EXPERT REVIEW
STATE-OF-THE-ART CORONARY INTERVENTIONS

State of the art: pressure wire and coronary functional assessment

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KEYWORDS

- coronary flow reserve
- fractional flow reserve
- instantaneous wave-free ratio

Abstract

The pressure wire has revolutionised cardiology by moving the focus of revascularisation from anatomy to physiology. This review provides a comprehensive viewpoint on the foundations of the field of intra-coronary physiology, with emphasis on the development and clinical evidence of fractional flow reserve (FFR). Additionally, we critically appraise clinical decision making based on the evolving area of resting coronary physiology. The emerging role of coronary flow reserve and its complementariness with FFR is also discussed, and the importance of the invasive assessment of the coronary microcirculation in outlining prognosis is put into perspective. Overall, this review summarises the capacity of invasive coronary physiology indices to guide revascularisation and to discriminate patients at high risk of an adverse cardiovascular outcome.

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Introduction

The pressure wire has revolutionised interventional cardiology by moving the focus of revascularisation from anatomy to physiology. This review provides a comprehensive viewpoint on the foundations of the intracoronary physiology field, critically appraises clinical decision making based on fractional flow reserve (FFR) and the evolving area of resting coronary physiology, puts into perspective the re-emerging role of coronary flow reserve and its complementariness with FFR, and finally describes some aspects of the importance of the invasive assessment of the coronary microcirculation. Overall, this review summarises the capacity of invasive coronary physiology to guide revascularisation and to discriminate patients at high risk of an adverse cardiovascular outcome **(Table 1)**.

Past of the pressure wire

For those who were medical students in the 1970s, the complex equation of Donald Young was the best approach to understand coronary physiology as described in his landmark paper in Circulation Research **(Figure 1)**[1]. Soon after, several authors applied these equations[2], but it was not until 1978 that Lance Gould firstly determined the applicability of these equations to vasoactive coronary arteries in the awake animal and secondly proposed a simplified and generalised form of the equations[3]. The Poiseuille principle was represented in the equation by the viscous friction (f) between layers of flow, and Bernoulli's principle by the loss of kinetic energy at the exit of the lesion, with vortex formation as a result of the separation (s) of laminar layers of flow. R. Kirkeeide popularised the equation in 1986, by introducing quantitative coronary angiography exit angle, entry angle and reference and minimum lumen areas; the drop of pressure could be inferred from the equation[4]. For those who like historical proof, in 1988 in the American Journal of Cardiology the haemodynamic results immediately after stenting were reported for the Bernoulli and Poiseuille resistance at coronary flows of 0.5, 1 and 3 ml/sec [5].

Around 1987, the Doppler wire was introduced and, although we could measure coronary flow velocity and coronary flow

Table 1. Overview of clinical coronary physiology

| 1. States	Resting	Sub-maximum hyperaemia (contrast)
	Maximum hyperaemic agent	Exercise
	Pacing	Other vasoactive or chronotropic drugs
2. Physiology variables measured	Aortic pressure (Pa)	Aortic pressure (Pa)
	Thermodilution mean transit time (Tmn)	Average peak Doppler flow velocity
	Electrocardiogram	Wedge and venous pressure
	Blood samples	Angiography parameters
3. 1 Pressure indices	Resting Pd/Pa	Rest Pd/rest Pa
	Instantaneous wave-free ratio (iFR)	Pd at wave-free period/Pa at wave-free period
	Contrast Pd/Pa	Mean Pd/mean Pa at contrast sub-maximum hypaemia
	Mean fractional flow reserve (FFR)	Mean Pd/mean Pa at maximum hypaemia
	Diastolic fractional flow reserve (dFFR)	Diastolic Pd/diastolic Pa at maximum hypaemia
3.2 Flow indices	Tmn (rest and hyperaemia)	Mean transit time (Tmn)
	APV (rest and hyperaemia)	Average peak Doppler flow velocity
	Coronary flow reserve (thermodilution)	Tmn rest/Tmn hyperaemia
	Coronary flow velocity reserve (Doppler)	Hyperaemia APV/rest APV
	Coronary flow capacity	Relationship between CFR and hyperaemic flow
	Pattern of thermodilution curve	Narrow unimodal, wide unimodal, bimodal
3.3 Stenosis resistance indices	Baseline stenosis resistance (thermodilution)	(Rest Pd-rest Pa)*Rest Tmn
	Baseline stenosis resistance (Doppler)	(Rest Pa-rest Pd)/rest APV
	Hyperaemic stenosis resistance (thermodilution)	(Hyperaemic Pa-hyperaemic Pd)*hyperaemic Tmn
	Hyperaemic stenosis resistance (Doppler)	(Hyperaemic Pa-hyperemic Pd)/hyperaemic APV
3.4 Microcirculatory resistance indices	Baseline microcirculatory resistance (thermodilution)	Rest Pd*Rest Tmn
	Baseline microcirculatory resistance (Doppler)	Rest Pd/rest APV
	Index of microcirculatory resistance (thermodilution)	Hyperaemic Pd*hyperaemic Tmn
	Hyperaemic microcirculatory resistance index (Doppler)	Hyperaemic Pd/hyperaemic APV
3.5 Phasic flow velocity and coronary pressure	IHDVPS	Slope of APV=a+β(Pd or Pa)
	Zero flow pressure (Pzf)	X axis intercept of y=a+βx
	Wave intensity analysis	Pressure velocity waves
4. Other	TIMI flow	TIMI frame count
	TIMI blush grade	TIMI blush grade
	Acetylcholine test	
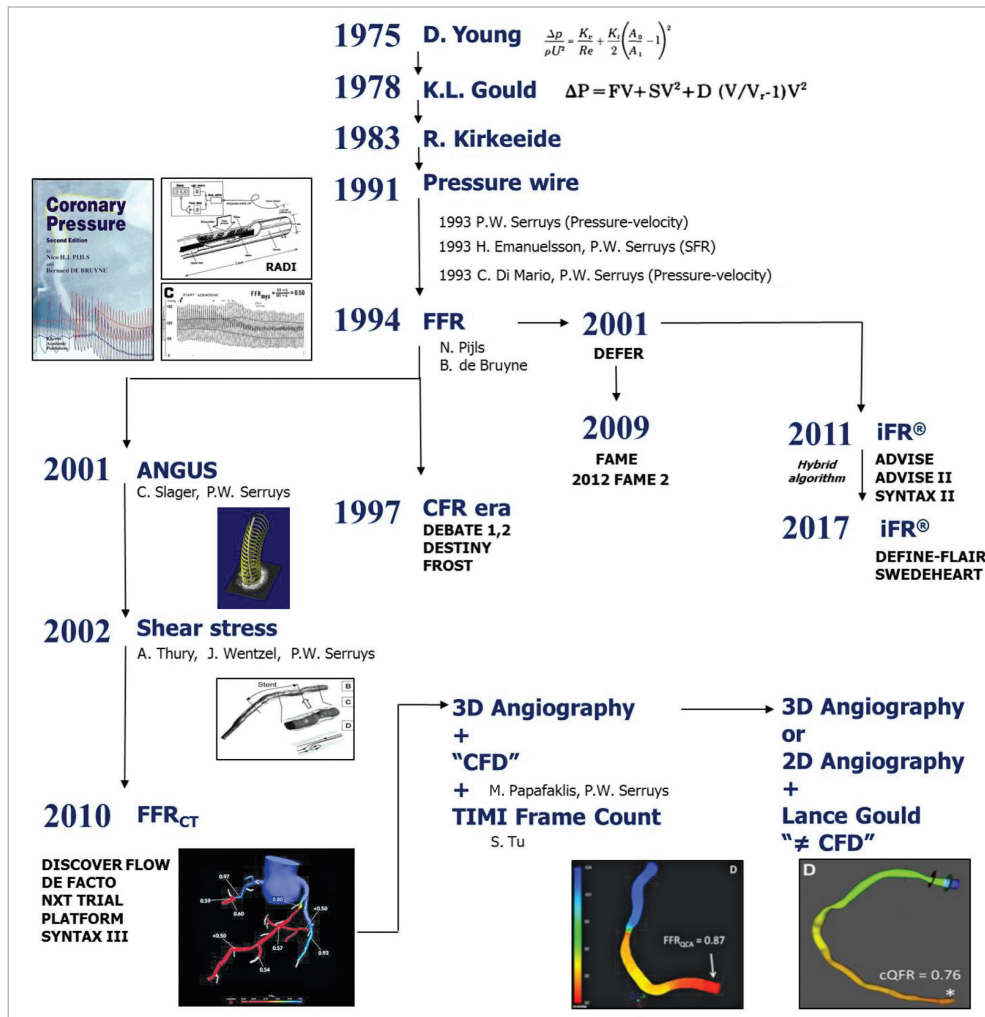
Figure 1. *A helicopter view of the field of coronary physiology, its development and ramifications.*

reserve (CFR)[6,7], it quickly became unclear which was the CFR criterion for normality[8]. In animal models, it was in the range of 4 to 5 but after the first human studies we saw the emergence of various CFR cut-offs. We may have forgotten, but important trials such as DEBATE I, II and DESTINY combined percent diameter stenosis with CFR to improve clinical decision making and help define which lesions could be safely deferred from percutaneous coronary intervention (PCI)[9,10].

