# The baseline instantaneous wave-free ratio as an index of coronary disease severity: relationship with fractional flow reserve and coronary flow reserve

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# DECLARATION OF ORIGINALITY

I hereby declare that the work presented in this thesis is my own.

Dr Ricardo Petraco

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# ABSTRACT

Over the last 30 years the development of invasive methods to directly measure the haemodynamic impact of individual coronary stenoses on blood flow has enabled the identification of vessel-specific and lesion-specific ischaemia. Fractional flow reserve (FFR) is the most commonly used technique, largely due to the simplification brought by its pressure-only methodology. Despite the evidence accumulated demonstrating the benefits of FFR-guided decisions, its adoption remains low worldwide (6-8%) and a large proportion of patients with coronary artery disease (CAD) still undergo percutaneous interventions without any objective evidence of myocardial ischaemia. This is partly due to FFR's reliance on the induction of coronary hyperaemia, a methodological step which adds time, cost and inconvenience for patients and clinicians.

Recently, our group presented a novel invasive pressure-only methodology, the instantaneous wave-free ratio (iFR), which differs from FFR as it can be calculated at baseline, without the need for vasodilator administration. In its initial validation studies, iFR demonstrated a close diagnostic agreement with FFR and with invasive coronary flow.

In this thesis, I will present a series of studies which aim to further evaluate the utility of iFR as an index coronary stenosis severity. Firstly, I will explore its diagnostic relationship with FFR in details and present a novel methodology to measure classification agreement between methods of clinical measurement. Secondly, I will evaluate the merits of utilising iFR and FFR in a common diagnostic pathway and quantify the potential benefits of such a strategy to spare patients from the need for vasodilator administration. Finally, I will investigate the

relationship between pressure-only indices (iFR and FFR) and coronary flow reserve, an extensively validated marker of prognosis in coronary disease.

# DEDICATION

I dedicate this thesis to four very especial people:

To my wife Angela, whose comprehension, support and affection have been unconditional over the last three years. Without her, this work would have been impossible.

To my son Leonardo, who probably has always wondered why daddy was spending so much time on the laptop, rather than building train tracks with him. The first three years of his life were also the three years of my PhD, a wonderful combination of exciting work and joyful evenings with him.

To my mum Leoni, whose dedication, abnegation and love have created the foundations for everything I achieved in life.

To my dad Alvaro, whose example of hard-work and thirst for knowledge has set the intellectual path which I want to follow.

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I am extremely grateful to my supervisors, whose support over the last years has been detrimental to the completion of this thesis.

Dr Justin Davies, a mentor who became a friend, has taught me coronary physiology, computer programming and English grammar. His guidance on my PhD has been masterful; whilst he gave me intellectual freedom to develop new ideas and to think independently, he was very hands-on when needed. Above all, he has taught me the importance of having a broad and long-term view of scientific aims and ambitions.

My admiration and gratitude to Professor Darrel Francis extends far beyond this thesis. He has been immensely supportive in all aspects of my career since we met 6 years ago. Whether writing a research grant, applying for jobs, reviewing manuscripts or even applying for a visa extension, he has always taken time out of his very busy schedule to help me. For that I could never thank him enough. Moreover, the most valuable lesson I learnt from Prof Francis over the last years is that scientific progress can only be achieved with a finely balanced recipe which includes intellectual freedom, scientific rigour and professional integrity; sprinkled of course with a good amount of cheekiness and sarcasm.

I thank Professor Jamil Mayet for his support both to my clinical and acadaemic careers. Since my arrival at St Marys Hospital in 2008 and up to the completion of my PhD in 2013, he has always made himself available. Polite, efficient and always motivated, he is a role model which I will always want to follow.

Professor Alun Hughes has provided me with the most comprehensive scientific support during every stage of my thesis. His insights on grant applications, thorough

feedback on manuscripts and almost limitless knowledge of statistics and cardiac physiology have all been invaluable to the completion of this work.

I am very grateful for the support from all of the consultants working in the cardiology department at Imperial NHS Trust. Particularly, Dr Sutaria, Dr Malik and Dr Mikhail have offered a friendly clinical environment for research to be undertaken. Without them, collecting good quality echo and haemodynamic data in a large busy tertiary centre would have been impossible.

I owe special thanks to all my research colleagues, who made my time during this PhD thesis fun and exciting. In particular, I have great admiration and respect for Drs Sayan Sen and Sukhjinder Nijjer, two extremely talented colleagues who have become close friends. The time spent in the “ICCH cave”, at cardiology meetings abroad and in the pub around the corner was truly unforgettable. With them I have learnt that whilst some things can be done easily, others need the encouragement of a good British pint. I hope this friendship continues for years to come.

I am thankful to the cardiology staff at the Echo and catheterization laboratories, including nurses, radiographers, physiologists and administrative staff. Their help and understanding during the long research cases were essential to the completion of this work.

I am extremely grateful to the British Heart Foundation and Imperial College Healthcare charity for the financial support required for this thesis.

Finally, I owe a debt of gratitude to the patients with heart disease who agreed to participate in this research project. Their involvement in this work was a true demonstration of altruism. Despite the anxieties and stresses caused by their

illnesses, they wholeheartedly volunteered to be part of this scientific journey, to the greater benefit of all patients with heart disease.

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# 1 INTRODUCTION

## 1.1 Global burden of coronary artery disease

Over the last 3 decades, more people have died from coronary artery disease (CAD) than from any other cause[1]. Whilst both incidence and mortality of CAD have been decreasing in the last decade in developing countries, they are expected to increase in developing nations as a result of increased longevity and urbanisation. Also, CAD is responsible for 10-18% of disability-adjusted life years (DALY) worldwide[2].

Optimal treatment of CAD requires a multi-dimensional approach which includes risk factor modification, pharmacological treatment and appropriate revascularisation of epicardial stenoses[3]. Therefore, accurate identification of those coronary lesions imposing limitation to coronary blood flow, causing symptoms of angina and increasing the risk of cardiac events is of crucial importance for patients and healthcare systems[4-6].

## 1.2 Coronary angiography and the limitations of anatomical assessment

Soon after coronary angiography was established as a routine diagnostic method for CAD, its limitations to predict the functional significance of epicardial stenoses became evident[7]. The fluid dynamic mechanisms behind energy dissipation of coronary blood flow are complex and cannot be predicted by simplified angiography-derived parameters such as stenosis length and percentage of luminal reduction [Figure 1.1][8]. Therefore, diagnostic methods which directly *measure* the functional impact of coronary narrowings are essential for a more accurate prediction of symptoms, disease severity and prognosis in patients with CAD[9-12]. Also, it has been demonstrated that coronary revascularisation decisions which are based on the presence of myocardial ischaemia or coronary flow limitation are beneficial to patients when compared to decisions guided purely on angiography[13-16].

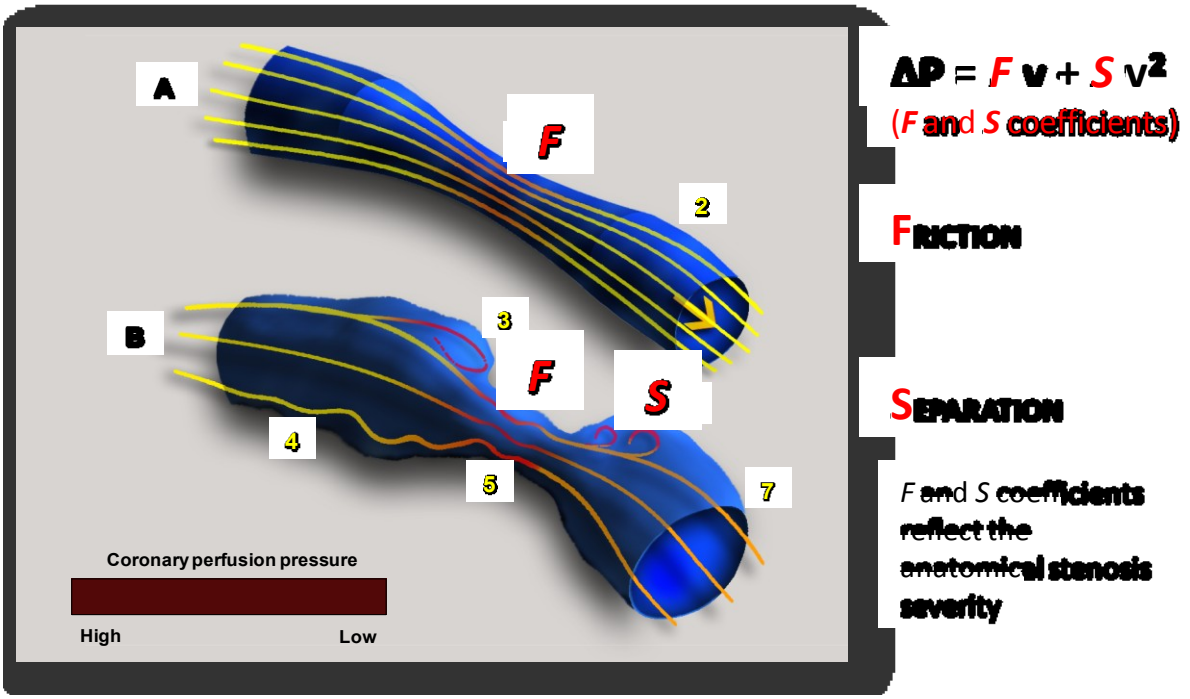


**Figure 1.1 Schematic representation of potential mechanisms for energy dissipation in coronary disease:** Computational fluid dynamic (CFD) three-dimensional reconstruction of an idealized smooth model of coronary stenosis (A) and of a patient-specific anatomy (B). Streamlines of flow are artificially represented as yellow lines. The smooth model (70% cross sectional area reduction) was created with smooth luminal surface and symmetrical and gradual inlet/outlet stenosis transitions. As blood flow crosses the stenosis (1) a temporary drop in pressure is observed as energy is converted into velocity. However, the smooth surface and the lack of morphological asymmetries allow almost full pressure recovery distal to the stenosis, with minimal reduction in perfusion pressure (yellow colour, 2). The patient specific model (with equal anatomical area reduction) shows potential sources of energy dissipation. As flow approaches the stenosis, part of it hits the abrupt inlet transition (3). Also, luminal roughness and wall irregularities lead to increased friction and flow disturbances outside (4) and, most importantly, inside the stenosis (5), which appears to be the main mechanism through which perfusion energy is lost. The abrupt outlet stenosis transition prevents flow re-attachment and leads to flow recirculation and disturbances (6), which also causes energy dissipation. Multiple sites of irreversible energy loss lead a reduction in perfusion pressure distal to the stenosis (orange colour, 7), leading to myocardial ischaemia. It can be therefore concluded that the reduction in cross sectional area per se is not the main limitation to coronary flow. This is the reason why, even when measured accurately, simple anatomical parameters such as percentage stenosis and minimal lumen area are weak predictors of physiology. The real anatomical obstacles to coronary flow (3-6) are not included in the standard criteria of disease severity.

## 1.3 Invasive coronary physiological assessment: lesion-specific quantification of functional disease severity

Non-invasive diagnostic methods of functional disease severity (such as stress ECG and echocardiography and myocardial perfusion methods) play an important role in the diagnosis and risk stratification of patients with CAD[17]. However, they have two major limitations. Firstly, they do not provide information on vessel-specific or lesion-specific ischaemia, which is relevant for patients with multi-vessel disease and when more than one coronary narrowing is present in a given coronary artery. Secondly, they do not *quantify* the amount of myocardial ischaemia or flow limitation imposed by stenoses. Therefore, invasive methods which use guide wires to directly measure the haemodynamic impact of an individual coronary stenosis can help clinical decision-making, by yielding information about *which* lesion(s) is(are) likely to be responsible for the patient's symptoms, the magnitude of ischaemia created by such lesions and, importantly, how likely it is that the symptoms will improve when the obstruction is removed by the means of revascularization[18, 19].

## 1.4 Fractional flow reserve: the establishment of pressure-only assessment

In stable coronary disease, myocardial ischaemia and symptoms of angina occur because of insufficient coronary blood *flow* for a given tissue demand[20]. Hence, invasive techniques which directly measure blood flow velocity with intra-coronary Doppler wires can provide valuable information about the underlying haemodynamics of lesions. However, since the development of the Doppler flow wire, adoption of flow-based methods in clinical practice has been largely restricted to research, mainly because of the demanding technical aspects of measuring invasive flow. Therefore, techniques which *estimate coronary flow* reduction by

*measuring coronary pressure* have been demonstrated to be more reproducible and easier to be applied clinically (Figure 1.2).

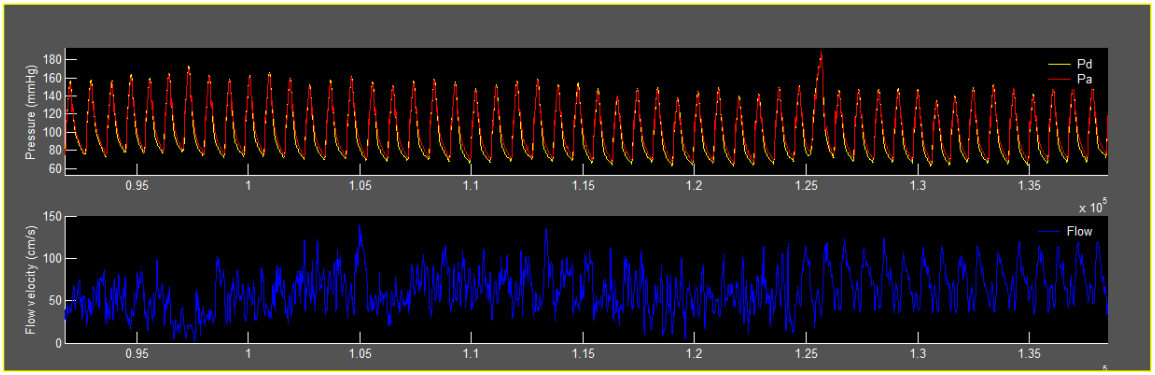


**Figure 1.2: Measurement of coronary pressure and flow velocity**

When compared to coronary flow velocity (bottom panel), pressure is much easier to measure (top panel). In this example it took approximately 30s for the operator to obtain a good flow trace, whilst pressure reading remained robust across the whole trace. This simplification brought by pressure-only measurements largely explains the establishment of fractional flow reserve as the most commonly used invasive index of disease severity.

Although the first invasive measurement of coronary pressure gradients was made in the 1970's[21], it wasn't until the mid 1990's, when advances in technology permitted the development of small, sophisticated high fidelity wires, that invasive functional assessment of coronary disease started to become clinically relevant[22, 23]. Seminal work by Pijls et al[24, 25] led to the development of fractional flow reserve (FFR), a pressure-only method of functional disease severity, which became the most adopted invasive technique in the catheterization laboratory.

FFR is calculated as the ratio of distal (Pd) to aortic (Pa) coronary pressures during conditions of vasodilator-induced coronary hyperaemia. In animal models free of native coronary disease, FFR was demonstrated to be capable of predicting the proportional reduction in maximal flow caused by focal epicardial stenoses[23]. In clinical populations of patients with coronary disease, FFR demonstrates a good

overall agreement with other functional modalities[26]. Finally, FFR has demonstrated its superiority over angiography alone to guide clinical decision-making in large clinical trials[14, 27]. The development of FFR, more than any other technique, has promoted a major shift in paradigm in the way cardiologists assess coronary stenoses severity in the cardiac catheterisation laboratory. The overall idea of revascularising all lesions which cause luminal reduction on angiography has been replaced by treating only those causing significant limitation to blood flow[28].

### 1.5 FFR dependency on the induction of coronary hyperaemia

Indices of stenosis severity which are based on pressure gradients, such as FFR, are only physiologically meaningful (and hence clinical useful) if measurements are obtained under certain conditions (Figure 1.3): firstly, the underlying flow needs to be constant (or stable) for the resulting pressure drop to reflect only the severity of the stenosis being interrogated; secondly, the underlying flow needs to be of a minimal magnitude to allow for sufficient discrimination between stenoses of different severities[29].

At the time of the development of FFR, it was believed that the only way to achieve such physiological status (stable and sufficient flow) was via the induction of coronary hyperaemia, as baseline coronary flow was deemed too variable and of low magnitude. FFR, therefore, by definition, can only be calculated under conditions of maximal hyperaemia, which is achieved in clinical practice by the administration of potent coronary vasodilators (most commonly adenosine), either intravenously or via the intracoronary route[30].

## Coronary pressure drop x flow curves

Each coronary stenosis has a specific pressure drop x flow curve, a finger print of its physiological severity.

Physiologically, a given pressure drop (ΔP) is a result of a stenosis being interrogated with a specific underlying flow (v).

In clinical practice, the pressure drop results can be interpreted in isolation when only pressure is measured (FFR, iFR). Alternatively, the *stenosis resistance* can be calculated (ΔP/flow), when measurement of flow is available (BSR, HSR).

## Why is a *minimal* underlying flow required?

If stenoses of different physiological severities are interrogated with a *very low* underlying flow (v low), the resulting pressure drop will be very similar (ΔP1, ΔP2, ΔP3).

Therefore, the results of indices based on pressure-drop (FFR, iFR) are only physiologically meaningful and clinically useful, when a *minimal* underlying flow is present (v min).

For a pressure-only index to be useful as a discriminator between stenoses of different severities, it is not necessary to achieve *maximal* flow in each underlying stenosis.

## Why does underlying flow need to be *stable*?

The same stenosis can have different pressure drop results (ΔP1, ΔP2, ΔP3), if interrogated with varying underlying flow (V1, V2, V3). Even stenoses of different severities can display the same pressure drop if flow is too variable (V4).

Therefore, in clinical practice, during stenosis interrogation, it is important that the variability in underlying flow (blue area) is low across a population of patients with different stenoses.

Alternatively, measures of stenosis resistance will account for this variability in underlying flow, because each pressure-drop result is indexed by its underlying flow (ΔP1/V1, ΔP2/V2, ΔP3/V3).

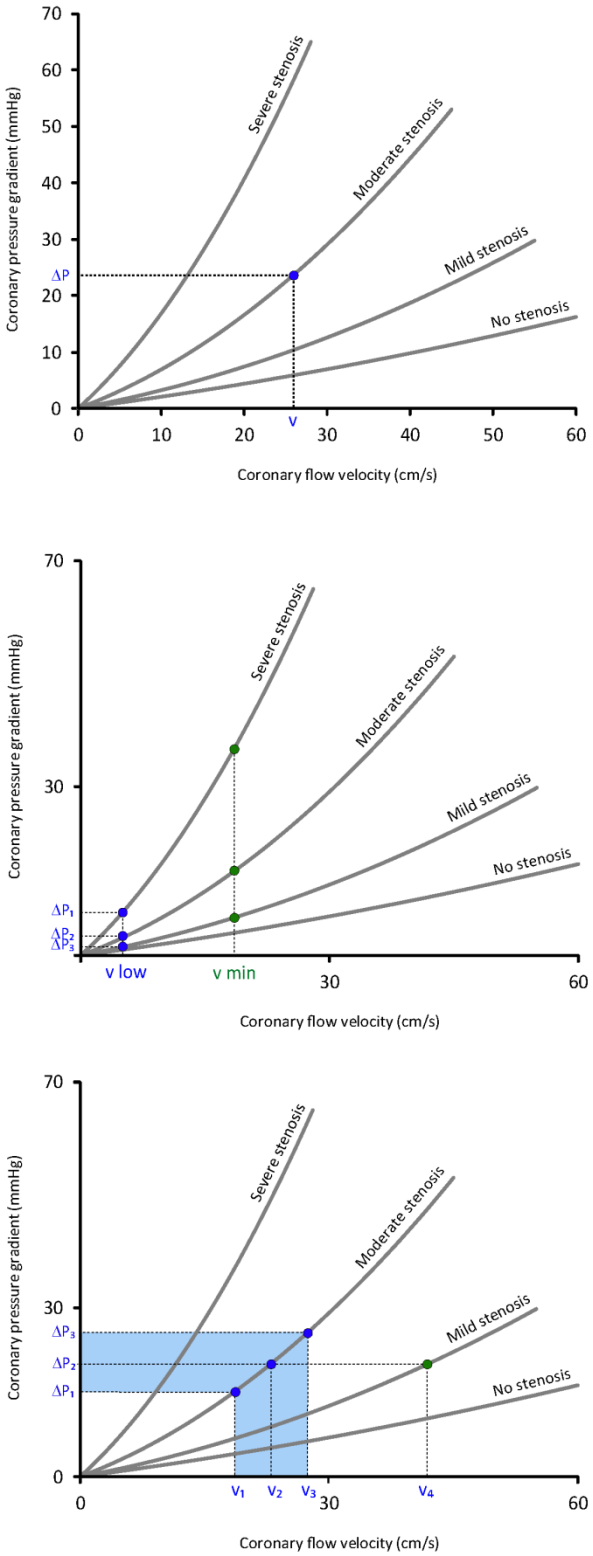


**Figure 1.3: Understanding the need for *stable* and *minimal* underlying coronary flow for accurate pressure-only assessment of stenosis severity**

## 1.6 Coronary flow reserve and prognosis stratification

Coronary flow reserve (CFR), defined as the ratio of hyperaemic flow to baseline flow, is a flow-only index of disease severity which quantifies the capacity of the coronary circulation to increase flow upon demand. Decades of research have consistently demonstrated the diagnostic and prognostic values of CFR in patients with CAD. Whether measured invasively or non-invasively, CFR has been shown to be able to identify patients with myocardial blood flow impairment, predict prognosis and stratify which lesions may benefit from revascularisation[11, 57-62]. More than any other physiological index of coronary disease severity, CFR has demonstrated its ability to predict hard events in patients with coronary disease, importantly death and myocardial infarction. Patients who demonstrate the capacity to double the amount of coronary flow upon demand (CFR >2) have excellent long term prognosis, regardless of the presence of other traditional risk factors, such as diabetes. Also, CFR's ability to predict events appears to be stronger than other markers of ischaemia, such as regional wall motion abnormalities on echocardiography[31] or the underlying FFR value of an epicardial stenosis[32]. CFR can therefore be seen as a safety marker in patients with CAD and an index against which novel diagnostic modalities should be tested.

