State-of-the-Art
by EuroIntervention

Functional coronary angiography for the assessment of the epicardial vessels and the microcirculation

Daniel Faria[1,2], MD; Breda Hennessey[1], MD; Asad Shabbir[1], MD; Hernán Mejía-Rentería[1], MD, PhD; Lin Wang[1], MD; Joo Myung Lee[3], MD, PhD; Hitoshi Matsuo[4], MD, PhD; Simone Biscaglia[5], MD; Bon-Kwon Koo[6], MD, PhD; Bo Xu[7], MD, PhD; Sergio Bravo Baptista[2,8], MD, PhD; Nieves Gonzalo[1], MD, PhD; Javier Escaned[1]*, MD, PhD

1. Hospital Clínico San Carlos IdISSC, Complutense University of Madrid, Madrid, Spain; 2. Interventional Cardiology Unit, Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal; 3. Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 4. Department of Cardiovascular Medicine, Gifu Heart Center, Gifu, Japan; 5. Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona, Italy; 6. Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea and Institute on Aging, Seoul National University, Seoul, Republic of Korea; 7. Department of Cardiology, Fuwai Hospital, National Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; 8. University Clinic of Cardiology, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00969

KEYWORDS

- non-invasive imaging
- innovation
- other technique
- QCA

Abstract

Over the last decade, steady progress has been made in the ability to assess coronary stenosis relevance by merging computerised analyses of angiograms with fluid dynamic modelling. The new field of functional coronary angiography (FCA) has attracted the attention of both clinical and interventional cardiologists as it anticipates a new era of facilitated physiological assessment of coronary artery disease, without the need for intracoronary instrumentation or vasodilator drug administration, and an increased adoption of ischaemia-driven revascularisation. This state-of-the-art review performs a deep dive into the foundations and rationale behind FCA indices derived from either invasive or computed angiograms. We discuss the currently available FCA systems, the evidence supporting their use, and the specific clinical scenarios in which FCA might facilitate patient management. Finally, the rapidly growing application of FCA to the diagnosis of coronary microvascular dysfunction is discussed. Overall, we aim to provide a state-of-the-art review not only to digest the achievements made so far in FCA, but also to enable the reader to follow the many publications and developments in this field that will likely take place in years to come.

**Corresponding author: Hospital Clínico San Carlos, Calle del Prof Martín Lagos, 28040 Madrid, Spain. E-mail: escaned@secardiologia.es*

SUBMITTED ON 04/11/2022 - REVISION RECEIVED ON 1st 08/02/2023 / 2nd 06/03/2023 - ACCEPTED ON 18/03/2023

Abbreviations

3D	three-dimensional
3D-QCA	3D quantitative coronary angiography
CAAS vFFR	vessel fractional flow reserve
CABG	coronary artery bypass grafting
CAD	coronary artery disease
caFRR	computational pressure-flow dynamics derived fractional flow reserve
CFD	computational fluid dynamics
CCTA	coronary computed tomography angiography
FCA	functional coronary angiography
FFR	fractional flow reserve
FFR_{CT}	coronary computed tomography-derived fractional flow reserve
FFR_{angio}	angiography-derived FFR
ICA	invasive coronary angiography
iFR	instantaneous free-wave ratio
ISR	in-stent restenosis
IVUS	intravascular ultrasound
MACE	major adverse cardiovascular events
MPP	myocardial perfusion pressure
MVD	microvascular disease
NHPR	non-hyperaemic pressure ratio
NPV	negative predictive value
OCT	optical coherence tomography
P_a	aortic pressure
PCI	percutaneous coronary intervention
P_d	distal pressure
PPV	positive predictive value
P_v	central venous pressure
QFR	quantitative flow ratio
SYNTAX	Synergy Between Percutaneous Coronary Intervention With Taxus And Cardiac Surgery
TIMI	Thrombolysis in Myocardial Infarction
vFAI	virtual functional assessment index
vFFR	virtual fractional flow reserve

Introduction

More than half a century after revolutionising clinical practice, coronary angiography remains the cornerstone for the evaluation and treatment of coronary artery disease (CAD). Notwithstanding its relevance as a diagnostic tool, coronary angiography is fraught with major limitations as a method to ascertain the functional relevance of coronary stenoses, particularly in lesions of intermediate angiographic severity[1].

Attempts to bridge the gap between the angiographic morphology and functional relevance of coronary stenoses were led in the 1970s by Lance Gould and other investigators. These authors used stenosis geometry data, objectively assessed with the then newly developed quantitative coronary angiography (QCA) methods, and incorporated these data into fluid dynamic equations used to predict translesional pressure loss over a range of flow values and resistances, ultimately founding the basis for the development of coronary physiology assessment[2].

However, the transition of this angiographic tool from the realm of research into clinical practice was hindered, on the one hand, by the lack of correlation with ischaemic and clinical outcomes[3] and, on the other, by the development of intracoronary physiology, particularly fractional flow reserve (FFR), which initiated the era of catheter guidewires for evaluation of ischaemia[4].

The additive benefit of FFR in clinical decision-making regarding revascularisation in patients with coronary stenoses has been clearly demonstrated in numerous dedicated randomised clinical trials[5,6,7]. Nevertheless, although this ultimately led to FFR being incorporated into international clinical practice guidelines over the following decade, coronary physiological interrogation remained largely underused in cardiac catheterisation laboratories[8].

Explanations for the low penetrance in clinical practice are twofold: inertial (i.e., the operator's apprehension about angiographic data and/or mistrust in coronary physiology) and technical (perceived complexity of adenosine infusion, procedural time and costs)[9]. The realisation that the adoption of invasive physiology was somewhat hampered by the requirement for vasodilatory drugs and coronary instrumentation has sparked two new developments in the last decade: 1) the introduction of non-hyperaemic indices, greatly simplifying the procedure by not mandating pharmacological hyperaemia induction; and, more recently, 2) the development of functional angiographic systems that can provide physiological information without either pressure guidewires or hyperaemic drugs **(Figure 1)**.

In this review, we revisit the physiological principles and technical aspects of the different modalities of wireless functional coronary angiography (FCA), focusing on invasive coronary angiography (ICA) and coronary computed tomography angiography (CCTA). We will also evaluate the existing evidence and discuss the clinical applicability of wireless FCA in specific clinical scenarios. Finally, we provide our vision for future prospects and how FCA will change current clinical practice.

Key principles of functional coronary imaging

BASIC CONCEPTS AND CAVEATS OF INVASIVE CORONARY PHYSIOLOGY

To fully understand the developments made in FCA, it is important to revisit some key concepts of coronary physiology.

FFR is the most widely used pressure-derived index of functional coronary stenosis severity; it expresses the percentage reduction in myocardial blood supply attributable to the interrogated stenosis. A translesional pressure ratio of 0.75 obtained during maximal hyperaemia indicates an impairment in myocardial blood supply of 25%, compared to the supply in the hypothetical absence of that same stenosis.

The cornerstone of FFR, which enables the use of pressure as a surrogate of flow, is the linearity of the pressure/flow relationship during hyperaemia. Under hyperaemic conditions, the fall in coronary pressure caused by a stenosis is proportional to the fall in maximal blood supply to the myocardium.

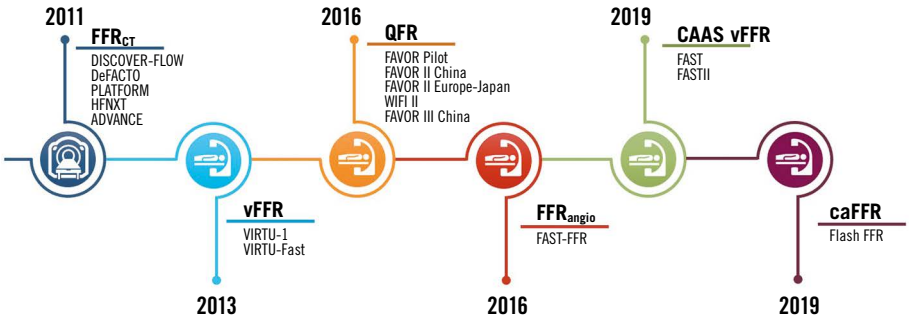


Figure 1. *Timeline of the evolution of non-invasive coronary physiology and the respective landmark studies. CAAS vFFR: vessel fractional flow reserve; caFFR: computational pressure-flow dynamics derived FFR; FFR: fractional flow reserve; FFR_{angio}: angiography-derived FFR; FFR_{CT}: computed tomography-derived FFR; QFR: quantitative flow ratio; vFFR: virtual fractional flow reserve*

In the epicardial coronary arteries, flow is driven by the myocardial perfusion pressure (MPP) and is equivalent to the difference between the aortic pressure (P_a) and the central venous pressure (P_v)[10]. Whenever there is an epicardial stenosis, the MPP is equivalent to the difference between the poststenotic distal pressure (P_d) and the P_v . Therefore, FFR can be estimated from pressure measurements as follows: $P_d - P_v/P_a - P_v$ or $\approx P_d/P_a$, as the effect of central venous pressure is usually negligible. Uniquely, FFR has a constant value of 1.0 in every normal coronary artery and is not influenced by variations in blood pressure, myocardial contractility, or heart rate[10].

The pressure loss across a coronary stenosis (ΔP) is dependent upon the severity of the narrowing and also on the magnitude of flow (Q) that goes through it[11]. Pressure loss across a stenosis is due to: 1) viscous friction (f) and 2) flow separation due to acceleration through the stenosis (t), which leads to blood swirling and reverse currents. The expression $\Delta P = fQ^2 + tQ^2$ explains why there is a quadratic increment in pressure loss through a stenosis with an increase in coronary flow[12].

ASSESSING FUNCTIONAL STENOSIS RELEVANCE FROM CORONARY ANGIOGRAMS

To derive patient-specific estimations of blood flow and pressure in coronary arteries from coronary angiography, three fundamental steps must be followed: 1) selection of a fluid equation solver (computational fluid dynamics or simplified fluid dynamics equations), 2) reconstruction of a three-dimensional (3D) model of the coronary arteries, and 3) definition of boundary conditions **(Figure 2)**[13].

SOLVING FLUID EQUATIONS

Most image-based FFR techniques utilise computational fluid dynamics (CFD), a generic term used for all the mathematical engineering that is required to describe and analyse fluid flow. Through computational processing, the governing equations of fluid dynamics, i.e., Navier-Stokes equations, can be solved for the unknown coronary pressure and blood velocity that vary in position and time[14]. Blood density and viscosity are usually assumed when solving these equations, as blood, despite its complex rheological properties, can be managed as a Newtonian fluid with constant viscosity, particularly in large arteries[15].

In order to reduce the computational power and time required to complete a full CFD analysis, and thus make it feasible for online vessel assessment in the catheterisation laboratory, a simplified version of CFD, using simpler mathematical coefficients, is frequently used in commercially available systems[16]. These approaches benefit from using actual blood flow velocity by using TIMI (Thrombolysis in Myocardial Infarction) frame count and aortic pressure values, which are directly accessible for online study, instead of standardised values[17].

CORONARY GEOMETRIC MODELS

A 3D reconstruction of the vessel lumen, which is used by most FCA systems, can be extracted from computed tomography (CT) images or from orthogonal invasive angiographic projections. Most systems integrate into the calculated metadata embedded in the DICOM image format, containing information on relevant parameters such as table/image intensifier height and frame rates. The obtained geometric model can then be divided into smaller entities, i.e., finite elements, forming the blocks of a virtual mesh, over which the equational unknowns are calculated[14]. It is important to keep in mind that friction losses causing flow limitation may be due to microhaemorrheological disturbances caused by diffuse disease. Capturing the haemodynamic effect of minute but extensive vessel irregularities with imaging techniques relies on a very accurate reconstruction of the arterial lumen, which may not be possible because of limits in angiographic resolution.

BOUNDARY FLOW CONDITIONS

The haemodynamics of epicardial vessels are strongly influenced by phenomena such as the cardiac cycle, intrinsic microvascular resistance, and extravascular compression. Boundary conditions are the mathematical limits (inlet and outlet) upon which haemodynamic models are applied to the entrance and exit of the reconstructed vessel segments, to simulate the influence of such factors[15]. Although the inlet boundary is usually easily obtainable (through directly measuring aortic pressures or by proving

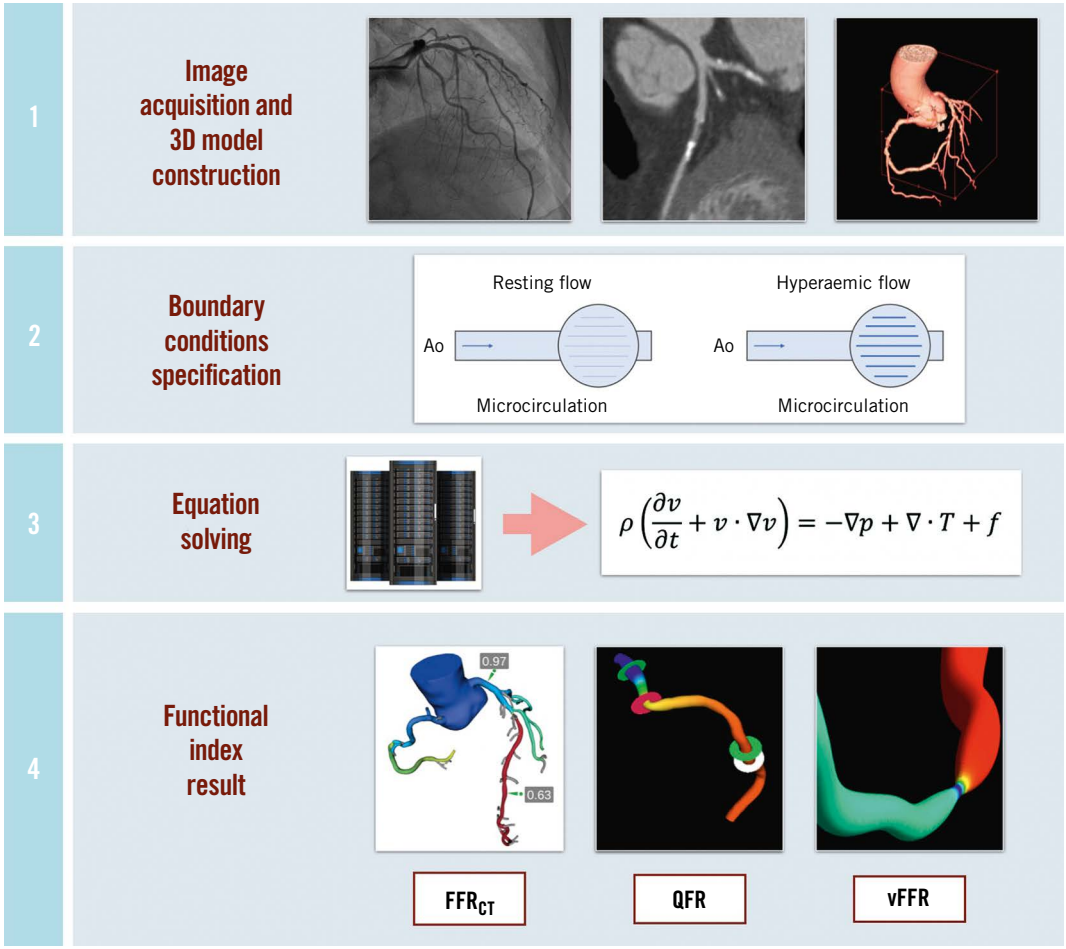


Figure 2. *Steps for obtaining a functional coronary imaging index. 1) Standard invasive coronary angiography or computed tomography angiography data are obtained. A quantitative 3-dimensional anatomical model is generated. 2) A physiological model of the coronary microcirculation is obtained from patient-specific data following specific principles: the resting coronary flow is proportional to the subtended myocardial mass; the microvascular resistance is inversely correlated with vessel size; the microvascular resistance is reduced during maximal hyperaemia. 3) Physical laws of fluid dynamics are applied to compute coronary blood flow, solving the Navier-Stokes equations or simplified equations. 4) The chosen functional index is calculated throughout the coronary artery. FFR$_{CT}$: computed tomography-derived fractional flow reserve; QFR: quantitative flow ratio; vFFR: virtual fractional flow reserve.*

a population average model) the same is not true for the outlet boundary, which includes terms such as microcirculatory resistance and central venous pressure. Preset conditions are frequently assumed, although, as previously discussed, the actual values of aortic pressure and flow velocity can be incorporated into the calculations to provide a more realistic estimate of boundary conditions[15].

