Optimising physiological endpoints of percutaneous coronary intervention

Rasha K. Al-Lamee[1,2]*, MA, MBBS, PhD; Christopher A. Rajkumar[1,2], BSc, MBBS; Sashiananthan Ganesananthan[1], BSc; Allen Jeremias[3], MD, MSc

1. National Heart and Lung Institute, Imperial College London, London, United Kingdom; 2. Imperial College Healthcare NHS Trust, London, United Kingdom; 3. Department of Cardiology, St. Francis Hospital, The Heart Center, Roslyn, NY, USA

Abstract

Invasive coronary physiology to select patients for coronary revascularisation has become established in contemporary guidelines for the management of stable coronary artery disease. Compared to revascularisation based on angiography alone, the use of coronary physiology has been shown to improve clinical outcomes and cost efficiency. However, recent data from randomised controlled trials have cast doubt upon the value of ischaemia testing to select patients for revascularisation. Importantly, 20-40% of patients have persistence or recurrence of angina after angiographically successful percutaneous coronary intervention (PCI). This state-of-the-art review is focused on the transitioning role of invasive coronary physiology from its use as a dichotomous test for ischaemia with fixed cut-points, towards its utility for real-time guidance of PCI to optimise physiological results. We summarise the contemporary evidence base for ischaemia testing in stable coronary artery disease, examine emerging indices which allow advanced physiological guidance of PCI, and discuss the rationale and evidence base for post-PCI physiological assessments to assess the success of revascularisation.

*Corresponding author: National Heart and Lung Institute, Imperial College London, 2nd Floor, B Block, Hammersmith Hospital, Du Cane Road, London, W12 0HS, United Kingdom. E-mail: r.al-lamee13@imperial.ac.uk

Abbreviations

CAD   coronary artery disease
FFR   fractional flow reserve
iFR   instantaneous wave-free ratio
IVUS   intravascular ultrasound
MI   myocardial infarction
OCT   optical coherence tomography
OMT   optimal medical therapy
PCI   percutaneous coronary intervention

Physiological justification of PCI

INTRODUCTION

Contemporary guidelines suggest that the principal remit of percutaneous coronary intervention (PCI) in stable coronary artery disease (CAD) is to treat symptoms refractory to optimal medical therapy (OMT)[1]. Recent data from the largest trial studying the impact of an early invasive strategy on hard outcomes in stable CAD support these recommendations[2]. Since we attribute symptoms not to the anatomic stenoses but to their association with myocardial perfusion, it intuitively follows that, to treat angina optimally, improvement of physiological, rather than anatomical characteristics of a diseased vessel should be the principal goal. Ischaemia-guided revascularisation with invasive coronary physiology has become a central component of modern-day evidence-based treatment algorithms for the management of stable CAD[1]. By offering real-time assessment of the ischaemic significance of epicardial stenoses, invasive coronary physiology identifies patients who can benefit from revascularisation by bridging the gap between anatomy, physiology and symptoms. However, recent placebo-controlled data have challenged this paradigm and it has become apparent that the link between ischaemia and symptoms may be more complex[3].

Physiological assessment allows vessel- and lesion-specific assessment for ischaemia. Therefore, in optimising post-PCI physiology, it may be possible to improve outcomes specific to that vessel or lesion. However, it must be remembered that cardiovascular events also occur from angiographically and physiologically non-significant lesions, so, even with the best physiological

results, secondary prevention with optimum medical therapy remains essential[4].

In this state-of-the-art review, we report the contemporary evidence base for revascularisation based on invasive physiology, the evolving role of physiology to guide PCI strategy, and the potential value of post-PCI physiological assessments. More broadly, we discuss the current role of ischaemia testing in the diagnosis and treatment of stable CAD and the implications for the future of coronary physiology.

CORONARY PHYSIOLOGY INDICES AND CLINICAL OUTCOME DATA

FRACTIONAL FLOW RESERVE

Summary characteristics and trial designs for landmark fractional flow reserve (FFR) trials are presented in **Table 1**.

In an era where interventionalists believed that anatomy was the gold standard and that treatment of moderate lesions was "preventative", the early FFR trials truly challenged dogma. The DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) trial demonstrated that, even in the presence of a significant single vessel anatomical stenosis, there were patients in whom it was safer to opt for conservative treatment[5]. The trial showed that, when FFR was ≥0.75, optimum medical therapy alone was equally safe to revascularisation with PCI and optimum medical therapy[5]. Importantly, it also showed that PCI did not lead to eradication of hard clinical outcomes because the reference group with FFR <0.75, in whom PCI was performed albeit in the bare metal stent era, had the worst outcomes among the three groups[6].

Once DEFER had shown that it was safe to leave non-physiologically significant lesions alone, the next step was to investigate whether FFR could be used to guide whom to treat with the larger FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial. The investigators this time chose a higher "clinical" FFR cut-point of 0.80 to ensure a safety margin for revascularisation at a time when the accepted belief was, "If you see it, you must treat it". They randomly assigned patients with multivessel CAD to revascularisation based on angiography

Table 1. Summary characteristics for patient outcome FFR trials.

Trial	Question	Subjects	Study population (n)	Primary endpoint	FFR cut-off	Mean FFR	Conclusion
DEFER[5]	Safety of deferral of PCI where FFR ≥0.75	SCD	325	24-month MACE	<0.75	Defer: 0.87±0.07 (n=91) Performance: 0.87±0.06 (n=90) Registry: 0.56±0.16 (n=144)	Deferral of PCI safe where FFR ≥0.75
FAME[7]	Efficacy of FFR-guided PCI vs PCI based on angiography alone	Multivessel SCD/ACS with non-culprit stenosis	1,005	12-month MACE	≤0.80	Overall cohort: 0.71±0.18 Ischaemic lesions: 0.60±0.14 Non-ischaemic lesions: 0.88±0.05	FFR-guided PCI superior to PCI based on angiography alone
FAME 2[9]	FFR-guided PCI+OMT vs OMT alone where FFR ≤0.80	Multivessel SCD	1,220	MACE (trial halted at 7-month follow-up)	≤0.80	FFR-guided PCI+OMT: 0.68±0.10 OMT alone: 0.68±0.15	FFR-guided PCI+OMT reduces urgent revascularisation compared to OMT alone

Values are mean±SD unless otherwise indicated. SCD: stable coronary disease

alone or to revascularisation for any vessel with FFR ≤0.80[7]. At 12-month follow-up, there was a significantly lower incidence of the primary composite endpoint of death, non-fatal myocardial infarction (MI) and repeat revascularisation in the FFR group, indicating superiority over angiography alone. Importantly, there was no difference in symptom improvement by Canadian Cardiovascular Society angina grade between the FFR- and angiography-guided groups[7].

The DEFER and FAME trials served to prove that, in stable CAD, PCI for stenoses deemed to be "non-ischaemic" according to FFR thresholds was less effective than conservative management, and possibly even harmful[5,7]. These landmark trials also importantly questioned the role of anatomically guided treatment and showed that reduction in number and length of stents was clinically advantageous in terms of both clinical outcomes and cost-effectiveness[8].

The FAME 2 (Fractional Flow Reserve guided PCI versus Medical Therapy in Stable Coronary Disease) trial was designed to answer whether a strategy of PCI in addition to medical therapy was superior to medical therapy alone for patients with significant ischaemia, defined as an FFR ≤0.80 in at least one vessel[9]. This unblinded trial was terminated early on ethical grounds because of a marked reduction in the rate of urgent revascularisation in the PCI+OMT group. The large majority of these unplanned revascularisation events were not associated with electrocardiographic (ECG) changes or biomarker elevation and, as a result, the endpoint was vulnerable to bias[10]. There was no significant difference in the incidence of all-cause mortality, cardiac death and MI, although there was a significant reduction in spontaneous MI among patients undergoing PCI at longer-term follow-up[11,12].

INSTANTANEOUS WAVE-FREE RATIO

Despite evidence that the use of FFR was clinically and economically efficacious, global adoption of FFR remained limited[13]. Added time, cost, and lack of familiarity with the techniques may have been barriers to its routine use[14]. A resting index, the instantaneous wave-free ratio (iFR), that did not require the induction of pharmacological hyperaemia, was developed to tackle some of these issues. The diagnostic accuracy of iFR to identify FFR-positive lesions was good and, when a third comparator was used as a reference standard, no significant differences were observed between FFR and iFR for their accuracy in identification of ischaemic stenoses[15]. Randomised controlled trials that were essential for the clinical validation of iFR are summarised in **Table 2**.

DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation)[16] and iFR-SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome)[17] were non-inferiority trials designed to test for equivalence between iFR- and FFR-guided revascularisation. The trials utilised identical cut-points for PCI (iFR ≤0.89 and FFR ≤0.80) with a harmonised primary endpoint of 12-month incidence of all-cause mortality, non-fatal MI and unplanned revascularisation.

With concordant results across the two trials, iFR-guided revascularisation was found to be non-inferior to an FFR-guided strategy. In a pooled patient-level analysis of the DEFINE-FLAIR and iFR-SWEDEHEART trials, it was found that significantly more patients were deferred in the iFR arm, with no impact on clinical outcomes[18].

Treatment reclassification occurs in 22-48% of studied populations when an FFR measurement is used in addition to the coronary angiogram to guide therapy in stable CAD[19]. In a substudy from iFR-SWEDEHEART, the use of iFR or FFR reclassified the initial angiogram-based treatment decision in approximately 40% of cases. The majority of these patients were reclassified from a strategy of revascularisation with PCI to conservative therapy with OMT[20]. No significant differences were observed between the reclassified iFR and FFR populations.

NOVEL NON-HYPERAEMIC PRESSURE RATIOS

Following the successful introduction and adoption of iFR in clinical practice, a number of alternative non-hyperaemic pressure ratios (NHPRs) have emerged in recent years. The commonality among these indices is a sub-cycle pressure measurement of the ratio of distal coronary to proximal aortic pressure (Pd/Pa). As these measurements are made independently of hyperaemia, they share in the principal advantage of iFR, namely, the lack of requirement of a vasodilator agent such as adenosine. The principal point of difference between each NHPR lies in the period of the cardiac cycle in which the Pd/Pa ratio is measured, the so-called "sampling window". The advantages and disadvantages of NHPRs in comparison to hyperaemic indices are presented in **Table 3**.

Several NHPRs have been shown to be closely related to iFR, both numerically and in terms of the accuracy of their classification when compared to a "gold standard" of FFR[21]. However, some indices, such as whole cycle Pd/Pa, may be more vulnerable to pressure wire drift causing increased diagnostic reclassification compared to iFR and FFR[22]. Despite evidence suggesting

Table 2. Summary characteristics of trials comparing FFR- versus iFR-guided revascularisation.

Trial	Study population (n)	FFR mean	iFR mean	Deferred by FFR (% total assessed)	Deferred by iFR (% total assessed)	FFR MACE (%)	iFR MACE (%)	*p*-value for non-inferiority
DEFINE-FLAIR[16]	2,492	0.83±0.09 (n=1,250)	0.91±0.09 (n=1,242)	583 (46.6)	652 (52.5)	7	6.8	<0.001
iFR-SWEDEHEART[17]	2,037	0.82±0.10 (n=1,019)	0.91±0.10 (n=1,018)	438 (43.5)	476 (46.7)	6.1	6.7	0.007

Values are mean±SD unless otherwise indicated.

Table 3. Advantages and disadvantages of hyperaemic and non-hyperaemic pressure ratios (NHPRs).

Pressure ratio	Advantages	Disadvantages
Hyperaemic	• Established cut-points • RCT clinical outcome data available	• Hyperaemic agent required • Associated cost, time and side effects • Inter-patient variation in microcirculatory response to adenosine • Haemodynamic "cross-talk" between serial stenoses
Non-hyperaemic	• No requirement for hyperaemic agent • RCT clinical outcome data for iFR • Individualised assessment of serial stenoses possible	• Some indices require proprietary software • RCT data not yet available for majority of NHPRs

diagnostic equivalence of NHPRs, there have been no prospective randomised clinical outcome trials of any of these newer NHPRs. Characteristics of the most commonly used NHPRs are presented in **Table 4**.

DEFINING THRESHOLDS

Defining a cut-point for treatment is a necessity when designing a clinical trial assessing the use of a measure of ischaemia. Trial investigators must follow strict algorithms in order to reduce the incidence of protocol deviation. Cut-points also aid statistical analysis and interpretation of the results. However, any measure of invasive physiology is continuous by its biological nature[23]. There can be no binary cut-point at which point the benefit of treatment suddenly appears or disappears. By definition, there must be a gradient of treatment response across the full spectrum of ischaemia. This gradient will apply to both subjective "soft" (e.g., symptoms) and objective "hard" (e.g., death) endpoints.

Initial FFR validation studies tested the index against non-invasive tests including exercise electrocardiogram testing, myocardial perfusion scintigraphy and dobutamine stress echocardiography. They showed an optimal threshold of 0.75, whereby, if FFR was positive, one or more of the other functional tests were also positive[24]. This was termed the "ischaemic threshold". The higher "clinical threshold" of FFR ≤0.80 was introduced in the clinical outcome trials to provide a "safety margin". It was felt that raising the threshold would increase the negative predictive value of this biological measurement compared to the previous cut-point of FFR <0.75[7].

Inadvertently, previous observations of decreased specificity in the FFR range of 0.75 to 0.80 and shifting thresholds have now led to the concept of a physiological "grey zone". Within the "grey zone", consideration of other diagnostic modalities and risk versus benefit analysis should be used to add clarity before a decision is made to pursue intervention, especially since measurements clustering around 0.77 to 0.83 demonstrate particular biological variability with respect to decision-making cut-points[25].

To define the cut-points for physiological measurements at rest (iFR), validation against FFR was required; therefore, the perpetuation of dichotomy continued. In the early development of the technique, iFR thresholds of 0.83 and 0.86 were reported to provide good agreement with an FFR of 0.80[26,27]. Before the clinical outcome data were available, hybrid algorithms were used for iFR[28]. For iFR <0.86, revascularisation was advised; for iFR >0.93, deferral was recommended and, for iFR 0.86 to 0.93, hyperaemic FFR measurements were required for adjudication, resulting in avoidance of hyperaemia in 57% of patients and 95% agreement with an FFR-only strategy[28]. Higher iFR thresholds of ≤0.89 (with diagnostic accuracy of 82.5%)[29] were eventually adopted for use in the landmark clinical trials[16,17].

Although decision making (to treat versus not to treat) is regarded as binary, the process of dichotomisation of biological measurements removes most of the information content and assumes discontinuity in response once these interval boundaries are crossed[23]. Hence, despite clinical trials adopting these thresholds, in clinical practice ischaemia should be regarded as a continuum in the context of a patient rather than as a definitive cut-off.

Table 4. Summary characteristics of non-hyperaemic pressure ratios.

	Sampling window	Hyperaemia required	Proposed cut-point	Vendor specific	RCT data
Phase specific					
iFR	Diastolic "wave-free" period	No	0.89	Yes	Yes
dPR	Diastolic period when dP/dt signal is flat	No	0.89	No	No
DFR	Diastolic period when Pa < mean Pa with a negative slope	No	0.89	Yes	No
Whole cycle					
Pd/Pa	Whole cycle	No	0.92	No	No
RFR	Whole cycle	No	0.89	Yes	No
DFR: diastolic hyperaemia-free ratio; dPR: diastolic pressure ratio; iFR: instantaneous wave-free ratio; RFR: resting full-cycle ratio					

CONSENSUS GUIDELINES

The importance of assessing the functional relevance of a coronary artery stenosis is central to European Society of Cardiology (ESC) guidance on decision making for myocardial revascularisation in stable CAD. Invasive functional testing, with FFR or iFR, has a class I, level of evidence "A" endorsement from the ESC to assess the severity of an intermediate lesion where evidence of ischaemia from non-invasive tests is not available[1]. Furthermore, FFR guidance of PCI is recommended with class IIa, level of evidence B for patients with multivessel disease undergoing PCI. Importantly, the ESC acknowledges a gap in the evidence base which prevents clear recommendations for FFR for the assessment of non-infarct-related artery (non-IRA) disease in the setting of ST-elevated MI (STEMI) with bystander disease[30]. Much like clinical trial design, nuanced directives are difficult for consensus guideline documents; therefore, dichotomous cut-offs are used but clinical judgement remains paramount. It is incumbent upon our guideline committees to continue to refine and reassess these recommendations in the light of increasing high-quality bias-resistant randomised controlled trial data.

