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Applied coronary physiology for planning and guidance of percutaneous coronary interventions. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology

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KEYWORDS

- fractional flow reserve
- intravascular ultrasound
- non-invasive imaging

Abstract

The clinical value of fractional flow reserve and non-hyperaemic pressure ratios are well established in determining an indication for percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD). In addition, over the last 5 years we have witnessed a shift towards the use of physiology to enhance procedural planning, assess post-PCI functional results, and guide PCI optimisation. In this regard, clinical studies have reported compelling data supporting the use of longitudinal vessel analysis, obtained with pressure guidewire pullbacks, to better understand how obstructive CAD contributes to myocardial ischaemia, to establish the likelihood of functionally successful PCI, to identify the presence and location of residual flow-limiting stenoses and to predict long-term outcomes. The introduction of new functional coronary angiography tools, which merge angiographic information with fluid dynamic equations to deliver information equivalent to intracoronary pressure measurements, are now available and potentially also applicable to these endeavours. Furthermore, the ability of longitudinal vessel analysis to predict the functional results of stenting has played an integral role in the evolving field of simulated PCI. Nevertheless, it is important to have an awareness of the value and challenges of physiology-guided PCI in specific clinical and anatomical contexts. The main aim of this European Association of Percutaneous Cardiovascular Interventions clinical consensus statement is to offer up-to-date evidence and expert opinion on the use of applied coronary physiology for procedural PCI planning, disease pattern recognition and post-PCI optimisation.

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Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
CCS	chronic coronary syndrome
CTCA	computed tomography coronary angiography
FCA	functional coronary angiography
FFR	fractional flow reserve
FFR_{CT}	computed tomography-derived fractional flow reserve
iFR	instantaneous wave-free ratio
IVUS	intravascular ultrasound
MACE	major adverse cardiovascular event
MVD	multivessel disease
NHPR	non-hyperaemic pressure ratio
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PPG_{index}	pressure pullback gradient index
QFR	quantitative flow ratio
RFR	resting full-cycle ratio
vFFR	virtual fractional flow reserve

Introduction

Intracoronary physiological assessment is acknowledged as a valuable strategy to identify the presence of flow-limiting epicardial stenoses in patients with chronic coronary syndromes (CCS) and to determine an indication for percutaneous coronary interventions (PCI)[1]. Yet, its role in procedural planning and in assessing the functional results of PCI is less clear.

In practice, it had been previously assumed that once the presence of flow-limiting disease was confirmed with a single pressure guidewire measurement, PCI guided by angiography should lead to effective restoration of vessel conductance. However, studies with physiological post-PCI evaluation based on fractional flow reserve (FFR) and non-hyperaemic pressure ratios (NHPR) demonstrate that this supposition is not correct and that relying on angiographic guidance alone can be associated with suboptimal functional results post-PCI in many cases[2-4].

This document addresses the use of coronary physiology to plan and guide PCI using physiological tools, providing evidence from the literature, expert opinion from operators, and revisiting available tools. The document provides an expert consensus on how to use commercially available physiology tools for these purposes. It has been reviewed and approved by the European Society of Cardiology (ESC) Clinical Guidelines Committee to ensure that no conflict exists with available guidelines. Many of the topics discussed herein pertain to the use of intracoronary pressure guidewires, which are the most widely used devices for physiological assessment in the cardiac catheterisation laboratory. Functional coronary angiography (FCA) tools, which merge angiographic information with fluid dynamic equations to deliver information equivalent to intracoronary pressure measurements and which constitute a valuable alternative to invasive tools in planning coronary revascularisation, are also discussed. A detailed and updated revision of the use of NHPR and FFR in different clinical scenarios is provided in **Supplementary Appendix 1**.

From confirming the indication to planning and guiding PCI

The limitations of coronary angiography in characterising the flow-limiting effect of coronary stenoses can be overcome by non-invasive and/or adjunctive invasive physiological assessments of coronary artery disease (CAD), the value of which are supported by evidence-based guideline recommendations[5]. When prior evidence of myocardial ischaemia is not available, FFR or instantaneous wave-free ratio (iFR) are recommended by the guidelines to assess the haemodynamic relevance of intermediate-grade coronary stenoses. FFR can also be considered in patients with multivessel disease (MVD) undergoing PCI[5].

Over the last decade, criticism concerning the use of angiography alone to guide revascularisation decisions has been extended to the decision of when an optimal functional result of the intervention has been achieved. Such criticism is supported by suboptimal functional results identified in vessels despite a satisfactory angiographic PCI result[2,3]. Prior and recent observations have shown that such functionally suboptimal PCI results carry prognostic relevance **(Supplementary Table 1)**[4,6-25]. Physiological guidance could contribute to improved PCI results in at least 3 ways: 1) improving preprocedural planning and simulation, 2) improving intraprocedural precision of PCI in addressing flow-limiting disease, and 3) guiding procedural optimisation of suboptimal PCI results **(Central illustration)**.

Despite the limited number of available studies in this field, there are now rational grounds to consider using physiological tools to plan effective PCI strategies to ideally remove all flow-limiting stenoses, to verify that functionally successful PCI has been achieved, and to contribute to procedural optimisation. **Table 1** provides key information on the physiological guidance of PCI.

Technological developments in applied coronary physiology in PCI

HYPERAEMIC AND NON-HYPERAEMIC PRESSURE INDICES

FFR is the most widely used intracoronary tool to define flow-limiting epicardial stenoses, with randomised clinical trials and observational studies supporting deferral[26-28] or performance[26,29] of revascularisation based on FFR values, predominately in patients with CCS. Contrast-based FFR, which relies upon submaximal myocardial hyperaemia induced by iodinated contrast administration, has been proposed as an adenosine-free alternative to FFR[30]. NHPR is increasingly utilised in clinical practice owing to a more favourable side-effect profile, reduced cost and procedure time, and ease of use compared with pharmacological hyperaemia. This facilitates multiple intraprocedural measurements either in different vessels or at different stages of the PCI procedure. Guidance by iFR, a widely utilised NHPR, was non-inferior to FFR guidance of revascularisation for major adverse cardiac events (MACE) at 1-year[31,32] and 5-year follow-ups[33]. Other diastolic NHPR correlate

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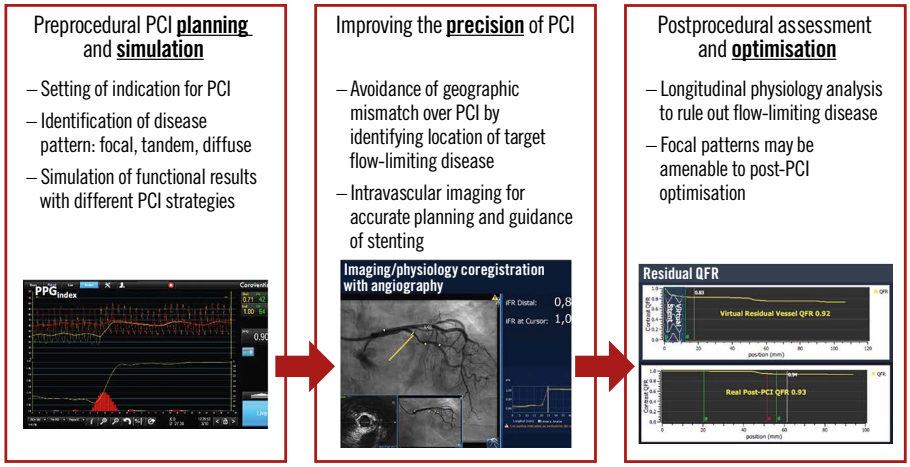
CENTRAL **ILLUSTRATION** **Applications of physiology in planning and guiding PCI procedures.**



iFR: instantaneous wave-free ratio; PCI: percutaneous coronary intervention; PPG: pullback pressure gradient; QFR: quantitative flow ratio

closely with the iFR, with a similar ischaemic cut-off of ≤0.89[34]. All NHPR have demonstrated significant association with the risk of 2-year vessel-oriented composite endpoints[35].

In the extended scenario of planning and guiding PCI, the use of pressure guidewires can be subject to specific caveats related to physiological assessment in complex clinical and anatomical

Table 1. Objectives of physiological planning and guidance of PCI.

Pre-PCI physiology assessment		
Objective	**Technique**	**Benefit**
Determining the indication for PCI	Pressure wire or FCA to identify the presence of flow-limiting disease	– Management of significant stenoses may confer prognostic or symptom benefit – Deferral of non-flow-limiting disease avoids unnecessary PCI
Identifying patterns of flow-limiting disease	Longitudinal physiological vessel analysis to identify focal, tandem, and diffuse patterns of flow-limiting disease	– Assists in gauging effectiveness of PCI – Aids with planning the length of stent and/or number of stents – Reconsider PCI when a suboptimal result is anticipated
Simulate impact of stenting in specific locations	NHPR and imaging-based functional assessments to simulate relief of stenosis virtually	– Plan effectiveness of PCI before stent deployment – Allows for several simulations prior to PCI
Facilitating precision stent deployment	Correlating physiology and angiography using either coregistration technologies or visual assessment, use of concomitant intracoronary imaging	– Avoidance of geographical miss during stenting, missing flow-limiting lesions – Accurate sizing of balloons and stents
Post-PCI physiology assessment		
Objective	**Technique**	**Benefit**
Ensuring an optimal functional result of PCI	Physiological measurements in PCI target vessel after satisfactory angiographic result, jailed side-branch interrogation	– Early identification of residual flow-limiting disease in the PCI target vessel after the intervention
Identifying potential targets of functional optimisation of PCI	Post-PCI longitudinal vessel analysis	– Establishing the cause of suboptimal functional PCI results – Establishing the feasibility and mode of PCI optimisation
Assessing the impact of PCI optimisation	Repeat physiological measurements after physiology-based optimisation	– Residual disease not amenable to PCI may identify need for directed medical therapy or surgical revascularisation

FCA: functional coronary angiography; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention

scenarios **(Table 2)**. Additional information detailing potential pitfalls in physiological assessment and considerations regarding the use of guide catheters, guide catheter extensions and microcatheters is provided in **Supplementary Appendix 1**.

FUNCTIONAL CORONARY ANGIOGRAPHY

The success of FFR and NHPR as indices to estimate functional stenosis severity has led to the development of new FCA technologies. These can derive similar information from an invasive coronary angiogram or non-invasive computed tomography coronary angiography (CTCA), with both approaches demonstrating good correlation with wire-based FFR. Computed tomography-derived FFR (FFR_{CT}) is obtained by merging a three-dimensional (3D) reconstruction of vessels from CTCA with computational fluid dynamics[36], thereby providing a reliable estimate of invasive FFR[37]. Similarly, several FFR-equivalent measurements can also be derived from invasive coronary angiograms[38-41]; these are supported by prospective validation studies. Quantitative flow ratio (QFR) is the only angiography-based physiological index that has been prospectively validated and has already been demonstrated to be associated with improved clinical outcomes when used to decide upon coronary revascularisation, compared with conventional angiography[42]. A distinct advantage of all FCA modalities is that they provide longitudinal vessel analysis, allowing accurate length measurements and localisation of flow-limiting disease to vessel anatomy. Detailed information on potential limitations of imaging-based functional coronary analysis is provided in **Supplementary Table 2**.

LONGITUDINAL PHYSIOLOGICAL VESSEL ANALYSIS

Customarily, indices of coronary physiology have been reported as a single value in the distal segment of the interrogated coronary

Table 2. Challenges and pitfalls related to physiological assessment.

Patient factors		
Challenges and pitfalls	**Comment**	**Solution**
Presence of significant ostial CAD	Identified with ventricularisation or "damping" pressure waveform on engagement, not assessable with some FCA modalities	Reposition guide catheter to a more proximal position, ensure coaxiality, consider downsizing guide catheter, use an additional guidewire or septal wire to control catheter tip position
Haemodynamic crosstalk in presence of tandem lesions	Sequential lesions along a vessel invariably physiologically influence the other lesions in the vessel	Consider simulated planning prior to undertaking PCI on 1 or 2 stenoses based on longitudinal vessel analysis obtained with functional coronary angiography, NHPR, or FFR
Procedural factors		
Challenges and pitfalls	**Comment**	**Solution**
Pressure wire drift	Offset of pressure reading during the procedure	Repeat procedure, use drift correction/re-normalise, or use image-based technique
Pseudostenosis caused by intracoronary wires	Straightening of tortuous vessels by intra-coronary wire may generate introsusceptions with haemodynamic relevance	Consider FCA as an alternative to intracoronary pressure guidewires
Ventricularisation/damping of aortic pressure	Guiding catheter engaged abutting the vascular lumen or in significant ostial lesions	Reposition guide catheter, ensure coaxiality, consider downsizing guide catheter, equalisation of pressure guidewire is advised
Use of guide catheter with side holes	False estimate of Pa at the tip of the guiding catheter	Advise not to use catheter with side holes for intracoronary assessment. If needed for clinical reasons, ensure catheter disengagement and use of IV adenosine.
Use of guide catheter extensions	May cause ventricularisation of Pa, if introduced after pressure equalisation, may modify Pa and affect measurements	Perform pressure equalisation with extension within guide catheter, withdraw guide extension at the time of physiological assessment
Use of coronary microcatheters	If used after pressure equalisation, may modify Pa and affect measurements	Perform pressure equalisation with microcatheter within guide catheter before measurements
Wire whipping	Pressure wire signal degrading through contact with vascular lumen	Repositioning of the pressure wire often resolves this issue
Transient microvascular dysfunction associated with the procedure	Rotational atherectomy and PCI tools generating microparticles may cause transient microvascular dysfunction, affecting pressure indices	Consider FCA as an alternative to intracoronary assessment if transient microvascular dysfunction is assumed or suspected
FFR measurement in region without stable hyperaemia	Whilst the software reports the lowest physiological reading, these might not be in stable hyperaemia and therefore overestimate lesion severity	Measure FFR in stable hyperaemia, and if needed adjust measurement points manually

CAD: coronary artery disease; IV: intravenous; FCA: functional coronary angiography; FFR: fractional flow reserve; NHPR: non-hyperaemic pressure ratio; Pa: aortic pressure; PCI: percutaneous coronary intervention

artery, reflecting cumulative pressure losses along the entire length of the epicardial vessel. Longitudinal assessment, utilising a pressure wire pullback, adds an additional dimension to the physiological analysis. Pullback manoeuvres can be performed manually[43] with either FFR or NHPR[44,45]. Accurate length measurements to the order of millimetres can be obtained by using either motorised pullback[46] or dedicated software that tracks the radiopaque wire tip during pullback[47]. Dedicated software is available to provide stable FFR, iFR, and resting full-cycle ratio (RFR) pullback curves, free of fluctuations due to the Venturi effect, where a drop in intracoronary pressure is seen as the sensor crosses the stenosis **(Supplementary Figure 1)**.

Prior to PCI, longitudinal vessel assessment informs on the distribution of pressure losses along the epicardial vessel and can differentiate focal and/or diffuse patterns of flow-limiting disease **(Figure 1)**. Longitudinal vessel analysis allows for the identification of focal and diffuse patterns of flow-limiting disease, either subjectively by visual inspection of the pullback curve or objectively by using the pressure pullback gradient index (PPG_{index})[45], which can be performed manually with high inter- and intraoperator reproducibility[48]. Differentiation of diffuse from focal disease is also feasible with an automated algorithm that analyses the instantaneous FFR gradient per time unit, the dFFR(t)/dt index[49]. Both the PPG_{index} and dFFR(t)/dt can be derived from QFR, and their prognostic relevance have been documented with post-PCI clinical outcomes[49,50]. The criteria used to define focal, tandem, and diffuse patterns, as well as supporting studies, can be found in **Table 3** and **Supplementary Table 3**, respectively[2,3,45,50-61]. The current definitions of focal and diffuse disease are largely qualitative, and research to formally define these lesion characteristics is awaited. The ability to discriminate between patterns of CAD carries immediate and relevant clinical implications; a focal pattern is associated with an optimal physiological result after PCI, with consequent good prognosis and relief of angina. On the contrary, a diffuse pattern of disease is associated with suboptimal post-PCI results and prognosis and more residual anginal symptoms[62].

After PCI, longitudinal physiological vessel interrogation may identify residual focal pressure gradients inside or outside the stent which might be amenable to additional stent post-dilatation or PCI[2]. Alternatively, a diffuse pattern of residual disease after PCI may discourage operators from further vessel instrumentation.

COREGISTRATION WITH ANGIOGRAPHY

Merging longitudinal vessel physiology with the coronary angiogram allows for accurate localisation of flow-limiting atherosclerotic disease and facilitates procedural planning[47]. The coregistered map provides signposts with a clear distribution of regions of pressure loss, enabling optimal localisation of specific target lesions that might benefit from PCI, and the implementation of length measurements **(Supplementary Figure 2)**. This technology can be used in conjunction with iFR and is particularly useful when forming strategies for intervention on tandem lesions and interrogating areas of diffuse disease.