Functional analysis of invasive coronary angiograms

By not requiring invasive measurements, pharmacological hyperaemia induction, or incurring additional costs, angiography-based techniques provide a promising solution for performing either online or offline functional evaluations of coronary stenosis in the catheterisation laboratory **(Central illustration)**. A number of different software approaches that estimate FFR from angiography have been developed with reported validation studies **(Supplementary Table 1, Table 1)**. Of note, only four of them have supporting evidence derived from prospective multicentric studies.

QUANTITATIVE FLOW RATIO (QFR)

QFR (QAngio XA 3D; Medis Medical Imaging Systems, and AngioPlus; Pulse Medical Imaging Technology) is an FFR computational method derived from 3D-QCA based on two orthogonal angiographic projections of the coronary vessel, usually separated by at least 25 degrees[17]. Once the vessel is reconstructed into a 3D model, the haemodynamic pressure drops are calculated at consecutive segments according to derived friction and turbulence pressure coefficients, and subsequently integrated into the whole analysed segment **(Figure 3)**. According to the type of flow value used for its calculation, QFR can be expressed in three different modes: 1) fixed-flow (fQFR) that uses a fixed value of population-averaged hyperaemic flow of 0.35 m/s, 2) contrast-flow (cQFR)

EuroIntervention

CENTRAL **ILLUSTRATION** Current commercially available functional indices based on invasive coronary angiography.

The columns from left to right show user interface display after index calculation; number of angiographic projections needed; need for mean aortic pressure input; capacity to provide microcirculatory resistance evaluation; simultaneous side branch physiological interrogation; and the quality and quantity of published evidence. Colour code: green=advantage; yellow: amenable; red=disadvantage. CAAS vFFR: vessel fractional flow reserve; caFFR: computational pressure-flow dynamics derived FFR; FFR: fractional flow reserve; FFR_{angio}: angiography-derived FFR; QFR: quantitative flow ratio; µQFR: Murray law-based QFR

that estimates flow velocity based on TIMI frame count, or 3) adenosine-flow (aQFR) that measures flow from hyperaemic coronary angiograms obtained during adenosine administration[18]. Most studies validating QFR utilised the cQFR method, which offers the best balance between diagnostic yield and technical ease of use[17].

Prior studies have shown a good correlation between QFR and FFR values in angiographically intermediate lesions, with a good diagnostic accuracy of QFR for assessing functional stenosis severity[19-39] **(Table 1)**. Two prospective, multicentre studies (Angiographic quantitative flow ratio-guided coronary intervention - FAVOR II China and FAVOR II Europe-Japan) have reported good diagnostic accuracies of QFR both at patient and vessel levels[16] and better sensitivity and specificity than 2D-QCA in assessing functional stenosis relevance[18]. In a patient-level meta-analysis of 16 high-quality studies comparing FFR and QFR, QFR demonstrated good positive and excellent negative predictive values in ascertaining the functional relevance of coronary stenoses with a cut-off FFR of ≤0.80[40].

Of note, QFR is the only functional angiographic system in which the clinical value has been tested in the setting of a randomised

Table 1. Technical aspects of the different FCA indices and respective validation studies.

	Technique	Imaging modality	Inlet	Outlet	Flow	Pattern	Equation solution	Other	Studies (Ref)	Year	Design	Vessels	Sensitivity	Specificity	PPV	NPV	Corr. with invasive FFR
COMMERCIALLY AVAILABLE	QFR	3D-QCA	Patient-averaged aortic pressure	Free	Fixed hyperaemic	Steady	Simplified equation	fQFR	FAVOR Pilot[17]	2016	Prospective offline	84	0.67	0.86	0.69	0.85	0.69
					TIMI frame count	Steady	Simplified equation	cQFR					0.74	0.91	0.80	0.88	0.77
					Adenosine-induced	Steady	Simplified equation	aQFR (hyperaemia)					0.78	0.91	0.81	0.90	0.72
			-	Free	TIMI frame count	Steady	Simplified equation	cQFR	FAVOR II China[16]	2017	Prospective online	328	0.95	0.92	0.86	0.97	0.86
									Yazaki et al[19]	2017	Retrospective offline	151	0.89	0.89	0.77	0.95	0.80
									FAVOR II Europe-Japan[18]	2018	Prospective online	317	0.87	0.87	0.76	0.93	0.83
									FAVOR III China[41]	2021	RCT	3,825	Lower events at 1-year follow-up: difference –3.0% [95% CI: –4.7 to –1.4]; hazard ratio 0.65 [95% CI: 0.51 to 0.83]				
									WIFI II[39]	2018	Prospective offline	240	0.77	0.86	0.75	0.87	0.70
				Free	Fixed hyperaemic	Steady	Simplified equation	fQFR	Ties et al[21]	2018	Retrospective offline	151	0.57	0.93	0.67	0.89	0.71
					TIMI frame count	Steady	Simplified equation	cQFR					0.67	0.96	0.82	0.92	0.70
				Free	Fixed hyperaemic	Steady	Simplified equation	fQFR	Koltowski et al[20]	2018	Retrospective offline	306	0.90	0.63	0.64	0.89	0.72
					TIMI frame count	Steady	Simplified equation	vQFR (vessel cQFR)					0.91	0.70	0.69	0.91	0.78
								iQFR (lesion cQFR)					0.49	0.97	0.91	0.72	0.70
								iQFR (index cQFR)					0.84	0.87	0.82	0.88	0.85
				Free	TIMI frame count	Steady	Simplified equation	cQFR	Mejía-Rentería et al[22]	2018	Retrospective offline	300	0.89	0.87	0.85	0.91	0.83
				Free	Fixed hyperaemic	Steady	Simplified equation	fQFR	Emori et al[25*]	2018	Retrospective offline	75	0.94	0.62	0.69	0.92	0.84
					TIMI frame count	Steady	Simplified equation	cQFR					0.92	0.82	0.83	0.91	0.88
				Free	TIMI frame count	Steady	Simplified equation	cQFR	Emori et al[23]	2018	Retrospective offline	100	0.97	0.87	0.94	0.93	0.89
									Spitaleri et al[36**]	2018	Prospective offline	45	0.88	0.97	0.94	0.94	0.90
									Smit et al[29***]	2018	Retrospective offline	82	0.71	0.95	0.85	0.89	0.74

Table 1. Technical aspects of the different FCA indices and respective validation studies (cont'd).

	Technique	Imaging modality	Inlet	Outlet	Flow	Pattern	Equation solution	Other	Studies (Ref)	Year	Design	Vessels	Sensitivity	Specificity	PPV	NPV	Corr. with invasive FFR
COMMERCIALLY AVAILABLE	QFR	3D-QCA	-	Free	TIMI frame count	Steady	Simplified equation	cQFR	Smit et al[24]	2019	Retrospective offline	334	0.70	0.92	0.77	0.89	0.81
									Stähli et al[26]	2019	Prospective offline	516	0.75	0.98	0.89	0.94	0.82
									Hwang et al[27]	2019	Retrospective offline	358	0.92	0.90	0.86	0.95	0.86
									Tanigaki et al[37]	2019	Retrospective offline	233	0.90	0.82	0.81	0.90	0.78
									Lauri et al[31]	2019	Retrospective offline	159	0.86	0.80	0.78	0.87	0.75
									Asano et al[35]	2019	Retrospective offline	310	0.74	0.74	0.86	0.57	-
									Rubimura et al[30]****	2019	Retrospective offline	93	-	-	-	-	0.79
COMMERCIALLY AVAILABLE	FFR_{angio}	ICA (2 views)	Measured mean aortic pressure	Resistance lumped model	Derived from healthy artery cross section + heart rate	Steady	CFD	-	Kornowski et al[45]	2016	Prospective offline	101	0.97	0.93	0.88	0.95	0.97
									Tröbs et al[57]	2016	Retrospective offline	113	0.79	0.94	0.85	0.92	0.85
		ICA (3 views)	Mean aortic pressure measured at hyperaemia	Resistance lumped model	Derived from 3D geometry and scaling	Steady	Fluid equation	-	Pellicano et al[46]	2017	Prospective offline	203	0.91	0.93	0.88	0.95	0.96
									FAST-FFR[47]	2019	Retrospective offline	319	0.94	0.91	0.89	0.95	0.80
									Omori et al[58]	2019	Prospective online	118	0.92	0.92	-	-	0.83
	vFFR	Rotational ICA + 3D reconstruction	Measured aortic pulsatile waveform	Resistance lumped model	-	Pulsatile	CFD	vFFR transient CFD	VIRTU-1[55]	2013	Prospective offline	35	0.86	1	1	0.97	0.84
			Measured aortic pulsatile waveform	Resistance lumped model	-	Pulsatile	CFD + fluid equation	vFFR pseudo-transient steady state	VIRTU-Fast[56]	2017	Prospective offline	73	1	1	1	1	1
			Measured mean aortic pressure	Resistance lumped model	-	Steady	CFD + fluid equation	vFFR steady state					1	1	1	1	1
	CAAS vFFR	ICA 3D-QCA	Measured mean aortic pressure at hyperaemia	Free	Derived from patient aortic pressure + 3D sizing	Steady	Fluid equation	-	FAST[49]	2019	Retrospective offline	319	-	-	-	-	0.89
									FASTII[50]	2021	Prospective observational	330	-	-	-	-	-
	FFR_{CT}	CTA	Lumped heart model	Resistance lumped model	-	Pulsatile/ steady	CFD/ simplified equations	-	DISCOVER-FLOW[64]	2011	Prospective offsite	159	0.88	0.82	0.74	0.92	0.72
									DeFACTO[65]	2012	Prospective offsite	407	0.90	0.54	0.67	0.84	0.63
									HFNXT[66]	2014	Prospective onsite	484	0.84	0.86	0.61	0.95	0.82

Table 1. Technical aspects of the different FCA indices and respective validation studies (cont'd).

	Technique	Imaging modality	Inlet	Outlet	Flow	Pattern	Equation solution	Other	Studies (Ref)	Year	Design	Vessels	Sensitivity	Specificity	PPV	NPV	Corr. with invasive FFR
NOT COMMERCIALLY AVAILABLE	caFFR	ICA (2 views)	Measured mean aortic pressure	Free	TIMI frame count	Steady	CFD	-	Flash FFR[51]	2019	Prospective online	328	0.90	0.99	0.97	0.95	0.89
	vFAI	ICA 3D-QCA	Average human aortic pressure (100 mmHg)	Free	Fixed	Steady	CFD	Derived from DP-flow curve	Papafaklis et al[54]	2014	Retrospective offline	139	0.90	0.86	0.80	0.94	0.78
	FFRQCA	ICA 3D-QCA	Measured mean aortic pressure	Free	TIMI frame count	Steady	CFD	Need of hyperaemia	Tu et al[59]	2014	Retrospective offline	80	0.78	0.93	0.92	0.91	0.81

*Postmyocardial infarction patients. **Patients with ST-elevation myocardial infarction from ARYOSTO. ***Patients with diabetes. ****Pre-percutaneous coronary intervention. 3D: three-dimensional; aQFR: adenosine-flow QFR; CAAS vFFR: vessel FFR; caFFR: computational pressure-flow dynamics derived FFR; CFD: computational fluid dynamics; cQFR: contrast-flow QFR; CTA: computed tomography angiography; DP: differential pressure; FFR: fractional flow reserve; FFR^{angio}: angiography-derived FFR; FFR^{CT}: coronary computed tomography-derived FFR; fQFR: fixed-flow QFR; ICA: invasive coronary angiography; NPV: negative predictive value; PPV: positive predictive value; ps-trans: vFFR computed with the pseudotransient steady-state method; QCA: quantitative coronary analysis; QFR: quantitative flow ratio; TIMI: Thrombolysis in Myocardial Infarction; trans: vFFR computed with full transient CFD; vFAI: virtual functional assessment index; vFFR: virtual FFR

clinical trial. The FAVOR III China Study randomised 3,825 patients with acute and chronic coronary syndromes, with at least one lesion with a diameter stenosis of 50-90% on angiography, to a QFR-guided strategy (PCI indicated if QFR ≤0.80) or a standard angiography-guided strategy.