The introduction of the pressure wire in 1991 by a Swedish company, RADI, ushered in a new era of coronary physiology. The work of Nico Pijls on coronary collaterals in dogs inaugurated the FFR era[11]. It took him some time to move from coronary collaterals to FFR but, together with Bernard de Bruyne, he was able to evaluate the diagnostic accuracy of FFR against exercise testing, thallium scintigraphy and stress echocardiography[12]. DEFER in 2001, FAME in 2009 and FAME 2 in 2012 translated the FFR concept from the bench to clinical practice, and finally, FFR has become an accepted parameter by the interventional community for clinical decision making[13-15].

In parallel to this rather simple FFR measurement, on both sides of the Atlantic, in Stanford, Boston and Rotterdam, techniques combining intravascular ultrasound and angiography were developed (the so-called ANGUS) able to measure shear stress in human coronary arteries[16]. It was a tedious and cumbersome procedure, since it involved a three-dimensional (3D) reconstruction of the vessel (with the correct positioning of the intravascular ultrasound cross-section on the centreline of the vessel filmed in biplane angiography), the creation of a mesh of finite elements, calculation of shear stress and drop in pressure. Around 2010, the community was "destabilised" by the introduction of FFR derived from computed tomography angiography (FFR-CT). This technology was developed by HeartFlow under the leadership of Charles Taylor, and a series of trials popularised the colour-coded assessment of FFR-CT[17]. Around the same time, we were also "destabilised" by the introduction of the instantaneous wave-free ratio (iFR) by Justin Davies, looking into diastole, where microcirculatory resistance is stable[18,19]. iFR triggered many debates, because for the pioneers it was difficult to be challenged by a new

technique not based on their "credo" – that both the epicardial vessel and microcirculation have to be fully dilated to assess the stenosis. Credit has to be given to the pioneers of the iFR, because very quickly they moved from ADVISE I and II, small clinical trials, to the large randomised DEFINE-FLAIR and iFR-SWEDE-HEART studies, aiming as trialists to evaluate the rate of major adverse cardiac events (MACE) with FFR or iFR guidance[19-22].

History is still not complete, since the colourful FFR-CT has triggered, in the most conventional field of angiography, attempts to create pseudo-FFRs, by combining angiographic data with computational fluid dynamics, including the Lance Gould equation. In 2014, the Boston group, together with Rotterdam and Ioannina, and Shengxian Tu, published the first non-commercial academic angiography-derived FFR, the so-called quantitative flow ratio (QFR)[23]. Whether large corporations will succeed in putting this technology online remains to be seen. While, at present, in 2017, it might look like we are going in circles, the reality is that we have made real progress in assessing the physiology of the coronary artery.

Present of the pressure wire
### FRACTIONAL FLOW RESERVE
CONCEPT
In 1993, Piljs et al described and experimentally validated the theoretical basis for the calculation of coronary flow from coronary pressure in the different components of the coronary circulation[11]. Here, it was shown that, at maximal hyperaemia, the ratio of distal-to-aortic pressure in a stenosed coronary artery was linearly and strongly correlated to the ratio of stenotic-to-normal mean arterial
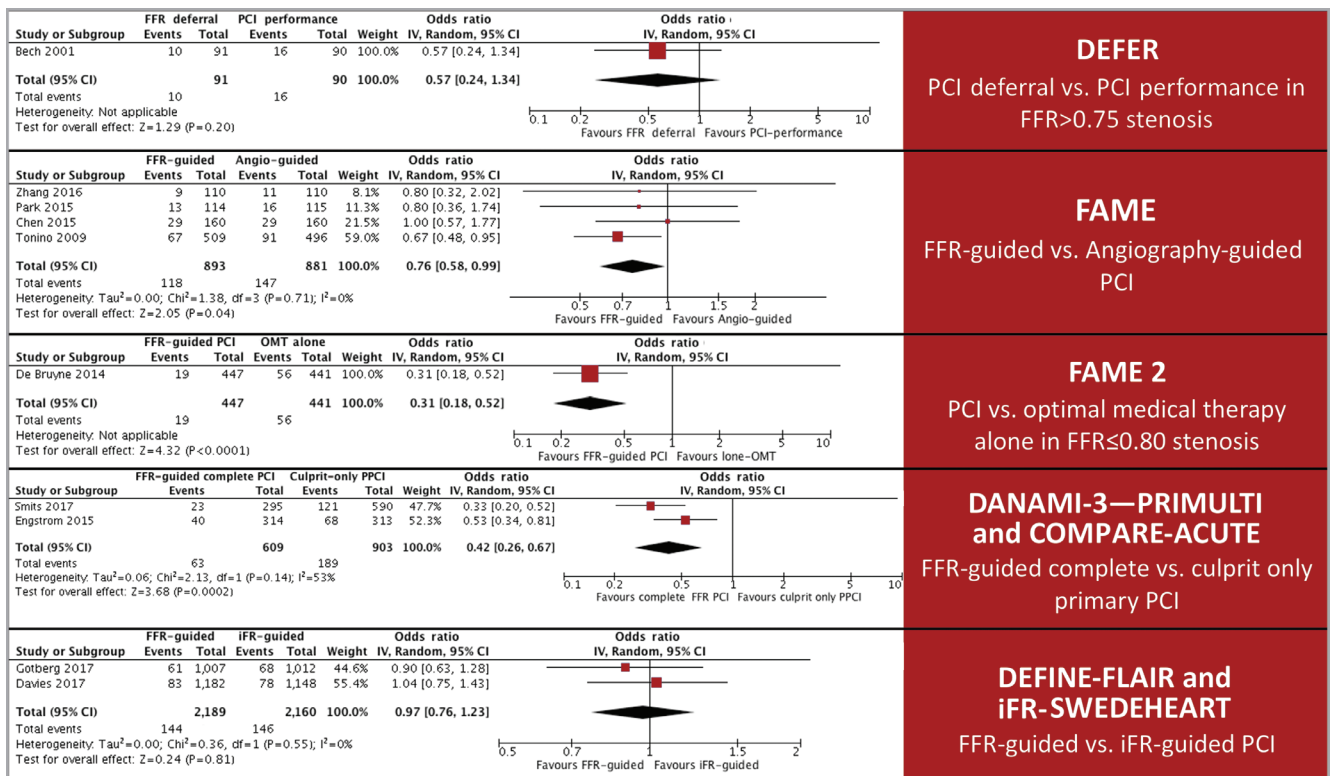
Doppler-derived blood flow velocity **(Figure 2)**. Consequently, the authors suggested that the derivation of flow reserve from pressures was possible. This was a dramatic step forward in the field, because coronary pressure is easier to measure than coronary flow. FFR was herein defined as the maximum achievable flow in the presence of a stenosis divided by the maximum flow expected in the same distribution in the absence of a stenosis[11]. Then, and because of the linear relationship between pressure and flow during hyperaemia, it was evidenced that FFR could be inferred from pressure, as the ratio of distal pressure (Pd) to aortic pressure (Pa) during maximum hyperaemia, assuming a negligible venous pressure. This elegant and clinically meaningful theory provided FFR with very useful characteristics. For example, the highest possible FFR value is 1.0, which denotes a normal epicardial conductance. An FFR value of 0.70 implies that the maximum flow to the distal myocardium only reaches 70% of what it would be if the artery were to be normal[11]. FFR takes into account the contribution of collaterals, is little influenced by systemic haemodynamics (although this argument has recently been challenged[24]), has reached a single cut-off prospectively validated in randomised trials, and displays a continuous relationship with MACE, such that the largest risk and revascularisation benefit accumulates in the most severe lesions[11,25]. All of these have made FFR an excellent index for clinical decision making in the catheterisation laboratory.