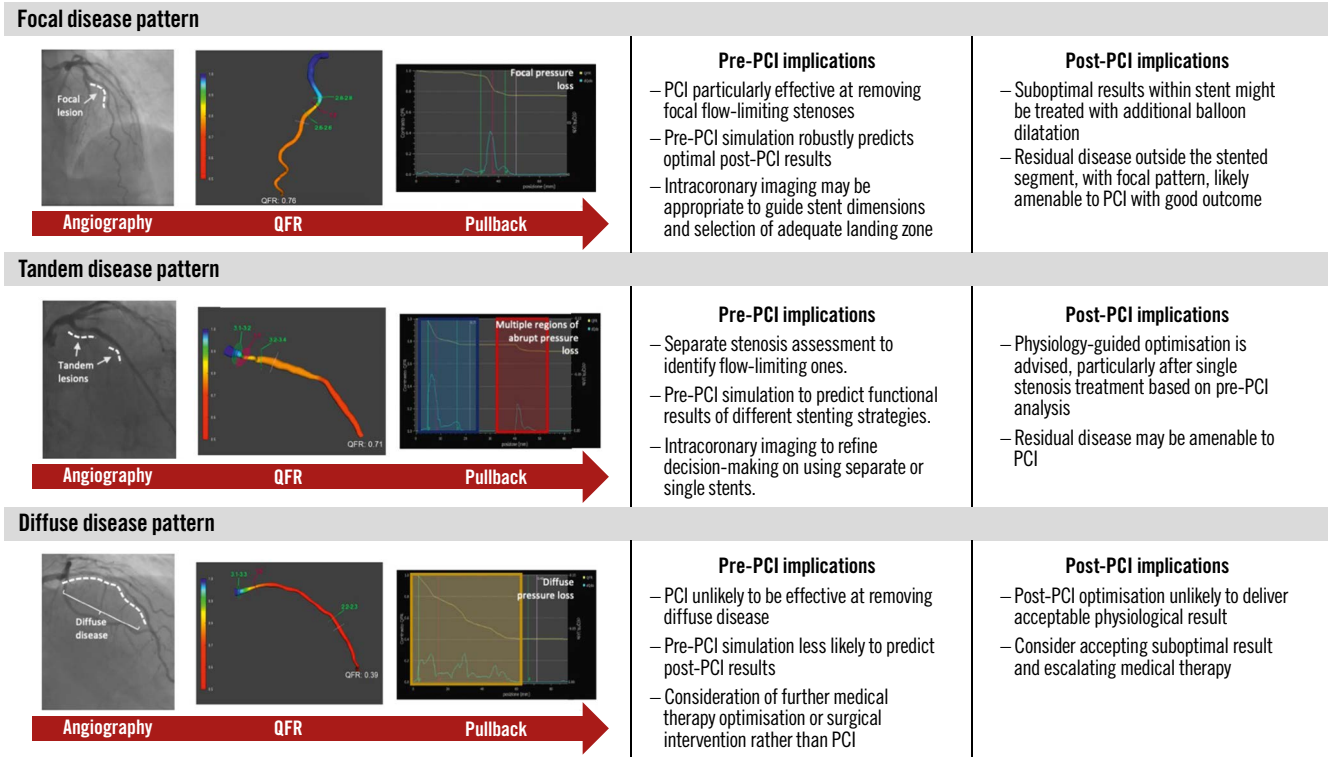


Figure 1. *Patterns of flow-limiting disease identified in longitudinal vessel analysis before and after PCI. PCI: percutaneous coronary intervention; QFR: quantitative flow ratio*

Table 3. Criteria used to define focal, tandem and diffuse patterns of obstructive coronary disease.

Pre-PCI physiology assessments			
Pattern	**FFR**	**NHPR**	**FCA**
Focal	FFR ≤0.80 at distal segment, abrupt single point of pressure loss.	iFR/RFR/DFR ≤0.89 at distal segment, with abrupt single point of ≥0.03 index units over ≤15 mm segment.	QFR/vFFR/FFR_{CT} ≤0.80 at distal segment, with single region of pressure loss of >0.05 in <10 mm segment.
Tandem	FFR ≤0.80 at distal segment, presence of ≥2 abrupt change of FFR values.	iFR/RFR/DFR ≤0.89, at distal segment, with presence of ≥2 abrupt changes of index values.	QFR/vFFR/FFR_{CT} ≤0.80 at distal vessel with presence of ≥2 abrupt changes of pressure loss.
Diffuse*	FFR ≤0.80 at distal segment with progressive and linear loss in FFR values over length of vessel.	iFR/RFR/DFR ≤0.89 at distal segment, with progressive and linear loss in pressure over length of vessel during iFR pullback.	Progressive and linear loss in QFR/vFFR/FFR_{CT} values over length of vessel during longitudinal analysis.
Post-PCI physiology assessments			
Pattern	**FFR**	**NHPR**	**FCA**
Focal	FFR with abrupt pressure loss at the stented site or elsewhere within the treated vessel.	Abrupt drop of iFR/RFR/DFR values at the stented site or elsewhere within the treated vessel.	Abrupt drop of QFR/vFFR values at the stented site or elsewhere within the treated vessel.
Tandem	Abrupt drop of FFR values at the level of an untreated tandem stenosis.	Abrupt drop of iFR/RFR/DFR values at the level of an untreated tandem stenosis.	Abrupt drop of QFR/vFFR values at the level of an untreated tandem stenosis.
Diffuse*	Progressive and linear loss in FFR values over length of stented vessel during pullback.	Progressive and linear loss in iFR/RFR/DFR values over length of stented vessel during pullback.	Progressive and linear loss in QFR/vFFR values over length of stented vessel.

*These criteria are clinical consensus statements and further validation is warranted. DFR: diastolic hyperaemia-free ratio; FCA: functional coronary angiography; FFR: fractional flow reserve; FFR_{CT}: computed tomography-derived FFR; iFR: instantaneous wave-free ratio; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; RFR: resting full-cycle ratio; vFFR: virtual FFR

SIMULATION OF FUNCTIONAL PCI RESULTS

Despite consistent evidence showing that suboptimal values of physiological indices after PCI are associated with poorer outcomes, there is a relative paucity of evidence regarding whether they can be used to guide PCI optimisation and, ultimately, to improve patient outcomes. Since the aim of PCI is the elimination of ischaemia-generating lesions, predicting the haemodynamic results of a given strategy before embarking on stenting appears to be a rational approach to avoid suboptimal results of the intervention. The concept of *in silico* simulation of PCI to predict functional results of an intervention is appealing, as it allows for both procedural planning and modelling of post-PCI physiology prior to undertaking the procedure.

There are different approaches to simulate functional PCI results from baseline longitudinal vessel analysis **(Figure 2)**. A simple mathematical approach to estimate the impact of PCI based on pullback curves can be followed: predicted NHPR ($NHPR_{pred}$)=pre-PCI NHPR (lowest value) + ∑intention-to-treat NHPR gradient(s). Pioneering studies with iFR pullback have demonstrated its ability to predict post-PCI results[63]. Subsequently, this has also been confirmed for other NHPR such as the RFR and diastolic pressure ratio[61]. Subtraction of the flow-limiting effect of one or more coronary stenoses can be readily performed with current software versions of iFR coregistration with angiography[31]. From the perspective of FCA, a dedicated virtual stenting tool has been developed for FFR_{CT}[64]. The FFR_{CT} Planner (HeartFlow) has been shown to be accurate and precise at predicting post-PCI FFR[65]. Analysis with QFR and virtual FFR (vFFR) provides an estimate of post-PCI values after treatment of a given stenosis (residual QFR and vFFR), which has been shown to predict post-PCI FFR[25,66,67]. **Figure 3** shows a pullback curve analysis performed with iFR and coregistration, including simulated stenting at a specific location.

CORONARY PRESSURE WIRES AND MEASURING TOOLS

Continued improvement in pressure guidewire technology has facilitated the accurate interrogation and measurement of complex coronary anatomies. Contemporary guidewire-based pressure indices are fitted with sensors that use either electrical or fibre-optic signal transmission. Advances in manufacturing processes have resulted in an improved accuracy and stability of the sensor, thus, minimising the drift phenomenon with workhorse guidewire-like characteristics, resulting in optimised torque control and manoeuvrability. The latter is critical for the safe wiring of the target vessel prior to the measurement of pressure loss and PCI. Microcatheter-based pressure measurement technology requires a 0.014" guidewire, according to anatomy or operator preference, but requires a 0.020" shaft profile for the microcatheter, which may interfere with measurements, especially in small vessels or severe stenoses, and can be difficult to navigate around tight angulations. The currently available and pending devices for invasive functional assessments are shown in **Supplementary Table 4**.

Physiological assessment of post-PCI results

Post-PCI intracoronary pressure measurements can identify residual flow-limiting disease, differentiate residual focal lesions from diffuse disease and provide prognostic information. Whilst

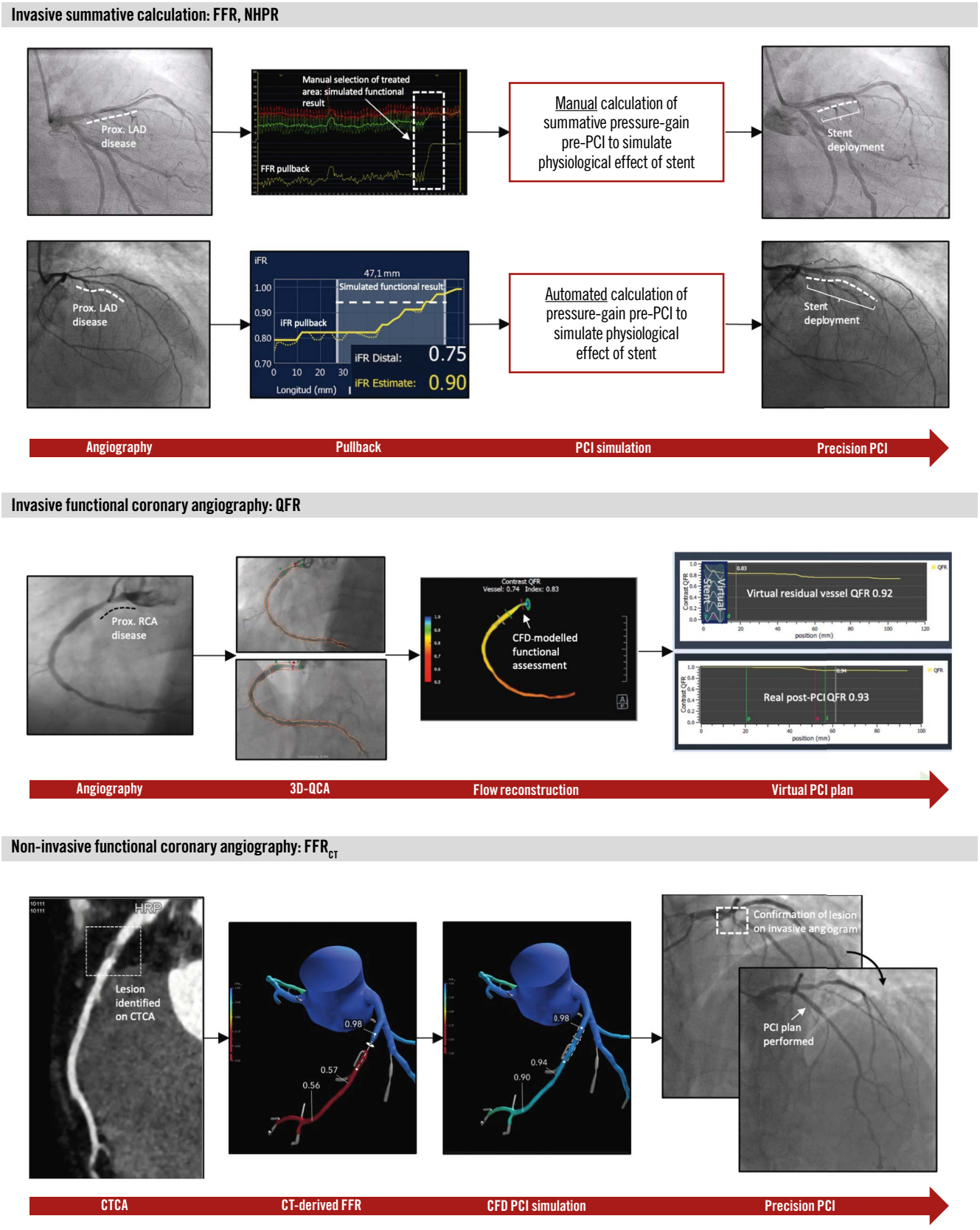


Figure 2. *Approaches for simulating functional PCI results based on longitudinal vessel analysis. 3D-QCA: three-dimensional quantitative coronary angiography; CFD: computational fluid dynamics; CTCA: computed tomography coronary angiography; FFR: fractional flow reserve; FFR_{CT}: computed tomography-derived FFR; iFR: instantaneous wave-free ratio; LAD: left anterior descending artery; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; RCA: right coronary artery*

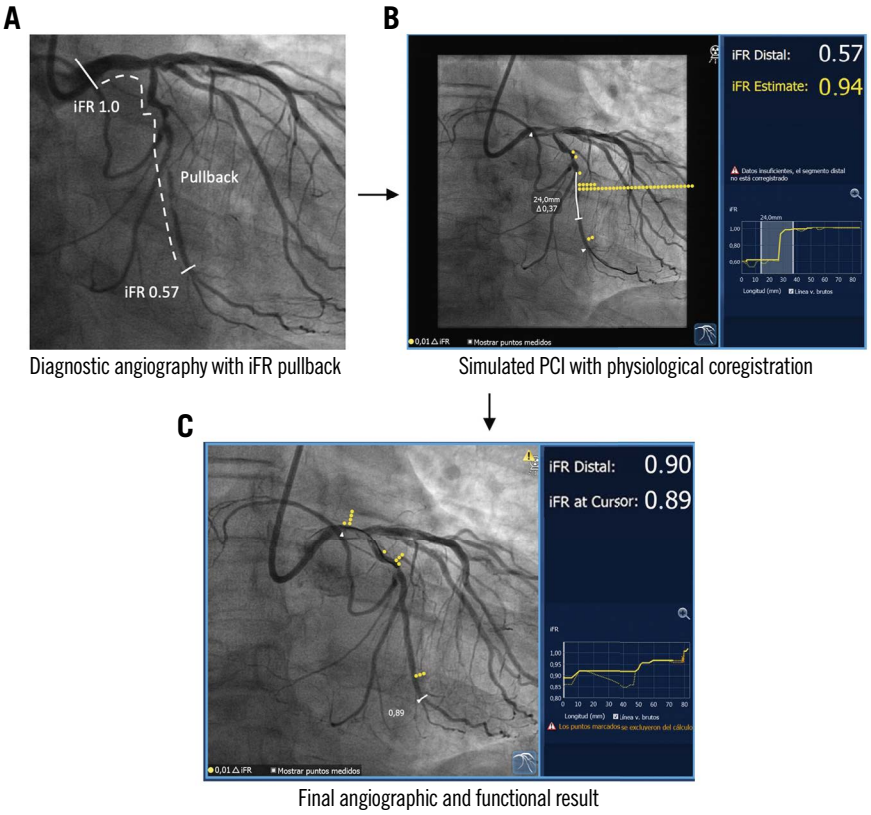


Figure 3. *Simulation of functional PCI results using coregistration of physiology and the coronary angiogram. A) Angiography of the left circumflex artery interrogated with longitudinal physiological assessment. B) The presence of flow-limiting disease in the vessel is demonstrated by a distal iFR of 0.57. Longitudinal vessel analysis revealed a focal disease phenotype. iFR coregistration with angiography allows accurate localisation of flow-limiting disease in the coronary anatomy. The PCI simulation suggests adequate functional results of the intervention, with a predicted post-PCI iFR of 0.94. C) Final co-registered angiographic-physiology result shown, with final iFR of 0.90. iFR: instantaneous wave-free ratio; PCI: percutaneous coronary intervention*

a higher post-PCI FFR is associated with a lower incidence of adverse clinical outcomes, the cut-off point for an optimal PCI result is still debated[68]. A post-PCI FFR ≥0.90 has been associated with a significantly lower risk of repeat PCI and MACE in a systematic review of 7,470 patients[69]. The most robust recent data, obtained in a patient-level meta-analysis of 5,869 vessels treated with modern drug-eluting stents, reported optimal post-PCI FFR cut-off values of 0.86 for target vessel failure and 0.80 for the composite of cardiac death or target vessel myocardial infarction[70]. For NHPR, a post-PCI iFR ≥0.95 was associated with improved patient outcomes in the DEFINE PCI study[3]. An optimal cut-off for post-PCI distal coronary pressure/aortic pressure (Pd/Pa) ratio of >0.96 has also been proposed[23].

Contemporary reports indicate that post-PCI physiology results might remain below the clinical revascularisation thresholds of ≤0.80 for FFR and <0.90 for NHPR in approximately 24-36% of cases[2,3,71]. Potential mechanisms of suboptimal post-PCI physiology results are outlined in **Figure 4**. Additional interventions guided by post-PCI coronary physiology assessments can improve the final result[2,10,71]. Caution should be exerted to avoid overtreatment, for example when the identified cause of suboptimal functional results entails treatment of long coronary segments or aggressive lesion manipulation. Intracoronary imaging may contribute to a better understanding of the cause of suboptimal functional results and to safer decision-making. Furthermore, it has to be kept in mind that cardiovascular risk may differ between patients despite having achieved an optimal functional result; this is largely dictated by the extension and characteristics of underlying atherosclerosis.