## 1.7 The baseline instantaneous wave-Free Ratio (iFR)

### 1.7.1 The need for a novel vasodilator-free index

Despite the robust evidence to support the use of FFR over angiography to guide revascularisation decisions, its adoption worldwide remains low[35, 36], estimated as 10-15% in Europe, 6-8% in the US and less than 1% in most developing countries (Figure 1.4). Undeniably, this low adoption is partly caused by the need for

vasodilator administration during FFR calculation, a step which adds time and cost to the procedure and inconvenience for the operator[33]. Also, in some countries, adenosine, the most commonly used vasodilator, is prohibitively expensive or simply not available, which prevents the benefits of invasive physiological assessment to reach many patients with coronary disease worldwide. Also, the administration of a potent systemic vasodilator such adenosine during stress testing is not free from side-effects and can induce hypotension, bradycardia, bronchospasm and acute coronary syndromes[34].

Finally, despite the clear benefits of FFR over angiography in identifying functionally significant stenoses which could be amenable to revascularization, there remain approximately 30% of cases in which FFR disagrees in stenoses classification with CFR, the most important predictor of cardiac events in CAD[35-37]. This disagreement with underlying flow suggests there might be scope for improvement in the current pressure-only approach to lesion selection using FFR.


**Figure 1.4: Estimated global adoption of fractional flow reserve in 2013**

Values in yellow represent the estimated utilization of fractional flow reserve to guide percutaneous intervention (%).

### 1.7.2 Initial development of iFR: the ADVISE study

Recently our research group presented a novel index of coronary disease severity, the instantaneous wave-Free Ratio (iFR), which fundamentally differs from FFR as it can be calculated from baseline coronary haemodynamics, without induction of hyperaemia[38]. iFR is the ratio of distal (Pd) to proximal (Pa) coronary pressures (Pd/Pa) at a specific part of the cardiac cycle, the baseline diastolic wave-free period (Figure 1.5 and Figure 1.6).

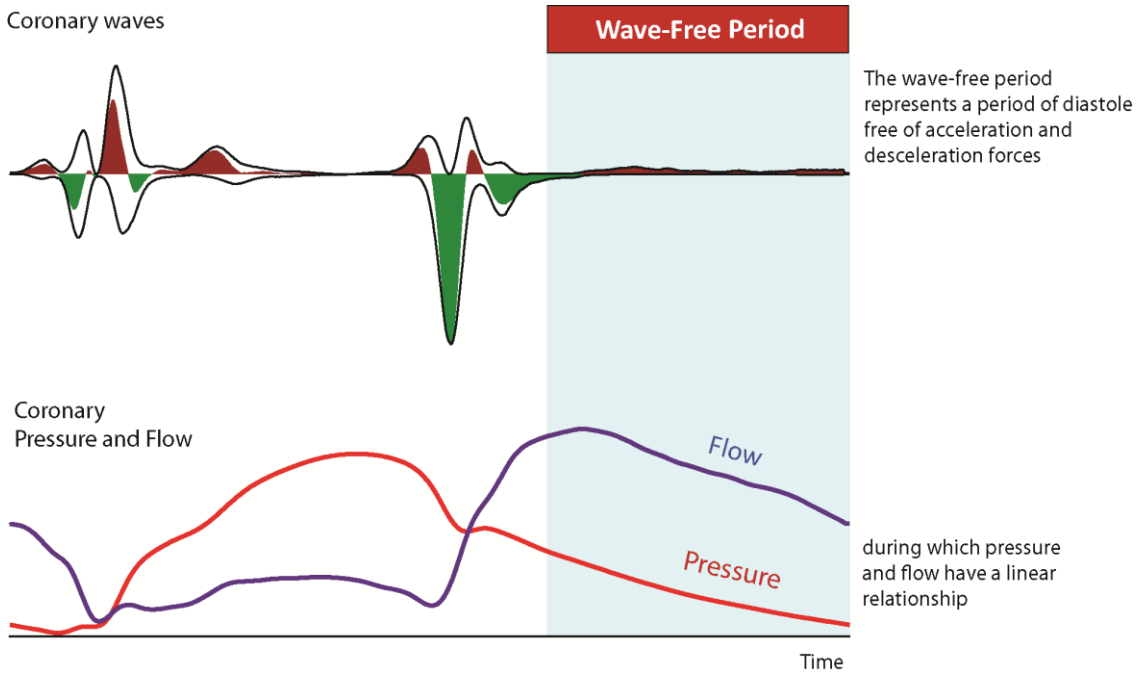


**Figure 1.5: Wave Intensity Analysis and the diastolic wave-free period:**

Pressure and flow are linearly related during the baseline diastolic wave-free period. This provides the physiological basis for the development of the instantaneous wave-free ratio (iFR) as an index of stenosis severity.

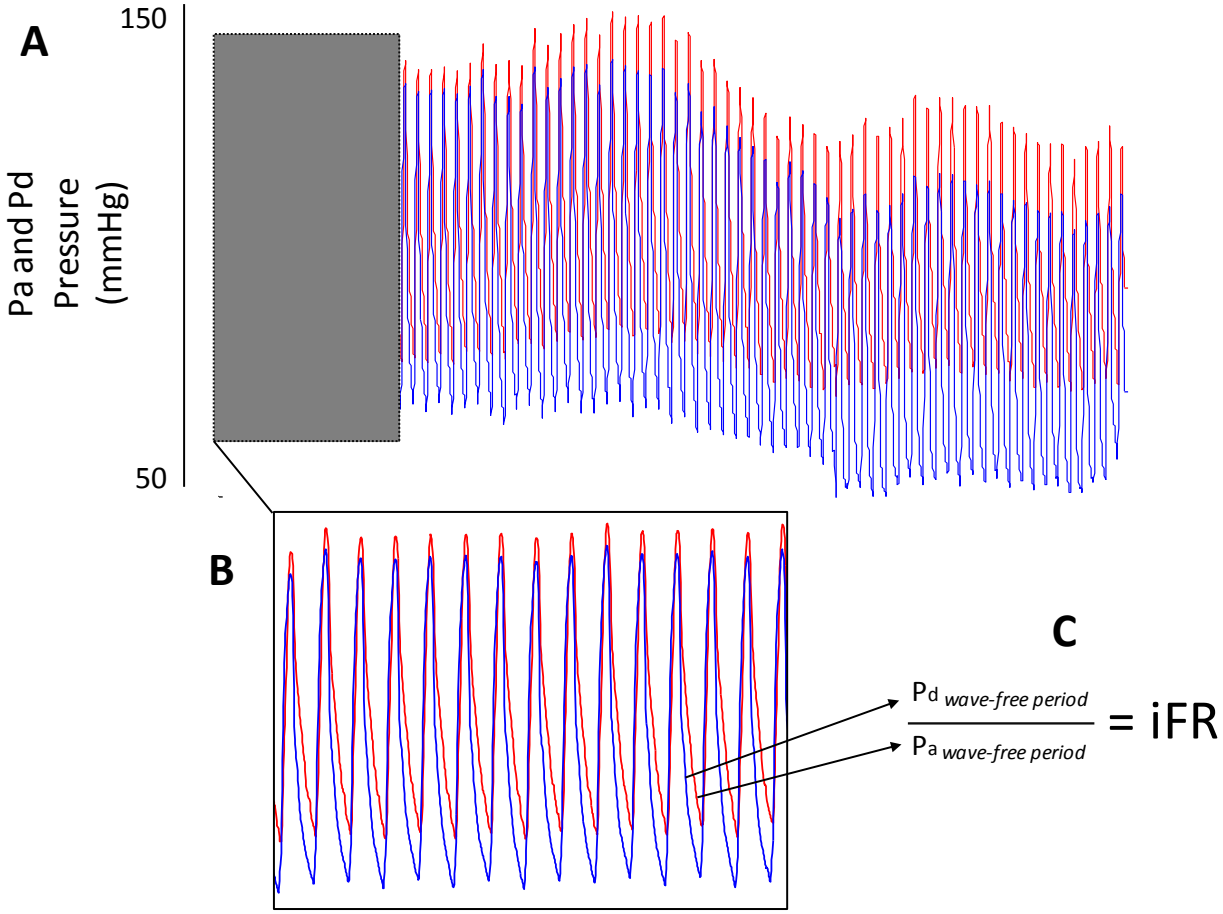


**Figure 1.6: The instantaneous wave-free ratio (iFR)**

iFR is calculated as a ratio of distal to proximal coronary pressures (Pd/Pa) at a specific period in baseline diastole – the wave-free period- without the need for hyperaemia induction

The physiological basis for iFR was described in the ADVISE study, which performed the first pilot comparison between iFR and FFR, using invasive coronary flow[38]. In ADVISE, iFR was found to have good agreement in stenoses classification with FFR across a wide spectrum of disease severity. Also, distal microvascular resistance during the baseline iFR window was found to be as stable as during whole cycle hyperaemia and FFR calculation. From ADVISE, these two initial encouraging findings set the foundations for further larger exploratory studies.

#### 1.7.3 iFR, FFR and magnitudes of distal microvascular resistance: the CLARIFY study

A subsequent study from our group extended the initial analysis from ADVISE to explore the haemodynamics underlying iFR and FFR, particularly the magnitudes of distal coronary resistance achieved during calculation of both indices[39]. This was a crucial analysis, as historical animal data from early 1990's suggested that FFR could provide better discriminatory power over baseline indices, because the induction of hyperaemia decreased distal microvascular resistance (and hence increased flow) by several fold[23]. Despite continuous development in FFR research, including its application in large outcome trials, the extent at which the induction of hyperaemia increases coronary flow in humans with coronary disease has never been explored in details. CLARIFY was therefore the first invasive study which evaluated the effects of adenosine on distal coronary resistance in patients undergoing FFR measurement. We found that the ability of adenosine to decrease resistance above baseline diastole was restricted to mild, not flow-limiting lesions. In stenoses which impose high resistance to blood flow (as measured by the hyperaemic stenosis resistance index HSR), baseline diastole offers a physiological environment with equal or even lower microvascular resistance than hyperaemia.

This finding provides strong physiological evidence to support the validity of baseline iFR, as it suggests that the magnitude of distal coronary resistance during baseline diastole is sufficiently low to enable identification of flow-limiting stenoses.

## 1.8 Aims of this thesis

The aim of this thesis is to provide further physiological and clinical validation for the utilisation of iFR as a functional index of stenosis severity.

Firstly, the relationship between iFR and FFR will be explored extensively in a larger and more clinically relevant sample. To that end, I evaluated the agreement in stenoses classification between iFR and FFR in patients undergoing routine FFR assessment in clinical practice.

Secondly, I will investigate the applicability of a hybrid decision-making strategy, in which both iFR and FFR are used in the same diagnostic pathway. In this analysis, I will explore the vasodilator-sparing capacity of iFR and the potential benefits to patients and healthcare systems associated with the reduction in the need for adenosine administration and FFR calculation.

Finally, I will further explore the underlying haemodynamics of both baseline iFR and hyperaemic FFR, using invasive coronary flow velocity and CFR as independent discriminators. In this final study, I will evaluate the agreement between pressure-only indices (iFR and FFR) and underlying CFR and quantify the magnitudes of underlying coronary flow achieved during their calculation.

# 2 MATERIALS AND METHODS

## 2.1 Funding

My work on this thesis was funded, in the first year, by the Imperial College Charity Grant. Funding for the years 2 and 3 were obtained via a personal Clinical Research Training Fellowship from the British Heart Foundation (Grant FS/11/46/28861).

## 2.2 Study sample

The final samples of the studies included in this thesis were a result of international collaborations between Imperial College Healthcare NHS Trust and other centres with extensive experience in invasive coronary physiology. This allowed exchange of expertise and increased power for each study. Whilst I have personally collected data which resulted from recruitment of 45 patients from Imperial College Healthcare NHS Trust, I was responsible in each study for pooling all data from all centres and performing all required subsequent analyses, which I describe in details below.

At our centre, potential patients were identified from the waiting list for coronary angiography at Imperial College Healthcare NHS Trust. Information about the study was provided at pre-assessment and consent was obtained at the day of the clinical procedure, once suitability for inclusion was confirmed. The study was approved by national and local ethics committees (NRES ref: 09/H0712/102 and 10/H0803/1; NCT01118481).

## 2.3 Set-up in the catheterization laboratory

### 2.3.1 Cardiac catheterization

Cardiac catheterization was performed according to standard clinical practice. 5000-10000 units of unfractionated intravenous heparin were given at the start of the procedure together with 300mcg-600mcg of intracoronary nitrates to minimize changes in epicardial artery diameters. Invasive physiological data was acquired after diagnostic angiography.

### 2.3.2 Aortic catheter

All aortic recordings were made via a 6 French guiding catheter. Guide catheters offer better inner coating, have a larger lumen and allow better torque control of the wire by the operator.

### 2.3.3 Medication

Since most patients studied were being investigated for possible coronary artery disease, it was deemed unethical to stop any of the medications they were taking prior to the procedure. Before the insertion of any intracoronary wire, 5000IU of heparin was given intravenously to reduce the risk of thrombosis. Furthermore, the activated clotting time (ACT) was measured at regular intervals and maintained above 250 seconds. Intracoronary GTN (300mcg) was administered to each artery before physiological assessment was performed to ensure no epicardial artery spasm.

### 2.3.4 Induction of hyperaemia

Current clinically used indices of coronary stenosis and microvascular resistance are measured during the administration of adenosine. The clinically recommended dose varies according to its route of administration. Intravenously a dose of 140mcg/Kg/min of adenosine via femoral venous line is recommended; intra-coronary a dose of 120mcg of adenosine by rapid bolus injection directly into the target vessel. Only an intravenous route of adenosine administration was used when simultaneous pressure and flow velocity measurements were made. This was done to ensure adequate time was available to achieve the best possible flow velocity envelope which is especially challenging in vessels with severe stenoses.

## 2.4 Data acquisition

### 2.4.1 Haemodynamic recording

Pressure and flow velocity were measured simultaneously with a 0.014inch combined pressure and Doppler sensor-tipped wire (ComboWire® XT, Volcano Corporation, San Diego, CA).

#### 2.4.1.1 The ComboWire XT

The ComboWire is a steerable guide wire which combines two different sensors. The guide wire has a diameter of 0.014" (0.36 mm) and a length of 185 cm. The CombTip type (model reference 9500) that was used in this study contains a pressure transducer and an ultrasound transducer, both mounted in a single housing at the tip of the guide wire (Figure 2.1). The ComboWire was connected to the ComboMap system via the patient interface module which conveyed the signals of Doppler and pressure from the wire to the console.

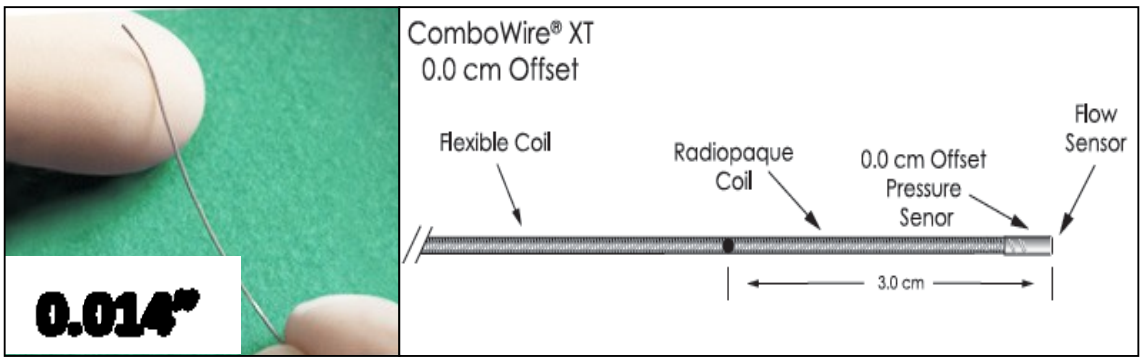


**Figure 2.1: The ComboWire XT**

#### 2.4.1.2 Electrocardiogram

Electrocardiogram (ECG) data was recorded throughout study. ECG analogue data was fed into the haemodynamic console. The ideal output lead was selected to ensure a dominant R wave was present. This is essential as the R wave provides the fiducial point against which the software would later identify each cardiac beat.

#### 2.4.1.3 Hemodynamic console

The ComboMap system 6800 (Volcano Corporation, San Diego, CA) processes the information it receives from the ComboWire, pressure transducer (from the catheterisation laboratory table) and ECG (Figure 2.2). Data recorded for subsequent analysis included the ECG, proximal aortic pressure (Pa) obtained from the aortic catheter used for coronary angiography, distal aortic pressure from the ComboWire pressure sensor (Pd) and instantaneous peak coronary flow velocity from the ComboWire Doppler sensor (IPV). All data was displayed in the console in real time (Figure 2.3). Pa, Pd, IPV and ECG were digitally stored in an .SDY file at a sampling frequency of 200Hz. Anonymized data was exported at the end of the procedure.


**Figure 2.2: Haemodynamic console used for data acquisition (ComboMap system 6800)**


**Figure 2.3: Haemodynamic data displayed at the console during data acquisition**

#### 2.4.1.4 Aortic pressure measurement

We used fluid-filled hollow guide catheters to measure aortic pressure (Pa) throughout the procedure. Pressure is transmitted through a tiny fluid column to an external pressure transducer, to which the fluid-filled system is connected. In order to maintain the highest level of quality of the pressure trace, the distance between the coronary artery to the pressure transducer was kept to the minimum and the catheter was kept free of bubbles. The pressure transducer was fixed to the catheter table to avoid erroneous readings of pressure due to height changes of the transducer. Before use, each of the fluid-filled catheters was zeroed at the right atrial level with the patient supine.

The pressure waveform was displayed continuously on a screen to be viewed by the operator together with minimum, maximum and mean values of aortic pressure. The standard procedure in the catheterization laboratory is to mount the pressure transducer of the guiding catheter at a height of 5 cm below the sternum, which is estimated to be the location of the aortic root. As this is merely estimation and can be incorrect, pressure readings may be also be incorrect. Therefore, by adjusting the height of the pressure transducer small errors in pressure can be corrected; decreasing the level of the transducer increases aortic pressure, increasing the height of the transducer will decrease aortic pressure. This manoeuvre was only carried out if during the verification process of comparing the fluid-filled pressure reading with that of the guide wire (at the time when the guide wire is positioned at the tip of the guide catheter while sitting at the coronary ostium) there was a pressure difference between the two readings. This step is explained on the section on equalizing pressure.

#### 2.4.1.5 Distal coronary pressure measurement

The ComboWire XT 0.0 guide wire (Volcano therapeutics) was used to measure coronary pressure (Pd) and a new sterile wire was used for each patient. Calibration of the pressure wire was carried out outside the body, with the wire positioned and rested on the table, through an automated process by the ComboMap. Once this was done, the 'ready' signal displayed on the touch screen enabled use of the wire. At baseline and with the wire outside the body, a check was carried out to ensure that Pd was reading zero pressure. If not, the wire was zeroed. Only then, was the wire removed from the spiral. Furthermore, to help with rotational movements and manipulation in the coronary arteries, the shapeable guide wire tip was carefully shaped using standard tip shaping practices. With experience, we found that for best results, the shaping of the tip had to be done in the direction of the sensor housing opening. Under fluoroscopic imaging, the wire was positioned in the coronary artery at the site of interest and on occasions torque was applied to facilitate this.

#### 2.4.1.6 Equalising pressure in the ascending aorta

At the coronary ostium, the pressure displayed by both the fluid-filled system and the pressure wire were compared. At this point to ensure wire pressure was equal to aortic pressure the wire pressure was equalised to aortic pressure. The next step of the protocol was only followed once it was confirmed that there was no difference in the two pressures. A guide wire introducer was placed in the Y-connector to facilitate wire manipulations in the coronary artery. The space around the wire within the introducer may leak and lead to aortic pressure measurements which are below the actual pressure. Although in every case we checked that the introducer was not leaking, we took the extra precaution of making all measurements with the introducer out and the Y-connector always locked in the closed position so that there was no leakage around the wire.

It should be noted that equalisation of pressure occurred in the aorta and therefore in the presence of a clear dicrotic notch on the pressure wave form. The presence of this notch was ensured throughout the measurement process to ensure no damping of aortic pressure was present which has been shown to result in inaccurate intra-coronary measurements.

#### 2.4.1.7 Checking for pressure drifting

One problem encountered during some of the procedures was signal drifting. This is a phenomenon which is frequently encountered during pressure wire measurements and a drift of <5mmHg per hour has been previously regarded as acceptable (25). However, due to the magnitude of the measurements we were making we refused to accept any drift in the measurements. As a result after each of the measurements the pressure sensor was returned to its original position in the aorta (where equalisation was performed) to ensure there was no drift. If any drift was detected the measurements were repeated. If the wire continued to drift it was replaced. No post hoc correction of drift was therefore necessary.

#### 2.4.1.8 Coronary flow velocity measurement

The ComboWire XT 0.0 guide wire (Volcano therapeutics) was used to measure instantaneous peak velocity of blood (IPV) simultaneously with Pd. A new sterile wire was used for each patient. Doppler velocity is measured approximately 5 mm from the tip of the wire. The pulsed Doppler beam angle is 45 degrees and insolates a sample volume of approximately 4 mm downstream of the Doppler probe. Fine rotational movements were carried out so that the Doppler beam captured the highest velocity. The intensity of the Doppler envelope was taken as indicative of this. Acquisition of the Doppler signal proved the most demanding aspect of the study acquisition process. With

experience we were able to get a strong, dense and steady signal even in the most challenging cases.

*2.4.1.8.1 Doppler calibration - Doppler spectrum input*

At each location, the wall filter function was used to reduce or eliminate low frequency noise returning in the Doppler spectrum when the transducer was near an artery wall. Available settings are 200, 400, 800 and 1600Hz, the optimum was found to be at 400Hz and this setting was used in the majority of the cases.

The IPV threshold is a signal to noise ratio, and establishes the signal threshold: signals below this level are considered noise and not displayed or used for flow measurements. The IPV threshold was set by optimizing the IPV envelope which is displayed as a blue envelope around the flow spectrum. This was adjusted manually in all patients and all vessels studied to ensure that the blue tracking envelope matched the outer edge of the velocity spectrum. A range of 0-3 was used for the majority of studies.

### 2.4.1.9 Reproducibility of measurements

Reproducibility of hemodynamic measurements has been demonstrated previously[40]. The mean and standard deviation of the difference between the separate 30-second recordings of blood pressure was 12.0±269 Pascal. The mean and standard deviation of the difference between the separate 30-second recordings of flow velocity was 0.007± 0.022 m/s[40].