EVIDENCE
FFR revolutionised cardiology by moving the focus of revascularisation from anatomy to physiology **(Figure 3)**. The three most important FFR trials are DEFER, FAME and FAME 2. In DEFER, if FFR was ≥0.75, patients with coronary artery disease (CAD)
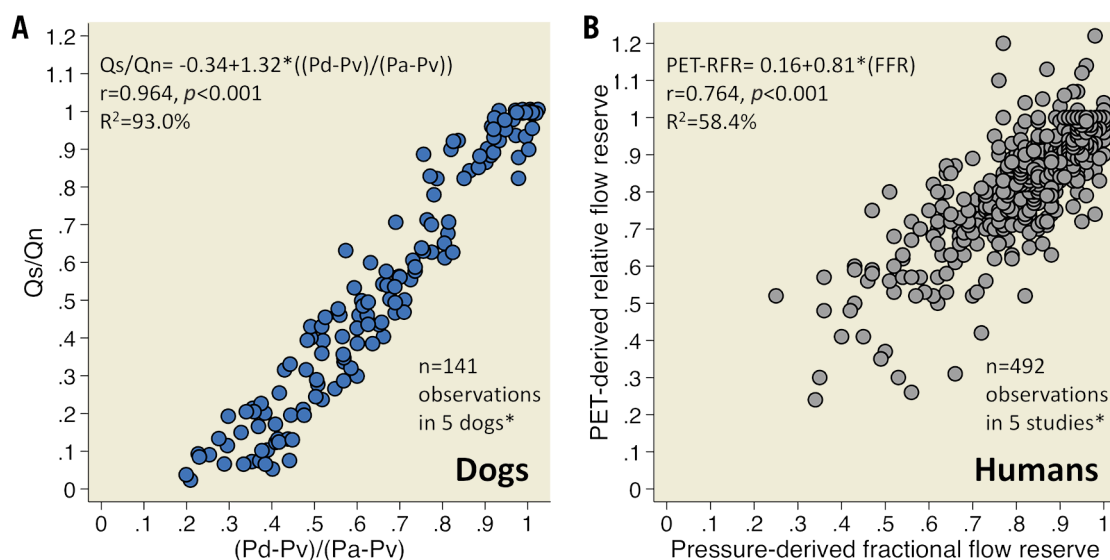
Figure 2. *Derivation of relative flow reserve from pressure. Summary of the relationship between relative flow reserve (RFR) and pressure-derived FFR in experimental and human studies. Individual data points were manually extracted from available scatters with dedicated software. Regressions are hence approximate*. Panel A summarises the five dogs of the FFR validation experiment[11]. Panel B summarises all available peer-reviewed scatters of the relationship between PET-derived RFR and FFR in humans[32,47-50]. A total of 563 vessels were included in these studies. However, only 492 (87.4%) vessels could be extracted and included in the Figure.*

DEFER — PCI deferral vs. PCI performance in FFR>0.75 stenosis

Study or Subgroup	FFR deferral Events	FFR deferral Total	PCI performance Events	PCI performance Total	Weight	Odds ratio IV, Random, 95% CI
Bech 2001	10	91	16	90	100.0%	0.57 [0.24, 1.34]
Total (95% CI)		91		90	100.0%	0.57 [0.24, 1.34]
Total events	10		16			

Heterogeneity: Not applicable
Test for overall effect: Z=1.29 (P=0.20)
Favours FFR deferral — Favours PCI-performance

FAME — FFR-guided vs. Angiography-guided PCI

Study or Subgroup	FFR-guided Events	FFR-guided Total	Angio-guided Events	Angio-guided Total	Weight	Odds ratio IV, Random, 95% CI
Zhang 2016	9	110	11	110	8.1%	0.80 [0.32, 2.02]
Park 2015	13	114	16	115	11.3%	0.80 [0.36, 1.74]
Chen 2015	29	160	29	160	21.5%	1.00 [0.57, 1.77]
Tonino 2009	67	509	91	496	59.0%	0.67 [0.48, 0.95]
Total (95% CI)		893		881	100.0%	0.76 [0.58, 0.99]
Total events	118		147			

Heterogeneity: Tau²=0.00; Chi²=1.38, df=3 (P=0.71); I²=0%
Test for overall effect: Z=2.05 (P=0.04)
Favours FFR-guided — Favours Angio-guided

FAME 2 — PCI vs. optimal medical therapy alone in FFR≤0.80 stenosis

Study or Subgroup	FFR-guided PCI Events	FFR-guided PCI Total	OMT alone Events	OMT alone Total	Weight	Odds ratio IV, Random, 95% CI
De Bruyne 2014	19	447	56	441	100.0%	0.31 [0.18, 0.52]
Total (95% CI)		447		441	100.0%	0.31 [0.18, 0.52]
Total events	19		56			

Heterogeneity: Not applicable
Test for overall effect: Z=4.32 (P<0.0001)
Favours FFR-guided PCI — Favours lone-OMT

DANAMI-3—PRIMULTI and COMPARE-ACUTE — FFR-guided complete vs. culprit only primary PCI

Study or Subgroup	FFR-guided complete PCI Events	Total	Culprit-only PPCI Events	Total	Weight	Odds ratio IV, Random, 95% CI
Smits 2017	23	295	121	590	47.7%	0.33 [0.20, 0.52]
Engstrom 2015	40	314	68	313	52.3%	0.53 [0.34, 0.81]
Total (95% CI)		609		903	100.0%	0.42 [0.26, 0.67]
Total events	63		189			

Heterogeneity: Tau²=0.06; Chi²=2.13, df=1 (P=0.14); I²=53%
Test for overall effect: Z=3.68 (P=0.0002)
Favours complete FFR PCI — Favours culprit only PPCI

DEFINE-FLAIR and iFR-SWEDEHEART — FFR-guided vs. iFR-guided PCI

Study or Subgroup	FFR-guided Events	Total	iFR-guided Events	Total	Weight	Odds ratio IV, Random, 95% CI
Gotberg 2017	61	1,007	68	1,012	44.6%	0.90 [0.63, 1.28]
Davies 2017	83	1,182	78	1,148	55.4%	1.04 [0.75, 1.43]
Total (95% CI)		2,189		2,160	100.0%	0.97 [0.76, 1.23]
Total events	144		146			

Heterogeneity: Tau²=0.00; Chi²=0.36, df=1 (P=0.55); I²=0%
Test for overall effect: Z=0.24 (P=0.81)
Favours FFR-guided — Favours iFR-guided

Figure 3. *FFR-randomised trials. Summary of all published FFR-randomised clinical trials with MACE as primary endpoint[13-15,21,22,51-55]. MACE of each individual study were combined with the random-effects model based on the DerSimonian and Laird method (RevMan 5.2 software) because of different inclusion criteria. FFR-guided PCI was associated with a lower risk of MACE compared to angiography-guided PCI and optimal medical therapy alone. FFR-guided complete PCI was also associated with a lower risk of MACE compared to culprit-only primary PCI. No differences were observed in the rate of MACE between FFR- and iFR-guided PCI.*

and intermediate stenosis were randomly assigned to deferral (n=91) or performance (n=90) of PCI[13]. If FFR was <0.75, PCI was performed (n=144). Event-free survival at five years was not different between the defer and perform groups (80% and 73%, respectively; p=0.52). Moreover, the risk of cardiac death or myocardial infarction related to FFR ≥0.75 stenosis was <1% per year, and not decreased by stenting. FAME randomised 1,005 patients with multivessel CAD to FFR-guided or angiographically guided complete PCI[14]. The MACE-oriented primary endpoint was 18.3% in the angiography group and 13.2% in the FFR group (p=0.02). FAME demonstrated that FFR-guided PCI results in better clinical outcomes as compared to angiography-guided complete PCI. FAME 2 hypothesised that, in patients with FFR-significant stenoses, PCI plus optimal medical therapy would be superior to medical therapy alone[15]. The study was positive and recruitment halted prematurely (n=1,220, ±54% of projected sample size), because of a significant difference in the percentage of patients who had a primary endpoint event (4.3% in the PCI group versus 12.7% in the medical therapy alone group, p<0.001), which was mostly driven by a lower rate of urgent revascularisation in the PCI group[15]. Altogether, these trials demonstrated that deferral of PCI on the basis of FFR is safe at long term and that FFR-guided PCI

improves patient outcome as compared to medical therapy alone and angiography-guided PCI. These are the reasons why FFR received a class 1A recommendation in the 2014 ESC EACTS guidelines on myocardial revascularisation for the identification of relevant stenosis when evidence of ischaemia is not otherwise available[26].

LIMITATIONS

The FFR model applies only during maximum hyperaemia when all resistances are constant and the derivation of flow reserve from pressure is possible[11]. The development of "true maximum hyperaemia" in clinical practice, however, is hampered by several factors, including a heterogeneous response to vasodilator agents and the functional status of the microcirculation. Indeed, only 84% of patients achieve "maximum" hyperaemia with intravenous adenosine when compared to intracoronary papaverine[27], and the functionality of the microcirculation may raise concerns, particularly in patients suffering from acute coronary syndromes, where local neurohumoral reflexes, epicardial spasm, microvascular vasoconstriction, compression and plugging, and elevated left ventricle end-diastolic pressure may lead to transitory microcirculatory dysfunction (MCD) in culprit and remote myocardial beds[28]. This is of paramount importance, because the proportion of patients with

acute coronary syndromes undergoing catheterisation is steadily increasing worldwide[28].