While functionally suboptimal PCI results are associated with adverse clinical outcomes and can be related to residual treatable disease, they may more frequently be an epiphenomenon of diffuse atherosclerosis that cannot be adequately addressed with revascularisation. This may explain why larger relative increases in FFR after stenting (typically achieved through treatment of focal, physiologically severe lesions) are associated with lower rates of target vessel failure, reduced incidence of angina and improved quality of life[14,21,72]. As not all residual flow-limiting disease is amenable to treatment with PCI, achieving optimal post-PCI FFR or NHPR target values can be challenging, or frequently impossible, in many patients[73]. Beyond the pattern of coronary artery disease, there are additional anatomical factors that may contribute to lower pressure-based indices. Evolving evidence suggests that post-PCI FFR values are consistently lower in left anterior descending (LAD) versus non-LAD vessels and might require vessel-specific optimal

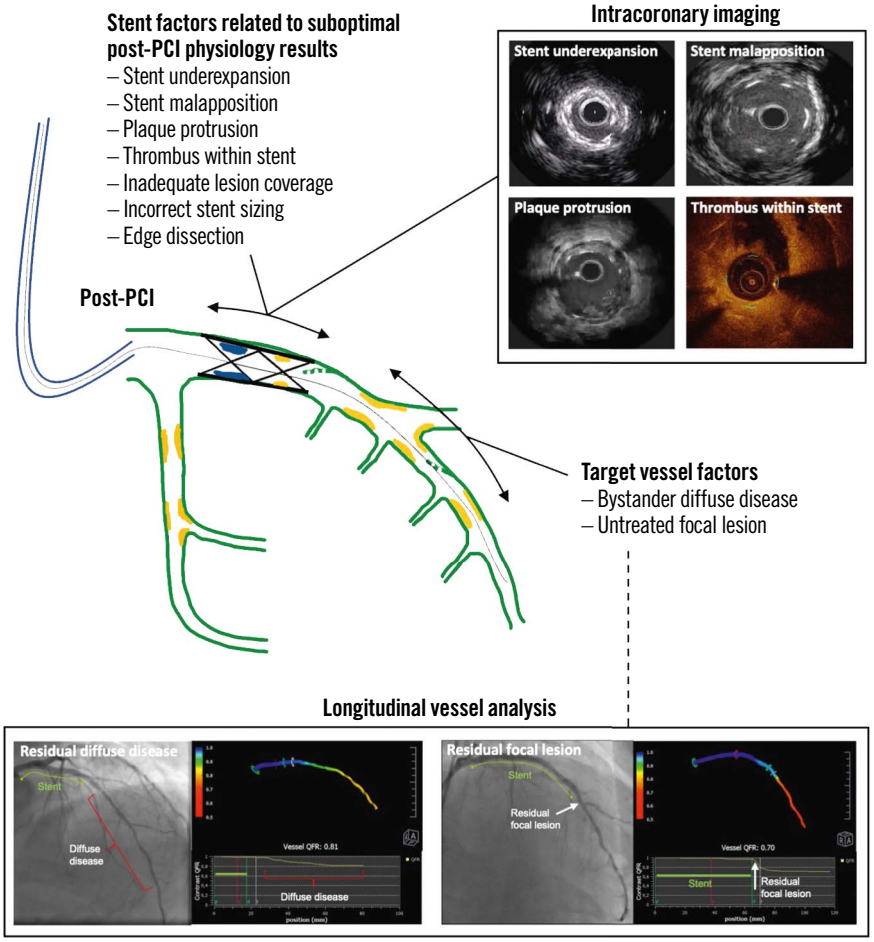


Figure 4. *Mechanisms of suboptimal post-PCI physiological results. PCI: percutaneous coronary intervention; QFR: quantitative flow ratio*

thresholds, adding a further level of complexity[2,22]. The lower LAD values likely occur because of the interplay of several factors, including the higher prevalence of intramuscular coronary tracts observed in the LAD **(Supplementary Figure 3)**, the impact of hydrostatic effects relating to coronary anatomy and the resultant height of the pressure wire sensor above or below the aortic pressure transducer (typically causing a hydrostatic offset of around 3.6 mmHg)[74], and higher coronary flow rates due to the larger myocardial mass subtended by the LAD (high flow across long segments of mild residual diffuse atheroma can generate an appreciable pressure gradient). Based on this, normal FFR values for the LAD have recently been shown to be 0.92, compared to 0.96 in non-LAD vessels[75]. Finally, in all anatomical locations, when NHPR are used, residual reactive hyperaemia induced by intervention-related vessel manipulation may render false positive measurements if performed immediately after stent implantation or contrast/saline injections.

Complementary role of combined imaging and physiology in PCI planning and guidance

Whilst the objective of PCI is the removal of flow-limiting disease, long-term results of interventions are strongly influenced by procedural factors that are better addressed with intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) − both of which provide detail on CAD patterns and guidance for PCI. A detailed description of these techniques and on their use in planning, guiding and optimising PCI is available elsewhere[76]. The results of comprehensive vessel imaging post-PCI compared with FFR and its effect on long-term outcomes have been reported[77]. In addition, there is growing interest in whether the presence of vulnerable atheroma in non-flow-limiting lesions might be associated with a higher risk of future events[78].

Merging information based on the presence and location of flow-limiting stenoses provided by physiology, with information on plaque characteristics and distribution, and vessel dimensions derived from imaging might aid in the selection of PCI devices and strategies in terms of lesion preparation, plaque-free landing zone for PCI, and the selection of stent diameter and length, all important aspects which ultimately improve long-term procedural results. Triregistration, with physiology and intracoronary imaging in conjunction with angiography, is currently available for IVUS and iFR. Coregistration with angiography is also feasible with OCT. Intracoronary imaging-derived physiology, such as OCT-derived FFR, currently lacks validation and is not available for clinical use.

In addition, there is extensive evidence suggesting that PCI optimisation with intravascular imaging improves long-term procedural outcomes[2,76,79-84]. This benefit is independent of the modest increase in FFR values noted in image-based PCI optimisation studies[79,85,86]. The synergistic use of intracoronary imaging and post-PCI longitudinal vessel pullback can be used to investigate causes of focal pressure loss after PCI and assist with decisions on how they could be rectified[86]. Imaging may also highlight the existence of high-risk morphological features of coronary disease − both at baseline and post-PCI − with prognostic implications, even when these are not ischaemia-generating[87], such as in instances of malapposition or significant edge dissection.

Integrating available tools and knowledge into algorithms for physiology-based planning and optimisation

The points discussed thus far can be tentatively integrated into algorithms for PCI planning and post-PCI evaluation. It is suggested that a comprehensive virtual analysis of the target vessel be performed prior to PCI, to support the indication for PCI and to assist in procedural planning and strategising, with the support of simulation if available. Following PCI, the result should be interrogated using a combination of physiology and/or imaging techniques, with post-PCI optimisation carried out when residual focal or tandem pressure loss remains. Suggested algorithms for comprehensive lesion assessment using pre- and post-PCI physiology are shown in **Figure 5** and **Figure 6**, respectively.

Applied coronary physiology in specific PCI scenarios

In addition to the general principles discussed above, the use of physiology to plan and guide PCI in specific scenarios is deserving of a separate discussion. **Supplementary Appendix 2** outlines applied coronary physiology for the following contexts: multivessel coronary artery disease, vessels with tandem lesions or diffusely diseased vessels, lesions in vessels providing collaterals to chronically occluded arteries, patients with acute coronary syndromes, bifurcation lesions and jailed side branches, left main stem stenosis, coronary lesions in patients with aortic stenosis, native vessel or surgical graft stenosis in patients with prior coronary artery bypass graft, and in vessels with myocardial bridge − all in greater detail.

Future directions and outlook

The use of physiology in procedural planning and simulation of PCI is an area of growing interest, though, as yet, supported only by a relatively small evidence base. Upcoming trials in the field

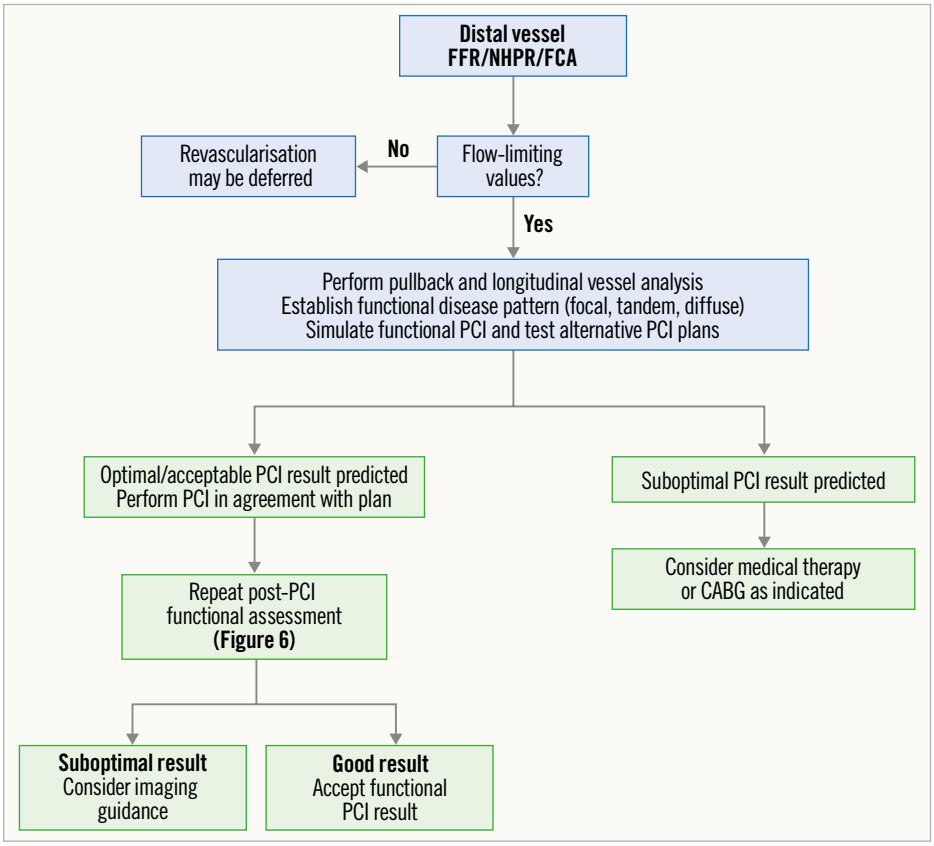


Figure 5. *Proposed algorithm for pre-PCI physiology assessment and planning of PCI based on physiological interrogation. CABG: coronary artery bypass graft; FCA: functional coronary angiography; FFR: fractional flow reserve; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention*

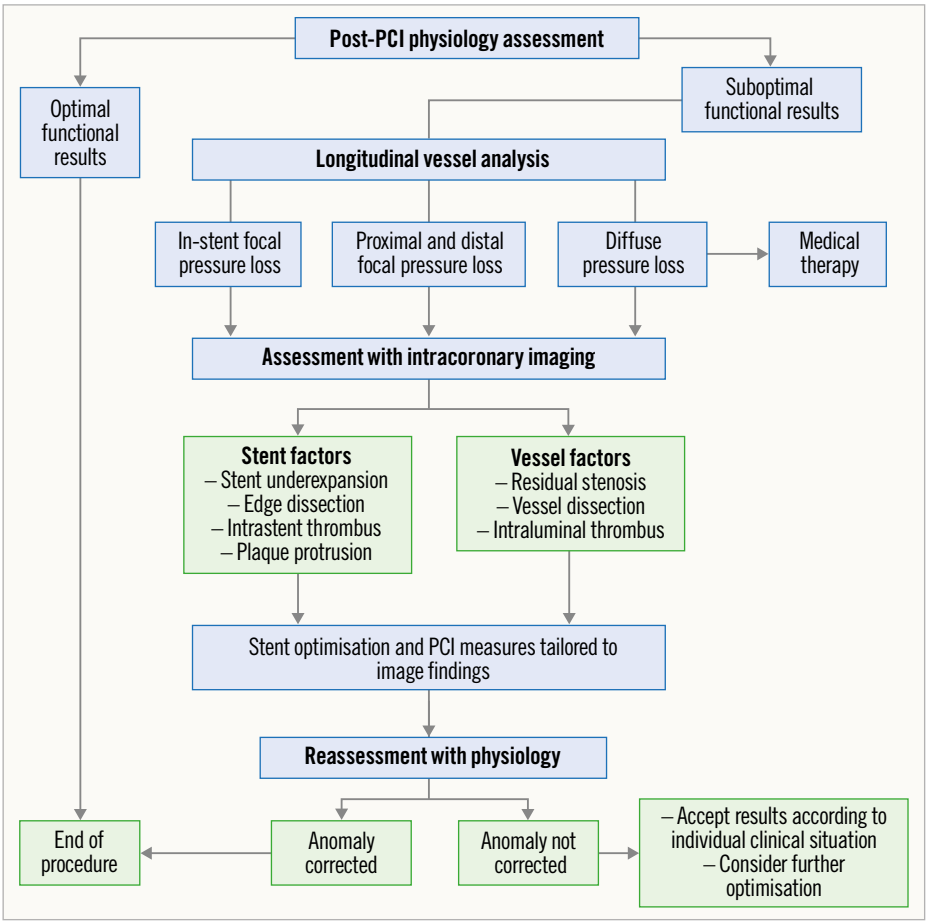


Figure 6. *Proposed algorithm for postprocedural assessment and optimisation of functional PCI results based on physiological interrogation. PCI: percutaneous coronary intervention*

will provide valuable evidence on the use of invasive physiology and FCA for this purpose. Whilst it is generally accepted that PCI is an appropriate therapy for patients with focal CAD, the optimal treatment strategy for patients with haemodynamically significant lesions in the presence of diffuse disease is a subject of ongoing investigation.

Prospective studies are also being conducted to assess the use of coregistration technology on stent deployment and patient outcomes. The DEFINE GPS (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting; ClinicalTrials.gov: NCT04451044) and iLARDI (Usefulness of the Use of Co-registration Strategy With iFR in Long and/or Diffuse Coronary Lesions; ClincalTrials.gov: NCT04283734) investigators aim to assess the impact of iFR coregistration (SyncVision; Philips) on guiding PCI and influencing the number and lengths of implanted stents, and in DEFINE GPS, whether this might influence the rate of MACE. The PPG Global Registry involves a prospective evaluation of the impact of the PPG index on clinical decision-making for PCI (or not) and related outcomes (ClinicalTrials.gov: NCT04789317). Future studies should better define the role of microvascular dysfunction in relation to PCI outcomes. Collectively, these studies will add significant value in objectively assessing the utility of pre-PCI simulation and planning using physiological indices.

Conclusions

The raison d'être of PCI is to abolish flow-limiting stenoses and ischaemia in order to improve patient symptoms and/or prognosis. In conjunction with angiographic findings, physiology determined by FFR, NHPR and FCA assists in weighing important decisions in procedural planning. Emerging studies hint at the application of *in silico* PCI simulation prior to intervening on a patient. This offers a novel perspective on planning the effectiveness of an intervention and could enable the adoption of revascularisation strategies associated with the highest physiological gain. Furthermore, identifying patients with little physiological gain after PCI, despite optimisation, is highly important, as they are at high risk of premature stent failure.

Physiology in the post-PCI setting facilitates procedural optimisation through descriptive longitudinal vessel analyses of stented segments, offering clarity on the presence of residual flow-limiting disease. These technologies, in combination with the ability to coregister anatomy with physiology and intravascular imaging, which allows for the identification of different disease phenotypes, have

revolutionised PCI in the modern era. Clinical trials assessing the effectiveness of these tools on clinical outcomes are eagerly awaited.

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

3. 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.

4. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H, De Bruyne B; Fractional Flow Reserve (FFR) Post-Stent Registry Investigators. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation.* 2002;105:2950-4.

5. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

6. Bech GJ, Pijls NH, De Bruyne B, Peels KH, Michels HR, Bonnier HJ, Koolen JJ. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. *Circulation.* 1999;99:883-8.

7. Klauss V, Erdin P, Rieber J, Leibig M, Stempfle HU, König A, Baylacher M, Theisen K, Haufe MC, Sroczynski G, Schiele T, Siebert U. Fractional flow reserve for the prediction of cardiac events after coronary stent implantation: results of a multivariate analysis. *Heart.* 2005;91:203-6.

8. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, Chung IS, Kim YN, Kim KB, Doh JH, Koo BK, Tahk SJ, Fearon WF. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. *Am J Cardiol.* 2011;107:1763-7.

9. Ito T, Tani T, Fujita H, Ohte N. Relationship between fractional flow reserve and residual plaque volume and clinical outcomes after optimal drug-eluting stent implantation: insight from intravascular ultrasound volumetric analysis. *Int J Cardiol.* 2014;176:399-404.

10. 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.

11. 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.

12. 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.

13. Kasula S, Agarwal SK, Hacioglu Y, Pothineni NK, Bhatti S, Ahmed Z, Uretsky B, Hakeem A. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. *Heart.* 2016;102:1988-94.

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

15. Azzalini L, Poletti E, Demir OM, Ancona MB, Mangieri A, Giannini F, Carlino M, Chieffo A, Montorfano M, Colombo A, Latib A. Impact of Post-Percutaneous Coronary Intervention Fractional Flow Reserve Measurement on Procedural Management and Clinical Outcomes: The REPEAT-FFR Study. *J Invasive Cardiol.* 2019;31:229-34.

16. Jensen LO, Thayssen P, Thuesen L, Hansen HS, Lassen JF, Kelbaek H, Junker A, Hansen KN, Boetker HE, Krusell LR, Pedersen KE. Influence of a pressure gradient distal to implanted bare-metal stent on in-stent restenosis after percutaneous coronary intervention. *Circulation.* 2007;116:2802-8.