Physiology to guide PCI

CHANGING DIRECTION FOR CORONARY PHYSIOLOGY

As the limitations of a dichotomised approach to the interpretation of ischaemia tests become increasingly apparent, the application of coronary physiology is moving away from simple justification of PCI using binary cut-points towards real-time guidance of PCI strategy. Advances in pressure wire software have allowed pressure wire pullback and co-registration technology to provide operators with in-cath lab physiological mapping to inform stenting strategy for the best haemodynamic result. This allows the identification of lesions with the largest pressure gradients and therefore the most favourable PCI targets. It also allows the operator to differentiate between focal stenoses, amenable to PCI, and diffuse disease which may result in an abnormal distal vessel physiology assessment but may not represent a technically suitable PCI target.

LIMITATIONS OF FFR PULLBACK

Pressure wire pullback using FFR is limited by the phenomenon of haemodynamic interdependence ("cross-talk") between serial stenoses or diffuse disease in the same vessel. This occurs because, under conditions of stable hyperaemia, the maximal flow achieved across one stenosis is limited by the haemodynamic characteristics of a sequential stenosis, resulting in a tendency to underestimate true stenosis severity for each of the lesions[31,32]. The problem this poses is that, once one stenosis is treated, hyperaemic flow, and therefore the pressure drop, across the second stenosis will increase. These haemodynamic characteristics make FFR less favourable for pullback assessments, particularly in the presence of tandem stenoses or diffusely diseased vessels.

iFR PULLBACK WITH CO-REGISTRATION

Under resting conditions, coronary flow is preserved across a wide spectrum of stenosis severity until a vessel is subtotally occluded[33].

Consequently, the benefit of performing pressure wire pullback assessments under resting conditions, without prerequisite hyperaemia, is that the assessment is less vulnerable to haemodynamic interdependence between sequential stenoses within the same vessel.

In this way, resting indices such as iFR, which are calculated on a beat-to-beat basis, permit a physiological map to be created with high spatial resolution during pressure wire pullback[34]. Through accurate quantification of the pressure gradient at each point within a vessel, iFR pullback can guide intervention by highlighting the stenoses which contribute the greatest pressure drop within the vessel. Equally important is the use of this technology to prevent unnecessary stenting of vessel segments which may angiographically appear significant, but do not contribute meaningfully to ischaemia in the vascular territory. iFR pullback, therefore, allows the pattern of CAD to be characterised as focal, diffuse or a mixed distribution.

The next derivation of this technology, iFR co-registration, is now able to track the movement of the pressure wire through the vessel in real time under continuous fluoroscopy. The data from an iFR pullback manoeuvre can be co-registered to the coronary angiogram, creating a physiological roadmap, whereby the pressure drop at any given stenosis is depicted visually on the patient's angiogram **(Figure 1A)**[32]. Furthermore, iFR co-registration enables modelling of custom stenting strategies in order to predict the post-PCI physiological result to a high degree of accuracy. This allows operators to plan their preferred stenting strategy in order to optimise the physiological gain per unit of stented segment **(Figure 1B)**.

Post-PCI physiology

FAILURES OF STANDARD APPROACH

Cardiologists have accepted that revascularisation decisions made on the visual appearance of the coronary angiogram alone are flawed. However, the success of coronary intervention is widely adjudicated with nothing more than this limited assessment technique. More rigorous measures of procedural success have not become well established and, as such, a contradiction exists between the methods we deem appropriate for justification of PCI and the methods by which we judge the success of our work. Despite angiographic success, further interrogation of stented lesions with optical coherence tomography (OCT), intravascular ultrasound (IVUS) and coronary physiology has shown that patients may have suboptimal PCI results, with residual ischaemia occurring in 18-25% of patients[35,36]. Frequency of recurrent angina with PCI guided by the angiogram alone can be as high as 50% at short-term follow-up[3] and around 30% at one year[37]. With physiology-guided revascularisation, one in five patients still reports symptoms of angina, and major adverse cardiac events (defined as death, non-fatal MI, and repeat revascularisation) remain relatively frequent after revascularisation with PCI (13% at 1 year and 28% at 5 years)[12]. While the link between invasive physiology and symptoms requires further study, if we utilise physiology to justify
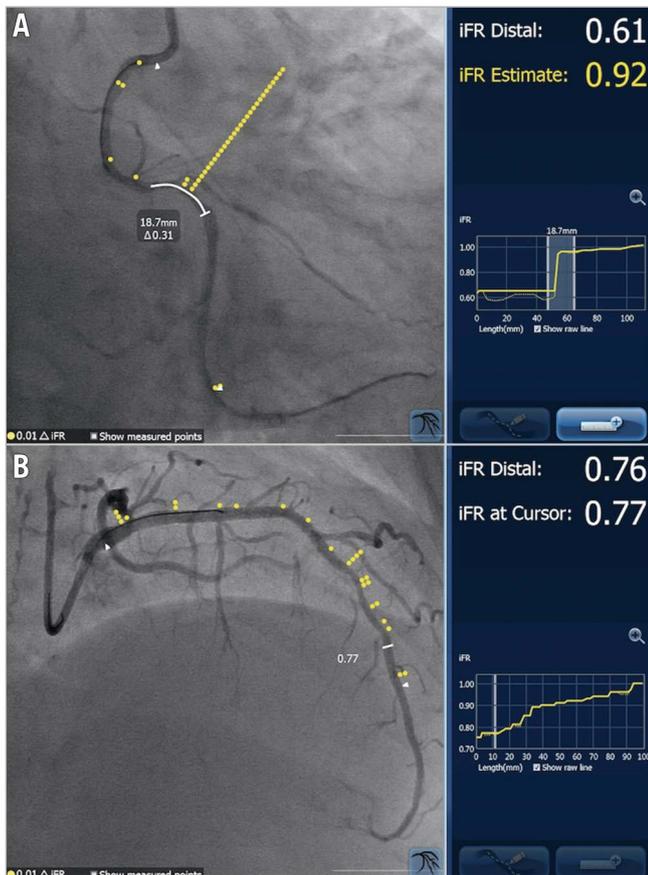
Figure 1. *iFR co-registration images. The yellow dots overlying each angiogram correspond to the location of a 0.01 iFR pressure drop. A) A focal stenosis in the right coronary artery. The operator has specified the planned stented segment, which results in a predicted physiological gain of 0.31 iFR units, resulting in an estimated post-PCI iFR of 0.92 for the vessel. B) A diffusely diseased left anterior descending artery. The cursor may be moved to any given location in the vessel to determine the estimated iFR at that position.*

revascularisation there may be a benefit to using the same tools to judge the success of coronary intervention.

RATIONALE FOR POST-PCI PHYSIOLOGY ASSESSMENTS

Observational evidence exists linking post-PCI physiology with clinical outcomes. A number of unblinded studies have now suggested that post-PCI physiology is independently associated with major adverse cardiovascular events, in particular target vessel failure **(Table 5)**.

Although various cut-off values have been suggested for post-PCI physiology, a meta-analysis of 970 lesions from 10 studies found that there was an independent and continuous relationship between post-PCI FFR and major adverse cardiovascular events without clear discontinuity in outcomes (Cox hazard ratio: 0.86, 95% confidence interval [CI]: 0.80 to 0.93; p<0.001)[38]. Interestingly, only post-PCI FFR retained prognostic value (adjusted Cox hazard ratio: 0.90, 95% CI: 0.82 to 0.99; p=0.032) compared to pre-PCI FFR (adjusted Cox hazard ratio: 0.97, 95% CI: 0.92 to 1.02; p=0.28)

after adjustment for pre- and post-PCI measurements. Hence, in corroboration with the concept of continuous ischaemic risk, further intervention in an effort to reduce ischaemia when post-PCI FFR values are suboptimal should be attempted. Individual studies are shown in **Table 5**[36,39-41].

It is pertinent to consider, however, that the post-PCI cut-off values in the individual studies are derived from observational data and *post hoc* analysis. It is therefore likely that there is a continuous post-PCI ischaemia spectrum with no dichotomous cut-point for an optimum post-PCI result. However, in order to test the use of post-PCI physiology formally, pre-specified optimum thresholds will be needed for clinical trials, just as was necessary with pre-PCI physiology trials. In the available post-PCI physiology studies, thresholds have been variously defined with margins above the currently accepted ischaemic threshold (FFR ≤0.80, iFR ≤0.89). A key limitation of the available evidence base is that blinded evaluation of post-PCI physiology among operators and patients was not always mandated. Hence, certain endpoints, such as urgent revascularisation, may be influenced by knowledge of post-PCI physiological results because they are vulnerable to bias.

