21.4	
Difference between groups (95% CI)	4.8 [-5.8 - 15.4]		0.37
Final IMRc ≥ 25			
Patients analysed (n)	122	126	
Proportion ≥ 25 (%)	24.6	19.8	
Difference between groups (95% CI)	4.8 [-5.6 - 15.1]		0.37

Change in SAQ Summary Score			
Patients analysed (n)	114	115	
Change between pre-PCI and 3-month follow-up scores	20.95 ± 25.04	21.51 ± 24.55	
Difference between groups (95% CI)	-0.56 [-5.9 – 7.0]		0.68
Change in EQ-5D-5L			
Patients analysed (n)	114	114	
Change between pre-PCI and 3-month follow-up scores	0.06 ± 0.22	0.03 ± 0.21	
Difference between groups (95% CI)	0.03 [-0.03 – 0.08]		0.64
Target Vessel Failure			
Target Vessel Failure	1	0	
Cardiac death	1	0	
Target vessel myocardial infarction	0	0	
Target vessel revascularisation	0	0	

Values are n (%) or mean ± SD. dPR=diastolic pressure ratio; RFR=Resting Full-cycle Ratio; TT rest=mean resting transit time; TT hyp=mean hyperaemic transit time; CFR=Coronary Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; FFR=Fractional Flow Reserve; SAQ=Seattle Angina Questionnaire; EQ-5D-5L= European Quality-of-Life–5 Dimensions–5 Levels questionnaire; PIOS=Physiology-guided Incremental Optimisation Strategy.

3.4 Safety analysis

A per-protocol procedural and safety analysis of patients in the PIOS group who underwent additional optimisation identified that this group had longer procedure durations with higher radiation, contrast, and adenosine doses. There were no differences in the incidence of procedural complications when compared to those patients who did not receive additional interventions (Table 3-5).

Table 3-5 - Per-protocol analysis of procedural characteristics and complications

	PIOS (n=40)	No PIOS (n=220)	p value
Procedural characteristics			
Procedure duration (mins)	94±23	67±24	< 0.0001
Total contrast dose (ml)	225±53	185±51	< 0.0001
Fluoroscopy time (mins)	23±8	16±8	< 0.0001
Dose Area Product (cGy.cm^2)	5236±2783	3780±2391	0.0007
Radiation dose (mGy)	921±551	686±462	0.0043
Total duration of adenosine infusions (sec)	439±87	290±73	< 0.0001
Total adenosine dose (mg)	93±25	62±32	< 0.0001
Procedural complications			
Coronary dissection	0	2 (0.9%)	0.54
Side branch occlusion	1 (2.5%)	8 (3.6%)	0.72
No flow / slow flow phenomenon	0	2 (0.9%)	0.54
Arm haematoma > 5cm	0	10 (4.5%)	0.17
Type 4a myocardial infarction	0	7 (3.2%)	0.60

3.5 Physiological effects of the PIOS intervention

Among patients who received further optimisation, both FFR and CFR increased significantly. Patients receiving an additional stent had a greater increase in FFR than those who received further post-dilation alone (Table 3-6).

Table 3-6 - Physiological effects of the PIOS intervention

	Initial Post-PCI		Final Post-PCI		Absolute Difference		Relative Difference (%)		p value
	N	Value	N	Value	N	Value	N	Value	
Any PIOS received (40)									
FFR	33	0.76±0.08	34	0.82±0.06	29	0.06±0.07	29	9±11.7	<0.0001
CFR	40	3.0±1.6	35	4.0±2.1	35	1.0±2.2	35	56.7±103.7	0.02
IMR	39	20±7	33	18±7	33	-3±8	33	-6.2±38.3	0.08
IMRc	39	19±7	33	17±7	33	-2±8	33	-3.2±41.3	0.17
Balloon only (23)									
FFR	18	0.79±0.07	19	0.83±0.05	15	0.03±0.05	15	4.4±7.6	0.03
CFR	23	3.1±1.6	19	3.6±1.5	19	0.4±1.4	19	32.9±62.1	0.21
IMR	22	19±6	17	16±6	17	-3±7	17	-8.9±34.1	0.11
IMRc	22	18±6	17	15±5	17	-2±7	17	-7.3±36.2	0.17
Stent only (12)									
FFR	11	0.72±0.09	10	0.80±0.05	10	0.09±0.08	10	14.3±15.8	0.01
CFR	12	2.8±1.8	11	5.4±2.6	11	2.5±2.8	11	127.1±142.8	0.01
IMR	12	24±9	11	18±10	11	-6±10	11	-19.6±35.3	0.10
IMRc	12	22±8	11	17±10	11	-4±10	11	-15.6±37.9	0.19
Post-dilation and stent (5)									
FFR	4	0.75±0.04	5	0.85±0.07	4	0.10±0.05	4	12.8±6.9	0.04
CFR	5	2.9±1.2	5	2.4±1.2	5	-0.5±1.6	5	-7.5±40	0.54
IMR	5	16±5	5	20±6	5	4±4	5	32.1±39.9	0.09
IMRc	5	15±5	5	20±6	5	5±5	5	38±47.1	0.09

Values are n (%) or mean ± SD. CFR=Coronary Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; FFR=Fractional Flow Reserve; PCI=Percutaneous Coronary Intervention; PIOS=Physiology-guided Incremental Optimisation Strategy

3.6 Physiology stratified by PCI indication

ACS-NSTEMI patients were medically stabilised and underwent PCI on a priority outpatient basis at a median of 3 weeks following their ACS presentation. Pre-PCI FFR values were lower in this cohort but there was no significant difference in microvascular resistance (as represented by corrected IMR) compared to patients undergoing PCI for either stable angina or staged completion of revascularisation in non-culprit vessels (Table 3-7).

Table 3-7 – Physiology stratified by PCI indication

	NSTEMI (N=104)		Stable Angina (N=88)		Staged Non-culprit (N=68)		p value
	N	Value	N	Value	N	Value	
Pre-PCI							
FFR	92	0.55±0.15	79	0.57±0.14	65	0.67±0.10	< 0.0001
CFR	90	1.9±0.9	80	1.8±0.9	63	2.3±0.9	0.005
IMR	86	29±13	76	28±12	61	24±11	0.02
IMRc	86	21±11	76	21±9	61	20±10	0.98
Initial Post-PCI							
FFR	97	0.86±0.10	80	0.83±0.08	61	0.85±0.09	0.11
CFR	104	3.3±1.7	87	3.5±2.1	66	2.9±1.5	0.15
IMR	103	23±17	85	19±11	66	24±19	0.13
IMRc	103	22±17	85	19±11	66	23±19	0.13

Values are n (%) or mean ± SD. Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; dPR=diastolic pressure ratio; iwFR=instantaneous wave-free ratio; RFR=Resting Full-cycle Ratio; FFR=Fractional Flow Reserve; CFR=Coronary Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; PCI=Percutaneous Coronary Intervention; NSTEMI=Non-ST-segment-Elevation Myocardial Infarction.

3.7 Physiology stratified by target vessel

When stratified by target vessel, there was no difference in mean pre-PCI FFR values between vessels, however, post-PCI FFR was significantly lower in the LAD (Table 3-8). The LAD had a lower proportion of patients with a final FFR ≥ 0.90 and a higher proportion with FFR ≤ 0.80 when compared to other vessels (Table 3-9).

Table 3-8 - Physiology stratified by target vessel

	LAD (N=150)		LCx (N=43)		RCA (N=67)		p value
	N	Value	N	Value	N	Value	
Pre-PCI							
FFR	135	0.58±0.14	39	0.61±0.11	62	0.59±0.16	0.52
CFR	132	2.1±1.1	41	1.8±0.8	60	1.8±0.6	0.06
IMR	131	26±10	38	27±13	54	32±15	0.02
IMRc	131	19±8	38	21±10	54	24±13	0.004
Initial Post-PCI							
FFR	140	0.80±0.07	38	0.92±0.07	60	0.91±0.07	< 0.0001
CFR	148	3.2±1.8	43	3.3±1.4	66	3.4±2.1	0.82
IMR	146	22±15	43	19±11	65	25±19	0.19
IMRc	146	21±15	43	19±11	65	25±19	0.14

Values are n (%) or mean ± SD. FFR=Fractional Flow Reserve; CFR=Coronary Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; PCI=Percutaneous Coronary Intervention; LAD=Left Anterior Descending artery; LCx=Left Circumflex artery; RCA=Right Coronary Artery

Table 3-9- Proportions of optimal (≥ 0.90) and suboptimal (≤ 0.80) final post-PCI FFR results stratified by target vessel

	LAD (N=138)	LCx (N=39)	RCA (N=62)	p value
Final FFR ≥ 0.90	10 (7.2%)	29 (74.4%)	40 (64.5%)	< 0.0001
Final FFR ≤ 0.80	52 (37.7%)	2 (5.1%)	4 (6.5%)	< 0.0001

FFR=Fractional Flow Reserve; PCI=Percutaneous Coronary Intervention; LAD=Left Anterior Descending artery; LCx=Left Circumflex artery; RCA=Right Coronary Artery

3.8 Association of FFR with angina at 3-month follow-up

The relative (percentage) change in FFR following PCI had a moderate but significant correlation with SAQ Angina Frequency score at 3 months follow-up (Spearman correlation coefficient 0.36, p< 0.0001). Larger relative increases in FFR were associated with a reduced burden of patient-reported angina at follow-up (Table 5).

Table 3-10 - Follow-up Seattle Angina Questionnaire (SAQ) scores stratified by tertiles of relative (percentage) change in FFR among patients with angina at baseline (CCS class I and above)

SAQ Domain	Low		Intermediate		High		p value
	N	Score	N	Score	N	Score	
Physical Limitation	47	71.81±30.07	48	83.16±24.76	52	85.90±23.89	0.02
Angina Frequency	50	78.60±23.56	55	85.09±21.33	57	94.39±13.89	< 0.001
Quality of Life	50	71.75±29.75	55	77.95±28.05	57	84.43±23.89	0.06
Summary Score	50	74.51±24.20	55	81.45±22.38	57	88.23±18.29	0.01

3.9 Clinical outcomes

There were no peri-procedural deaths. At a median (interquartile range) follow-up of 2 years there had been only one target vessel failure event. This patient, who was in the PIOS group but had not received any additional optimisation, suffered a presumed cardiac death in the community 17 months after their procedure (Table 3-11). Other clinical endpoints of interest are presented in Table 3-12.

Table 3-11 – Target Vessel Failure [median (IQR) follow-up duration of 2.1 (0.9) years]

	PIOS n/131 (%)	Control n/129 (%)
Target Vessel Failure	1 (0.8)	0
Cardiac Death	1 (0.8)	0
Target Vessel Myocardial Infarction	0	0
Target Vessel Revascularisation	0	0

Table 3-12 - Other clinical endpoints of interest

	PIOS n/131 (%)	Control n/129 (%)
All-Cause Mortality	1 (0.8)	2 (1.6)
Non-Cardiac Death	1 (0.8)	2 (1.6)
Myocardial Infarction	7 (5.3)	8 (6.2)
Type 1 Myocardial Infarction	1 (0.8)	4 (3.1)
Type 2 Myocardial Infarction	0	1 (0.8)
Type 3 Myocardial Infarction	1 (0.8)	0
Type 4a Myocardial Infarction	4 (3.1)	3 (2.3)
Type 4c Myocardial Infarction	1 (0.8)	0
Non-Target Vessel Revascularisation	5 (3.8)	4 (3.1)
Stroke	2 (1.5)	1 (0.8)
Bleeding	2 (1.5)	2 (1.6)

3.10 Discussion

In this randomised controlled trial of a coronary physiology-guided PCI optimisation strategy, additional FFR-guided intervention after stenting did not significantly increase the proportion of patients achieving the optimal post-PCI FFR result of ≥ 0.90 but did reduce the proportion of patients with a final FFR ≤ 0.80 (the guideline-directed threshold for revascularisation) when compared to the angiography-guided control group.

There is a gap in clinical trial evidence on strategies to optimise PCI outcomes. In a retrospective, single-centre registry of 664 vessels from 574 patients, 118 (17.8%) vessels were found to have a post-PCI FFR ≤ 0.80.(44) Additional interventions were performed in 87/118 (73.7%) of these vessels which increased the final FFR to ≥ 0.80 in 58/87 (66.7%). In the overall population, additional post-dilation or stenting reduced the proportion of vessels with post-PCI FFR ≤ 0.80 from 118 (17.8%) to 63 (9.5%). In total, 137 vessels (20.6%) underwent further treatment for what were perceived to be suboptimal post-PCI FFR results with further post-dilatation (42%) and/or additional stenting (33%) or both (18%). FFR was repeated in all 137 lesions with an overall improvement from 0.78± 0.07 to 0.87 ± 0.05. Amongst patients who received post-dilation only, FFR improved from 0.75±0.06 to 0.85 ± 0.06. This is perhaps not surprising when the particulars of the index PCI procedure are examined. Just over half of lesions (n=352, 53%) were pre-dilated, the mean diameter of implanted stents was 2.87mm and only 200 (30.1% of vessels) received post-dilation. By comparison, in TARGET-FFR, the mean stent diameter was 3.23mm with 100% and 98.1% rates of pre-dilation and post-dilation (with on average a 0.5mm larger non-compliant balloon) respectively (Table 3-2). The yield from additional post-dilation alone in TARGET-FFR was more modest (FFR increased from 0.79±0.07 to 0.83±0.05, Table 3-6) and could suggest a higher incidence of initial stent under-expansion and/or malapposition in the previous registry.

A recent prospective registry supports the findings from TARGET-FFR.(52) In this registry, 84/230 vessels (36.5%) had an initial post-PCI FFR ≤ 0.80 while just 49/230 (21.3%) achieved a value > 0.90. FFR pullback identified targets for further optimisation in 29/84 (34.5%). After further intervention, FFR increased

from 0.73 (IQR: 0.69-0.77) to 0.80 (IQR: 0.77-0.85) and reduced the overall incidence of post-PCI FFR ≤ 0.80 by 6.1% (36.5% to 30.4%). The number of vessels with a final FFR > 0.90 increased by 5 (2.1%). In TARGET-FFR's PIOS group, additional FFR-guided optimisation measures reduced the overall incidence of FFR ≤ 0.80 by 10.5% and increased the proportion of vessels with post-PCI FFR ≥ 0.90 by 2.2%.

Why is it so difficult to achieve a post-PCI FFR ≥ 0.90? The answer may be influenced by characteristics of the target coronary artery. PCI on a lesion in the LAD has previously been identified as an independent predictor of suboptimal post-PCI FFR results(19, 21, 44, 52, 82) and the LAD was the target vessel in 150/260 (57.7%) of patients in TARGET-FFR. The TARGET-FFR data confirm that both absolute post-PCI FFR values and the proportion of patients achieving a final FFR value ≥ 0.90 are significantly lower in the LAD than either the left circumflex or right coronary arteries. There were, however, no significant differences between vessels in post-PCI CFR or corrected microvascular resistance. It has been postulated that lower FFR values in the LAD relate to the larger area of myocardium subtended by this vessel. Higher flow rates across long segments of residual mild diffuse atheroma can result in large pressure gradients. Hydrostatic factors relating to coronary anatomy and the height of the pressure wire sensor above or below the aortic pressure transducer may also contribute to this phenomenon. Given that achieving a post-PCI FFR ≥ 0.90 in the LAD in anything other than a minority of patients appears unlikely, does this threshold represent a realistic target or definition of a functionally optimal PCI result in this vessel? In a registry of 835 patients who had post-PCI FFR measured, Hwang et al reported that the optimal cut-off values for predicting target vessel failure at 2 years were lower in LAD than in non-LAD vessels (0.82 vs. 0.88).(22)

In TARGET-FFR, use of intracoronary imaging (ICI) during the index PCI was not associated with higher post-PCI FFR values when compared to cases guided by angiography alone. IVUS or OCT was utilised in 16.2% (42/260) of PCI procedures which exceeds the UK national average of 10.7% in 2018/19. The DOCTORS study previously randomised 240 patients with NSTEMI to either OCT- or angiography-guided PCI and reported a marginally higher post-PCI FFR in the OCT arm (0.94▫0.04 vs. 0.92▫0.05, p=0.005).(42) It is worth noting that observational data

from a number of non-randomised studies in which IVUS was routinely used before and after PCI(12, 14, 56) have reported mean/median post-PCI FFR values within the same range as those from cohorts with lower rates of adjunctive ICI than in TARGET-FFR.(15, 23, 50)

Even well-expanded stents manifest a pressure gradient during maximal hyperaemia. In TARGET-FFR, we theorised that a trans-stent gradient of > 0.05 FFR units would be of sufficient magnitude to detect change/improvement related to additional post-dilation of the stent. Yang et al have reported that trans-stent gradients ≥ 0.04 FFR units are associated with increased rates of MACE. The authors found that despite successful PCI, 98.5% of stents in their study had a hyperaemic trans-stent gradient (HTG) > 0, with single stents having a mean HTG of 0.03 ± 0.02 and overlapping stents a mean of 0.05 ± 0.02.(83) These findings support our hypothesis that intervening on stents with HTG < 0.05 units would have been unlikely to achieve an appreciable change in final FFR.

Currently, there are no generally accepted definitions of focal or diffuse disease with respect to pressure-wire pullback curves. To date, such definitions have been arbitrary, vary from study to study, and are often very much in the eye of the beholder. The DEFINE PCI study examined post-PCI iFR pullbacks and arbitrarily categorised trans-stenotic pressure gradients ≥ 0.03 iFR units as focal lesions when their length was ≤ 15 mm, and as diffuse disease when their length exceeded 15 mm.(60) 15mm is not an insignificant length of vessel and a plausible argument could be made that a relatively small pressure loss (0.03 units) over such length should be considered diffuse. Adopting such a broad definition of focality led the authors to the unprecedented conclusion that 81.6% of patients with post-PCI iFR < 0.90 had ‘focal’ residual disease. The signal to noise ratio is lower with hyperaemic pullbacks than with resting assessments. Had we chosen to define focal disease as a gradient of ≥ 0.03 FFR units over 15mm, the data from Yang et al illustrates how a pre-PCI gradient of 0.03 within a vessel could end up being replaced by a HTG of 0.03 post-stenting. This would achieve no overall functional gain in the vessel yet expose the patient to the risk of additional coronary intervention. As one can observe from the case examples provided in the Appendix, truly focal lesions cause an obvious and abrupt drop in pressure. Accordingly, we felt that an abrupt pressure drop ≥ 0.05 FFR units was

an appropriate definition of focal disease when utilising FFR assessment (with anything else being considered generally diffuse).

TARGET-FFR provides the first randomised data on the incidence of physiologically suboptimal results following standard-of-care PCI and confirms the feasibility of routine post-PCI FFR assessment. It found that persistently abnormal post-PCI FFR values are common and that a strategy of routine post-PCI physiology guidance can safely and effectively improve the final FFR values in a significant number of the worst-affected patients. Importantly, larger relative increases in FFR were associated with a reduced frequency of angina at 3-month follow-up.

The study has several limitations. It is a single-centre study with a relatively homogenous PCI practice, including high rates of lesion pre-dilatation and high-pressure stent post-dilation. On average, FFR is performed prior to PCI in 9.4% of cases in the UK. In our study the rate of pre-PCI FFR guidance (including pullback assessment) was 35%. This may have influenced or altered operators' stenting strategy and consequently reduced the incidence of focal, physiologically significant residual disease post-PCI. A larger multicentre trial incorporating a wider range of PCI strategies and techniques may have had a different outcome. With just 40 of the 131 patients randomised to the PIOS arm receiving additional optimisation measures, the study was ultimately underpowered to detect a significant between-group difference for its primary endpoint. Excluding patients with post-PCI FFR ≥ 0.90 (29% of the PIOS group) from randomisation would have increased the power for the primary endpoint but overestimated the effect physicians could expect from measuring post-PCI physiology. Ultimately, TARGET-FFR was a trial of a strategy of routine post-PCI FFR assessment versus standard of care, without selection based on the post-PCI FFR value. This approach permits an evaluation of the effects of the PIOS intervention, regardless of the baseline post-PCI FFR. By randomising all-comers, the design allowed a comprehensive, and generalisable evaluation of the effects of physiology-guided PCI optimisation. The incidence of target vessel failure at a median follow-up of 2 years was very low and the study was not powered for clinical outcomes. Larger randomised trials would be required to test if physiology-guided optimisation of PCI results can improve patient outcomes compared to standard angiographic assessment alone.

Chapter 4 Results – Impact of the baseline pattern of coronary artery disease on post-PCI coronary physiology and patient-reported outcome measures

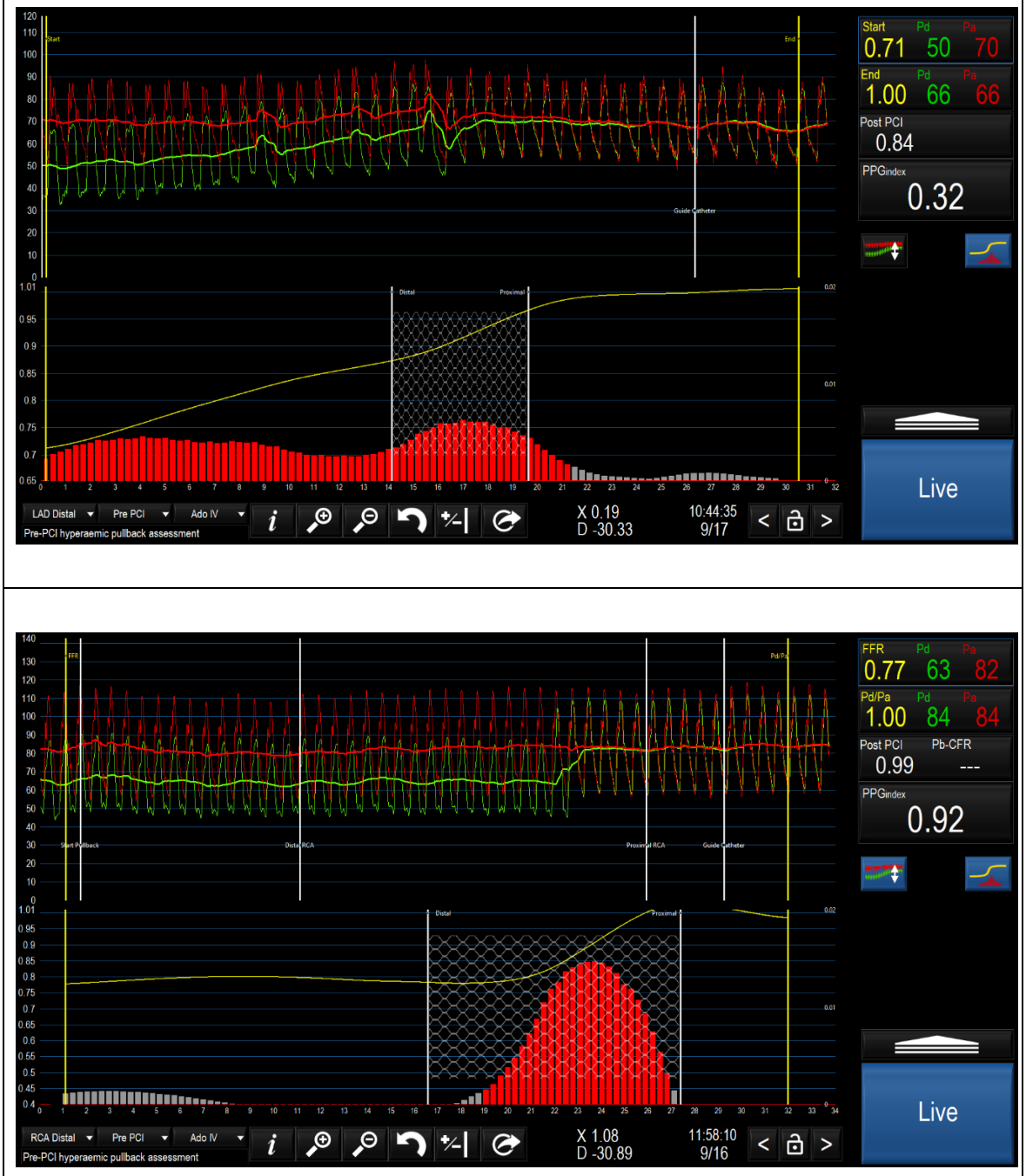
4.1 The Pullback Pressure Gradient (PPG) index

The PPG index, a continuous metric derived from the maximal pressure gradient over 20% of the pullback duration and the length of functional disease, was calculated from a post hoc analysis of the pre-PCI FFR pullback recordings using Coroflow v3.5 software (Coroventis Research AP, Uppsala, Sweden). The core lab applied the following exclusion criteria to the pullback recordings: absence of a dicrotic notch from the pressure waveforms; ventricularisation; pressure wire drift of more than 0.05 FFR units after pullback to the guide catheter; unstable hyperaemic conditions during the pullback manoeuvre; pullback duration less than 15 seconds, and pullback curves with major artifacts. PPG values range from 0 to 1.0 with those close to 1.0 representing focal coronary artery disease and nearer to 0 indicating a diffuse pattern of disease.(84) Examples of focal and diffuse patterns of coronary disease are provided in Figure 4-1. The median PPG value was used to differentiate focal from diffuse CAD. To adjust for baseline disease severity, the percentage change in pressure ratios was also normalised by the pre-PCI value (i.e., [post-PCI value minus pre-PCI value] / [1 minus pre-PCI value]).