17. Shin D, Lee SH, Lee JM, Choi KH, Hwang D, Lee HJ, Jang HJ, Kim HK, Kwak JJ, Ha SJ, Song YB, Shin ES, Doh JH. Prognostic Implications of Post-Intervention Resting Pd/Pa and Fractional Flow Reserve in Patients With Stent Implantation. *JACC Cardiovasc Interv.* 2020;13:1920-33.

18. 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.

19. Zhang R, Xu B, Dou K, Guan C, Zhao Y, Wang X, Zou T, Qiao Z, Xie L, Wang H, Yuan S, Song L, Tu S, Wang Y, Wijns W. Post-PCI outcomes predicted by pre-intervention simulation of residual quantitative flow ratio using augmented reality. *Int J Cardiol.* 2022;352:33-9.

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

21. Fournier S, Ciccarelli G, Toth GG, Milkas A, Xaplanteris P, Tonino PAL, Fearon WF, Pijls NHJ, Barbato E, De Bruyne B. Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention. *JAMA Cardiol.* 2019;4:370-4.

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

23. 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.

24. 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.

25. Lee HJ, Mejía-Rentería H, Escaned J, Doh JH, Lee JM, Hwang D, Yuasa S, Choi KH, Jang HJ, Jeon KH, Lee J, Nam CW, Shin ES, Koo BK. Prediction of functional results of percutaneous coronary interventions with virtual stenting and quantitative flow ratio. *Catheter Cardiovasc Interv.* 2022;100:1208-17.

26. 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.

27. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, Kim JH, Chae IH, Yoon JH, Her SH, Seung KB, Chung WY, Yoo SY, Lee JB, Choi SW, Park K, Hong TJ, Lee SY, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ; IRIS-FFR Investigators†. Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation.* 2017;135:2241-51.

28. 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.

29. 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.

30. Leone AM, Martin-Reyes R, Baptista SB, Amabile N, Raposo L, Franco Pelaez JA, Trani C, Cialdella P, Basile E, Zimbardo G, Burzotta F, Porto I, Aurigemma C, Rebuzzi AG, Faustino M, Niccoli G, Abreu PF, Slama MS, Spagnoli V, Telleria Arrieta M, Amat Santos IJ, de la Torre Hernandez JM, Lopez Palop R, Crea F. The Multi-center Evaluation of the Accuracy of the Contrast MEdium INduced Pd/Pa RaTiO in Predicting FFR (MEMENTO-FFR) Study. *EuroIntervention.* 2016;12:708-15.

31. 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-SWEDEHEART Investigators. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med.* 2017;376:1813-23.

32. 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.

33. Götberg M, Berntorp K, Rylance R, Christiansen EH, Yndigegn T, Gudmundsdottir IJ, Koul S, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Venetsanos D, James SK, Kåregren A, Carlsson J, Jensen J, Karlsson AC, Erlinge D, Fröbert O. 5-Year Outcomes of PCI Guided by Measurement of Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve. *J Am Coll Cardiol.* 2022;79:965-74.

34. 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.

35. Lee JM, Choi KH, Park J, Hwang D, Rhee TM, Kim J, Park J, Kim HY, Jung HW, Cho YK, Yoon HJ, Song YB, Hahn JY, Nam CW, Shin ES, Doh JH, Hur SH, Koo BK. Physiological and Clinical Assessment of Resting Physiological Indexes. *Circulation.* 2019;139:889-900.

36. Kim KH, Doh JH, Koo BK, Min JK, Erglis A, Yang HM, Park KW, Lee HY, Kang HJ, Kim YJ, Lee SY, Kim HS. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovasc Interv.* 2014;7:72-8.

37. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, Leipsic JA, Knuuti J, Underwood SR, van de Ven PM, van Rossum AC, Taylor CA, Knaapen P. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. *J Am Coll Cardiol.* 2019;73:161-73.

38. Gosling RC, Morris PD, Silva Soto DA, Lawford PV, Hose DR, Gunn JP. Virtual Coronary Intervention: A Treatment Planning Tool Based Upon the Angiogram. *JACC Cardiovasc Imaging.* 2019;12:865-72.

39. Papafaklis MI, Muramatsu T, Ishibashi Y, Lakkas LS, Nakatani S, Bourantas CV, Ligthart J, Onuma Y, Echavarria-Pinto M, Tsirka G, Kotsia A, Nikas DN, Mogabgab O, van Geuns RJ, Naka KK, Fotiadis DI, Brilakis ES, Garcia-Garcia HM, Escaned J, Zijlstra F, Michalis LK, Serruys PW. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. *EuroIntervention.* 2014;10:574-83.

40. Li J, Gong Y, Wang W, Yang Q, Liu B, Lu Y, Xu Y, Huo Y, Yi T, Liu J, Li Y, Xu S, Zhao L, Ali ZA, Huo Y. Accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR. *Cardiovasc Res.* 2020;116:1349-56.

41. 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.

42. Xu B, Tu S, Song L, Jin Z, Yu B, Fu G, Zhou Y, Wang J, Chen Y, Pu J, Chen L, Qu X, Yang J, Liu X, Guo L, Shen C, Zhang Y, Zhang Q, Pan H, Fu X, Liu J, Zhao Y, Escaned J, Wang Y, Fearon WF, Dou K, Kirtane AJ, Wu Y, Serruys PW, Yang W, Wijns W, Guan C, Leon MB, Qiao S, Stone GW; FAVOR III China study group. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet.* 2021;398:2149-59.

43. Ando H, Takashima H, Suzuki A, Sakurai S, Kumagai S, Kurita A, Waseda K, Amano T. Impact of lesion characteristics on the prediction of optimal poststent fractional flow reserve. *Am Heart J.* 2016;182:119-24.

44. 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;16:1 67-71.

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

46. Matsuo A, Shimoo S, Takamatsu K, Tsuji Y, Kyodo A, Mera K, Koide M, Isodono K, Tsubakimoto Y, Sakatani T, Inoue K, Fujita H. Visualization of the improvement of myocardial perfusion after coronary intervention using motorized fractional flow reserve pullback curve. *Cardiovasc Interv Ther.* 2018;33:99-108.

47. Higashioka D, Shiono Y, Kubo T, Kitabata H, Nishi T, Terada K, Emori H, Takahata M, Wada T, Shimamura K, Matsuo Y, Ino Y, Tanaka A, Hozumi T, Akasaka T. The inter-study reproducibility of instantaneous wave-free ratio and angiography coregistration. *J Cardiol.* 2020;75:507-12.

48. Sonck J, Mizukami T, Johnson NP, Nagumo S, Gallinoro E, Candreva A, Mileva N, Munhoz D, Shinke T, Svanerud J, Barbato E, De Bruyne B, Collet C. Development, validation, and reproducibility of the pullback pressure gradient (PPG) derived from manual fractional flow reserve pullbacks. *Catheter Cardiovasc Interv.* 2022;99:1518-25.

49. Lee SH, Shin D, Lee JM, Lefieux A, Molony D, Choi KH, Hwang D, Lee HJ, Jang HJ, Kim HK, Ha SJ, Kwak JJ, Park TK, Yang JH, Song YB, Hahn JY, Doh JH, Shin ES, Nam CW, Koo BK, Choi SH, Gwon HC. Automated Algorithm Using Pre-Intervention Fractional Flow Reserve Pullback Curve to Predict Post-Intervention Physiological Results. *JACC Cardiovasc Interv.* 2020;13:2670-84.

50. Shiono Y, Kubo T, Honda K, Katayama Y, Aoki H, Satogami K, Kashiyama K, Taruya A, Nishiguchi T, Kuroi A, Orii M, Kameyama T, Yamano T, Yamaguchi T, Matsuo Y, Ino Y, Tanaka A, Hozumi T, Nishimura Y, Okamura Y, Akasaka T. Impact of functional focal versus diffuse coronary artery disease on bypass graft patency. *Int J Cardiol.* 2016;222:16-21.

51. van Beek KAJ, van Steenbergen GJ, Vervaat FE, Mulders BCJH, van Straten BH, van Nunen LX, Wijnbergen IF. Single center experience in the treatment of hemodynamically significant diffuse coronary artery disease of the left anterior descending. *Int J Cardiol.* 2022;352:40-4.

52. Biscaglia S, Uretsky B, Barbato E, Collet C, Onuma Y, Jeremias A, Tebaldi M, Hakeem A, Kogame N, Sonck J, Escaned J, Serruys PW, Stone GW, Campo G. Invasive Coronary Physiology After Stent Implantation: Another Step Toward Precision Medicine. *JACC Cardiovasc Interv.* 2021;14:237-46.

53. Candreva A, Mizukami T, Sonck J, Munhoz D, Nagumo S, Di Gioia G, Gallinoro E, Mileva N, Bartunek J, Wyffels E, Barbato E, De Bruyne B, Perera D, Collet C. Hyperemic hemodynamic characteristics of serial coronary lesions assessed by pullback pressure gradients. *Catheter Cardiovasc Interv.* 2021;98:E647-54.

54. Warisawa T, Howard JP, Cook CM, Ahmad Y, Doi S, Nakayama M, Goto S, Yakuta Y, Karube K, Seike F, Uetani T, Murai T, Kikuta Y, Shiono Y, Kawase Y, Shun-Shin MJ, Kaihara T, Higuma T, Ishibashi Y, Matsuda H, Nishina H, Matsuo H, Escaned J, Akashi YJ, Davies JE. Inter-observer differences in interpretation of coronary pressure-wire pullback data by non-expert interventional cardiologists. *Cardiovasc Interv Ther.* 2021;36:289-97.

55. Matsuo A, Kasahara T, Ariyoshi M, Irie D, Isodono K, Tsubakimoto Y, Sakatani T, Inoue K, Fujita H. Utility of angiography-physiology coregistration maps during percutaneous coronary intervention in clinical practice. *Cardiovasc Interv Ther.* 2021;36:208-18.

56. Scarsini R, Fezzi S, Pesarini G, Del Sole PA, Venturi G, Mammone C, Marcoli M, Gambaro A, Tavella D, Pighi M, Ribichini F. Impact of physiologically diffuse versus focal pattern of coronary disease on quantitative flow reserve diagnostic accuracy. *Catheter Cardiovasc Interv.* 2022;99:736-45.

57. Tang J, Chu J, Hou H, Lai Y, Tu S, Chen F, Yao Y, Ye Z, Gao Y, Mao Y, Zhuang S, Liu X. Clinical implication of QFR in patients with ST-segment elevation myocardial infarction after drug-eluting stent implantation. *Int J Cardiovasc Imaging.* 2021;37:755-66.

58. Biscaglia S, Uretsky BF, Tebaldi M, Erriquez A, Brugaletta S, Cerrato E, Quadri G, Spitaleri G, Colaiori I, Di Girolamo D, Scoccia A, Zucchetti O, D'Aniello E, Manfrini M, Pavasini R, Barbato E, Campo G. Angio-Based Fractional Flow Reserve, Functional Pattern of Coronary Artery Disease, and Prediction of Percutaneous Coronary Intervention Result: a Proof-of-Concept Study. *Cardiovasc Drugs Ther.* 2022;36:645-53.

59. Shin D, Dai N, Lee SH, Choi KH, Lefieux A, Molony D, Hwang D, Kim HK, Jeon KH, Lee HJ, Jang HJ, Ha SJ, Park TK, Yang JH, Song YB, Hahn JY, Choi SH, Doh JH, Shin ES, Nam CW, Koo BK, Gwon HC, Ge J, Lee JM. Physiological Distribution and Local Severity of Coronary Artery Disease and Outcomes After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2021;14:1771-85.

60. Kőszegi Z, Berta B, Tóth GG, Tar B, Üveges Á, Ágoston A, Szücs A, Szabó GT, Barta J, Szük T, Czuriga D, Komócsi A, Ruzsa Z. Anatomical Assessment vs. Pullback REsting full-cycle rAtio (RFR) Measurement for Evaluation of Focal and Diffuse CoronarY Disease: Rationale and Design of the "READY Register". *Front Cardiovasc Med.* 2021 Dec;8:784220.

61. Omori H, Kawase Y, Mizukami T, Tanigaki T, Hirata T, Kikuchi J, Ota H, Sobue Y, Miyake T, Kawamura I, Okubo M, Kamiya H, Hirakawa A, Kawasaki M, Nakagawa M, Tsuchiya K, Suzuki Y, Ito T, Terashima M, Kondo T, Suzuki T, Escaned J, Matsuo H. Comparisons of Nonhyperemic Pressure Ratios: Predicting Functional Results of Coronary Revascularization Using Longitudinal Vessel Interrogation. *JACC Cardiovasc Interv.* 2020;13:2688-98.

62. Collet C, Collison D, Mizukami T, McCartney P, Sonck J, Ford T, Munhoz D, Berry C, De Bruyne B, Oldroyd K. Differential Improvement in Angina and Health-Related Quality of Life After PCI in Focal and Diffuse Coronary Artery Disease. *JACC Cardiovasc Interv.* 2022;15:2506-18.

63. 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.

64. Modi BN, Sankaran S, Kim HJ, Ellis H, Rogers C, Taylor CA, Rajani R, Perera D. Predicting the Physiological Effect of Revascularization in Serially Diseased Coronary Arteries. *Circ Cardiovasc Interv.* 2019;12:e007577.

65. Sonck J, Nagumo S, Norgaard BL, Otake H, Ko B, Zhang J, Mizukami T, Maeng M, Andreini D, Takahashi Y, Jensen JM, Ihdayhid A, Heggermont W, Barbato E, Mileva N, Munhoz D, Bartunek J, Updegrove A, Collinsworth A, Penicka M, Van Hoe L, Leipsic J, Koo BK, De Bruyne B, Collet C. Clinical Validation of a Virtual Planner for Coronary Interventions Based on Coronary CT Angiography. *JACC Cardiovasc Imaging.* 2022;15:1242-55.

66. van Diemen PA, de Winter RW, Schumacher SP, Bom MJ, Driessen RS, Everaars H, Jukema RA, Somsen YB, Popelkova L, van de Ven PM, van Rossum AC, van de Hoef TP, de Haan S, Marques KM, Lemkes JS, Appelman Y, Nap A, Verouden NJ, Opolski MP, Danad I, Knaapen P. Residual Quantitative Flow Ratio to Estimate Post-Percutaneous Coronary Intervention Fractional Flow Reserve. *J Interv Cardiol.* 2021;2021:4339451.

67. Tomaniak M, Neleman T, Ziedses des Plantes A, Masdjedi K, van Zandvoort LJC, Kochman J, den Dekker WK, Wilschut JM, Diletti R, Kardys I, Zijlstra F, Van Mieghem NM, Daemen J. Diagnostic Accuracy of Coronary Angiography-Based Vessel Fractional Flow Reserve (vFFR) Virtual Stenting. *J Clin Med.* 2022;11:1397.

68. 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.

69. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, Costerousse O, Bertrand OF. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. *Am Heart J.* 2017;183:1-9.

70. Hwang D, Koo BK, Zhang J, Park J, Yang S, Kim M, Yun JP, Lee JM, Nam CW, Shin ES, Doh JH, Chen SL, Kakuta T, Toth GG, Piroth Z, Johnson NP, Pijls NHJ, Hakeem A, Uretsky BF, Hokama Y, Tanaka N, Lim HS, Ito T, Matsuo A, Azzalini L, Leesar MA, Neleman T, van Mieghem NM, Diletti R, Daemen J, Collison D, Collet C, De Bruyne B. Prognostic Implications of Fractional Flow Reserve After Coronary Stenting: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2022;5:e2232842.

71. Uretsky BF, Agarwal SK, Vallurupalli S, Al-Hawwas M, Hasan R, Miller K, Hakeem A. Prospective Evaluation of the Strategy of Functionally Optimized Coronary Intervention. *J Am Heart Assoc.* 2020;9:e015073.

72. Nishi T, Piroth Z, De Bruyne B, Jagic N, Möbius-Winkler S, Kobayashi Y, Derimay F, Fournier S, Barbato E, Tonino P, Jüni P, Pijls NHJ, Fearon WF. Fractional Flow Reserve and Quality-of-Life Improvement After Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease. *Circulation.* 2018;138:1797-804.

73. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, Zijlstra F, de Jaegere P, Daemen J, van Mieghem NM. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. *Circ Cardiovasc Interv.* 2019;12:e007428.

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

75. Fournier S, Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, Mizukami T, Nagumo S, Kodeboina M, El Farissi M, Zelis JM, Sonck J, Collet C, Pijls NHJ, De Bruyne B. Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans. *EuroIntervention.* 2021;17:e309-16.

76. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, Radu MD, Joner M, Yu B, Jia H, Meneveau N, de la Torre Hernandez JM, Escaned J, Hill J, Prati F, Colombo A, di Mario C, Regar E, Capodanno D, Wijns W, Byrne RA, Guagliumi G; ESC Scientific Document Group. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J.* 2018;39:3281-300.

77. Burzotta F, Leone AM, Aurigemma C, Zambrano A, Zimbardo G, Arioti M, Vergallo R, De Maria GL, Cerracchio E, Romagnoli E, Trani C, Crea F. Fractional Flow Reserve or Optical Coherence Tomography to Guide Management of Angiographically Intermediate Coronary Stenosis: A Single-Center Trial. *JACC Cardiovasc Interv.* 2020;13:49-58.

78. Ferraro RA, van Rosendael AR, Lu Y, Andreini D, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, de Araújo Gonçalves P, Hadamitzky M, Kim YJ, Leipsic J, Maffei E, Marques H, Plank F, Pontone G, Raff GL, Villines TC, Lee SE, Al'Aref SJ, Baskaran L, Cho I, Danad I, Gransar H, Budoff MJ, Samady H, Stone PH, Virmani R, Narula J, Berman DS, Chang HJ, Bax JJ, Min JK, Shaw LJ, Lin FY. Non-obstructive high-risk plaques increase the risk of future culprit lesions comparable to obstructive plaques without high-risk features: the ICONIC study. *Eur Heart J Cardiovasc Imaging.* 2020;21:973-80.