Most studies have not evaluated further intervention to optimise physiological measurements, as these procedures were deemed angiographically successful. Therefore, the mechanisms for suboptimal post-PCI physiology remain unknown. Before incorporating the logical construct of post-PCI physiology into guideline recommendations, randomised controlled trials are needed to define the utility of post-PCI physiology and the additive benefit of subsequent intervention on clinical endpoints.

MECHANISMS FOR POST-PCI ISCHAEMIA

Determining the mechanism of post-PCI ischaemia is fundamental to an operator's ability to target further intervention and optimise the result. Equally important is the possibility that discovering the mechanism of post-PCI ischaemia may confirm that additional treatment would be futile in achieving further incremental gains in the haemodynamic properties of the vessel, such as in the setting of diffuse disease. This may save the patient unnecessary additional intervention.

An excellent final angiographic result may frequently co-exist with residual post-PCI ischaemia. Clues regarding the mechanism of a poor physiological result may not be forthcoming from the angiogram alone. As a lumenogram, the coronary angiogram often hides diffuse disease within an artery: the "normal" reference diameter of the vessel may therefore be underestimated and, without intravascular imaging, this will not be appreciated. Secondly, following PCI, an increase in flow to the distal vessel may result in an angiographically moderate tandem stenosis taking on greater physiological significance.

Imperfections with PCI itself must also be recognised as important causes of post-intervention ischaemia. At worst, a geographic miss of the culprit lesion may have occurred **(Figure 2)**. Experienced operators remain vulnerable to this if ancillary tools such as pullback and co-registration are not used to guide PCI by

Table 5. Recent studies linking post-PCI physiology and clinical outcomes.

Study	Intervention group	Physiology outcomes	Comments
Agarwal 2016[36]	574 patients with mean FFR 0.65±0.14, treated with DES (79%)	Post-PCI FFR ≤0.86 had the best predictive accuracy for MACE and ≤0.85 for TVR. Patients with post-PCI FFR >0.86 had lower MACE compared to FFR ≤0.86 group (17% vs 23%; p=0.02).	Final FFR ≤0.86 had incremental prognostic value over clinical and angiographic variables for prediction of MACE.
Li 2017[39]	1,476 patients with baseline FFR <0.8 treated with DES	At one year, 40 (4.0%) TVFs occurred in the post-PCI FFR >0.88 and 48 (8.0%) in the post-PCI FFR ≤0.88 group (p=0.001), driven mainly by TVR (3.8% vs 8.8%; p=0.005) and cardiac death (0.2% vs 1.3%; p=0.017).	The difference in TVF between the 2 groups was maintained up to 3-year follow-up (p=0.002). Disease in the LAD, stent diameter, and stent length were independent predictors of impaired post-PCI FFR.
Piroth 2017[40]	639 patients from FAME 1 and FAME 2 who had post-PCI FFR measured	Two-year overall vessel-oriented composite endpoint was significantly higher for lower tertile (<0.88) compared to upper tertile (>0.92) post-PCI FFR (9.2% vs 3.8%, respectively; p=0.037) and target vessel revascularisation (7.0% vs 2.4%, respectively; p=0.037).	Post-PCI FFR of 0.92 was found to have the highest diagnostic accuracy for the vessel-orientated composite endpoint; however, the positive likelihood ratio was low (<1.4).
Hakeem 2019[41]	574 patients with post-PCI FFR and Pd/Pa measurements	A post-PCI FFR of ≤0.86 had the best predictive accuracy for MACE (17% vs 23%; p=0.02). For post-PCI Pd/Pa, a threshold ≤0.96 was the best predictor of MACE (15% vs 24%; p=0.0006).	Patients with Pd/Pa ≤0.96 and FFR ≤0.86 had the highest event rate (25%), whereas those with Pd/Pa >0.96 and FFR >0.86 had the lowest event rate (15%).
Patel 2020[42]	467 patients treated in the DEFINE-PCI study with post-PCI iFR measurements	At 1-year follow-up, post-PCI iFR ≥0.95 was associated with a significant reduction in the composite endpoint of cardiac death, spontaneous MI and clinically driven TVR, compared with patients with post-PCI iFR<0.95 (1.8% vs 5.7%, respectively, p=0.04).	Highly symptomatic patients at baseline derived significantly greater angina relief at 12 months if a post-PCI iFR ≥0.95 was achieved compared to patients with residual ischaemia. Non-randomised data; however, patients and physicians were blinded to post-PCI physiology.

DES: drug-eluting stents; iFR: instantaneous wave-free ratio; TVF: target vessel failure; TVR: target vessel revascularisation

localising the regions of maximal pressure loss. More commonly, undersized or underexpanded stents may impair the physiological result and may be confirmed with intravascular imaging. Finally, proximal or distal stent edge dissections may meaningfully impede flow to the distal vessel and should always be considered in the setting of post-PCI ischaemia.

The DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) study examined the frequency and mechanism of residual post-PCI ischaemia using blinded post-PCI iFR-pullback assessments[35]. After angiographically successful PCI, 24.0% of patients in the study were found to have residual ischaemia, as defined by post-PCI iFR <0.90. When this was stratified by the pattern of disease on iFR pullback, 81.6% had one or more focal areas of pressure loss and only 18.4% of patients had diffuse disease. Where residual focal stenoses existed, these were geographically distributed within (38.4%), proximal (31.5%) and distal (30.1%) to the stented segment. These residual focal pressure gradients were poorly correlated to core lab quantitative coronary
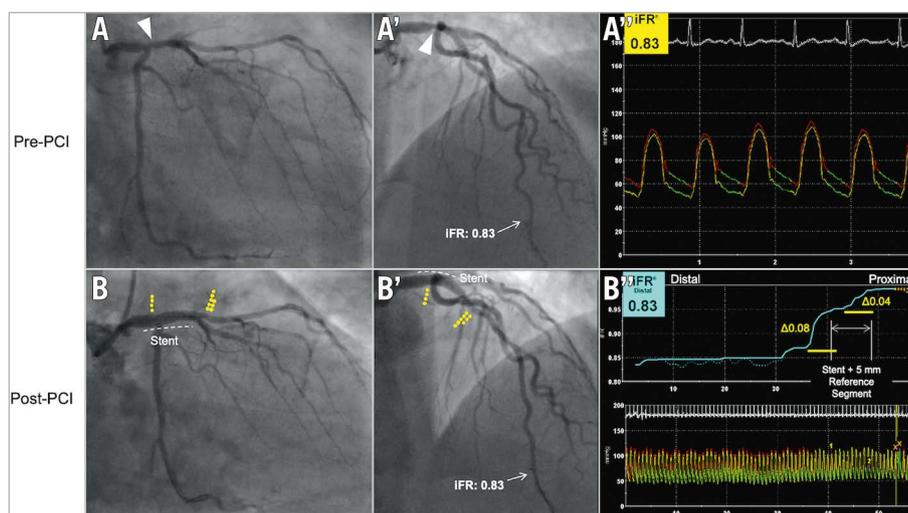

Figure 2. *An example of a geographic miss during PCI to the proximal left anterior descending (LAD) artery and left main stem (LMS). A) A moderate stenosis noted in the distal left main stem. A') The distal iFR in the LAD is 0.83. The operator performs PCI to the LMS, extending into the proximal LAD. B) Post-PCI iFR co-registration shows localised focal pressure loss at the entry of the stent, but also a second, larger pressure loss distal to the stented segment. B') The distal iFR remains the same (0.83) as pre-PCI due to geographic miss.*

angiography (QCA) analysis of minimum lumen diameter or percent residual stenosis, demonstrating the inability of coronary angiography to determine physiological lesion severity. DEFINE PCI therefore served to prove that post-PCI residual ischaemia is common, even after contemporary, angiographically successful PCI. Secondly, it found that residual focal lesions, potentially amenable to further treatment, were most commonly the cause.

The one-year outcomes of DEFINE-PCI showed that achieving a post-PCI iFR ≥0.95 was associated with a significant reduction in a composite endpoint of cardiac death, spontaneous MI, or clinically driven target vessel revascularisation[42], albeit with the limitations of an observational study design.

TECHNICAL CONSIDERATIONS
PITFALLS IN PHYSIOLOGICAL ASSESSMENTS
Adherence to meticulous technique is the cornerstone of accurate physiological assessments, in the pre- or post-PCI setting. Pitfalls in the optimal assessment technique are frequently encountered, but are often easily resolved. In **Table 6** and **Figure 3**, we highlight the most common errors for any physiological assessment, their physiological consequences, and techniques to resolve the problem.
TECHNICAL CONSIDERATIONS SPECIFIC TO POST-PCI PHYSIOLOGICAL ASSESSMENTS
Coronary vasospasm is common following PCI as the vessel reacts to stenting. It follows that administration of intracoronary nitrates before repeating physiological assessment is particularly pertinent after PCI, regardless of the physiological assessment technique.