4.2 Relationship between PPG and other coronary physiology metrics.

Valid PPG measurements were obtained from 121 patients. Correlation between PPG and other coronary physiology metrics is outlined in Table 4-1. Apart from Coronary Flow Reserve, PPG had no relationship to other pre-PCI coronary physiology metrics. It had significant correlations to post-PCI and delta values (absolute, percentage and normalised percentage change) for almost all indices expect resting transit times.

Figure 4-1 – Examples of diffuse (low PPG) and focal (high PPG) patterns of coronary artery disease



Top panel: Example of a diffuse pressure gradient during an FFR pullback manoeuvre in a left anterior descending artery with a low PPG index of 0.32, displayed graphically below the yellow FFR line as a wide spread of red histogram bars representing a diffuse pressure gradient. Bottom panel: Focal lesion in the proximal right coronary artery yielding a high PPG index of 0.92 and a peaked histogram pattern representing an abrupt, focal pressure gradient across the lesion.

Table 4-1 – Spearman correlation between PPG and other coronary physiology metrics (all patients)

Coronary Physiology Metric	Timepoint (n)	Correlation Coefficient	P value
Pd/Pa	Pre-PCI (117)	0.04	0.70
	Post-PCI (115)	0.55	< 0.001
	Absolute Change (111)	0.31	0.001
	Percentage Change (111)	0.27	0.004
	Normalised % Change (109)	0.60	< 0.001
dPR	Pre-PCI (117)	0.01	0.89
	Post-PCI (115)	0.56	< 0.001
	Absolute Change (111)	0.32	< 0.001
	Percentage Change (111)	0.28	0.003
	Normalised % Change (109)	0.62	< 0.001
iFR_{sim}	Pre-PCI (117)	0.00	1.00
	Post-PCI (115)	0.57	< 0.001
	Absolute Change (111)	0.32	< 0.001
	Percentage Change (111)	0.29	0.002
	Normalised % Change (109)	0.60	< 0.001
RFR	Pre-PCI (117)	-0.02	0.87
	Post-PCI (115)	0.57	< 0.001
	Absolute Change (111)	0.34	< 0.001
	Percentage Change (111)	0.30	0.001
	Normalised % Change (111)	0.58	< 0.001
FFR	Pre-PCI (118)	-0.08	0.42
	Post-PCI (115)	0.47	< 0.001
	Absolute Change (112)	0.41	< 0.001
	Percentage Change (112)	0.37	< 0.001
	Normalised % Change (112)	0.58	< 0.001
Resting Transit Time	Pre-PCI (115)	-0.10	0.26
	Post-PCI (120)	-0.14	0.14
	Absolute Change (114)	0.01	0.88
	Percentage Change (114)	-0.03	0.73
Hyperaemic Transit Time	Pre-PCI (115)	0.10	0.28
	Post-PCI (119)	-0.36	< 0.001
	Absolute Change (113)	-0.34	< 0.001
	Percentage Change (113)	-0.41	< 0.001
CFR	Pre-PCI (113)	-0.26	0.005
	Post-PCI (119)	0.26	0.005
	Absolute Change (111)	0.40	< 0.001
	Percentage Change (111)	0.40	< 0.001
IMR	Pre-PCI (110)	0.07	0.48
	Post-PCI (119)	-0.23	0.01
	Absolute Change (108)	-0.30	0.002
	Percentage Change (108)	-0.33	< 0.001
IMRc	Pre-PCI (110)	-0.02	0.83
	Post-PCI (119)	-0.19	0.036
	Absolute Change (108)	-0.19	0.051
	Percentage Change (108)	-0.20	0.04

The post-PCI value reported is the initial result, prior to any additional optimisation measures being performed. Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; dPR=diastolic pressure ratio; RFR=Resting Full-cycle Ratio; CFR=Coronary Flow Reserve; iFR_{sim}=Simulated instantaneous wave-Free Ratio; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; FFR=Fractional Flow Reserve

4.3 Relationship between PPG and patient-reported outcome measures

101 patients with available PPG values had angina at baseline (CCS class I or above). The cohort was dichotomised by the median PPG value into groups of focal (PPG ≥ 0.65) and diffuse (PPG < 0.65) patterns of coronary artery disease. Baseline clinical characteristics are presented in Table 4-2. Patients with a diffuse pattern of CAD had a higher incidence of previous myocardial infarction and nicorandil use but the groups were otherwise evenly matched. Table 4-3 compares procedural and coronary physiology characteristics between patients with focal and diffuse disease. The LAD was the target vessel in a significantly larger proportion of patients in the diffuse group. Vessels with a focal pattern of disease contained stenoses which were angiographically and physiologically more severe than those in the diffuse group. Vessels with diffuse disease patterns received longer stented segments and were associated with a higher rate of intracoronary imaging use during PCI. Absolute post-PCI values and percentage improvement of both hyperaemic and non-hyperaemic pressure ratios were significantly higher in vessels with focal disease patterns.

There was no relationship between the PPG value and patient-reported angina or quality-of-life scores pre-PCI. 3 months post-PCI, the PPG value had weak, but significant, positive correlations with SAQ – Angina Frequency (SAQ-AF) score, SAQ – Summary Score (SAQ-SS) and the EQ-5D-5L weighted health index score (Table 4-4). Follow-up SAQ-AF and SAQ-SS scores were significantly higher in patients with focal disease. The rate of residual angina (follow-up SAQ-AF score < 100) was higher in patients with diffuse disease (Table 4-5). Follow-up EQ-5D-5L scores were lower and weighted health index scores higher (indicating better health status) in the focal disease group.

Table 4-2 – Baseline clinical characteristics stratified by PPG-defined focal vs. diffuse disease in patients with angina (CCS Class 1 or above)

Variables	Total	Focal (PPG ≥ 0.65)	Diffuse (PPG < 0.65)	p-value
Number of patients	101	51	50	
Male, n (%)	84 (83.2)	43 (84.3)	41 (82)	0.76
Age years, mean (SD)	60.6 ± 8.2	59.9 ± 7.5	61.3 ± 8.9	0.37
BMI, mean (SD)	29.9 ± 4.6	29.4 ± 4.4	30.3 ± 4.8	0.34
Family history of CAD, n (%)	68 (67.3)	36 (70.6)	32 (64)	0.48
Smoking status, n (%)				0.17
Non-smoker	28 (27.7)	11 (21.6)	17 (34)	
Current Smoker	17 (16.8)	7 (13.7)	10 (20)	
Ex-smoker	56 (55.4)	33 (64.7)	23 (46)	
Hypertension, n (%)	44 (43.6)	19 (37.3)	25 (50)	0.20
Dyslipidaemia, n (%)	59 (58.4)	32 (62.7)	27 (54)	0.37
Heart Failure, n (%)	30 (29.7)	11 (21.6)	19 (38)	0.07
Diabetes, n (%)	22 (21.8)	9 (17.6)	13 (26)	0.31
Atrial Fibrillation, n (%)	8 (7.9)	5 (9.8)	3 (6)	0.72
Chronic Kidney Disease, n (%)	3 (3)	2 (3.9)	1 (2)	1.00
Indication for PCI, n (%)				0.08
Stable Angina	28 (27.7)	13 (25.5)	15 (30)	
ACS – UA/NSTEMI	41 (40.6)	26 (51)	15 (30)	
Staged Completion of Revascularisation	32 (31.7)	12 (23.5)	20 (40)	
Previous MI	40 (39.6)	15 (29.4)	25 (50)	0.03
Previous PCI, n (%)	42 (41.6)	17 (33.3)	25 (50)	0.09
Baseline CCS Class, n (%)				0.32
CCS 1	24 (23.8)	15 (29.4)	9 (18)	
CCS 2	50 (49.5)	22 (43.1)	28 (56)	
CCS 3	27 (26.7)	14 (27.5)	13 (26)	
Baseline SAQ-AF = 100	19 (18.8)	10 (19.6)	9 (18)	0.84
Medications				
Any antiplatelet, n (%)	100 (99)	50 (98)	50 (100)	1.00
DAPT, n (%)	77 (76.2)	39 (76.5)	38 (76)	0.96
Oral anticoagulant, n (%)	7 (6.9)	4 (7.8)	3 (6)	1.00
Statins, n (%)	97 (96)	49 (96.1)	48 (96)	1.00
ACEI, n (%)	74 (73.3)	36 (70.6)	38 (76)	0.54
ARB, n (%)	7 (6.9)	4 (7.8)	3 (6)	1.00
Diuretics, n (%)	10 (9.9)	4 (7.8)	6 (12)	0.52
Number of Anti-anginal Agents, mean (SD)	1.9 ± 0.8	1.8 ± 0.7	2.0 ± 0.9	0.34
Beta-blocker, n (%)	94 (93.1)	49 (96.1)	45 (90)	0.27
Calcium channel blocker, n (%)	22 (21.8)	10 (19.6)	12 (24)	0.59

Nicorandil, n (%)	11 (10.9)	2 (3.9)	9 (18)	0.02
Ivabradine, n (%)	2 (2)	1 (2)	1 (2)	1.00
Oral Nitrates, n (%)	30 (29.7)	13 (25.5)	17 (34)	0.35
Frequency of GTN spray use, n (%)				0.47
None	40 (39.6)	21 (41.2)	19 (38)	
Daily	10 (9.9)	4 (7.8)	6 (12)	
Weekly	36 (35.6)	16 (31.4)	20 (40)	
Monthly	15 (14.9)	10 (19.6)	5 (10)	

Values are n (%), median (IQR), or mean ± SD. ACEI=Angiotensin Converting Enzyme Inhibitor; ACS – UA/NSTEMI=Acute Coronary Syndrome – Unstable Angina/Non-ST-segment-Elevation Myocardial Infarction; APT=Antiplatelet Therapy; ARB=Angiotensin II-Receptor Blocker; BMI=Body Mass Index; CABG= Coronary Artery Bypass Graft surgery; CAD=Coronary Artery Disease; CCB=Calcium Channel Blocker; CCS=Canadian Cardiovascular Society; CKD=Chronic Kidney Disease; GTN=Glyceryl Trinitrate; MI=Myocardial Infarction; OAC=Oral Anticoagulant; PCI=Percutaneous Coronary Intervention; PIOS=Physiology-guided Incremental Optimisation Strategy; STEMI=ST-segment-Elevation Myocardial Infarction.

Table 4-3 – Procedural and coronary physiology characteristics stratified by PPG-defined focal vs. diffuse disease in patients with angina (CCS Class 1 or above)

Variables	Overall	Focal (PPG ≥ 0.65)	Diffuse (PPG < 0.65)	p-value
Target Vessel				< 0.001
LAD	62 (61.4)	17 (33.3)	45 (90)	
LCx	18 (17.8)	16 (31.4)	2 (4)	
RCA	21 (20.8)	18 (35.3)	3 (6)	
Diameter stenosis (%), mean ± SD	61.7 ± 15.6	66.1 ± 16.2	57.1 ± 13.7	0.003
Lesion length, mean ± SD	11.8 ± 5.4	11.2 ± 5.2	12.4 ± 5.5	0.29
AHA/ACC Lesion type, n (%)				0.24
A	17 (16.8)	8 (15.7)	9 (18)	
B1	42 (41.6)	26 (51)	16 (32)	
B2	36 (35.6)	15 (29.4)	21 (42)	
C	6 (5.9)	2 (3.9)	4 (8)	
SYNTAX score, mean ± SD	11.3 ± 8.1	9.3 ± 7.6	13.3 ± 8.3	0.01
BCIS Jeopardy score, mean ± SD	5.2 ± 3.1	4.8 ± 3.0	5.6 ± 3.2	0.15
Pre-PCI Pd/Pa, mean ± SD	0.81 ± 0.13	0.80 ± 0.16	0.83 ± 0.11	0.20
Pre-PCI dPR, mean ± SD	0.76 ± 0.17	0.74 ± 0.20	0.79 ± 0.14	0.13
Pre-PCI iwFR, mean ± SD	0.75 ± 0.19	0.72 ± 0.21	0.78 ± 0.16	0.10
Pre-PCI RFR, mean ± SD	0.74 ± 0.19	0.71 ± 0.21	0.77 ± 0.16	0.10
Pre-PCI FFR, mean ± SD	0.62 ± 0.13	0.59 ± 0.15	0.65 ± 0.11	0.03
Pre-PCI resting TT	1.03 ± 0.42	0.99 ± 0.41	1.08 ± 0.44	0.32
Pre-PCI hyperaemic TT	0.57 ± 0.35	0.63 ± 0.39	0.50 ± 0.28	0.06
Pre-PCI CFR, mean ± SD	2.2 ± 1.0	1.8 ± 0.7	2.5 ± 1.2	< 0.001
Pre-PCI IMR, mean ± SD	26 ± 13	27 ± 15	25 ± 11	0.43
Pre-PCI IMRc, mean ± SD	20 ± 11	20 ± 13	21 ± 9	0.90
PPG, mean ± SD	0.65 ± 0.14	0.77 ± 0.06	0.53 ± 0.07	< 0.001
Pre-dilatation, n (%)	101 (100)	51 (100.0)	50 (100.0)	NS
Post-dilatation, n (%)	99 (98)	49 (96.1)	50 (100)	0.50
Intravascular imaging, n (%)	22 (21.8)	4 (7.8)	18 (36)	< 0.001
PIOS Applied, n (%)	18 (17.8)	4 (7.8)	14 (28)	0.008
Number of stents (per vessel), mean ± SD	1.45 ± 0.62	1.37 ± 0.53	1.52 ± 0.71	0.24
Stent diameter, mean ± SD	3.22 ± 0.40	3.21 ± 0.41	3.22 ± 0.39	0.81
Total stent length (mm), mean ± SD	41.91 ± 21.18	37.78 ± 19.42	46.12 ± 22.24	0.047
Residual diameter stenosis, mean ± SD	14.9 ± 8.8	14.0 ± 8.6	15.9 ± 9.0	0.30
Residual SYNTAX score, mean ± SD	2.0 ± 3.9	2.7 ± 4.9	1.3 ± 2.6	0.06

Post-PCI Pd/Pa, mean ± SD	0.93 ± 0.05	0.96 ± 0.05	0.91 ± 0.04	< 0.001
Post-PCI dPR	0.92 ± 0.06	0.95 ± 0.06	0.89 ± 0.05	< 0.001
Post-PCI iwFR	0.92 ± 0.07	0.95 ± 0.06	0.89 ± 0.05	< 0.001
Post-PCI RFR	0.91 ± 0.06	0.94 ± 0.06	0.89 ± 0.05	< 0.001
Post-PCI FFR, mean ± SD	0.85 ± 0.09	0.88 ± 0.07	0.84 ± 0.05	< 0.001
Post-PCI resting TT	0.89 ± 0.41	0.81 ± 0.37	0.97 ± 0.44	0.05
Post-PCI hyperaemic TT	0.31 ± 0.20	0.25 ± 0.17	0.32 ± 0.17	0.05
Post-PCI CFR, mean ± SD	3.5 ± 1.8	3.7 ± 1.7	3.4 ± 1.9	0.32
Post-PCI IMR	20 ± 15	18 ± 16	21 ± 14	0.28
Post-PCI IMRc	20 ± 15	18 ± 15	20 ± 14	0.36
Delta Pd/Pa	0.13 ± 0.13	0.17 ± 0.14	0.08 ± 0.10	0.002
% Delta Pd/Pa, mean ± SD	19.9 ± 28.9	27.1 ± 33.6	12.5 ± 21.0	0.01
Normalised % Delta Pd/Pa	63.1 ± 54.3	90.3 ± 57.0	36.0 ± 34.5	< 0.001
Delta dPR	0.16 ± 0.17	0.22 ± 0.18	0.11 ± 0.14	0.001
% Delta dPR, mean ± SD	34.2 ± 66.4	47.2 ± 80.4	21.0 ± 45.3	0.06
Normalised % Delta dPR	61.4 ± 45.2	86.0 ± 43.9	37.4 ± 31.6	< 0.001
Delta iFR_{sim}	0.17 ± 0.19	0.24 ± 0.20	0.11 ± 0.15	0.001
% Delta iFR_{sim}, mean ± SD	43.8 ± 107	61.9 ± 136.5	25.3 ± 60.5	0.10
Normalised % Delta iFR_{sim}	61.0 ± 45.8	86.1 ± 44.0	36.6 ± 32.6	< 0.001
Delta RFR	0.18 ± 0.18	0.24 ± 0.19	0.12 ± 0.15	0.001
% Delta RFR, mean ± SD	42.5 ± 96.1	59.6 ± 122.0	25.0 ± 55.1	0.08
Normalised % Delta RFR	58.5 ± 40.0	80.0 ± 34.3	36.6 ± 33.0	< 0.001
Delta FFR, mean ± SD	0.24 ± 0.14	0.30 ± 0.14	0.19 ± 0.11	< 0.001
% Delta FFR, mean ± SD	47.6 ± 41.8	61.3 ± 48.0	33.4 ± 28.3	< 0.001
Normalised % Delta FFR	60.6 ± 21.7	70.7 ± 19.7	50.2 ± 18.7	< 0.001
Delta resting TT	-0.15 ± 0.38	-0.18 ± 0.39	-0.12 ± 0.37	0.43
% Delta resting TT, mean ± SD	-8.8 ± 41.8	-9.6 ± 50.1	-7.9 ± 32.3	0.84
Delta hyperaemic TT	-0.29 ± 0.34	-0.40 ± 0.37	-0.17 ± 0.24	< 0.001
% Delta hyperaemic TT, mean ± SD	-39 ± 41.6	-51.1 ± 41.9	-26.1 ± 37.6	0.004
Delta CFR, mean ± SD	1.4 ± 1.8	1.9 ± 1.6	0.8 ± 1.8	0.004
% Delta CFR, mean ± SD	85.3 ± 103	119.9 ± 109.1	49.9 ± 83.5	0.001
Delta IMR	-7 ± 12	-10 ± 13	-3 ± 11	0.01
% Delta IMR, mean ± SD	-17.8 ± 48.5	-25.7 ± 54.5	-10.0 ± 40.9	0.13
Delta IMRc	-2 ± 11	-4 ± 11	-1 ± 10	0.14
% Delta IMRc, mean ± SD	-1.7 ± 54.1	-5.8 ± 56.8	2.2 ± 51.7	0.50

Values are n (%) or mean ± SD. CFR=Coronary Flow Reserve; dPR=diastolic pressure ratio; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; LAD=Left Anterior

Descending; LCx=Left Circumflex; MI=Myocardial Infarction; NS=Non-Significant; PCI=Percutaneous Coronary Intervention; Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; PIOS=Physiology-guided Incremental Optimisation Strategy; RCA=Right Coronary Artery; RFR=Resting Full-cycle Ratio; TT=mean Transit Time

Table 4-4 – Spearman correlation between PPG and Patient Reported Outcome Measure scores among patients with angina at baseline (CCS Class I or above)

Patient Reported Outcome Measure	Timepoint (n)	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline (93)	0.09	0.38
	Follow-Up (81)	0.17	0.12
	Absolute Change (76)	0.02	0.85
SAQ Angina Frequency Score (SAQ7-AF)	Baseline (101)	0.04	0.71
	Follow-Up (88)	0.27	0.01
	Absolute Change (88)	0.21	0.05
SAQ Quality of Life Score (SAQ7-QL)	Baseline (101)	0.11	0.26
	Follow-Up (88)	0.19	0.08
	Absolute Change (88)	0.06	0.58
SAQ Summary Score (SAQ7-SS)	Baseline (101)	0.10	0.31
	Follow-Up (88)	0.25	0.02
	Absolute Change (88)	0.13	0.24
EQ-5D-5L UK Weighted Health State	Baseline (101)	0.11	0.26
	Follow-Up (88)	0.27	0.01
	Absolute Change (88)	0.15	0.16

CCS=Canadian Cardiovascular Society; EQ-5D-5L= European Quality-of-Life-5 Dimension-5 Level questionnaire; PCI=Percutaneous Coronary Intervention; PPG=Pullback Pressure Gradient; SAQ=Seattle Angina Questionnaire.

Table 4-5 – Baseline, Follow-Up and Change in SAQ-7 scores stratified by PPG-defined focal vs. diffuse disease in patients with angina (CCS Class 1 or above)

Variables	Overall	Focal (PPG ≥ 0.65)	Diffuse (PPG < 0.65)	p-value
n	101	51	50	
Baseline SAQ-7				
Physical Limitation score, mean ± SD	60.98 ± 25.39	64.63 ± 25.57	57.55 ± 25.00	0.18
Physical Limitation categories				0.65
Very Poor to Poor, n (%)	5/93 (5.4)	2/45 (4.4)	3/48 (6.3)	
Poor to Fair, n (%)	23/93 (24.7)	9/45 (20)	14/48 (29.2)	
Fair to Good, n (%)	29/93 (31.2)	14/45 (31.1)	16/48 (31.3)	
Good to Excellent, n (%)	36/93 (38.7)	20/45 (44.4)	16/48 (33.3)	
Angina Frequency score, mean ± SD	65.05 ± 26.14	66.67 ± 25.82	63.40 ± 26.62	0.53
Angina Frequency categories				0.69
Daily, n (%)	14 (13.9)	5 (9.8)	9 (18)	
Weekly, n (%)	39 (38.6)	21 (41.2)	18 (36)	
Monthly, n (%)	29 (28.7)	15 (29.4)	14 (28)	
None, n (%)	19 (18.8)	10 (19.6)	9 (18)	
Quality-of-Life score, mean ± SD	40.35 ± 26.51	42.65 ± 26.95	38.00 ± 26.12	0.38
Quality-of-Life categories				0.77
Very Poor to Poor, n (%)	26 (25.7)	13 (25.5)	13 (26)	
Poor to Fair, n (%)	34 (33.7)	16 (31.4)	18 (36)	
Fair to Good, n (%)	25 (24.8)	12 (23.5)	13 (26)	
Good to Excellent, n (%)	16 (15.8)	10 (19.6)	6 (12)	
Summary Score, mean ± SD	55.61 ± 22.08	58.04 ± 22.59	53.13 ± 21.50	0.27
Summary Score categories				0.38
Very Poor to Poor, n (%)	8 (7.9)	5 (9.8)	3 (6)	
Poor to Fair, n (%)	36 (35.6)	14 (27.5)	22 (44)	
Fair to Good, n (%)	36 (35.6)	20 (39.2)	16 (32)	
Good to Excellent, n (%)	21 (20.8)	12 (23.5)	9 (18)	
Follow-up SAQ				
Physical Limitation score, mean ± SD	78.40 ± 27.94	83.53 ± 26.07	72.59 ± 29.18	0.08

Physical Limitation categories				0.20
Very Poor to Poor, n (%)	5/81 (6.2)	3/43 (7)	2/38 (5.3)	
Poor to Fair, n (%)	7/81 (8.6)	1/43 (2.3)	6/38 (15.8)	
Fair to Good, n (%)	12/81 (14.8)	6/43 (14)	6/38 (15.8)	
Good to Excellent, n (%)	57/81 (70.4)	33/43 (76.7)	24/38 (63.2)	
Angina Frequency score, mean ± SD	83.52 ± 23.69	89.35 ± 19.37	77.14 ± 26.44	0.02
Angina Frequency categories				0.08
Daily, n (%)	4/88 (4.5)	1/46 (2.2)	3/42 (7.1)	
Weekly, n (%)	16/88 (18.2)	5/46 (10.9)	11/42 (26.2)	
Monthly, n (%)	19/88 (21.6)	9/46 (19.6)	10/42 (23.8)	
None, n (%)	49/88 (55.7)	31/46 (67.4)	18/42 (42.9)	
Quality-of-Life score, mean ± SD	75.28 ± 29.48	80.98 ± 26.58	69.05 ± 31.51	0.06
Quality-of-Life categories				0.56
Very Poor to Poor, n (%)	7/88 (8)	2/46 (4.3)	5/42 (11.9)	
Poor to Fair, n (%)	7/88 (8)	3/46 (6.5)	4/42 (9.5)	
Fair to Good, n (%)	15/88 (17)	8/46 (17.4)	7/42 (16.7)	
Good to Excellent, n (%)	59/88 (67)	33/46 (71.7)	26/42 (61.9)	
Summary Score, mean ± SD	78.88 ± 24.02	84.50 ± 22.46	72.72 ± 24.42	0.02
Summary Score categories				0.09
Very Poor to Poor, n (%)	3/88 (3.4)	2/46 (4.3)	1/42 (2.4)	
Poor to Fair, n (%)	11/88 (12.5)	3/46 (6.5)	8/42 (19)	
Fair to Good, n (%)	14/88 (15.9)	5/46 (10.9)	9/42 (21.4)	
Good to Excellent, n (%)	60/88 (68.2)	36/46 (78.3)	24/42 (57.1)	
Change in SAQ Scores				
Change in Physical Limitation score, mean ± SD	14.20 ± 28.13	16.88 ± 30.74	11.37 ± 25.21	0.40
Change in Angina Frequency score, mean ± SD	19.09 ± 25.89	23.04 ± 28.12	14.76 ± 22.76	0.14
Change in Quality-of-Life score, mean ± SD	34.52 ± 30.15	38.04 ± 31.51	30.66 ± 28.45	0.25
Change in Summary Score, mean ± SD	23.09 ± 23.42	26.43 ± 25.68	19.42 ± 20.33	0.16
Residual Angina (Follow-Up SAQ-AF < 100), n (%)	39/88 (44.3)	15/46 (32.6)	24/42 (57.1)	0.02

SAQ=Seattle Angina Questionnaire

Table 4-6 – Baseline and follow-up EQ-5D-5L scores stratified by PPG-defined focal vs. diffuse disease in patients with angina (CCS Class 1 or above)

Variables	Total	Focal (PPG ≥ 0.65)	Diffuse (PPG < 0.65)	p-value
Baseline EQ-5D-5L				
Mobility score, mean ± SD	1.9 ± 1.1	1.8 ± 1.1	2.0 ± 1.0	0.31
Self-care score, mean ± SD	1.3 ± 0.6	1.3 ± 0.6	1.4 ± 0.6	0.46
Usual activities score, mean ± SD	2.4 ± 1.2	2.4 ± 1.2	2.4 ± 1.2	0.94
Pain score, mean ± SD	2.2 ± 0.9	2.1 ± 0.9	2.4 ± 1.0	0.19
Anxiety and depression score, mean ± SD	1.9 ± 0.9	1.9 ± 0.9	1.9 ± 1.0	0.68
Visual Analogue Scale, mean ± SD	67 ± 19	68 ± 20	66 ± 19	0.53
EQ-5D-5L index, mean ± SD	0.75 ± 0.20	0.76 ± 0.21	0.73 ± 0.20	0.53
Follow-Up EQ-5D-5L				
Mobility score, mean ± SD	1.7 ± 1.1	1.4 ± 0.9	2.0 ± 1.2	0.012
Self-care score, mean ± SD	1.4 ± 0.8	1.2 ± 0.7	1.6 ± 0.9	0.042
Usual activities score, mean ± SD	1.8 ± 1.1	1.6 ± 1.0	2.0 ± 1.1	0.047
Pain score, mean ± SD	1.8 ± 1.0	1.5 ± 0.8	2.2 ± 1.0	< 0.001
Anxiety and depression score, mean ± SD	1.8 ± 1.1	1.6 ± 0.9	1.9 ± 1.2	0.16
Visual Analogue Scale, mean ± SD	74 ± 22	79 ± 20	69 ± 23	0.031
Change in Visual Analogue Scale, mean ± SD	7 ± 22	11 ± 20	3 ± 24	0.07
EQ-5D-5L index, mean ± SD	0.80 ± 0.25	0.87 ± 0.22	0.73 ± 0.27	0.012
Change in Weighted Health Index	0.05 ± 0.20	0.10 ± 0.21	-0.001 ± 0.18	0.019

CCS=Canadian Cardiovascular Society; EQ-5D-5L=European Quality-of-Life–5 Dimensions–5 Levels questionnaire; PPG=Pullback Pressure Gradient index

4.4 Discussion

Percutaneous coronary intervention on a vessel with a focal pattern of coronary artery disease (as defined by a high PPG value on pre-PCI FFR pullback) was associated with larger improvements in coronary physiology metrics and improved angina and quality-of-life scores at 3-month follow-up.