79. Meneveau N, Souteyrand G, Motreff P, Caussin C, Amabile N, Ohlmann P, Morel O, Lefrançois Y, Descotes-Genon V, Silvain J, Braik N, Chopard R, Chatot M, Ecarnot F, Tauzin H, Van Belle E, Belle L, Schiele F. Optical Coherence Tomography to Optimize Results of Percutaneous Coronary Intervention in Patients with Non-ST-Elevation Acute Coronary Syndrome: Results of the Multicenter, Randomized DOCTORS Study (Does Optical Coherence Tomography Optimize Results of Stenting). *Circulation.* 2016;134:906-17.

80. Tian NL, Gami SK, Ye F, Zhang JJ, Liu ZZ, Lin S, Ge Z, Shan SJ, You W, Chen L, Zhang YJ, Mintz G, Chen SL. Angiographic and clinical comparisons of intravascular ultra-sound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions: two-year results from a randomised AIR-CTO study. *EuroIntervention.* 2015;10:1409-17.

81. Hong SJ, Mintz GS, Ahn CM, Kim JS, Kim BK, Ko YG, Kang TS, Kang WC, Kim YH, Hur SH, Hong BK, Choi D, Kwon H, Jang Y, Hong MK; IVUS-XPL Investigators. Effect of Intravascular Ultrasound-Guided Drug-Eluting Stent Implantation: 5-Year Follow-Up of the IVUS-XPL Randomized Trial. *JACC Cardiovasc Interv.* 2020;13:62-71.

82. Hong SJ, Kim D, Kim BK, Ahn CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y. Acute and one-year clinical outcomes of pre-stenting intravascular ultrasound: a patient-level meta-analysis of randomised clinical trials. *EuroIntervention.* 2021;17:202-11.

83. Hong SJ, Zhang JJ, Mintz GS, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Kan J, Pan T, Gao X, Ge Z, Chen SL, Hong MK. Improved 3-Year Cardiac Survival After IVUS-Guided Long DES Implantation: A Patient-Level Analysis From 2 Randomized Trials. *JACC Cardiovasc Interv.* 2022;15:208-16.

84. Shin DH, Hong SJ, Mintz GS, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Hong MK. Effects of Intravascular Ultrasound-Guided Versus Angiography-Guided New-Generation Drug-Eluting Stent Implantation: Meta-Analysis With Individual Patient-Level Data From 2,345 Randomized Patients. *JACC Cardiovasc Interv.* 2016;9:2232-39.

85. Wijns W, Shite J, Jones MR, Lee SW, Price MJ, Fabbiocchi F, Barbato E, Akasaka T, Bezerra H, Holmes D. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. *Eur Heart J.* 2015;36:3346-55.

86. Neleman T, van Zandvoort LJC, Tovar Forero MN, Masdjedi K, Ligthart JMR, Witberg KT, Groenland FTW, Cummins P, Lenzen MJ, Boersma E, Nuis RJ, den Dekker WK, Diletti R, Wilschut J, Zijlstra F, Van Mieghem NM, Daemen J. FFR-Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care: The FFR REACT Trial. *JACC Cardiovasc Interv.* 2022;15:1595-1607.

87. Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, IJsselmuiden AJJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Al Nooryani A, Rivero F, Malinowski K, De Luca G, Garcia Garcia H, Granada JF, Wojakowski W. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J.* 2021;42:4671-79.

88. Van Belle E, Gil R, Klauss V, Balghith M, Meuwissen M, Clerc J, Witzenbichler B, Cercek M, Vlachojannis M, Lang I, Commeau P, Vincent F, Testa L, Wasek W, Debry N, Kische S, Gabrielli G, Sardella G. Impact of Routine Invasive Physiology at Time of Angiography in Patients With Multivessel Coronary Artery Disease on Reclassification of Revascularization Strategy: Results From the DEFINE REAL Study. *JACC Cardiovasc Interv.* 2018;11:354-65.

89. Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Ej West N, Piek JJ, Zaman A, Fath-Ordoubadi F, Stables RH, Appleby C, van Mieghem N, van Geuns RJ, Uren N, Zueco J, Buszman P, Iñiguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Hanratty C, Cavalcante R, Kappetein AP, Taggart DP, van Es GA, Morel MA, de Vries T, Onuma Y, Farooq V, Serruys PW, Banning AP. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J.* 2017;38:3124-34.

90. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary

artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol.* 2010;56:177-84.

91. Banning AP, Serruys P, De Maria GL, Ryan N, Walsh S, Gonzalo N, Jan van Geuns R, Onuma Y, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Piek JJ, Appleby C, Fath-Ordoubadi F, Zaman A, Van Mieghem NM, Uren N, Zueco J, Buszman P, Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, de Vries T, Taggart D, Farooq V, Spitzer E, Tijssen J, Escaned J. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. *Eur Heart J.* 2022;43:1307-16.

92. Fearon WF, Zimmermann FM, De Bruyne B, Piroth Z, van Straten AHM, Szekely L, Davidavičius G, Kalinauskas G, Mansour S, Kharbanda R, Östlund-Papadogeorgos N, Aminian A, Oldroyd KG, Al-Attar N, Jagic N, Dambrink JE, Kala P, Angerås O, MacCarthy P, Wendler O, Casselman F, Witt N, Mavromatis K, Miner SES, Sarma J, Engstrøm T, Christiansen EH, Tonino PAL, Reardon MJ, Lu D, Ding VY, Kobayashi Y, Hlatky MA, Mahaffey KW, Desai M, Woo YJ, Yeung AC, Pijls NHJ; FAME 3 Investigators. Fractional Flow Reserve-Guided PCI as Compared with Coronary Bypass Surgery. *N Engl J Med.* 2022;386:128-37.

93. Thuesen AL, Riber LP, Veien KT, Christiansen EH, Jensen SE, Modrau I, Andreasen JJ, Junker A, Mortensen PE, Jensen LO. Fractional Flow Reserve Versus Angiographically-Guided Coronary Artery Bypass Grafting. *J Am Coll Cardiol.* 2018;72:2732-43.

94. Toth GG, De Bruyne B, Kala P, Ribichini FL, Casselman F, Ramos R, Piroth Z, Fournier S, Piccoli A, Van Mieghem C, Penicka M, Mates M, Nemec P, Van Praet F, Stockman B, Degriek I, Barbato E. Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting: the GRAFFITI trial. *EuroIntervention.* 2019;15:e999-e1005.

95. Glineur D, Grau JB, Etienne PY, Benedetto U, Fortier JH, Papadatos S, Laruelle C, Pieters D, El Khoury E, Blouard P, Timmermans P, Ruel M, Chong AY, So D, Chan V, Rubens F, Gaudino MF. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. *Eur Heart J.* 2019;40:2421-8.

96. Toth GG, Mizukami T, Collet C, Thuesen AL, Casselman F, Jensen LO, De Bruyne B, Barbato E. Impact of Functional Severity of Coronary Artery Disease on Arterial Versus Venous Graft Patency. *JACC Cardiovasc Interv.* 2022;15:1098-100.

97. Hara H, Gao C, Kogame N, Ono M, Kawashima H, Wang R, Morel MA, O'Leary N, Sharif F, Möllmann H, Reiber JHC, Sabaté M, Zaman A, Wijns W, Onuma Y, Serruys PW. A randomised controlled trial of the sirolimus-eluting biodegradable polymer ultra-thin Supraflex stent versus the everolimus-eluting biodegradable polymer SYNERGY stent for three-vessel coronary artery disease: rationale and design of the Multivessel TALENT trial. *EuroIntervention.* 2020;16:e997-e1004.

98. Collet C, Miyazaki Y, Ryan N, Asano T, Tenekecioglu E, Sonck J, Andreini D, Sabate M, Brugaletta S, Stables RH, Bartorelli A, de Winter RJ, Katagiri Y, Chichareon P, De Maria GL, Suwannasom P, Cavalcante R, Jonker H, Morel MA, Cosyns B, Kappetein AP, Taggart DT, Farooq V, Escaned J, Banning A, Onuma Y, Serruys PW. Fractional Flow Reserve Derived From Computed Tomographic Angiography in Patients With Multivessel CAD. *J Am Coll Cardiol.* 2018;71:2756-69.

99. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, La Meir M, Miyazaki Y, de Mey J, Gaemperli O, Ouda A, Maureira JP, Mandry D, Camenzind E, Macron L, Doenst T, Teichgräber U, Sigusch H, Asano T, Katagiri Y, Morel MA, Lindeboom W, Pontone G, Lüscher TF, Bartorelli AL, Serruys PW. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J.* 2018;39:3689-98.

100. Andreini D, Modolo R, Katagiri Y, Mushtaq S, Sonck J, Collet C, De Martini S, Roberto M, Tanaka K, Miyazaki Y, Czapla J, Schoors D, Plass A, Maisano F, Kaufmann P, Orry X, Metzdorf PA, Folliguet T, Färber G, Diamantis I, Schönweiß M, Bonalumi G, Guglielmo M, Ferrari C, Olivares P, Cavallotti L, Leal I, Lindeboom W, Onuma Y, Serruys PW, Bartorelli AL; SYNTAX III REVOLUTION Investigators. Impact of Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography on Heart Team Treatment Decision-Making in Patients With Multivessel Coronary Artery Disease: Insights From the SYNTAX III REVOLUTION Trial. *Circ Cardiovasc Interv.* 2019;12:e007607.

101. Pijls NH, De Bruyne B, Bech GJ, Liistro F, Heyndrickx GR, Bonnier HJ, Koolen JJ. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation.* 2000;102:2371-7.

102. Warisawa T, Howard JP, Kawase Y, Tanigaki T, Omori H, Cook CM, Ahmad Y, Francis DP, Akashi YJ, Matsuo H, Davies JE. Difference in functional assessment of individual stenosis severity in serial coronary lesions between resting and hyperemic pressure-wire pullback: Insights from the GIFT registry. *Int J Cardiol.* 2020;312:10-5.

103. Kim HL, Koo BK, Nam CW, Doh JH, Kim JH, Yang HM, Park KW, Lee HY, Kang HJ, Cho YS, Youn TJ, Kim SH, Chae IH, Choi DJ, Kim HS, Oh BH, Park YB. Clinical and physiological outcomes of fractional flow reserve-guided percutaneous coronary intervention in patients with serial stenoses within one coronary artery. *JACC Cardiovasc Interv.* 2012;5:1013-8.

104. Ahn JM, Nakayoshi T, Hashikata T, Kashiyama K, Arashi H, Kweon J, Van't Veer M, Lyons J, Fearon WF. Impact of Serial Coronary Stenoses on Various Coronary Physiologic Indices. *Circ Cardiovasc Interv.* 2022;15:e012134.

105. Kikuta Y, Cook CM, Sharp ASP, Salinas P, Kawase Y, Shiono Y, Giavarini A, Nakayama M, De Rosa S, Sen S, Nijjer SS, Al-Lamee R, Petraco R, Malik IS, Mikhail GW, Kaprielian RR, Wijntjens GWM, Mori S, Hagikura A, Mates M, Mizuno A, Hellig F, Lee K, Janssens L, Horie K, Mohdnazri S, Herrera R, Krackhardt F, Yamawaki M, Davies J, Takebayashi H, Keeble T, Haruta S, Ribichini F, Indolfi C, Mayet J, Francis DP, Piek JJ, Di Mario C, Escaned J, Matsuo H, Davies JE. Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome In Humans With Coronary Artery Disease: Primary Results of the International Multicenter iFR GRADIENT Registry. *JACC Cardiovasc Interv.* 2018;11:757-67.

106. Rubimbura V, Guillon B, Fournier S, Amabile N, Chi Pan C, Combaret N, Eeckhout E, Kibler M, Silvain J, Wijns W, Schiele F, Muller O, Meneveau N, Adjedj J. Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population. *Catheter Cardiovasc Interv.* 2020;96:1145-53.

107. Guan S, Gan Q, Han W, Zhai X, Wang M, Chen Y, Zhang L, Li T, Chang X, Liu H, Hong W, Li Z, Tu S, Qu X. Feasibility of Quantitative Flow Ratio Virtual Stenting for Guidance of Serial Coronary Lesions Intervention. *J Am Heart Assoc.* 2022;11:e025663.

108. van der Hoeven NW, Janssens GN, de Waard GA, Everaars H, Broyd CJ, Beijnink CWH, van de Ven PM, Nijveldt R, Cook CM, Petraco R, Ten Cate T, von Birgelen C, Escaned J, Davies JE, van Leeuwen MAH, van Royen N. Temporal Changes in Coronary Hyperemic and Resting Hemodynamic Indices in Nonculprit Vessels of Patients With ST-Segment Elevation Myocardial Infarction. *JAMA Cardiol.* 2019;4:736-44.

109. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv.* 2010;3:1274-81.

110. Musto C, De Felice F, Rigattieri S, Chin D, Marra A, Nazzaro MS, Cifarelli A, Violini R. Instantaneous wave-free ratio and fractional flow reserve for the assessment of nonculprit lesions during the index procedure in patients with ST-segment elevation myocardial infarction: The WAVE study. *Am Heart J.* 2017;193:63-9.

111. Thim T, Götberg M, Fröbert O, Nijveldt R, van Royen N, Baptista SB, Koul S, Kellerth T, Bøtker HE, Terkelsen CJ, Christiansen EH, Jakobsen L, Kristensen SD, Maeng M. Non-culprit Stenosis Evaluation Using Instantaneous Wave-Free Ratio in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv.* 2017;10:2528-35.

112. Cuculi F, De Maria GL, Meier P, Dall'Armellina E, de Caterina AR, Channon KM, Prendergast BD, Choudhury RP, Forfar JC, Kharbanda RK, Banning AP. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. *J Am Coll Cardiol.* 2014;64:1894-904.

113. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, Van Crombrugge P, Heyndrickx GR, Wijns W. Fractional flow reserve in patients with prior myocardial infarction. *Circulation.* 2001;104:157-62.

114. Smits PC, Abdel-Wahab M, Neumann FJ, Boxmade Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med.* 2017;376:1234-44.

115. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L; DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet.* 2015;386:665-71.

116. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, le Bras A, Gallet R, Khalife K, Morelle JF, Motreff P, Lemesle G, Dillinger JG, Lhermusier T, Silvain J, Roule V, Labèque JN, Rangé G, Ducrocq G, Cottin Y, Blanchard D, Charles Nelson A, De Bruyne B, Chatellier G, Danchin N; FLOWER-MI Study Investigators. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. *N Engl J Med.* 2021;385:297-308.

117. Piróth Z, Boxma-de Klerk BM, Omerovic E, Andréka P, Fontos G, Fülöp G, Abdel-Wahab M, Neumann FJ, Richardt G, Abdelghani M, Smits PC. The Natural

History of Non-culprit Lesions in STEMI: An FFR Substudy of the Compare-Acute Trial. *JACC Cardiovasc Interv.* 2020;13:954-61.

118. Denormandie P, Simon T, Cayla G, Steg PG, Montalescot G, Durand-Zaleski I, le Bras A, le Breton H, Valy Y, Schiele F, Cuisset T, Vanzetto G, Levesque S, Goube P, Nallet O, Angoulvant D, Roubille F, Charles Nelson A, Chatellier G, Danchin N, Puymirat E. Compared Outcomes of ST-Segment-Elevation Myocardial Infarction Patients With Multivessel Disease Treated With Primary Percutaneous Coronary Intervention and Preserved Fractional Flow Reserve of Nonculprit Lesions Treated Conservatively and of Those With Low Fractional Flow Reserve Managed Invasively: Insights From the FLOWER-MI Trial. *Circ Cardiovasc Interv.* 2021;14:e011314.

119. Leone AM, Liuzzo G. No blossom for fractional flow reserve in FLOWER-MI. *Eur Heart J.* 2021;42:2971-2.

120. Leone AM, Cialdella P, Lassandro Pepe F, Basile E, Zimbardo G, Arioti M, Ciriello G, D'Amario D, Buffon A, Burzotta F, Porto I, Aurigemma C, Niccoli G, Rebuzzi AG, Trani C, Crea F. Fractional flow reserve in acute coronary syndromes and in stable ischemic heart disease: clinical implications. *Int J Cardiol.* 2019;277:42-6.

121. Van Belle E, Baptista SB, Raposo L, Henderson J, Rioufol G, Santos L, Pouillot C, Ramos R, Cuisset T, Calé R, Teiger E, Jorge E, Belle L, Machado C, Barreau D, Costa M, Hanssen M, Oliveira E, Besnard C, Costa J, Dallongeville J, Pipa J, Sideris G, Fonseca N, Bretelle C, Guardado J, Lhoest N, Silva B, Barnay P, Sousa MJ, Leborgne L, Silva JC, Vincent F, Rodrigues A, Seca L, Fernandes R, Dupouy P; PRIME-FFR Study Group. Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes: PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries - Implementation of FFR [Fractional Flow Reserve] in Routine Practice). *Circ Cardiovasc Interv.* 2017;10:e004296.

122. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, Pijls NH. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. *JACC Cardiovasc Interv.* 2011;4:1183-9.