In the post-PCI setting, advancement of the pressure wire may be technically challenging, particularly through more complex stented segments. Passing the pressure wire alongside the workhorse wire can be an effective strategy. Consideration should also be given to the possible risk of advancing a pressure wire through concealed ruptures or dissections which may not be apparent angiographically if there is significant post-PCI haziness. For this reason, a potential advantage may be offered by the use of a miniaturised dual lumen catheter for wire exchange distal to the stented segment, although damping of the proximal aortic pressure tracing through the guiding catheter affects the accuracy of this technique. Dedicated microcatheter-based pressure sensors have been developed, but systematically overestimate lesion severity due to a pressure effect of the catheter across the vessel segment under assessment[43]. To avoid these sources of inaccuracy, a small outer diameter over-the-wire microcatheter may be used to exchange the workhorse wire for a pressure wire, with use of a trapping balloon technique inside the guiding catheter to remove the microcatheter. This more complex solution is helpful to ensure accurate haemodynamic measurements.

Previous discussion has centred upon the validity of NHPRs in the post-PCI setting. A theoretical concern was raised regarding the period of hyperaemia that follows balloon inflation during PCI. NHPRs are susceptible to residual hyperaemia, which will reduce the NHPR result if resting conditions are not restored before measurement. However, based on current evidence, hyperaemia following transitory coronary occlusion only persists for approximately one minute on average[44]. Hence, in the time it takes

Table 6. Common pitfalls in physiological assessment technique and methods of resolution.

| Pitfall in assessment technique	Description	Physiological consequence	Remedy
Omission of therapeutic heparin dose	Subtherapeutic anticoagulation prior to instrumentation of coronary artery	Thrombus formation in catheter or on pressure wire	Ensure therapeutic dose unfractionated heparin administration for every pressure wire assessment
Omission of intracoronary nitrates	Spasm of coronary artery during instrumentation	↓Pd=↓FFR Stenosis severity overestimated	Intracoronary bolus glyceryl trinitrate titrated to blood pressure prior to normalisation
Failure to perform normalisation	Poor calibration of Pa and Pd trace	Fixed error in Pd/Pa ratio	Normalise every assessment and ensure Pd/Pa=1.00 before passing wire distally
Failure to remove needle introducer	Presence of the needle introducer in the haemostatic valve precludes accurate Pa assessment	Needle introducer ↓Pa=↑FFR Stenosis severity underestimated	Always remove needle introducer prior to normalisation and again prior to measurement of FFR
Damped Pa trace (Figure 3A)	Guiding catheter "wedged" trace occurs when the guiding catheter position abuts the arterial wall	↓Pa=↑FFR Stenosis severity underestimated	Ensure coaxial catheter position, use smaller guiding catheter
Ostial stenosis	Ventricularisation of Pa trace due to catheter damping in presence of ostial stenosis	↓Pa=↑FFR Stenosis severity underestimated	Retract catheter into aorta. Perform normalisation with pressure sensor in aorta
Use of side hole catheter	Pa pressure inaccurately measured due to the presence of side holes in the aortic root	↑Pa=↓FFR Stenosis severity overestimated	Do not use side hole catheter for physiological assessments
Whipping artefact (Figure 3B)	During systole the pressure wire contacts the arterial wall creating Pd artefact	↑Pd=↑FFR Stenosis severity underestimated	Easily recognised, retract or advance several millimetres to new position and retest
Wire signal drift	Development of piezoelectric pressure sensor electronic signal offset during assessment	Inaccurate FFR measurement in either direction. Stenosis severity underestimated or overestimated	Always perform a "drift check". Where Pd/Pa falls outside 1.00±0.02, re-normalise and repeat assessment
Incorrect FFR assessment point	Consoles typically report the lowest Pd/Pa measured, but FFR should be measured at stable hyperaemia	↓FFR Stenosis severity overestimated	Manually adjust the FFR assessment point to the period of stable hyperaemia
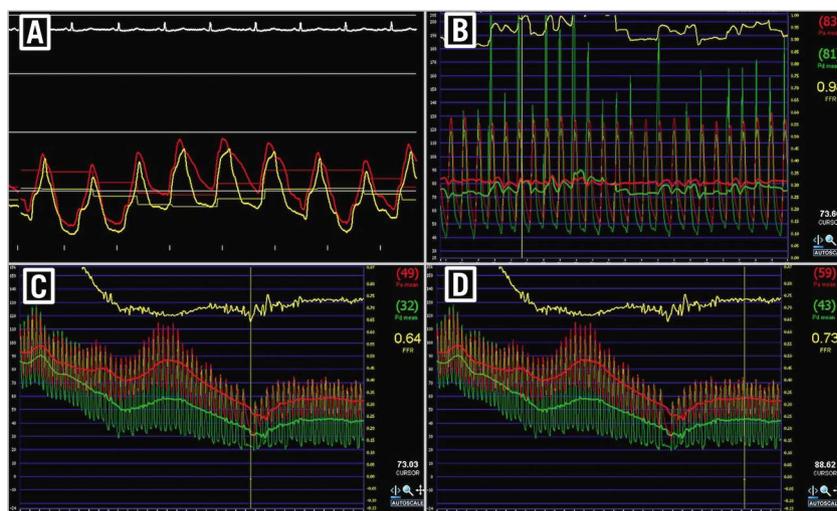
Figure 3. *Pitfalls in the assessment of coronary physiology. A) Example of damped Pa trace with a characteristic waveform. B) Example of whipping artefact. C) Example of an incorrect cursor position to measure FFR. The console may default measurement to the lowest Pd/Pa value. However, this position does not correspond to stable hyperaemia and will overestimate stenosis severity. D) The cursor has now been adjusted to ensure that FFR is measured at a period of stable hyperaemia.*

to carry out physiological assessments post PCI, resting conditions are typically restored.

On a more practical note, the purpose of carrying out post-PCI physiological assessment is twofold – to diagnose a suboptimal haemodynamic result and, secondly, to elicit its cause. We propose that for the first objective available data would suggest that either FFR or an NHPR could be used. However, where post-PCI ischaemia is found, an NHPR is more robust for performance of pullback and co-registration which will provide focus on the underlying mechanism of ischaemia. The use of a hyperaemic pressure ratio for pullback assessments in the post-PCI setting is likely to be vulnerable to the same limitations as in the pre-PCI setting, namely haemodynamic cross-communication between diseased segments of the same vessel[32].

METHODS OF OPTIMISATION
For post-PCI physiology to be useful, operators must be equipped with a strategy to intervene on the results of a suboptimal post-PCI physiology result. This strategy will vary on a case-by-case basis but, when performed effectively, post-intervention optimisation can reclassify vessels from "ischaemic" to "non-ischaemic" physiological criteria. In the largest study to date, Agarwal et al[36] examined post-PCI FFR in 574 patients (664 lesions); 21% of these lesions had a post-PCI FFR ≤0.81, again highlighting the frequency of post-PCI ischaemia. Repeat interventions were carried out in the majority of this group, including post-dilation of the implanted stent (42%), another stent implantation (33%) and further stenting with further balloon post-dilation (18%). As a result of these interventions, the mean post-PCI FFR in this group increased from 0.78±0.07 to 0.87±0.05.

As previously discussed, the optimal method for any further post-PCI intervention will depend upon the mechanism of the suboptimal result. The importance of intravascular imaging with IVUS or OCT to determine this mechanism cannot be overstated. Reliance on angiographic views alone to assess the success of revascularisation is particularly limited in the setting of post-PCI haziness which may preclude visualisation of concealed ruptures or dissections. Operators must therefore be confident with the interpretation of post-PCI intravascular imaging in order to determine an effective optimisation strategy. Stent underexpansion, malapposition and entry and exit site dissections may only be identified with this approach. Randomised data are now available to support a reduction in target vessel failure when PCI is guided by intravascular imaging as opposed to angiography alone[45,46]. Trials specific to post-PCI imaging optimisation have not been conducted; however, it is a reasonable assumption that the benefits would extend to this setting. Ultimately, synergistic data from intravascular imaging and adjunctive tools such as physiology co-registration will afford the operator the best opportunity to target any post-PCI intervention to where it is most needed **(Central illustration)**.