Another fundamental limitation of FFR stems from its lone-pressure nature. Although coronary pressure and flow are closely related, flow is primarily more important for the maintenance of myocardial function[25]. It should be emphasised that FFR was designed to assess the relative contribution of the stenosis to the overall degree of myocardial flow impairment[11]. If myocardial flow is truly impaired in the myocardium, however, it cannot be known from FFR alone[25,29]. That is to say, even if a stenosis is contributing significantly to myocardial flow impairment (i.e., FFR ≤0.80), the maximum achievable flow might suffice to avoid ischaemia. On the other hand, even if a stenosis is not contributing significantly to myocardial flow impairment (i.e., FFR >0.80), the maximum achievable flow might not suffice and ischaemia may be present **(Figure 4)**. Both conditions are not anecdotal and could exist in as many as 30% of clinically assessed vessels[29]. These limitations of FFR theory indicate room for further refinement and clearly support the need for a more comprehensive invasive diagnosis of CAD.

INSTANTANEOUS WAVE-FREE RATIO
CONCEPT
In 2010 it was recognised that the resting Pd/Pa ratio was strongly correlated with FFR[30]. At that time, Davies et al had already shown how wave intensity analysis could be used to identify and quantify the pressure-velocity waves in normal human coronary arteries[18]. A detailed analysis of these waves in stenosed coronary arteries was later performed by Sen et al, who identified that, during mid to late diastole, there is a finite period of time where the formation of new pressure-velocity waves is absent[19]. Within this wave-free period, the authors observed that microvascular resistance was lower than mean whole-cycle resting resistance, and not statistically different from mean hyperaemic whole-cycle resistance. Moreover, the coefficients of variation of the wave-free microvascular resistance and the hyperaemic whole-cycle resistance were not significantly different. Therefore, the authors postulated that, during the wave-free period, microcirculatory resistance is naturally stable and minimised which, as discussed above, are the theoretical prerequisites for the derivation of flow reserve from pressure. The iFR was therefore proposed as a vasodilator-free index of stenosis severity comparable to FFR, and defined as the ratio of mean Pd to mean Pa both during the wave-free period[19].

EVIDENCE
Several groups put iFR through scrutiny. Most of these were summarised in RESOLVE, a comprehensive (n=1,593 retrospective pressure traces) core-laboratory analysis of the diagnostic accuracy of iFR and resting Pd/Pa against FFR[31]. RESOLVE documented a moderate linear relationship between both iFR and Pd/Pa with FFR (R^2=0.66 and 0.69, respectively), with an overall, and non-statistically different, diagnostic accuracy of ~80% for both
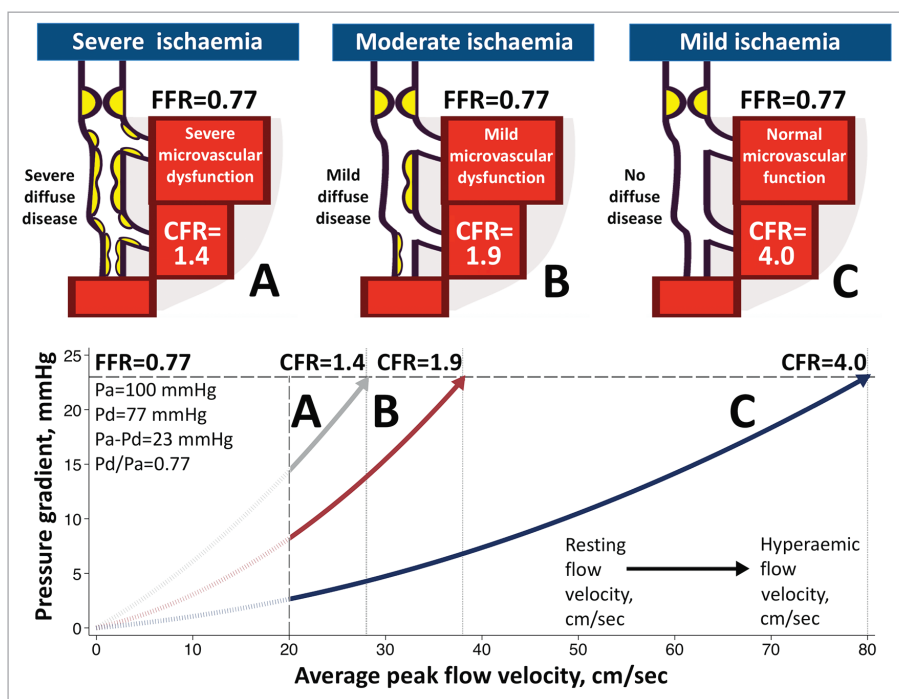
Figure 4. *FFR and CFR discordance. This figure conceptually illustrates three scenarios of a same hypothetical FFR value within the FFR grey zone. In vessel C, diffuse and microvascular disease are minimal. CFR is normal and ischaemia unlikely. Vessel B represents the most common case, where moderate diffuse and microvascular disease contribute, in addition to the stenosis, to exhausting the CFR. Vessel A is highly affected by diffuse and microvascular disease. Here, CFR is severely exhausted and profound ischaemia highly likely, even if FFR is only moderately affected.*

non-hyperaemic indices. RESOLVE results were similar to the findings of the meticulous and prospective ADVISE II study[20], that permits to conclude that the iFR and FFR relationship in clinical populations is weaker than that reported in the original iFR description, and that, for FFR diagnosis, iFR is not statistically superior to resting Pd/Pa[20,31]. In this interpretation, however, it should be kept in mind that, despite the clinical benefits of FFR, there is no gold standard for the detection of myocardial ischaemia, and that many other ischaemia tests are also supported by vast outcome data. Investigators thus decided to evaluate the diagnostic accuracy of iFR, Pd/Pa and FFR against alternative arbiters of myocardial flow impairment **(Figure 5)**[32-34]. Notably, and as compared to most of the alternative tests, both iFR and Pd/Pa were found to be non-inferior to FFR for the detection of ischaemia-generating stenosis. This strongly suggests that resting pressure indices provide enough – although physiologically incomplete – information for appropriate triggering of revascularisation. JUSTIFY CFR, the largest (n=216) of these studies, demonstrated that, of all pressure indices, iFR had the highest diagnostic accuracy against CFR, and that, as compared to Pd/Pa, iFR was statistically better for detecting an exhausted flow reserve[34]. This is important because CFR is emerging as a powerful tool for MACE discrimination[25]. This higher agreement with CFR, a larger range of possible values and a smaller vulnerability to pressure drift made iFR the best resting index for randomised clinical testing.

The effectiveness of iFR to guide revascularisation, as compared to FFR, was put to the test in DEFINE-FLAIR and iFR-SWEDE-HEART, the largest coronary physiology randomised clinical trials performed to date[21,22]. Herein, >4,500 patients were randomised in two different studies in a 1:1 fashion to either iFR-guided or FFR-guided PCI, with iFR ≤0.89 and FFR ≤0.80 as pre-specified

treatment thresholds. Both studies were designed to show the non-inferiority of iFR to FFR with respect to the subsequent risk of MACE. The primary endpoint, a composite of death from any cause, non-fatal myocardial infarction, or unplanned revascularisation at one year, occurred in DEFINE-FLAIR and iFR-SWEDE-HEART, in 6.8% and 6.7% in the iFR groups, and in 7.0% and 6.1% in the FFR groups, respectively. Since the differences in event rates fell within the trials' pre-specified non-inferiority margins, it can be concluded that revascularisation guided by iFR is non-inferior to revascularisation guided by FFR with respect to the risk of MACE at one year **(Figure 6)**. Moreover, in the iFR groups, the number of functionally significant stenoses and rates of revascularisation were lower, the duration of the procedure was shorter, and the percentage of patients who reported adverse procedural symptoms was smaller. These additional advantages and the robustness of the two trials have set the basis for the inclusion of iFR as an appropriate substitute for FFR in the recent ACC 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease[35].