After 1 year of follow-up, patients randomised to the QFR-guided strategy had fewer myocardial infarctions and ischaemia-driven revascularisations (hazard ratio [HR] 0.65, 95% confidence interval [CI]: 0.51-0.83; p=0.0004)[41]. Moreover, the recently published 2-year follow-up analysis showed that QFR-guided patients had better outcomes in terms of major adverse cardiovascular events (MACE; HR 0.66, 95% CI: 0.54-0.81; p<0.0001)[42]. The FAVOR III Europe Japan Study (ClinicalTrials.gov: NCT03729739) will assess 1-year clinical outcomes comparing a QFR-based strategy to a strategy of pressure wire-based FFR.

Several studies have shown that QFR values correlate better with FFR than with non-hyperaemic pressure ratios (NHPR)[43]. This may be due to the fact that, compared with FFR, NHPR are more sensitive to friction losses of intracoronary pressure[44] which, as discussed above, may be more difficult to identify with FCA. As a matter of fact, a significant difference in the correlation between both invasive indices and QFR has been shown to occur only in vessels with a diffuse pattern of disease, as assessed with guidewire-based longitudinal vessel interrogation[43].

CORONARY ANGIOGRAPHY-DERIVED FFR

Coronary angiography-derived FFR (FFR_{angio}; FFR_{angio} System; CathWorks Ltd.) involves the creation of a 3D representation of the entire coronary arterial tree, using at least three single-plane angiographic projections, and estimates flow through a stenosis by solving simplified fluid equations[45,46]. The microcirculatory resistance is estimated based on scaling formulas. The expected hyperaemic flow is estimated through the calculated microcirculation resistance and the total volume and length of the reconstructed coronary arterial system. The FFR_{angio} is then obtained by dividing the expected hyperaemic flow rate in the stenotic artery with the hyperaemic flow rate calculated for a healthy artery **(Supplementary Figure 1)**. Some advantages of FFR_{angio}, compared with other invasive physiological systems, include the possibility of assessing the entire coronary vessel tree, including side branches, in a single analysis, without the need of intravenous nitrate administration.

After smaller prospective offline studies validated and reported a good diagnostic accuracy of FFR_{angio}[45,46], the multicentre FFR_{angio} Accuracy vs. Standard FFR (FAST-FFR) Trial prospectively enrolled 301 patients and reported an excellent per-vessel sensitivity (94%) and specificity (91%), with invasive FFR as the reference. Interestingly, even for "grey zone" FFR values (0.75-0.85), the diagnostic accuracy was high (87%)[47].

The clinical value of FFR_{angio} has recently been announced in a cohort of 518 patients. The cumulative incidence of death, myocardial infarction and repeat revascularisation after 2 years of follow-up was 3.6% in patients with an FFR_{angio}-guided deferred strategy and 6.7% in patients treated with PCI[48].

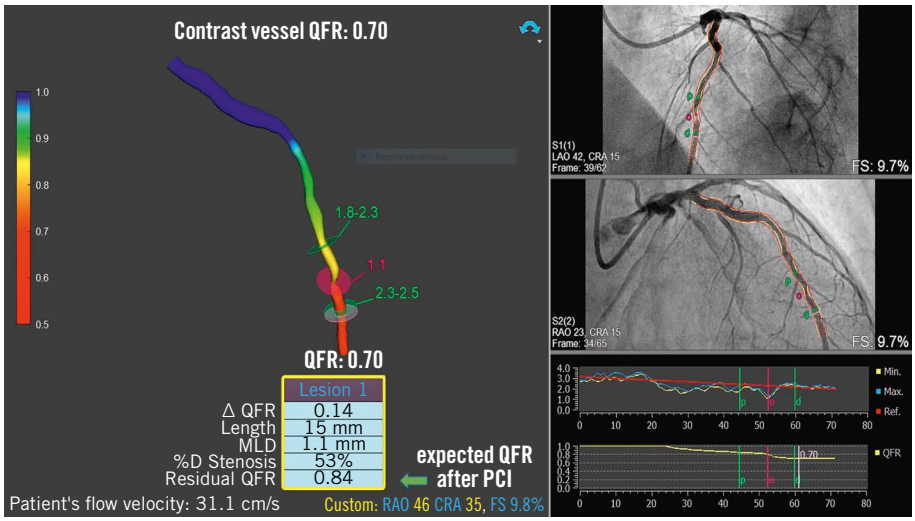


Figure 3. *Contrast QFR for the left anterior descending artery. Coronary angiography showed an intermediate lesion in mid-left anterior descending artery. Contrast QFR in the same vessel was positive for significant functional ischaemia (0.70). Virtual angioplasty in a small segment (between the green markers) showed an expected final QFR of 0.84 after stenting. MLD: minimum lumen diameter; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; %D: % diameter*

VESSEL FRACTIONAL FLOW RESERVE

Vessel fractional flow reserve (CAAS vFFR; Pie Medical Imaging) is calculated using 3D-QCA and simplified fluid equations. The inlet is determined by the aortic root pressure in hyperaemia, and flow velocity is derived by applying the measured pressure to the reconstructed 3D coronary geometry **(Supplementary Figure 2)**. Based on the good linear correlation with wire-derived FFR in the Fast Assessment of STenosis severity (FAST) study[49], the CAAS vFFR system was the first invasive angiography-based physiology system to obtain U.S. Food and Drug Administration market clearance. The recently reported FASTII trial results showed that CAAS vFFR has a high diagnostic accuracy to detect FFR ≤0.80[50]. The ongoing FAST III trial (ClinicalTrials.gov: NCT04931771) will address its prognostic impact compared with FFR.

COMPUTATIONAL PRESSURE-FLOW DYNAMICS DERIVED FFR

Computational pressure-flow dynamics derived FFR (caFFR; FlashAngio caFFR System; RainMed Ltd.) uses 3D angiographic reconstructions based on two orthogonal views, which are subsequently merged with computational fluid dynamics **(Supplementary Figure 3)**. Patient-specific aortic pressure, applied at the inlet boundary, and resting flow velocities, determined by the TIMI frame count method, are integrated into the calculations to solve the Navier-Stokes equations[51]. In the Accuracy of Computational Pressure-Fluid Dynamics applied to Coronary Angiography to Derive Fractional Flow Reserve (Flash FFR) Study, caFFR demonstrated good diagnostic accuracy for the identification of functionally significant lesions, with wire-based FFR as the reference[51].

MURRAY LAW-BASED QFR

Recently, a new approach to quantify functional stenosis severity from a single angiographic view has been proposed **(Supplementary Figure 4)**. With the support of artificial intelligence algorithms, the Murray law-based QFR (μQFR) enables FFR estimation with a single, good quality angiographic projection, adjusting both the reference vessel diameter and the outgoing flow through side branches according to fractal geometry rules. After reporting an excellent agreement between μQFR and FFR in a *post hoc* analysis of the FAVOR II China study[52], Tu et al demonstrated an almost perfect agreement with 3D-QFR in a small cohort[53].

OTHER SYSTEMS FOR FUNCTIONAL ASSESSMENT OF CORONARY STENOSES BASED ON INVASIVE ANGIOGRAPHY

In addition to the commercially available indices discussed above, other systems have also been reported.

The Virtual Functional Assessment Index (vFAI) uses 3D-QCA technology and CFD equations[54]. Average aortic pressure is applied at the inlet boundary. Blood flow is calculated by simulating pressures at 1 and 3 ml/s (average flow at rest and in hyperaemic conditions in human coronary arteries). Unlike the other systems described previously, virtual FFR (vFFR; Philips) is based upon rotational coronary angiography (RoCA; Philips)[55]. The system uses a CFD analysis in which aortic pressure waveforms are measured and applied at the inlet boundary, and the outlet boundary is derived by coupling a model of microcirculation. A simplified version of vFFR using steady-state CFD and simplified fluid dynamics equations has been described[56].

Angiographic FFR (AngioFFR) uses CFD Simulation software (Siemens) and performs calculations using two angiographic projections of the coronary vessel, patient-specific heart rate and blood pressure; it is supported by artificial intelligence algorithms[57]. In a study including 253 lesions (200 patients), AngioFFR resulted in a good overall sensitivity and specificity, with a shorter processing time than invasive FFR[58].

Tu et al developed an angiographic index from 3D quantitative coronary angiography and TIMI frame count (FFRQCA) with an overall good discrimination capacity to predict FFR ≤0.80[59].

Limitations of angiography-derived FFR

TECHNICAL ISSUES

Current versions of most angiography-derived techniques are highly operator dependent and require multiple steps (manual indication of landmarks, correction of vessel contours and indication of the target vessel start and endpoints, which account for significant interobserver variation in non-trial settings[40]. As accuracy depends directly on the quality of images and optimal projections, overlapped or highly tortuous vessels cannot be correctly evaluated.

In systems in which TIMI frame count is used as an estimate of coronary flow, the quality of contrast injection might influence the accuracy of estimations. The lack of standardisation of contrast injections might account for the differences in the reported correlations with invasive FFR[20]. The adoption of systems requiring rotational coronary angiography is limited by the availability of angiographic hardware with this feature. Since rotational angiography provides fewer images per projection, the number of end diastolic frames available for analysis is reduced[55].

Angiography-derived FFR using simplified fluid equations is reportedly less time-consuming when compared with wire-based FFR. However, the same reports did not account for the time needed and spent in acquiring the prespecified images to make the analysis possible, which is often challenging[20].

ISSUES RELATED TO REPORTED EVIDENCE

Most published studies had a retrospective offline design, with a limited number of patients and were not powered for hard clinical endpoints **(Table 1)**. Currently, only QFR have published data demonstrating improved outcomes from randomised controlled trials.

As with most clinical trials and validation studies, the number of exclusion criteria applied resulted in a highly selected population whose representability in real-world practice is somewhat hindered. This results in the exclusion of approximately 15% of screened patients (for the following reasons: aorto-ostial lesions, bifurcation lesions, presence of coronary bypass grafts, left main disease, chronic total occlusions, stent restenosis or diffuse disease) **(Supplementary Table 2)**.

CONFOUNDING FACTORS

Important discrepancies between FFR and QFR are found in patients with chronic kidney disease and diabetes, which might be related to the increased prevalence of microvascular dysfunction[60]. A recent study from Mejía-Rentería et al demonstrated that microcirculatory dysfunction, defined by an index of microvascular resistance (IMR) ≥23, decreased the diagnostic performance of QFR to detect functionally significant lesions as determined by FFR. Nevertheless, QFR was still superior to angiography alone in ascertaining functional stenosis severity[22]. Hwang et al demonstrated discordance between QFR and instantaneous wave-free ratio (iFR) when considering abnormal coronary flow reserve (CFR) values[27]. Additionally, Westra et al demonstrated that resting P_d/P_a and FFR functional classification disagreement is associated with a reduced diagnostic accuracy of QFR[61].

Functional angiography based on coronary computed tomography

Merging CCTA with FFR by using advanced computational analysis allows a complete haemodynamic and anatomical evaluation of a coronary lesion in one single non-invasive test, improving clinical outcomes, although without significantly reducing costs[62].

CORONARY COMPUTED TOMOGRAPHY-DERIVED FRACTIONAL FLOW RESERVE

In the last decade, CCTA has been shown to be a highly accurate and non-invasive method for the evaluation of CAD and the assessment of plaque. Coronary computed tomography-derived fractional flow reserve (FFR_{CT}; HeartFlow FFR_{CT} Analysis; HeartFlow) is based on the application of CFD methods to solve the Navier-Stokes equations to simulate flow, pressure and velocity during rest and hyperaemia **(Figure 4)**.

Contrary to FCA based on invasive angiograms, a full CFD analysis is performed using a supercomputer. The coronary 3D modelling is obtained by conventional CCTA and the patient-specific boundary conditions are determined as lumped models for the heart (time varying elastance model – inlet) and coronary microcirculation (outlet). Recently, reduced-order and steady-state models have been introduced to compensate for the limitations of supercomputer dependence and offsite calculation, averaging the Navier-Stokes equations over vessel cross-sections. Machine learning models have also recently materialised utilising artificial intelligence algorithms to calculate stenosis severity based on a multilayer neural network architecture and offline training[63].

A number of prospective studies have been conducted to validate FFR_{CT} using wire-based FFR as the gold standard reference. The Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW) study found good correlation between FFR_{CT} and FFR and a higher diagnostic performance of FFR_{CT} compared to CCTA alone[64]. Similar results were found in the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study[65].

The Analysis of Coronary Blood Flow Using CT Angiography (HTNXT) study scheduled high-quality CCTA (beta blocker and nitroglycerine administration) prior to ICA, and used a refined FFR_{CT} algorithm which resulted in considerable enhancement of diagnostic accuracy on a per-patient and per-lesion basis for FFR_{CT}, compared with CCTA alone, and subsequently higher specificity with comparable sensitivity[66].

The Prospective LongitudinAl Trial of FFT_{CT}: Outcome and Resource Impacts (PLATFORM) Study prospectively randomised

584 patients with a planned ICA to receive usual care testing or CCTA/FFR_{CT}. The results showed that 61% of ICA procedures were deferred after receiving the CCTA/FFR_{CT} results, with low rates of clinical events at 90 days in both arms[67]. The 1-year outcome data from this trial showed that care guided by the CCTA/FFR_{CT} was associated with lower costs but equivalent quality of life and clinical outcomes[68].

Finally, the Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary CarE (ADVANCE) registry prospectively enrolled 5,083 patients with coronary atherosclerosis identified on CCTA to evaluate the clinical significance of functionally significant stenosis with FFR_{CT}. Revascularisation and MACE events occurred more frequently in patients with an FFR_{CT} ≤0.80, than with patients with an FFR_{CT} >0.80 (risk ratio [RR] 6.87; 95% CI: 5.59-8.45; p<0.001 and RR: 1.81; 95% CI: 0.96-3.43; p=0.06, respectively)[69].

Limitations of computed tomography-derived FFR

TECHNICAL ISSUES

Currently, FFR_{CT} is time-consuming and analysed offsite. Furthermore, the accuracy of FFR_{CT} is dependent upon a high-quality CCTA, which requires new-generation CT scans that are not always readily available. The analysis is also strictly dependent on the absence of artefacts (motion, intracoronary stents, pacemakers, internal defibrillators, prosthetic heart valves, excessive coronary calcification, uncontrolled atrial arrhythmias or frequent ventricular ectopic beats), resulting in significant dataset rejection in the validation studies (11-33%) due to poor image quality[64,65,66]. Limited information is available on whether FFR_{CT} is cost-effective.