## 2.5 Post-acquisition haemodynamic data analysis

Once exported from the console, haemodynamic data was imported to customized software written in Matlab (Mathworks, Inc.). This software was written by me using a combination of new coding with a foundation of codes from previous researchers in the group. The software automatically performed specific processes with the haemodynamic data:

### 2.5.1 Correction of pressure-flow delay

For accurate analysis of phasic coronary haemodynamics it was vital that measurements of pressure and velocity were correctly aligned in time. Previous studies have demonstrated this delay to be 43ms (mean 42.5±3.8ms)[40]. This delay was subtracted from the timing of the pressure data in all subsequent analyses, so that both pressure and Doppler signals were synchronous.

### 2.5.2 Data filtering

All data was passed through a Savitzky-Golay smoothing filter. This filter is ideal for smoothing haemodynamic signals whose frequency span (without noise) is large. This is typical of haemodynamic data where it is common for peaks and troughs to occur rapidly in succession within a short time period. The Savitzky-Golay filter fits a polynomial to each frame of data to minimize the least of squares error. It is thus more effective at preserving pertinent high frequency components of a signal than standard averaging filters. However, whilst the Savitzky-Golay is very good at preserving high frequency components, it is less good than standard averaging filters at removing noise. Savitzky-Golay polynomial order and frame width constants were set at 3 and 31 respectively in all data analysis.

### 2.5.3 Calculation of coronary haemodynamic indices

The software automatically calculated a series of haemodynamic indices, with minimal operator input. The diastolic iFR window was identified using fully automated algorithms acting over ECG-gated, time-aligned pressure traces, as described in the ADVISE study[38]. A screenshot example of the software used for analysis is presented in Figure 2.4.

### 2.5.3.1 Definition of physiological indices

Pa = Proximal (aortic) pressure (mmHg)

Pd = Distal (coronary) pressure (mmHg)

Fractional Flow Reserve (FFR) = $\frac{Pd}{Pa}$ at whole-cycle hyperaemia

Instantaneous wave-Free Ratio (iFR) = $\frac{Pd}{Pa}$ at baseline iFR window

Instantaneous wave-Free Ratio during adenosine administration (iFRa) = $\frac{Pd}{Pa}$ at hyperaemic iFR window

Baseline Flow = Mean baseline whole-cycle coronary flow velocity (cm/s)

Flow $_{FFR}$ = Mean whole-cycle coronary flow velocity at stable hyperaemia (cm/s)

Flow $_{iFR}$ = Mean coronary flow velocity during the baseline iFR window (mid-diastole) (cm/s)

Coronary flow velocity reserve (CFVR) ** = $\frac{Whole{-}cycle\ hyperaemic\ flow\ velocity}{Whole{-}cycle\ baseline\ flow\ velocity}$

Hyperaemic Stenosis Resistance (HSR) = $\frac{Whole{-}cycle\ hyperaemic\ pressure\ gradient\ (mmHg)}{Whole{-}cycle\ hyperaemic\ flow\ velocity\ (\frac{cm}{s})}$

Distal hyperaemic coronary resistance = $\frac{Whole{-}cycle\ hyperaemic\ distal\ pressure\ (Pd)}{Whole{-}cycle\ hyperaemic\ flow\ velocity\ (\frac{cm}{s})}$

Distal baseline iFR window resistance = $\frac{iFR\ window\ distal\ pressure\ (iFR\ Pd)}{iFR\ window\ flow\ velocity\ (\frac{cm}{s})}$

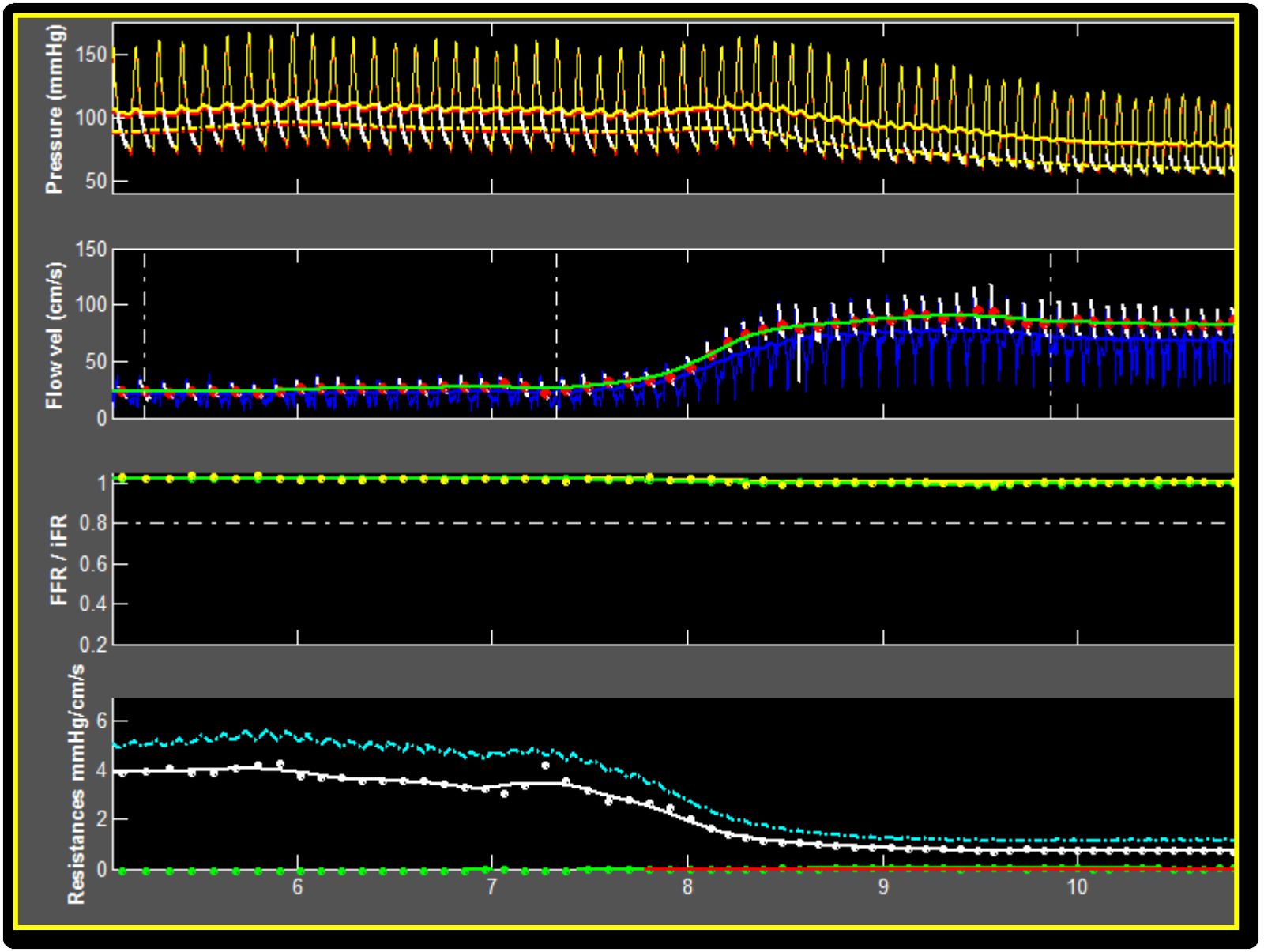


**Figure 2.4: Screenshot of customized software used for off-line hemodynamic analysis:**

The operator selects the time window to be analysed and all indices are calculated automatically.

# 3 Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses

## 3.1 Introduction

Instantaneous wave-Free Ratio (iFR) is a recently proposed invasive pressure-derived index of coronary stenosis severity. It differs from fractional flow reserve (FFR) as it does not require the administration of vasodilators for its calculation. iFR is calculated from trans-stenotic pressure measurements as the ratio of distal to proximal coronary pressures during a specific wave-free period of the cardiac cycle, when microvascular resistance is intrinsically stable and minimised[38].

The physiological foundations of iFR and its diagnostic efficiency in identifying FFR-significant stenoses have been recently reported in the ADVISE study[38]. As a validation study, ADVISE evaluated iFR's performance across a broad range of coronary stenosis severities, which included tight and mild coronary narrowings, in the same line as pioneering studies of FFR[24, 25, 41]. However, in everyday practice, and in agreement with clinical practice guideline recommendations[3, 5, 42], functional intracoronary assessment of stenosis severity is predominantly used to interrogate intermediate stenoses with unclear severity. A critical difference of these two scenarios is that, in clinical evaluation of angiographically intermediate stenoses, FFR values tend to be distributed closer to the 0.80 established cut-off. It is likely that these differences in frequency distribution of stenosis severity could influence the intrinsic agreement between repeated FFR measurements and the overall agreement between iFR and FFR on classifying coronary stenoses[43-45] (Figure 3.1).

In the present study we evaluated the level of agreement between iFR and FFR in a cohort of patients with intermediate coronary stenoses investigated with pressure guide wires as part of their clinical assessment. The agreement between iFR and FFR was interpreted in light of the intrinsic variability of FFR, and the underlying characteristics of FFR data distribution encountered in this registry.

## 3.2 Methods

### 3.2.1 iFR and FFR data from this clinical registry

#### 3.2.1.1 iFR registry study population

The study included 312 patients with 339 coronary stenoses that, as part of clinical management, required functional intracoronary assessment with pressure guide wires at three large European tertiary cardiac centres (Hospital Clínico San Carlos in Madrid, Spain; Guy's and St Thomas' NHS Foundation Trust, London; and the Academic Health Science System of Imperial College London, UK). Anatomical severity of coronary stenoses was measured using quantitative coronary angiography (QCA).

#### 3.2.1.2 Haemodynamic data collection and analysis

Acquisition of physiological data for FFR calculation was performed according to conventional practice[42] using commercially available FFR systems (RadiView console and PressureWire Certus, St. Jude Medical, Minneapolis, Minnesota; and Combomap console and Prestige pressure guide wire, Volcano Corporation, San Diego, California). Adenosine was used for the calculation of FFR; in 99% of the cases it was administered via a central line, with doses ranging from 140mcg/Kg/min to 200mcg/Kg/min; in the remaining 1% of the cases the intra-coronary route was used. Digital data was extracted from FFR console platforms and processed off-line in a core laboratory (International Centre for Circulatory Health, National Heart and Lung Institute, UK) using a custom software package with Matlab (Mathworks, Inc., Natick, Massachusetts)

as described elsewhere[38]. It was possible to calculate iFR in all cases, using fully automated algorithms applied to the wave-free period over a minimum of 5 beats, before adenosine administration, as previously described[38] (Figure 1.6).

### 3.2.2 FFR intrinsic variability data from landmark FFR reproducibility study

The FFR reproducibility data from the DEFER study[15] was obtained from a previously published scientific statement on physiological assessment of coronary stenoses from the American Heart Association, containing the correlation between 2 consecutive FFR measurements within 10 minutes in 325 selected subjects[42]. Data was digitised using semi-automatic bitmap-to-digital software (Matlab, Mathworks, Inc.).

### 3.2.3 Steps for establishing the overall classification agreement between iFR and FFR

For the purpose of general understanding of our methodology, we have schematically divided this study in 5 steps, as summarised in the flowchart presented in Figure 3.2:

The first step was to identify the optimal iFR cut-off (Step 1, Figure 3.2): A receiver-operating characteristic (ROC) curve was applied to this iFR registry to identify the optimal iFR cut-off value to agree with an FFR of 0.8. Next, the FFR repeatability agreement was assessed (Step 2, Figure 3.2) using data from the DEFER reproducibility study. Mean FFR values were divided in 0.05 quantiles, from 0.2 to 1 and the agreement (diagnostic accuracy) between the first and second FFR measurements calculated in each quantile. Agreement between FFR values was considered when *both* FFR values were below (or equal to) or

above the established cut-off of 0.80. Next, the agreement between iFR and FFR was assessed (Step 3, Figure 3.2) using data from this iFR registry, the same method to that described in step 2. Then, the overall level of agreement (total diagnostic accuracy) between iFR and FFR and between repeated measurements of FFR was than calculated for the sample of this clinical registry (Step 4, Figure 3.2). For both iFR-FFR and FFR-FFR relationships, the total agreement was calculated by multiplying the agreement in each 0.05 quantile (from step 2 and 3) by the percentage of data points in each 0.05 quantile encountered in this registry. Finally, an estimation of the overall iFR-FFR agreement and FFR repeatability agreement in different populations was performed using the same methodology applied in step 4 to estimate the overall level of agreement (total diagnostic accuracy) between iFR and FFR and between repeated measurements of FFR in different samples, from previous validation studies of iFR and FFR (Step 5, Figure 3.2). The frequency distribution of FFR values in the ADVISE trial, FFR reproducibility study and the landmark study which validated FFR against positron emission tomography (PET) were obtained from their original publications[38, 41, 42].

### 3.2.4 Statistical analysis

Statistical calculations were performed using Matlab (Mathworks, Inc.) and STATA version 11 (StataCorp, College Station, Texas). The Hartigan's Dip Test was used to test for unimodality for the samples of this clinical iFR registry, the FFR reproducibility study and the ADVISE study. The Hartigan's Dip Test could not be applied to the FFR study against PET due to insufficient data points

across the entire range of FFR values. The areas under ROC curves were compared using a nonparametric method[46].

## 3.3 Results

### 3.3.1 Patient characteristics of this clinical iFR registry

Demographic, clinical and angiographic data of the iFR registry population are shown in Table 3-1. The mean diameter stenosis was 48% (standard deviation 13%), indicating a predominantly intermediate anatomical stenosis grade. The interrogated stenoses were located most frequently in the left anterior descending artery (71%). The vast majority of patients presented with stable symptoms; in 7 % of cases, the pressure guide wire was used to interrogate non-culprit stenoses in the context of an acute coronary event. There were no complications related to pressure guide wire interrogation of the stenoses. Analysis of the registry data revealed a unimodal distribution of FFR values with mean 0.81 (standard deviation 0.09) and median 0.82, with a preponderance of intermediate physiological severity: 71% of FFR values fell between 0.7 and 0.9 and only 10% were < 0.7. The Hartigan's Dip Test confirmed the unimodality of the data (dip test=0.027, p=0.1).

### 3.3.2 Identification of optimal iFR cut-off

To match an FFR value of 0.8, the ROC curve identified an optimal iFR cut-off value of 0.89. The area under the ROC curve for iFR was 0.86 (Figure 3.3), whilst for mean resting Pd/Pa was 0.80 (p=0.01). For an FFR value of 0.75, the ROC curve identified an optimal iFR cut-off value of 0.79.

### 3.3.3 Assessment of the agreement between iFR and FFR after accounting for the intrinsic variability of FFR

3.3.3.1 Per-range classification agreement between repeated FFR measurements

The FFR reproducibility study reveals the classification agreement between the first and second FFR measurements (the ability of *both* measurements to classify a lesion as significant or not based on a 0.8 cut-off). This repeatability agreement is shown in Figure 3.4 for each 0.05 quantile of the disease spectrum. In general, the ability of the 1$^{st}$ FFR measurement to agree with the classification of the second FFR measurement was strong across almost the whole range of disease. However, close to its established 0.80 cut-off, the FFR repeatability agreement fell, reaching a nadir of around 50%. Overall, for the population of this clinical iFR registry, the level of classification agreement between repeated FFR measurements was 85%.

3.3.3.2 Per-range classification agreement between iFR and FFR

The classification agreement between iFR and FFR (their ability to *both* classify a lesion as significant or not based on a 0.89 and 0.8 cut-off, respectively) is shown in Figure 3.5 for each 0.05 quantile of the disease spectrum. iFR - FFR categorisation agreement followed a similar pattern to the agreement of repeated measurements of FFR. iFR agreement with FFR was strong (100%) across almost the whole range of disease, except for the zone around their established cut-off where intrinsic FFR-FFR classification agreement was also lowest. Overall, for the population of this clinical iFR registry, the level of classification agreement between iFR and FFR was 80%.

### 3.3.4 Overall agreement between iFR and FFR in this clinical registry

When the intrinsic variability of FFR is taken into account, the overall level of classification agreement between iFR and FFR in this registry population is 94% (80% observed iFR – FFR agreement as a fraction of the 85% FFR repeatability agreement) (Table 3-2). Amongst the stenoses classified as non-significant by iFR (> 0.89) and as significant by FFR (≤ 0.8), 81% had associated FFR values located within the FFR "gray-zone" (0.75 - 0.8) and 41% within the 0.79 - 0.80 FFR range.

### 3.3.5 Overall agreement between iFR and FFR across different populations

To assess the agreement between repeated FFR measurements and between iFR and FFR in populations with different distributions of FFR values, comparisons were made for the samples of the ADVISE study, the FFR reproducibility study and the FFR-PET study, using the same methodology as applied to this clinical registry. The population characteristics of these studies are summarised in Table 3-2 and their frequency distribution of FFR values is presented in Figure 3.6, with a comparison histogram of this clinical iFR registry. The overall level of classification agreement between iFR and FFR in different studies is presented in Table 3-2 and Figure 3.7. The magnitude of agreement between repeated FFR measurements and between iFR and FFR changes significantly depending on the underlying population studied. However, across all different samples, when the intrinsic variability of FFR is taken into account, iFR accuracy is almost identical, ranging from 94% to 96% (Table 3-2).

## 3.4 Discussion

The present study finds an excellent classification agreement between iFR and FFR in a registry population that is formed by coronary stenoses with predominantly intermediate physiological and angiographic severities, the most frequent clinical context of FFR use. The agreement between iFR and FFR was analysed taking into account the intrinsic variability of repeated FFR measurements (from DEFER) in the same population. We have also found that the close relationship between iFR and FFR is maintained across populations with different distributions of FFR values, such as in previous validation studies of FFR and iFR. The overall agreement between iFR and FFR mirrors the agreement between repeated FFR measurements and varies significantly depending on the type of population being studied. However, for multiple types of population distribution, if the intrinsic variability of FFR is accounted for, iFR accuracy ranges from 94% to 96%.

### 3.4.1 iFR and FFR: continuous variables interpreted dichotomously

Despite the pressure gradient across a coronary stenosis being a continuous variable, assessment of stenosis severity with FFR is interpreted dichotomously ("significant" versus "non-significant"). One of the consequences of comparing two techniques that use dichotomous classification based on continuous values, such as FFR and iFR, is that the classification agreement between measurements will decrease when the values studied are close to the established cut-off (i.e. 0.8 for FFR). This concept, which is schematically depicted in Figure 3.1, is valid for comparisons between techniques (iFR versus

FFR) and, as we found in this present study, also affects the repeatability performance of an index (repeated FFR measurements). For instance, a small difference between measurements near the FFR cut-off value of 0.80 (for example, 0.79 versus 0.81) will have a direct effect on the stenosis classification. The same absolute difference in measurements when encountered away from the cut point (for example 0.50 versus 0.52, or 0.95 versus 0.97) will have no impact on the classification of a lesion. Figure 3.4 illustrates how the agreement between 2 repeated FFR measurements decreases around its established cut-off value. This observation is of paramount importance, since comparisons against FFR (newly proposed modalities such as iFR or even established techniques such as intravascular ultrasound) cannot, on average, perform better than FFR would perform against itself[47]. This phenomenon also demonstrates that, despite contrary belief[48], a coronary pressure index sometimes can lie – even to itself.

### 3.4.2 Effects of data distribution on overall agreement between iFR and FFR

As a consequence of the above phenomenon, the frequency distribution of values in any study population has a major influence on the overall classification agreement between tests. Direct comparison of the overall percentage agreement (total accuracy) between tests is therefore only valid when applied to samples with the same type of data distribution. To circumnavigate this we applied a method which allows the overall agreement between iFR and FFR to be estimated in any type of data distribution and interpreted in the context of FFR intrinsic variability in the same sample. First, we demonstrated that within each quantile of physiological disease severity, the agreement between iFR and FFR follows a similar pattern to the intrinsic or intra-technique agreement of FFR

(Figure 3.4 and Figure 3.5). Subsequently, we calculated the overall agreement (or total accuracy) between iFR and FFR and the overall self-agreement (intrinsic accuracy) between repeated FFR measurements for the population encountered in this clinical registry. Finally, we extended this analysis to other populations, with different distributions of FFR values and demonstrated that iFR and FFR have a level of agreement which is as close as the FFR intrinsic agreement, when comparisons are made in the same type of population.

### 3.4.3 iFR performance in a representative clinical population

iFR was first tested as a diagnostic index in the ADVISE study. Being a methodological validation study, the main aim of ADVISE was to test iFR performance using FFR as a reference, over a wide range of stenosis severity. Indeed, 41% of the patients in ADVISE had FFR values < 0.7. This pattern of distribution, with an almost equal proportion of significant and non-significant stenoses, is a common feature of validation studies, including those which compared FFR against invasive coronary flow[24], non-invasive functional tests[25] and positron emission tomography[41]. The ADVISE study documented a high level of agreement between iFR and FFR, setting the foundations of iFR as a coronary diagnostic modality.

This registry constitutes a second step in the validation of iFR, applied in this occasion to a clinically representative population of individuals undergoing coronary physiological assessment in the catheter laboratory. Although one of the messages arising from the FAME study[14] was that even angiographically severe stenoses may have an associated FFR > 0.80, most physicians currently

limit the use FFR to the evaluation of angiographically intermediate stenoses, in agreement with the recommendation made by clinical practice guidelines[3, 5, 42]. This attitude is reflected in the characteristics of clinical cohorts, formed predominantly by physiologically intermediate stenoses. In the case of this clinical iFR registry the distribution of FFR data revealed that most FFR values (81%) fell between 0.60 and 0.90 (Figure 3.6), a pattern consistently shown in data from the three participating institutions. In this population of physiologically intermediate coronary stenoses, iFR maintained excellent classification agreement with FFR.

### 3.4.4 The effects of data distribution on the optimal iFR cut-off

In this clinical iFR registry, the optimal established cut-off value for iFR to identify stenoses with FFR of 0.80 was 0.89. This value is higher than the 0.83 optimal iFR cut-off observed in the ADVISE study but similar to the one observed in other studies comparing iFR and FFR in clinical populations[49]. As these cut-offs were identified using receiver-operating characteristic curves, accurate determination is highly dependent on adequate powering around the cut-off. As this iFR registry had the majority of its lesions in the intermediate zone (81%), it is both reflective of the population in which such physiological assessments are routinely made, and is well powered to explore the iFR cut-off best reflecting FFR 0.8. Therefore, the iFR 0.89 cut-off represents the value of iFR which will more often agree with dichotomous classification of stenoses by FFR in clinical populations, and can therefore be considered the best iFR cut-off to identify 0.8 FFR stenoses in clinical practice.