LIMITATIONS

Shortly after its introduction, the foundation premises of iFR were challenged and not reproduced in a larger cohort of human coronary arteries. Here, wave-free resting microvascular resistance significantly and consistently exceeded mean whole-cycle hyperaemic resistance[36]. Whilst a definitive answer to this conundrum is lacking, it seems that the most plausible explanation is a significant difference in the physiology severity of the investigated vessels[19,36]. A report from the Iberian-Dutch-English (IDEAL) collaborators sheds some light on this issue, by demonstrating in humans how, with progressive anatomic stenosis severity, trans-stenotic pressure gradient increases, hyperaemic flow decreases, while resting
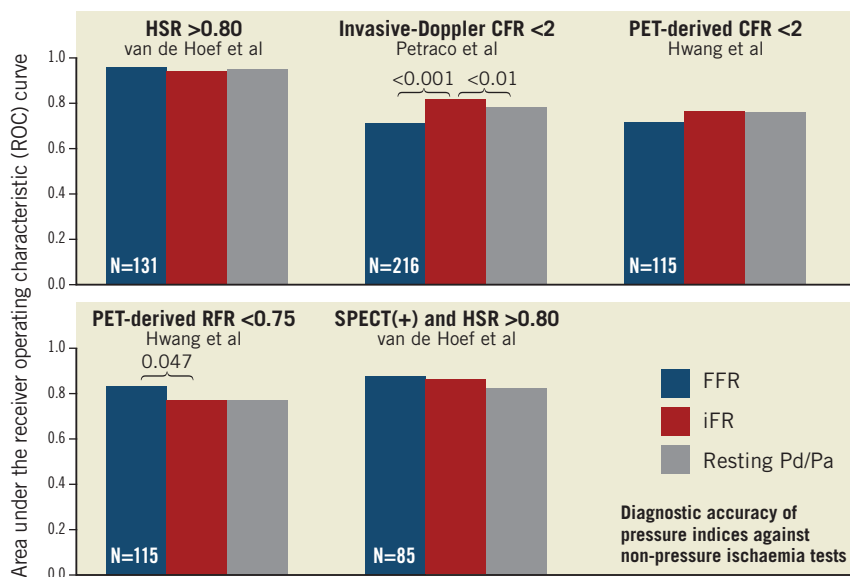
Figure 5. *Diagnostic accuracy of pressure indices against non-pressure ischaemia tests. All published studies comparing the diagnostic accuracy of FFR, iFR and resting Pd/Pa against non-pressure ischaemia tests are summarised in this Figure[33,34,50,56]. Only p<0.05 are shown. HSR: hyperaemic stenosis resistance; SPECT: single photon emission computed tomography; PET: positron emission tomography*
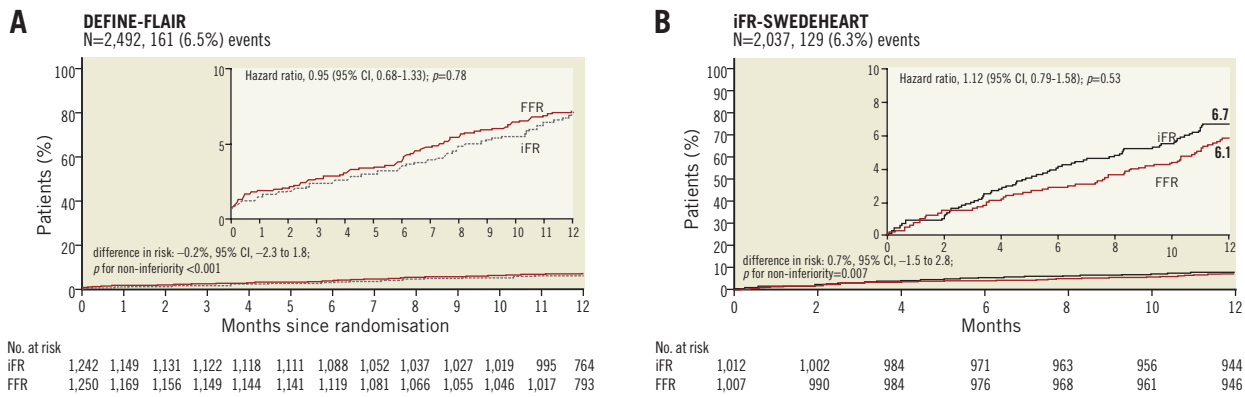
Figure 6. *iFR as tool to guide revascularisation. Cumulative risk of the composite of death from any cause, non-fatal myocardial infarction, or unplanned revascularisation at one year in DEFINE-FLAIR (A) and iFR-SWEDEHEART (B). Reprinted with permission from Davies et al and Götberg et al[21,22].*

coronary flow is maintained, by compensatory reduction in microvascular resistance[37]. Additionally, hyperaemic microvascular resistance remains unchanged with increasing stenosis severity, whereas resting microvascular resistance decreases, to levels as low as those achieved with hyperaemia. Thus, resting microvascular resistance will fall dramatically in response to vasodilators in mildly stenosed vessels while it will not decrease further in tightly stenosed vessels. Whether these findings explain the above-mentioned conundrum on the iFR foundation premises remains to be proved. An interesting proposal of the IDEAL investigators is that, since resting flow is preserved at the expense of distal coronary pressure, changes in distal pressure could represent to what degree the stenosis is exhausting autoregulation, and could hence represent the true physiological impact of the stenosis in the distal myocardium[37]. This

argumentation provides further support for the use of resting indices but should be challenged by future research.

CFR AND FFR ASSESSMENT
EMERGING PROGNOSTIC ROLE OF CFR
CFR is the ratio of hyperaemic to baseline flow, and reflects the capacity of both the epicardial vessel and the microcirculation to satisfy demand, by increasing flow[25]. Therefore, and because CFR interrogates the coronary circulation as a whole, CFR can identify whether, and in spite of an epicardial stenosis, myocardial flow supply is or is not normal. This is a key diagnostic characteristic, intimately related to risk, because ultimately myocardial function thrives on flow, as assessed by CFR, and not on perfusion pressure, as assessed by FFR[25,29]. This physiology foundation has received
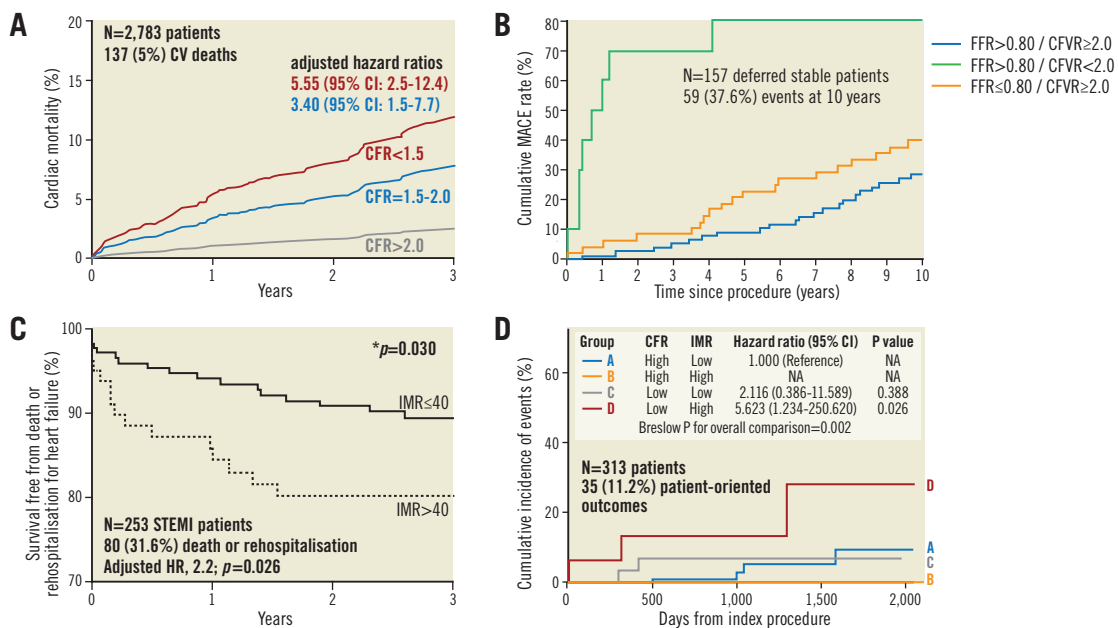
Figure 7. *Risk discriminative capacity of CFR and IMR. Murthy et al[38] (A), van de Hoef et al[42] (B), Fearon et al[44] (C), and Lee et al[45] (D) provide supportive data for CFR and IMR as tools for risk discrimination. CFR: coronaray flow reserve; CVFR: Coronary flow velocity reserve; IMR: index of microvascular resistance. All reprinted with permission.*

reassuring sustenance from a wealth of clinical data **(Figure 7)**. For example, in a large clinical cohort (n=2,783) investigated with positron emission tomography, a CFR <1.5 was associated with an univariate 16-fold increased risk in mortality at medium term, as compared to a normal flow supply (CFR >2)[38]. In a different study, where 4,313 patients with known or suspected CAD were evaluated with stress echocardiography including CFR evaluation of the left anterior descending artery, the four-year mortality was markedly higher in patients with CFR ≤2, in both the group with (39% vs. 7%, p<0.001) and the group without (12% vs. 3%, p<0.001) inducible ischaemia, as compared to patients with preserved flow supply (CFR >2)[39]. Since the capacity of CFR to stratify the risk for mortality hence extends beyond the presence or absence of stress-induced ischaemia – the ultimate objective of FFR – little doubt now exists on the incremental information that CFR provides to FFR assessment.