Compared to patients with diffuse disease, those with focal disease had angiographically more severe target lesions with lower FFR and CFR values prior to stenting, however, there were no significant between-group differences in patient-reported symptom or quality-of-life scores at baseline.

Recent data on the physiological distribution and local severity of coronary artery disease as determined by quantitative flow ratio (QFR) virtual pullbacks identified associations between the pattern of coronary artery disease and clinical outcomes after PCI. Among 341 patients, the proportions of suboptimal post-PCI physiology results (defined as post-PCI FFR ≤ 0.85 AND percentage FFR increase ≤ 15%) and the cumulative incidence of Target Vessel Failure at 2 years were significantly higher in patients with predominantly diffuse patterns of coronary disease.(85) Furthermore, a subsequent analysis of 1685 vessels from 1395 patients in whom both pre-PCI QFR-PPG and post-PCI QFR were calculated found that the prognostic implication of pre-PCI functional disease pattern assessed by QFR-PPG index is retained even after successful PCI, and this prognostic value is mostly explained by its direct effect, which is independent of the mediation effect of post-PCI QFR.(86) The prognostic ability of invasively measured PPG for clinical and patient-reported outcomes will be prospectively assessed in the ongoing PPG Global registry (NCT04789317).

Chapter 5 Results – Patient and procedural predictors of residual angina after percutaneous coronary intervention

5.1 Introduction – the impact of residual angina

Residual angina is associated with long-term anxiety, depression, impaired physical function and quality of life.(87) Percutaneous coronary intervention (PCI) achieves greater reductions in myocardial ischaemia than optimal medical therapy alone.(88) The greater the degree of ischaemia in a myocardial territory, the greater the improvement in symptoms following PCI.(51) Patients with moderate or severe ischaemia randomised to an initial invasive strategy in the ISCHEMIA trial had greater improvement in angina-related health status than those assigned to the conservative strategy and larger differences were observed in patients who actually had anginal symptoms at baseline.(89) Nevertheless, persistence or recurrence of angina after PCI is well-recognised and may affect 20-40% of patients during short-to-medium-term follow-up.(57, 90) Total healthcare costs in the first year after an index PCI can be up to 1.8 times greater for patients with angina or chest pain after stenting, with cost differentials continuing out to 36 months post-PCI.(91) Understanding patient factors associated with residual angina may support different approaches to revascularisation.(92) Conflicting data exist regarding the association between invasive coronary measurements and patient-reported outcome measures at follow-up.(93-95) In this chapter, we examine the incidence and associates of residual angina at 3 months post-PCI in the TARGET-FFR trial.

5.2 Definition of angina

The presence of residual angina post-PCI was defined by a patient-reported follow-up Seattle Angina Questionnaire - Angina Frequency (SAQ-AF) score of < 100. Patients with a follow-up of SAQ-AF score = 100 were classified as having no angina.(89, 92) Prior to PCI, in addition to patient-reported SAQ scores, anginal symptoms were also assessed and adjudicated by a physician with a Canadian Cardiovascular Society (CCS) score of Class I or above defining the presence of

angina at baseline. This definition was used for subgroup analyses of patients with anginal symptoms at baseline.

5.3 Statistical analysis

Continuous variables are presented as mean ± SD, and categorical data as counts and percentages. A two-sample t-test was used to compare patient-level characteristics with continuous variables. Categorical variables were compared using the chi-square test without continuity correction. Whenever appropriate, a Fisher's exact test was used instead. 95% confidence intervals (CI) for between-group differences were calculated using the Wald method without continuity correction. Follow-up PROM scores stratified by FFR tertiles were analysed with an ANCOVA model on the parameter's follow-up value adjusted for FFR tertiles and baseline value. Relationship between variables was assessed using Spearman's correlation coefficient.

5.4 Population and baseline demographics

Of 260 participants, 230 (88.5%) provided follow-up SAQ-AF scores 3 months (median [IQR] 105 [31] days) post-PCI. For the purposes of this analysis, patients were stratified by the presence of residual angina. Eighty-eight (38.3%) of 230 patients had residual angina as determined by a SAQ-AF score < 100. 10.2% of those patients (9/88) had a baseline SAQ-AF score of 100 prior to undergoing PCI. Clinical characteristics at baseline are presented in Table 5-1. Patients with residual angina had higher rates of previous myocardial infarction (MI) and PCI. The incidence of atrial fibrillation and current cigarette smoking were also higher in the residual angina group. Patients with residual angina had significantly higher CCS scores at baseline and were prescribed more anti-anginal drugs with greater utilization of oral nitrate tablets and more frequent use of reliever sublingual nitrate spray.

Table 5-1 – Baseline clinical characteristics stratified by presence of residual angina 3 months post-PCI

Variables	Total	No Residual Angina	Residual Angina	p-value
Number of patients, n (%)	230	142 (61.7)	88 (38.3)	
Male, n (%)	202 (87.8)	127 (89.4)	75 (85.2)	0.34
Age years, mean (SD)	60.9 ± 8.6	60.9 ± 8	61 ± 9.5	0.91
BMI, mean (SD)	29.8 ± 5.5	29 ± 4.8	31 ± 6.3	0.013
Family history of CAD, n (%)	153 (66.5)	94 (66.2)	59 (67)	0.90
Smoking status, n (%)				0.04
Non-smoker	72 (31.3)	48 (33.8)	24 (27.3)	
Current Smoker	37 (16.1)	16 (11.3)	21 (23.9)	
Ex-smoker	121 (52.6)	78 (54.9)	43 (48.9)	
Hypertension, n (%)	103 (44.8)	57 (40.1)	46 (52.3)	0.07
Dyslipidaemia, n (%)	128 (55.7)	84 (59.2)	44 (50)	0.17
Heart Failure, n (%)	53 (23)	31 (21.8)	22 (25)	0.58
Diabetes, n (%)	39 (17)	19 (13.4)	20 (22.7)	0.066
Atrial Fibrillation, n (%)	18 (7.8)	6 (4.2)	12 (13.6)	0.01
Chronic Kidney Disease, n (%)	4 (1.7)	2 (1.4)	2 (2.3)	0.64
Indication for PCI, n (%)				0.39
Stable Angina	67 (29.1)	40 (28.2)	27 (30.7)	
ACS – UA/NSTEMI	91 (39.6)	61 (43)	30 (34.1)	
Staged Completion of Revascularisation	72 (31.3)	41 (28.9)	31 (35.2)	
Previous MI	83 (36.1)	43 (30.3)	40 (45.5)	0.02
Previous PCI, n (%)	86 (37.4)	45 (31.7)	41 (46.6)	0.02
Baseline CCS Angina Class, n (%)				< 0.001
CCS 0	36 (15.7)	31 (21.8)	5 (5.7)	
CCS 1	56 (24.3)	45 (31.7)	11 (12.5)	
CCS 2	85 (37)	44 (31)	41 (46.6)	
CCS 3	52 (22.6)	21 (14.8)	31 (35.2)	
CCS 4	1 (0.4)	1 (0.7)	0	
Baseline SAQ-AF = 100	62 (27)	53 (37.3)	9 (10.2)	< 0.001
Medications				
Any antiplatelet, n (%)	223 (97)	141 (99.3)	82 (93.2)	0.014
DAPT, n (%)	160 (69.6)	97 (68.3)	63 (71.6)	0.60
Oral anticoagulant, n (%)	16 (7)	3 (2.1)	13 (14.8)	< 0.001
Statins, n (%)	221 (96.1)	139 (97.9)	82 (93.2)	0.09
ACEI, n (%)	150 (65.2)	95 (66.9)	55 (62.5)	0.50
ARB, n (%)	23 (10)	10 (7)	13 (14.8)	0.06
Diuretics, n (%)	27 (11.7)	12 (8.5)	15 (17)	0.049
Number of Anti-anginal Agents, mean (SD)	1.73 ± 0.82	1.58 ± 0.78	1.97 ± 0.84	< 0.001
Beta-blocker, n (%)	208 (90.4)	126 (88.7)	82 (93.2)	0.26

Calcium channel blocker, n (%)	45 (19.6)	26 (18.3)	19 (21.6)	0.54
Nicorandil, n (%)	17 (7.4)	8 (5.6)	9 (10.2)	0.20
Ivabradine, n (%)	4 (1.7)	2 (1.4)	2 (2.3)	0.64
Oral Nitrates, n (%)	66 (28.7)	33 (23.2)	33 (37.5)	0.02
Frequency of GTN spray use, n (%)				< 0.001
None	115 (50)	89 (62.7))	26 (29.5))	
Daily	29 (12.6)	11 (7.7)	18 (20.5)	
Weekly	61 (26.5)	27 (19)	34 (38.6)	
Monthly	25 (10.9)	15 (10.6)	10 (11.4)	

ACEI=Angiotensin-Converting Enzyme Inhibitor; ACS-UA/NSTEMI=Acute Coronary Syndrome-Unstable Angina/Non-ST segment Elevation Myocardial Infarction; ARB=Angiotensin-Receptor Blocker; BMI=Body Mass Index; CCS=Canadian Cardiovascular Society; DAPT=Dual Anti-Platelet Therapy; GTN=Glyceryl Trinitrate; PCI=Percutaneous Coronary Intervention

5.5 Procedural outcomes

Procedural and coronary physiology characteristics are presented in Table 5-2. There were no differences between groups in the angiographic severity of stenoses or procedural characteristics such as lesion preparation, stent length, post-dilation, and use of intracoronary imaging. Patients who were angina-free at follow-up had physiologically more severe lesions prior to PCI and achieved significantly larger improvements in hyperaemic and non-hyperaemic pressure ratios after stenting. There were no between-group differences in either post-PCI physiology metrics or in the proportion of patients who received additional intervention through the study's post-PCI physiology-guided optimisation protocol.

Table 5-2 – Baseline procedural and coronary physiology characteristics stratified by presence of residual angina 3 months post-PCI

Variables	Overall	No Residual Angina	Residual Angina	p-value
n	230	142	88	
Diameter stenosis (%), mean ± SD	65.9 ± 15.4	67 ± 15.3	64.1 ± 15.4	0.17
Lesion length, mean ± SD	12.2 ± 6.0	12.3 ± 6.4	12.1 ± 5.4	0.77
AHA/ACC Lesion type, n (%)				0.08
A	40 (17.4)	31 (21.8)	9 (10.2)	
B1	83 (36.1)	44 (31)	39 (44.3)	
B2	91 (39.6)	57 (40.1)	34 (38.6)	
C	16 (7)	10 (7)	6 (6.8)	
SYNTAX score, mean ± SD	11.2 ± 8.1	11.6 ± 8.4	10.5 ± 7.6	0.29
BCIS Jeopardy score, mean ± SD	5.0 ± 3.0	4.9 ± 3.1	5.1 ± 2.9	0.70
Pre-PCI Pd/Pa, mean ± SD	0.75 ± 0.18	0.73 ± 0.19	0.79 ± 0.15	0.008
Pre-PCI FFR, mean ± SD	0.58 ± 0.14	0.56 ± 0.15	0.62 ± 0.13	0.003
Pre-PCI resting TT	1.13 ± 0.44	1.16 ± 0.43	1.08 ± 0.47	0.21
Pre-PCI hyperaemic TT	0.69 ± 0.40	0.75 ± 0.41	0.60 ± 0.35	0.005
Pre-PCI CFR, mean ± SD	1.9 ± 0.9	1.8 ± 0.8	2.1 ± 1.0	0.008
Pre-PCI IMR	28 ± 12	29 ± 12	27 ± 13	0.22
Pre-PCI IMRc	21 ± 11	20 ± 10	21 ± 11	0.69
Pre-dilatation, n (%)	230 (100)	142 (100.0)	88 (100.0)	NA
Post-dilatation, n (%)	225 (97.8)	138 (97.2)	87 (98.9)	0.65
Intravascular imaging, n (%)	36 (15.7)	22 (15.5)	14 (15.9)	0.93
PIOS Applied, n (%)	33 (14.3)	24 (16.9)	9 (10.2)	0.16
Number of stents (per vessel), mean ± SD	1.46 ± 0.66	1.45 ± 0.67	1.47 ± 0.66	0.87
Stent diameter (mm) mean ± SD	3.22 ± 0.43	3.19 ± 0.42	3.26 ± 0.44	0.20
Total stent length (mm), mean ± SD	41.8±20.1	41.2±19.7	42.7±20.8	0.57
Residual diameter stenosis (%), mean ± SD	14.2 ± 8.6	13.9 ± 8.8	14.6 ± 8.4	0.52
Residual SYNTAX score, mean ± SD	2.31 ± 4.38	2.27 ± 4.12	2.37 ± 4.82	0.87
Post-PCI Pd/Pa, mean ± SD	0.94 ± 0.05	0.94 ± 0.06	0.94 ± 0.05	0.51
Post-PCI FFR, mean ± SD	0.86 ± 0.08	0.86 ± 0.09	0.86 ± 0.07	0.87
Post-PCI resting TT	0.91 ± 0.42	0.95 ± 0.44	0.85 ± 0.38	0.09
Post-PCI hyperaemic TT	0.32 ± 0.21	0.33 ± 0.21	0.32 ± 0.20	0.79
Post-PCI CFR, mean ± SD	3.4 ± 1.9	3.4 ± 1.8	3.4 ± 2.2	0.90
Post-PCI IMR	22 ± 17	22 ± 17	22 ± 16	0.86
Post-PCI IMRc	21 ± 16	21 ± 17	21 ± 16	0.88

Delta Pd/Pa	0.19 ± 0.18	0.22 ± 0.19	0.15 ± 0.15	0.004
% Delta Pd/Pa, mean ± SD	37 ± 57.4	44.1 ± 63.3	25.4 ± 44.2	0.014
Delta FFR, mean ± SD	0.28 ± 0.15	0.30 ± 0.16	0.23 ± 0.13	0.001
% Delta FFR, mean ± SD	58.3 ± 46.5	67.0 ± 50.7	43.1 ± 33.5	< 0.001
Delta resting TT	-0.22 ± 0.46	-0.21 ± 0.48	-0.23 ± 0.42	0.77
% Delta resting TT, mean ± SD	-11.8 ± 43.2	-11.2 ± 44.6	-12.8 ± 41.1	0.79
Delta hyperaemic TT	-0.38 ± 0.41	-0.44 ± 0.42	-0.29 ± 0.37	0.008
% Delta hyperaemic TT, mean ± SD	-43.3 ± 41.9	-48.8 ± 32.1	-34.9 ± 52.7	0.036
Delta CFR, mean ± SD	1.5 ± 1.8	1.7 ± 1.8	1.3 ± 1.9	0.18
% Delta CFR, mean ± SD	103.8 ± 131	122.7 ± 147.2	75.1 ± 95.8	0.006
Delta IMR	-7 ± 16	-9 ± 15	-5 ± 18	0.12
% Delta IMR, mean ± SD	-16 ± 66	-23.2 ± 47.8	-6 ± 87.4	0.12
Delta IMRc	-1 ± 15	-1 ± 14	0 ± 16	0.72
% Delta IMRc, mean ± SD	14 ± 126	11.8 ± 128.3	16.2 ± 122	0.82
Periprocedural MI, n (%)	7 (3)	3 (2.1)	4 (4.5)	0.43

ACC=American College of Cardiology; AHA=American Heart Association; BCIS=British Cardiovascular Intervention Society; CFR=Coronary Flow Reserve; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc=Index of Microcirculatory Resistance corrected for epicardial stenosis (Yong's formula); Pd/Pa=Ratio of resting distal coronary to aortic pressure; PIOS=Physiology-guided Optimisation Protocol; PPG=Pullback Pressure Gradient; SD=Standard Deviation; TT=Transit Time. Percentage change was defined as ([Post-PCI Value – Pre-PCI Value] / Pre-PCI Value x 100).

5.6 Patient-Reported Outcome Measures

Patients with residual angina had significantly lower SAQ scores at baseline and follow-up compared to patients free from angina (Table 5-3) and no change in the mean EQ-5D-5L health index score (Table 5-4) post-PCI. Among patients who had angina at baseline (CCS Class I and above), FFR and CFR correlated with the absolute PROM scores at follow-up. FFR had a moderate, positive correlation with follow-up SAQ-AF scores. CFR had a similar, albeit weaker, correlation. This reflected negative correlations with the pre-PCI SAQ-AF score rather than positive correlations with post-PCI values (Table 5-5 & 5-7). Pre-PCI and percentage change in FFR both also had significant, albeit somewhat weaker, correlations with the other SAQ domains and the EQ-5D-5L weighted health index score (Tables 5-5 & 5-6). The magnitude of change in pressure ratios was predicated by the pre- rather than post-PCI value and patients with residual angina tended to have achieved smaller changes in FFR following PCI (Figures 5-1 & 5-2). There was no correlation between IMR (corrected for epicardial stenosis) and patient-reported outcome measures (Tables 5-9 & 5-10).

5.7 Clinical outcomes

The rate of target vessel failure at a median [IQR] follow-up of 3 [0.9] years was 1.7% (4/230) with no significant difference between groups (No Angina, 0.7% vs. Residual Angina, 3.4%, p=0.16).

Table 5-3 – Baseline, Follow-Up and Change in SAQ-7 scores stratified by presence of residual angina (SAQ-AF score < 100 at follow-up)

Variables	Overall	No Residual Angina	Residual Angina	p-value
n	230	142	88	
Baseline SAQ-7				
Physical Limitation score, mean ± SD	68.61±26.66	76.24±24.71	57.34±25.53	< 0.001
Physical Limitation categories				< 0.001
Very Poor to Poor, n (%)	7/208 (3.4)	2/124 (1.6)	5/84 (6)	
Poor to Fair, n (%)	38/208 (18.3)	14/124 (11.3)	24/84 (28.6)	
Fair to Good, n (%)	58/208 (27.9)	31/124 (25)	27/84 (32.1)	
Good to Excellent, n (%)	105/208 (50.5)	77/124 (62.1)	28/84 (33.3)	
Angina Frequency score, mean ± SD	68.83±28.73	76.27±27.20	56.82± 7.15	< 0.001
Angina Frequency categories				< 0.001
Daily, n (%)	35 (15.2)	13 (9.2)	22 (25)	
Weekly, n (%)	63 (27.4)	30 (21.1)	33 (37.5)	
Monthly, n (%)	70 (30.4)	46 (32.4)	24 (27.3)	
None, n (%)	62 (27)	53 (37.3)	9 (10.2)	
Quality of Life score, mean ± SD	48.75±30.54	56.07±30.61	36.93±26.59	< 0.001
Quality of Life categories				< 0.001
Very Poor to Poor, n (%)	46 (20)	18 (12.7)	28 (31.8)	
Poor to Fair, n (%)	69 (30)	38 (26.8)	31 (35.2)	
Fair to Good, n (%)	50 (21.7)	33 (23.2)	17 (19.3)	
Good to Excellent, n (%)	65 (28.3)	53 (37.3)	12 (13.6)	
Summary Score, mean ± SD	62.10±25.30	69.48±24.12	50.20±22.59	< 0.001
Summary Score categories				< 0.001
Very Poor to Poor, n (%)	17 (7.4)	6 (4.2)	11 (12.5)	
Poor to Fair, n (%)	61 (26.5)	25 (17.6)	36 (40.9)	
Fair to Good, n (%)	69 (30)	41 (28.9)	28 (31.8)	
Good to Excellent, n (%)	83 (36.1)	70 (49.3)	13 (14.8)	
Follow-up SAQ				
Physical Limitation score, mean ± SD	81.69±25.73	91.20±18.88	66.82±27.99	< 0.001
Physical Limitation categories				< 0.001

Very Poor to Poor, n (%)	10/205 (4.9)	3/125 (2.4)	7/80 (8.8)	
Poor to Fair, n (%)	15/205 (7.3)	3/125 (2.4)	12/80 (15)	
Fair to Good, n (%)	24/205 (11.7)	8/125 (6.4)	16/80 (20)	
Good to Excellent, n (%)	156/205 (76.1)	111/125 (88.8)	45/80 (56.3)	
Angina Frequency score, mean ± SD	87.65±19.84	100±0	67.73±19.64	< 0.001
Angina Frequency categories				< 0.001
Daily, n (%)	5 (2.2)	0	5 (5.7)	
Weekly, n (%)	32 (13.9)	0	32 (36.4)	
Monthly, n (%)	51 (22.2)	0	51 (58)	
None, n (%)	142 (61.7)	142 (100)	0	
Quality-of-Life score, mean ± SD	80.11±27.16	93.66±13.95	58.24±28.92	< 0.001
Quality-of-Life categories				< 0.001
Very Poor to Poor, n (%)	12 (5.2)	0	12 (13.6)	
Poor to Fair, n (%)	19 (8.3)	2 (1.4)	17 (19.3)	
Fair to Good, n (%)	28 (12.2)	8 (5.6)	20 (22.7)	
Good to Excellent, n (%)	171 (74.3)	132 (93)	39 (44.3)	
Summary Score, mean ± SD	83.24±21.47	95.16±8.72	64.01±22	< 0.001
Summary Score categories				< 0.001
Very Poor to Poor, n (%)	3 (1.3)	0	3 (3.4)	
Poor to Fair, n (%)	22 (9.6)	0	22 (25)	
Fair to Good, n (%)	36 (15.7)	7 (4.9)	29 (33)	
Good to Excellent, n (%)	169 (73.5)	135 (95.1)	34 (38.6)	
Change in SAQ Scores				
Change in Physical Limitation score, mean ± SD	13.81±27.64	17.69±27.27	8.28±27.38	0.02
Change in Angina Frequency score, mean ± SD	18.83±28.13	23.73±27.20	10.91 ± 27.94	< 0.001
Change in Quality-of-Life score, mean ± SD	31.36±30.75	37.59±29.27	21.31±30.57	< 0.001
Change in Summary Score, mean ± SD	21.14±24.73	25.68±24.25	13.81±23.85	< 0.001

SAQ=Seattle Angina Questionnaire

Table 5-4 – Baseline and follow-up EQ-5D-5L scores stratified by presence of residual angina 3 months post-PCI

Variables	Total	No Residual Angina	Residual Angina	p-value
Baseline EQ-5D-5L				
Mobility score, mean ± SD	1.8 ± 1.0	1.6 ± 0.9	2.2 ± 1.0	< 0.001
Self-care score, mean ± SD	1.2 ± 0.5	1.1 ± 0.3	1.4 ± 0.6	< 0.001
Usual activities score, mean ± SD	2.2 ± 1.2	2.0 ± 1.1	2.6 ± 1.1	< 0.001
Pain score, mean ± SD	2.0 ± 1.0	1.7 ± 0.9	2.4 ± 1.0	< 0.001
Anxiety and depression score, mean ± SD	1.8 ± 0.9	1.6 ± 0.8	2.2 ± 0.9	< 0.001
Visual Analogue Scale, mean ± SD	69.8 ± 18.2	74.2 ± 16.6	62.9 ± 18.7	< 0.001
EQ-5D-5L index, mean ± SD	0.78 ± 0.20	0.84 ± 0.15	0.69 ± 0.22	< 0.001
Follow-Up EQ-5D-5L				
Mobility score, mean ± SD	1.6 ± 1.0	1.3 ± 0.8	2.1 ± 1.1	< 0.001
Self-care score, mean ± SD	1.3 ± 0.7	1.1 ± 0.4	1.6 ± 0.9	< 0.001
Usual activities score, mean ± SD	1.7 ± 1.0	1.4 ± 0.7	2.3 ± 1.1	< 0.001
Pain score, mean ± SD	1.7 ± 0.9	1.4 ± 0.8	2.3 ± 0.9	< 0.001
Anxiety and depression score, mean ± SD	1.7 ± 1.1	1.4 ± 0.7	2.3 ± 1.3	< 0.001
Visual Analogue Scale, mean ± SD	76.9 ±18.3	83.5 ±12.4	66.2 ± 21.2	< 0.001
EQ-5D-5L index, mean ± SD	0.82 ± 0.23	0.91 ± 0.17	0.69 ± 0.26	< 0.001
Change in Weighted Health Index	0.04 ± 0.22	0.07 ± 0.18	-.001 ± 0.26	0.03

EQ-5D-5L: European Quality-of-Life–5 Dimensions–5 Levels questionnaire

Table 5-5 – Spearman correlation between FFR and follow-up Patient Reported Outcome Measure scores among patients with angina at baseline (CCS class I and above)

Patient Reported Outcome Measure	FFR	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.21	0.008
	Post-PCI	0.07	0.39
	Absolute Change	0.26	0.002
	Percentage Change	0.26	0.001
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.31	< 0.0001
	Post-PCI	0.07	0.35
	Absolute Change	0.35	<0.0001
	Percentage Change	0.36	< 0.0001
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.17	0.02
	Post-PCI	0.03	0.70
	Absolute Change	0.21	0.008
	Percentage Change	0.22	0.006
SAQ Summary Score (SAQ7-SS)	Baseline	-0.26	0.0004
	Post-PCI	0.01	0.90
	Absolute Change	0.29	0.0002
	Percentage Change	0.30	< 0.0001
EQ-5D-5L UK Weighted Health State	Baseline	-0.15	0.04
	Post-PCI	0.02	0.80
	Absolute Change	0.20	0.011
	Percentage Change	0.21	0.008

FFR=Fractional Flow Reserve; PCI=Percutaneous Coronary Intervention; SAQ=Seattle Angina Questionnaire. Percentage change was defined as ([Post-PCI Value – Pre-PCI Value] / Pre-PCI Value x 100).