123. Burzotta F, Lassen JF, Lefèvre T, Banning AP, Chatzizisis YS, Johnson TW, Ferenc M, Rathore S, Albiero R, Pan M, Darremont O, Hildick-Smith D, Chieffo A, Zimarino M, Louvard Y, Stankovic G. Percutaneous coronary intervention for bifurcation coronary lesions: the 15th consensus document from the European Bifurcation Club. *EuroIntervention.* 2021;16:1307-17.

124. Koo BK, Kang HJ, Youn TJ, Chae IH, Choi DJ, Kim HS, Sohn DW, Oh BH, Lee MM, Park YB, Choi YS, Tahk SJ. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol.* 2005;46:633-7.

125. Kumsars I, Narbute I, Thuesen L, Niemelä M, Steigen TK, Kervinen K, Sondore D, Holm NR, Lassen JF, Christiansen EH, Maeng M, Jegere S, Juhnevica D, Erglis A; Nordic-Baltic PCI study group. Side branch fractional flow reserve measurements after main vessel stenting: a Nordic-Baltic Bifurcation Study III substudy. *EuroIntervention.* 2012;7:1155-61.

126. Chen SL, Ye F, Zhang JJ, Xu T, Tian NL, Liu ZZ, Lin S, Shan SJ, Ge Z, You W, Liu YQ, Qian XS, Li F, Yang S, Kwan TW, Xu B, Stone GW. Randomized Comparison of FFR-Guided and Angiography-Guided Provisional Stenting of True Coronary Bifurcation Lesions: The DKCRUSH-VI Trial (Double Kissing Crush Versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions VI). *JACC Cardiovasc Interv.* 2015;8:536-46.

127. Omori H, Kawase Y, Hara M, Tanigaki T, Okamoto S, Hirata T, Kikuchi J, Ota H, Sobue Y, Miyake T, Kawamura I, Okubo M, Kamiya H, Tsuchiya K, Suzuki T, Pijls NHJ, Matsuo H. Feasibility and safety of jailed-pressure wire technique using durable optical fiber pressure wire for intervention of coronary bifurcation lesions. *Catheter Cardiovasc Interv.* 2019;94:E61-6.

128. Warisawa T, Cook CM, Rajkumar C, Howard JP, Seligman H, Ahmad Y, El Hajj S, Doi S, Nakajima A, Nakayama M, Goto S, Vera-Urquiza R, Sato T, Kikuta Y, Kawase Y, Nishina H, Petraco R, Al-Lamee R, Nijjer S, Sen S, Nakamura S, Lerman A, Matsuo H, Francis DP, Akashi YJ, Escaned J, Davies JE. Safety of Revascularization Deferral of Left Main Stenosis Based on Instantaneous Wave-Free Ratio Evaluation. *JACC Cardiovasc Interv.* 2020;13:1655-64.

129. Cerrato E, Echavarria-Pinto M, D'Ascenzo F, Gonzalo N, Quadri G, Quirós A, de la Torre Hernández JM, Tomassini F, Barbero U, Nombela-Franco L, Nuñez-Gil I, Biondi-Zoccai G, Macaya C, Varbella F, Escaned J. Safety of intermediate left main stenosis revascularization deferral based on fractional flow reserve and intravascular ultrasound: A systematic review and meta-regression including 908 deferred left main stenosis from 12 studies. *Int J Cardiol.* 2018;271:42-8.

130. Bech GJ, Droste H, Pijls NH, De Bruyne B, Bonnier JJ, Michels HR, Peels KH, Koolen JJ. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart.* 2001;86:547-52.

131. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation.* 2009;120:1505-12.

132. Yong AS, Daniels D, De Bruyne B, Kim HS, Ikeno F, Lyons J, Pijls NH, Fearon WF. Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv.* 2013;6:161-5.

133. Fearon WF, Yong AS, Lenders G, Toth GG, Dao C, Daniels DV, Pijls NHJ, De Bruyne B. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. *JACC Cardiovasc Interv.* 2015;8:398-403.

134. Ahmad Y, Götberg M, Cook C, Howard JP, Malik I, Mikhail G, Frame A, Petraco R, Rajkumar C, Demir O, Iglesias JF, Bhindi R, Koul S, Hadjiloizou N, Gerber R, Ramrakha P, Ruparelia N, Sutaria N, Kanaganayagam G, Ariff B, Fertleman M, Anderson J, Chukwuemeka A, Francis D, Mayet J, Serruys P, Davies J, Sen S. Coronary Hemodynamics in Patients With Severe Aortic Stenosis and Coronary Artery Disease Undergoing Transcatheter Aortic Valve Replacement: Implications for Clinical Indices of Coronary Stenosis Severity. *JACC Cardiovasc Interv.* 2018;11:2019-31.

135. Zelis JM, Tonino PAL, Pijls NHJ, De Bruyne B, Kirkeeide RL, Gould KL, Johnson NP. Coronary Microcirculation in Aortic Stenosis: Pathophysiology, Invasive Assessment, and Future Directions. *J Interv Cardiol.* 2020;2020:4603169.

136. Schuijf JD, Wijns W, Jukema JW, Atsma DE, de Roos A, Lamb HJ, Stokkel MP, Dibbets-Schneider P, Decramer I, De Bondt P, van der Wall EE, Vanhoenacker PK, Bax JJ. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. *J Am Coll Cardiol.* 2006;48:2508-14.

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

138. Mejía-Rentería H, Nombela-Franco L, Paradis JM, Lunardi M, Lee JM, Amat-Santos IJ, Veiga Fernandez G, Kalra A, Bansal EJ, de la Torre Hernandez JM, Rodés-Cabau J, Ribichini FL, Escaned J; Collaborators. Angiography-based quantitative flow ratio versus fractional flow reserve in patients with coronary artery disease and severe aortic stenosis. *EuroIntervention.* 2020;16:e285-92.

139. Kleczynski P, Dziewierz A, Rzeszutko L, Dudek D, Legutko J. Quantitative flow ratio for evaluation of borderline coronary lesions in patients with severe aortic stenosis. *Rev Esp Cardiol (Engl Ed).* 2022;75:472-8.

140. Sejr-Hansen M, Christiansen EH, Ahmad Y, Vendrik J, Westra J, Holm NR, Thim T, Seligman H, Hall K, Sen S, Terkelsen CJ, Eftekhari A. Performance of quantitative flow ratio in patients with aortic stenosis undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2022;99:68-73.

141. Gohmann RF, Pawelka K, Seitz P, Majunke N, Heiser L, Renatus K, Desch S, Lauten P, Holzhey D, Noack T, Wilde J, Kiefer P, Krieghoff C, Lücke C, Gottschling S, Ebel S, Borger MA, Thiele H, Panknin C, Horn M, Abdel-Wahab M, Gutberlet M. Combined cCTA and TAVR Planning for Ruling Out Significant CAD: Added Value of ML-Based CT-FFR. *JACC Cardiovasc Imaging.* 2022;15:476-86.

142. Michail M, Ihdayhid AR, Comella A, Thakur U, Cameron JD, McCormick LM, Gooley RP, Nicholls SJ, Mathur A, Hughes AD, Ko BS, Brown AJ. Feasibility and Validity of Computed Tomography-Derived Fractional Flow Reserve in Patients With Severe Aortic Stenosis: The CAST-FFR Study. *Circ Cardiovasc Interv.* 2021;14:e009586.

143. Allahwala UK, Brilakis ES, Byrne J, Davies JE, Ward MR, Weaver JC, Bhindi R. Applicability and Interpretation of Coronary Physiology in the Setting of a Chronic Total Occlusion. *Circ Cardiovasc Interv.* 2019;12:e007813.

144. Iqbal MB, Shah N, Khan M, Wallis W. Reduction in myocardial perfusion territory and its effect on the physiological severity of a coronary stenosis. *Circ Cardiovasc Interv.* 2010;3:89-90.

145. Kurisu S, Mitsuba N, Ishibashi K, Kato Y, Dohi Y, Nishioka K, Kihara Y. A pitfall of fractional flow reserve associated with the presence of collateral circulation. *Intern Med.* 2011;50:2811-3.

146. Matsuo H, Kawase Y. Physiological impact of CTO recanalization assessed by coronary pressure measurement: a case report. *Catheter Cardiovasc Interv.* 2013;82:E459-64.

147. Sachdeva R, Agrawal M, Flynn SE, Werner GS, Uretsky BF. Reversal of ischemia of donor artery myocardium after recanalization of a chronic total occlusion. *Catheter Cardiovasc Interv.* 2013;82:E453-8.

148. Sachdeva R, Uretsky BF. The effect of CTO recanalization on FFR of the donor artery. *Catheter Cardiovasc Interv.* 2011;77:367-9.

149. Fournier S, Toth GG, De Bruyne B, Johnson NP, Ciccarelli G, Xaplanteris P, Milkas A, Strisciuglio T, Bartunek J, Vanderheyden M, Wyffels E, Casselman F, Van Praet F, Stockman B, Degrieck I, Barbato E. Six-Year Follow-Up of Fractional Flow

Reserve-Guided Versus Angiography-Guided Coronary Artery Bypass Graft Surgery. *Circ Cardiovasc Interv.* 2018;11:e006368.

150. Toth G, De Bruyne B, Casselman F, De Vroey F, Pyxaras S, Di Serafino L, Van Praet F, Van Mieghem C, Stockman B, Wijns W, Degrieck I, Barbato E. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. *Circulation.* 2013;128:1405-11.

151. Spadaccio C, Glineur D, Barbato E, Di Franco A, Oldroyd KG, Biondi-Zoccai G, Crea F, Fremes SE, Angiolillo DJ, Gaudino M. Fractional Flow Reserve-Based Coronary Artery Bypass Surgery: Current Evidence and Future Directions. *JACC Cardiovasc Interv.* 2020;13:1086-96.

152. Lopes NH, Paulitsch Fda S, Gois AF, Pereira AC, Stolf NA, Dallan LO, Ramires JA, Hueb WA. Impact of number of vessels disease on outcome of patients with stable coronary artery disease: 5-year follow-up of the Medical, Angioplasty, and bypass Surgery study (MASS). *Eur J Cardiothorac Surg.* 2008;33:349-54.

153. Tarantini G, Barioli A, Nai Fovino L, Fraccaro C, Masiero G, Iliceto S, Napodano M. Unmasking Myocardial Bridge-Related Ischemia by Intracoronary Functional Evaluation. *Circ Cardiovasc Interv.* 2018;11:e006247.

154. Tarantini G, Migliore F, Cademartiri F, Fraccaro C, Iliceto S. Left Anterior Descending Artery Myocardial Bridging: A Clinical Approach. *J Am Coll Cardiol.* 2016;68:2887-99.

155. Waterbury TM, Tarantini G, Vogel B, Mehran R, Gersh BJ, Gulati R. Non-atherosclerotic causes of acute coronary syndromes. *Nat Rev Cardiol.* 2020;17:229-41.

Supplementary data

Supplementary Appendix 1. Guiding catheters, guide catheter extensions and microcatheters.

Supplementary Appendix 2. Applied coronary physiology in specific PCI scenarios.

Supplementary Table 1. Studies supporting the prognostic impact of functional PCI results.

Supplementary Table 2. Limitations related to image-based functional coronary analysis.

Supplementary Table 3. Supporting studies used to define focal, tandem and diffuse disease patterns.

Supplementary Table 4. Currently available and pending devices for invasive functional coronary assessment.

Supplementary Figure 1. Correction of intracoronary pressure pullback curves with dedicated software addressing fluctuations caused by the Venturi effect.

Supplementary Figure 2. Longitudinal iFR mapping coregistered with coronary angiography.

Supplementary Figure 3. Pre- and post-PCI functional test in the presence of myocardial bridge.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00194

Supplementary data

Supplementary Appendix 1. Guiding catheters, guide catheter extensions and microcatheters.

Operators should be aware that intracoronary pressure measurements can be influenced by PCI hardware. The integrity of measured FFR and NHPR in PCI procedures depends on the accuracy of the measured aortic (Pa) and intracoronary (Pd) pressures, and the persistence of pressure calibration during the procedure. This is particularly important in instances when the pressure guidewire is used as a workhorse wire during the entirety of the PCI procedure. Damping of the catheter pressure waveform may affect mean Pa pressure measurements or generate a mismatch with the Pd waveform, translating into diastolic pressure gradients. Careful attention should be paid to the choice, sizing, and position of the guide catheter. Guide catheter extensions or catheters with side holes may not provide sufficiently accurate Pa measurements. Microcatheters inserted over the pressure guidewire might also affect pressure equalisation. Intracoronary hyperaemic drugs should be avoided if the guide catheter is disengaged, to prevent the loss of drug in the aorta. Drift is often caused by technical and/or procedural issues related to the distal pressure sensor, the aortic pressure setup, or both.

Supplementary Appendix 2. Applied coronary physiology in specific PCI scenarios.

Multivessel coronary artery disease

Invasive physiology in patients with MVD leads to a reclassification of revascularisation strategy in approximately 30% of patients, and investigation of more vessels is associated with higher reclassification rates (up to 66%) [88]. In patients with MVD and truly intermediate disease, physiological PCI planning decreases the number of lesions indicated for intervention by approximately 20-30% [88], leading to fewer stents implanted and a lower number of complex lesions treated [89,90]. In the SYNTAX II study, the combined use of physiology and other contemporary PCI techniques in patients with three-vessel disease was associated with improved five-year outcomes with regard to MACE, MI, and stent thrombosis, when compared with a matched patient population from the original SYNTAX study [92]. In the FAME III trial, FFR-guided PCI was not non-inferior to CABG concerning the one-year incidence of death from any cause, myocardial infarction, stroke, or repeat revascularisation [92]. However, a differential effect according to the SYNTAX score was apparent, suggesting that revascularisation decisions based on FFR in this setting may be nuanced and that CAD complexity should also be taken into consideration. Nevertheless, regarding patients with MVD in whom surgical revascularisation is planned, several studies have demonstrated that high FFR values in the native coronary arteries prior to CABG are associated with increased rates of arterial surgical conduit occlusion within the first year [93-96].

Functional coronary angiography might play an important role in planning and guiding MVD due to its ability to evaluate all major vessels (avoiding intracoronary instrumentation multiple times) and suitability for off-line analysis of diagnostic angiograms thus potentially enabling post-hoc analysis and decision making, even in cases when invasive physiology was not performed [57,58]. Ongoing studies are exploring the value of FCA guidance to decide upon revascularisation in patients with MVD [97]. Functional evaluation of MVD based on CTCA FFR_{CT} has been tested in several studies [98,99]. The SYNTAX III REVOLUTION study reported the additive utility of FFR_{CT} in assisting heart team decisions (18.3% adjustment in

procedural planning), allowing further characterisation and simplification of disease patterns with fewer patients classified with MVD (13.5% absolute reduction in numbers of patients with MVD with the assistance of FFR_{CT}) [100].

Vessels with tandem lesions or diffusely diseased vessels

Physiologic assessment of vessels with tandem stenoses aims to identify the haemodynamic contribution of each stenosis. As each stenosis in series limits hyperaemic flow across the other [101], haemodynamic stenosis crosstalk may occur, generally causing underestimation of individual stenosis severity [53,102]. As such, interpretation of lesion-specific pressure gradients is challenging in this setting and a definitive recommendation on how to quantify severity based on each individual value cannot be made.

Assessment of tandem stenoses with FFR is typically performed using pressure wire pullbacks with intravenous administration of adenosine. Based on the obtained curve, treatment of the most haemodynamically significant lesion can be performed, followed by reassessment of the vessel to ensure any residual disease is not haemodynamically significant [103]. NHPRs such as iFR are less prone to haemodynamic crosstalk between stenoses [63], although experimental studies have shown that both NHPR and FFR are equally affected by hemodynamic interdependence in cases in which the functional significance of serial coronary stenoses is very severe [104]. The haemodynamic contribution of separate stenosis can be established from longitudinal NHPR pullback, and prediction of the haemodynamic result of intervening on one or both stenoses can be based on mathematical calculation, or on virtual stenting tools [55,105]. The same approach can be followed using longitudinal vessel analysis derived from FCA [106,107].

Patients with acute coronary syndromes

Most of the evidence addressing the safety of decision-making based on FFR stems from trials and cohorts made up of patients primarily with CCS. The physiological implications of acute coronary syndrome (ACS) may interfere with some basic assumptions made in the theoretical framework of FFR, such as fixed stenosis geometry, stable microcirculatory status, and an adequate hyperaemic response to adenosine. The enhanced adrenergic drive associated with ACS might also interfere with NHPRs. These effects disappear quickly, and their magnitude depends on the haemodynamic derangement of the patient.

The reproducibility of FFR and iFR measurements in ACS has been investigated previously [108–111]. More recent studies suggest that in patients with ST-segment elevation myocardial infarction (STEMI), FFR and NHPR values in non-culprit vessels can shift in the transition from the acute to subacute STEMI phases [108]. Due to major dynamic changes in the coronary microcirculation downstream of the infarct-related lesion, FFR or invasive physiologic indices may not be used in the acute phase to guide PCI of the culprit lesion [112]. Thus, FFR might be considered to determine the significance of the lesion in the culprit artery after acute and subacute phases [113]. Prior studies have shown that the default use of FFR to guide revascularisation of non-culprit lesions in STEMI patients reduces revascularisation rates [114-116], and carries prognostic information [117]. However, FFR-guided complete revascularisation in patients with STEMI was not superior to angiography guidance in terms of one-year MACE in the large FLOWER MI trial [116]. Fewer stents were used in the physiology guided arm. A substudy of that trial demonstrated that the avoidance of revascularisation of non-culprit lesions based on an FFR >0.80 is associated with an excess of events [118]. However, several limitations should be considered in the interpretation of the trial and sub-studies; the study included a highly selected population, the functional evaluation was performed as a

staged procedure in the majority of patients limiting the potential FFR advantage in reducing unnecessary procedures and the observed rate of adverse events was significantly lower than expected. In addition, PCI was performed in 20% of lesions with FFR>0.80, FFR values were missing in 25%, and it is unknown which lesions (treated or untreated) were responsible for events during follow-up [119]. The role of iFR-guided complete revascularisation in acute STEMI patients with MVD is being evaluated in the Instantaneous wave-free ratio guided Multivessel revascularizatiOn During percutaneous coronary intervEntion for acute myocaRdial infarctioN (iMODERN) randomised trial (NCT03298659).