CONTEMPORARY REINTERPRETATION OF THE FFR AND CFR RELATIONSHIP

FFR and CFR were both envisaged to estimate coronary stenosis severity. However, it was quickly evidenced that FFR and CFR disagree in around 30% of vessels **(Figure 8)**[29,40]. A recent model proposed by Johnson et al suggests that this discordance is not due to methodology but is rather a consequence of the complex interaction between focal stenosis, diffuse atherosclerosis and MCD[29]. **Figure 8** explains this model. A non-ischaemic lesion will be characterised by both adequate and concordant FFR and CFR (red in **Figure 8**). A severe flow-limiting stenosis (blue in **Figure 8**) will exhaust flow supply (CFR <2), because autoregulation cannot compensate for high epicardial resistance (FFR

≤0.80). In the discordant group with FFR ≤0.80 and CFR ≥2, the theoretical substrate is a focal lesion with minimum diffuse disease and a functionally preserved microcirculation. A CFR >2.0 would reflect that flow supply suffices to avoid ischaemia, even if FFR is ≤0.80 (orange in **Figure 8**). Finally, the discordant group with FFR >0.80 and CFR <2 would be explained by predominant diffuse atherosclerosis (yellow in **Figure 8**) or MCD if the pressure loss is trivial (<5 mmHg) (grey in **Figure 8**). In this quadrant, the flow supply is significantly impaired (CFR <2) and ischaemia highly likely, even if the relative contribution of the stenosis to the overall degree of flow impairment is only minor (FFR >0.80). On the basis of the preserved myocardial function at low perfusion pressures when flow remains sufficient, and of the above-mentioned encouraging clinical data for preserved CFR, the ongoing DEFINE-FLOW study (clinicaltrials. gov NCT02328820) hypothesises that deferring revascularisation in stenosis with low FFR but preserved CFR is safe. Results are expected in one year.

ASSESSMENT OF THE CORONARY MICROCIRCULATION

A sizeable body of evidence nowadays substantiates how the coronary microcirculation contributes to ischaemia and influences patient symptoms and outcomes. For example, more than half of women and around one third of men with stable angina undergoing coronary angiography are found to have non-obstructive CAD[41]. MCD seems to account for at least one third of these cases[41]. Furthermore, the quality of life of patients with MCD is significantly affected, as >40% are admitted for recurrent angina[28,41]. This means high healthcare costs, similar to those of obstructive
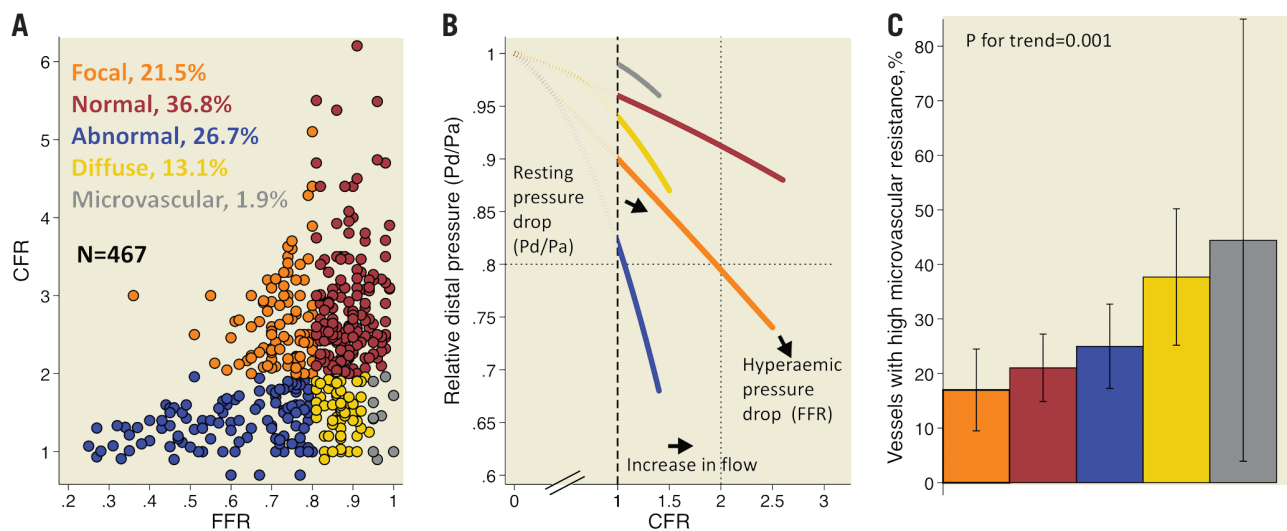
Figure 8. *CFR and FFR relationship. Synopsis of 467 vessels: 299 assessed with Doppler in the AMC Heartcentre, Amsterdam, the Netherlands; 167 assessed with thermodilution in the Hospital Clínico San Carlos, Madrid, Spain. Panel A shows the overall CFR and FFR relationship, with CFR <2 and FFR ≤0.80 as cut-offs. Panel B exhibits a quadratic fit that starts at a hypothetical zero flow and zero pressure drop, crosses the vertical dotted line at the median resting Pd/Pa observed in each category, and ends at each category median CFR and FFR values. Panel C shows the prevalence of vessels with high microcirculatory resistance (above the 75th percentile in each Doppler and thermodilution data set) in the CFR and FFR regions. Modified with permission from: Coronary Stenosis Imaging and Physiology - ISBN 978-2-37274-007-4.*

CAD[41]. Although some non-invasive tests inform on the functional status of the coronary microcirculation, its most certain evaluation remains invasive, because non-invasive techniques cannot differentiate between epicardial and microvascular disease.

The first technology able to assess intracoronary flow in humans was Doppler-flow velocity, and most of our basic understanding of the function of the coronary artery and microcirculation in health and disease stemmed from these sensors[28]. Although its clinical use is still limited by a difficult acquisition of appropriate signals, recent studies are renewing interest in the technology[28,42]. For example, a recent study (n=160) observed that the Doppler-derived hyperaemic microcirculatory resistance index measured immediately after primary PCI was a strong independent predictor of microvascular injury defined with cardiac magnetic resonance and MACE at three years[43]. The second available technology capable of assessing coronary flow is the thermodilution method[28]. Advantages over Doppler-flow velocity are its technical ease and a better correlation with absolute coronary flow. The thermodilution-derived index of microcirculatory resistance (IMR) is reproducible, and mounting evidence supports its value as a meaningful diagnostic tool **(Figure 7)**. In patients with acute myocardial infarction, high IMR values are associated with larger infarct size, worse wall motion scores, and decreased myocardial viability and left ventricle recovery[28]. A multicentre study (n=253) of patients with ST-elevation myocardial infarction observed that patients with IMR >40 U immediately after primary PCI had higher rates of death or re-hospitalisation for heart failure at one year than patients with IMR ≤40 (17.1% versus 6.6%, p=0.027)[44]. Likewise, a recent prospective natural history study of stable patients (n=313) with CAD and FFR-negative stenosis addressed the prognostic capacity of CFR and IMR[45]. Herein, both CFR and IMR improved risk stratification, and patients with low CFR and high IMR had a worse prognosis. IMR thus seems capable of correctly discriminating patients at higher risk, in both acute and stable clinical settings. It is important to state, however, that, as with all intracoronary physiology tests, the coronary thermodilution method carries intrinsic limitations, such as a high sensitivity of the measurements to the displacement of the sensor, an inherent variability in the thermodilution curve, and the necessity of an adequate mixture of the indicator with blood before the bolus reaches the sensor. Finally, and in spite of the growing evidence supporting the value of the invasive assessment of the coronary microcirculation (especially with microcirculatory resistance indices), specific treatment options for MCD are very limited.

Future

Pressure guidewires are still used predominantly to ascertain the functional relevance of intermediate coronary stenoses. It is foreseeable that interrogation will be expanded to vessels with severe CAD to obtain relevant information to plan PCI. Intracoronary pressure mapping allows identification of the segments that contribute more to haemodynamic impairment caused by diffuse narrowing and that, therefore, should constitute the primary revascularisation target. This is facilitated by the use of resting indices such as iFR, which do not require hyperaemia and have less haemodynamic crosstalk between stenoses[46].

Translation of intracoronary physiology findings to angiography-based actions, such as identification of the coronary segment to be treated and subsequent stent deployment, will be facilitated by co-registration of physiological data with angiography. Currently, this can be done with static coronary images, but technological improvements in dynamic roadmapping will most likely enable such physiological guidance to be performed also using moving images **(Figure 9)**.

Physiological interrogation after PCI will be performed routinely to document the haemodynamic result of the intervention[25]. This might lead to further optimisation or to documenting the residual haemodynamic effect of non-treatable lesions.