Table 5-6 – Follow-Up PROM scores stratified by tertiles of FFR at baseline, post-PCI, and percentage change among patients with angina at baseline (CCS class I and above)

FFR		Low		Intermediate		High		p value
	Patient Reported Outcome	**N**	**Score**	**N**	**Score**	**N**	**Score**	
Baseline	SAQ Physical Limitation Score	55	83.79±25.68	53	81.05±24.98	51	75.82±24.80	0.30
	SAQ Angina Frequency Score	61	93.77±13.31	59	82.71±23.48	54	80.74±23.14	0.001
	SAQ Quality of Life Score	61	84.02±23.62	59	75.64±29.94	54	74.31±28.98	0.12
	SAQ Summary Score	61	87.60±17.75	59	79.17±24.47	54	77.02±23.61	0.02
	EQ-5D-5L Health State (UK)	61	0.84±0.25	59	0.78±0.27	54	0.79±0.24	0.35
Post-PCI	SAQ Physical Limitation Score	51	81.54±23.94	57	77.92±26.70	54	80.86±28.94	0.75
	SAQ Angina Frequency Score	58	84.48±21.70	62	86.29±20.74	59	87.29±19.99	0.76
	SAQ Quality of Life Score	58	77.59±29.22	62	76.41±26.31	59	77.54±29.89	0.97
	SAQ Summary Score	58	81.62±22.46	62	80.25±20.72	59	81.17±24.12	0.94
	EQ-5D-5L Health State (UK)	58	0.82±0.24	62	0.81±0.21	59	0.79±0.29	0.87
Percentage Change	SAQ Physical Limitation Score	47	71.81±30.07	48	83.16±24.76	52	85.90±23.89	0.02
	SAQ Angina Frequency Score	50	78.60±23.56	55	85.09±21.33	57	94.39±13.89	< 0.001
	SAQ Quality of Life Score	50	71.75±29.75	55	77.95±28.05	57	84.43±23.89	0.06

	SAQ Summary Score	50	74.51±24.20	55	81.45±22.38	57	88.23±18.29	0.006
	EQ-5D-5L Health State (UK)	50	0.76±0.26	55	0.81±0.24	57	0.84±0.26	0.29

FFR=Fractional Flow Reserve; PCI=Percutaneous Coronary Intervention; SAQ=Seattle Angina Questionnaire.

Table 5-7 – Spearman correlation between CFR and follow-up Patient Reported Outcome Measure scores among patients with angina at baseline (CCS Class I and above)

Patient Reported Outcome Measure	CFR	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.08	0.32
	Post-PCI	0.10	0.21
	Absolute Change	0.18	0.02
	Percentage Change	0.21	0.008
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.24	0.002
	Post-PCI	0.08	0.26
	Absolute Change	0.20	0.009
	Percentage Change	0.26	< 0.001
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.13	0.10
	Post-PCI	0.03	0.64
	Absolute Change	0.12	0.12
	Percentage Change	0.16	0.036
SAQ Summary Score (SAQ7-SS)	Baseline	-0.16	0.03
	Post-PCI	0.07	0.37
	Absolute Change	0.17	0.03
	Percentage Change	0.21	0.005
EQ-5D-5L UK Weighted Health Index	Baseline	-0.06	0.40
	Post-PCI	0.09	0.21
	Absolute Change	0.17	0.025
	Percentage Change	0.20	0.01

CCS=Canadian Cardiovascular Society; CFR=Coronary Flow Reserve; EQ-5D-5L=European Quality-of-Life-5 Dimension-5 Level questionnaire; PCI=Percutaneous Coronary Intervention; SAQ=Seattle Angina Questionnaire.

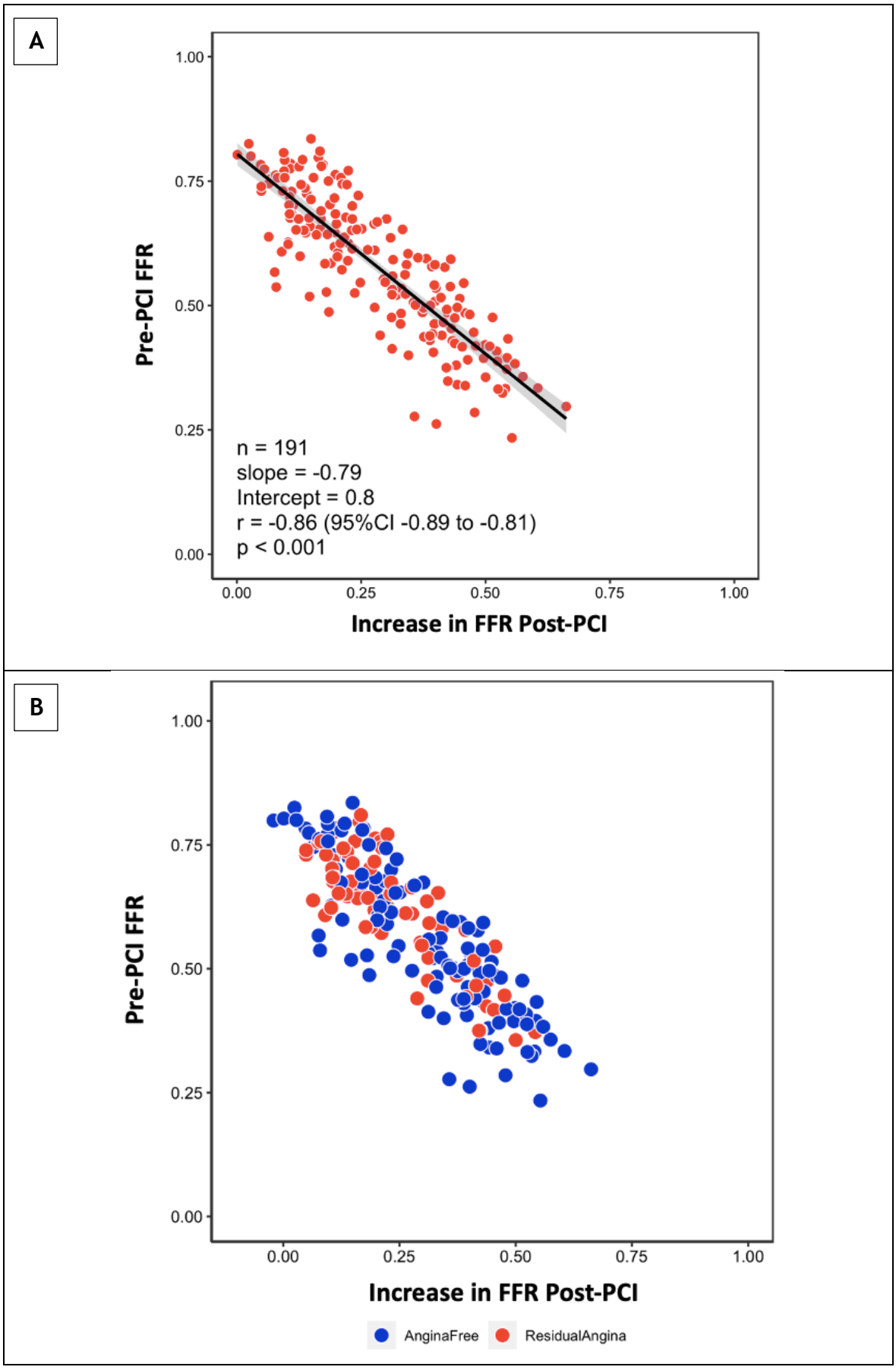
Table 5-8 – PROM scores 3 months post-PCI stratified by tertiles of CFR at baseline, post-PCI, and percentage change among patients with angina at baseline

CFR		Low		Intermediate		High		p value
	Patient Reported Outcome	**N**	**Score**	**N**	**Score**	**N**	**Score**	
Baseline	SAQ Physical Limitation Score	52	81.57±26.58	53	78.77±27.23	54	78.32±26.59	0.80
	SAQ Angina Frequency Score	61	91.31±16.48	56	83.04±22.96	57	80.53±23.18	0.015
	SAQ Quality of Life Score	61	81.56±25.88	56	75.67±31.21	57	74.12±28.14	0.32
	SAQ Summary Score	61	85.00±19.86	56	78.70±25.58	57	77.65±21.99	0.16
	EQ-5D-5L Health State (UK)	61	0.80±0.27	56	0.84±0.19	57	0.77±0.27	0.34
Post-PCI	SAQ Physical Limitation Score	56	75.52±26.83	51	83.99±23.62	63	81.22±27.80	0.23
	SAQ Angina Frequency Score	62	83.55±21.36	61	85.41±23.49	64	88.75±16.57	0.36
	SAQ Quality of Life Score	62	75.81±30.52	61	77.05±30.21	64	79.88±24.05	0.71
	SAQ Summary Score	62	77.93±23.95	61	82.09±23.16	64	83.38±20.10	0.37
	EQ-5D-5L Health State (UK)	62	0.80±0.23	61	0.80±0.23	64	0.82±0.27	0.86
Percentage Change	SAQ Physical Limitation Score	50	70.58±27.00	51	86.93±22.25	52	80.61±27.89	0.007
	SAQ Angina Frequency Score	55	76.18±25.35	55	90.00±15.87	58	89.14±18.28	< 0.001
	SAQ Quality of Life Score	55	68.18±33.14	55	85.45±19.80	58	78.88±28.02	0.005

	SAQ Summary Score	55	71.90±25.71	55	87.38±16.11	58	82.58±22.47	0.006
	EQ-5D-5L Health State (UK)	55	0.72±0.25	55	0.88±0.17	58	0.81±0.27	< 0.001

CFR=Coronary Flow Reserve; EQ-5D-5L=European Quality-of-Life-5 Dimension-5 Level questionnaire; PCI=Percutaneous Coronary Intervention; PROM=Patient-Reported Outcome Measure; SAQ=Seattle Angina Questionnaire

Figure 5-1 – Correlation between pre-PCI and change in FFR values with stratification by presence of residual angina 3 months post-PCI



Correlation between pre-PCI FFR and change in FFR values (Panel A) with stratification by presence of residual angina (Panel B). Figures courtesy of Dr Takuya Mizukami.

Figure 5-2 – Change in FFR from pre- to post-PCI stratified by presence of residual angina 3 months post-PCI

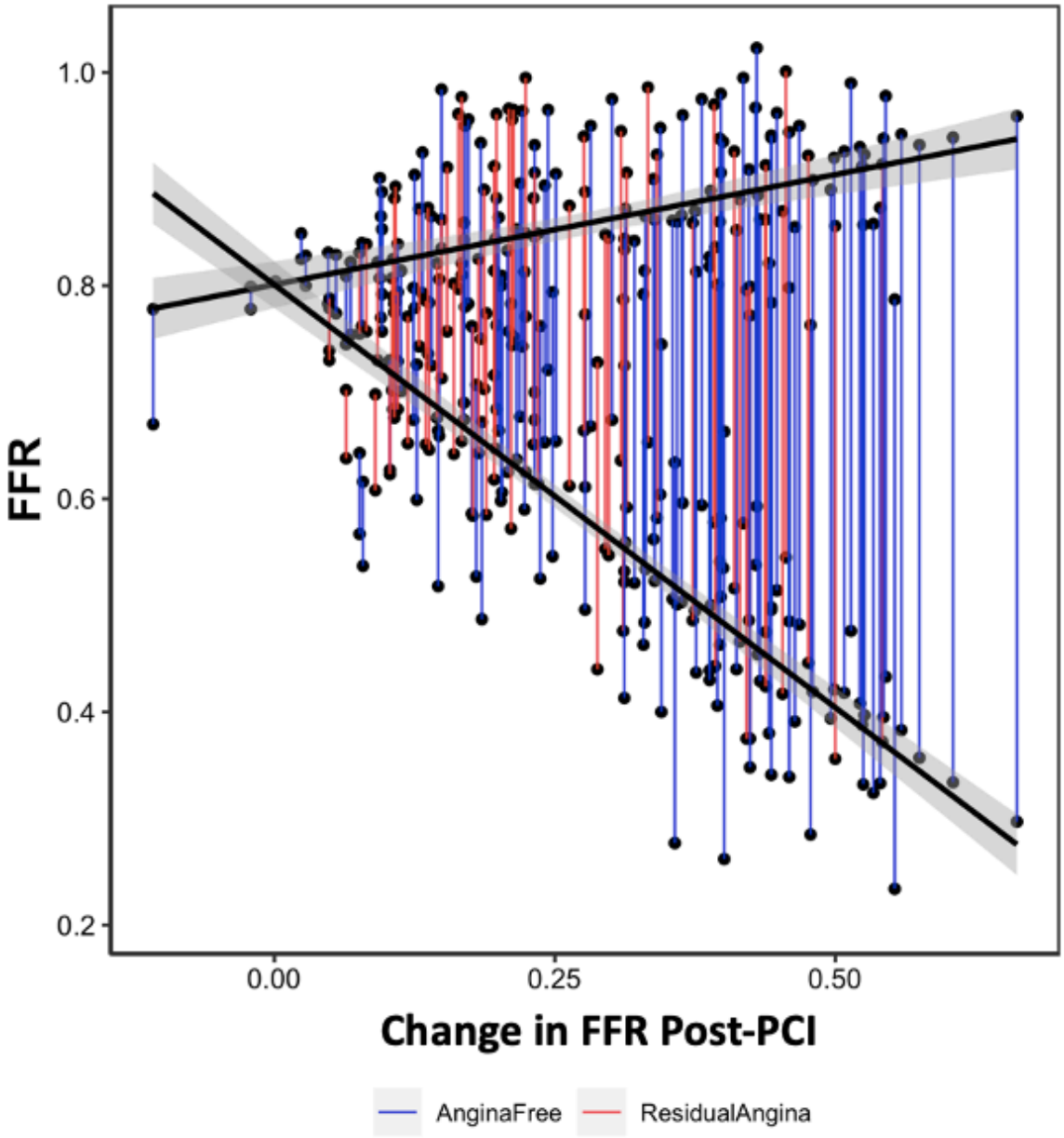


Figure courtesy of Dr Takuya Mizukami.

Table 5-9 – Spearman correlation between corrected IMR (IMRc) and Patient Reported Outcome Measure scores 3 months post-PCI among patients with angina at baseline (CCS Class I and above)

Patient Reported Outcome Measure	IMRc	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.02	0.82
	Post-PCI	0.02	0.70
	Absolute Change	-0.02	0.85
	Percentage Change	0.04	0.64
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.04	0.62
	Post-PCI	-0.05	0.54
	Absolute Change	-0.03	0.67
	Percentage Change	-0.03	0.73
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.04	0.59
	Post-PCI	-0.04	0.59
	Absolute Change	0.02	0.84
	Percentage Change	0.04	0.64
SAQ Summary Score (SAQ7-SS)	Baseline	-0.03	0.68
	Post-PCI	-0.04	0.56
	Absolute Change	-0.01	0.88
	Percentage Change	0.02	0.78
EQ-5D-5L UK Weighted Health Index	Baseline	-0.08	0.29
	Post-PCI	-0.08	0.26
	Absolute Change	-0.02	0.81
	Percentage Change	0.01	0.95

CCS=Canadian Cardiovascular Society; IMRc=Index of Microcirculatory Resistance corrected for epicardial stenosis (Yong's formula); EQ-5D-5L= European Quality-of-Life-5 Dimension-5 Level questionnaire; PCI=Percutaneous Coronary Intervention; SAQ=Seattle Angina Questionnaire.

Table 5-10 – PROM scores 3 months post-PCI stratified by tertiles of IMRc at baseline, post-PCI, and percentage change among patients with angina at baseline

IMRc		Low		Intermediate		High		p value
	Patient Reported Outcome	**N**	**Score**	**N**	**Score**	**N**	**Score**	
Baseline	SAQ Physical Limitation Score	53	83.73±25.32	47	78.37±26.28	50	76.83±29.66	0.40
	SAQ Angina Frequency Score	56	86.61±20.56	53	83.58±21.93	56	84.82±22.07	0.76
	SAQ Quality of Life Score	56	80.58±25.99	53	74.29±28.42	56	77.01±30.60	0.51
	SAQ Summary Score	56	83.59±20.09	53	79.12±22.84	56	79.42±25.14	0.51
	EQ-5D-5L Health State (UK)	56	0.84±0.24	53	0.79±0.23	56	0.78±0.27	0.39
Post-PCI	SAQ Physical Limitation Score	60	77.50±27.07	51	86.60±23.57	55	76.59±27.95	0.10
	SAQ Angina Frequency Score	63	85.08±21.01	60	88.67±18.91	60	83.83±22.33	0.42
	SAQ Quality of Life Score	63	76.98±27.42	60	80.83±27.47	60	74.79±30.14	0.50
	SAQ Summary Score	63	80.18±21.63	60	85.13±22.06	60	77.87±23.71	0.20
	EQ-5D-5L Health State (UK)	63	0.81±0.23	60	0.84±0.26	60	0.77±0.23	0.37
Absolute Change	SAQ Physical Limitation Score	47	79.61±27.68	50	80.67±25.22	46	78.17±28.75	0.90
	SAQ Angina Frequency Score	53	85.85±20.80	55	87.27±19.76	50	82.00±22.95	0.43
	SAQ Quality of Life Score	53	76.65±29.83	55	79.32±26.38	50	76.50±28.86	0.85

	SAQ Summary Score	53	80.46±24.03	55	82.81±21.01	50	78.84±23.48	0.67
	EQ-5D-5L Health State (UK)	53	0.80±0.28	55	0.83±0.19	50	0.78±0.26	0.54
Percentage Change	SAQ Physical Limitation Score	47	77.84±29.61	48	82.29±24.04	48	78.39±27.57	0.68
	SAQ Angina Frequency Score	54	85.19±21.61	53	88.30±18.99	51	81.76±22.60	0.29
	SAQ Quality of Life Score	54	75.69±29.78	53	81.37±26.47	51	75.49±28.39	0.48
	SAQ Summary Score	54	79.50±24.77	53	84.34±20.74	51	78.39±22.52	0.36
	EQ-5D-5L Health State (UK)	54	0.79±0.28	53	0.84±0.19	51	0.78±0.25	0.46

EQ-5D-5L= European Quality-of-Life-5 Dimension-5 Level questionnaire; IMRc=Index of Microcirculatory Resistance corrected for epicardial stenosis (Yong's formula); PCI=Percutaneous Coronary Intervention; PROM=Patient-Reported Outcome Measure; SAQ=Seattle Angina Questionnaire

5.8 Discussion

One in three patients in the TARGET-FFR randomised trial reported residual angina three months after undergoing PCI which, while a substantial proportion, is not unprecedented. In the ABSORB IV trial, 39% (494/1265) of patients in the drug-eluting stent arm had physician-adjudicated angina or angina-equivalent symptoms at 1-year follow-up.(57)

The process of defining residual angina presents its own challenges and alternative definitions could have been applied in the present study with a resultant variation in the reported incidence. For example, when considering angina at baseline, 71.9% of patients (187/260) had angina as defined by a patient-reported SAQ-Angina Frequency score < 100; 82.7% (215/260) had angina as defined by physician-adjudicated CCS Class 1 and above; and 90.8% (236/260) had angina as defined by a patient-reported SAQ-Summary Score < 100. The rates of residual angina as defined by SAQ-AF score < 100 and SAQ-SS score < 100 were 38.3% (88/230) and 62.2% (143/230) respectively. CCS Class at follow-up is not available.

As the impact of anginal symptoms is inherently subjective, we concluded that attempting to define a level of residual angina that might be acceptable to patients or represent a clinically meaningful improvement would be arbitrary and ultimately futile. Improved but persistent symptoms may be considered a success by some patients yet completely unacceptable to others, so we therefore determined a complete absence of patient-reported angina to represent the gold standard. The SAQ-Angina Frequency domain asks patients to report the frequency of “chest pain, chest tightness or anginal attacks” over the preceding 4 weeks with a score < 100 indicating at least one anginal episode within that period. Accordingly, we adopted an SAQ-AF score of < 100 as the definition of residual angina at follow-up after rationalising that the binary absence or presence of patient-reported chest pain symptoms would provide a more objective assessment of residual angina than the subjective physical limitation and quality-of-life scores which also influence the SAQ-Summary Score.

One in ten participants reporting angina after stenting did not have symptoms prior to their intervention which highlights the importance of ascertaining the indication for and appropriateness of PCI with patients prior to embarking upon the procedure, particularly for those who are asymptomatic.

Patients with residual angina post-PCI had a higher burden of cardiovascular risk factors, including cigarette smoking, prior MI, and atrial fibrillation. Atrial fibrillation may limit a patient's capacity for physical activity due to symptoms of palpitations, dyspnoea and/or a sensation of chest tightness. Such symptoms are common during paroxysmal high ventricular rate episodes but are also frequently reported by patients in atrial fibrillation even when pulse rates are adequately controlled and unlikely to be provoking myocardial ischaemia. In the presence of atrial fibrillation, these symptoms can occur either in isolation or combination and be perceived and reported as anginal symptoms. Disentangling which symptoms relate to myocardial ischaemia in this setting is difficult and serves to highlight the challenges encountered when analysing angina. The higher rates of oral anticoagulants and concomitant lower rate of antiplatelets prescribed at baseline among patients with residual angina are likely just commensurate with the higher incidence of atrial fibrillation in this group. As there was no difference in the incidence of the heart failure or hypertension, the higher rate of diuretic therapy may relate to prescriptions for dyspnoea thought to represent an angina-equivalent symptom.

Patients with residual angina had more severe symptoms at baseline (higher incidence of both CCS class 2 and 3 angina and self-reported rates of daily and weekly angina) and were prescribed more anti-anginal agents with greater use of oral and sublingual nitrates than those who were angina-free post procedure. Patients with residual angina reported no change in quality-of-life as assessed by the EQ-5D-5L weighted health index score and had significantly lower SAQ Quality-of-Life scores compared to those who were angina-free. These findings are contrary to a previous report concluding that preprocedural angina frequency is the most important prognostic indicator of quality-of-life after PCI.(96)

Procedural and Intracoronary Physiology Characteristics

There were no significant differences between groups in angiography-based parameters of coronary artery disease severity either pre- or post-PCI. Counterintuitively, patients with residual angina had a higher burden of angina at baseline yet less physiologically severe lesions than those who were angina-free at follow-up. Patients with residual angina had significantly higher pre-PCI FFR and CFR values and faster hyperaemic transit times. There were no differences in absolute post-PCI physiology values between groups and, among patients with angina at baseline, there was no correlation between post-PCI values and patient-reported outcome measures at follow-up. Coronary microvascular dysfunction has been proposed as a potential mechanism for persistent angina post-PCI.(90) In this population of patients with obstructive epicardial coronary disease, there were no differences in mean post-PCI CFR or IMR values between those patients with or without residual angina. Based on currently accepted thresholds, the mean post-PCI CFR and IMRc values in the residual angina group of 3.4 and 21 respectively were not suggestive of coronary microvascular dysfunction (CMD). Furthermore, there was no correlation between corrected IMR and patient-reported outcome measures. It seems unlikely that these patients went on to develop de novo CMD over the following three months, however, the study design did not include invasive or non-invasive assessments of microvascular function at this timepoint. Acetylcholine provocation testing was not performed therefore the incidence of coronary vasospasm is unknown.