ISSUES RELATED TO REPORTED EVIDENCE

As previously described for the angiography-derived FFR techniques, the application of FFR_{CT} analysis is not available for all patients. According to the proprietary company specifications, FFR_{CT} is currently not recommended for patients with acute coronary syndromes (ACS) or recent myocardial infarction (MI), prior coronary artery bypass grafting (CABG), complex congenital heart disease, body mass index >35 kg/m^2 or haemodynamic instability.

In the ADVANCE registry, baseline medications were not reported and optimised medical therapy was not considered in the core lab recommendations. Therefore, the primary outcome results do not reflect current recommended practice by international guidelines[69]. Furthermore, based on the presented studies, FFR_{CT} was validated in a particular low-risk subgroup of patients and the performance of FFR_{CT} in intermediate- or high-risk populations is currently unknown[70]. Importantly, neither core lab readers nor site investigators were blinded to the study aims, creating an opportunity for potential information bias on post-CCTA management by both entities[69].

Clinical scenarios for functional coronary angiography

In **Figure 5**, we propose a decision-making algorithm for the use of FCA in everyday practice. It should be kept in mind that most of the validation studies discussed have been performed in patients with chronic coronary syndromes and intermediate coronary stenoses located in a major coronary branch. However, many researchers have explored the value of FCA in other relevant clinical and anatomical scenarios. These are discussed in greater detail below.

NON-CULPRIT VESSEL EVALUATION IN ACUTE CORONARY SYNDROMES

Approximately half of patients presenting with ST-segment elevation myocardial infarction (STEMI) have multivessel disease with non-culprit lesions (NCL)[71]. Repeated invasive tests are associated with increased risk, cost, and time, especially in non-functionally significant NCL. The ability to estimate the functional relevance of NCL offline after primary percutaneous coronary intervention (PCI) could greatly facilitate the management of these patients and optimise the catheterisation laboratory workflow.

Overall, the available evidence is concordant and supports the value of QFR for this indication. Lauri et al published a retrospective, observational, multicentre study demonstrating that QFR has excellent diagnostic accuracy when assessing the functional relevance of NCL during primary PCI[31]. Sejr-Hanse et al performed

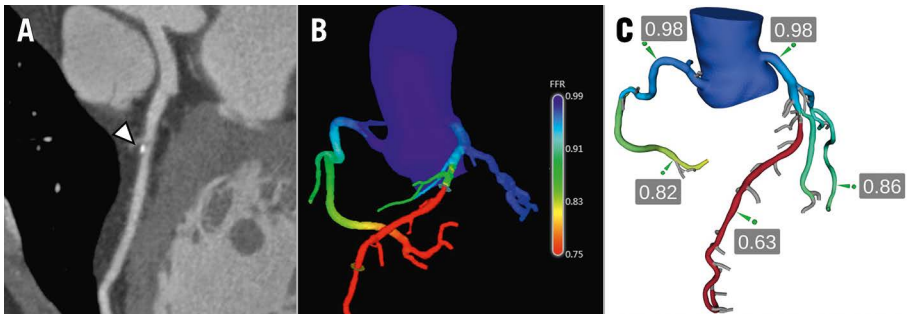


Figure 4. *Coronary computed tomography-derived fractional flow reserve. A) CCTA of the LAD artery is shown. Arrowhead indicates a calcified plaque in the middle segment with 50% diameter stenosis. B) A quantitative 3D colour-coded anatomical model is generated. C) FFR_{CT} is calculated throughout the coronary tree. The FFR_{CT} value of 0.63 in the distal LAD artery suggests the presence of a functionally significant stenosis after the emergence of the first diagonal branch. Courtesy of Dr Joo Myung Lee. CCTA: coronary computed tomography angiography; FFR: fractional flow reserve; FFR_{CT}: coronary computed tomography-derived FFR; LAD: left anterior descending*

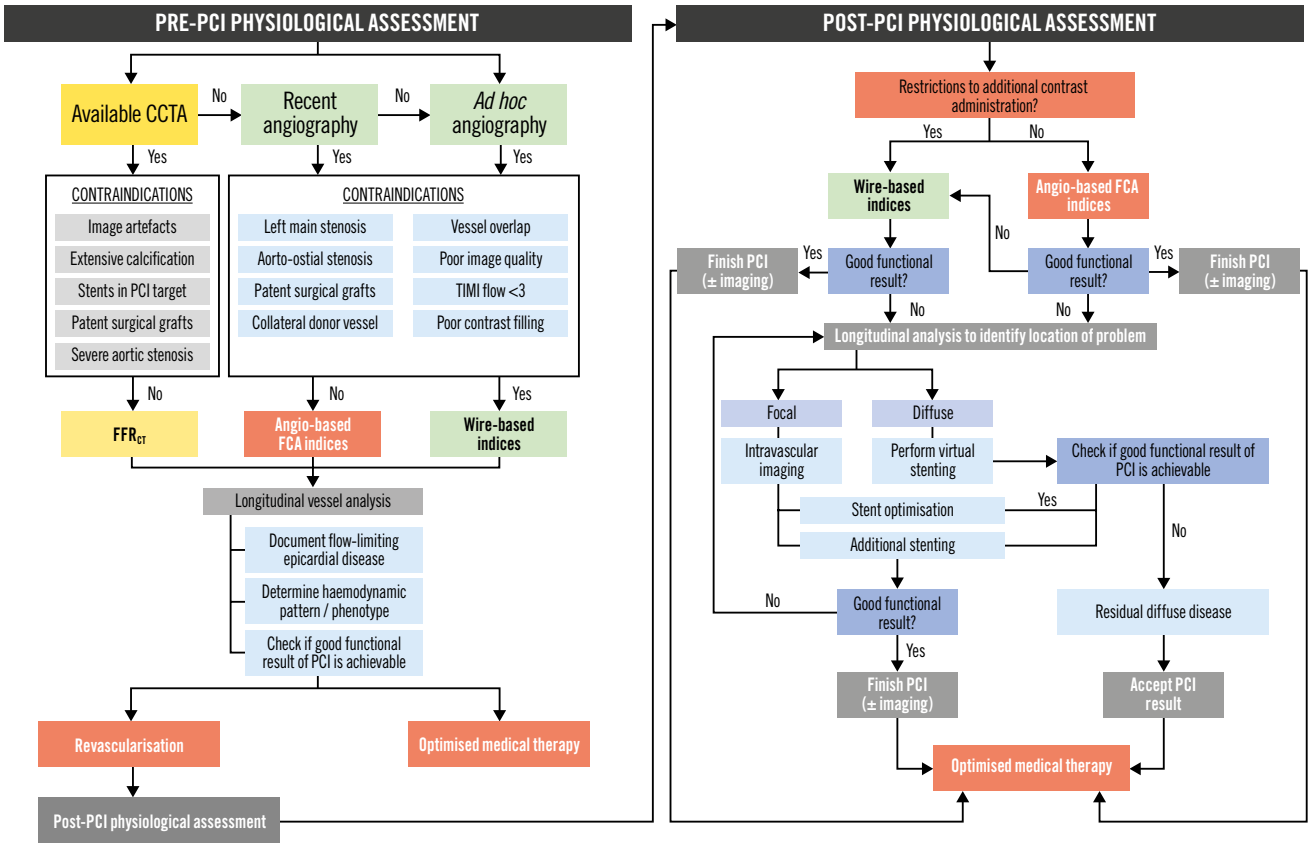


Figure 5. *Utilisation of FCA in clinical practice. Decision-making algorithm for the usage of FCA in pre- and post-PCI settings. CCTA: coronary computed tomography angiography; FCA: functional coronary angiography; FFR_{CT}: computed tomography-derived fractional flow reserve; LM: left main; PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction*

a *post hoc* analysis of the Intravascular Ultrasound Guided PCI in STEMI (iSTEMI) study and demonstrated that acute phase QFR has a very good diagnostic performance with staged FFR as reference[33]. Finally, Spitaleri et al, in a proof-of-concept study performed in patients with STEMI with NCL, found excellent correlation and agreement between QFR and FFR values in acute and subacute procedures. They also found that a QFR value ≤0.80 was associated with a higher risk of adverse events (HR 2.3, 95% CI: 1.2-4.5; p=0.01)[36].

Choi et al, in a multicentre retrospective registry, identified that QFR consistently showed high diagnostic performance in predicting the functional significance of epicardial coronary stenosis, regardless of vessel location, lesion length, or various clinical presentations including ACS with NCL (n=153), previous MI (n=30), or diabetes mellitus (n=190)[38].

Erbay et al studied the prognostic impact of QFR analysis in postinterventional culprit and non-culprit vessels in 792 patients with ACS. The results showed that an abnormal QFR is an independent predictor of 2-year MACE in both non-culprit arteries (odds ratio [OR] 3.78, 95% CI: 2.21-6.45; p<0.001) and post-PCI culprit arteries (OR 3.60, 95% CI: 2.09-6.20; p<0.001)[72].

Duguay et al retrospectively investigated the prognostic value of FFR_{CT} based on machine learning in patients with ACS and multivessel disease in 48 patients. Receiver operating characteristics including the framing risk score (FRS), the Coronary Artery Disease-Reporting and Data System (CAD-RADS) classification and FFR_{CT} showed a discriminatory power superior to the FRS alone for the prediction of MACE (area under the curve [AUC] 0.66; p=0.032)[73].

Thus, for the time being, FCA has the potential to deliver equivalent measurements to FFR in non-culprit lesions in the context of ACS. It has to be kept in mind that the value of FFR in this context is a matter of current debate, with discordant results in trials[74]. The existence of time-dependent changes in microcirculatory status, or higher prevalence of vulnerable lesions, have been proposed to explain why recent trials failed in demonstrating the value of FFR in decision-making in this context[75]. Further research will show whether in this context QFR mirrors FFR-linked outcomes or, alternatively, if FCA has any advantages.

In the setting of non-functionally significant lesions, intravascular imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) is the gold standard for the detection of vulnerable plaques. However, by measuring CT attenuation in Hounsfield units, CCTA can detect plaque composition with similar accuracy. Plaques with high CT attenuation correspond to calcified lesions, whilst low-attenuation plaques correspond to the existence of time-dependent changes in high-risk lipid-rich lesions on virtual histography IVUS[76]. In addition, the

pattern of CT attenuation can also be used to detect plaque vulnerability. The presence of the "napkin-ring" sign in CCTA is associated with thin-cap fibroatheromas in OCT. Furthermore, Otsuka et al demonstrated this sign is an independent strong predictor of future ischaemic events at 2-year follow-up, including cardiac death, myocardial infarction and unstable angina (HR 5.55, 95% CI: 2.10-14.7; p<0.001)[77].

HYBRID APPROACH OF QFR/FFR IN CLINICAL DECISION-MAKING

A strategy based on primary QFR-FFR, using FFR only when QFR values are in the "grey zone" could reduce procedural time, associated costs, and complications. Lauri et al reported that using a hybrid QFR-FFR approach − primarily using QFR if values are <0.75 or >0.85, and FFR only when QFR values were within these boundaries − would result in an overall classification agreement of 96.7% in post-ACS NCL[31]. Compared to the iFR/FFR strategy, validated in the ADVISE II registry[78], the main advantage of the reported QFR/FFR approach is the avoidance of unnecessary pressure wire evaluation, avoiding repeated diagnostic procedures in 58.5% of patients[31].

PLANNING PERCUTANEOUS CORONARY REVASCULARISATION

In addition to identifying flow-limiting disease, FFR_{CT} might prove useful in guiding and planning coronary revascularisation. Jensen et al recently confirmed an increase in the PCI/ICA ratio in the high-risk population, with more ICA cancelled on the basis of FFR_{CT}[79]. This study introduces the possibility of decision-making during PCI without the need to confirm ischaemia invasively, because of a high concordance between invasive and non-invasive measures of ischaemia. Van Belle et al also demonstrated that adding FFR_{CT} to the strategy algorithm changes the treatment decision in one-third of lesions[80]. Another important aspect in PCI planning is the ability to simulate the post-PCI coronary artery, allowing the calculation of post-PCI FFR_{CT} **(Figure 6)**. In the original feasibility study, virtual post-PCI FFR_{CT} demonstrated good overall correlation with invasive post-PCI FFR[81]. This method still has limited clinical utility, as the current computational requirements do not allow for a timely evaluation. With future developments in computation, this method could be performed online by onsite physicians, further aiding revascularisation decision-making.

THE VALUE OF FCA IN PLANNING INTERVENTIONS EXTENDS TO HEART TEAM DECISIONS ON REVASCULARISATION OF MULTIVESSEL DISEASE

By being able to provide a non-invasive functional Synergy Between Percutaneous Coronary Intervention With Taxus And Cardiac Surgery (SYNTAX) score, FFR_{CT} offers significant potential to reduce the need of ICA or invasive adjudication of ischaemia for Heart Team decisions.