### 3.5 Clinical implications

Supported by multiple clinical studies demonstrating the benefits of physiology-guided revascularisation, FFR utilisation has expanded significantly over the recent years and has culminated in recent proposals of interrogating every suitable stenosis, irrespective of its angiographic severity[14, 15, 50]. However, FFR is performed in only 6% of all coronary intervention procedures in the United States[3]. Undoubtedly, the need for adenosine administration is a contributor to this low adoption rate. As iFR is a pressure-derived index which does not require adenosine administration for its calculation, it is an attractive tool for the interventionalist, since it may simplify even further the utilisation of coronary physiology in the cardiac catheterisation laboratory. The idea of adenosine-free interrogation of coronary stenoses is also supported by recent demonstration that resting coronary haemodynamics can be used to infer the physiological significance of coronary lesions[51].

#### 3.5.1 Data distribution of future iFR and FFR studies with clinical outcomes

We believe that our results highlight the foremost importance of knowing the type of data distribution when quoting the overall performance of diagnostic tests such as accuracy and predictive values. For a valid interpretation of the meaningfulness of study results, we suggest that future trials, especially those evaluating clinical endpoints[15, 27] such as FAME II study, present their data distribution for universal comparison.

### 3.6 Limitations

Our study has limitations. The investigators had no control over the technique for measuring FFR across all three institutions. The recording of each FFR trace was performed relying solely on the clinicians' expertise, which could potentially increase the chance for measuring error. However, this real-life method of data collection helps to strengthen the external validity of our results and its interpretation directly into clinical practice.

This registry included patients in whom FFR was performed using either intravenous (99%) or intracoronary (1%) routes. Whilst differences in methodology may introduce theoretical differences between the groups, these differences are small, and reflect the real world assessment practices of the institutions in the study.

Finally, iFR was compared to FFR within the same digital pressure trace, whilst the FFR intrinsic variability was established in repeated FFR measurements, 10 minutes apart. It is unknown whether this time delay could influence the iFR-FFR relationship. iFR reproducibility studies are ongoing and will help clarify this discussion.

### 3.7 Conclusions

iFR demonstrated a high level of classification agreement with FFR in a large group of patients with intermediate coronary stenoses, typical of individuals undergoing cardiac catheterization and invasive coronary physiological assessment. The agreement between iFR and FFR mirrors the intrinsic agreement of repeated FFR measurements when the same sample is being studied.

## 3.8 Tables

**Table 3-1: Patient Demographic Data**

| | |
|---|---|
| No. of stenoses | 339 |
| Age, yrs ± SD | 62 ± 10 |
| Male, n (%) | 261 (77) |
| Co-morbidities, n (%) | |
| Diabetes | 105 (31) |
| Hypertension | 210 (62) |
| Hypercholesterolaemia | 237 (70) |
| Smoking history | 152 (45) |
| Chronic kidney disease | 24 (7) |
| Severe LV dysfunction (EF < 30%) | 7 (2) |
| Clinical presentation, n (%) | |
| Stable angina | 315 (93) |
| Unstable angina | 24 (7) |
| Coronary anatomy, n (%) | |
| Single vessel CAD | 264 (78) |
| Multivessel CAD | 75 (22) |
| LAD | 241 (71) |
| LCx | 44 (13) |
| RCA | 44 (13) |
| LMS | 10 (3) |
| Proximal vessel | 162 (48) |
| Diameter stenosis, % ± SD | 48 ± 13 |
| Reference vessel, mm ± SD | 2.9 ± 0.6 |
| Adenosine route, n (%) | |
| Intravenous | 332 (98) |
| Intracoronary | 7 (2) |

EF = Ejection Fraction; CAD = Coronary artery disease; LAD = Left anterior descending artery; LCx = Left circumflex artery; RCA = Right coronary artery; LMS = Left main stem; SD = Standard deviation of the mean. Diagnosis of diabetes, hypertension, hypercholesterolaemia and chronic kidney disease was obtained from the history described in the medical notes. Smoking history includes current and previous cigarette smoking.

**Table 3-2: Observed and adjusted iFR-FFR agreement in different populations**

| Population from | Distribution of FFR values | | | Overall classification agreement between | | iFR accuracy |
|---|---|---|---|---|---|---|
| | Mean FFR ± SD | FFR < 0.7 | FFR 0.7 - 0.9 | Repeated FFR measurements | iFR and FFR (observed) | |
| **iFR clinical registry** | 0.81 ± 0.09 | 10 % | 71 % | 85 % | 80 % | 94 % (80/85) |
| **FFR reproducibility study** | 0.75 ± 0.14 | 36 % | 46 % | 91 % | 86 % | 94 % (86/91) |
| **ADVISE study** | 0.72 ± 0.2 | 41 % | 41 % | 93 % | 88 % | 94 % (88/93) |
| **FFR - PET study** | 0.63 ± 0.19 | 73 % | 14 % | 100 % | 96 % | 96 % (96/100) |

SD = Standard deviation of the mean

## 3.9 Figures

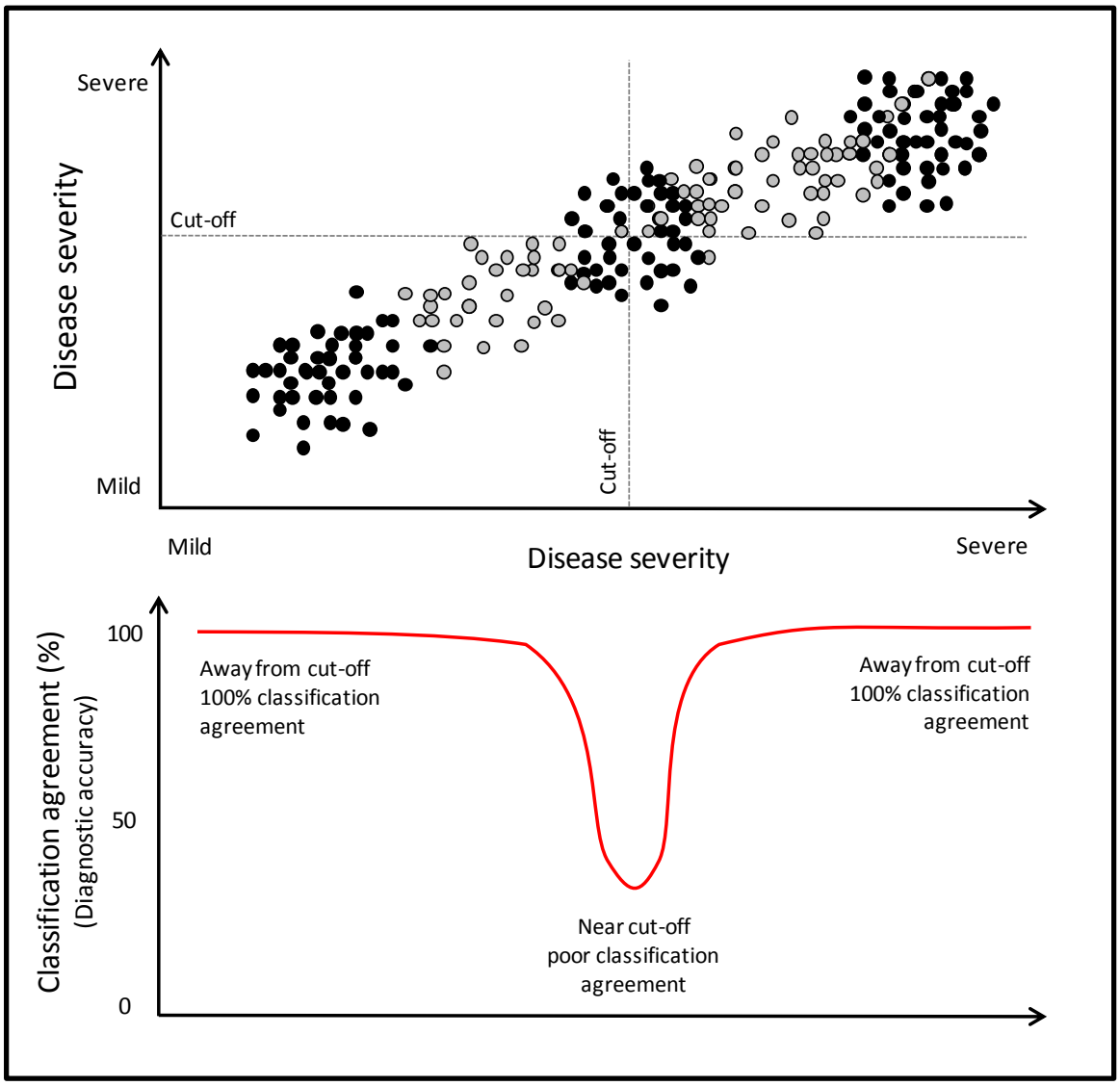


**Figure 3.1: Classification agreement between two measurements depends on the data distribution**

The level of agreement between two measurements - when they are *both* "significant" or "non significant" – will vary within each range of disease severity (from mild to severe), depending on how close the data points are to the established cut-off (clusters of black dots). The overall agreement between them (the overall diagnostic accuracy) will therefore be influenced by the data distribution of the sample and depend on the proportional number of data points away from/close to diagnostic cut-off.

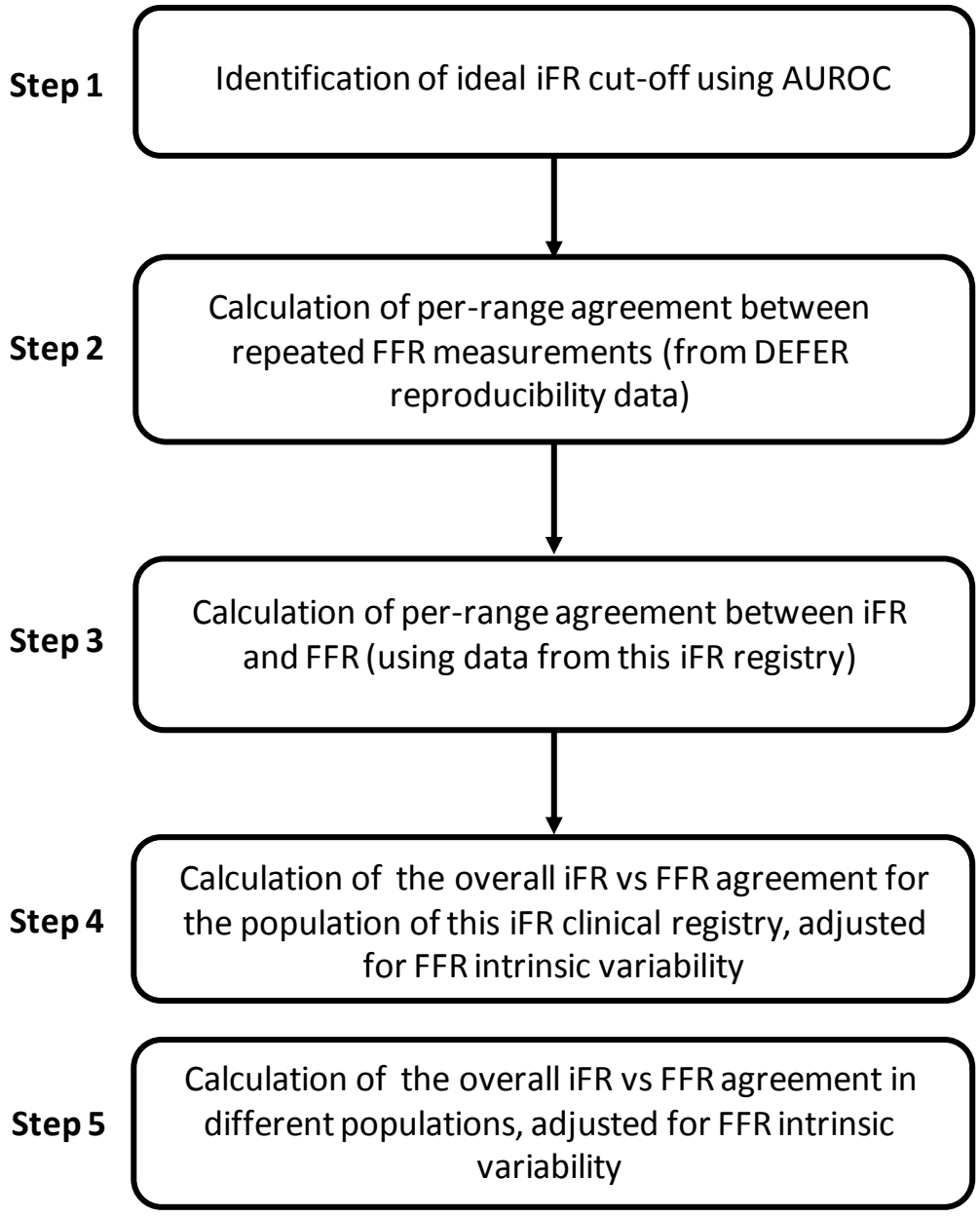


**Figure 3.2: Study flowchart**

Overview of study methodology

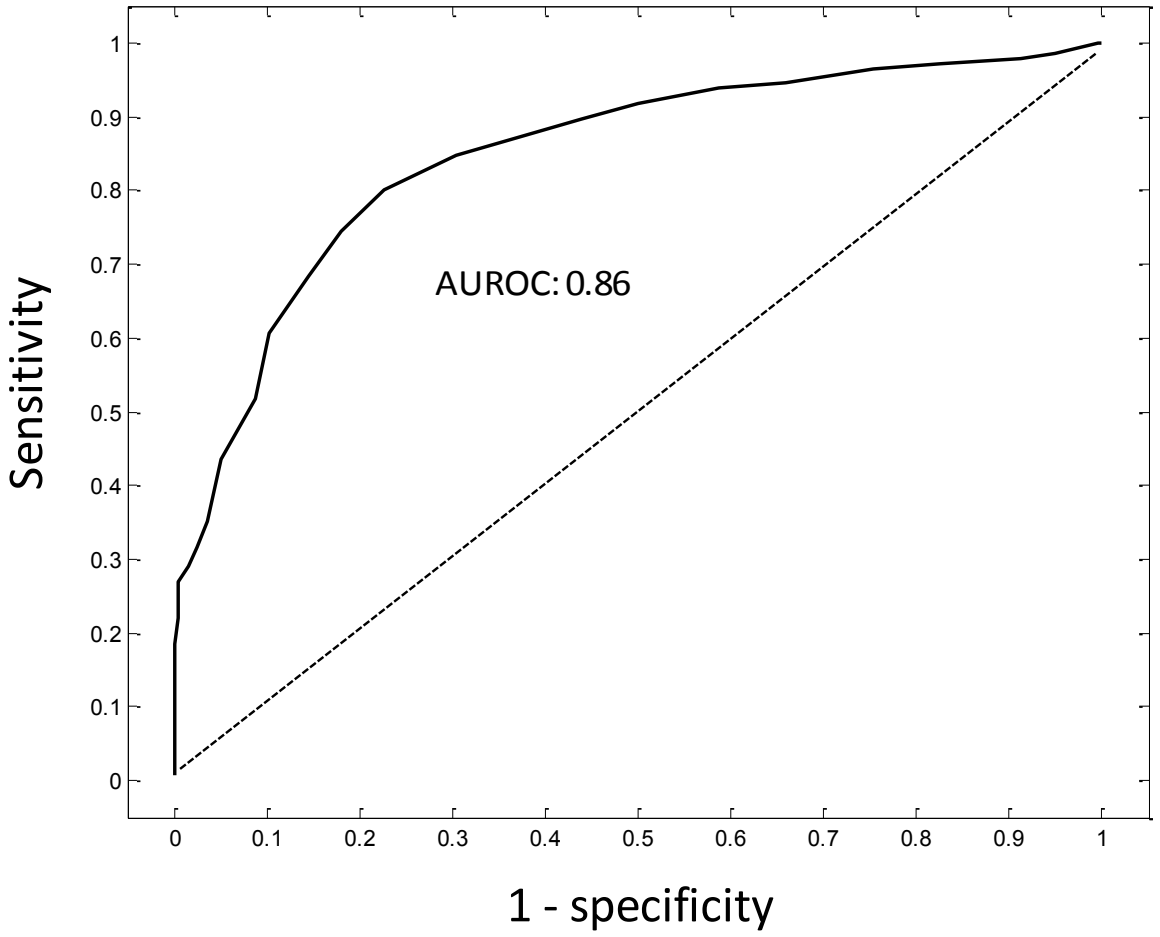


**Figure 3.3: Area under receiver-operating characteristic curve (ROC).**

Classification agreement between iFR and FFR in this clinical iFR registry, demonstrated using the area under the receiver-operating characteristic curve (FFR cut-off 0.8). The optimal iFR cut-off identified for the population of this study was 0.89.

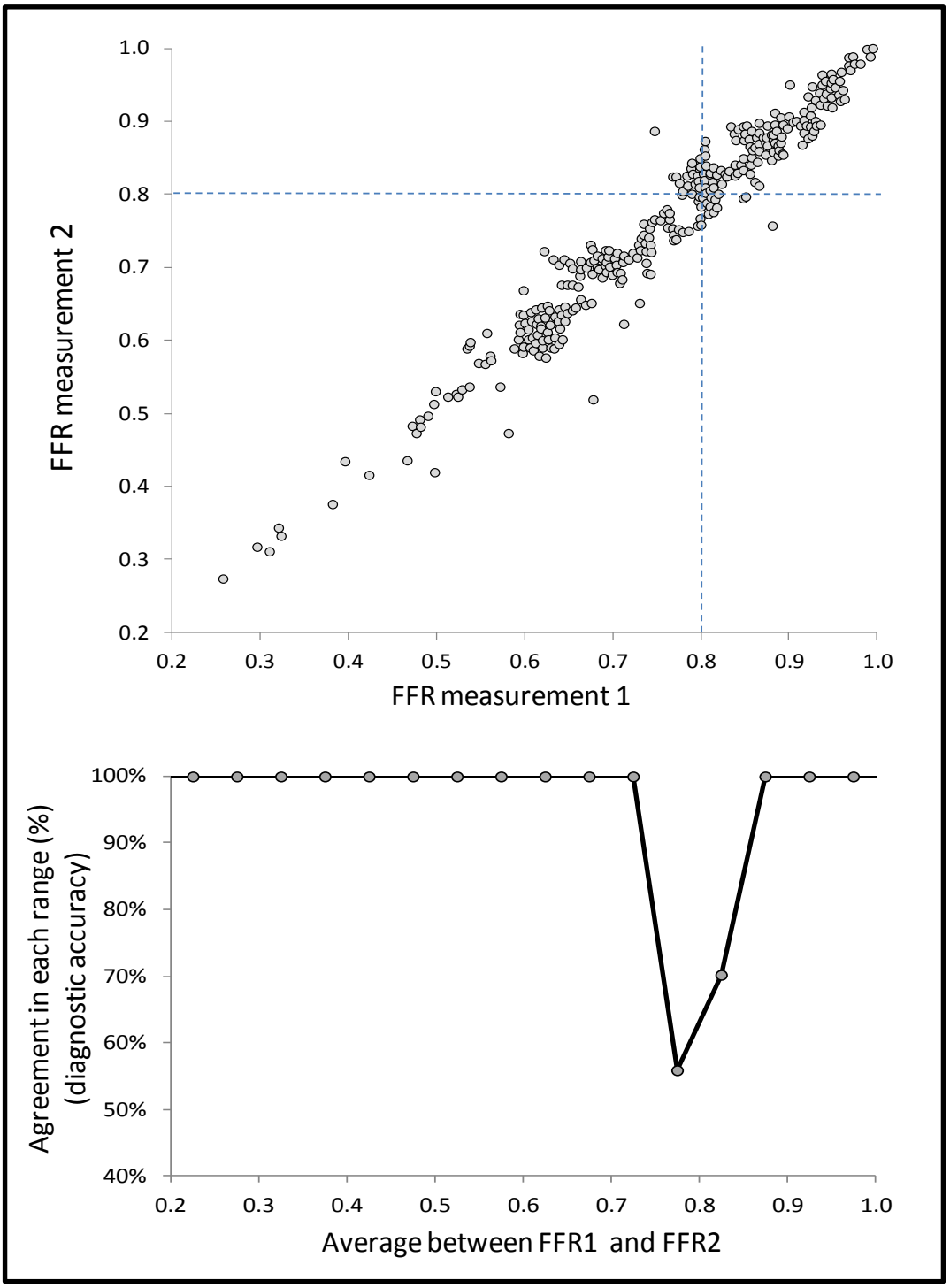


**Figure 3.4: Per-range agreement between repeated measurements of FFR**

The top panel is a scatter plot of two repeated FFR measurements, taken 10 minutes apart, digitised from reference 5. Bottom panel reveals the level of agreement ("diagnostic accuracy") between the two measurements for each quantile of disease (from 0.2 to 1 in bands of 0.05). At extremes, agreement is excellent (100%). Close to the established cut-off, however, FFR starts to disagree with itself, with its intrinsic accuracy falling to approximately 55%. Gray dots in bottom panel mark the centre of each 0.05 quantile. Agreement between FFR values was considered when *both* FFR values were below (or equal to) or above the established cut-off of 0.80.