A physiology-stratified analysis of the ORBITA trial assessed paired SAQ and EQ-5D-5L data from 189 patients and found that pre-PCI FFR and iFR did not predict the effect of placebo-controlled PCI on anginal symptoms or quality-of-life.(93) A subsequent analysis of pooled data from the FAME 1 and 2 trials reported that larger improvements in FFR with PCI were associated with an increased probability of improvement of at least two CCS classes at 1-month follow-up but did not find any correlation between pre-PCI FFR values and symptom improvement.(95) Latterly, another pooled analysis of FAME 1 and 2 data found that lower pre-PCI FFR, higher delta FFR and higher percentage delta FFR were associated with significantly larger change from baseline EQ-5D index score at both 1 month and 1 year post-PCI.(94)

In the present analysis, among patients who had angina at baseline (CCS class I and above), pre-PCI and percentage change in FFR values had significant correlations with patient-reported outcome measures at follow-up. Post-PCI values had no correlation with angina or quality-of-life at follow-up indicating that, as demonstrated in Figures 5-1and 5-2, pre-PCI values drove the magnitude of the change. Larger change in FFR following PCI was associated with higher PROMs scores at follow-up. In keeping with these findings, significantly lower absolute and percentage change values for FFR were observed in the residual angina group. PCI provides greater improvement in symptoms and quality-of-life if it is performed in patients with physiologically severe disease. Patients with a higher symptom burden and lower quality of life at baseline are more likely to have residual angina, particularly where PCI can only achieve a small improvement in physiology metrics, such as in those with diffuse patterns of coronary disease and borderline or ‘grey-zone’ pre-PCI values. Accordingly, this analysis supports the concept that intracoronary physiology assessment can inform expectations of angina relief and quality-of-life improvement after stenting and thereby help to determine the appropriateness of PCI intended to alleviate symptoms. Patients with physiologically severe lesions can expect a larger improvement in intracoronary pressure ratios following PCI which is associated with a higher likelihood of angina relief and improved quality-of-life.

Chapter 6 Results – Non-Hyperaemic Pressure Ratios

6.1 Introduction

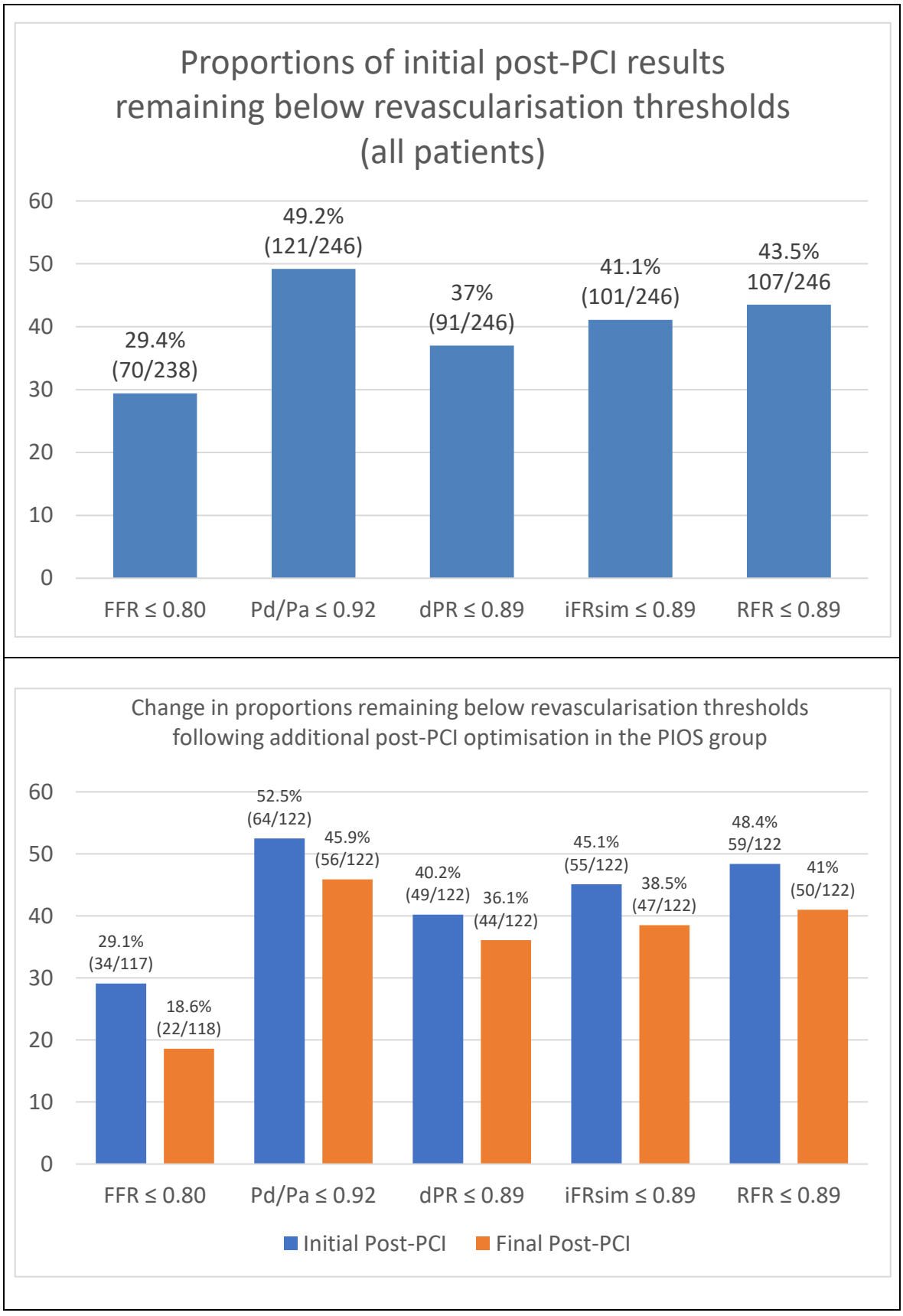
Non-hyperaemic pressure ratios (NHPRs), such as the instantaneous wave-free ratio (iFR), have potential to be used as objective measures of improvement in coronary haemodynamics following PCI.(97) The original NHPR, the ratio of distal coronary to aortic pressure (Pd/Pa) is routinely available with all diagnostic guidewires and has been shown to have excellent agreement with iFR.(98) A retrospective analysis reported that a post-PCI Pd/Pa value ≤ 0.96 was an independent predictor of MACE at a median follow-up time of 30 months.(61) Additional resting physiology indices have subsequently been developed which have diagnostic equivalence to iFR. These include the diastolic pressure ratio (dPR) and the resting full-cycle ratio (RFR).(62, 63) The observational DEFINE PCI study undertook blinded post-PCI iFR assessments and identified persistently abnormal iFR values (< 0.90) in 21.9% (114/520) of vessels despite angiographically successful stenting results. The authors concluded that most of these cases (81.6%) were due to inapparent focal lesions potentially amenable to treatment with additional PCI. No further optimisation was attempted, however, it was hypothesised that additional PCI to this focal disease could reduce the proportion of vessels with a residual iFR < 0.90 from 21.9% to 4.4%.(60) Follow-up at a median duration of one year found that a post-PCI iFR ≥ 0.95 was associated with a lower risk of MACE. This was driven primarily by a lower incidence of spontaneous (but not target vessel) myocardial infarction.(75) While an NHPR-guided PCI optimisation strategy facilitating multiple physiological assessments without the need to repeatedly induce hyperaemia might be more appealing to patients and clinicians, data on the incidence of suboptimal post-PCI results across the range of NHPRs and the efficacy of additional optimisation measures are currently lacking. While TARGET-FFR was designed to assess the efficacy of a post-PCI physiology-guided incremental optimisation strategy (PIOS) vs. standard angiographic guidance in achieving final post-PCI FFR values ≥ 0.90, a range of NHPRs were also recorded at each phase of PCI. For the first time, this has enabled an assessment of the impact of additional PCI on final post-PCI NHPR values. As presented in Chapter 3, there were no significant difference

between randomised groups with respect to the secondary outcomes of patients with final post-PCI dPR and RFR ≥ 0.90. In this chapter we expand the analysis of non-hyperaemic pressure ratios to explore the incidence of suboptimal results across a range of NHPRs, the effect of additional PCI, and provide novel data on the association of NHPRs with patient symptoms at follow-up.

6.2 Proportions of optimal and suboptimal post-PCI NHPR results and the impact of the PIOS intervention

Following core lab adjudication, initial post-PCI non-hyperaemic pressure recordings from 246 patients were included for analysis. The proportions of initial post-PCI FFR and NHPR values below clinical revascularisation thresholds and above proposed optimal cut-offs among the entire study population are presented in Figure 6-1 & Table 6-1 respectively. 30.5% (40/131) of patients randomised to the optimisation arm had further intervention performed based on a suboptimal post-PCI FFR result of ≤ 0.90. The effect of these additional interventions on the various coronary physiology indices is outlined in Table 6-2. Modest increases in the proportion of patients with NHPR values above clinical and optimal cut-offs were observed when comparing overall initial and final post-PCI results, however, there was no significant difference in NHPR values between randomised groups (Figure 6-1 & Tables 6-1 – 6-3).

Figure 6-1 Proportions of suboptimal post-PCI values across hyperaemic and non-hyperaemic pressure ratios



dPR=diastolic Pressure Ratio; FFR=Fractional Flow Reserve; iFRsim=simulated instantaneous wave-Free Ratio; NHPR=Non-Hyperaemic Pressure Ratio; Pd/Pa=ratio of resting distal coronary pressure (Pd) to aortic pressure (Pa); RFR=Resting Full-cycle Ratio

Table 6-1 – Distribution of proportions of initial and final post-PCI NHPRs across clinical & proposed optimal thresholds

	Initial Post-PCI % (n)	Final Post-PCI % (n)
Clinical Cut-offs		
Pd/Pa ≤ 0.92	49.2% (121/246)	45.9% (113/246)
dPR (whole diastole) ≤ 0.89	37% (91/246)	35% (86/246)
iFR_{sim} ≤ 0.89	41.1% (101/246)	37.8% (93/246)
RFR ≤ 0.89	43.5% (107/246)	39.8% (98/246)
Optimal Cut-offs		
Pd/Pa > 0.96	32.1% (79/246)	32.9% (81/246)
dPR (whole diastole) ≥ 0.95	36.6% (90/246)	38.2% (94/246)
iFR_{sim} ≥ 0.95	35% (86/246)	36.6% (90/246)
RFR ≥ 0.95	33.7% (83/246)	35% (86/246)

dPR=diastolic Pressure Ratio; FFR=Fractional Flow Reserve; iFR_{sim}=simulated instantaneous wave-Free Ratio; NHPR=Non-Hyperaemic Pressure Ratio; Pd/Pa=ratio of resting distal coronary pressure (Pd) to aortic pressure (Pa); RFR=Resting Full-cycle Ratio

Table 6-2 – Physiological effects of the PIOS intervention

	Initial Post-PCI		Final Post-PCI		Absolute Difference		Relative Difference (%)		p value
	N	Value	N	Value	N	Value	N	Value	
Any PIOS received (40)									
Pd/Pa	35	0.89 ± 0.03	35	0.91 ± 0.03	31	0.02 ± 0.03	31	2.2 ± 3.4	0.001
dPR	35	0.87 ± 0.04	35	0.90 ± 0.04	31	0.02 ± 0.04	31	3 ± 4.4	0.001
iFR_{sim}	35	0.87 ± 0.04	35	0.89 ± 0.04	31	0.03 ± 0.04	31	3.1 ± 4.8	0.001
RFR	35	0.87 ± 0.04	35	0.89 ± 0.04	31	0.03 ± 0.04	31	3.2 ± 4.9	0.001
FFR	33	0.76 ± 0.08	34	0.82 ± 0.06	29	0.06 ± 0.07	29	9 ± 11.7	< 0.0001
CFR	40	3.0 ± 1.6	35	4.0 ± 2.1	35	1.0 ± 2.2	35	56.7 ± 103.7	0.02
IMR	39	20 ± 7	33	18 ± 7	33	-3 ± 8	33	-6.2 ± 38.3	0.08
IMRc	39	19 ± 7	33	17 ± 7	33	-2 ± 8	33	-3.2 ± 41.3	0.17
Balloon only (23)									
Pd/Pa	19	0.90 ± 0.03	19	0.91 ± 0.03	16	0.01 ± 0.02	16	1.6 ± 2	0.01
dPR	19	0.88 ± 0.04	19	0.89 ± 0.04	16	0.01 ± 0.02	16	1.7 ± 2.9	0.03
iFR_{sim}	19	0.87 ± 0.04	19	0.89 ± 0.04	16	0.01 ± 0.03	16	1.6 ± 3	0.06
RFR	19	0.87 ± 0.04	19	0.89 ± 0.04	16	0.01 ± 0.02	16	1.6 ± 2.8	0.03
FFR	18	0.79 ± 0.07	19	0.83 ± 0.05	15	0.03 ± 0.05	15	4.4 ± 7.6	0.03
CFR	23	3.1 ± 1.6	19	3.6 ± 1.5	19	0.4 ± 1.4	19	32.9 ± 62.1	0.21
IMR	22	19 ± 6	17	16 ± 6	17	-3 ± 7	17	-8.9 ± 34.1	0.11
IMRc	22	18 ± 6	17	15 ± 5	17	-2 ± 7	17	-7.3 ± 36.2	0.17
Stent only (12)									
Pd/Pa	12	0.89 ± 0.04	11	0.92 ± 0.02	11	0.03 ± 0.04	11	3.9 ± 4.2	0.01
dPR	12	0.87 ± 0.05	11	0.91 ± 0.03	11	0.04 ± 0.04	11	5 ± 5.2	0.01
iFR_{sim}	12	0.86 ± 0.05	11	0.90 ± 0.03	11	0.05 ± 0.05	11	5.7 ± 5.8	0.01
RFR	12	0.86 ± 0.05	11	0.90 ± 0.03	11	0.05 ± 0.05	11	5.8 ± 5.8	0.01
FFR	11	0.72 ± 0.09	10	0.80 ± 0.05	10	0.09 ± 0.08	10	14.3 ± 15.8	0.01
CFR	12	2.8 ± 1.8	11	5.4 ± 2.6	11	2.5 ± 2.8	11	127.1 ± 142.8	0.01
IMR	12	24 ± 9	11	18 ± 10	11	-6 ± 10	11	-19.6 ± 35.3	0.10
IMRc	12	22 ± 8	11	17 ± 10	11	-4 ± 10	11	-15.6 ± 37.9	0.19
Post-dilation and stent (5)									
Pd/Pa	4	0.90 ± 0.02	5	0.91 ± 0.05	4	0 ± 0.03	4	-0.3 ± 3.7	0.89
dPR	4	0.87 ± 0.03	5	0.90 ± 0.06	4	0.02 ± 0.05	4	2.2 ± 5.9	0.49
iFR_{sim}	4	0.86 ± 0.03	5	0.90 ± 0.07	4	0.02 ± 0.05	4	2.3 ± 6	0.49

RFR	4	0.86 ± 0.03	5	0.89 ± 0.07	4	0.02 ± 0.06	4	2.3 ± 7	0.55
FFR	4	0.75 ± 0.04	5	0.85 ± 0.07	4	0.10 ± 0.05	4	12.8 ± 6.9	0.04
CFR	5	2.9 ± 1.2	5	2.4 ± 1.2	5	-0.5 ± 1.6	5	-7.5 ± 40	0.54
IMR	5	16 ± 5	5	20 ± 6	5	4 ± 4	5	32.1 ± 39.9	0.09
IMRc	5	15 ± 5	5	20 ± 6	5	5 ± 5	5	38 ± 47.1	0.09

Values are n (%) or mean ± SD. dPR=diastolic Pressure Ratio; CFR=Coronary Flow Reserve; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; iFR_{sim}=simulated instantaneous wave-Free Ratio; NHPR=Non-Hyperaemic Pressure Ratio; PCI=Percutaneous Coronary Intervention; Pd/Pa= ratio of mean distal coronary to aortic pressure at rest; PIOS=Physiology-guided Incremental Optimisation Strategy; RFR=Resting Full-cycle Ratio

Table 6-3 – Proportions of suboptimal and optimal final post-PCI physiology results per randomised group

Cut-off	Total		Control		PIOS		p value
	N	n (%)	N	n (%)	N	n (%)	
Suboptimal							
Final Pd/Pa ≤ 0.92	246	113 (45.9)	124	57 (46)	122	56 (45.9)	0.99
Final dPR ≤ 0.89	246	86 (35)	124	42 (33.9)	122	44 (36.1)	0.72
Final iFR_{sim} ≤ 0.89	246	93 (37.8)	124	46 (37.1)	122	47 (38.5)	0.82
Final RFR ≤ 0.89	246	98 (39.8)	124	48 (38.7)	122	50 (40)	0.72
Final FFR ≤ 0.80	239	58 (24.3)	121	36 (29.8)	118	22 (18.6)	0.045
Final CFR < 2.0	252	55 (21.8)	127	28 (22)	125	27 (21.6)	0.93
Final CFR < 2.5	252	87 (34.5)	127	47 (37)	125	40 (32)	0.40
Final IMR > 25	248	59 (23.8)	126	27 (21.4)	122	32 (26.2)	0.37
Final IMRc > 25	248	55 (22.2)	126	25 (19.8)	122	30 (24.6)	0.37
Optimal							
Final Pd/Pa > 0.96	246	81 (32.9)	124	41 (33.1)	122	40 (32.8)	0.96
Final dPR ≥ 0.95	246	94 (38.2)	124	44 (35.5)	122	50 (41)	0.37
Final iFR_{sim} ≥ 0.95	246	90 (36.6)	124	43 (34.7)	122	47 (38.5)	0.53
Final RFR ≥ 0.95	246	86 (35)	124	42 (33.9)	122	44 (36.1)	0.72
Final FFR ≥ 0.90	239	79 (33.1)	121	34 (28.1)	118	45 (38.1)	0.099
Final CFR ≥ 2.0	252	197 (78.2)	127	99 (78)	125	98 (78.4)	0.93
Final CFR ≥ 2.5	252	165 (65.5)	127	80 (63)	125	85 (68)	0.40
Final IMR ≤ 25	248	189 (76.2)	126	99 (78.6)	122	90 (73.8)	0.37
Final IMRc ≤ 25	248	193 (77.8)	126	101 (80.2)	122	92 (75.4)	0.37

dPR=diastolic Pressure Ratio; CFR=Coronary Flow Reserve; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; iFR_{sim}=simulated instantaneous wave-Free Ratio; NHPR=Non-Hyperaemic Pressure Ratio; PCI=Percutaneous Coronary Intervention; Pd/Pa= ratio of mean distal coronary to aortic pressure at rest; PIOS=Physiology-guided Incremental Optimisation Strategy; RFR=Resting Full-cycle Ratio. FFR=Fractional Flow Reserve; PCI=Percutaneous Coronary Intervention

Table 6-4 – Proportions of suboptimal and optimal initial and final post-PCI physiology results in the PIOS intervention arm

Cut-off	Initial Post-PCI		Final Post-PCI		Difference
	N	n (%)	N	n (%)	(%)
Suboptimal					
Final Pd/Pa ≤ 0.92	122	64 (52.5)	122	56 (45.9)	-6.6
Final dPR ≤ 0.89	122	49 (40.2)	122	44 (36.1)	-4.1
Final iFR_{sim} ≤ 0.89	122	55 (45.1)	122	47 (38.5)	-6.6
Final RFR ≤ 0.89	122	59 (48.4)	122	50 (41)	-7.4
Final FFR ≤ 0.80	117	34 (29.1)	118	22 (18.6)	-10.4
Final CFR < 2.0	130	34 (26.2)	125	27 (21.6)	-4.6
Final CFR < 2.5	130	55 (42.3)	125	40 (32)	-10.3
Final IMR ≥ 25	128	34 (26.6)	122	32 (26.2)	-0.3
Final IMRc ≥ 25	128	32 (25)	122	30 (24.6)	-0.4
Optimal					
Final Pd/Pa > 0.96	122	38 (31.1)	122	40 (32.8)	1.6
Final dPR ≥ 0.95	122	46 (37.7)	122	50 (41)	3.3
Final iFR_{sim} ≥ 0.95	122	43 (35.2)	122	47 (38.6)	3.3
Final RFR ≥ 0.95	122	41 (33.6)	122	44 (36.1)	2.5
Final FFR ≥ 0.90	117	42 (35.9)	118	45 (38.1)	2.2
Final CFR ≥ 2.0	130	96 (73.8)	125	98 (78.4)	4.6
Final CFR ≥ 2.5	130	75 (57.7)	125	85 (68)	10.3
Final IMR < 25	128	94 (73.4)	122	90 (73.8)	0.3
Final IMRc < 25	128	96 (75)	122	92 (75.4)	0.4

dPR=diastolic Pressure Ratio; CFR=Coronary Flow Reserve; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; iFR_{sim}=simulated instantaneous wave-Free Ratio; NHPR=Non-Hyperaemic Pressure Ratio; PCI=Percutaneous Coronary Intervention; Pd/Pa= ratio of mean distal coronary to aortic pressure at rest; PIOS=Physiology-guided Incremental Optimisation Strategy; RFR=Resting Full-cycle Ratio. FFR=Fractional Flow Reserve; PCI=Percutaneous Coronary Intervention;

6.3 Impact of clinical indication & target vessel on NHPRs

When stratified by the indication for stenting, pre-PCI NHPR values were significantly lower in ACS culprit vessels than in cases of stable angina or staged non-culprit vessel revascularisation, however, there were no significant differences in post-PCI values (Table 6-5). When stratified by target vessel, pre-PCI iFR_{sim}, dPR, RFR and IMRc were significantly higher in the right coronary than in the left coronary branches. As with FFR, both the initial post-PCI NHPR values and the final proportions above their respective optimal cut-off points were significantly lower in the LAD than in non-LAD vessels (Table 6-6 and 6-7).