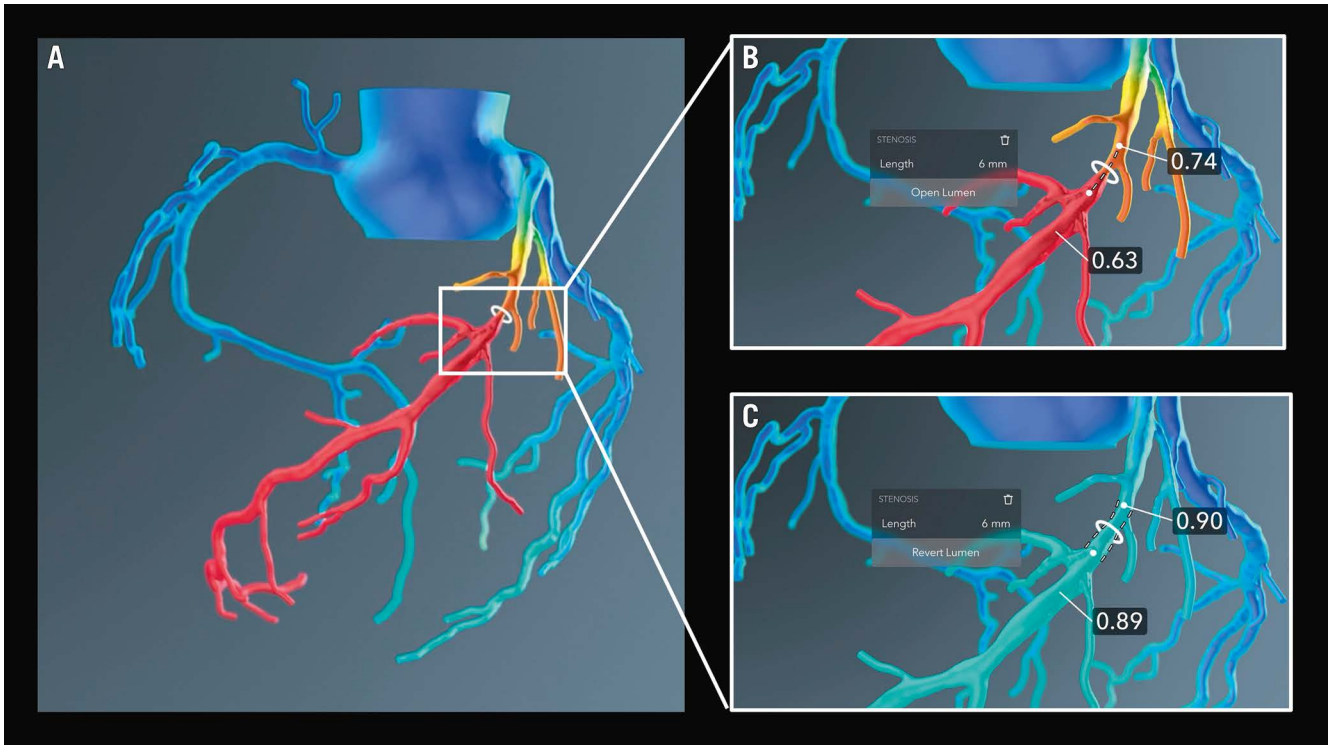


Figure 6. *Simulation of PCI results using FFR_{CT}. A) CT-based functional coronary angiography showing a flow-limiting stenosis in the mid-segment of the left anterior descending artery. B) Simulation of PCI results after choosing the target segment to treat and C) expected haemodynamic results after achieving revascularisation. FFR_{CT}: coronary computed tomography derived fractional flow reserve; PCI: percutaneous coronary intervention*

The incremental value of a functional assessment of CAD, beyond solely anatomical ICA imaging, was highlighted in a study published by the Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention (FAME) study investigators, showing that adding FFR into the classic anatomical SYNTAX score reclassifies over 30% of patients[82]. The advantages of state-of-the art PCI guided by hybrid assessment with iFR and FFR in improving clinical outcomes in patients with *de novo* 3-vessel disease were also demonstrated in the SYNTAX II trial[83].

Asano et al derived a functional SYNTAX score based on QFR (fSS_{QFR}) by retrospectively screening and analysing all lesions interrogated by iFR/FFR in the SYNTAX II trial. According to the 2-year patient-oriented composite endpoint (all-cause death, myocardial infarction, or any revascularisation), fSS_{QFR} reclassified 26.1% of patients into the low-risk group (net reclassification improvement 0.32; p<0.001), and its accuracy to predict this composite endpoint was higher than that of the classic anatomical SYNTAX score (0.68 vs 0.56; p=0.002)[35].

The calculation of the SYNTAX score derived from coronary CCTA (CT SYNTAX score) has been shown to have similar accuracy when compared to the one derived from ICA[84]. By being able to provide a non-invasive fSS, FFR_{CT} offers significant potential to reduce the need of ICA or invasive adjudication of ischaemia. The SYNTAX III trial, which randomised patients to non-invasive and invasive adjudication of ischaemia, identified that in patients with left main or 3-vessel CAD, agreement concerning treatment choices (PCI or CABG) between coronary CCTA and ICA was high (Cohen's kappa 0.82, 95% CI: 0.74-0.91). FFR_{CT} also changed the treatment decision in 7% of patients[85].

Despite the potential role of FCA in this setting, evidence of a clear benefit in clinical practice is lacking. In addition, the results of the FAME 3 trial showed that FFR-guided PCI was inferior to CABG in patients with 3-vessel CAD regarding death, myocardial infarction, stroke or repeat revascularisations at 1 year[86]. Given that all the FCA indices were validated against FFR, we do not recommend using FCA to decide the revascularisation strategy (PCI vs CABG) until further evidence is available.

IN-STENT RESTENOSIS

The performance of QFR in in-stent restenosis (ISR) was evaluated retrospectively in a multicentre, international, blinded study by Liontou et al, showing a reasonably high classification agreement between FFR and QFR (0.83), comparable to those reported with *de novo* lesions. Additionally, the reported performance of QFR to establish ISR relevance, with wire-based FFR as reference, was high (AUC 0.90, 95% CI: 0.83-0.97)[87].

To date, there is no available evidence regarding the use of FFR_{CT} in evaluating ISR. Recently published studies highlighted relevant limitations of CCTA imaging in the presence of coronary stents due to artificial lumen narrowing, ranging between 10 and 60%, being more pronounced in small diameter stents (<3 mm)[88]. Despite having a very high negative predictive value (NPV) for the exclusion of ISR, its positive predictive value (PPV) is markedly worse[89]. With the recent introduction of dual source CT scanners, there has been a significant improvement in the reported performances.

FUNCTIONAL EVALUATION IN THE PRESENCE OF AORTIC STENOSIS

Concomitant CABG surgery is performed in approximately 40% of patients undergoing surgical aortic valve replacement and the prevalence of significant CAD in patients undergoing transcatheter aortic valve implantation (TAVI) is greater than in surgical series, with a reported prevalence of over 60%[90]. However, despite being recommended by international guidelines, the safety and benefit of revascularisation in this group of patients is yet to be proven.

The prognostic impact of CAD in this setting is still unclear and PCI before TAVI has not been associated with improved hard endpoints or symptoms during follow-up[91]. The increased imposed afterload in this setting is responsible for a complex array of macro- and microcellular transformations that culminate in left ventricular hypertrophy, increased diastolic pressures, interstitial fibrosis, and microvascular dysfunction. These maladaptive modifications ultimately compromise the microcirculatory response to pharmacological vasodilation and, therefore, might explain the underestimation of intermediate stenosis functional significance with FFR[92]. Interestingly, the PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION (ACTIVATION) trial showed that coronary revascularisation in patients without angina and undergoing TAVI is not beneficial[93]. The role of image-based physiology will be assessed in the Quantitative Flow Ratio Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease (FAVOR4-QVAS) trial testing a QFR-guided revascularisation strategy in patients undergoing aortic valve replacement. Nevertheless, the use of FFR_{CT} is of particular interest, since currently all patients undergoing TAVI require CT prior to evaluating their suitability and procedural planning.

FUNCTIONAL ISCHAEMIA AFTER PCI

Clinical outcomes regarding clinical decision-making based on non-intracoronary physiology remain to be published. Nevertheless, the prognostic value of QFR in successfully revascularised patients was investigated prospectively by Biscaglia et al in the Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation (HAWKEYE) study. In this trial, a 3-fold increase in the vessel-oriented composite endpoint was identified (cardiovascular death, myocardial infarction or ischaemia-driven target vessel revascularisation) in vessels with offline post-PCI QFR ≤0.89 (HR 2.91, 95% CI: 1.63-5.19; p<0.001), with significant differences in all three composites[94]. Most importantly, owing to the integrated pullback trace, QFR was able to discriminate the mechanism underlying the suboptimal functional result **(Figure 7)**. The relevance of this field is likely to increase based on reported studies using post-PCI invasive functional assessment, which have shown worse prognosis if functionally significant obstructive disease is left untreated, even after angiographically successful PCI[95].

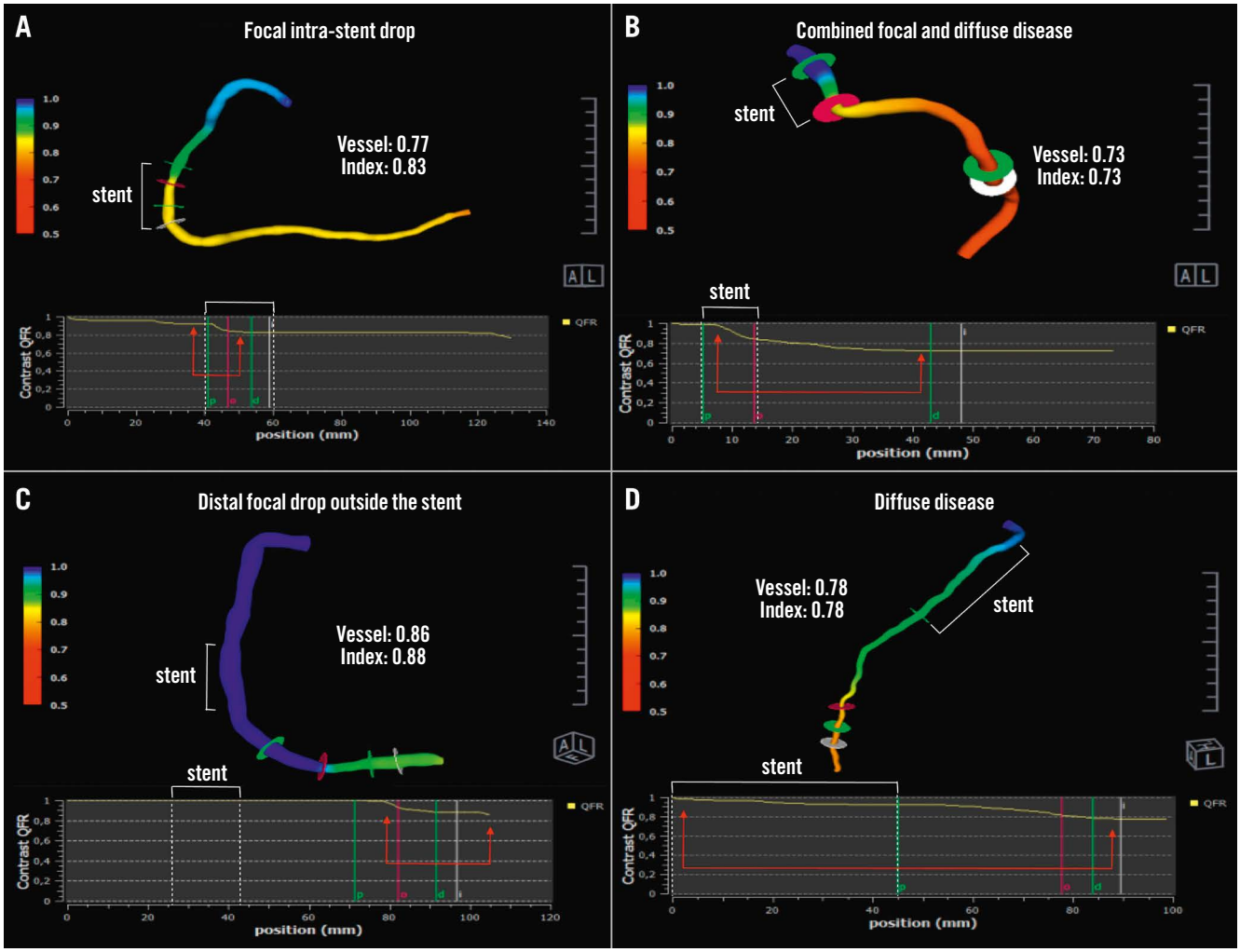


Figure 7. *Establishing the cause of suboptimal functional PCI results with QFR. The white brackets indicate the stented segment. The red arrows point to the major QFR drop during pullback. A) Focal intra-stent drop. B) Combined intra-stent focal drop and distal diffuse disease. C) Distal focal drop outside the stent. D) Diffuse disease. Courtesy of Dr Simone Biscaglia. PCI: percutaneous coronary intervention; QFR: quantitative flow ratio*

MICROCIRCULATORY CORONARY RESISTANCE

Recently, two proof-of-concept studies were conducted to test angiography-derived indices of microcirculatory resistance. De Maria et al developed and validated an angiography-derived index of microcirculatory resistance (IMR_{angio}) in STEMI, demonstrating good correlation between conventional IMR and IMR_{angio} measured immediately before stenting in primary PCI[96].

Tebaldi et al validated another angio-based IMR (A-IMR), using IMR as a gold standard, in patients with chronic coronary syndrome and an intermediate left anterior descending (LAD) artery lesion, showing good correlation between the two indices[97].

Recently, Mejía-Rentería et al developed a wire- and adenosine-free IMR (angio-IMR) that exhibited good correlation with invasive IMR and its feasibility in interpreting functional stenosis assessed by QFR **(Figure 8)**[98].

Finally, Choi et al confirmed the prognostic value of an elevated angio-IMR calculated using computational flow and pressure simulations in two cohorts of STEMI patients that were followed up for 10 years, demonstrating that patients with an angio-IMR >40 had a significantly increased risk of cardiac death and hospitalisation for heart failure[99].

Conclusions

In recent years, major technical developments in the field of coronary imaging (invasive angiography and CCTA) have made it possible to obtain functional information from a primary anatomical examination. FCA and CCTA now allow a wireless-based evaluation, with preliminary studies demonstrating good correlation with invasive FFR and overall good reproducibility and feasibility. The developments in both modalities and their clinical adoption worldwide could move FCA from the research field to clinical practice in the coming years. Issues regarding the time burden and costs, particularly with CT_{FFR}, might hinder their broad applicability in routine clinical practice. The significant number of predetermined assumptions when computing flow by FCA are reflected in a wide "grey zone" of measurements that will still require confirmation by invasive physiology. Studies and trials are required to assess major clinical endpoints and the cost-effectiveness of FCA.