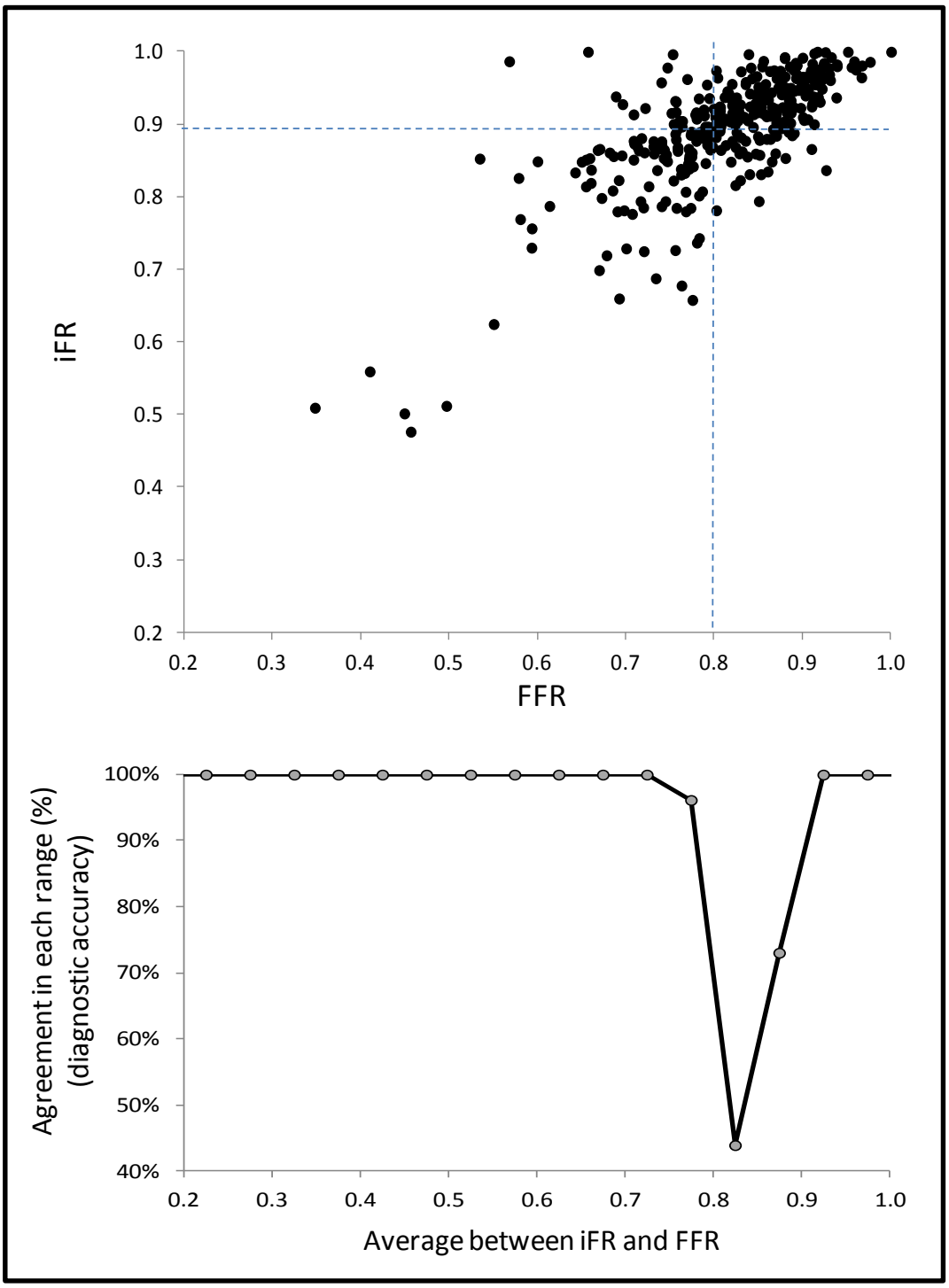


**Figure 3.5: Per-range agreement between iFR and FFR**

The top panel is the scatter plot of iFR and FFR values from this clinical iFR registry. Bottom panel reveals the level of agreement ("diagnostic accuracy") between the iFR and FFR for each range of disease (from 0.2 to 1 in bands of 0.05). At extremes, agreement is excellent (100%). Close to their established cut-offs, however, iFR-FFR classification agreement falls significantly. Gray dots in bottom panel mark the centre of each 0.05 quantile. Agreement between iFR and FFR values was considered when *both* tests were below (or equal to) or above their established cut-off.

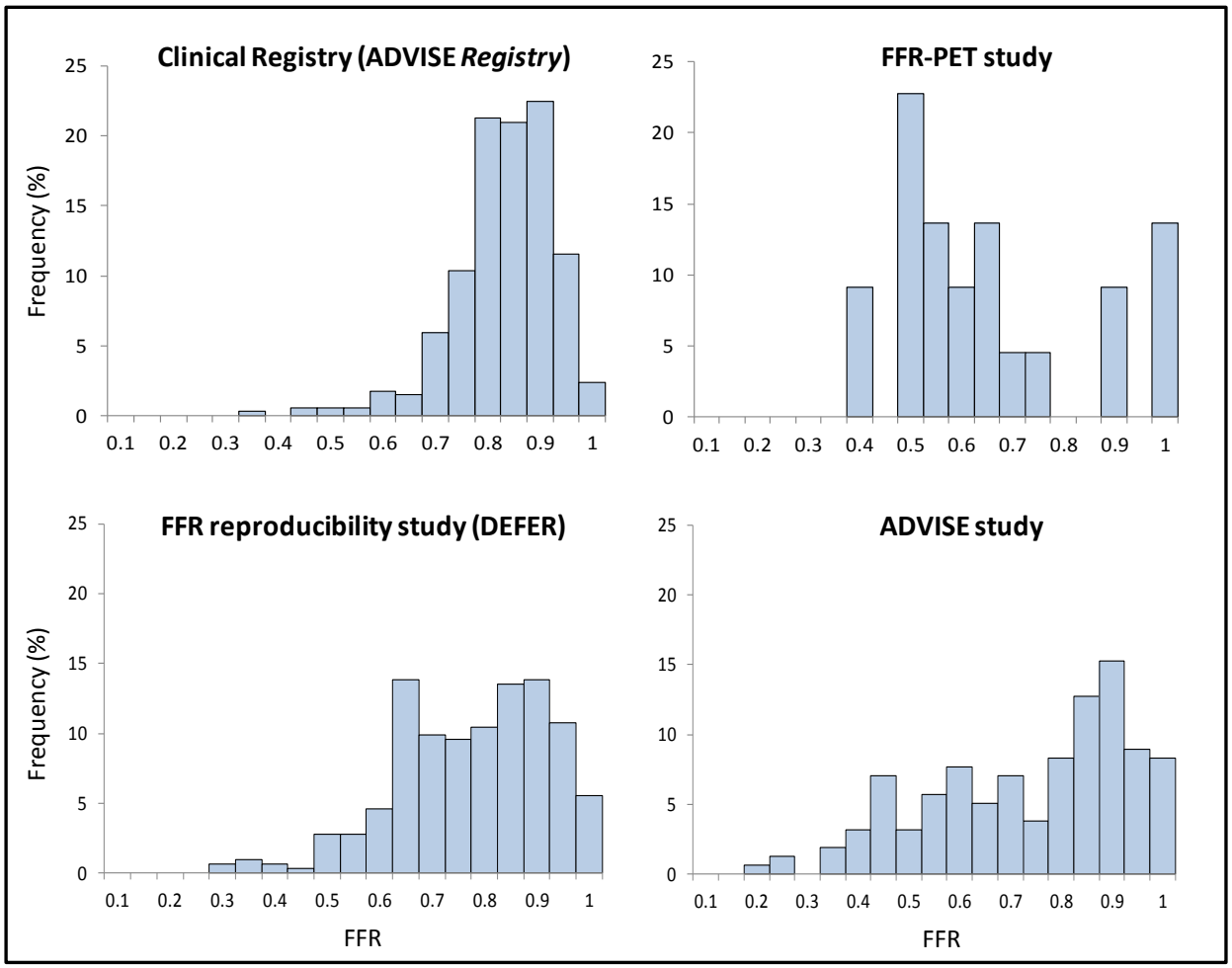


**Figure 3.6: Distribution of data in different FFR studies**

Frequency histograms reveal the unimodal type of data distribution of this clinical iFR registry, with predominantly higher FFR values (top left). This contrasts with the bimodal pattern of data distribution observed in the FFR reproducibility study (lower left); the more widely spread data seen in the ADVISE study (bottom right); and with the extreme type of distribution from the study which validated FFR against PET (top right). These contrasts highlight the differences between the study populations of methodological validation studies and patients undergoing routine coronary physiological assessment in clinical practice included in this iFR registry. Each bar represents one 0.05 FFR quantile and the symbol (*) identifies the most frequent FFR quantile in each population.

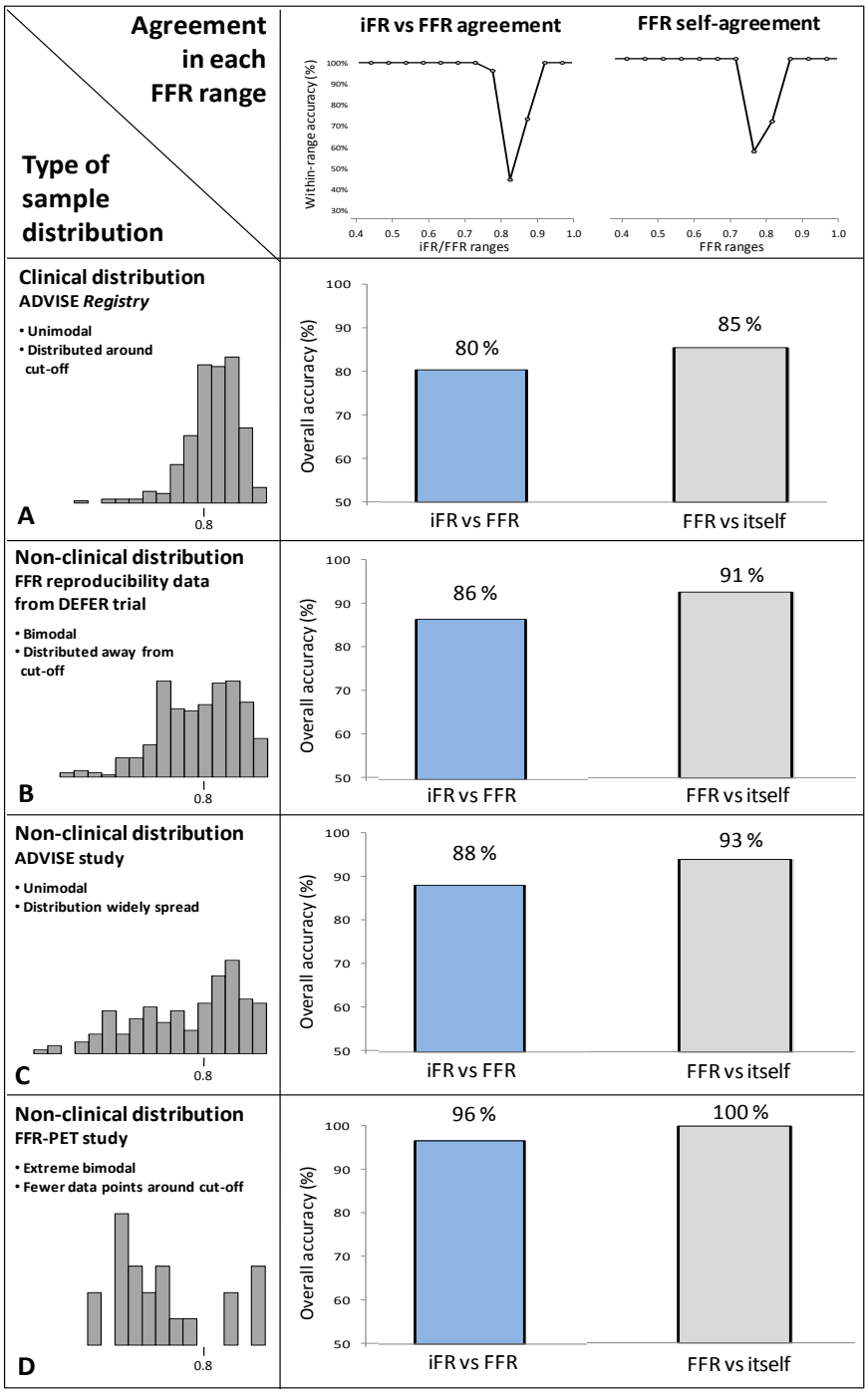


**Figure 3.7: Overall classification agreement between iFR and FFR**

Top panels are the per-range agreement charts (from Figures 4 and 5) for iFR versus FFR (left) and repeated FFR measurements (right). The overall level of agreement (or total accuracy) between iFR and FFR and the intrinsic agreement of FFR are derived for different types of data distribution (left histograms, from Figure 6). In clinical samples such as this iFR registry (A), where values are distributed unimodally around the cut-off point, both iFR-FFR and FFR-FFR level of agreement are lower than those observed in samples where data is distributed bimodally, away from the cut-off area (B and D) or more widely (C). Agreement was considered when *both* tests were below (or equal to) or above their established cut-offs

# 4 The V-test: a novel, sample-independent statistical approach to describe agreement between methods of clinical measurement

## 4.1 Introduction

In chapter 03, a new approach to compare diagnostic accuracies between iFR and FFR in different samples was introduced. In this study, this new statistical concept is explained in details using a simplified model of cardiovascular disease, which aims to demonstrate its utility in other areas of cardiology and clinical medicine.

The performance of a clinical diagnostic test is often quantified by its *diagnostic accuracy,* and the directly-related *sensitivity*, *specificity* and *predictive values*[52]. Physicians often choose diagnostic methods based on their published diagnostic accuracy, an example of a statistical concept having a direct influence in patient care and even equipment purchase[53]. However, relying on diagnostic accuracy as an ideal measure of a test's performance may forget a serious limitation, which is that for any given test and its reference gold standard, diagnostic accuracy can have any value from 50% to 100% depending on whether the sample studied is formed by intermediate or extremes forms of disease.

Almost all clinically useful biological measurements are fundamentally quantifiable as continuous variables, such as serum sodium, plasma glucose and blood cholesterol. For clinical convenience, however, many are interpreted qualitatively, by a dichotomous classification into *normal* versus *abnormal,* based on a fixed cut-off. For instance, although serum levels of cholesterol can be quantified and displayed across a wide spectrum of values, patients are usually given a diagnosis of "hypercholesterolaemia or not" based on a fixed cut-off value. Dichotomising results into positive versus negative is common in daily clinical practice because of the perceived pressure of information overload, and sometimes with the reason given that clinical decisions are themselves

dichotomous (treat versus not treat). However, dichotomising quantitative data of diagnostic methods has consequences that may not have been considered and may be extremely undesirable[54].

### 4.1.1 Dependency of *accuracy* on distribution of patients

Classification agreement between two methods of measurement is called *diagnostic accuracy* if one test is considered the reference gold standard. Rarely considered is how largely this value depends on the distribution of disease severity is the sample of patients studied (Figure 4.1). In short, very severely diseased and very healthy individuals are likely to be concordantly classified by both tests as positive or negative. A sample consisting of such extremes is likely to show a high diagnostic accuracy that may even approach 100%. In contrast, in the intermediate zone of disease severity, near the boundary between normal and abnormal, tests will always show classification disagreement. Naturally, therefore, samples formed predominantly by intermediate values are likely to show diagnostic accuracy values which could nadir close to 50%.

Even worse is the situation when the two tests report values in the same physical units and are of potentially equal status, prompting the average of the two tests to be used as the consensus marker of severity, as recommended by Bland and Altman. For patients just at the boundary on this “average-of-two” scale, whenever one test is positive the other test must be negative. Thus for these individuals diagnostic accuracy is forced to be 0%.

Mixtures of patients from these types, and other types in between, can generate any degree of diagnostic accuracy from 100% down to 50% for all diagnostic tests and definitions of severity.

### 4.1.2 Pioneering studies and clinical samples

Studies which first evaluate diagnostic methods are often performed in samples whose distribution is very different from the populations in which the test will be applied in clinical practice[55, 56]. Commonly, pioneering research is performed in patients who either definitely have or definitely don't have a condition, in a "case-control" fashion. However, if the focus is on diagnostic accuracy (and the related indices sensitivity, specificity, predictive values and receiver-operator characteristic (ROC) curves), researchers may unknowingly be presenting values that cannot be directly compared between studies, nor are applicable to routine clinical practice.

We give a practical example of why a single value of diagnostic accuracy cannot be a universal measure of a test performance, because of extreme dependence of the accuracy upon where in the spectrum the patients are drawn from.

We then introduce the V-test, a simple visual approach to demonstrate classification agreement between methods of measurement, which is easy to calculate and interpret, and allows diagnostic accuracy to be derived for any sample distribution.

## 4.2 Practical example: a new diagnostic method for the screening of hypercholesterolaemia[Y]

Imagine investigators developed a new method to measure serum cholesterol which utilizes an infra-red scan of the finger and yields an immediate value. The expectation was that this new test ($Chol_{rapid}$) could be used in the primary care to screen for hypercholesterolaemia without the need for a needle or formal laboratory test, and would enable identification of patients at high risk of cardiovascular events and lead to early initiation of therapy.

A landmark, large validation study was required before its implementation in clinical practice, so $Chol_{rapid}$ had to be tested against the gold-standard method of measuring cholesterol in the biochemistry laboratory ($Chol_{gold}$). The landmark study tested $Chol_{rapid}$ performance across a wide range of cholesterol values. Therefore, 238 patients were recruited from multiple clinical settings: healthy young volunteers with no history of cardiac disease, patients with multiple risk factors from a cardiovascular clinic and patients from a specialised hyperlipidaemia out-patient service. For the purpose of diagnostic classification, a cholesterol result of 5.7 mmol/L[¥] or above was considered hypercholesterolaemia.

The results of this final clinical study confirmed early expectations, with $Chol_{rapid}$ showing an accuracy of 95% to diagnose hypercholesterolaemia, with a sensitivity of 95% and an area under the ROC curve of 0.99. Figure 4.2A shows a scatter plot between the two methods and summarizes $Chol_{rapid}$ diagnostic performance.

As a result, $Chol_{rapid}$ was approved to be implemented in a large primary care unit for a period of trial. For one year, patients from the community with at least one risk factor for cardiovascular disease started having their cholesterol

measured with $Chol_{rapid}$. During this initial clinical evaluation, however, blood samples were still sent for standard laboratory analysis ($Chol_{gold}$), for a period of real-world comparison.

At the end of the first year of its utilisation, investigators re-evaluated $Chol_{rapid}$ diagnostic performance, comparing it against the same gold standard measurement $Chol_{gold}$. The results of this second, retrospective analysis were very disappointing. $Chol_{rapid}$ diagnostic accuracy to identify patients with hypercholesterolaemia fell to 83%, with a significant drop in sensitivity (84%), and an area under ROC curve of 0.89 (Figure 4.2B). As a result, a primary care safety committee decided to temporarily withhold $Chol_{rapid}$ utilisation until a comprehensive assessment of its reliability was carried out.

The health authority look into the reasons for such discrepancy between the final validation study and its first year of implementation, but found nothing obvious: the technique applied was exactly the same, with comparisons made against $Chol_{gold}$ tested in the same biochemistry laboratory.

### 4.3 Diagnostic accuracy: a population-dependent measure of agreement

The fundamental relationship between $Chol_{rapid}$ and $Chol_{gold}$ remained unaltered in the two studies, as shown by the degree of vertical dispersion of values (raw measurement disagreement) in both scatter plots (Figure 4.3A). The stable relationship between the two methods can also be demonstrated in the form of Bland-Altman plots (Figure 4.3B), which reveals that the limits of agreement were very similar in the two studies[57].

Therefore, the significant reduction in $Chol_{rapid}$ diagnostic performance between studies (accuracy, ROC curve, sensitivity, etc) can be entirely explained by how

differently cholesterol values were distributed in the two samples (Figure 4.4). The specific explanation is that the studies differed severely in what proportion of patients had cholesterol values close to the diagnostic cut-off of 5.7mmol/L: whilst the final validation study included patients with a wide range of cholesterol values (and so a large proportion of them far away from the cut point), the primary care study was mainly formed by patients with intermediate values of cholesterol, straddling the cut-off value, i.e. the region where most disagreements occur. Differences in the distribution of cholesterol values, rather than in the actual measurement performance of $Chol_{rapid}$, were responsible for the different accuracy values (Figure 4.1).

Our example highlights two important principles for any diagnostic modality. First, for the relationship between any two methods of clinical measurement, there are no universal values of *diagnostic accuracy, sensitivity, specificity, predictive values or ROC curve,* because classification agreement between methods can change greatly with the distribution of the patient sample. These parameters are only meaningful to demonstrate the *effects* of the raw measurement disagreement between the two methods (vertical scatter, Figure 4.3) in a *specific* population when a *specific* classification cut-off is used to define what is normal / abnormal.

Secondly, pioneering work very commonly uses a much wider spread of patients than is found in routine clinical practice[25]. While the desire to examine the whole spectrum is understandable, clinicians should realise that clinical populations often have substantially more patients in the middle zone, and therefore would show a much lower rate of classification match or diagnostic accuracy[58]. Therefore, when choosing a diagnostic modality based on its reported diagnostic

accuracy, an eye should be kept on whether this value was obtained from a clinically representative sample or instead one that artificially enhanced accuracy, even if unintentionally.

### 4.4 The V-test: a sample-independent method to measure classification agreement between tests

The concept of *diagnostic accuracy* is appealing because it gives clinicians a standardised, dimensionless measure of how good a test is (out of 100%)[59]. Neither the simple measurement of the vertical scatter in a correlation plot (the true measure of numerical disagreement) nor the calculation of limits of agreement using with Bland-Altman plots are as instantly appreciated by all clinicians. However, diagnostic accuracy and related parameters are flawed when quoted in isolation because values from one study may have no relationship to values in another cohort whose patients are distributed differently. We therefore present a way to combine the simplicity and clinical usefulness of parameters such as diagnostic accuracy with an additional information which makes it easy to apply to any population.

### 4.5 The V-plot: a display of per-quantile accuracies

To circumvent this sample-dependency, instead of simply calculating an *overall* value of diagnostic accuracy for the whole study population, we should calculate the classification agreement between methods in *each part of the spectrum* of disease severity. This results in several *per-quantile* values of “accuracies”, which can be displayed across the entire range of disease severity to generate a V-shaped plot, which gives name to the test (Figure 4.5). The V-plot has this shape because, as demonstrated in Figure 4.1, patients at extremes usually

show good diagnostic agreement between modalities producing plateaus near 100% at the left and right, but close to the classification cut-off agreement plunges to around 50% (or even lower if severity is defined by the average of the two tests).

The V-plot is, therefore, a universal fingerprint of per-quantile classification agreement between two methods of measurement, which can be expressed independently of the distribution of values of the underlying sample. This can be demonstrated by displaying the V-plot from the two $Chol_{rapid}$ studies (Figure 4.5). Despite marked differences in the distribution of cholesterol values and very different diagnostic accuracies, the V-plots from the two studies are almost identical. This can be interpreted as the two studies showing the same degree of classification agreement between $Chol_{rapid}$ and $Chol_{gold}$ across the spectrum of cholesterol values. Figure 4.6 explains in details the steps for the calculation of the V-plot and the application of the V-test accuracy in a sample.

### 4.6 Application of the V-test to any population

Once the V-plot has been established for the relationship between any two indices, the *overall agreement* between them can be projected to any other distribution of severity. For example, once a V-plot is derived from either of the two $Chol_{rapid}$ studies, it is possible to calculate the classification agreement between $Chol_{rapid}$ and $Chol_{gold}$ for a specialised outpatient lipid clinic, which is mainly formed by very high cholesterol levels (Figure 4.7). Ability to infer properties for a new cohort is clinically valuable because clinicians often need to use tests in cohorts whose distributions are very different from those in which major studies have been conducted.

The mathematical approach to the V-test calculation is described in Figure 4.6.