Perhaps the major pending advance in clinical coronary physiology will be the adoption of a comprehensive assessment of the coronary circulation, which will address both the epicardial vessel and the microcirculation[29,42]. Previous paragraphs have discussed the advantages of this approach but, to be adopted by the majority of cardiologists, at least two requirements will have to be fulfilled. The first will be the availability of new user-friendly technologies for measuring coronary flow and calculating combined press-flow indices in the catheterisation laboratory. Current technologies for coronary flow estimation are too complex and time-consuming for most interventionalists, and are available on old guidewire platforms. Phasic information will be required to perform interrogation of specific intervals of the cardiac cycle. The second will be the existence of conclusive evidence supporting the benefit of such assessment for the patient.

One of the clinical scenarios in which physiological interrogation may potentially play an important role is in acute myocardial infarction. Recent and ongoing studies are investigating the potential value of FFR and iFR in assessing non-culprit stenoses in such patients. However, in addition, there is growing evidence that interrogation of the culprit vessel immediately after primary PCI with specific indices informs on the degree of microcirculatory and myocardial damage caused by ongoing myocardial no-reflow, which can occur despite the achievement of angiographic normal flow[28]. In particular, estimation of the zero flow pressure can be important, as this has been shown to be a predictor of myocardial damage[28]. Determining which therapeutic actions, implemented at the time of primary PCI or immediately after, may reduce myocardial damage constitutes an area of current interest[28].

Over the last 10 years, the theoretical framework of FFR and iFR has been adopted by post-processing of coronary imaging, either non-invasive (FFR-CT) or invasive (QFR). It is quite likely that these techniques will be used to circumvent the limitations of planar coronary angiography in assessing functional stenotic relevance. Yet, as these approaches will not be able to address many of the advantages of invasive physiological assessment discussed above, it is foreseeable that the use of intracoronary guidewires fitted with sensors will continue to expand.
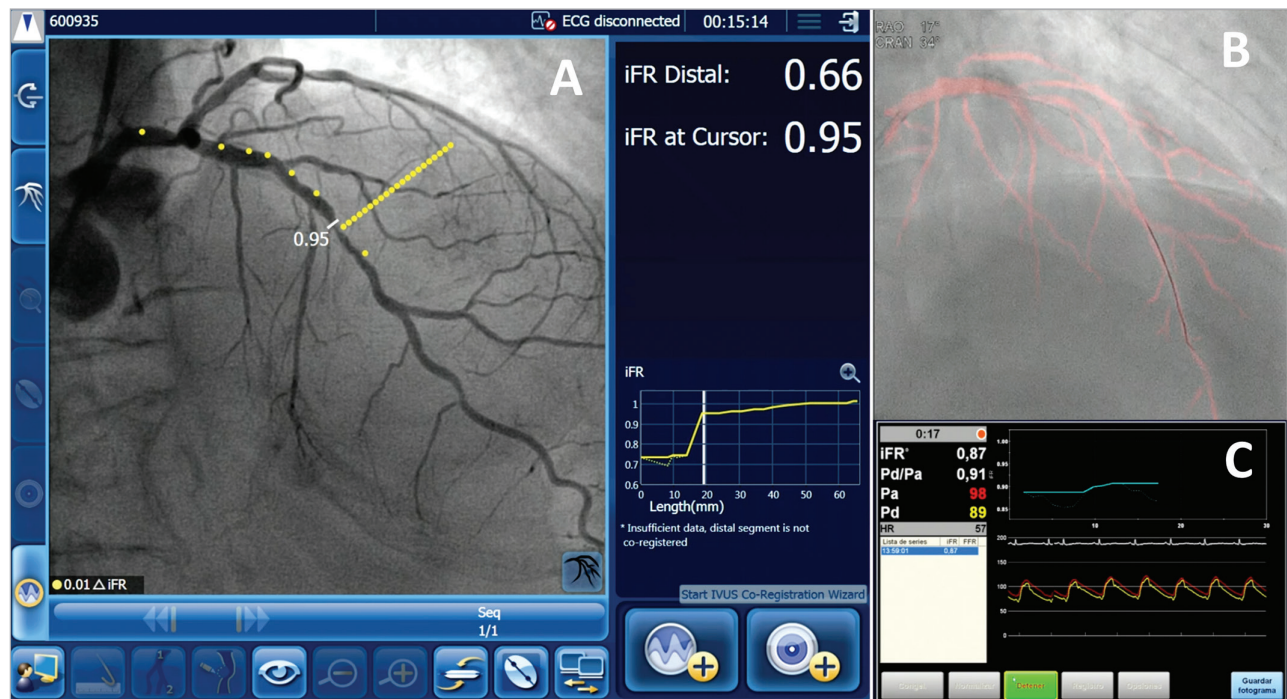
Figure 9. *Future of the pressure wire. Panel A shows the result of co-registering iFR pullback data with coronary angiography in a left anterior descending coronary artery with several irregularities. Each yellow dot represents a modification of 0.01 iFR units. The co-registered image shows with clarity the vessel region accounting for most of the haemodynamic impairment, allowing identification of the PCI target segment and translation to angiography during stent deployment. Panel B and Panel C show an iFR pullback performed during dynamic roadmapping (pink colour moving mask generated from prior angiographic run), allowing clear correlation between changes in iFR and specific anatomical landmarks.*

Conclusions

Coronary physiology indices are more than ever important for the interventional cardiologist. They allow a further refinement in the selection of revascularisation targets and have the potential to identify patients at high risk for MACE.

Authors' perspective

Physiology has always been at the core of interventional cardiology and is now more than ever at the front line of the diagnostic and therapeutic evaluation. The field is evolving quickly and is exposed to a double tension: to simplify physiology as FFR and iFR have done, to foster its adoption and thus to translate to more patients the benefits that have been demonstrated in trials, or, on the contrary, to confront the intricacy of CAD, with combined pressure and flow indices. Which approach is the more successful remains to be seen.

Conflict of interest statement

M. Echavarria-Pinto has served as speaker at educational events organised by St. Jude Medical and Volcano Corporation. C. Collet reports a research grant from HeartFlow Inc. J. Escaned has served as speaker at educational events organised by St. Jude Medical and Volcano Corporation. J.J. Piek is a consultant for Philips/Volcano Corporation. P.W. Serruys is a member of the International Advisory Board of Abbott Vascular.

References

1. Young DF, Cholvin NR, Roth AC. Pressure drop across artificially induced stenoses in the femoral arteries of dogs. *Circ Res.* 1975;36:735-43.

2. Tyberg JV, Massie BM, Botvinick EH, Parmley W. The hemodynamics of coronary arterial stenosis. *Cardiovasc Clin.* 1977;8:71-84.

3. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res.* 1978;43:242-53.

4. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VII. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. *J Am Coll Cardiol.* 1986;7: 103-13.

5. Puel J, Juilliere Y, Bertrand ME, Rickards AF, Sigwart U, Serruys PW. Early and late assessment of stenosis geometry after coronary arterial stenting. *Am J Cardiol.* 1988;61:546-53.

6. Di Mario C, de Feyter PJ, Slager CJ, de Jaegere P, Roelandt JR, Serruys PW. Intracoronary blood flow velocity and transstenotic pressure gradient using sensor-tip pressure and Doppler guidewires: a new technology for the assessment of stenosis severity in the catheterization laboratory. *Cathet Cardiovasc Diagn.* 1993;28: 311-9.

7. Di Mario C, Krams R, Gil R, Serruys PW. Slope of the instantaneous hyperemic diastolic coronary flow velocity-pressure relation. A new index for assessment of the physiological significance of coronary stenosis in humans. *Circulation.* 1994;90:1215-24.

8. Serruys PW, Mario CD, Meneveau N, de Jaegere P, Strikwerda S, de Feyter PJ, Emanuelsson H. Intracoronary pressure and flow velocity with sensor-tip guidewires: a new methodologic approach for assessment of coronary hemodynamics before and after coronary interventions. *Am J Cardiol.* 1993;71:41D-53D.

9. Di Mario C, Moses JW, Anderson TJ, Bonan R, Muramatsu T, Jain AC, Suarez de Lezo J, Cho SY, Kern M, Meredith IT, Cohen D, Moussa I, Colombo A. Randomized comparison of elective stent implantation and coronary balloon angioplasty guided by online quantitative angiography and intracoronary Doppler. DESTINI Study Group (Doppler Endpoint STenting INternational Investigation). *Circulation.* 2000;102:2938-44.

10. Serruys PW, di Mario C, Piek J, Schroeder E, Vrints C, Probst P, de Bruyne B, Hanet C, Fleck E, Haude M, Verna E, Voudris V, Geschwind H, Emanuelsson H, Mühlberger V, Danzi G, Peels HO, Ford AJ Jr, Boersma E. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: the DEBATE Study (Doppler Endpoints Balloon Angioplasty Trial Europe). *Circulation.* 1997;96:3369-77.

11. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation.* 1993;8:1354-67.

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

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

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

15. De Bruyne B, Fearon WF, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371:1208-17.

16. Krams R, Wentzel JJ, Oomen JA, Vinke R, Schuurbiers JC, de Feyter PJ, Serruys PW, Slager CJ. Evaluation of endothelial shear stress and 3D geometry as factors determining the development of atherosclerosis and remodeling in human coronary arteries in vivo. Combining 3D reconstruction from angiography and IVUS (ANGUS) with computational fluid dynamics. *Arterioscler Thromb Vasc Biol.* 1997;17:2061-5.

17. 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;2:803-810.

18. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation.* 2006;113:1768-78.

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

20. 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.

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

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

23. 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 JH, Holm NR, Wijns W; FAVOR Pilot Trial Study Group. Diagnostic Accuracy of Fast Computational Approach to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. *JACC Cardiovasc Interv.* 2016;9:2024-35.

24. Nijjer SS, Sen S, Petraco R, Davies JE. Advances in coronary physiology. *Circ J Off J Jpn Circ Soc.* 2015;79:1172-84.

25. Johnson NP, Gould KL, Di Carli MF, Taqueti VR. Invasive FFR and Noninvasive CFR in the Evaluation of Ischemia: What Is the Future? *J Am Coll Cardiol.* 2016;67:2772-88.

26. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

27. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation.* 1990;82:1595-606.

28. Echavarría-Pinto M, Serruys PW, Garcia-Garcia HM, Broyd C, Cerrato E, Macaya C, Escaned J. Use of intracoronary physiology indices in acute coronary syndromes. *Interventional Cardiology.* 2015;7:483-95.

29. Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? *JACC Cardiovasc Imaging.* 2012;5:193-202.

30. Mamas MA, Horner S, Welch E, Ashworth A, Millington S, Fraser D, Fath-Ordoubadi F, Neyses L, El-Omar M. Resting Pd/Pa measured with intracoronary pressure wire strongly predicts fractional flow reserve. *J Invasive Cardiol.* 2010;22:260-5.

31. Jeremias A, Maehara A, Généreux P, Asrress KN, Berry C, De Bruyne B, Davies JE, Escaned J, Fearon WF, Gould KL, Johnson NP, Kirtane AJ, Koo BK, Marques KM, Nijjer S, Oldroyd KG, Petraco R, Piek JJ, Pijls NH, Redwood S, Siebes M, Spaan JA, van 't Veer M, Mintz GS, Stone GW. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol.* 2014;63:1253-61.

32. Hwang D, Jeon KH, Lee JM, Park J, Kim CH, Tong Y, Zhang J, Bang JI, Suh M, Paeng JC, Na SH, Cheon GJ, Cook CM, Davies JE, Koo BK. Diagnostic Performance of Resting and Hyperemic Invasive Physiological Indices to Define Myocardial Ischemia: Validation With 13N-Ammonia Positron Emission Tomography. *JACC Cardiovasc Interv.* 2017;10:751-760.

33. van de Hoef TP, Meuwissen M, Escaned J, Sen S, Petraco R, van Lavieren MA, Echavarria-Pinto M, Nolte F, Nijjer S, Chamuleau SA, Voskuil M, van Eck-Smit BL, Verberne HJ, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Davies JE, Piek JJ. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. *EuroIntervention.* 2015;11:914-25.

34. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Foin N, Malik IS, Mikhail GW, Hughes AD, Francis DP, Mayet J, Di Mario C, Escaned J, Piek JJ, Davies JE. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv.* 2014;7:492-502.

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

36. Johnson NP, Kirkeeide RL, Asrress KN, Fearon WF, Lockie T, Marques KM, Pyxaras SA, Rolandi MC, van 't Veer M, De Bruyne B, Piek JJ, Pijls NH, Redwood S, Siebes M, Spaan JA, Gould KL. Does the instantaneous wave-free ratio approximate the fractional flow reserve? *J Am Coll Cardiol.* 2013;61:1428-35.

37. Nijjer SS, de Waard GA, Sen S, van de Hoef TP, Petraco R, Echavarría-Pinto M, van Lavieren MA, Meuwissen M, Danad I, Knaapen P, Escaned J, Piek JJ, Davies JE, van Royen N. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. *Eur Heart J.* 2016;37:2069-80.

38. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011;124:2215-24.

39. Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Molinaro S, Picano E, Sicari R. Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. *JACC Cardiovasc Imaging.* 2012;5:1079-85.

40. Meuwissen M, Chamuleau SA, Siebes M, Schotborgh CE, Koch KT, de Winter RJ, Bax M, de Jong A, Spaan JA, Piek JJ. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. *Circulation.* 2001;103:184-7.

41. Radico F, Cicchitti V, Zimarino M, De Caterina R. Angina pectoris and myocardial ischemia in the absence of obstructive coronary artery disease: practical considerations for diagnostic tests. *JACC Cardiovasc Interv.* 2014;7:453-63.

42. van de Hoef TP, van Lavieren MA, Damman P, Delewi R, Piek MA, Chamuleau SA, Voskuil M, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Meuwissen M, Piek JJ. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv.* 2014;7:301-11.

43. de Waard GA, Fahrni G, de Wit D, Kitabata H, Williams R, Patel N, Teunissen PF, van de Ven PM, Umman S, Knaapen P, Perera D, Akasaka T, Sezer M, Kharbanda RK, van Royen N. Hyperaemic microvascular resistance predicts clinical outcome and microvascular injury after myocardial infarction. *Heart.* 2017 June 29. [Epub ahead of print].

44. Fearon WF, Low AF, Yong AS, McGeoch R, Berry C, Shah MG, Ho MY, Kim HS, Loh JP, Oldroyd KG. Prognostic value of the Index of Microcirculatory Resistance measured after primary percutaneous coronary intervention. *Circulation.* 2013; 127:2436-41.

45. Lee JM, Jung JH, Hwang D, Park J, Fan Y, Na SH, Doh JH, Nam CW, Shin ES, Koo BK. Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis. *J Am Coll Cardiol.* 2016;67:1158-69.

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

47. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, Paulus WJ, Heyndrickx GR, Wijns W. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation.* 1994;89:1013-22.

48. Marques KM, Knaapen P, Boellaard R, Lammertsma AA, Westerhof N, Visser FC. Microvascular function in viable myocardium after chronic infarction does not influence fractional flow reserve measurements. *J Nucl Med.* 2007;48:1987-92.

49. Stuijfzand WJ, Uusitalo V, Kero T, Danad I, Rijnierse MT, Saraste A, Raijmakers PG, Lammertsma AA, Harms HJ, Heymans MW, Huisman MC, Marques KM, Kajander SA, Pietilä M, Sörensen J, van Royen N, Knuuti J, Knaapen P. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. *Circ Cardiovasc Imaging.* 2015;8(1).

50. Lee JM, Kim CH, Koo BK, Hwang D, Park J, Zhang J, Tong Y, Jeon KH, Bang JI, Suh M, Paeng JC, Cheon GJ, Na SH, Ahn JM, Park SJ, Kim HS. Integrated Myocardial Perfusion Imaging Diagnostics Improve Detection of Functionally Significant Coronary Artery Stenosis by 13N-ammonia Positron Emission Tomography. *Circ Cardiovasc Imaging.* 2016;9(9).

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

52. Park SH, Jeon KH, Lee JM, Nam CW, Doh JH, Lee BK, Rha SW, Yoo KD, Jung KT, Cho YS, Lee HY, Youn TJ, Chung WY, Koo BK. Long-Term Clinical Outcomes of Fractional Flow Reserve-Guided Versus Routine Drug-Eluting Stent Implantation in Patients With Intermediate Coronary Stenosis: Five-Year Clinical Outcomes of DEFER-DES Trial. *Circ Cardiovasc Interv.* 2015;8: e002442.

53. Zhang Z, Li K, Tian J. Efficacy and safety outcomes of fractional flow reserve in guiding clinical therapy of non-ST-segment elevation myocardial infarction compared with angiography alone in elderly Chinese patients. *Clin Interv Aging.* 2016;11:1751-4.

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

55. 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;376:1234-1244.

56. van de Hoef TP, Petraco R, van Lavieren MA, Nijjer S, Nolte F, Sen S, Echavarria-Pinto M, Henriques JP, Koch KT, Baan J Jr, de Winter RJ, Siebes M, Spaan JA, Tijssen JG, Meuwissen M, Escaned J, Davies JE, Piek JJ. Basal stenosis resistance index derived from simultaneous pressure and flow velocity measurements. *EuroIntervention.* 2016;12:e199-207.