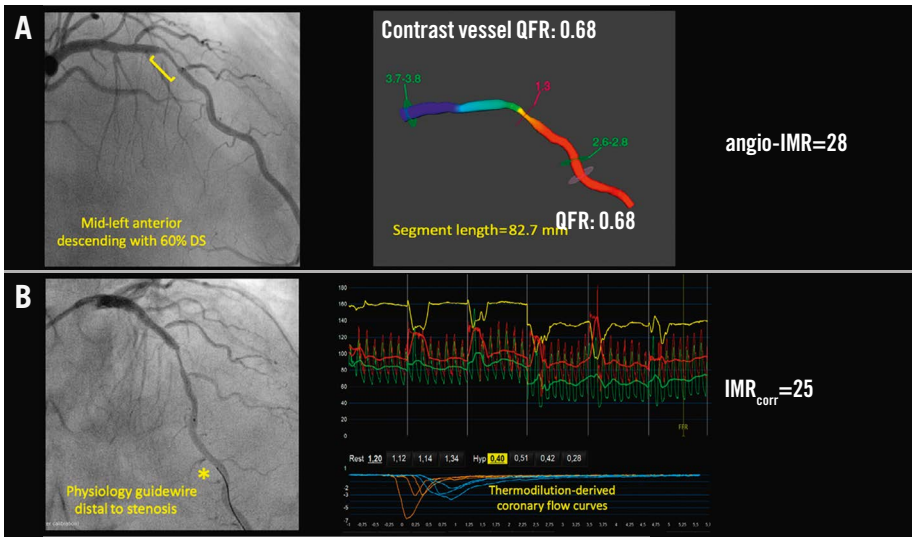


Figure 8. *Derivation of coronary microvascular resistance from FCA. A) Steps and formulas for calculating the hyperaemic index of coronary microvascular resistance without the need for guidewires or hyperaemic drug administration. B) Invasive assessment of IMR by thermodilution-derived coronary flow curves. angio-IMR: wire- and adenosine-free IMR; DS: diameter stenosis; FCA: functional coronary angiography; IMR: index of microvascular resistance; IMR$_{corr}$: IMR adjusted by Young's formula; QFR: quantitative flow ratio*

Conflict of interest statement

H. Mejía-Rentería has received speaker fees from Abbott Vascular, Boston Scientific, and Philips Healthcare. J.M. Lee received a research grant from Abbott Vascular and Philips/Volcano. H. Matsuo has received speaker fees from Philips, Boston Scientific, Abbott Vascular, and Zeon Medical. S. Baptista has received personal fees from Abbott, Boston Scientific, and HeartFlow. N. Gonzalo has received consultancy and speaker fees from Abbott Vascular, Boston Scientific, Philips/Volcano, and Shockwave Medical. J. Escaned has received speaker and/or advisory board member fees from Abbott Vascular, Boston Scientific, Medis, and Philips. The other authors have no conflicts of interest to declare.

References

1. Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DG, Kerber RE. Visual estimates of percent diameter coronary stenosis: "a battered gold standard". *J Am Coll Cardiol.* 1988;11:882-5.

2. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol.* 1974;33:87-94.

3. Wijns W, Serruys PW, Reiber JHC, van den Brand M, Simoons ML, Kooijman CJ, Balakumaran K, Hugenholtz PG. Quantitative angiography of the left anterior descending coronary artery: Correlations with pressure gradient and results of exercise thallium scintigraphy. *Circulation.* 1985;71:273-9.

4. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJRM, Bartunek J, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703-8.

5. Tonino PAL, De Bruyne B, Pijls NHJ, 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.

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

7. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de 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.

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

9. Tebaldi M, Biscaglia S, Fineschi M, Musumeci G, Marchese A, Leone AM, Rossi ML, Stefanini G, Maione A, Menozzi A, Tarantino F, Lodolini V, Gallo F, Barbato E, Tarantini G, Campo G. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. *JACC Cardiovasc Interv.* 2018;11:1482-91.

10. Leone AM, Scalone G, De Maria GL, Tagliaferro F, Gardi A, Clemente F, Basile E, Cialdella P, De Caterina AR, Porto I, Aurigemma C, Burzotta F, Niccoli G, Trani C, Rebuzzi AG, Crea F. Efficacy of contrast medium induced Pd/Pa ratio in predicting functional significance of intermediate coronary artery stenosis assessed by fractional flow reserve: insights from the RINASCI study. *EuroIntervention.* 2015;11:421-7.

11. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol.* 1974;34:48-55.

12. Corcoran D, Hennigan B, Berry C. Fractional flow reserve: a clinical perspective. *Int J Cardiovasc Imaging.* 2017;33:961-74.

13. Tu S, Westra J, Adjedj J, Ding D, Liang F, Xu B, Holm NR, Reiber JHC, Wijns W. Fractional flow reserve in clinical practice: from wire-based invasive measurement to image-based computation. *Eur Heart J.* 2020;41:3271-9.

14. Zhong L, Zhang JM, Su B, Tan RS, Allen JC, Kassab GS. Application of Patient-Specific Computational Fluid Dynamics in Coronary and Intra-Cardiac Flow Simulations: Challenges and Opportunities. *Front Physiol.* 2018;9:742.

15. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol.* 2013;61:2233-41.

16. 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.

17. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JHC, Holm NR, Wijns W; FAVOR Pilot Trial Study Group. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. *JACC Cardiovasc Interv.* 2016;9:2024-35.

18. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, Nef H, Naber C, Barbierato M, Tu S, Neghabat O, Madsen M, Tebaldi M, Tanigaki T, Kochman J, Somi S, Esposito G, Mercone G, Mejia-Renteria H, Ronco F, Bøtker HE, Wijns W, Christiansen EH, Holm NR. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan study. *J Am Heart Assoc.* 2018;7:e009603.

19. Yazaki K, Otsuka M, Kataoka S, Kahata M, Kumagai A, Inoue K, Koganei H, Enta K, Ishii Y. Applicability of 3-Dimensional Quantitative Coronary Angiography-Derived Computed Fractional Flow Reserve for Intermediate Coronary Stenosis. *Circ J.* 2017;81:988-92.

20. Kołtowski Ł, Zaleska M, Maksym J, Tomaniak M, Soliński M, Puchta D, Holm NR, Opolski G, Kochman J. Quantitative flow ratio derived from diagnostic coronary angiography in assessment of patients with intermediate coronary stenosis: a wire-free fractional flow reserve study. *Clin Res Cardiol.* 2018;107:858-67.

21. Ties D, van Dijk R, Pundziute G, Lipsic E, Vonck TE, van den Heuvel AFM, Vliegenthart R, Oudkerk M, van der Harst P. Computational quantitative flow ratio to assess functional severity of coronary artery stenosis. *Int J Cardiol.* 2018;271:36-41.

22. Mejía-Rentería H, Lee JM, Lauri F, van der Hoeven NW, de Waard GA, Macaya F, Pérez-Vizcayno MJ, Gonzalo N, Jiménez-Quevedo P, Nombela-Franco L, Salinas P, Núñez-Gil I, del Trigo M, Goto S, Lee HJ, Liontou C, Fernández-Ortiz A, Macaya C, van Royen N, Koo BK, Escaned J. Influence of Microcirculatory Dysfunction on Angiography-Based Functional Assessment of Coronary Stenoses. *JACC Cardiovasc Interv.* 2018;11:741-53.

23. Emori H, Kubo T, Kameyama T, Ino Y, Matsuo Y, Kitabata H, Terada K, Katayama Y, Aoki H, Taruya A, Shimamura K, Ota S, Tanaka A, Hozumi T, Akasaka T. Diagnostic Accuracy of Quantitative Flow Ratio for Assessing Myocardial Ischemia in Prior Myocardial Infarction. *Circ J.* 2018;82:807-14.

24. Smit JM, Koning G, van Rosendael AR, Dibbets-Schneider P, Mertens BJ, Jukema JW, Delgado V, Reiber JHC, Bax JJ, Scholte AJ. Relationship Between Coronary Contrast-Flow Quantitative Flow Ratio and Myocardial Ischemia Assessed by SPECT MPI. *Eur J Nucl Med Mol Imaging.* 2017;44:1888-96.

25. Emori H, Kubo T, Kameyama T, Ino Y, Matsuo Y, Kitabata H, Terada K, Katayama Y, Taruya A, Shimamura K, Shiono Y, Tanaka A, Hozumi T, Akasaka T. Quantitative flow ratio and instantaneous wave-free ratio for the assessment of the functional severity of intermediate coronary artery stenosis. *Coron Artery Dis.* 2018; 29:611-7.

26. Stähli BE, Erbay A, Steiner J, Klotsche J, Mochmann HC, Skurk C, Lauten A, Landmesser U, Leistner DM. Comparison of resting distal to aortic coronary pressure with angiography-based quantitative flow ratio. *Int J Cardiol.* 2019;279:12-7.

27. Hwang D, Choi KH, Lee JM, Mejía-Rentería H, Kim J, Park J, Rhee TM, Jeon KH, Lee HJ, Kim HK, Park TK, Yang JH, Song Y Bin, Shin ES, Nam CW, Kwak JJ, Doh JH, Hahn JY, Choi JH, Choi SH, Escaned J, Koo BK, Gwon HC. Diagnostic Agreement of Quantitative Flow Ratio With Fractional Flow Reserve and Instantaneous Wave-Free Ratio. *J Am Heart Assoc.* 2019;8:e011605.

28. Huang J, Emori H, Ding D, Kubo T, Yu W, Huang P, Zhang S, Gutiérrez-Chico JL, Akasaka T, Wijns W, Tu S. Comparison of diagnostic performance of intracoronary optical coherence tomography-based versus angiography-based fractional flow reserve for the evaluation of coronary lesions. *EuroIntervention.* 2020;16:568-76.

29. Smit JM, Koning G, van Rosendael AR, El Mahdiui M, Mertens BJ, Schalij MJ, Jukema JW, Delgado V, Reiber JHC, Bax JJ, Scholte AJ. Referral of patients for fractional flow reserve using quantitative flow ratio. *Eur Heart J Cardiovasc Imaging.* 2019;20:1231-8.

30. 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.

31. Lauri F, Macaya F, Mejía-Rentería H, Goto S, Yeoh J, Nakayama M, Quirós A, Liontou C, Pareek N, Fernández-Ortíz A, Macaya C, MacCarthy P, Escaned J; Collaborators. Angiography-derived functional assessment of non-culprit coronary stenoses in primary percutaneous coronary intervention. *EuroIntervention.* 2020;15: e1594-601.

32. Watarai M, Otsuka M, Yazaki K, Inagaki Y, Kahata M, Kumagai A, Inoue K, Koganei H, Enta K, Ishii Y. Applicability of quantitative flow ratio for rapid evaluation of intermediate coronary stenosis: comparison with instantaneous wave-free ratio in clinical practice. *Int J Cardiovasc Imaging.* 2019;35:1963-9.

33. Sejr-Hansen M, Westra J, Thim T, Christiansen EH, Eftekhari A, Kristensen SD, Jakobsen L, Götberg M, Frøbert O, van der Hoeven NW, Holm NR, Maeng M. Quantitative flow ratio for immediate assessment of nonculprit lesions in patients with ST-segment elevation myocardial infarction-An iSTEMI substudy. *Catheter Cardiovasc Interv.* 2019;94:686-92.

34. Smit JM, El Mahdiui M, van Rosendael AR, Jukema JW, Koning G, Reiber JHC, Bax JJ, Scholte AJ. Comparison of Diagnostic Performance of Quantitative Flow Ratio in Patients With Versus Without Diabetes Mellitus. *Am J Cardiol.* 2019;123:1722-8.

35. Asano T, Katagiri Y, Chang CC, Kogame N, Chichareon P, Takahashi K, Modolo R, Tenekecioglu E, Collet C, Jonker H, Appleby C, Zaman A, van Mieghem N, Uren N, Zueco J, Piek JJ, Reiber JHC, Farooq V, Escaned J, Banning AP, Serruys PW, Onuma Y. Angiography-Derived Fractional Flow Reserve in the SYNTAX II Trial: Feasibility, Diagnostic Performance of Quantitative Flow Ratio, and Clinical Prognostic Value of Functional SYNTAX Score Derived From Quantitative Flow Ratio in Patients With 3-Vessel Disease. *JACC Cardiovasc Interv.* 2019;12:259-70.

36. Spitaleri G, Tebaldi M, Biscaglia S, Westra J, Brugaletta S, Erriquez A, Passarini G, Brieda A, Leone AM, Picchi A, Ielasi A, Di Girolamo D, Trani C, Ferrari R, Reiber JHC, Valgimigli M, Sabatè M, Campo G. Quantitative Flow Ratio Identifies Nonculprit Coronary Lesions Requiring Revascularization in Patients with ST-Segment-Elevation Myocardial Infarction and Multivessel Disease. *Circ Cardiovasc Interv.* 2018;11: e006023.

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

38. Choi KH, Lee SH, Lee JM, Hwang D, Zhang J, Kim J, Im SY, Kim HK, Nam CW, Doh JH, Shin ES, Mejía-Rentería H, Park TK, Yang JH, Song Y Bin, Hahn JY, Choi SH, Gwon HC, Escaned J, Koo BK. Clinical relevance and prognostic implications of contrast quantitative flow ratio in patients with coronary artery disease. *Int J Cardiol.* 2021;325:23-9.

39. Westra J, Tu S, Winther S, Nissen L, Vestergaard MB, Andersen BK, Holck EN, Maule CF, Johansen JK, Andreasen LN, Simonsen JK, Zhang Y, Kristensen SD, Maeng M, Kaltoft A, Terkelsen CJ, Krusell LR, Jakobsen L, Reiber JHC, Lassen JF, Bøttcher M, Bøtker HE, Christiansen EH, Holm NR. Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio during Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II). *Circ Cardiovasc Imaging.* 2018;11:e007107.

40. Westra J, Tu S, Campo G, Qiao S, Matsuo H, Qu X, Koltowski L, Chang Y, Liu T, Yang J, Andersen BK, Eftekhari A, Christiansen EH, Escaned J, Wijns W, Xu B, Holm NR. Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: An individual patient-data meta-analysis. *Catheter Cardiovasc Interv.* 2019;94:693-701.

41. 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.

42. Song L, Xu B, Tu S, Guan C, 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, Zhang R, Liu J, Zhao Y, Wang Y, Dou K, Kirtane AJ, Wu Y, Wijns W, Yang W, Leon MB, Qiao S, Stone GW; FAVOR III China Study Group. 2-Year Outcomes of Angiographic Quantitative Flow Ratio-Guided Coronary Interventions. *J Am Coll Cardiol.* 2022;80: 2089-101.

43. Wienemann H, Ameskamp C, Mejía-Rentería H, Mauri V, Hohmann C, Baldus S, Adam M, Escaned J, Halbach M. Diagnostic performance of quantitative flow ratio versus fractional flow reserve and resting full-cycle ratio in intermediate coronary lesions. *Int J Cardiol.* 2022;362:59-67.

44. Warisawa T, Cook CM, Howard JP, Ahmad Y, Doi S, Nakayama M, Goto S, Yakuta Y, Karube K, Shun-Shin MJ, Petraco R, Sen S, Nijjer S, Al Lamee R, Ishibashi Y, Matsuda H, Escaned J, di Mario C, Francis DP, Akashi YJ, Davies JE. Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance. *Circ Cardiovasc Interv.* 2019;12:e007494.