Unresolved questions regarding myocardial ischaemia
Recent randomised controlled trials have cast doubt on the practice of ischaemia testing as a method of selecting patients able to benefit from revascularisation. It is important to consider these broader data to contextualise the evolving roles of invasive coronary physiology.

Scientifically it seems logical that the degree of ischaemia may be associated with clinical outcomes. Early observational studies showed that, in order to obtain a survival benefit from revascularisation over and above medical therapy, greater than 10% of the myocardium needed to be ischaemic[47]. However, this was based on retrospective data assessing the difference in outcomes
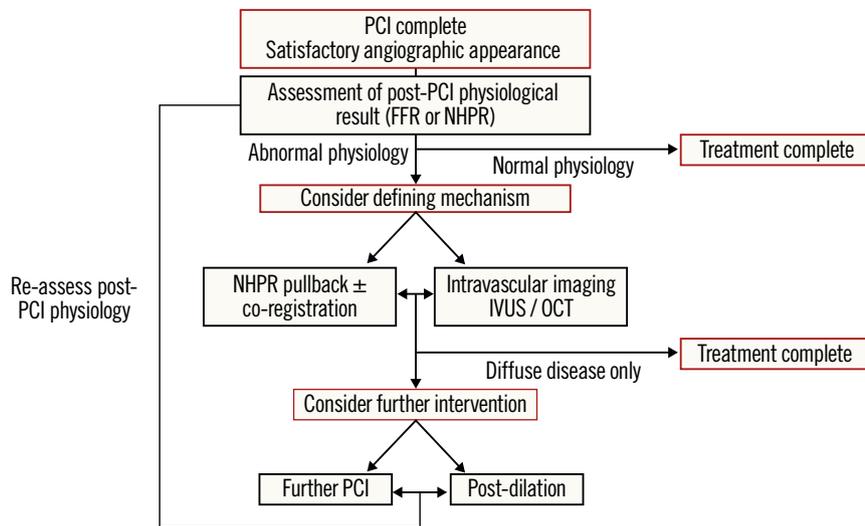
Central illustration. *Proposed potential algorithm for post-PCI physiological assessment and treatment.*

according to the degree of ischaemia with patients allocated to two groups depending on whether or not PCI was performed. Patients were not randomised, and the data were therefore potentially confounded. It is quite possible that the drivers for conservative management were unmeasured and highly influential. Nevertheless, these limited data informed clinical guidelines and set the precedent for widespread practice of ischaemia-guided revascularisation[1,48].

Subsequent randomised data emerged from a nuclear substudy of the COURAGE (Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation) trial[49,50]. While a substudy of patients who underwent serial myocardial perfusion scintigraphy demonstrated that adding PCI to OMT resulted in greater reduction in ischaemia compared with OMT alone[50], there was no evidence that PCI reduced the primary endpoint of death or MI in patients with moderate to severe ischaemia[49].

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial was designed to answer definitively the question of whether an early invasive strategy offered additive clinical benefit versus conservative management in patients with moderate to severe ischaemia for hard clinical endpoints[2]. Overall, there was no significant difference between an initial invasive approach with cardiac catheterisation and revascularisation in comparison to a conservative approach for a five-component composite endpoint of death, MI, hospitalisation for heart failure or unstable angina and resuscitated cardiac arrest (HR 0.93, p=0.34). In the group randomised to an early invasive approach, there was a significant reduction in spontaneous MI when compared to the control arm, a benefit that was offset by a significant increase in the risk of periprocedural MI which resulted in no difference between the groups in overall MI or cardiovascular death. This highlights the potential trade-off in risk between early (periprocedural) and late (spontaneous) MI that

may be observed with an invasive approach. A similar reduction in spontaneous MI was also observed in the extended follow-up of the FAME 2 trial[12]. While the implications of a spontaneous MI may be of greater clinical relevance than a periprocedural MI, these differences have not translated into a difference in the overall rates of cardiovascular death in those trials. Longer-term follow-up will be required to understand the clinical implications of these results fully.

These data should allow us to be confident that treatment of myocardial ischaemia with OMT is safe and effective. PCI has been prognostically neutral in the patient populations studied. The principal driver for revascularisation in stable coronary disease is, therefore, not the presence of residual ischaemia but the persistence of angina, despite OMT.

A simple linear relationship between the severity of ischaemia and symptomatic angina again seems scientifically logical. However, clinical practice would suggest that this reasonable assumption is misplaced. The physiology-stratified sub-analysis of the ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial showed that the greater the degree of ischaemia measured by FFR and the iFR at baseline, the greater the extent of myocardial perfusion improvement seen on stress echocardiography following revascularisation[51]. However, while these tests of ischaemia were very well correlated, the correlation of baseline ischaemia with exercise time and the symptom and quality-of-life endpoints of ORBITA were less clear[51]. Further research in broader patient populations is required to understand more fully the relationship between ischaemia and symptom severity. The clearest message of ORBITA was the importance of blinding, with placebo control, when symptoms are the endpoint under investigation. Unblinded assessments of symptoms in trials of revascularisation should be disregarded, as knowledge of treatment allocation profoundly affects physician and patient reporting[10].

Taken together, it is incumbent upon all in our community to reflect upon these trial results and to consider carefully the indication for PCI on an individual patient basis. It also seems timely now to reconsider the value of ischaemia testing. If the presence of ischaemia does not predict poor clinical outcomes and these outcomes are not mitigated by resolution of ischaemia, what is the value of these tests? Their role may be predominantly in the diagnosis of symptoms that are the result of cardiac disease and the guidance of where to treat rather than in selecting those patients who stand to benefit the most. Most importantly, in the absence of symptoms, they may have a limited role in the prediction of risk.

Future directions and recommendations

A number of upcoming trials will investigate the association between post-PCI physiology and clinical outcomes. DEFINE-GPS (Distal Evaluation of Functional performance with Intravascular sensors to assess the Narrowing Effect: Guided Physiologic Stenting [NCT04451044]) is a randomised controlled trial that aims to randomise ~3,000 participants to PCI guided by iFR co-registration or angiography alone[52]. The primary endpoint will be major adverse cardiac events or rehospitalisation for unstable angina at two years. The DEFINE-GPS trial will improve our understanding of the utility of NHPR co-registration techniques in guiding PCI and subsequent intervention as coronary stenting is increasingly applied to more complex patients.

The double-blind ORBITA-2 trial (NCT03742050) is currently randomising patients with single and multivessel CAD to PCI versus placebo for the treatment of stable angina. Post-PCI physiological assessments will be performed allowing, for the first time, the association between post-PCI physiological results and subsequent angina relief to be tested in a cohort of patients blinded to treatment allocation.

ORBITA-STAR (NCT04280575) is an "n-of-1" study assessing whether placebo-controlled verification of angina symptoms during induced ischaemia can more accurately predict a positive response to PCI. This may offer the potential to maximise the therapeutic efficacy of PCI by identifying the patients most able to benefit symptomatically from treatment.

The role of artificial intelligence is increasing in prominence in a number of settings in cardiology; coronary physiology is no exception to this trend. It has been shown that around 30% of coronary physiology data is excluded after core laboratory assessment due to signal drift or abnormal waveforms[53]. Artificial intelligence has been identified as an approach to real-time identification of abnormal waveforms to alert the interventionist and avoid diagnostic errors in measurements. Arterial waveform analysis using neural networks has been shown to identify rapidly and accurately (98.7% to 99.4% accurate) the presence of damping, demonstrating how machine learning can aid in ensuring the quality and safety of routine clinical practice[54]. Future research will determine whether neural networks can be trained to guide the optimum site of revascularisation based on physiology and pullback data.

We also envisage that novel techniques for physiological assessment that eliminate additional pharmacology or even coronary wire use may supersede current practice and further enhance both operator and patient experiences. Quantitative flow reserve (QFR), initially described in the FAVOR (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis) pilot study, uses a three-dimensional angiographic reconstruction of the stenosed vessel and the contrast flow frame count to make an assessment of FFR. Studies have shown promising results regarding the ability of QFR to identify the presence of functionally significant stenosis[55], and a possible prognostic value of post-PCI QFR[56,57]. This, along with FFR-CT[58], may offer newer technologies that encompass anatomic and physiological assessment of CAD with reduced procedural risk.