## 4.7 Conclusions

For any given clinical test being compared with a gold standard, there is no universal value of diagnostic accuracy. It will always vary progressively from almost 100% at the extremes (of health and disease) to approximately 50% (close to pure chance) near the diagnostic cut-point. The make-up of the sample of patients being studied (extremes versus intermediate) can therefore completely control the obtained value for diagnostic accuracy. This means that reports of diagnostic accuracy in isolation are an unsafe basis to evaluate a clinical test. Sensitivity, specificity, predictive values and ROC curves are just as controllable by the make-up of patient sample.

Authors and readers should therefore focus on whether a studied sample is particularly rich in extreme patients or intermediate patients.

The V-test approach described here exposes the variation of diagnostic accuracy along the spectrum of disease and makes it easy to use classification agreement drawn from one distribution of patients (v-plot) to derive the expected diagnostic accuracy for any other distribution of interest.

## 4.8 Figures

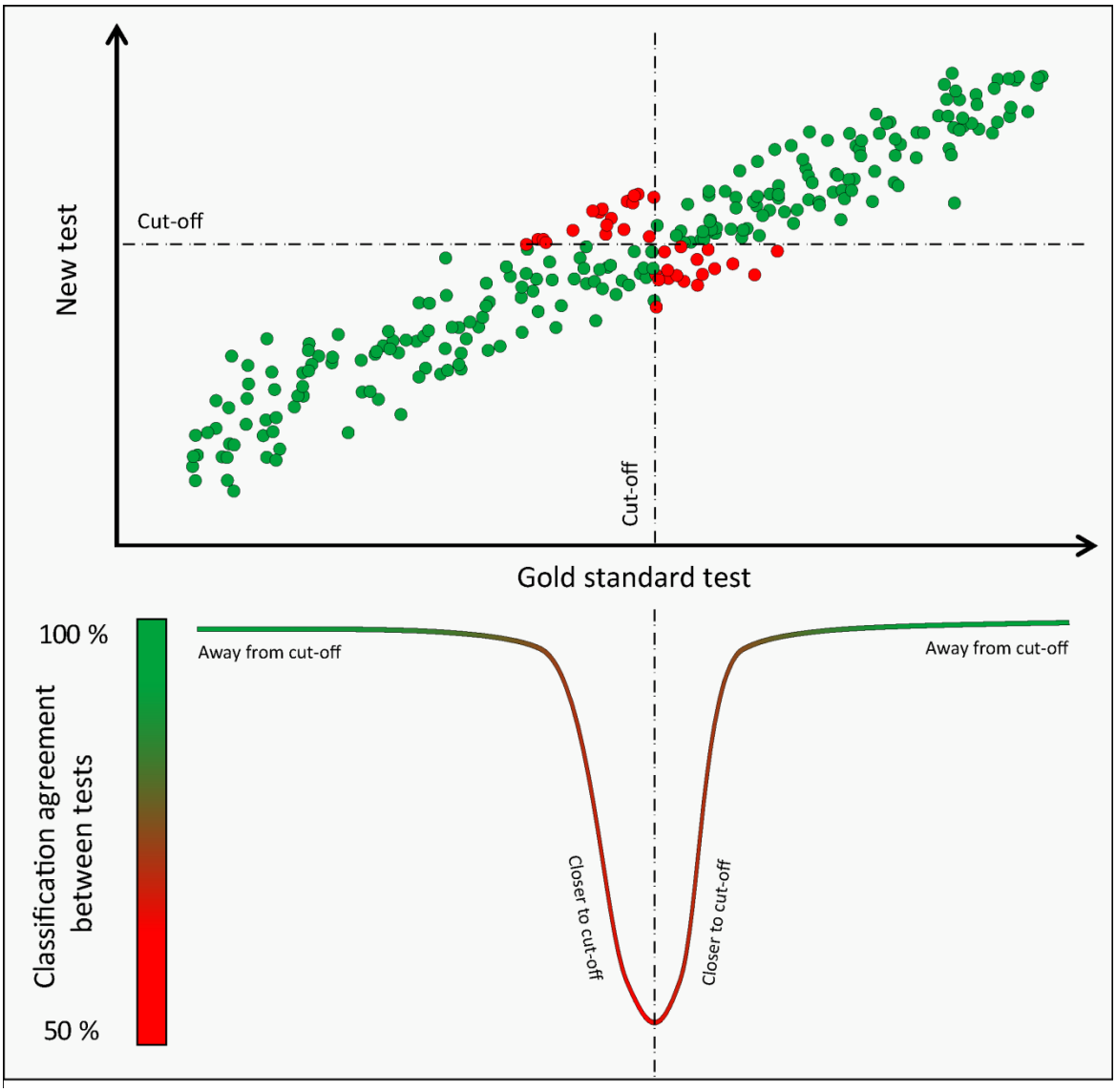


**Figure 4.1: Disease severity and classification agreement between methods**

Schematic representation of the principle that classification agreement between two methods of measurement vary across the range of disease severity. At the extremes of disease and health agreement is 100%. Close to the classification cut-off, around the intermediate range of disease severity, agreement falls, reaching a nadir which can be as lower as 50%.

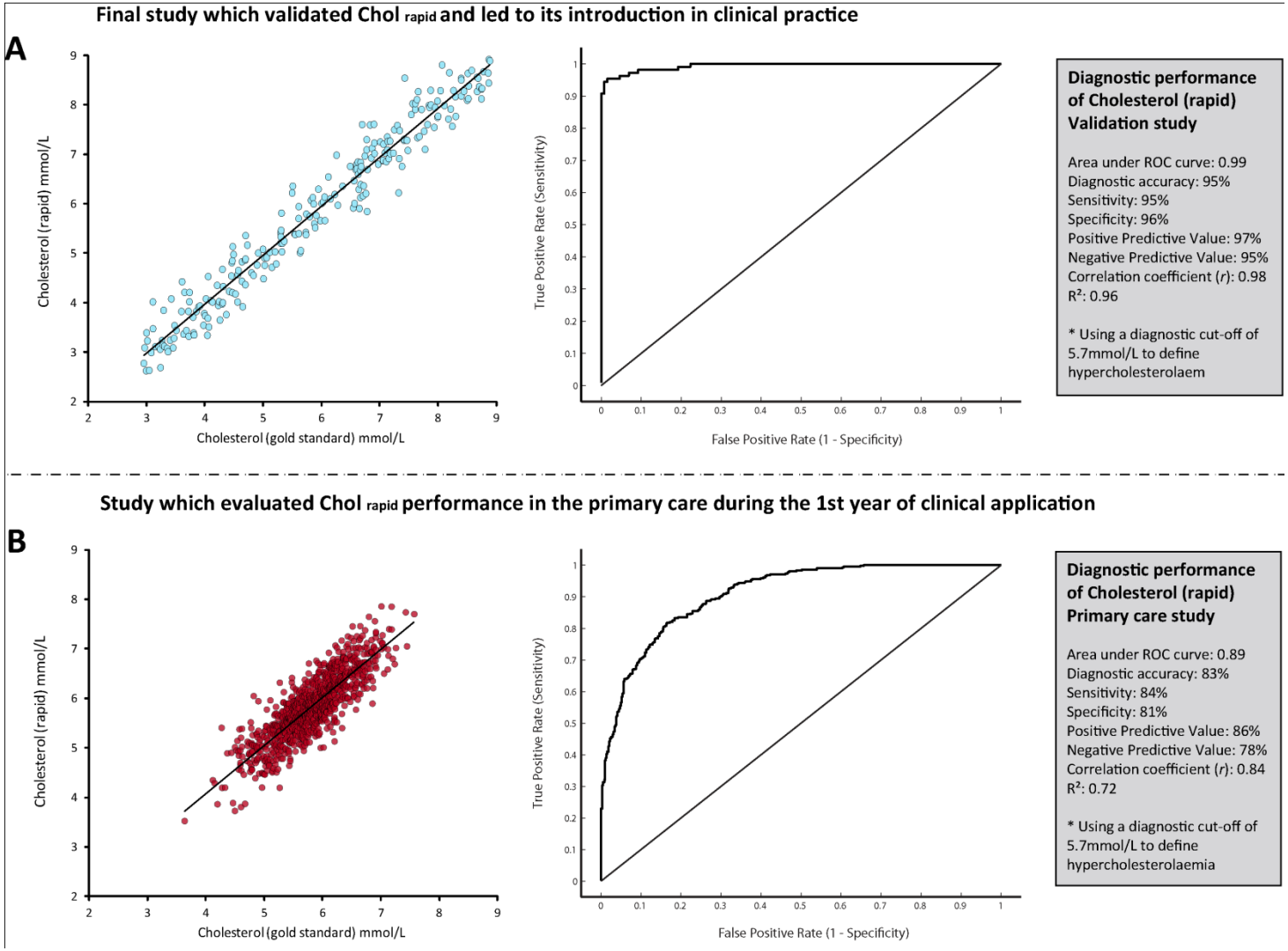


**Figure 4.2: Diagnostic performance of the new cholesterol test**

The performance of the new cholesterol test (Chol $_{rapid}$) changed significantly between the two studies. The overall accuracy of Chol $_{rapid}$ to diagnose hypercholesterolaemia fell in the primary care retrospective cohort (B), when compared to the initial validation study (A). Values of area under ROC curve, sensitivity, specificity and predictive values were also largely different.

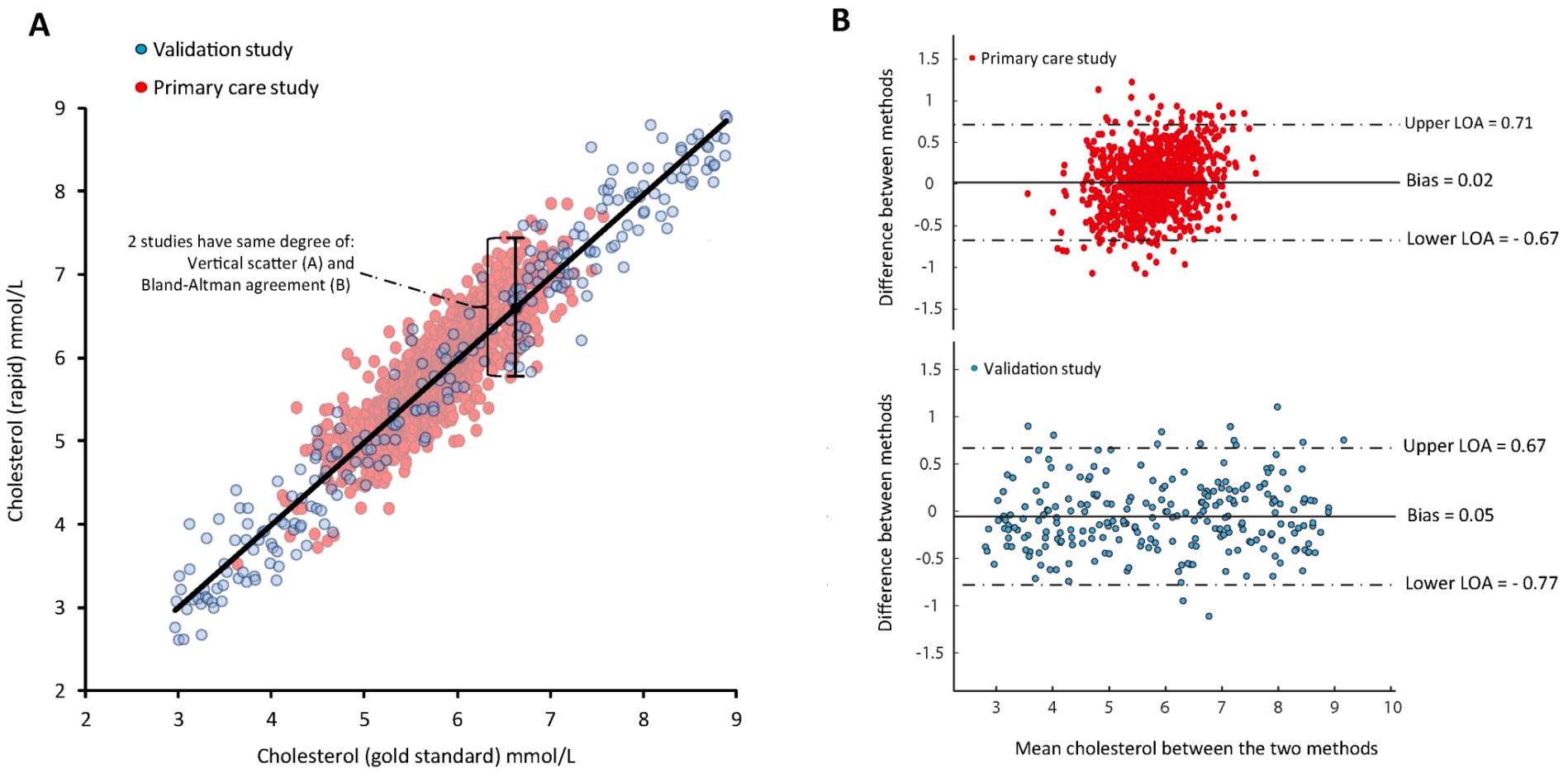


**Figure 4.3: Measurement agreement between Chol $_{rapid}$ and Cho $_{gold}$ is equal between studies**

Despite different magnitudes of classification agreement (diagnostic accuracy) between Chol rapid and Chol gold in the two studies, the raw measurement disagreement between the two methods remained unchanged. This can be appreciated from the vertical scatter of plot A and from Bland-Altman plots (B). It can be inferred that the observed drop in Chol $_{rapid}$ performance in the primary care study cannot be explained by a change in its true measurement performance.

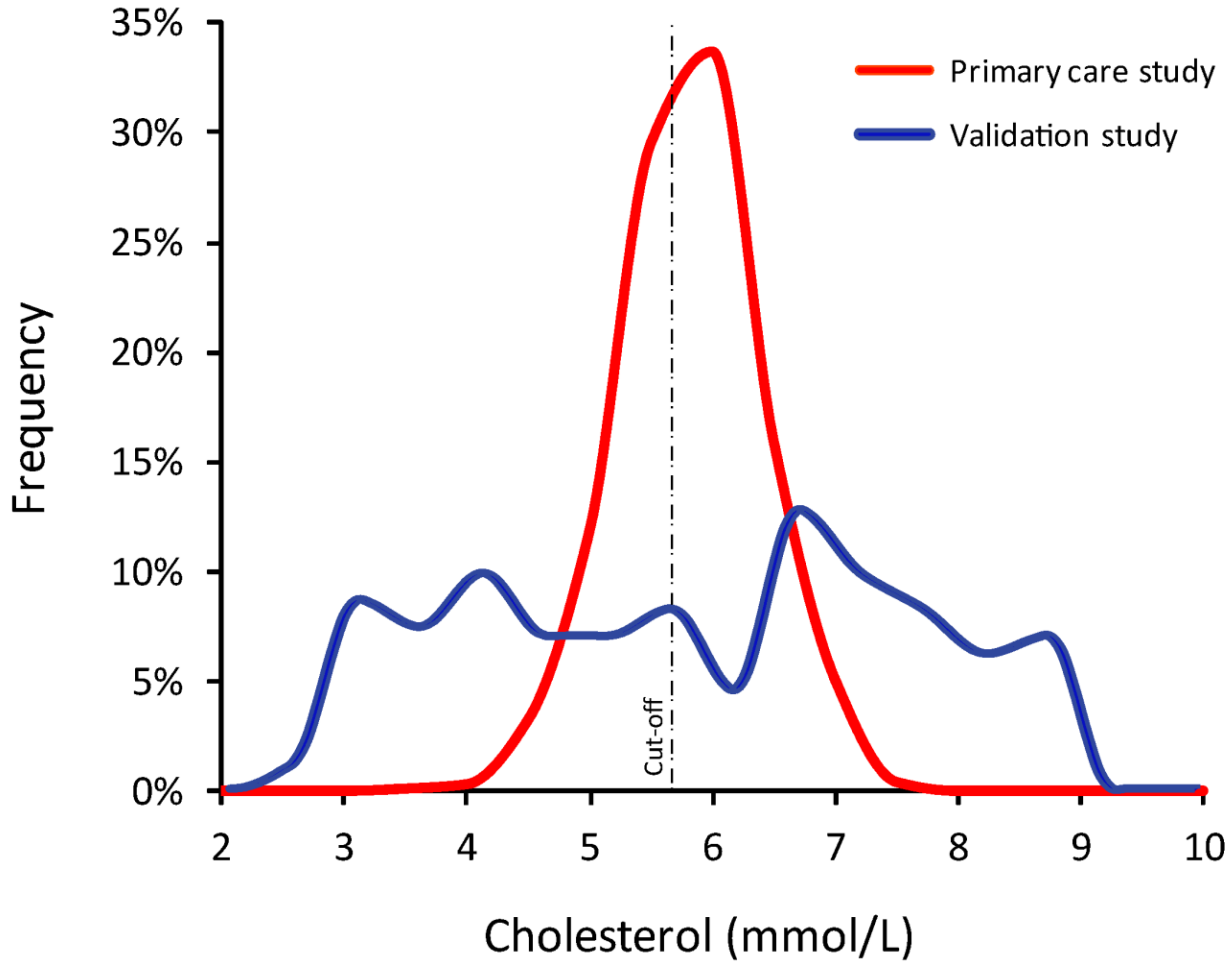


**Figure 4.4: Histogram of cholesterol values from both studies**

Whilst the validation study included patients with a wide range of cholesterol values, the primary care cohort was formed predominantly of patients with intermediate values of cholesterol. This difference was responsible for the significant drop in Chol $_{rapid}$ accuracy reported in the primary care study.

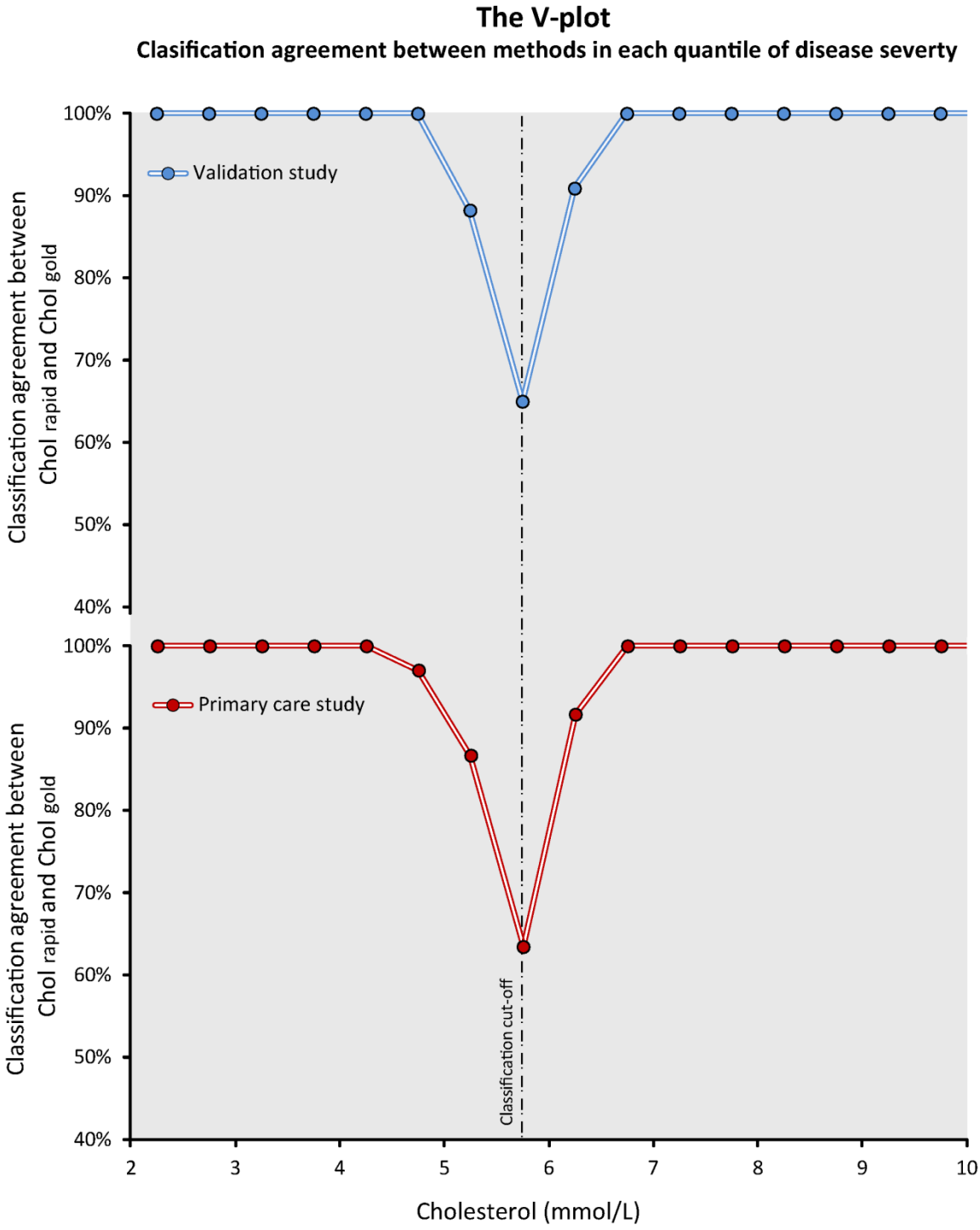


**Figure 4.5: The V-plot agreement between Chol $_{rapid}$ and Chol $_{gold}$**

The V-plot permits a visual demonstration that the classification agreement between Chol $_{rapid}$ and Chol $_{gold}$ is equal in the two studies, in each quantile of disease severity. The *overall* classification agreement (diagnostic accuracy of Chol $_{rapid}$) could change between studies, depending on the proportion of patients in each quantile.