Table 6-5 – Pre- and post-PCI physiology values stratified by PCI indication

	NSTEMI (N=104)		Stable Angina (N=88)		Staged Non-culprit (N=68)		P value
	N	Value	N	Value	N	Value	
Pre-PCI							
Pd/Pa	96	0.71 ± 0.21	82	0.75 ± 0.16	64	0.85 ± 0·10	< 0.0001
dPR	96	0.64 ± 0.24	82	0.69 ± 0.20	64	0.82 ± 0·13	< 0.0001
iFR_{sim}	96	0.62 ± 0.26	82	0.67 ± 0.22	64	0.81 ± 0·14	< 0.0001
RFR	96	0.61 ± 0.26	82	0.66 ± 0.22	64	0.80 ± 0·14	< 0.0001
FFR	92	0.55 ± 0.15	79	0.57 ± 0.14	65	0.67 ± 0·10	< 0.0001
CFR	90	1.9 ± 0.9	80	1.8 ± 0.9	63	2.3 ± 0·9	0.005
IMR	86	29 ± 13	76	28 ± 12	61	24 ± 11	0.02
IMRc	86	21 ± 11	76	21 ± 9	61	20 ± 10	0.98
Initial Post-PCI							
Pd/Pa	99	0.94 ± 0.06	83	0·93 ± 0.05	64	0.93 ± 0.05	0.18
dPR	99	0.93 ± 0.07	83	0·91 ± 0.06	64	0.92 ± 0.06	0.10
iFR_{sim}	99	0.93 ± 0.07	83	0·91 ± 0.07	64	0.91 ± 0.06	0.10
RFR	99	0.92 ± 0.07	83	0·90 ± 0.07	64	0.91 ± 0.06	0.07
FFR	97	0.86 ± 0.10	80	0·83 ± 0.08	61	0.85 ± 0.09	0.11
CFR	104	3.3 ± 1.7	87	3.5 ± 2.1	66	2.9 ± 1.5	0.15
IMR	103	23 ± 17	85	19 ± 11	66	24 ± 19	0.13
IMRc	103	22 ± 17	85	19 ± 11	66	23 ± 19	0.13

Values are mean ± SD. CFR=Coronary Flow Reserve; dPR=diastolic pressure ratio; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; iFR_{sim}=instantaneous wave-free ratio; NSTEMI=Non-ST-segment-Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; RFR=Resting Full-cycle Ratio

Table 6-6 – Physiology stratified by target vessel

	LAD (N=150)		LCx (N=43)		RCA (N=67)		p value
	N	Value	N	Value	N	Value	
Pre-PCI							
Pd/Pa	137	0.74 ± 0.17	41	0.76 ± 0.19	64	0.79 ± 0.19	0.18
dPR	137	0.68 ± 0.21	41	0.69 ± 0.21	64	0.76 ± 0.21	0.03
iFR_{sim}	137	0.66 ± 0.23	41	0.67 ± 0.22	64	0.75 ± 0.22	0.02
RFR	137	0.65 ± 0.23	41	0.65 ± 0.23	64	0.74 ± 0.22	0.03
FFR	135	0.58 ± 0.14	39	0.61 ± 0.11	62	0.59 ± 0.16	0.52
CFR	132	2.1 ± 1.1	41	1.8 ± 0.8	60	1.8 ± 0.6	0.06
IMR	131	26 ± 10	38	27 ± 13	54	32 ± 15	0.02
IMRc	131	19 ± 8	38	21 ± 10	54	24 ± 13	0.004
Initial Post-PCI							
Pd/Pa	144	0.90 ± 0.03	39	0.98 ± 0.03	63	0.98 ± 0.04	< 0.0001
dPR	144	0.88 ± 0.04	39	0.98 ± 0.04	63	0.98 ± 0.05	< 0.0001
iFR_{sim}	144	0.88 ± 0.04	39	0.98 ± 0.04	63	0.98 ± 0.05	< 0.0001
RFR	144	0.87 ± 0.04	39	0.97 ± 0.04	63	0.97 ± 0.05	< 0.0001
FFR	140	0.80 ± 0.07	38	0.92 ± 0.07	60	0.91 ± 0.07	< 0.0001
CFR	148	3.2 ± 1.8	43	3.3 ± 1.4	66	3.4 ± 2.1	0.82
IMR	146	22 ± 15	43	19 ± 11	65	25 ± 19	0.19
IMRc	146	21 ± 15	43	19 ± 11	65	25 ± 19	0.14

Values are mean ± SD. CFR=Coronary Flow Reserve; dPR=diastolic pressure ratio; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; iFRsim=instantaneous wave-free ratio; LAD=Left Anterior Descending artery; LCx=Left Circumflex artery; PCI=Percutaneous Coronary Intervention; Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; RCA=Right Coronary Artery; RFR=Resting Full-cycle Ratio

Table 6-7 – Proportions of suboptimal and optimal final post-PCI physiology results stratified by target vessel

Threshold	Total		LAD		LCx		RCA		p value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Suboptimal									
Final Pd/Pa ≤ 0·92	246	113 (45.9)	142	108 (76.1)	40	2 (5)	64	3 (4.7)	< 0.0001
Final dPR ≤ 0·89	246	86 (35)	142	81 (57)	40	2 (5)	64	3 (4.7)	< 0.0001
Final iFR_{sim} ≤ 0·89	246	93 (37.8)	142	88 (62)	40	2 (5)	64	3 (4.7)	< 0.0001
Final RFR ≤ 0·89	246	98 (39.8)	142	92 (64.8)	40	2 (5)	64	4 (6.3)	< 0.0001
Final FFR ≤ 0·80	239	58 (24.3)	138	52 (37.7)	39	2 (5.1)	62	4 (6.5)	< 0.0001
CFR < 2.0	252	55 (21.8)	144	27 (18.7)	43	7 (16.3)	65	21 (32.3)	0.0561
CFR < 2.5	252	87 (34.5)	144	50 (34.7)	43	12 (27.9)	65	25 (38.5)	0.5270
IMR > 25	248	59 (23.8)	141	29 (20.6)	43	9 (20.9)	64	21 (32.8)	0.1440
IMRc > 25	248	55 (22.2)	141	25 (17.7)	43	9 (20.9)	64	21 (32.8)	0.0537
Optimal									
Final Pd/Pa > 0·96	246	81 (32.9)	142	0 (0)	40	31 (77.5)	64	50 (78.1)	< 0.0001
Final dPR ≥ 0·95	246	94 (38.2)	142	3 (2.1)	40	34 (85)	64	57 (89.1)	< 0.0001
Final iFR_{sim} ≥ 0·95	246	90 (36.6)	142	1 (0.7)	40	35 (87.5)	64	54 (84.4)	< 0.0001
Final RFR ≥ 0·95	246	86 (35)	142	1 (0.7)	40	34 (85)	64	51 (79.7)	< 0.0001
Final FFR ≥ 0·90	239	79 (33.1)	138	10 (7.2)	39	29 (74.4)	62	40 (65.4)	< 0.0001
CFR ≥ 2.0	252	197 (78.2)	144	117 (81.3)	43	36 (83.7)	65	44 (67.7)	0.0561
CFR ≥ 2.5	252	165 (65.5)	144	94 (65.3)	43	31 (72.1)	65	40 (61.5)	0.5270
IMR ≤ 25	248	189 (76.2)	141	112 (79.4)	43	34 (79.1)	64	43 (67.2)	0.1440
IMRc ≤ 25	248	193 (77.8)	141	116 (82.3)	43	34 (79.1)	64	43 (67.2)	0.0537

Values n (%). CFR=Coronary Flow Reserve; dPR=diastolic pressure ratio; FFR=Fractional Flow Reserve; IMR=Index of Microcirculatory Resistance; IMRc= Index of Microcirculatory Resistance corrected for epicardial stenosis; iFR_{sim}=instantaneous wave-free ratio; LAD=Left Anterior Descending artery; LCx=Left Circumflex artery; PCI=Percutaneous Coronary Intervention; Pd/Pa=Ratio of mean distal coronary to aortic pressure at rest; RCA=Right Coronary Artery; RFR=Resting Full-cycle Ratio

6.4 Association between NHPRs and Patient-Reported Outcome Measures

82.7% (215/260) patients reported anginal symptoms pre-PCI. Among these patients with angina at baseline, both pre-PCI and absolute change in NHPR values correlated with change in SAQ-7 and EQ-5D-5L at follow-up, however, post-PCI NHPR values did not (Tables 6-8 — 6-11). Lower pre-PCI values and larger absolute change in NHPR were associated with larger improvements in patient-reported SAQ-7 & EQ-5D-5L scores (Tables 6-12 — 6-15) and a lower incidence of residual angina (defined as SAQ-Angina Frequency score < 100 — Figures 6-2 and 6-3) at 3-month (median [IQR] 105 [31] days) follow-up.

Table 6-8 – Spearman correlation between Pd/Pa and Change in Patient Reported Outcome Measures at follow-up among patients with angina at baseline

Patient Reported Outcome Measure	Pd/Pa	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.23	< 0.01
	Post-PCI	-0.02	0.78
	Absolute Change	0.28	< 0.001
	Percentage Change	0.28	<0.001
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.28	< 0.001
	Post-PCI	0.03	0.71
	Absolute Change	0.33	< 0.001
	Percentage Change	0.33	< 0.001
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.18	0.02
	Post-PCI	-0.05	0.51
	Absolute Change	0.20	< 0.01
	Percentage Change	0.20	< 0.01
SAQ Summary Score (SAQ7-SS)	Baseline	-0.25	< 0.001
	Post-PCI	0.002	0.98
	Absolute Change	0.30	< 0.001
	Percentage Change	0.30	< 0.001
EQ-5D-5L UK Weighted Health State	Baseline	-0.21	0.004
	Post-PCI	-0.02	0.82
	Absolute Change	0.23	0.002
	Percentage Change	0.24	0.002

PCI=Percutaneous Coronary Intervention; Pd/Pa= ratio of mean distal coronary to aortic pressure at rest; SAQ=Seattle Angina Questionnaire.

Table 6-9 – Spearman correlation between dPR and Change in Patient Reported Outcome Measures at follow-up among patients with angina at baseline

Patient Reported Outcome Measure	dPR	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.25	< 0.01
	Post-PCI	-0.03	0.68
	Absolute Change	0.29	< 0.001
	Percentage Change	0.29	< 0.001
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.27	< 0.001
	Post-PCI	0.02	0.76
	Absolute Change	0.32	< 0.001
	Percentage Change	0.32	< 0.001
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.18	0.02
	Post-PCI	-0.06	0.45
	Absolute Change	0.20	0.01
	Percentage Change	0.20	< 0.01
SAQ Summary Score (SAQ7-SS)	Baseline	-0.25	< 0.001
	Post-PCI	-0.003	0.97
	Absolute Change	0.30	< 0.001
	Percentage Change	0.30	< 0.001
EQ-5D-5L UK Weighted Health State	Baseline	-0.23	0.002
	Post-PCI	-0.02	0.79
	Absolute Change	0.24	0.001
	Percentage Change	0.24	0.001

PCI=Percutaneous Coronary Intervention; dPR=diastolic Pressure Ratio; SAQ=Seattle Angina Questionnaire

Table 6-10 – Spearman correlation between iFR_{sim} and Change in Patient Reported Outcome Measures at follow-up among patients with angina at baseline

Patient Reported Outcome Measure	iFR_{sim}	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.25	< 0.01
	Post-PCI	-0.03	0.70
	Absolute Change	0.28	< 0.001
	Percentage Change	0.28	< 0.001
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.28	< 0.001
	Post-PCI	0.03	0.73
	Absolute Change	0.32	< 0.001
	Percentage Change	0.32	< 0.001
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.19	0.01
	Post-PCI	-0.06	0.41
	Absolute Change	0.20	< 0.01
	Percentage Change	0.20	<0.01
SAQ Summary Score (SAQ7-SS)	Baseline	-0.26	< 0.001
	Post-PCI	-0.005	0.95
	Absolute Change	0.30	< 0.001
	Percentage Change	0.30	< 0.001
EQ-5D-5L UK Weighted Health State	Baseline	-0.23	0.002
	Post-PCI	-0.02	0.76
	Absolute Change	0.25	0.001
	Percentage Change	0.25	0.001

iFR_{sim}=simulated instantaneous wave-Free Ratio; PCI=Percutaneous Coronary Intervention; SAQ=Seattle Angina Questionnaire

Table 6-11 – Spearman correlation between RFR and Change in Patient Reported Outcome Measures at follow-up among patients with angina at baseline

Patient Reported Outcome Measure	RFR	Correlation Coefficient	P value
SAQ Physical Limitation Score (SAQ7-PL)	Baseline	-0.24	< 0.01
	Post-PCI	-0.01	0.93
	Absolute Change	0.29	< 0.001
	Percentage Change	0.28	< 0.001
SAQ Angina Frequency Score (SAQ7-AF)	Baseline	-0.28	< 0.001
	Post-PCI	0.03	0.69
	Absolute Change	0.32	< 0.001
	Percentage Change	0.32	< 0.001
SAQ Quality of Life Score (SAQ7-QL)	Baseline	-0.18	0.01
	Post-PCI	-0.03	0.64
	Absolute Change	0.20	< 0.01
	Percentage Change	0.21	< 0.01
SAQ Summary Score (SAQ7-SS)	Baseline	-0.26	< 0.001
	Post-PCI	0.02	0.82
	Absolute Change	0.30	< 0.001
	Percentage Change	0.30	< 0.001
EQ-5D-5L UK Weighted Health State	Baseline	-0.24	0.002
	Post-PCI	-0.006	0.94
	Absolute Change	0.25	0.001
	Percentage Change	0.25	0.001

PCI=Percutaneous Coronary Intervention; RFR=Resting Full-cycle Ratio; SAQ=Seattle Angina Questionnaire

Table 6-12 – Change in PROMS stratified by tertiles of Pd/Pa at baseline, post-PCI, and absolute change among patients with angina at baseline

Pd/Pa		Low		Intermediate		High		p value
	Patient Reported Outcome	**N**	**Change**	**N**	**Change**	**N**	**Change**	
Baseline	SAQ Physical Limitation Score	52	22.6±31.02	52	16.19±29.02	48	11.63±23.43	0.149
	SAQ Angina Frequency Score	63	33.33±28.62	62	16.77±31.19	54	16.48±24.27	0.001
	SAQ Quality of Life Score	63	43.45±29.26	62	29.84±33.75	54	31.25±30.01	0.03
	SAQ Summary Score	63	33.02±24.33	62	20.87±27.79	54	20.12±21.41	0.006
	EQ-5D-5L Health State (UK)	63	0.08±0.28	62	0.06±0.23	54	0±0.19	0.20
Post-PCI	SAQ Physical Limitation Score	47	18±28.92	54	16.82±20.83	53	17.85±33.30	0.97
	SAQ Angina Frequency Score	57	23.16±29.35	63	20.32±30.21	63	24.92±28.62	0.68
	SAQ Quality of Life Score	57	38.16±33.77	63	33.13±31.68	63	35.52±29.80	0.69
	SAQ Summary Score	57	27.04±26.74	63	22.75±22.68	63	25.76±26.39	0.63
	EQ-5D-5L Health State (UK)	57	0.08±0.24	63	0.02±0.18	63	0.07±0.27	0.38
Absolute Change	SAQ Physical Limitation Score	45	9.26±23.18	49	16.84±30.06	50	25.83±28.68	0.02
	SAQ Angina Frequency Score	52	13.85±28.02	58	17.93±26.74	60	35.17±29.66	< 0.001
	SAQ Quality of Life Score	52	28.37±31.22	58	32.76±34.32	60	43.96±28.51	0.03

SAQ Summary Score	52	17.61±22.81	58	22.33±26.72	60	34.65±24.30	0.001
EQ-5D-5L Health State (UK)	52	-0.01±0.19	58	0.08±0.26	60	0.09±0.25	0.052

Table 6-13 – Change in PROMS stratified by tertiles of dPR at baseline, post-PCI, and absolute change among patients with angina at baseline

dPR		Low		Intermediate		High		p value
	Patient Reported Outcome	**N**	**Change**	**N**	**Change**	**N**	**Change**	
Baseline	SAQ Physical Limitation Score	52	21.96±32.42	55	15.45±26.70	45	12.96±24.59	0.26
	SAQ Angina Frequency Score	64	33.75±28.59	62	13.71±30.26	53	19.25±24.80	< 0.001
	SAQ Quality of Life Score	64	42.38±31.23	62	28.83±31.74	53	33.49±30.50	0.049
	SAQ Summary Score	64	32.51±25.54	62	19.31±26.35	53	22.31±21.95	< 0.01
	EQ-5D-5L Health State (UK)	64	0.09±0.28	62	0.06±0.22	53	0±0.19	0.096
Post-PCI	SAQ Physical Limitation Score	56	18.68±27.62	46	15.40±20.86	52	18.19±33.53	0.82
	SAQ Angina Frequency Score	67	23.43±29.98	53	18.68±30.00	63	25.56±28.04	0.44
	SAQ Quality of Life Score	67	39.55±33.26	53	29.95±31.33	63	35.91±29.83	0.26
	SAQ Summary Score	67	27.64±26.27	53	20.65±22.35	63	26.21±26.21	0.30
	EQ-5D-5L Health State (UK)	67	0.07±0.24	53	0.03±0.18	63	0.06±0.27	0.60
Absolute Change	SAQ Physical Limitation Score	47	11.44±24.07	47	14.27±29.34	50	26.50±29.05	0.02
	SAQ Angina Frequency Score	54	13.52±27.62	56	18.75±26.50	60	34.83±30.28	< 0.001
	SAQ Quality of Life Score	54	29.17±30.81	56	31.03±34.79	60	45.00±28.11	0.01

SAQ Summary Score	54	18.33±23.04	56	21.35±26.32	60	35.07±24.51	< 0.001
EQ-5D-5L Health State (UK)	54	0.00±0.18	56	0.05±0.24	60	0.11±0.27	0.03

Table 6-14 – Change in PROMS stratified by tertiles of iFR_{sim} at baseline, post-PCI, and absolute change among patients with angina at baseline

iFR_{sim}		Low		Intermediate		High		p value
	Patient Reported Outcome	**N**	**Change**	**N**	**Change**	**N**	**Change**	
Baseline	SAQ Physical Limitation Score	51	22.22±32.69	54	16.51±26.21	47	11.70±24.80	0.18
	SAQ Angina Frequency Score	63	34.29±28.50	60	14.83±21.33	56	17.50±26.44	< 0.001
	SAQ Quality of Life Score	63	42.86±31.25	60	30.21±30.90	56	31.47±31.44	0.049
	SAQ Summary Score	63	32.92±25.54	60	20.42±25.55	56	20.74±23.09	< 0.01
	EQ-5D-5L Health State (UK)	63	0.09±0.29	60	0.07±0.20	56	-0.02±0.20	0.03
Post-PCI	SAQ Physical Limitation Score	52	17.39±27.91	51	16.99±21.01	51	18.22±33.86	0.98
	SAQ Angina Frequency Score	62	21.61±29.15	60	21.33±30.61	61	25.41±28.44	0.69
	SAQ Quality of Life Score	62	38.10±34.06	60	32.08±30.91	61	36.27±29.90	0.56
	SAQ Summary Score	62	26.24±26.43	60	22.81±22.58	61	26.27±26.62	0.69
	EQ-5D-5L Health State (UK)	62	0.07±0.24	60	0.03±0.17	61	0.07±0.27	0.61
Absolute Change	SAQ Physical Limitation Score	43	11.05±24.85	51	14.38±28.37	50	26.50±29.05	0.02
	SAQ Angina Frequency Score	49	13.67±28.63	61	18.20±25.79	60	34.83±30.28	< 0.001
	SAQ Quality of Life Score	49	28.83±31.99	61	31.15±33.59	60	45.00±28.11	0.01

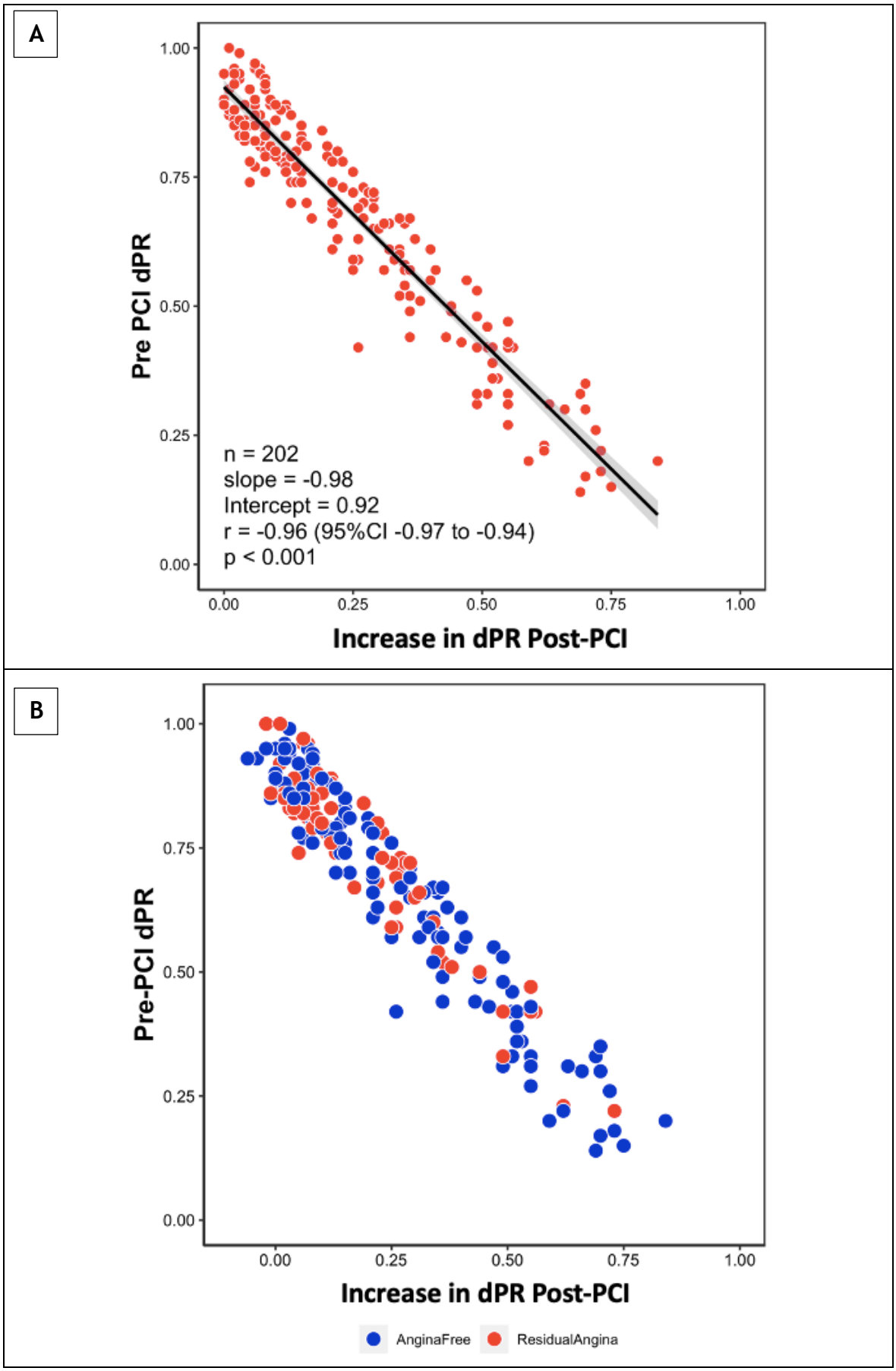
SAQ Summary Score	49	18.25±24.07	61	21.17±25.31	60	35.07±24.51	< 0.001
EQ-5D-5L Health State (UK)	49	0.00±0.19	61	0.05±0.24	60	0.11±0.27	0.04

Table 6-15 – Change in PROMS stratified by tertiles of RFR at baseline, post-PCI, and absolute change among patients with angina at baseline

RFR		Low		Intermediate		High		P value
	Patient Reported Outcome	**N**	**Change**	**N**	**Change**	**N**	**Change**	
Baseline	SAQ Physical Limitation Score	51	22.06±32.74	53	17.14±26.21	48	11.28±24.70	0.17
	SAQ Angina Frequency Score	63	33.65±28.81	60	15.83±29.24	56	17.14±26.54	< 0.001
	SAQ Quality of Life Score	63	41.67±30.95	60	31.04±31.93	56	31.92±31.16	0.12
	SAQ Summary Score	63	32.27±25.67	60	21.19±25.69	56	20.65±23.14	0.02
	EQ-5D-5L Health State (UK)	63	0.09±0.29	60	0.08±0.20	56	-0.02±0.20	0.03
Post-PCI	SAQ Physical Limitation Score	53	17.22±27.66	51	16.18±22.14	50	19.25±33.39	0.86
	SAQ Angina Frequency Score	64	21.88±28.78	59	21.36±30.88	60	25.17±28.61	0.74
	SAQ Quality of Life Score	64	37.70±33.89	59	32.20±30.81	60	36.46±30.12	0.61
	SAQ Summary Score	64	26.09±26.09	59	22.64±22.74	60	26.53±26.77	0.66
	EQ-5D-5L Health State (UK)	64	0.07±0.24	59	0.02±0.18	60	0.07±0.27	0.42
Absolute Change	SAQ Physical Limitation Score	47	11.08±24.36	47	14.63±29.06	50	26.50±29.05	0.02
	SAQ Angina Frequency Score	54	13.89±27.64	56	18.39±26.55	60	34.83±30.28	< 0.001
	SAQ Quality of Life Score	54	28.94±30.98	56	31.25±34.62	60	45.00±28.11	0.01

SAQ Summary Score	54	18.28±23.01	56	21.41±26.33	60	35.07±24.51	< 0.001
EQ-5D-5L Health State (UK)	54	0.01±0.18	56	0.04±0.25	60	0.11±0.27	0.052

Figure 6-2 – Correlation between pre-PCI and change in dPR values with stratification by presence of residual angina 3 months post-PCI



Correlation between pre-PCI dPR and change in dPR values (Panel A) with stratification by presence of residual angina (Panel B). Figures courtesy of Dr Takuya Mizukami.