When considering prognostic endpoints, it must be remembered that many adverse cardiac events originate from angiographically and physiologically non-significant lesions. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study showed that, after acute coronary syndrome (ACS), the majority of non-culprit lesions responsible for major adverse cardiac events during follow-up were angiographically mild, non-flow-limiting lesions at baseline, but with high-risk features such as thin-cap fibroatheromas or large plaque volumes[4]. More recently, the LRP (lipid-rich plaque) and PROSPECT ABSORB (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II combined with a randomised, controlled, intervention trial) studies have demonstrated the utility of intravascular imaging including near-infrared spectroscopy (NIRS) for the identification of vulnerable lipid-rich plaques, which may be physiologically non-flow-limiting, but pose high risk of rupture and associated MACE[59,60]. Whether preventative treatment of these lipid-rich plaques can translate into improved clinical outcomes remains to be determined and requires further dedicated trials. Nevertheless, together these data suggest that physiological optimisation of PCI can only achieve so much: development of clinical tools to identify the vulnerable plaque will be pivotal for meaningful steps to be made towards the aim of cardiac risk reduction through revascularisation. These tools, in combination with truly optimum medical therapy, will allow prognostic endpoints to be optimised in stable CAD.

Conclusion

More than 30 years ago, the concept of FFR was developed in order to help coronary interventionalists decide whom to treat with revascularisation. It was an attractive technique which offered immediate numerical results and unambiguous interpretation with a clear-cut threshold for treatment.

More recently, based on randomised data including many thousands of patients, our understanding of myocardial ischaemia and coronary physiology and their association with prognostic and symptomatic endpoints in stable coronary artery disease has begun to evolve. The simplistic relationships between myocardial

ischaemia, coronary revascularisation and long-term outcomes are much more complex than previously thought.

Coronary physiology is now evolving to support new roles in the catheterisation laboratory, and its use to optimise physiological results of PCI should be encouraged. Nevertheless, randomised, blinded data examining these new roles should be considered essential to their long-term success as tools to optimise clinical outcomes for patients.

Acknowledgements

Conflict of interest statement

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41:407-77.

2. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE Jr, Rockhold FW, Broderick S, Ferguson TB Jr, Williams DO, Harrington RA, Stone GW, Rosenberg Y; ISCHEMIA Research Group. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med.* 2020;382: 1395-407.

3. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP; ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet.* 2018;391:31-40.

4. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med.* 2011;364:226-35.

5. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation.* 2001;103:2928-34.

6. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon HC, Remkes WS, Stella PR, van

Schaardenburgh P, Bech GJ, De Bruyne B, Pijls NH. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J.* 2015;36:3182-8.

7. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213-24.

8. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, Jüni P, Pijls NHJ, Hlatky MA; FAME 2 Trial Investigators. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation.* 2018;137:480-7.

9. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991-1001.

10. Rajkumar CA, Nijjer SS, Cole GD, Al-Lamee R, Francis DP. 'Faith Healing' and 'Subtraction Anxiety' in Unblinded Trials of Procedures: Lessons from DEFER and FAME-2 for End Points in the ISCHEMIA Trial. *Circ Cardiovasc Qual Outcomes.* 2018;11:e004665.

11. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve–guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371:1208-17.

12. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, Engstrøm T, Kääb S, Dambrink JH, Rioufol G, Toth GG, Piroth Z, Witt N, Fröbert O, Kala P, Linke A, Jagic N, Mates M, Mavromatis K, Samady H, Irimpen A, Oldroyd K, Campo G, Rothenbühler M, Jüni P, De Bruyne B; FAME 2 Investigators. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med.* 2018;379:250-9.

13. Götberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *J Am Coll Cardiol.* 2017;70:1379-402.

14. Kleiman NS. Bringing it all together: integration of physiology with anatomy during cardiac catheterization. *J Am Coll Cardiol.* 2011;58:1219-21.

15. De Rosa S, Polimeni A, Petraco R, Davies JE, Indolfi C. Diagnostic Performance of the Instantaneous Wave-Free Ratio: Comparison With Fractional Flow Reserve. *Circ Cardiovasc Interv.* 2018;11:e004613.

16. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Härle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med.* 2017;376:1824-34.

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

18. Escaned J, Ryan N, Mejía-Rentería H, Cook CM, Dehbi HM, Alegria-Barrero E, Alghamdi A, Al-Lamee R, Altman J, Ambrosia A, Baptista SB,

Bertilsson M, Bhindi R, Birgander M, Bojara W, Brugaletta S, Buller C, Calais F, Silva PC, Carlsson J, Christiansen EH, Danielewicz M, Di Mario C, Doh JH, Erglis A, Erlinge D, Gerber RT, Going O, Gudmundsdottir I, Härle T, Hauer D, Hellig F, Indolfi C, Jakobsen L, Janssens L, Jensen J, Jeremias A, Kåregren A, Karlsson AC, Kharbanda RK, Khashaba A, Kikuta Y, Krackhardt F, Koo BK, Koul S, Laine M, Lehman SJ, Lindroos P, Malik IS, Maeng M, Matsuo H, Meuwissen M, Nam CW, Niccoli G, Nijjer SS, Olsson H, Olsson SE, Omerovic E, Panayi G, Petraco R, Piek JJ, Ribichini F, Samady H, Samuels B, Sandhall L, Sapontis J, Sen S, Seto AH, Sezer M, Sharp ASP, Shin ES, Singh J, Takashima H, Talwar S, Tanaka N, Tang K, Van Belle E, van Royen N, Varenhorst C, Vinhas H, Vrints CJ, Walters D, Yokoi H, Fröbert O, Patel MR, Serruys P, Davies JE, Götberg M. Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease and Acute Coronary Syndromes. *JACC Cardiovasc Interv.* 2018;11:1437-49.

19. Nagaraja V, Mamas M, Mahmoudi M, Rogers C, Curzen N. Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: How consistent is the effect? *Cardiovasc Revasc Med.* 2017;18:320-7.

20. Andell P, Berntorp K, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Venetsanos D, Erlinge D, Fröbert O, Koul S, Reitan C, Götberg M. Reclassification of Treatment Strategy With Instantaneous Wave-Free Ratio and Fractional Flow Reserve: A Substudy From the iFR-SWEDEHEART Trial. *JACC Cardiovasc Interv.* 2018;11:2084-94.

21. Van't Veer M, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, Zimmermann FM, van Nunen LX, Barbato E, Berry C, Oldroyd KG. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? *J Am Coll Cardiol.* 2017;70:3088-96.

22. Cook CM, Ahmad Y, Shun-Shin MJ, Nijjer S, Petraco R, Al-Lamee R, Mayet J, Francis DP, Sen S, Davies JE. Quantification of the Effect of Pressure Wire Drift on the Diagnostic Performance of Fractional Flow Reserve, Instantaneous Wave-Free Ratio, and Whole-Cycle Pd/Pa. *Circ Cardiovasc Interv.* 2016;9:e002988.

23. Harrell FE Jr. Regression Modeling Strategies - With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. Berlin, Germany: Springer International Publishing; 2015.

24. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, Koolen JJ. Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary-Artery Stenoses. *N Engl J Med.* 1996;334: 1703-8.

25. Petraco R, Sen S, Nijjer S, Echavarria-Pinto M, Escaned J, Francis DP, Davies JE. Fractional flow reserve-guided revascularization: practical implications of a diagnostic gray zone and measurement variability on clinical decisions. *JACC Cardiovasc Interv.* 2013;6:222-5.

26. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol.* 2012;59:1392-402.

27. Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, Mikhail GW, Foin N, Broyd C, Hadjiloizou N, Sethi A, Al-Bustami M, Hackett D, Khan MA, Khawaja MZ, Baker CS, Bellamy M, Parker KH, Hughes AD, Francis DP, Mayet J, Di Mario C, Escaned J, Redwood S, Davies JE. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol.* 2013;61:1409-20.

28. Petraco R, Park JJ, Sen S, Nijjer SS, Malik IS, Echavarría-Pinto M, Asrress KN, Nam CW, Macías E, Foale RA, Sethi A, Mikhail GW, Kaprielian R, Baker CS, Lefroy D, Bellamy M, Al-Bustami M, Khan MA, Gonzalo N, Hughes AD, Francis DP, Mayet J, Di Mario C, Redwood S, Escaned J, Koo BK, Davies JE. Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. *EuroIntervention.* 2013;8:1157-65.

29. Escaned J, Echavarría-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, Raveendran G, Altman JD, Kurz HI, Brechtken J, Tulli M, Von Birgelen C, Schneider JE, Khashaba AA, Jeremias A, Baucum J, Moreno R, Meuwissen M, Mishkel G, van Geuns RJ, Levite H, Lopez-Palop R, Mayhew M, Serruys PW, Samady H, Piek JJ, Lerman A; ADVISE II Study Group. Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance: Results of ADVISE II International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II). *JACC Cardiovasc Interv.* 2015;8:824-33.

30. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-77.

31. De Bruyne B, Pijls NH, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. *Circulation.* 2000;101:1840-7.

32. Nijjer SS, Sen S, Petraco R, Escaned J, Echavarria-Pinto M, Broyd C, Al-Lamee R, Foin N, Foale RA, Malik IS, Mikhail GW, Sethi AS, Al-Bustami M, Kaprielian RR, Khan MA, Baker CS, Bellamy MF, Hughes AD, Mayet J, Francis DP, Di Mario C, Davies JE. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. *JACC Cardiovasc Interv.* 2014;7:1386-96.

33. Gould KL, Lipscomb K, Calvert C. Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. *Circulation.* 1975;51:1085-94.

34. Nijjer SS, Sen S, Petraco R, Mayet J, Francis DP, Davies JE. The Instantaneous wave-Free Ratio (iFR) pullback: a novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions. *Cardiovasc Revasc Med.* 2015;16:167-71.

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

36. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. *JACC Cardiovasc Interv.* 2016; 9:1022-31.

37. Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P, Vrakking MM, Wang K, Mahoney EM, Audi S, Leadley K, Dawkins KD, Kappetein AP; Synergy between PCI with Taxus and Cardiac Surgery Investigators. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med.* 2011;364:1016-26.

38. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Domínguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jiménez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, López-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodés-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol.* 2014;64: 1641-54.

39. Li SJ, Ge Z, Kan J, Zhang JJ, Ye F, Kwan TW, Santoso T, Yang S, Sheiban I, Qian XS, Tian NL, Rab TS, Tao L, Chen SL. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. *JACC Cardiovasc Interv.* 2017;10:986-95.

40. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N, Rioufol G, Pijls NHJ, Fearon WF, Jüni P, De Bruyne B. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. *Circ Cardiovasc Interv.* 2017;10:e005233.

41. Hakeem A, Ghosh B, Shah K, Agarwal S, Kasula S, Hacioglu Y, Bhatti S, Ahmed Z, Uretsky B. Incremental Prognostic Value of Post-Intervention Pd/Pa in Patients Undergoing Ischemia-Driven Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2019;12:2002-14.

42. Patel M, Jeremias A, Davies J, Maehara A, Matsumura M, Seto A, Samady H, Sharp A, Schneider J, Tang K, Ali Z, Talwar S, and Stone GW on behalf of the DEFINE PCI Investigators. 1-Year Outcomes of Patients with Residual Physiologic Ischemia After Percutaneous Coronary Intervention: The DEFINE PCI Trial [Internet]. TCT CONNECT 2020; 2020.

43. Seligman H, Shun-Shin MJ, Vasireddy A, Cook C, Ahmad YY, Howard J, Sen S, Al-Lamee R, Nijjer S, Chamie D, Davies J, Mayet J, Francis DP, Petraco R. Fractional flow reserve derived from microcatheters versus standard pressure wires: a stenosis-level meta-analysis. *Open Heart.* 2019;6:e000971.

44. Kawase Y, Omori H, Kawasaki M, Tanigaki T, Hirata T, Okamoto S, Ota H, Kikuchi J, Okubo M, Kamiya H, Hirakawa A, Suzuki T, Matsuo H. Postocclusional Hyperemia for Fractional Flow Reserve After Percutaneous Coronary Intervention. *Circ Cardiovasc Interv.* 2017;10:e005674.

45. Gao XF, Ge Z, Kong XQ, Kan J, Han L, Lu S, Tian NL, Lin S, Lu QH, Wang XY, Li QH, Liu ZZ, Chen Y, Qian XS, Wang J, Chai DY, Chen CH, Pan T, Ye F, Zhang JJ, Chen SL; ULTIMATE Investigators. 3-Year Outcomes of the ULTIMATE Trial Comparing Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation. *JACC Cardiovasc Interv.* 2021;14:247-57.

46. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes With Intravascular Ultrasound-Guided Stent Implantation: A Meta-Analysis of Randomized Trials in the Era of Drug-Eluting Stents. *Circ Cardiovasc Interv.* 2016;9:e003700.

47. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LEJ, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J.* 2011;32:1012-24.

48. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, Smith PK. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2017;69:2212-41.

49. Shaw LJ, Weintraub WS, Maron DJ, Hartigan PM, Hachamovitch R, Min JK, Dada M, Mancini GBJ, Hayes SW, O'Rourke RA, Spertus JA, Kostuk W, Gosselin G, Chaitman BR, Knudtson M, Friedman J, Slomka P, Germano G, Bates ER, Teo KK, Boden WE, Berman DS. Baseline stress myocardial perfusion imaging results and outcomes in patients with stable ischemic heart disease randomized to optimal medical therapy with or without percutaneous coronary intervention. *Am Heart J.* 2012;164:243-50.

50. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation.* 2008;117:1283-91.

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

52. Philips announces DEFINE GPS global multicenter study to assess outcomes of PCI procedures guided by integrated iFR and interventional X-ray images [Internet]. Philips. [last accessed 28 July 2020]. Available from: https://www. philips.com/a-w/about/news/archive/standard/news/press/2020/20200211-philips-announces-define-gps-global-multicenter-study-to-assess-outcomes-of-pci-procedures-guided-by-integrated-ifr-and-interventional-x-ray-images.html

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

54. Howard JP, Cook CM, van de Hoef TP, Meuwissen M, de Waard GA, van Lavieren MA, Echavarria-Pinto M, Danad I, Piek JJ, Götberg M, Al-Lamee RK, Sen S, Nijjer SS, Seligman H, van Royen N, Knaapen P, Escaned J, Francis DP, Petraco R, Davies JE. Artificial Intelligence for Aortic Pressure Waveform Analysis During Coronary Angiography: Machine Learning for Patient Safety. *JACC Cardiovasc Interv.* 2019;12:2093-101.

55. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F, Fang W, Chen J, Li W, Guan C, Holm NR, Wijns W, Hu S. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. *J Am Coll Cardiol.* 2017;70:3077-87.

56. Kogame N, Takahashi K, Tomaniak M, Chichareon P, Modolo R, Chang CC, Komiyama H, Katagiri Y, Asano T, Stables R, Fath-Ordoubadi F, Walsh S, Sabaté M, Davies JE, Piek JJ, van Geuns RJ, Reiber JHC, Banning AP, Escaned J, Farooq V, Serruys PW, Onuma Y. Clinical Implication of Quantitative Flow Ratio After Percutaneous Coronary Intervention for 3-Vessel Disease. *JACC Cardiovasc Interv.* 2019;12:2064-75.

57. Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, Ielasi A, Spitaleri G, Di Girolamo D, Mezzapelle G, Geraci S, Manfrini M, Pavasini R, Barbato E, Campo G. Prognostic Value of QFR Measured Immediately After Successful Stent Implantation: The International Multicenter Prospective HAWKEYE Study. *JACC Cardiovasc Interv.* 2019;12:2079-88.

58. Tanigaki T, Emori H, Kawase Y, Kubo T, Omori H, Shiono Y, Sobue Y, Shimamura K, Hirata T, Matsuo Y, Ota H, Kitabata H, Okubo M, Ino Y, Matsuo H, Akasaka T. QFR Versus FFR Derived From Computed Tomography for Functional Assessment of Coronary Artery Stenosis. *JACC Cardiovasc Interv.* 2019;12:2050-9.

59. Waksman R, Di Mario C, Torguson R, Ali ZA, Singh V, Skinner WH, Artis AK, Cate TT, Powers E, Kim C, Regar E, Wong SC, Lewis S, Wykrzykowska J, Dube S, Kazziha S, van der Ent M, Shah P, Craig PE, Zou Q, Kolm P, Brewer HB, Garcia-Garcia HM; LRP Investigators. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet.* 2019;394:1629-37.

60. Stone GW, Maehara A, Ali ZA, Held C, Matsumura M, Kjøller-Hansen L, Bøtker HE, Maeng M, Engstrøm T, Wiseth R, Persson J, Trovik T, Jensen U, James SK, Mintz GS, Dressler O, Crowley A, Ben-Yehuda O, Erlinge D; PROSPECT ABSORB Investigators. Percutaneous Coronary Intervention for Vulnerable Coronary Atherosclerotic Plaque. *J Am Coll Cardiol.* 2020;76: 2289-301.