On occasion, the culprit lesion in patients with non-ST-segment elevation myocardial infarction (NSTEMI) cannot be clearly identified. FFR-based deferral of revascularisation in NSTEMI with an unclear culprit lesion is associated with worse outcomes [120]. It should be noted that ACS patients derive similar advantages from FFR-guidance (compared to angio-guidance) as stable angina patients [121,122]. Further details regarding the interpretation of physiology with microcirculatory changes are available in the **Supplementary Appendix 3** below.

Bifurcation lesions and jailed side branches

There is a paucity of studies evaluating bifurcation lesions with invasive physiology or FCA. Angiographic guidance, the standard approach to guide PCI of bifurcation lesions [123], frequently overestimates side branch (SB)-lesion severity [124]. Physiologic assessment of bifurcation anatomy may further assist PCI strategy and indicate the necessity of adopting a non-provisional strategy in some instances. In the Nordic-Baltic Bifurcation Study III, systematic kissing-balloon (KB) led to higher SB FFR values (0.92 versus 0.85 with no-KB; *P*=0.011), but the difference was not clinically relevant, and attenuated over time (0.91 versus 0.87; *P*=0.19) [125].

Compared with an angiography-guided approach, an FFR-guided PCI strategy in bifurcation PCI provided similar rates of functionally adequate revascularisation and hard cardiac events with less stent implantation and was associated with numerically lower rates of TVF and stent thrombosis [126]. In the DKCRUSH-VI study, patients were randomly assigned to FFR or angiography guided SB-PCI, which led to fewer stents being placed (25.9% in the FFR arm versus 38.1% in the angiography arm, *P*=0.01), less main branch (MB) restenosis in the physiology guided group (1.2% versus 9.2%, *P*=0.01), and no difference in MACE [126]. Thus, provided that coronary flow is normal, and signs of acute ischemia are absent after main-branch stenting, current evidence suggests that a pressure-wire based provisional approach is feasible, yielding reliable clinical outcomes.

Recent work has also supported the use of jailed pressure guidewires for continuous SB monitoring [127], which seems safe and feasible, even with high-pressure MB inflations using non-compliant balloons, however large prospective studies are lacking.

Left main stenosis

Safety of deferral of revascularisation in left main stem (LMS) stenosis when FFR or iFR values are non-ischaemic has been reported [128-130]. Of note, LMS stenosis <50% was associated with positive FFR values (<0.80) in 23% of the cases, whilst the presence of a significant LMS stenosis (>50%) was rarely (6% of the cases) associated with negative FFR values (>0.80) [131].

Avoidance of technical pitfalls for wire-based interrogation in this location is particularly important. Overall, the effect of downstream stenosis on FFR assessment of LMS disease has been reported to be small, unless the downstream stenosis is proximal and very severe [132,133]. Longitudinal vessel analysis may provide a richer picture of the individual contribution of LMS and downstream stenoses. Likewise, no studies on physiological optimisation of LMS PCI are currently available. Information on the use of FCA in the LMS is scarce.

Coronary lesions in patients with aortic stenosis

The main challenge when assessing the functional relevance of coronary stenoses prior to aortic valve replacement is that the boundary of haemodynamic and microvascular conditions will shift owing to the intervention on the aortic valve [134,135]. Thus, there is uncertainty regarding whether intracoronary measurements made as part of diagnostic work-up of aortic stenosis (AS) reliably predict stenosis relevance once such boundary conditions have been modified by transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement, or whether intracoronary indices are equally affected by changes in cardiac physiology. One study has reported that both iFR and FFR [54]correlate well with ischaemia demonstrated with single-photon emission computerised tomography (SPECT) imaging [136]. Studies in patients with AS using FFR as a comparator for iFR are fraught by the fact that discordance between both indices are compatible with a similar diagnostic efficiency against non-invasive tests [137].

Although reduced adenosine-induced hyperaemia has been observed in patients with AS, FFR-guided PCI was superior to angiographic-guided PCI in retrospective trials, and it has been demonstrated that an FFR>0.85 effectively excludes the presence of ischaemia-generating stenosis. Non-hyperaemic indices such as iFR do not rely on the effect of adenosine, yet since basal coronary flow may be increased in AS, NHPR indices might overestimate stenosis severity. The use of functional angiography has been explored in these patients using FFR obtained at baseline or after TAVI as a comparator, reporting a good diagnostic yield of QFR [138-140]. One study suggests that severe AS (valve area <0.6 cm^2) is a major determinant of the discrepancy between QFR and FFR values [138]. Also, FFR_{CT} values have been shown to correlate well with invasive FFR values in patients with AS [141,142].

Lesions in vessels providing collaterals to chronically occluded arteries

As collateral donor vessels have an increased subtended myocardial bed, angiographically mild or moderate stenoses may show disproportionally low FFR/iFR values [143]. The impact of a CTO on FFR measurements in the collateral donor vessel is highly variable, as it depends on the magnitude of hyperaemic flow downstream to the occluded artery, which might be decreased if myocardial scar or microvascular dysfunction are present. Reversal of the above-described phenomenon and its impact on FFR values in the donor vessel must be taken into account if CTO PCI is planned [144-148]. In cases when myocardial viability is proven downstream to a CTO, and PCI is not planned or possible, PCI of the donor vessel with significant FFR/iFR, but only modest or moderate stenosis, might be beneficial. This scenario deserves further investigation. Of note, assessment of stenosis severity utilising functional angiography does not consider the increase in coronary flow linked to collateral blood supply, thus it may potentially predict the functional stenosis relevance of the stenosis only once CTO revascularisation has been performed.

Native vessel or surgical graft stenoses in patients with prior CABG

Assessing functional stenosis severity in patients with prior coronary artery bypass grafts (CABG) is challenging due to complex hydraulic circuits generated by patent grafts, frequent

presence of CTO lesions with collateral supply, and tortuous mammary artery grafts. As patients with patent surgical grafts have been excluded from most clinical trials pertaining to the investigation of FFR or iFR to assist in decision making, with the exception of a few retrospective studies [149], the safety of revascularisation deferral based on physiology has not been adequately established in these patients also with the exception of few retrospective studies [150]. Relevant consideration in this regard is that the natural history of surgical graft disease is different from that of native CAD [94,151]. As a matter of principle, distal coronary flow is the summed supply of the native vessel and the conduit. Currently, no studies are available on the use of functional coronary angiography in patients with prior CABG and as such, interpretation and clinical decisions must be judged according to the specificities of each individual case. Functionally diffuse disease, demonstrated with physiological pullback, might infer an increased risk of graft failure in patients undergoing CABG [50].

Vessels with myocardial bridge

The role of invasive functional testing in the evaluation of the impact of myocardial bridging on coronary flow has not yet been standardised. Given the dynamic characteristics of myocardial bridge stenosis, the traditional use of FFR requiring two mean pressures to be obtained during maximal (adenosine-induced) hyperaemia is largely inadequate for the assessment of their haemodynamic significance [152]. In this regard it has been demonstrated that the systolic pressure over-estimation in the distal segments of the vessel, with ventricularisation of the pressure wave distal to the bridge, might artificially lead to a negative FFR evaluation caused by a systolic distal pressure greater than systolic proximal pressure [88,153,154]. Hence, diastolic FFR in conjunction with dobutamine has been demonstrated as the most appropriate approach for testing the haemodynamic significance of a myocardial bridge, whereas standard mean FFR should be used with caution [155]. Recently, it has been suggested that iFR correlates more closely with respect to symptoms/non-invasive tests than FFR, at rest and during dobutamine infusion, even if in this latter setting a specific cut-off value has not yet been established [89]. Furthermore, the use of the pullback scouting analysis during iFR measurement might provide additional information on the length and the location of a myocardial bridge. This may be due to the hydrostatic effect related to the vessel distribution and also to a higher prevalence of intracoronary microvascular tracts.

Periprocedural systemic and microcirculatory changes

Transient haemodynamic changes at systemic and coronary level can influence measurements made with intracoronary pressure indices. Hyperaemic indices may be transiently blunted by microvascular embolisation of plaque components, adrenergic activation, or profound ischaemia, potentially leading to false negative readings. NHPR readings might be affected by adrenergic responses and reactive hyperaemia (for example due to contrast injection and transient flow interruption during device inflation/implantation), potentially causing false positive results.

SUPPLEMENTARY TABLE 1. Studies supporting the prognostic impact of functional PCI results.

First author	Year	Index	Study aim	No. of patients	CAD type	Comments
Bech *et al.*	1999	FFR	Prognostic value of FFR post balloon angioplasty (PTCA), 2-year follow up	60	CCS	Post-PCI FFR≥0.90 associated with lower rate of composite MACE (death, MI, repeat PTCA, recurrent ischemia) compared with FFR<0.90; 12% versus 41% respectively, *P*=0.0122
Pijls *et al.*	2002	FFR	Correlation of post-PCI FFR with MACE, 6-month follow up	750	CCS, ACS	Residual low FFR post-PCI correlates with MACE outcome at 6-months. Composite MACE outcome OR (adjusted for stent length) 7.35 (95%CI, 3.04-17.73) for FFR<0.80, 1.25 (95%CI, 0.58-2.70) for FFR>0.91
Klauss *et al.*	2005	FFR	Prognostic implications of post-PCI FFR on MACE, 6-month follow up	119	CCS	Post-PCI FFR higher in patients without events versus with MACE; FFR>0.95 (±0.05) versus FFR<0.88 (±0.08) respectively (*P*=0.001). Post-PCI FFR<0.95 (OR 6.22, 95%CI 1.79-21.62) predictor of MACE (calculated using logistical regression model)
Nam *et al.*	2011	FFR	Correlation of post-PCI FFR with MACE, 1-year follow up	80	CCS, ACS	No difference in death, MI or stent thrombosis at 1-year. Adverse MACE in low FFR group (FFR≤0.90) driven by target vessel revascularisation compared with high-FFR group (FFR>0.90) 17.5% versus 2.5% (*P*<0.01)
Ito *et al.*	2014	FFR	Impact of clinical outcomes with FFR after IVUS assisted PCI, 1.5-year follow up	97	CCS	No difference in death, MI or stent thrombosis between post-PCI FFR≤0.90 and FFR>0.90 groups. Increased rate of target vessel revascularisation in low-FFR group compared with high-FFR group; 15% versus 2% respectively (*P*=0.04)
Agarwal *et al.*	2016	FFR	Influence of post-PCI FFR on prognosis after PCI, with analyses for different disease patterns, 2.5-year follow up	574	CCS, ACS	ROC analysis suggests optimal post-PCI cut-off for death is ≤0.87, with patients with a post-PCI FFR>0.87 experiencing lower rates (13.5% versus 9%, *P*=0.03). Differences more profound in patients with multi-vessel disease
Piroth *et al.*	2017	FFR	Post-PCI FFR to predict clinical outcome from patients in FAME 1 and FAME 2, 1-year follow up (with exploratory 2-year MACE outcomes)	639	CCS	Higher rate of vessel orientated cardiac events in patients with FFR<0.88 compared with FFR>0.92 (HR 1.46, 95%CI 1.02-2.08), and target vessel revascularisation (HR 1.59, 95%CI 1.03-2.46) at 2-years
Li *et al.*	2017	FFR	Post-PCI FFR cut-off for prediction of 3-year TVF, 3-year follow up	1476	CCS	FFR≤0.88 correlates with TVF and cardiac death, compared with FFR>0.88. By 1 year, 4% versus 8% in the FFR>0.88 compared with FFR≤0.88 respectively (*P*=0.001). Cardiac death in FFR>0.88 0.2% versus FFR≤0.88 1.3% (*P*=0.017)
Kasula *et al.*	2016	FFR	Prognostic utility of post-PCI FFR in setting of ACS, 2.4-year follow up	390	CCS, ACS	In setting of ACS, post-PCI FFR associated with increased MACE (calculated with Cox regression model), optimal cut-off of FFR≤0.91 (ROC analysis). Higher observed rate of MACE in low-FFR group; 19% versus 30%, *P*=0.03
Lee *et al.*	2018	FFR	Correlations between pre- and post-PCI FFR and long-term prognostic implications, 2-year follow up	621	CCS	No differences in cardiac death between FFR<0.84 and FFR≥0.84. Failure of resolution of flow limiting disease associated with TVF between groups at 2 years; (driven by revascularisation) 11.5% versus 0% in low %FFR increase compared with high %FFR increase respectively (*P*=0.002)

Azzalini *et al.*	2019	FFR	Effect of routine post-PCI FFR on decision making and MACE, 1-year follow up	65	CCS, ACS	FFR≥0.90 associated with significant reduction in 1-year composite MACE (9.1% versus 31.6%, *P*=0.047). No significant difference observed in individual hard endpoints of cardiac death, MI or TVF
Fournier *et al.*	2019	FFR	If an improvement in FFR (ΔFFR) bears prognostic benefit, 2-year follow up	639	CCS	No difference in death or myocardial infarction by ΔFFR. Highest rate of TVR observed in patients with lowest tertile of ΔFFR (adjusted *P*=0.002)
Hwang *et al.*	2019	FFR	Prognostic relevance of post-PCI FFR and identify an optimal cut-off value depending on target vessel (LAD or non-LAD), 2-year follow up	835	CCS, ACS	Different post-PCI FFR between LAD and non-LAD vessels (*P*<0.001). Optimum LAD post-PCI FFR cut-off to predict TVF is 0.82, and 0.88 in non-LAD. TVF higher in patients with lower post-PCI FFR in LAD (10.9% versus 2.5%, P<0.001) and non-LAD (8% versus 1.9%, *P*<0.004). No difference in cardiac death or MI.
Jensen *et al.*	2007	Pd/Pa	Predictive capacity of FFR, Pd/Pa and pullback to determine risks of in-stent restenosis, 9-month follow up	98	CCS	Distal residual abnormal Pd/Pa ratio post-PCI predictor of in-stent restenosis; OR 4.58 (95%CI 1.11-18.84) *P*=0.034 (multivariate analysis).
Hakeem *et al.*	2019	Pd/Pa, FFR	Long-term prognostic value of post-PCI Pa/Pd and FFR, 2.5-year follow up	574	CCS, ACS	Post-PCI Pd/Pa>0.96 associated with reduced composite MACE, with additive benefit beyond post-PCI FFR alone (calculated using adjusted Cox regression analysis)
Shin *et al.*	2019	Pd/Pa, FFR	Evaluate prognostic implications of post-PCI Pd/Pa compared with post-PCI FFR, 2-year follow up	588	CCS, ACS	26.3% discordance between post-PCI Pd/Pa and post-PCI FFR. Post-PCI Pd/Pa≤0.92 with FFR>0.80 associated with 3.5% TVF and FFR≤0.80 10.4%, *P*=0.045.
Biscaglia *et al.*	2019	QFR	Whether post-PCI QFR correlates with adverse events in patients undergoing complete revascularisation with PCI, 1.7-year follow up (median)	602	CCS, ACS	Lower QFR post-PCI correlates with adverse patient outcomes. Post-PCI QFR≤0.89 associated with increased VOCE (cardiovascular death, vessel-related MI, TVR) with HR 2.91, 95%CI 1.63-5.19 (calculated using adjusted Cox regression analysis).
Kogame *et al.*	2019	QFR	Assess post-PCI QFR in 3-vessel disease on clinical outcomes	440	CCS, ACS	Higher post-PCI QFR associated with more favourable clinical outcomes in de novo 3-vessel CAD, with optimal cutoff of 0.91 predicting 2-year VOCE.
Lee *et al.*	2022	QFR	Assessment of the clinical value of residual QFR (rQFR) in the prediction of residual ischaemia after virtual PCI	274	CCS, ACS	Estimated rQFR from pre-PCI diagnostic coronary angiography and virtual PCI over-estimated functional benefit of PCI with good prediction of suboptimal functional results and long-term VOCE.
Zhang *et al.*	2022	QFR	Retrospective analysis of PANDA III cohort, correlation between pre-PCI residual QFR and actual post-PCI QFR, 2-year outcomes	2348	CCS, ACS	Actual post-PCI and residual (simulated) post-PCI QFR correlate. Optimal simulated residual QFR>0.92, with 2-year VOCE higher in suboptimal residual QFR≤0.92, 2% versus 10.7% respectively, HR 5.58 (95%CI 3.55-8.79), driven by vessel-related cardiac death (HR 4.38, 95%CI 2-9.6, *P*<0.0002), MI (HR 4.30, 95%CI 1.75-10.6, *P*<0.001) and TVF.
Patel *et al.*	2020	iFR	Prospective assessment of post-PCI iFR and clinical outcomes quantified by MACE, 1-year outcomes	500	CCS, ACS	Post-PCI iFR correlates with composite MACE at 1-year. Post-PCI iFR≥0.95 associated with improved symptoms of angina and MACE (1.8% versus 5.7%, *P*=0.04)