Figure 6-3 – Change in dPR from pre- to post-PCI stratified by presence of residual angina 3 months post-PCI

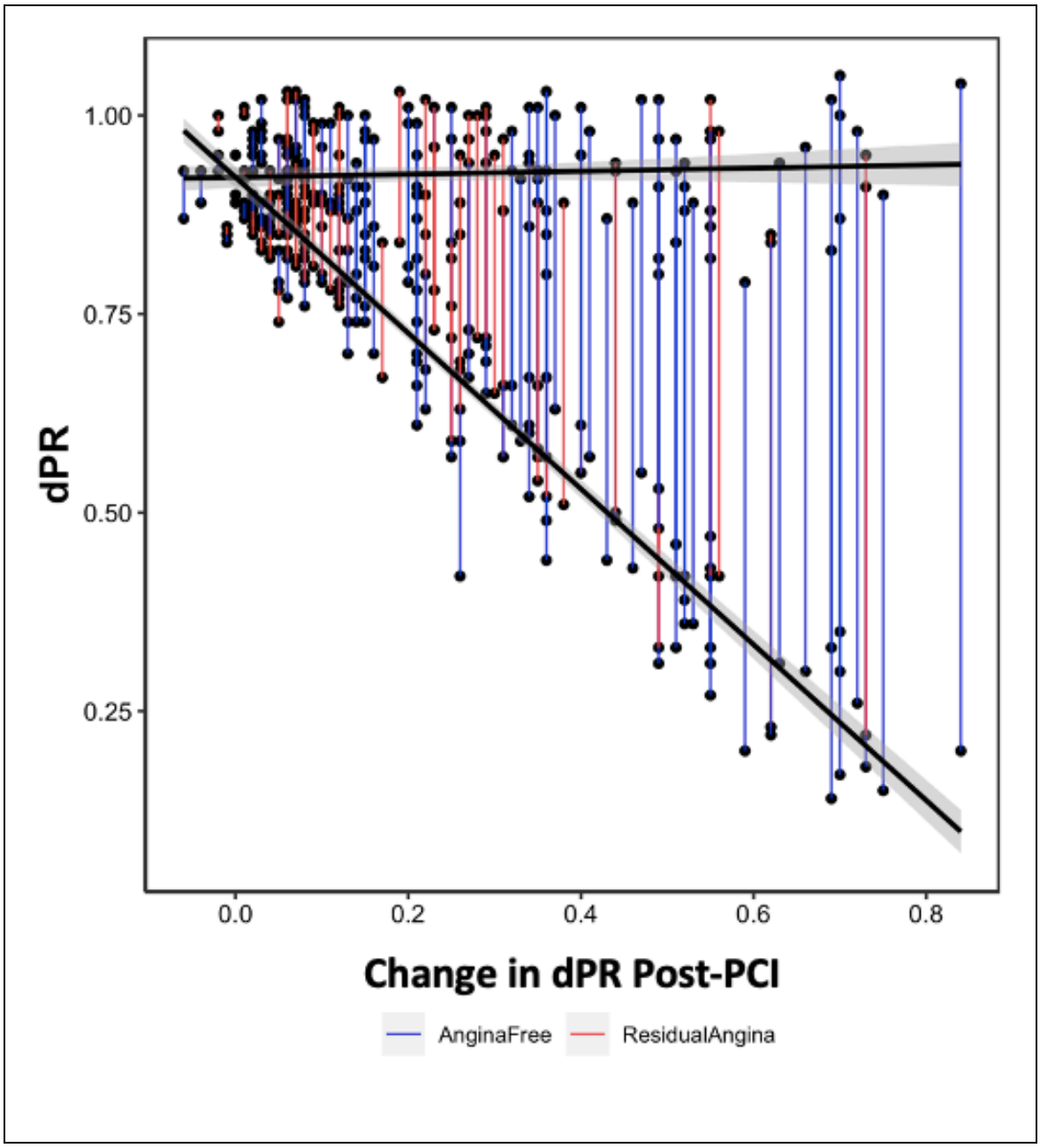
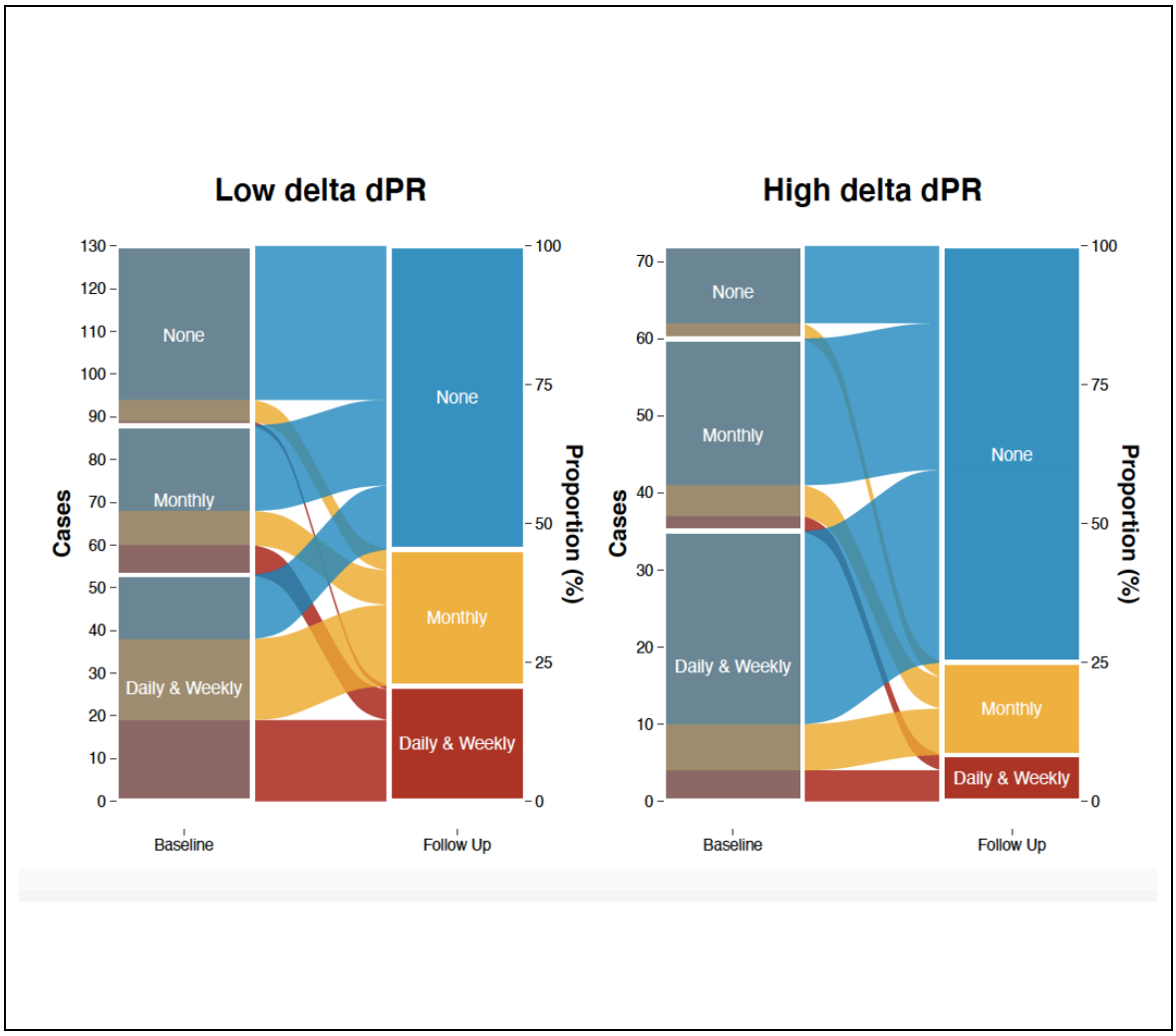


Figure courtesy of Dr Takuya Mizukami.

Figure 6-4 – Change in frequency of angina at 3-month follow-up stratified by magnitude of change in dPR after PCI



Sankey diagram depicting changes in angina frequency (daily or weekly, monthly or none) between baseline and 3-month follow-up stratified by low and high delta dPR (dichotomised by the 66th percentile value). Figure courtesy of Dr Takuya Mizukami.

6.5 Discussion

Previous studies have reported excellent agreement between NHPRs (and resting diastolic indices in particular).(62, 98-100) Nevertheless, when employing a dichotomous cut-off, the prevalence of positive studies has been shown to vary between NHPRs which may influence revascularisation decisions according to the resting pressure index utilized.(101, 102) In the present analysis this variation was also evident in the proportions of optimal and suboptimal post-PCI NHPR values (Table 6-1). A previous blinded observational study reported 21% (114/542) of vessels had a residual iFR ≤ 0.89 following standard-of-care PCI. Substantially higher proportions of suboptimal post-PCI NHPR values (ranging from 37 – 49.2%) were observed in this sub-analysis of the TARGET-FFR randomised controlled trial. By comparison, the proportion of vessels with residual suboptimal FFR (≤ 0.80) was 24.3% (58/239). The accompanying microvascular assessment with CFR and IMR reassures that the lower proportion of suboptimal FFR was not the result of acute microvascular dysfunction leading to a blunted hyperaemic effect post-PCI. In any event, such a phenomenon would also have affected the resting indices and we would expect higher, not lower, NHPR values in that case. The more likely explanation is that, following the hyperaemic stimuli of repeated transient balloon occlusions of the vessel, it is not possible to re-establish true resting conditions in the immediate post-PCI phase. There is precedence for this observation among non-culprit vessels in the STEMI setting. After successful primary culprit intervention for STEMI, Thim et al evaluated iFR in 157 non-culprit vessels, deferred treatment and performed follow-up assessments at a median of 16 [5–32] days. Median acute iFR was 0.89 [0.82–0.94] and median follow-up iFR 0.91 [0.86–0.96]. With follow-up ≥ 16 days after STEMI, acute iFR was shown to be lower than follow-up iFR and had a classification agreement of only 70%.(103) Data from a subsequent study evaluating FFR, CFR and IMR in the non-infarct-related arteries (IRA) of patients with ST-segment elevation myocardial infarction (STEMI) found lower CFR values in non-IRA compared with stable angina (SA) vessels (1.77 [1.25–2.76] versus 2.44 [1.63–4.00], P=0.018), primarily driven by an increased resting flow in non-IRA (rest mean transit time 0.58 [0.32–0.83] versus 0.65 seconds [0.39–1.20], P=0.045). Hyperaemic flow was similar (hyperaemic mean transit time 0.26 [0.20–0.42] versus 0.26 seconds [0.18–0.35], P=0.873) and there were no differences in IMR (15.6 [10.4–21.8] in non-IRA versus 16.7 [11.6–23.6] in SA

vessels, P=0.559).(104) In TARGET-FFR, median post-PCI resting transit times were 10% faster than those prior to PCI (1.12 ± 0.45 [Pre] vs. 0.93 ± 0.42 seconds [Post], difference -0.20 ± 0.45, relative difference -10 ± 43%, Table 3-3) Conceptually, these findings support the theory that, when measured in the immediate post-PCI phase, NHPR values may be underestimated (thereby overestimating the physiological significance of residual disease) due to higher resting coronary flow. This has implications for operators using post-PCI NHPR results (particularly across the dichotomous cut-off points where these values cluster) to guide additional PCI optimisation in a vessel.

Impact of Target Vessel on NHPRs

The target vessel had a significant impact on NHPR results. Pre-PCI dPR, iFR_{sim} and RFR were all significantly higher in the right coronary artery. This may be partly explained by the higher levels of microvascular resistance (assessed by corrected IMR) observed in this artery. There was no difference in pre-PCI FFR between vessels. For values close to the clinical cut-off, this could lead to vessel-specific discordance in revascularisation decisions between non-hyperaemic and hyperaemic indices, however, previous data suggest that deferred lesions with discordant results between NHPRs and FFR did not have a higher risk of vessel-oriented composite outcomes at 5 years than revascularised vessels.(105) As previously reported with FFR (Table 3-8), post-PCI NHPR values in the present analysis were also systematically lower in the LAD than non-LAD arteries. Assuming that the majority of focal epicardial stenoses have been successfully treated by PCI, the lower NHPR values observed in the LAD post-PCI most likely relate to the interplay of hydrostatic forces, the ratio of coronary artery volume to myocardial mass subtended and higher flow rates in the LAD (which will generate larger pressure gradients over any residual diffuse disease).(106-108) While these factors are of course also present pre-PCI, their influence is obscured by the effect of a haemodynamically significant stenosis which is several orders of magnitude greater.

Association between NHPRs and Patient-Reported Outcome Measures

There is a paucity of data on the association between post-PCI NHPRs and patient-reported outcome measures such as angina. A previous study identified an iFR of < 0.95 as the best cut-off value to discriminate cardiac death or

spontaneous MI during a median 1-year follow-up. When the relationship between this cut-off for composite clinical outcomes and changes in Seattle Angina Questionnaire (SAQ) scores was examined, the only significant between-group difference identified was in a single SAQ domain (Angina Frequency) in a very specific subgroup of patients. In what the authors classified as highly symptomatic patients (baseline SAQ-AF score ≤ 60), SAQ-AF score increased by ≥ 10 points more frequently in patients with versus without post-PCI iFR ≥ 0.95 (100% vs 88.5%; P =0.01).(75)

Rather than focus on this previously proposed threshold or attempt to identify our own optimal dichotomous cut-off value, in the present analysis we opted instead to examine the association between NHPRs and the change in patient-reported outcome measures among patients who reported angina at baseline. Significant, albeit weak-to-moderate, positive correlations were observed between the change in NHPR values following PCI and patient-reported outcomes at 3-month follow-up (across EQ-5D-5L weighted health state and all domains of the SAQ-7). This was predominantly driven by negative correlations with the pre-PCI NHPR value. Interestingly, no association was observed between the absolute post-PCI NHPR values and PROMs which likely explains why previous investigators found little to link post-PCI NHPR results with SAQ scores at follow-up.

Limitations

Resting Pd/Pa, dPR and RFR were recorded prospectively at each phase of PCI, however, the additional PCI optimisation measures in the intervention arm were directed based on FFR measurement and a hyperaemic pressure-wire pullback assessment. The rationale for the study's definition of focal disease (an abrupt pressure drop ≥ 0.05 FFR units) has been outlined previously. Hyperaemia magnifies pressure gradients, making residual focal disease more apparent. It is therefore most likely that even less optimisation would have been attempted had these measures been directed by a non-hyperaemic pullback assessment.

Chapter 7 Conclusion

In the TARGET-FFR trial, blinded, routine assessment of coronary physiology after standard-of-care percutaneous coronary intervention identified that a substantial proportion of patients have persistently suboptimal post-PCI FFR results (68% < 0.90, 29% ≤ 0.80). The pattern of residual disease, as assessed by FRR pullback gradients, was predominantly diffuse in nature. A post-PCI physiology-guided incremental optimisation strategy (PIOS) based on reducing hyperaemic trans-stent pressure gradients and stenting residual untreated, focal disease achieved modest improvements in final FFR values. Compared to a control group, the PIOS intervention significantly reduced the proportion of patients with post-PCI FFR remaining below the clinical threshold for revascularisation (FFR ≤ 0.80) but did not increase the proportion above the proposed optimal post-PCI threshold of ≥ 0.90. With just 30.5% (40/131) of patients randomised to the PIOS group considered eligible and suitable to receive additional intervention, the study was ultimately underpowered for its primary outcome and should be interpreted in that context.

Additional optimisation measures also achieved small improvements in post-PCI non-hyperaemic pressure ratios (NHPRs) but there were no significant differences between randomised groups in the proportion of patients with suboptimal results. Higher resting coronary flow in the immediate post-PCI phase may lead to NHPR values being underestimated (thereby overestimating the physiological significance of residual disease). This has implications for operators using non-hyperaemic post-PCI results (particularly across the dichotomous clinical revascularisation cut-off points where these values cluster) to guide additional PCI optimisation in a vessel.

Post-PCI FFR was systematically lower where the LAD was the target vessel for intervention (57.4% of patients). Achieving a post-PCI FFR value ≥ 0.90 may simply not be possible in the majority of LAD arteries. Previous studies found no excess in clinical events for LAD target vessels compared to non-LAD target vessels which may support adopting a separate, lower cut-off value to represent an optimal post-PCI FFR result in the LAD.

Post-PCI coronary physiology had no significant correlation with patient-reported angina or quality-of-life scores at 3-month follow-up. Rather, it was the magnitude of change in hyperaemic and non-hyperaemic indices which predicted improvement in patient-reported outcome measures (PROMs). The change was predominantly driven by pre-PCI values which were found to have significant negative correlations with PROMs scores (i.e., lower pre-PCI values correlating with larger improvements in PROMs scores). PCI on focal patterns of coronary artery disease (as defined by the Pullback Pressure Gradient index) was associated with larger improvements in coronary physiology indices and patient-reported outcome measures.

In conclusion, the findings of the TARGET-FFR randomised controlled trial can be summarised as follows:

- Suboptimal post-PCI results are common, particularly in the LAD artery, and most frequently relate to diffuse-pattern residual pressure gradients

- A strategy of routine post-PCI FFR-guided optimisation is feasible and safe and can reduce the proportion of patients with a final FFR remaining below the clinical revascularisation threshold

- Patients with physiologically severe and focal lesions can expect a larger improvement in intracoronary pressure ratios following PCI which is associated with a higher likelihood of angina relief and improved quality-of-life

- The scope to further optimise post-PCI physiology results with additional intervention in vessels with diffuse patterns of coronary disease is limited

- Accordingly, physiology-guided optimisation of PCI may be more effective when directed upstream to provide a comprehensive pre-PCI assessment. Quantifying the pattern of coronary disease can predict which vessels are likely to achieve large improvements in coronary physiology metrics after stenting and thereby determine the appropriateness of PCI intended to alleviate symptoms. Planning stent deployment based on the findings of a

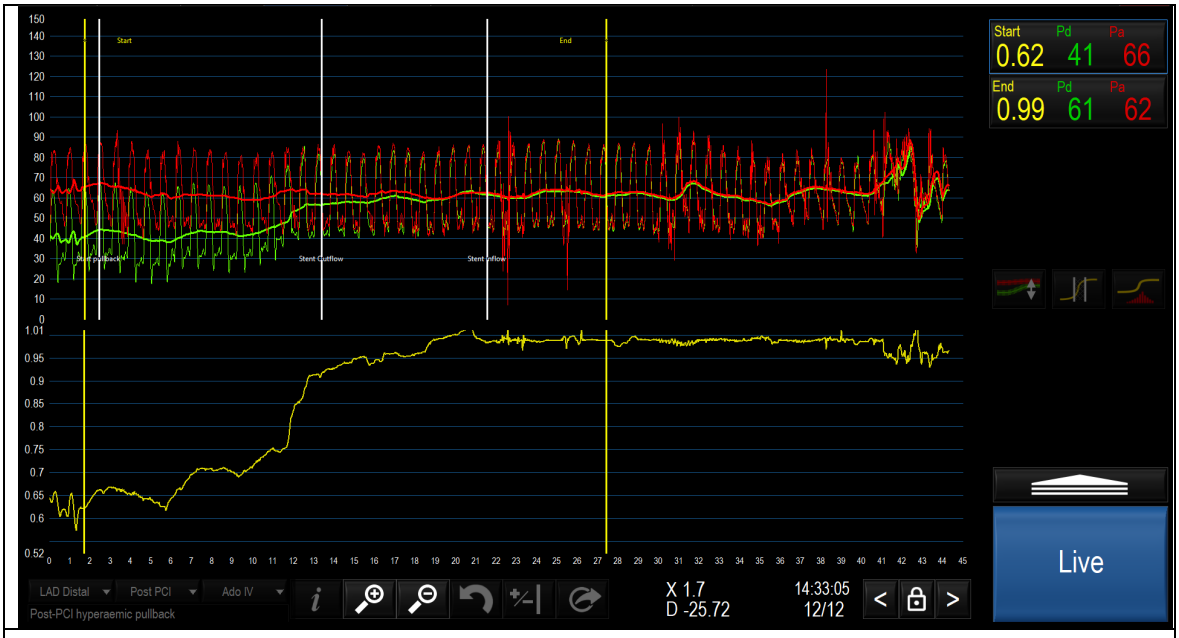
detailed pre-PCI pullback is also likely to decrease the incidence of residual focal disease and need for additional optimisation.

Appendices

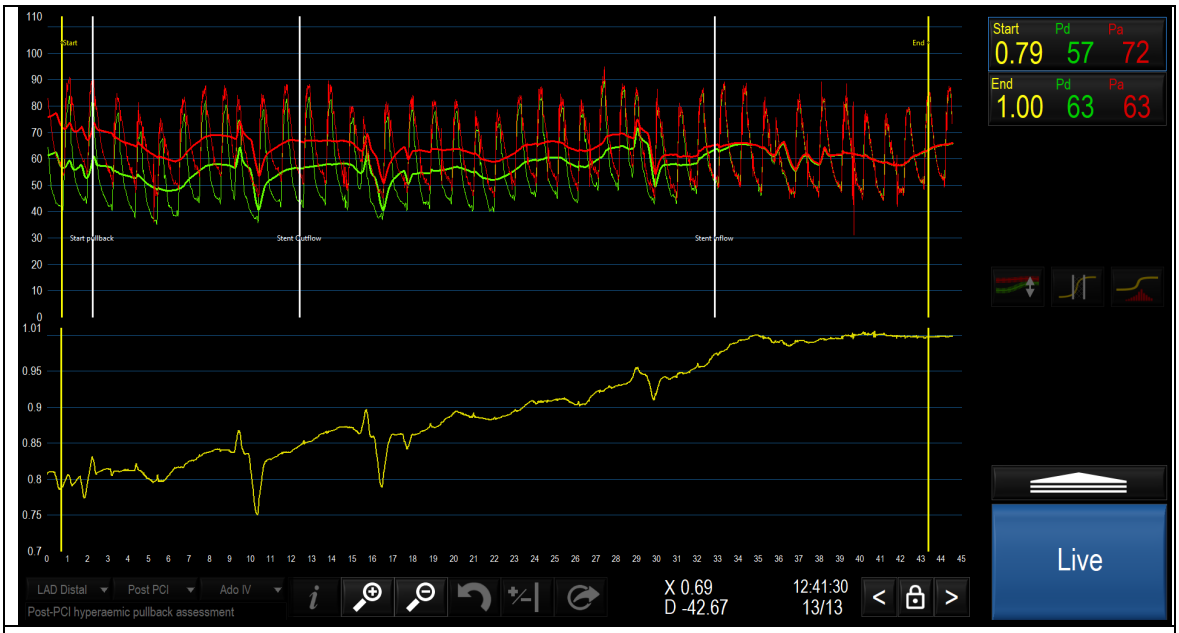
Protocol Deviations

The following section contains summaries of all 20 cases in the PIOS group where additional optimisation measures were advised by the study protocol but were not performed due to operator and/or patient factors.

The pullback recordings also serve to provide examples of predominantly diffuse (but occasionally focal) residual disease patterns and some of the pressure waveform artefacts encountered during pullback assessments.



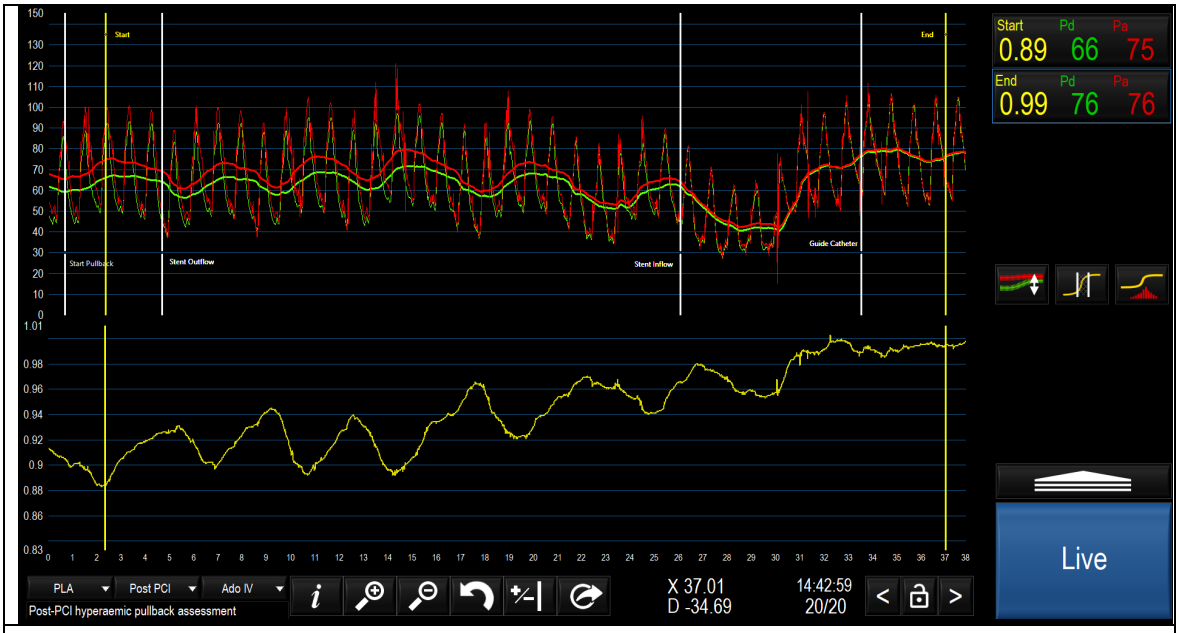
Case 1. Post-PCI FFR 0.61. A 3.0/33mm stent, post-dilated with 4mm non-compliant (NC) balloon to 18atm proximally. Diffuse residual gradient with hyperaemic trans-stent gradient (HTG) of 0.07 units and a focal pressure loss of 0.16 units at distal stent edge. Largest pressure drop occurred at the stent outflow in the mid LAD at the edge of segment with marked intramyocardial bridging. Operator felt stenting into the intramyocardial segment would be inappropriate and potentially hazardous



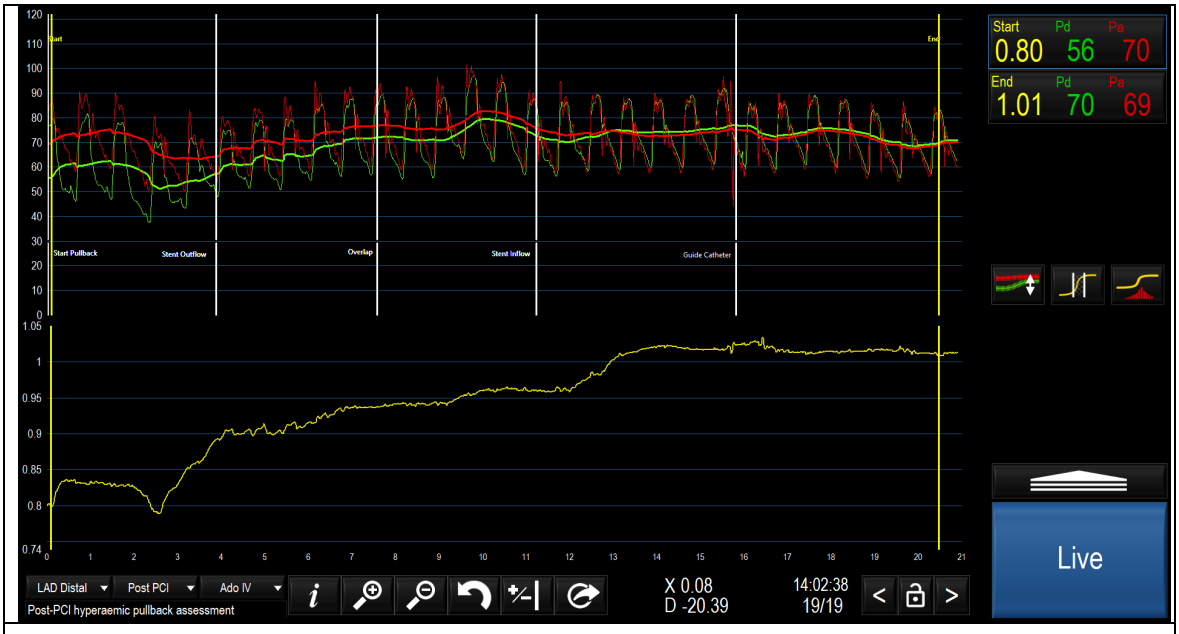
Case 2. Post-PCI FFR 0.78. Overlapping 3.0/32mm and 3.5/32mm stents post-dilated with 3.5mm NC balloon to 18atm. Diffuse residual gradient with HTG of 0.12 units. Operator felt sub-optimal post-PCI represented diffuse gradient in distal vessel and through the stented segment with no focus for additional optimisation following initial high pressure post-dilation with non-compliant balloons. Note pressure waveform artefacts from ectopic heartbeats.