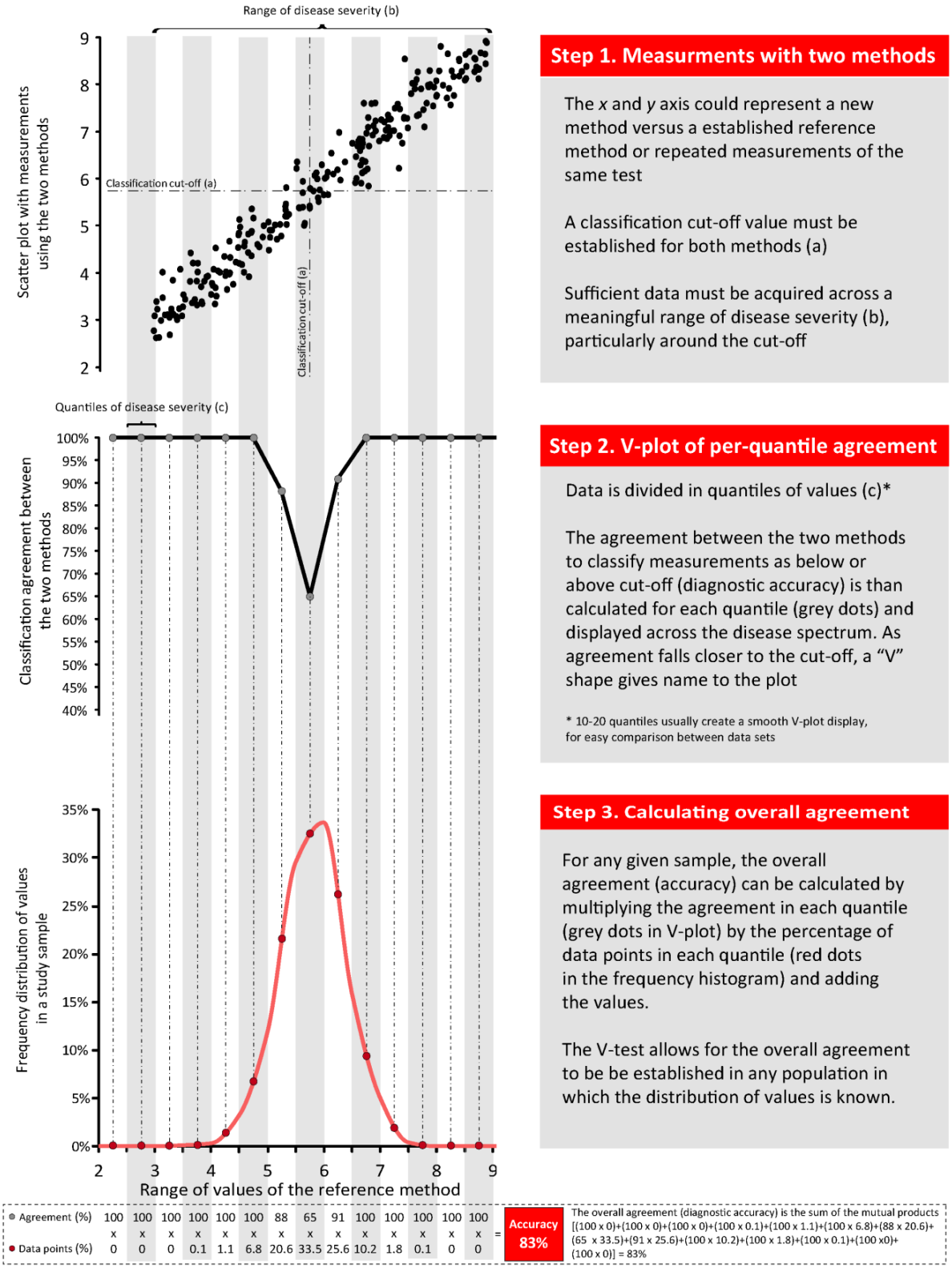


**Figure 4.6: V-test methodology explained**

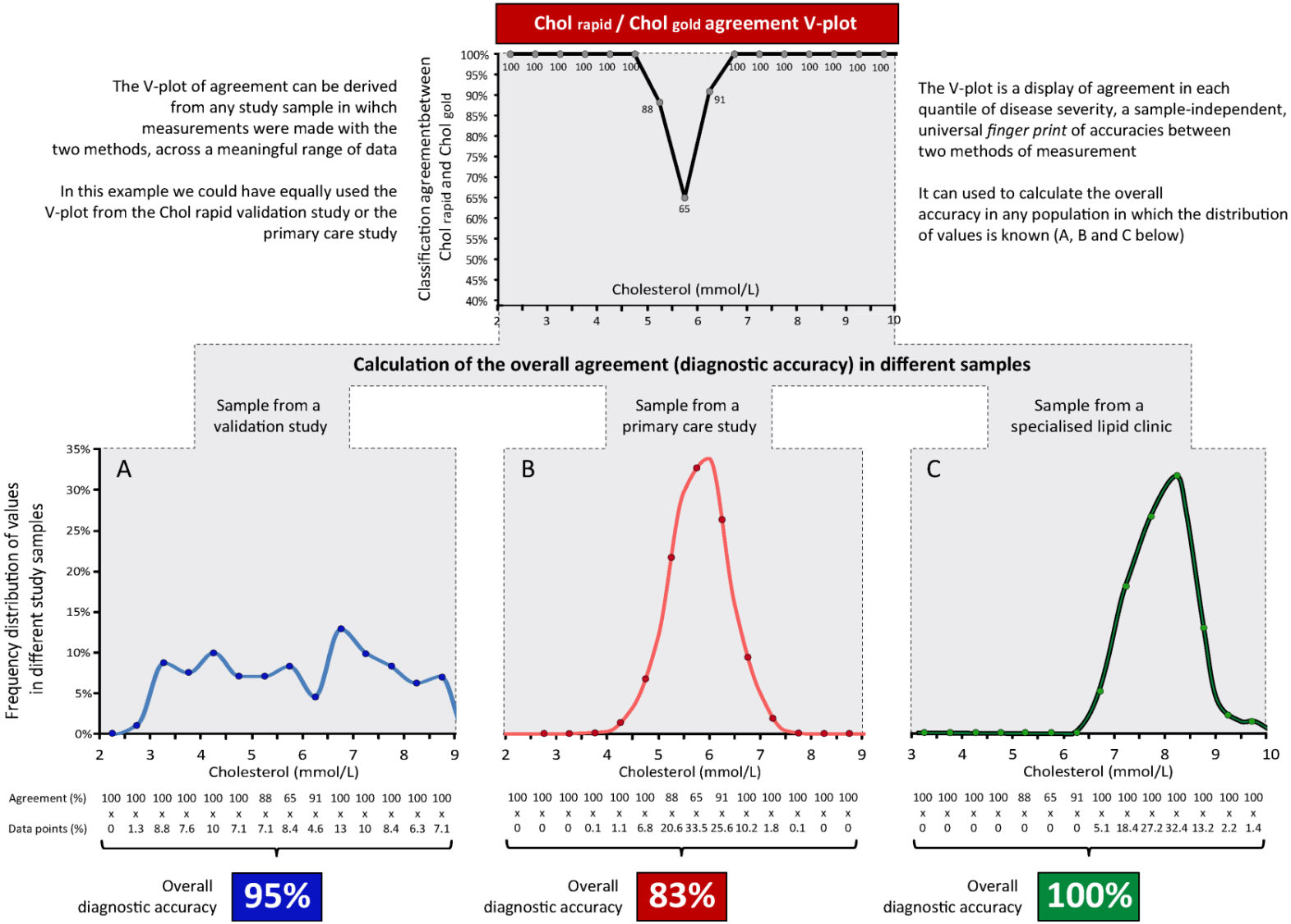


**Figure 4.7: Calculating the overall accuracy in different samples using the V-plot**

The V-plot agreement between Chol $_{rapid}$ and Chol $_{gold}$ can be derived from any study which compared the two methods (top panel). It can be used as a fingerprint of classification agreement to calculate the overall agreement between Chol $_{rapid}$ and Chol $_{gold}$ in any sample in which the distribution of cholesterol values is known (samples A, B and C).

# 5 Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation

## 5.1 Introduction

Despite the evidence demonstrating the benefits of coronary revascularisation guided by fractional flow reserve (FFR)[13-15], its adoption into widespread clinical practice remains low; estimated as 6-8% worldwide[33, 60]. The reasons for this are multi-factorial[33], including incomplete reimbursement, lack of widespread easy access to vasodilator drugs and challenges associated with technicalities of the procedure.

The need for vasodilator administration for FFR calculation is perhaps a common contributor to all these factors. Therefore, a diagnostic strategy which decreases the proportion of patients which needs vasodilator administration could potentially simplify assessment and reduce procedural time and costs. Such an approach would have the potential to bring physiology-guided revascularisation to many more patients, thereby improving clinical outcomes and improving healthcare cost-efficiency[61].

The instantaneous wave-Free Ratio (iFR) is a novel pressure-only invasive index of coronary stenosis severity which does not require the administration of vasodilator drugs, such as adenosine[38]. Like FFR, iFR uses only pressure and is performed with a standard coronary pressure guide wire. However, in contrast to FFR, iFR is calculated at rest, without pharmacological provocation. Recent studies which directly compared the classification of intermediate coronary stenoses by iFR and FFR[38, 49] revealed a consistent pattern of agreement between the two methods: 1) outside of the intermediate range of iFR and FFR values agreement is very high (> 90%), whilst 2) disagreements are of small magnitude and concentrated in the zone near their cut-offs[58]. Trials with clinical

endpoints will evaluate whether these small disagreements in the uncertain zone around the current FFR cut-off affect patient outcome.

Meanwhile, the high classification agreement between FFR and iFR outside of the intermediate zone may provide the opportunity for a staged, hybrid iFR-FFR decision-making strategy, in which only patients within a certain range of intermediate iFR values would require adenosine for FFR classification of lesions. This hybrid iFR-FFR strategy might achieve a high classification agreement with an FFR-only approach (and thus continue to deliver an FFR-based classification of lesions), whilst significantly reducing the number of patients who require vasodilator administration.

In this study, we sought to evaluate the proportion of patients in clinical practice which could be free from vasodilator administration in a hybrid iFR-FFR decision-making strategy of revascularisation whilst matching the stenoses classification of an FFR-only strategy.

## 5.2 Methods

### 5.2.1 Patient population

This study evaluated 577 coronary stenoses from 550 patients in which iFR and FFR was compared. Studies and centres contributing data were: the European ADVISE Registry study population (Hospital Clínico San Carlos in Madrid, Spain; Guy's and St Thomas' NHS Foundation Trust, London; and the Academic Health Science System of Imperial College London, UK; N=339)[58]; and an independent South Korean study (Seoul National University Hospital and Keimyung University Dongsan Medical Center; N=238)[49].

### 5.2.2 Haemodynamic data collection and analysis

Acquisition of physiological data for FFR calculation was performed according to conventional practice[42] using commercially available FFR systems (RadiView console and PressureWire Certus, St. Jude Medical, Minneapolis, Minnesota; and Combomap console and Prestige pressure guide wire, Volcano Corporation, San Diego, California). In the European cohort (N=339), intravenous adenosine was used for the calculation of FFR in 98% of the cases, administered via a central line, with doses ranging from 140mcg/Kg/min to 200mcg/Kg/min; in the remaining 2% of the cases the intra-coronary route was used. In the South Korean cohort, both intravenous and intracoronary routes were used in each patient (140mcg/Kg/min intravenously and 40mcg - 80mcg for intracoronary), and the lowest value of FFR was chosen for analysis. Digital data was extracted from FFR console platforms and processed off-line in a core laboratory (International Centre for Circulatory Health, National Heart and Lung Institute, UK) using a custom software package with Matlab (Mathworks, Inc., Natick,

Massachusetts). Each iFR trace was evaluated blinded from its FFR counterpart. iFR was calculated using fully automated algorithms applied to time-aligned pressure traces over the wave-free period of diastole over a minimum of 5 beats, before adenosine administration, as previously described[38]. iFR is defined as the ratio of distal coronary pressure to proximal coronary pressure during the wave-Free period in diastole. Resting Pd/Pa was calculated from baseline traces, as the ratio of mean distal (Pd) to proximal (Pa) coronary pressures, over the entire cardiac cycle.

### 5.2.3 Comparison between hybrid iFR-FFR strategy and FFR-only strategy

This study retrospectively compared two possible strategies to guide coronary revascularisation:

**Strategy 1: FFR-only strategy:** This strategy was used as the reference. All interrogated stenoses received adenosine for FFR calculation and all decisions were based on the final FFR result using the currently recommended 0.8 cut-off value. No decision was taken based on the iFR result.

**Strategy 2: Hybrid iFR-FFR strategy:** A series of two independent iFR values were identified: one with a high negative predictive value (exceeding 90%) to exclude FFR-significant stenoses (defer iFR value) and another with a high positive predictive value (exceeding 90%) to identify FFR-significant stenoses (treatment iFR value). A positive result was defined as FFR or iFR ≤ 0.8 and it was assumed that only stenoses with iFR values between the defer and

treatment iFR values would have been given adenosine and followed standard FFR classification of lesions (Figure 5.1).

### 5.2.4 Endpoints for comparison between FFR-only and hybrid iFR-FFR strategies

This study used the following endpoints to compare the two strategies:

**Overall classification agreement between strategies:** Give its proven safety as a guide to revascularisation, the classification of stenoses by the FFR-only strategy was used as the reference. The overall classification agreement (when *both* strategies classified a stenosis as significant or not significant) between the iFR-FFR strategy and the FFR-only strategy was calculated. An overall agreement of 95% was considered ideal.

**Proportion of patients adenosine-free:** In the hybrid iFR-FFR strategy, the proportion of stenoses which fell outside the adenosine requirement zone (which would be free from adenosine in a hybrid iFR-FFR strategy) was calculated for each level of overall agreement with the FFR-only strategy. For comparison, in the FFR-only strategy, all interrogated stenoses (100%) required adenosine administration. In the hybrid iFR-FFR strategy, the size of the zone between the defer and treatment iFR values was calculated (in 0.01 iFR units). This zone represented the iFR values within which administration of adenosine was required for FFR calculation.

### 5.2.5 Comparison with a hybrid Pd/Pa-FFR strategy

The same methodology was then applied for the evaluation of a Pd/Pa-FFR hybrid strategy. The proportion of vessels which would be free from adenosine

with a hybrid Pd/Pa-FFR strategy was compared to the iFR-FFR strategy, for each level of agreement with the FFR-only strategy.

### 5.2.6 Statistical analysis

Statistical calculations were performed using Matlab (Mathworks, Inc.). Data were expressed as mean ± standard deviation for continuous variables and percentages for categorical variables.

## 5.3 Results

### 5.3.1 Population characteristics

Patient demographics and stenosis characteristics are summarised in Table 5-1. The majority of stenoses were physiologically intermediate, representative of patients undergoing FFR assessment of intermediate lesions in daily clinical practice. Mean FFR was 0.81 ± 0.10; 80% of stenoses had FFR between 0.6 and 0.9; and only 13% had FFR ≤ 0.7 (Figure 5.2).

### 5.3.2 Overall classification agreement between hybrid iFR-FFR strategy and FFR-only strategy

Using a deferral iFR value of > 0.93, a treatment iFR value of < 0.86 and with adenosine only given to stenoses with iFR values between 0.86 and 0.93, resulted in an overall 95% agreement with the FFR-only strategy (Figure 5.3). A deferral value of iFR > 0.93 demonstrated a negative predictive value of 91% to exclude FFR-significant stenoses and a treatment iFR value of < 0.86 had a positive predictive value of 92% to identify FFR-significant stenoses.

### 5.3.3 Reduction in adenosine requirement with hybrid iFR-FFR strategy

The utilisation of a hybrid iFR-FFR strategy would have significantly reduced the number of patients in whom adenosine was required. For an overall classification agreement of 95% with the FFR-only (adenosine-to-all) strategy, in the hybrid iFR-FFR strategy 57% of the stenoses would have become adenosine-free (Figure 5.3 and Figure 5.4). For a classification agreement between the strategies of 85% and 90%, respectively, the stenosis population predicted to be free of adenosine was 88% and 74% respectively (Figure 5.4 and Figure 5.5).

### 5.3.4 Size of adenosine requirement zone

For a hybrid iFR-FFR strategy with a 95% classification agreement with the FFR-only strategy the width of the adenosine requirement zone was 0.08 iFR points (from 0.86 to 0.93), which represented 43% of this study population. The larger the adenosine requirement zone, the higher the overall agreement between a hybrid iFR-FFR strategy and the FFR-only strategy. However, increasing the adenosine zone also decreased the proportion of stenoses which became adenosine-free (Figure 5.5).

### 5.3.5 Incremental benefits of a hybrid iFR-FFR strategy compared to a hybrid PdPa-FFR strategy

iFR is superior to PdPa when used in a staged approach with FFR. For the same level of agreement with the FFR-only strategy, a hybrid iFR-FFR strategy significantly increased the number of adenosine-free patients when compared to a hybrid PdPa-FFR strategy. For magnitudes of agreement of 90%, 96%, respectively, the proportion of adenosine-free patients gained with iFR (over Pd/Pa) was 21%, and 28% (Figure 5.6).

## 5.4 Discussion

Whilst we await for clinical trials which evaluate the safety of iFR as an independent tool to guide to coronary revascularisation, this study shows that a hybrid decision-making strategy of coronary revascularisation with iFR and FFR has the potential to foster adoption of physiology-guided PCI. Our results demonstrate that such an approach has the potential to drastically reduce the need for adenosine administration whilst maintaining a 95% classification agreement with an FFR-only strategy.

### 5.4.1 Implications to increased adoption of physiology-guided PCI

Adding to the evidence already provided by the DEFER and FAME trials[14, 15, 27], the FAME II study recently demonstrated that, when compared to medical therapy alone, percutaneous coronary intervention (PCI) can reduce coronary events, when flow limiting lesions are identified by FFR[13]. It is therefore unfortunate that currently 92 to 94% of all coronary interventions worldwide are performed without any invasive physiological guidance[3, 33, 60], and it is clearly in the patients' interest to make physiology-guided PCI available to all. As the need for the administration of adenosine is one of the impediments to FFR utilisation[30, 33, 62, 63], a hybrid strategy with iFR could potentially facilitate the application of pressure wire interrogation, decrease procedural time[62], costs[61], avoid the small risks associated with central venous access and adenosine administration and minimise patient inconvenience. Also, as the need for a femoral venous sheath would be avoided in the majority of patients, a hybrid iFR-FFR strategy could potentially increase the number of radial procedures, which is in itself associated with improved outcomes[64]. Our results, therefore, suggest that a hybrid

revascularisation strategy with iFR and FFR has the potential to significantly increase adoption of physiology-guided PCI in clinical practice, by combining iFR and FFR in the same diagnostic pathway (Figure 5.3).

### 5.4.2 Adenosine-free population depends on desired agreement with FFR

The desired magnitude of agreement between a hybrid iFR-FFR strategy and an FFR-only strategy will determine the proportion of adenosine-free patients in any given population and the iFR values chosen to make deferral or treatment decisions (Figure 5.4).

If limits of iFR were chosen to achieve an overall 95% agreement with FFR we found that this would free 57% of patients from adenosine during physiological assessment in the catheterization laboratory. We believe this represents a safe and clinically meaningful balance between classification match and potential for increase adoption of physiology-guided procedures. However, If a 90% overall match with an FFR-only strategy was to be accepted, the proportion of patients free from adenosine would increase to 74%, with iFR values to defer and treat of $< 0.89$ and $> 0.92$, respectively (adenosine would be required when iFR falls between 0.89 and 0.92). Finally, if clinicians were only happy to accept a 99% agreement between strategies, 31% of patients would still be spared from administration of adenosine if iFR and FFR were used in a staged approach (Figure 5.4 and Figure 5.5).

### 5.4.3 Clinically representative study population

The results of our study are relevant to the daily clinical application of physiological interrogation of angiographic intermediate stenoses, as our sample

was formed by two independent populations of patients undergoing clinical FFR measurement from sites in Europe and Asia[49, 58]. Importantly, patients in this sample were not specifically recruited for a research study, and therefore reflect the daily clinical practice of physiological interrogation of angiographically intermediate coronary stenoses. Because the majority of our patients had physiologically intermediate stenoses straddling the FFR treatment cut-off (mean FFR of 0.81, with 80% of FFR values falling between 0.6 and 0.9), 43% of them would still have to receive adenosine for a 95% agreement with an FFR-only strategy. It is likely that in other study populations, which included patients with more severe lesions (away from the intermediate range) even more patients would be free of adenosine for the same magnitude of agreement with an FFR-only strategy.

For instance, if we apply the same hybrid iFR-FFR strategy to the ADVISE study population[38] (which had mean FFR of 0.72 ± 0.2, with only 41% of stenoses between 0.7 and 0.9), using the same iFR values to defer and treat stenoses (> 0.93 and < 0.86, respectively) we would obtain a similar classification match with an FFR only strategy (96%). However, the proportion of adenosine-free patients would significantly increase to 77%.

This example demonstrates that, in populations which include more patients with physiologically severe stenoses, such as the ones encountered in the DEFER[15] (mean FFR 0.73), FAME[14] (mean FFR 0.71) and FAME II[13] (mean FFR 0.68) studies, the application of a hybrid iFR-FFR strategy is likely to free a proportionally higher percentage of patients from adenosine.

### 5.4.4 Allowing for an FFR 0.75 – 0.8 grey zone

The analysis presented in this study was performed using a fixed FFR cut-off of 0.8, as mandated by current clinical guidelines[3, 42] as a result of the FAME[14] and FAME II[13] studies. However, the DEFER trial[15] and, more importantly, its 5 years follow up results[27], left little doubt about the safety of deferring stenosis with FFR ≥ 0.75. This overlap between FAME and DEFER FFR cut-offs is the widely acknowledged 0.75 - 0.8 FFR grey zone[65], within which it is both mandated to treat, and known to be safe to defer, coronary lesions.

Therefore, if clinicians opt to use a hybrid iFR-FFR strategy which accounts for this FFR grey zone, the number of patients free of adenosine would increase to 76% (Figure 5.7). For this purpose, an iFR value of > 0.90 could be used to defer revascularisation in stenoses (with 94% negative predictive value to exclude stenoses with FFR < 0.75), whilst an iFR value of < 0.86 would be used to treat stenoses (with a 93% positive predictive value to identify stenoses with FFR ≤ 0.8).

A summary of the results is presented in Figure 5.8.

### 5.4.5 Disagreement between strategies is infrequent and of small magnitude

The overall 95% agreement between the hybrid iFR-FFR strategy and the FFR-only strategy in practice means that only 1 in 20 stenosis would have a different classification with the two approaches. Although this number is small (95% agreement between test modalities being unusual in clinical practice), it is still clinically relevant to understand the magnitude of such disagreement, when it occurs.

At the upper range of iFR values (negative iFR), disagreements only represented 3.1% of the overall population (18 out of 577 cases). Out of those cases, 67% (12) fell within the FFR grey zone of 0.75 - 0.8 and only in 3 cases FFR was < 0.7. At the lower range of iFR results (positive iFR), disagreements represented only 1.7% of the overall population. Out of those cases, in 60% FFR fell between 0.8 and 0.85, and only 1 above 0.88.