SUPPLEMENTARY TABLE 2. Limitations related to image-based functional coronary analysis.	
Invasive angiography derived	
QFR	• Reliant on adequate projections with good vessel opacification • Not applicable in ostial and left main lesions, major bifurcations, myocardial bridges • Single vessel analysis • Nitrates required as angiographically derived • Need for proprietary software • Manual vessel contouring may be needed
vFFR	• Similar limitations to QFR • High quality diagnostic angiography required with orthogonal views • Limited evidence to assess diagnostic accuracy or utility currently
caFFR	• Similar limitations to QFR • Relatively high-powered hardware required to compute simultaneous coronary arteries
FFR_{angio}	• Needs three angiographic projections
$IVUS_{FFR}$	• Requires vessel instrumentation • Need to change to guide catheter to facilitate imaging • Limited data on usage
OCT_{FFR}	• Similar to $IVUS_{FFR}$
Non-invasive angiography derived	
FFR_{CT}	• Analysis performed out of the hospital • Relatively time consuming to obtain results • Latest generation CT scanners required acquire images and avoid step artifact • Patients often require beta-blockade to facilitate scan • Awaiting prognostic validation

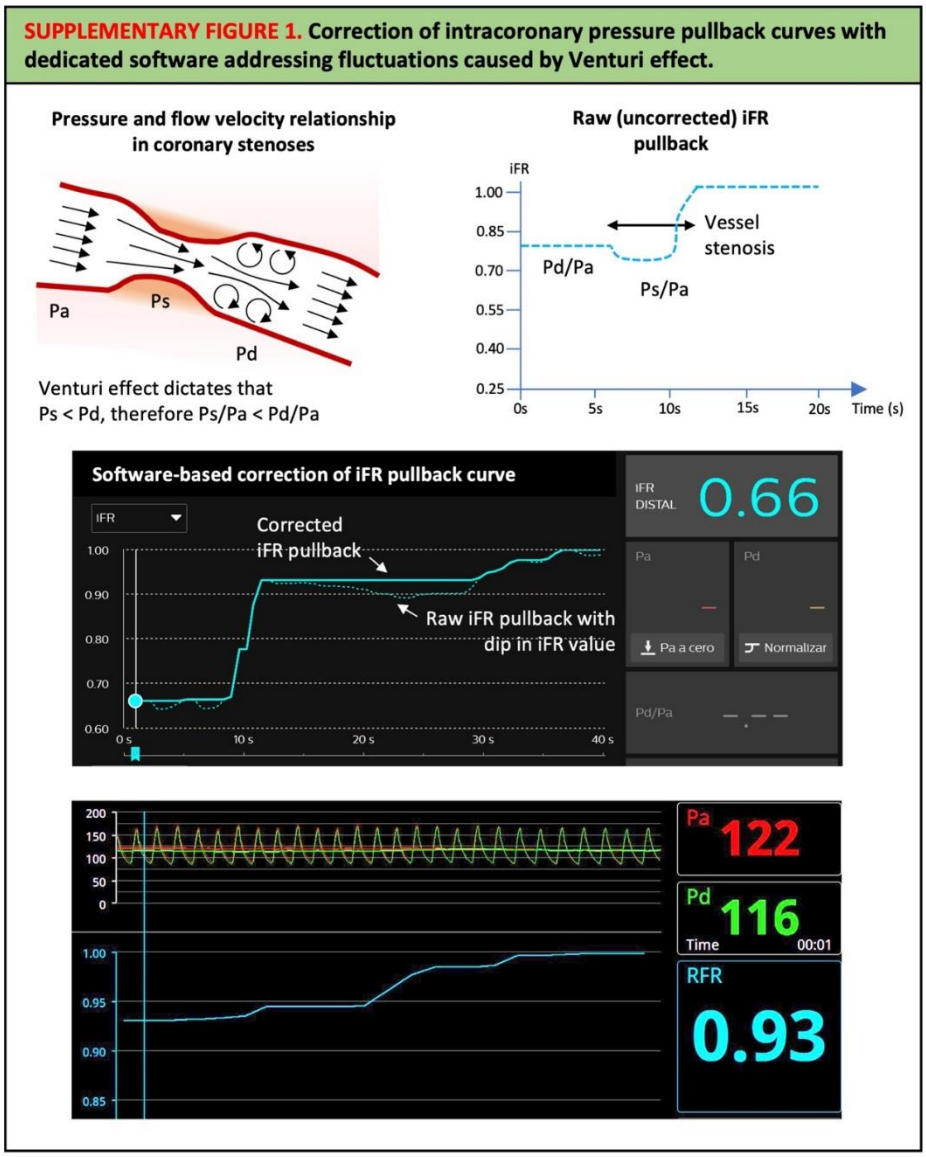
SUPPLEMENTARY TABLE 3. Supporting studies used to define focal, tandem and diffuse disease patterns.

	Study title	First author	Year	Ref no.	Study type	Technique	No. of patients	Focal disease	Diffuse disease
1	Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis	Collet C *et al.*	2019	45	Prospective, multicentre	FFR, PPG_{index}	79	Continuous metric, values approaching 1.0 represent focal haemodynamically focal CAD, whereas values close to 0 diffuse CAD.	
2	Differential improvement in angina and health-related quality of life after PCI in focal and diffuse coronary artery disease	Collet C *et al.*	2022	62	Sub-study of TARGET-FFR	FFR, PPG_{index}	103	Focal coronary artery disease (CAD) was defined as a pullback pressure gradient (PPG) value ≥0.66 and diffuse CAD as PPG <0.66. Increased residual angina post-PCI with low PPG (diffuse disease).	
3	Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR)	Collison D *et al.*	2021	2	Prospective, single centre, randomised	FFR	260	Change ≥0.05 FFR units.	Anything else was considered diffuse.
4	Single center experience in the treatment of hemodynamically significant diffuse coronary artery disease of the left anterior descending	van Beek K *et al.*	2022	51	Retrospective single centre	FFR	59	1 or 2 abrupt changes with ≥0.10 FFR units.	Anything else was considered diffuse.
5	Automated algorithm using pre-intervention fractional flow reserve pullback curve to predict post-intervention physiological results	Lee SH *et al.*	2020	49	Prospective, multicentre	dFFR(t)/dt	234	Major FFR gradient dFFR(t)/dt ≥0.035/second.	Signal noise in the absence of lesion dFFR(t)/dt <0.015/second. Minor FFR gradient dFFR(t)/dt 0.015-0.034/second.
6	Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention (DEFINE PCI)	Jeremias A *et al.*	2019	3	Prospective, multicentre	iFR	494	Change ≥0.03 iFR units within 15mm.	Change ≥0.03 iFR units >15mm.
7	Inter-observer differences in interpretation of coronary pressure-wire pullback data by non-expert interventional cardiologists	Warisawa T *et al.*	2020	54	Retrospective multicentre	iFR	545	Change ≥0.03 iFR units within 15mm.	Change ≥0.03 iFR units >15mm.
8	Utility of angiography–physiology co-registration maps during percutaneous coronary intervention in clinical practice	Matsuo A *et al.*	2021	55	Prospective, single centre	iFR	70	Change ≥0.03 iFR units within 20mm.	Change ≥0.03 iFR units with a length ≥20mm.
9	Impact of physiologically diffuse versus focal pattern of coronary disease on quantitative flow reserve diagnostic accuracy	Scarsini R *et al.*	2021	56	Retrospective single centre	iFR	194	Change ≥0.03 iFR units within 15mm.	Progressive and constant iFR change.
						QFR	194	Abrupt change in QFR of ≥0.05 units in length <10 mm.	Progressive and constant QFR change.

10	Clinical implication of QFR in patients with ST-segment elevation myocardial infarction after drug-eluting stent implantation	Tang J *et al.*	2021	57	Retrospective Multicentre	QFR	186	Abrupt change in QFR of ≥0.03 units in length <20 mm.	Abrupt change in QFR of ≥0.03 units in length ≥20 mm.
11	Angio-Based Fractional Flow Reserve, Functional Pattern of Coronary Artery Disease, and Prediction of Percutaneous Coronary Intervention Result: a Proof-of-Concept Study	Biscaglia S *et al.*	2021	58	Retrospective Multicentre	QFR	111	Abrupt change in QFR of ≥0.05 units in length <10 mm.	Progressive and constant QFR change without significant focal change in QFR units.
12	Physiological Distribution and Local Severity of Coronary Artery Disease and Outcomes After Percutaneous Coronary Intervention	Shin D *et al.*	2021	59	Retrospective Multicentre	QFR	341	The median value of QFR PPG index ≥0.78 used to define focal disease, and <0.78 to define diffuse disease. Major gradient determined to be dQFR/ds ≥0.025/mm.	
13	Anatomical Assessment vs. Pullback resting full-cycle ratio (RFR) Measurement for Evaluation of Focal and Diffuse coronary Disease: Rationale and Design of the "READY Register"	Koszegi Z *et al.*	2021	60	Retrospective ?centre	RFR	-	Change in RFR of >0.05 units in length <25 mm.	Change in RFR of >0.05 units in length >25 mm.
14	Comparisons of Non-hyperaemic pressure Ratios	Omori H *et al.*	2020	61	Prospective, multicentre, randomized	iFR, RFR, dPR	140	Change of index units ≥0.03 within 15 mm length.	Anything else was considered diffuse.

SUPPLEMENTARY TABLE 4. Currently available and pending devices for invasive functional coronary assessment.				
Device name	**Manufacturer**	**FDA approval**	**Available**	**Functional index**
ComboWire™	Volcano	2004	Yes	FFR, CFR, HSR, HMR
Volcano Verrata™	Philips Volcano	2014	Yes	FFR, iFR
COMET™	Boston Scientific	2015	Yes	FFR, DFR
Volcano Verrata™ PLUS	Philips Volcano	2016	Yes	FFR, iFR
PressureWire™ X	Abbott	2016	Yes	FFR, RFR, IMR, CFR
COMET™ II	Boston Scientific	2019	Yes	FFR, DFR
Pressure Guidewire System Model 100™	Zurich Medical	2019	Yes	FFR
OmniWire	Philips Volcano	2019	Yes	FFR, iFR
Navvus® Rapid Exchange FFR microcatheter	Acist Medical Systems	2019	Yes	FFR
OptoWire 3	OpSens Medical	2020	Yes	FFR, dPR
Wirecath®	Cavis Technologies	-	Undergoing clinical trial, NCT04776577	FFR
TruePhysio™ pressure microcatheter	Insight Lifetech	-	Undergoing clinical trial, NCT05437900, NCT05417763	FFR

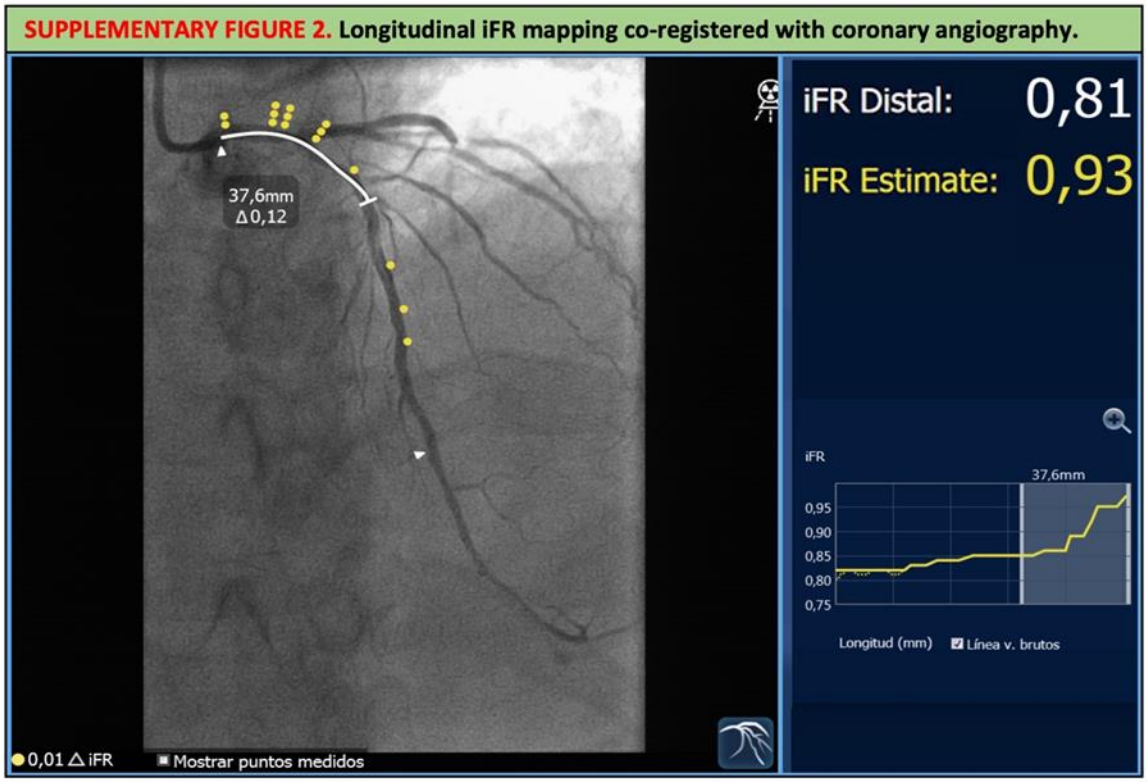
Previous versions of these devices have that are no longer available have not been included.



Supplementary Figure 1.

Correction of intracoronary pressure pullback curves with dedicated software addressing fluctuations caused by the Venturi effect.

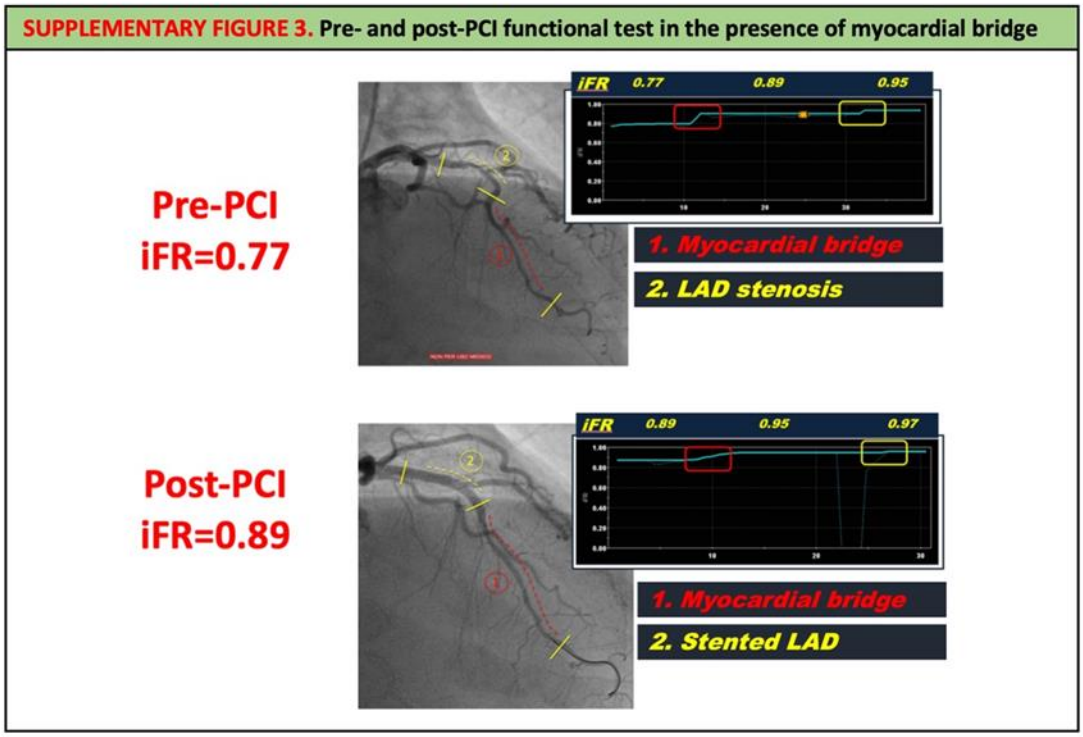
The pressure pullback curve obtained with intracoronary guidewires over a vessel with stenoses typically show ups and downs caused by pressure – flow velocity relationships (Venturi effect). Over the pullback, intraluminal pressure within the reference segment distal to a stenosis (Pd) will decrease when reaching an intra-stenotic location with high flow velocity (Ps). This translates into a dip of translesional pressure ratios like FFR, iFR and others. The figure shows how software-based correction of the pullback curve omits such dip in iFR values, facilitating interpretation of the longitudinal vessel analysis. See also an example of software-based correction of RFR pullback curve below.



Supplementary Figure 2.

Longitudinal iFR mapping coregistered with coronary angiography.

Co-registration of iFR with angiography, showing flow limiting disease in the left main stem and left anterior descending artery with a physiologically significant iFR of 0.81, and predicted post-PCI iFR of 0.93 after successful treatment of selected segment.



Supplementary Figure 3.

Pre- and post-PCI functional test in the presence of myocardial bridge.

iFR analysis of a proximal LAD stenosis with a distal myocardial bridge. Longitudinal vessel analysis allowed outlining the separate contribution of a coronary stenosis and a subtended myocardial bridge to abnormal coronary haemodynamics. Post-PCI physiology confirmed the residual flow-limiting effect of the myocardial bridge after stenting of the proximal atherosclerotic lesion.