Case 3. Post-PCI FFR 0.88. 2.75/18mm stent deployed to mid vessel lesion, post-dilated with 3mm NC balloon to 16atm. 3.0/28mm stent to proximal lesion, post-dilated with 3.5mm NC balloon (14-18atm). HTG of 0.07 units across distal stent and 0.05 across proximal stent. Operator felt there were no further targets for optimisation and that the distal stent had been adequately post-dilated already

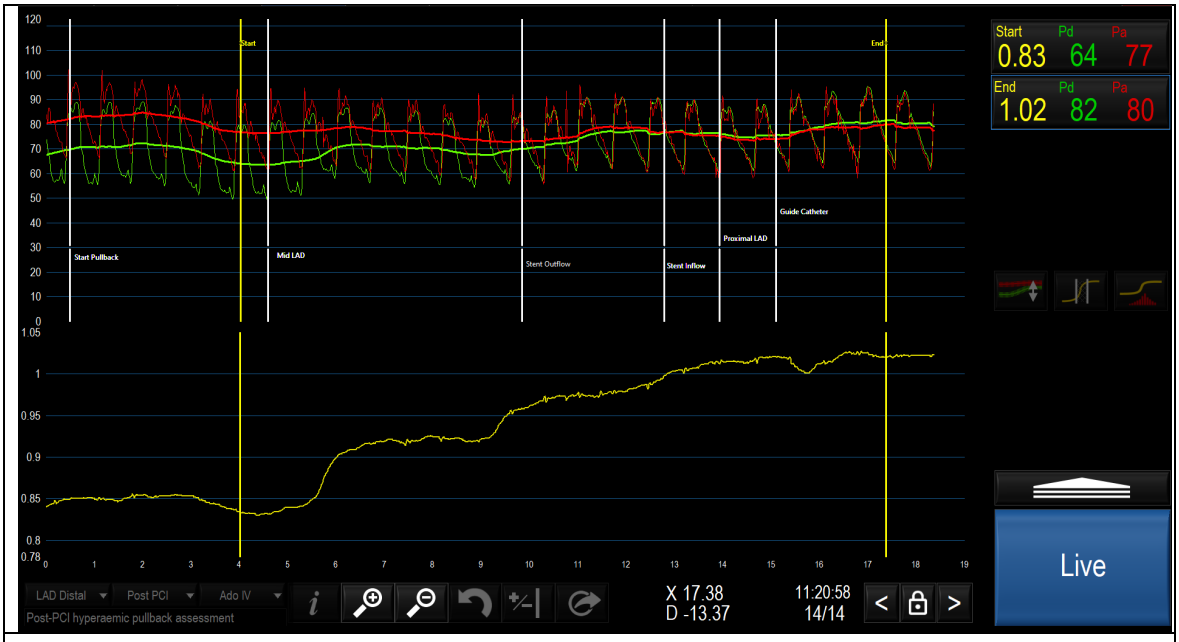
Case 4. Post-PCI FFR 0.87. Previous proximal LAD stent. New 3.0/32mm stent deployed to overlap distally, post-dilated with 3.5mm NC balloon to 22atm. Diffuse gradient with HTG of 0.05 units. Long stented segment with borderline HTG value. Operator felt further aggressive post-dilation had potential for an adverse outcome and declined to attempt further optimisation.



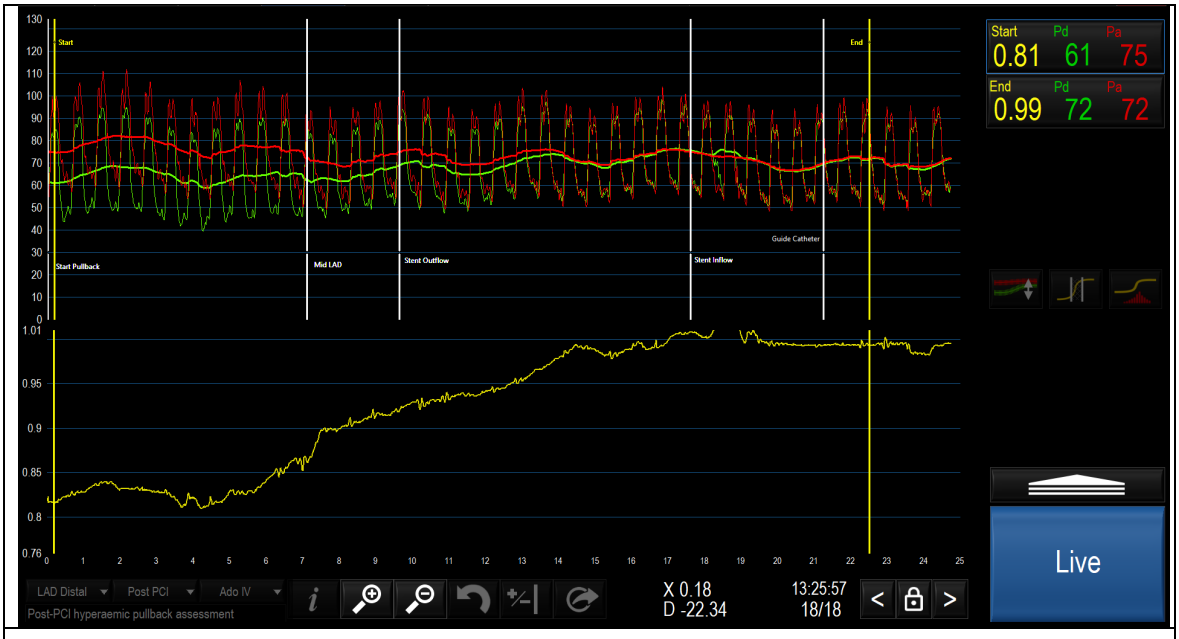
Case 5. Post-PCI FFR 0.86. Borderline HTG of 0.05 units across a 2.75/48mm stent which had been post-dilated with a 3mm NC balloon to 20atm. Operator felt appropriate post-dilation had been performed and that residual diffuse gradient related to stent length. Note undulating pressure waveform artefact related to pattern of adenosine response.



Case 6. Post-PCI FFR 0.80. 3.0/23mm stent post-dilated with 3.25mm NC balloon at target lesion. Additional 3.5/23mm stent overlapping proximally to cover inflow disease. Diffuse residual gradient with HTG of 0.07 units and a relatively focal drop of 0.10 units at stent outflow. Operator unwilling to perform further optimisation/post-dilate proximal stent as deployment had resulted in acute closure of a small, diseased septal branch which provoked seemingly disproportionate ischaemic chest pain and ECG changes (ST elevation in I and AVL, downsloping inferior ST depression)

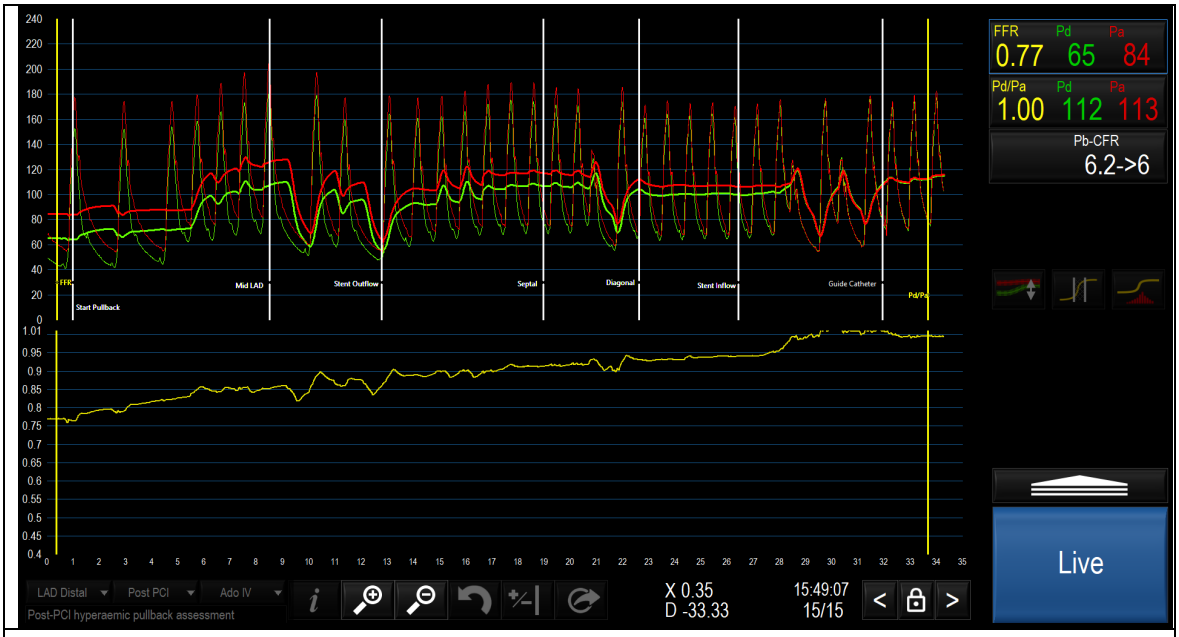


Case 7. Post-PCI FFR 0.81. 3.5/18mm stent proximally post-dilated with 3.75mm NC balloon to 16atm. HTG of 0.04 units. Focal pressure drop at stent outflow with larger focal drop of 0.09 units distally. Operator unwilling to stent either the disease at stent outflow or the more distal focal lesion as FFR already > 0.80 and distal lesion was located at a bifurcation point.



Case 8. Post-PCI FFR 0.81. 3.0/48mm stent post-dilated with 3.5mm NC balloon to 14atm. Diffuse residual gradient with HTG of 0.07 units. Operator felt stent had been adequately post-dilated, reluctant to post-dilate with larger balloon and felt diffuse HTG was attributed to stent length.

Case 9. Post-PCI FFR 0.82. 3.5/23mm stent deployed at target lesion. Overlapping 3.0/48mm stent distally to cover long segment of diffuse disease. Post-dilation of both stents with 3.5mm NC balloon to 16atm. Further post-dilation with 3.75mm NC balloon to 20atm in proximal segment for optimisation of stent above the origin of main diagonal branch. Diffuse residual gradient with HTG of 0.05 units. Operator felt stents had been adequately post-dilated and unlikely to be able to further reduce HTG due to length of stented segment.



Case 10. Post-PCI FFR 0.78. 3.0/38mm stent post-dilated with 3.25mm NC balloon to 18atm. Diffuse residual gradient with HTG of 0.05 units. Operator felt stent had already been appropriately post-dilated and that further intervention would not reduce HTG significantly. Note pressure waveform artefact due to intermittent heart block.

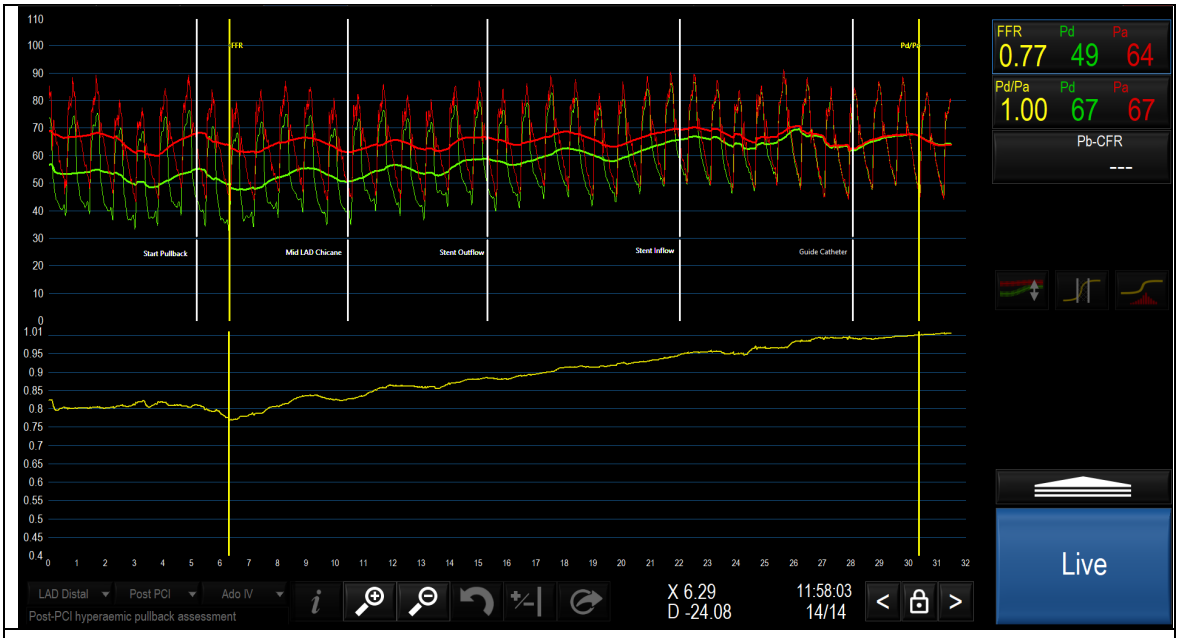
No post-PCI pullback performed

Case 11. Post-PCI FFR 0.71. Medina 1,1,0 bifurcation lesion involving proximal LAD and diagonal branch. Culotte technique. 2.75/38 stent from LAD into diagonal. Proximal optimisation with 3.5mm NC balloon. 3.5/38mm stent in LAD. Final kissing balloon angioplasty with 3.5/ NC balloon in LAD (10atm) and 2.75mm NC balloon into diagonal (10atm). Computer software failure mandating system restart after during post-PCI measurements. Operator unwilling to remove pressure wire to re-zero or continue with repeat measurements and optimisation protocol. No post-PCI pullback performed and therefore no optimisation attempted.

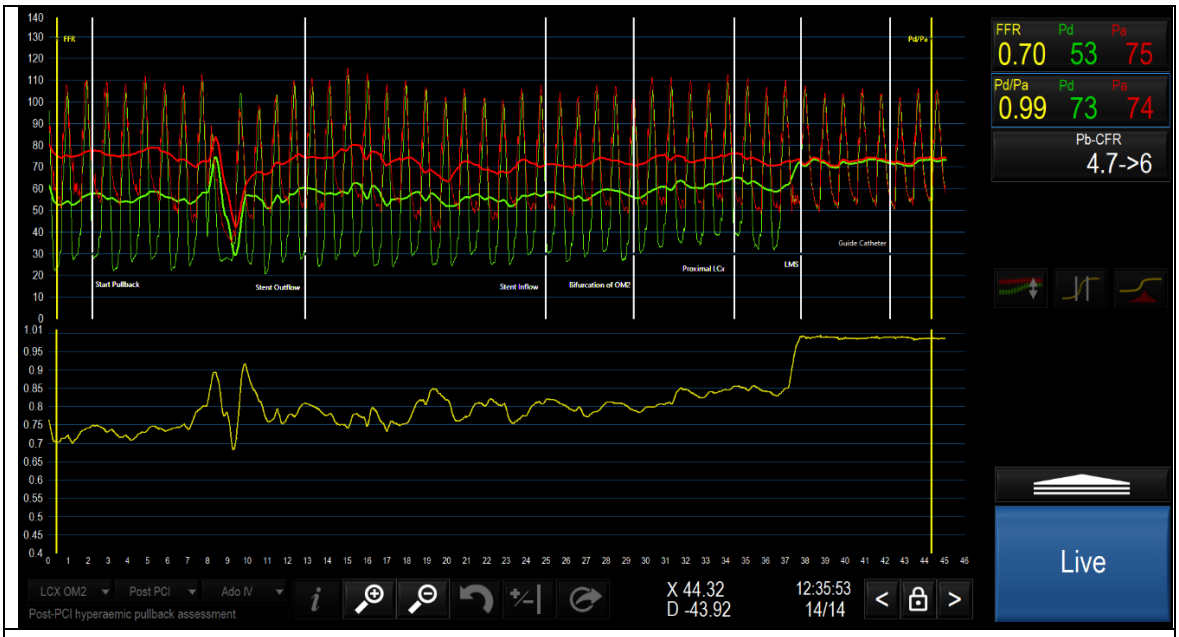
Case 12. Post-PCI FFR 0.87. 3.5/20mm stent at target lesion. Additional 3.0/32mm stent overlapping distally to treat second lesion downstream. Distal-to-mid stent segment post-dilated with 3.25 NC balloon (18-22atm) and proximal segment with 3.75/15mm NC balloon (18-20atm) Diffuse residual gradient with HTG of 0.05 units. Operator felt stent had been adequately post-dilated and that further dilatation with larger balloons may be harmful

Case 13. Post-PCI FFR 0.84. 3.5/48mm stent post-dilated with a 3.5mm NC balloon to 18atm. Diffuse residual gradient with HTG of 0.06 units. Operator believed stent was adequately post-dilated and that further expansion attempts with a larger balloon would not significantly reduce the gradient in a long stent and may be hazardous.

Case 14. Post-PCI FFR 0.80. 3.0/38mm stent deployed at target lesion. Additional 3.0/23mm stent overlapping proximally to cover disease at stent inflow. Post-dilation with 3.25mm NC balloon up to 20atm. Diffuse residual gradient with HTG of 0.06 units. Operator felt stent had been adequately post-dilated and that residual HTG of was related to total stent length of 60mm and unlikely to change with further post-dilation.

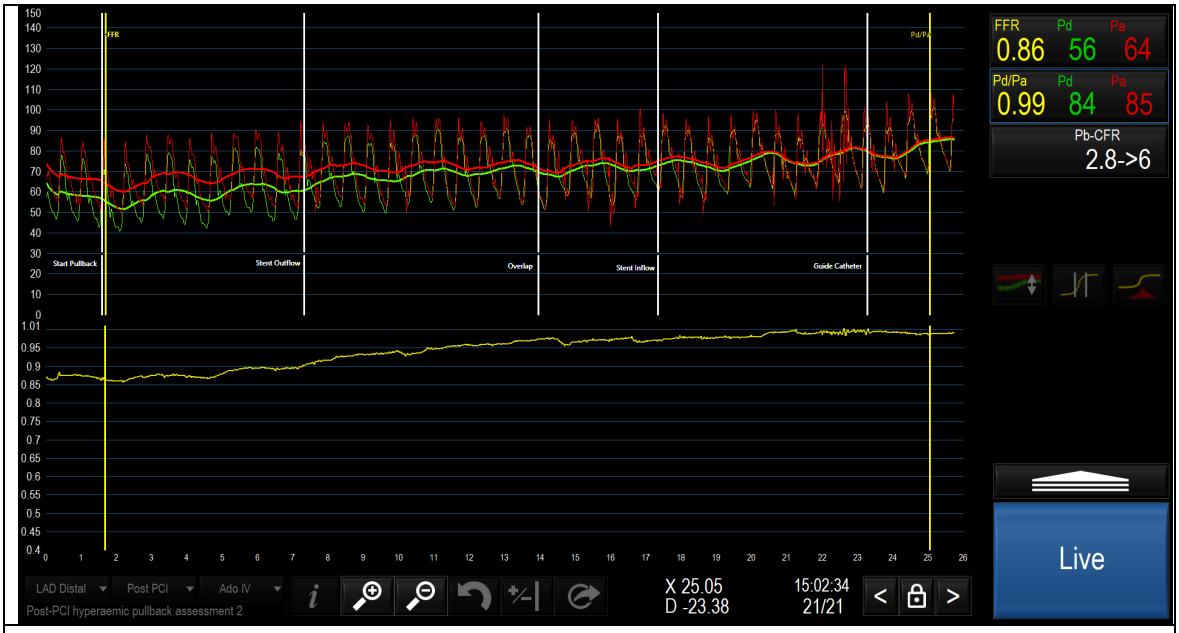


Case 15. Post-PCI FFR 0.76. 3.5/33mm stent. Post-dilated with 3.75/12mm NC balloon (16atm) distally and 4.0/20mm NC balloon (18atm) proximally. Diffuse residual gradient with HTG of 0.07 units. Operator felt stent had been adequately post-dilated and that further aggressive efforts at expansion may be harmful.

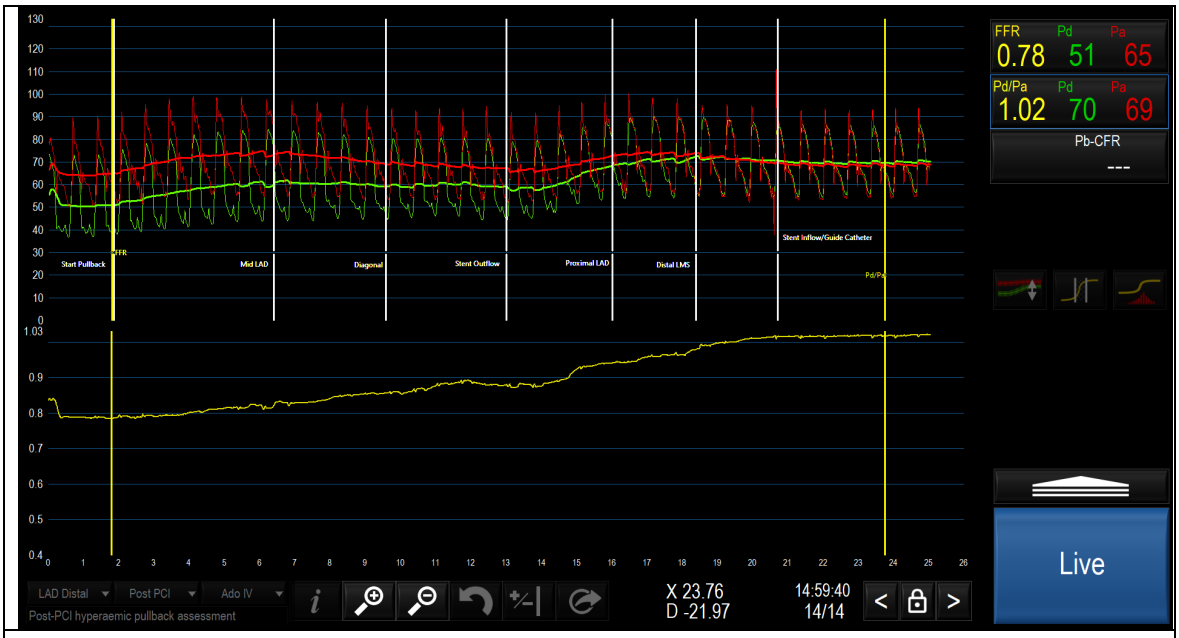


Case 16. Post-PCI FFR 0.70. 3.0/28mm stent post-dilated with 3.25mm NC balloon to 20atm. Diffuse residual gradient distally with HTG of 0.02 units. Focal step-up of 0.16 units proximally at ostial vessel back in to left main stem. Operator did not wish to proceed to PCI of left main stem. Pressure waveform artefact distally relating to ectopic heartbeat.

Case 17. Post-PCI FFR 0.82. 3.5/48mm stent deployed at target lesion. Additional 3.5/15mm stent overlapped proximally to cover inflow disease. Post-dilated with 3.75mm NC balloon up to 14atm. Diffuse residual gradient distally with HTG of 0.05 units. Relatively focal step-up of 0.07 units back into left main stem. Operator believed stent was adequately post-dilated and borderline residual HTG related to stent length. Did not feel stenting back into LMS was warranted. Note pressure waveform artefacts related to ectopic heart beats.



Case 18. Post-PCI FFR 0.80. 3.0/38mm stent to target lesion. Additional 4.0/20mm stent overlapping proximally to cover disease at stent inflow. Sequential post-dilation: 3.5/15mm NC balloon (16-20atm) to first stent then 4.0/12mm NC balloon (18-24tm) to second stent and overlap. Finally, a 3.25 NC balloon (14-16atm) applied to an area of eccentric under-expansion at stent overlap. Diffuse residual gradient with HTG of 0.07 units. Following high-pressure post-dilations guided by Intravascular Ultrasound (IVUS) imaging, the operator was satisfied with stent deployment and felt no further optimisation achievable by additional post-dilation. Residual gradient felt to be due to length of stented segment.



Case 19. Post-PCI FFR 0.77. 3.5/38mm stent deployed from LAD back into Left Main Stem. Sequential post-dilation initially with 3.5/15mm NC balloon (16atm) in LAD and 4.5/8mm NC balloon (10-14atm) in LMS. Following IVUS assessment, a 4.0/12mm NC balloon applied to segment in proximal LAD (16atm) and a 5.0/12mm NC balloon (8-12atm) to segment in left main. Diffuse residual gradient with HTG of 0.07 units. Based on IVUS appearances, operator was satisfied stent had been appropriately post-dilated with large diameter NC balloons to high pressure and further aggressive post-dilation may have been harmful

Case 20. Post-PCI FFR 0.87. 3.0/38mm stent deployed at target lesion in LAD back into left main stem. Additional 2.75/48mm stent deployed to overlap distally due to distal stent edge dissection and to treat diffuse outflow disease with further discrete lesion downstream. Sequential post-dilation of stents with 3.0/15mm NC balloon (14-18atm), followed by 3.5/20mm (12-16atm) and 4.0/15mm NC (14atm) in proximal LAD segment. Finally, following OCT assessment, a 4.0/12mm NC balloon was applied to LMS segment at high pressure (16-18atm). Diffuse residual gradient with HTG of 0.08 units. Patient intolerant of further adenosine, satisfactory, no further intervention attempted and result accepted. Note pressure waveform artefacts related to ectopic beats.

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