45. Kornowski R, Lavi I, Pellicano M, Xaplanteris P, Vaknin-Assa H, Assali A, Valtzer O, Lotringer Y, De Bruyne B. Fractional Flow Reserve Derived From Routine Coronary Angiograms. *J Am Coll Cardiol.* 2016;68:2235-7.

46. Pellicano M, Lavi I, De Bruyne B, Vaknin-Assa H, Assali A, Valtzer O, Lotringer Y, Weisz G, Almagor Y, Xaplanteris P, Kirtane AJ, Codner P, Leon MB, Kornowski R. Validation Study of Image-Based Fractional Flow Reserve During Coronary Angiography. *Circ Cardiovasc Interv.* 2017;10:e005259.

47. Fearon WF, Achenbach S, Engstrom T, Assali A, Shlofmitz R, Jeremias A, Fournier S, Kirtane AJ, Kornowski R, Greenberg G, Jubeh R, Kolansky DM, McAndrew T, Dressler O, Maehara A, Matsumura M, Leon MB, De Bruyne B; FAST-FFR Study Investigators. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. *Circulation.* 2019;139:477-84.

48. Witberg G, Bental T, Levi A, Talmor-Barkan Y, Rotholz A, Tanigaki T, Nakayama M, Omori H, Itakura R, Kawase Y, Matsuo H, Kornowski R. Clinical

Outcomes of FFRangio-Guided Treatment for Coronary Artery Disease. *JACC Cardiovasc Interv.* 2022;15:468-70.

49. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, Lemmert ME, Wilschut J, Diletti R, de Jaegere P, Zijlstra F, Van Mieghem NM, Daemen J. Validation of three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. *EuroIntervention.* 2020;16:591-9.

50. Masdjedi K, Tanaka N, Van Belle E, Porouchani S, Linke A, Woitek FJ, Bartorelli AL, Ali ZA, den Dekker WK, Wilschut JM, Diletti R, Zijlstra F, Boersma E, Van Mieghem NM, Spitzer E, Daemen J. Vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study. *EuroIntervention.* 2022;17:1498-505.

51. 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.

52. Tu S, Ding D, Chang Y, Li C, Wijns W, Xu B. Diagnostic accuracy of quantitative flow ratio for assessment of coronary stenosis significance from a single angiographic view: A novel method based on bifurcation fractal law. *Catheter Cardiovasc Interv.* 2021;97 Suppl 2:1040-7.

53. Cortés C, Liu L, Berdin SL, Fernández-Corredoira PM, Zhang R, Schäfer U, López M, Diarte JA, Tu S, Gutiérrez-Chico JL. Agreement between Murray law-based quantitative flow ratio (μQFR) and three-dimensional quantitative flow ratio (3D-QFR) in non-selected angiographic stenosis: A multicenter study. *Cardiol J.* 2022;29:388-95.

54. 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.

55. Morris PD, Ryan D, Morton AC, Lycett R, Lawford PV, Hose DR, Gunn JP. Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary lesions. Results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. *JACC Cardiovasc Interv.* 2013;6:149-57.

56. Morris PD, Silva Soto DA, Feher JFA, Rafiroiu D, Lungu A, Varma S, Lawford PV, Hose DR, Gunn JP. Fast Virtual Fractional Flow Reserve Based Upon Steady-State Computational Fluid Dynamics Analysis: Results From the VIRTU-Fast Study. *JACC Basic Transl Sci.* 2017;2:434-46.

57. Tröbs M, Achenbach S, Röther J, Redel T, Scheuering M, Winneberger D, Klingenbeck K, Itu L, Passerini T, Kamen A, Sharma P, Comaniciu D, Schlundt C. Comparison of Fractional Flow Reserve Based on Computational Fluid Dynamics Modeling Using Coronary Angiographic Vessel Morphology Versus Invasively Measured Fractional Flow Reserve. *Am J Cardiol.* 2016;117:29-35.

58. Omori H, Witberg G, Kawase Y, Tanigaki T, Okamoto S, Hirata T, Sobue Y, Ota H, Kamiya H, Okubo M, Valzer O, Kornowski R, Matsuo H. Angiogram based fractional flow reserve in patients with dual/triple vessel coronary artery disease. *Int J Cardiol.* 2019;283:17-22.

59. Tu S, Barbato E, Köszegi Z, Yang J, Sun Z, Holm NR, Tar B, Li Y, Rusinaru D, Wijns W, Reiber JH. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. *JACC Cardiovasc Interv.* 2014;7:768-77.

60. Murai T, Lee T, Yonetsu T, Isobe M, Kakuta T. Influence of microvascular resistance on fractional flow reserve after successful percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2015;85:585-92.

61. Westra J, Eftekhari A, Tu S, Campo G, Escaned J, Winther S, Matsuo H, Qu X, Koltowski L, Chang Y, Liu T, Yang J, Andersen BK, Wijns W, Böttcher M, Christiansen EH, Xu B, Holm NR. Resting distal to aortic pressure ratio and fractional flow reserve discordance affects the diagnostic performance of quantitative flow ratio: Results from an individual patient data meta-analysis. *Catheter Cardiovasc Interv.* 2021:97:825-32.

62. Curzen N, Nicholas Z, Stuart B, Wilding S, Hill K, Shambrook J, Eminton Z, Ball D, Barrett C, Johnson L, Nuttall J, Fox K, Connolly D, O'Kane P, Hobson A, Chauhan A, Uren N, Mccann G, Berry C, Carter J, Roobottom C, Mamas M, Rajani R, Ford I, Douglas P, Hlatky M. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial. *Eur Heart J.* 2021;42:3844-52.

63. Tesche C, De Cecco CN, Albrecht MH, Duguay TM, Bayer RR, Litwin SE, Steinberg DH, Schoepf UJ. Coronary CT angiography-derived fractional flow reserve. *Radiology.* 2017;285:17-33.

64. Koo BK, Erglis A, Doh JH, Daniels D V., Jegere S, Kim HS, Dunning A, Defrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol.* 2011;58:1989-97.

65. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, Van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GBJ, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA.* 2012;308:1237-45.

66. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Bøtker HE, Achenbach S; NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol.* 2014;63:1145-55.

67. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U, Schuchlenz HW, Feuchtner G, Gilard M, Andreini D, Jensen JM, Hadamitzky M, Chiswell K, Cyr D, Wilk A, Wang F, Rogers C, De Bruyne B; PLATFORM Investigators. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J.* 2015;36:3359-67.

68. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U, Schuchlenz HW, Feuchtner G, Gilard M, Andreini D, Jensen JM, Hadamitzky M, Chiswell K, Cyr D, Wilk A, Wang F, Rogers C, Hlatky MA; PLATFORM Investigators. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. *J Am Coll Cardiol.* 2016;68:435-45.

69. Patel MR, Nørgaard BL, Fairbairn TA, Nieman K, Akasaka T, Berman DS, Raff GL, Hurwitz Koweek LM, Pontone G, Kawasaki T, Sand NPR, Jensen JM, Amano T, Poon M, Øvrehus KA, Sonck J, Rabbat MG, Mullen S, De Bruyne B, Rogers C, Matsuo H, Bax JJ, Leipsic J. 1-Year Impact on Medical Practice and Clinical Outcomes of FFR_{CT}: The ADVANCE Registry. *JACC Cardiovasc Imaging.* 2020;13: 97-105.

70. Cook CM, Petraco R, Shun-Shin MJ, Ahmad Y, Nijjer S, Al-Lamee R, Kikuta Y, Shiono Y, Mayet J, Francis DP, Sen S, Davies JE. Diagnostic Accuracy of Computed Tomography-Derived Fractional Flow Reserve: A Systematic Review. *JAMA Cardiol.* 2017;2:803-10.

71. Thim T, van der Hoeven NW, Musto C, Nijveldt R, Götberg M, Engstrøm T, Smits PC, Oldroyd KG, Gershlick AH, Escaned J, Baptista SB, Raposo L, van Royen N, Maeng M. Evaluation and Management of Nonculprit Lesions in STEMI. *JACC Cardiovasc Interv.* 2020;13:1145-54.

72. Erbay A, Penzel L, Abdelwahed YS, Klotsche J, Heuberger A, Schatz AS, Steiner J, Haghikia A, Sinning D, Fröhlich GM, Landmesser U, Stähli BE, Leistner DM. Prognostic Impact of Pancoronary Quantitative Flow Ratio Assessment in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes. *Circ Cardiovasc Interv.* 2021;14:e010698.

73. Duguay TM, Tesche C, Vliegenthart R, De Cecco CN, Lin H, Albrecht MH, Varga-Szemes A, De Santis D, Ebersberger U, Bayer RR, Litwin SE, Hoffmann E, Steinberg DH, Schoepf UJ. Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve Based on Machine Learning for Risk Stratification of Non-Culprit Coronary Narrowings in Patients with Acute Coronary Syndrome. *Am J Cardiol.* 2017;120:1260-6.

74. 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.

75. Cerrato E, Mejía-Rentería H, Dehbi HM, Ahn JM, Cook C, Dupouy P, Baptista SB, Raposo L, Van Belle E, Götberg M, Davies JE, Park SJ, Escaned J. Revascularization Deferral of Nonculprit Stenoses on the Basis of Fractional Flow Reserve: 1-Year Outcomes of 8,579 Patients. *Cardiovasc Interv.* 2020;13:1894-903.

76. Marwan M, Taher MA, El Meniawy K, Awadallah H, Pflederer T, Schuhbäck A, Ropers D, Daniel WG, Achenbach S. In vivo CT detection of lipid-rich coronary artery atherosclerotic plaques using quantitative histogram analysis: a head to head comparison with IVUS. *Atherosclerosis.* 2011;215:110-5.

77. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, Shimada K, Yoshiyama M. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging.* 2013;6:448-57.

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

79. Jensen JM, Bøtker HE, Mathiassen ON, Grove EL, Øvrehus KA, Pedersen KB, Terkelsen CJ, Christiansen EH, Maeng M, Leipsic J, Kaltoft A, Jakobsen L, Sørensen JT, Thim T, Kristensen SD, Krusell LR, Nørgaard BL. Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris: influence on downstream rate of invasive coronary angiography. *Eur Heart J Cardiovasc Imaging.* 2018;19:405-14.

80. Van Belle E, Raposo L, Bravo Baptista S, Vincent F, Porouchani S, Cosenza A, Rogers C, Leipsic J. Impact of an Interactive CT/FFR_{CT} Interventional Planner on Coronary Artery Disease Management Decision Making. *JACC Cardiovasc Imaging.* 2021;14:1068-70.

81. Ihdayhid AR, White A, Ko B. Assessment of Serial Coronary Stenoses With Noninvasive Computed Tomography-Derived Fractional Flow Reserve and Treatment Planning Using a Novel Virtual Stenting Application. *JACC Cardiovasc Interv.* 2017;10:e223-5.

82. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PAL, De Bruyne B, Pijls NH, Fearon WF; FAME Study Investigators. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol.* 2011;58: 1211-8.

83. Escaned J, Collet C, Ryan N, Luigi De Maria G, 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.

84. Papadopoulou SL, Girasis C, Dharampal A, Farooq V, Onuma Y, Rossi A, Morel MA, Krestin GP, Serruys PW, De Feyter PJ, Garcia Garcia HM. CT-SYNTAX score: A feasibility and reproducibility Study. *JACC Cardiovasc Imaging.* 2013;6: 413-5.

85. 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.

86. 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.

87. Liontou C, Mejía-Rentería H, Lauri F, Goto S, Lee HJ, Nakayama M, Quirós A, Macaya F, Gonzalo N, Núñez-Gil I, Salinas P, Del Trigo M, Escaned J. Quantitative flow ratio for functional evaluation of in-stent restenosis. *EuroIntervention.* 2021;17: e396-8.

88. Maintz D, Seifarth H, Raupach R, Flohr T, Rink M, Sommer T, Ozgün M, Heindel W, Fischbach R. 64-slice multidetector coronary CT angiography: in vitro evaluation of 68 different stents. *Eur Radiol.* 2006;16:818-26.

89. Mahnken AH. CT Imaging of Coronary Stents: Past, Present, and Future. *ISRN Cardiol.* 2012;2012:139823.

90. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-98.

91. Kotronias RA, Kwok CS, George S, Capodanno D, Ludman PF, Townend JN, Doshi SN, Khogali SS, Généreux P, Herrmann HC, Mamas MA, Bagur R. Transcatheter Aortic Valve Implantation With or Without Percutaneous Coronary Artery Revascularization Strategy: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2017;6:e005960.

92. Pesarini G, Scarsini R, Zivelonghi C, Piccoli A, Gambaro A, Gottin L, Rossi A, Ferrero V, Vassanelli C, Ribichini F. Functional Assessment of Coronary Artery Disease in Patients Undergoing Transcatheter Aortic Valve Implantation: Influence of Pressure Overload on the Evaluation of Lesions Severity. *Circ Cardiovasc Interv.* 2016;9:e004088.

93. Khawaja MZ, Wang D, Pocock S, Redwood SR, Thomas MR. The percutaneous coronary intervention prior to transcatheter aortic valve implantation (ACTIVATION) trial: study protocol for a randomized controlled trial. *Trials.* 2014;15:300.

94. 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.

95. 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.

96. De Maria GL, Scarsini R, Shanmuganathan M, Kotronias RA, Terentes-Printzios D, Borlotti A, Langrish JP, Lucking AJ, Choudhury RP, Kharbanda R, Ferreira VM; Oxford Acute Myocardial Infarction (OXAMI) Study Investigators; Channon KM, Garcia-Garcia HM, Banning AP. Angiography-derived index of microcirculatory resistance as a novel, pressure-wire-free tool to assess coronary microcirculation in ST elevation myocardial infarction. *Int J Cardiovasc Imaging.* 2020;36:1395-406.

97. Tebaldi M, Biscaglia S, Di Girolamo D, Erriquez A, Penzo C, Tumscitz C, Campo G. Angio-Based Index of Microcirculatory Resistance for the Assessment of the Coronary Resistance: A Proof of Concept Study. *J Interv Cardiol.* 2020;2020: 8887369-8887369.

98. Mejia-Renteria H, Lee JM, Choi KH, Lee SH, Wang L, Kakuta T, Koo BK, Escaned J. Coronary microcirculation assessment using functional angiography: Development of a wire-free method applicable to conventional coronary angiograms. *Catheter Cardiovasc Interv.* 2021;98:1027-37.

99. Choi KH, Dai N, Li YL, Kim J, Shin D, Lee SH, Joh HS, Kim HK, Jeon KH, Ha SJ, Kim SM, Jang MJ, Park TK, Yang JH, Song Y Bin, Hahn JY, Doh JH, Shin ES, Choi SH, Gwon HC, Lee JM. Functional Coronary Angiography-Derived Index of Microcirculatory Resistance in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv.* 2021;14:1670-84.

Supplementary data

Supplementary Table 1. Patient exclusion rates across studies.

Supplementary Table 2. Exclusion criteria across the studies.

Supplementary Figure 1. User interface of an FFR_{angio} evaluation of the left anterior descending artery.

Supplementary Figure 2. CAAS vFFR in the diagnostic assessment of intermediate stenosis functional significance.

Supplementary Figure 3. caFFR interrogation of a left anterior descending artery.

Supplementary Figure 4. μQFR interrogation of a left anterior descending artery.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00969

Supplementary data

Supplementary Table 1. Patient exclusion rates across studies.

Technique	Study	Patients Screened	Patients included	% Excluded
QFR	FAVOR Pilot (17)	88	72	18,2
	FAVOR II China (16)	335	307	8,4
	FAVOR II Europe Japan (18)	329	272	17,3
	WIFI II (39)	292	172	41,1
	Yazaki et al. (19)	-	142	-
	Ties et al. (21)	274	128	53,3
	Koltowski et al. (20)	740	268	63,8
	Mejía-Renteria et al. (22)	304	248	18,4
	Emori et al. (23)*	163	150	8,0
	Emori et al. (25)	106	100	5,7
	Smit et al. (29)***	-	259	-
	Smit et al. (24)	-	290	-
	Stähli et al. (26)	493	436	11,6
	Hwang et al. (27)	118	82	30,5
	Tanigaki et al (37)	172	152	11,6
	Lauri et al. (31)	136	82	39,7
	Asano et al. (35)	454	386	15,0
	Rubimura et al. (30)	240	84	65,0
FFR_{angio}	FAST-FFR (47)	352	301	14,5
	Kornowski et al. (45)	-	88	-
	Trobs et al. (57)	86	73	15,1
	Pellicano et al. (46)	199	184	7,5
	Omori et al. (58)	67	50	25,4
vFFR	VIRTU-1 (55)	20	19	5,0
	VIRTU-FAST (56)	-	20	-
CAAS-vFRR	FAST (49)	-	100	-
caFRR	FLASH-FFR (51)	330	328	0,6
vFAI	Papafaklis et al.(54)	-	120	-
FFRQCA	Tu et al. (59)	71	68	4,2
FFR_{CT}	DISCOVER-FLOW (64)	-	103	-
	DeFACTO (65)	285	252	11,6
	HFNXT trial (66)	365	254	30,4

Legend: QFR -Quantitative Flow Ratio; FFR_{angio} - Angiography-derived FFR ;- vFFR - Virtual Fractional Flow Reserve; CAAS-vFFR - Vessel fractional flow reserve; caFFR- Computational pressure-flow dynamics derived FFR, vFAI - Virtual Functional Assessment Index; FFRQCA – Fractional Flow Reserve calculated from 3-

dimentional Quantitative Coronary Angiography; FFR_{CT}- FFR_{CT} - Coronary Computed Tomography derived Fractional Flow Reserve

Supplementary Table 2. Exclusion criteria across the studies.

	Number of studies
Angiographical	
Aorto-ostial lesions	23
CABG	21
Vessel Overlap	12
Tortuosity	5
Bifurcations	7
Poor image quality/contrast filling	16
No nitrates given	4
Bridging	2
<2 projections	10
CTO	6
Left Main	12
Recent PCI	3
Stent restenosis	7
Diffuse disease	4
Target vessel collaterals	5
TIMI flow grade < 3	2
Thrombus	2
Small reference vessel (<2mm)	2
Aneurysm	1
Clinical	
Allergy	7
Heart Failure	6
Recent MI	9
CKD	3
Atrial arrhythmias/Tachycardia	5
Heart transplant	2
Heart valve surgery	2
Aortic stenosis	1
CCS Class IV angina	1
Intracardiac devices	1
BMI>35Kg.m^{-2}	1

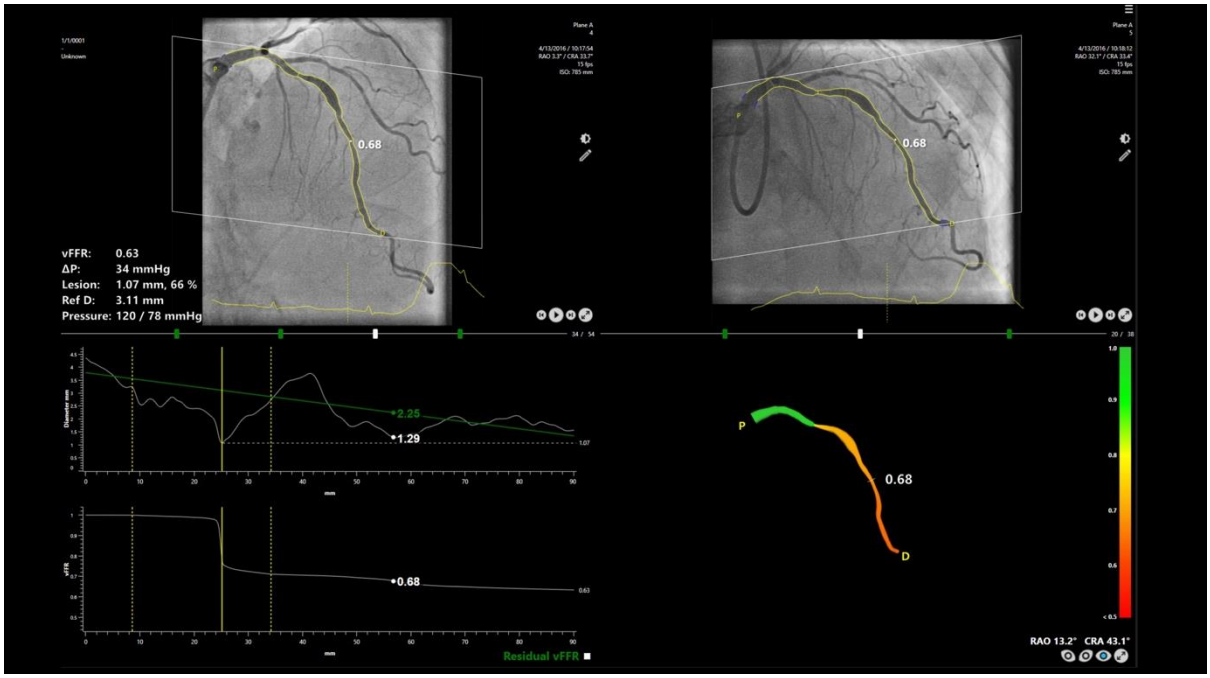
Legend: CABG – Coronary Artery Bypass Grafting; CTO – Chronic Total Occlusion; PCI – Percutaneous Coronary Intervention; TIMI – Thrombolysis in Myocardial Infarction; CKD – Chronic Kidney Disease; CCS – Canadian Cardiovascular Society; BMI – Body Mass Index.

Supplementary Figure 1.

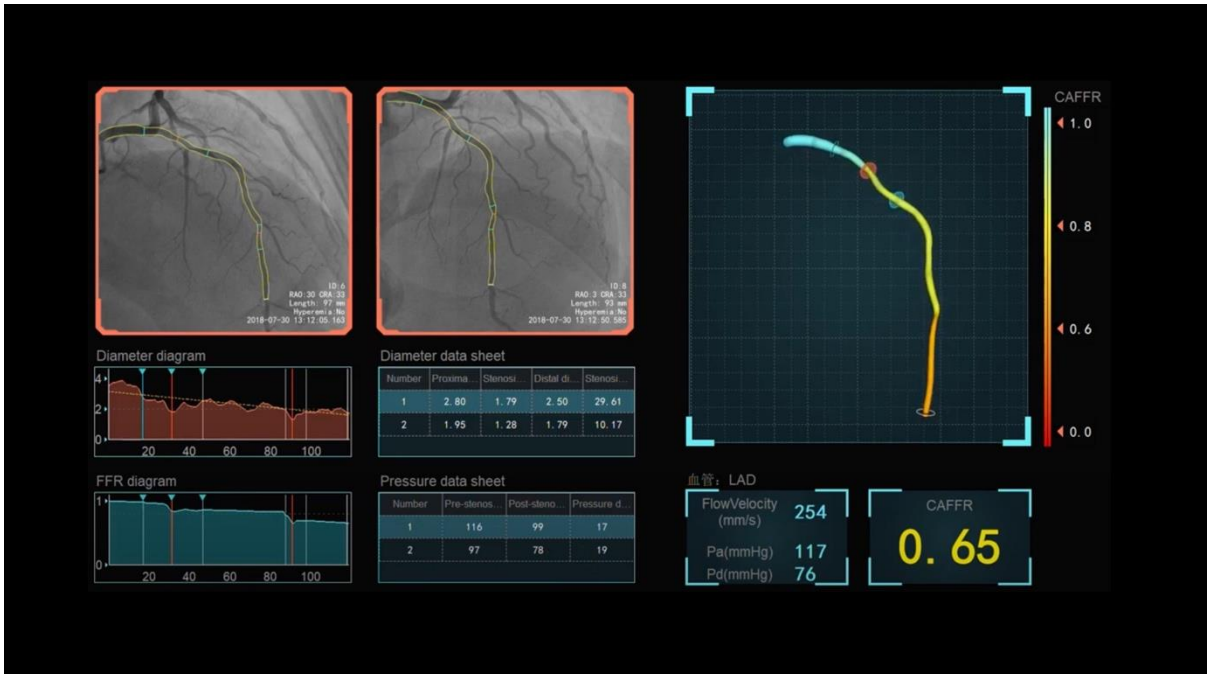
User interface of an FFR_{angio} evaluation of the left anterior descending artery.

Caption: Left Panel) 3-dimension reconstruction of the left coronary artery and left anterior descending artery evaluation showing significant ischemia (FFR=0.72) in the mid-distal segment. Right Upper Panel) Three different coronary angiograms are needed for the model reconstruction. Right Lower Panel) Virtual QCA pullback analysis showing the expected vessel diameter (green line) and the observed vessel diameter (white line) showing a 55% diameter stenosis in the analyzed segment.

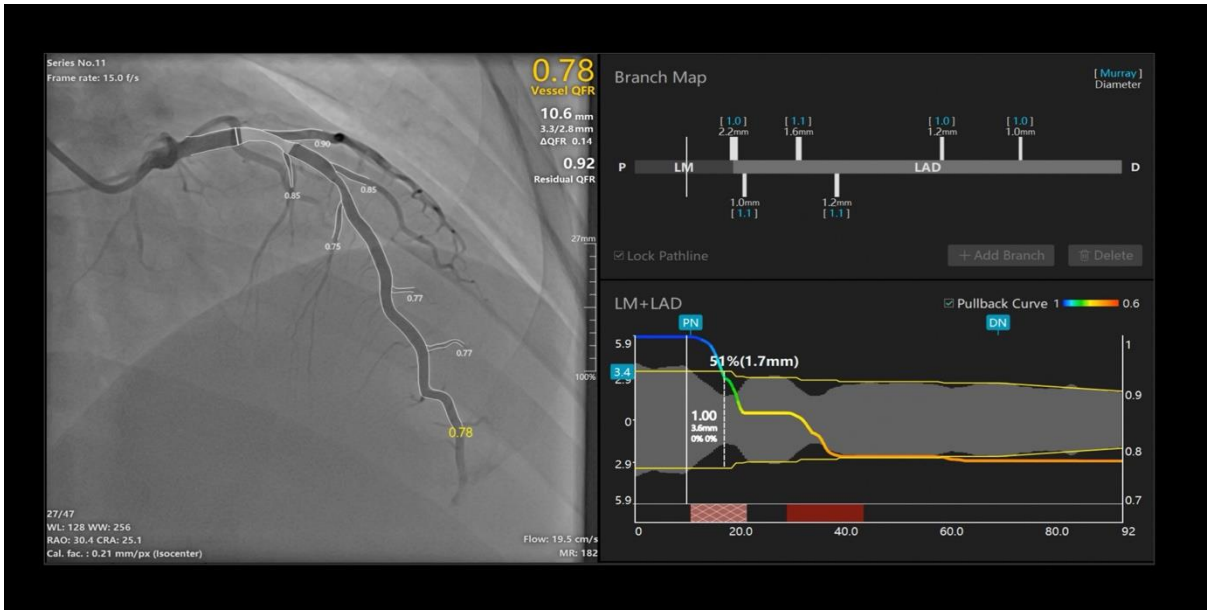
Legend: FFR_{angio} - Angiography-derived FFR; FFR – Fractional Flow Reserve; QCA – Quantitative Coronary Angiography.



Supplementary Figure 2.
CAAS vFFR in the diagnostic assessment of intermediate stenosis functional significance.
Caption: Reconstruction of the left anterior descending artery and computation of vessel FFR, using two angiographic projections at least 30 degrees apart and invasively measured aortic root pressure. *Courtesy of Pie Medical Imaging.*
Legend: CAAS-vFFR - Vessel fractional flow reserve; FFR – Fractional Flow Reserve.



Supplementary Figure 3.
caFFR interrogation of a left anterior descending artery.
Caption: Upper Left Panel: Selection of 2 different angiographic projections of the left anterior descending artery; Lower Left Panel: Diameter by QCA and FFR estimation pullback of the interrogated vessel. Right Panel: Graphical representation of the evaluated segment and estimated FFR result.
Legend: caFFR- Computational pressure-flow dynamics derived FFR; QCA – Quantitative Coronary Angiography; FFR – Fractional Flow Reserve.



Supplementary Figure 4.

µQFR interrogation of a left anterior descending artery.

Caption: Right panel: Right Cranial View of the LAD artery with an intermediate stenosis in de mid-segment with direct functional interrogation of the main vessel and respective side branches. Upper Left Panel: Side branch map evaluation with respective functional index result and vessel diameter. Lower Left Panel: Virtual Pullback showing a focal drop on the corresponding mid-segment lesion.

Legend: Murray-based Quantitative Flow Ratio; LM – Left Main; LAD -Left Anterior Descending