Therefore, given the small magnitude of disagreement between strategies compared with the range of uncertainty within trial-based FFR-guided management itself, it might be speculated that classification of the small number of lesions differently by the hybrid iFR-FFR strategy from the FFR-to-all strategy, will not have a significant effect on the risk of cardiac events. The scope for such small disagreements would need to be taken in the context of the opportunity for bringing rapid, symptom-free physiological targeting of PCI to a significantly higher number of patients with coronary disease.

The relationship between iFR and FFR across different study populations reveals that the majority of differences in stenosis classification occur close to the iFR and FFR cut points, which could potentially have little or no effect on patient outcome[58]. However, prior to the application of a single dichotomous iFR cut point and implementation of iFR into clinical practice as an independent method to guide coronary revascularisation, clinical studies are warranted to demonstrate the safety and efficacy of iFR. Until such studies clarify the usefulness of iFR as an independent diagnostic modality, a hybrid iFR-FFR strategy provides a pragmatic strategy to increase adoption of physiology-guided revascularisation in the catheter laboratories.

## 5.5 Limitations

This study was a retrospective analysis performed on data collected from two clinical cohorts of patients who underwent FFR evaluation, using different doses and routes for adenosine administration. The proposed hybrid iFR-FFR revascularisation strategy was not tested prospectively against clinical outcomes. The positive side of this real-world, retrospective analysis is that our proposed FFR-only strategy (with varying doses of adenosine) reflects the clinical practice of interventionists in catheterisation laboratories across centres in Europe and Asia."

The comparison between the classification of coronary stenoses by the two revascularisation strategies was made without an independent discriminator, such as a non invasive perfusion modality or invasive coronary flow. Therefore, when strategies disagreed in classifying a lesion as significant / non-significant, it is not possible to infer which of them correctly identified or excluded flow limiting lesions.

## 5.6 Conclusions

Whilst we await the results of clinical trials which evaluate efficacy of iFR as a sole method to guide coronary revascularisation, a hybrid decision-making revascularisation strategy guided by iFR and FFR could drastically reduce the need for adenosine administration in clinical practice and maintain a high diagnostic agreement (≥ 95%) with FFR classification of stenoses. Therefore, the adoption of a hybrid iFR-FFR approach could expand the utilisation of physiology-guided revascularisation in clinical practice and improve patient outcome.

## 5.7 Tables

**Table 5-1: Patient demographic data**

| | |
|---|---|
| Population from, n (%) | |
| ADVISE Registry study | 339 (59%) |
| South Korean study | 238 (41%) |
| Age, yrs ± SD | 62 ± 8 |
| Male, n (%) | 422 (73%) |
| Hypertension, n (%) | 343 (59%) |
| Diabetes mellitus, n (%) | 171 (30%) |
| Dyslipidemia, n (%) | 385 (67%) |
| Chronic kidney disease, n (%) | 37 (6%) |
| Left anterior descending artery lesions, n (%) | 414 (72%) |
| Diameter stenosis (%) | 50.2 ± 13 |

SD= Standard deviation of the difference

## 5.8 Figures

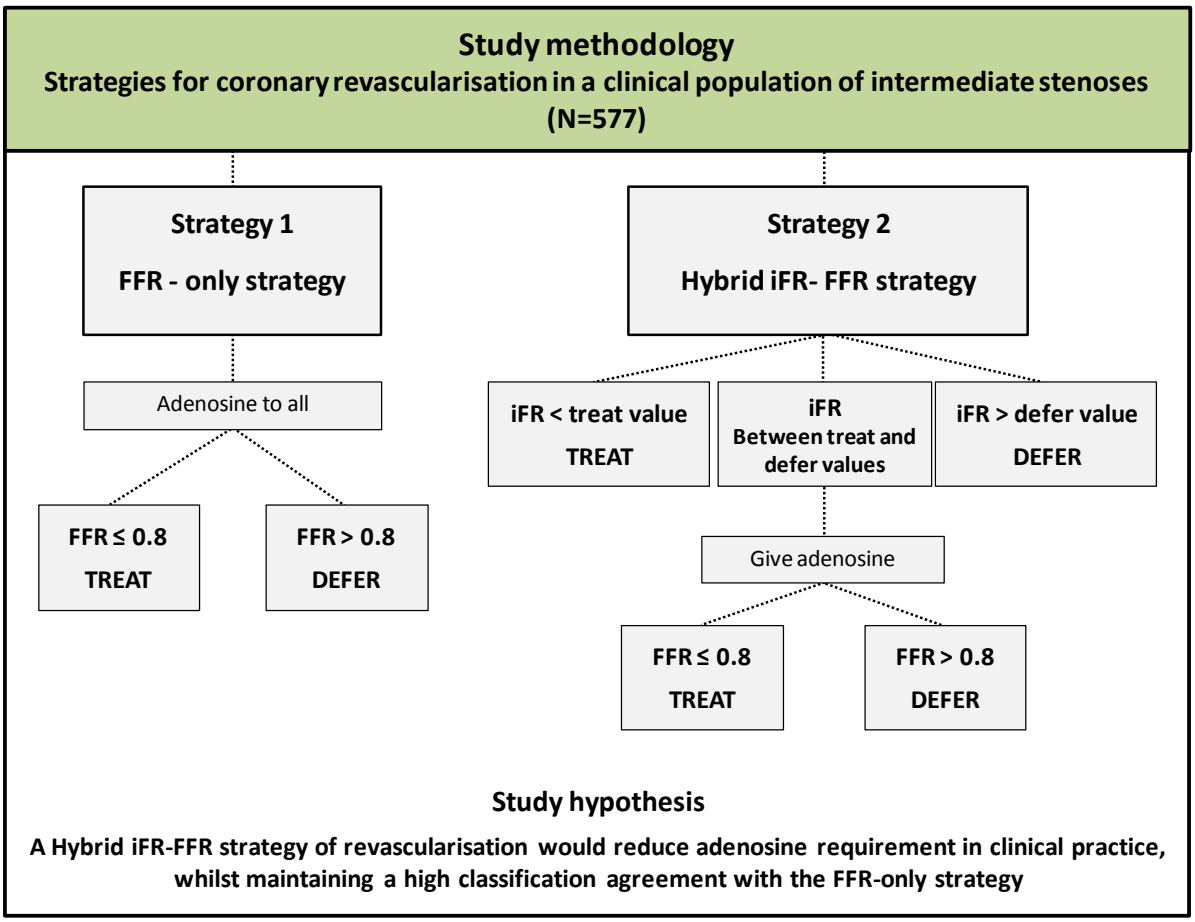


**Figure 5.1: Study methodology flowchart and study hypothesis**

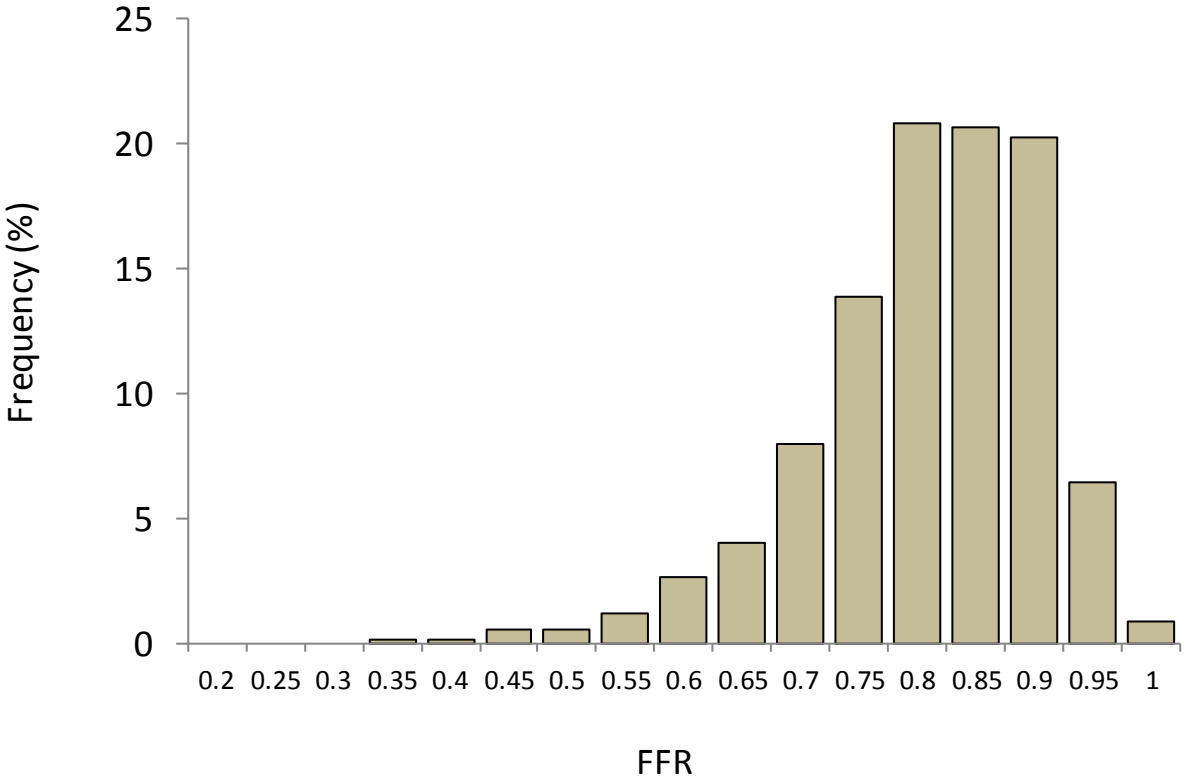


**Figure 5.2: Frequency histogram of study population**

Distribution of FFR values. The majority of lesions were classified as physiologically intermediate, with mean FFR 0.81 ± 0.1 and 80% of FFR values between 0.6 and 0.9.

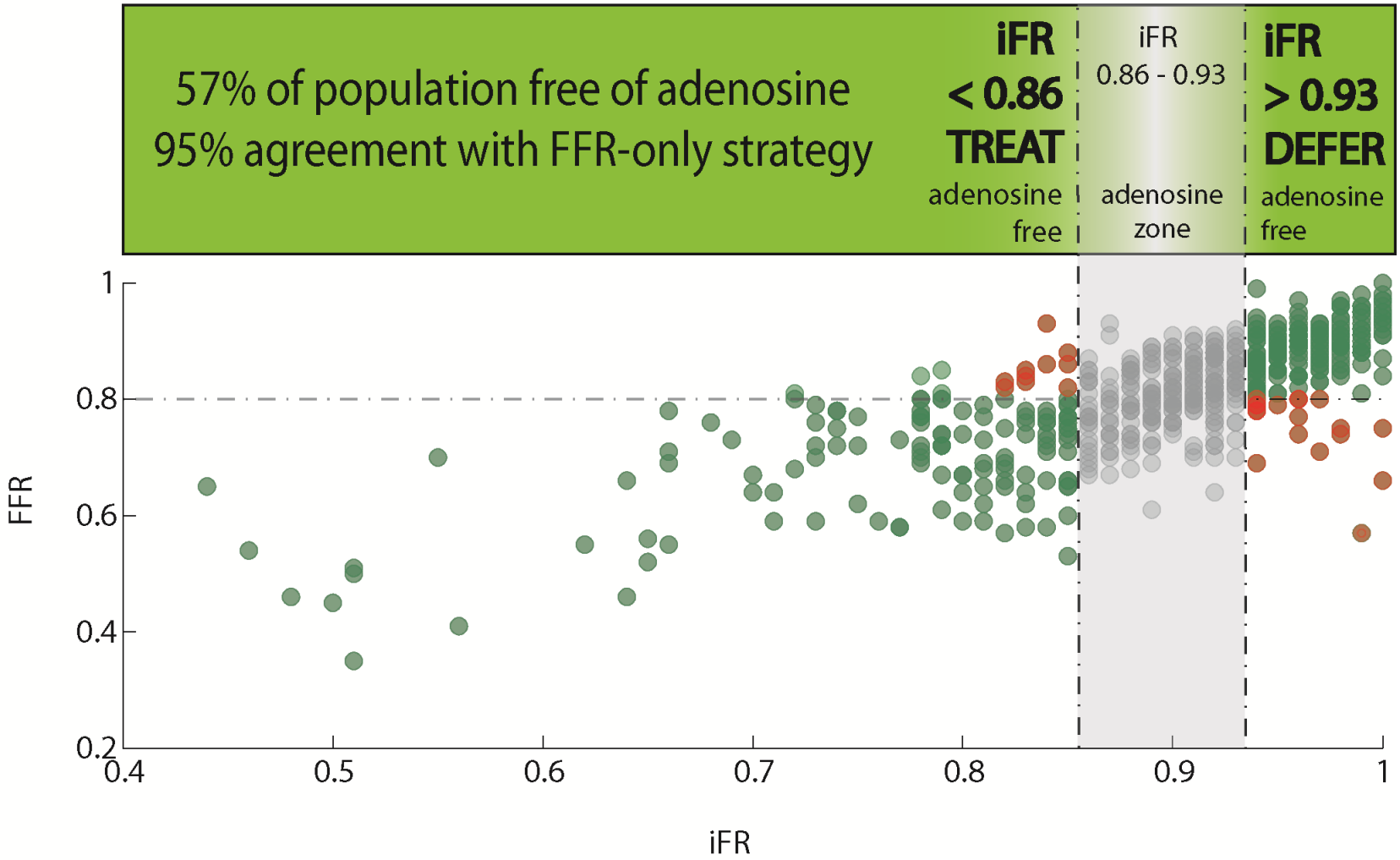


**Figure 5.3: Hybrid revascularisation strategy with instantaneous wave-Free Ratio (iFR) and fractional flow reserve reduces the adenosine requirement in clinical practice**

Coronary revascularisation decisions can be made without adenosine when iFR is < 0.86 (positive predictive value of 92%) or when iFR is > 0.93 (negative predictive value of 91%). In clinical practice, such iFR-based decisions can be made in 57% of patients. When iFR values fall between 0.86 and 0.93, adenosine is given and the FFR cut-off of 0.8 is used to guide revascularisation. This hybrid iFR-FFR approach has a 95% classification agreement with an FFR-only, adenosine-to-all, strategy. Green dots represent the agreement between iFR and FFR and red dots show disagreement points. Grey dots inside the grey zone represent the stenoses which will be classified by FFR, following adenosine administration.

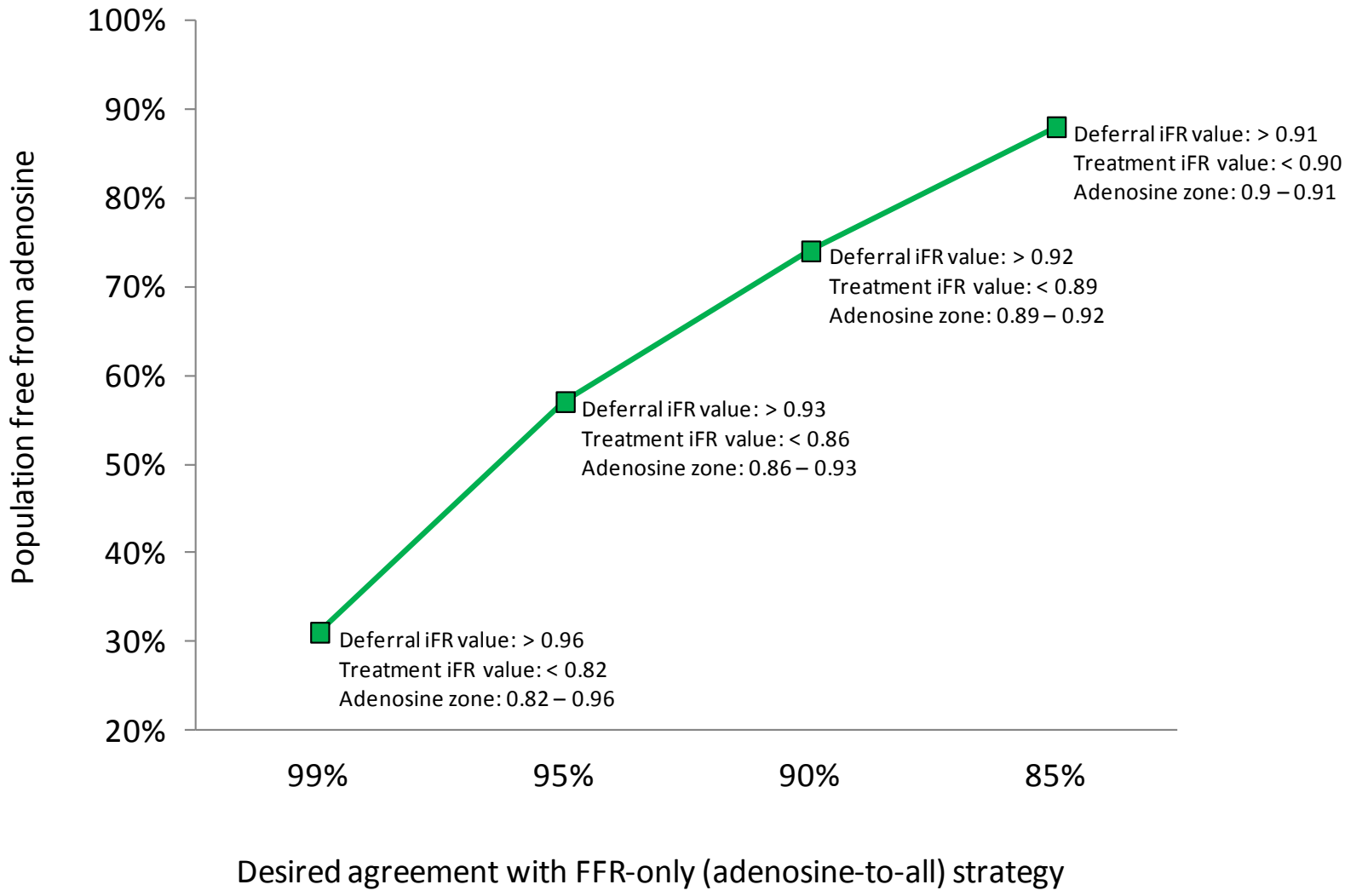


**Figure 5.4: Hybrid iFR–FFR strategy reduces the number of patients requiring adenosine for any desired agreement with an FFR-only strategy**

Using a hybrid iFR-FFR approach can reduce adenosine requirement in clinical practice by 74% with a 90% agreement with an FFR-only, adenosine-to-all, approach. For 95% and 99% agreement, the reduction in adenosine requirement would be 57% and 31%, respectively.

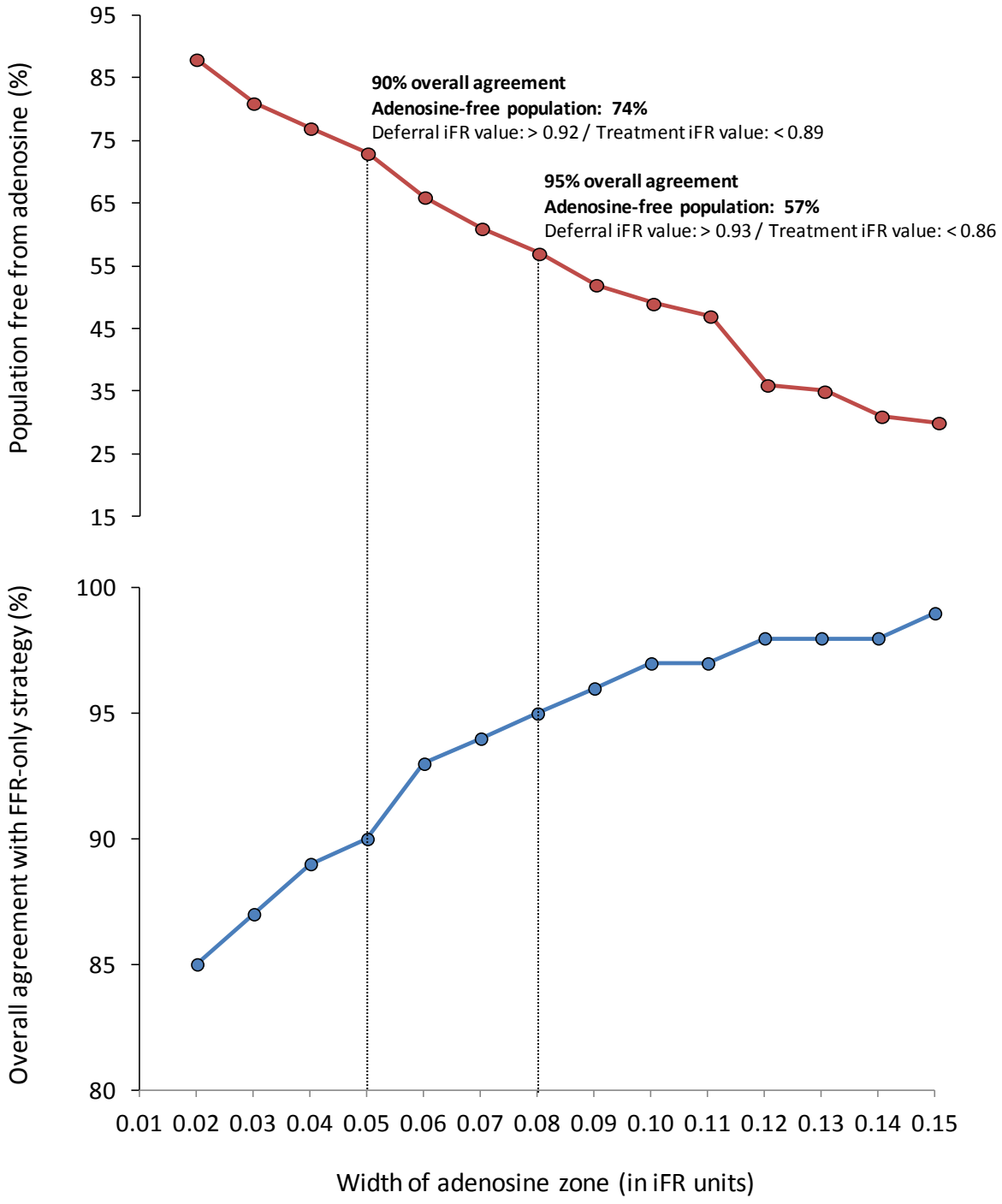


**Figure 5.5: Population free from adenosine and the overall agreement with an FFR-only strategy depends on the size of the adenosine requirement zone**

If adenosine is given to a larger window of iFR values, the diagnostic agreement with a FFR-only strategy increases (lower panel), albeit at a cost of less patients being free from adenosine (upper panel).

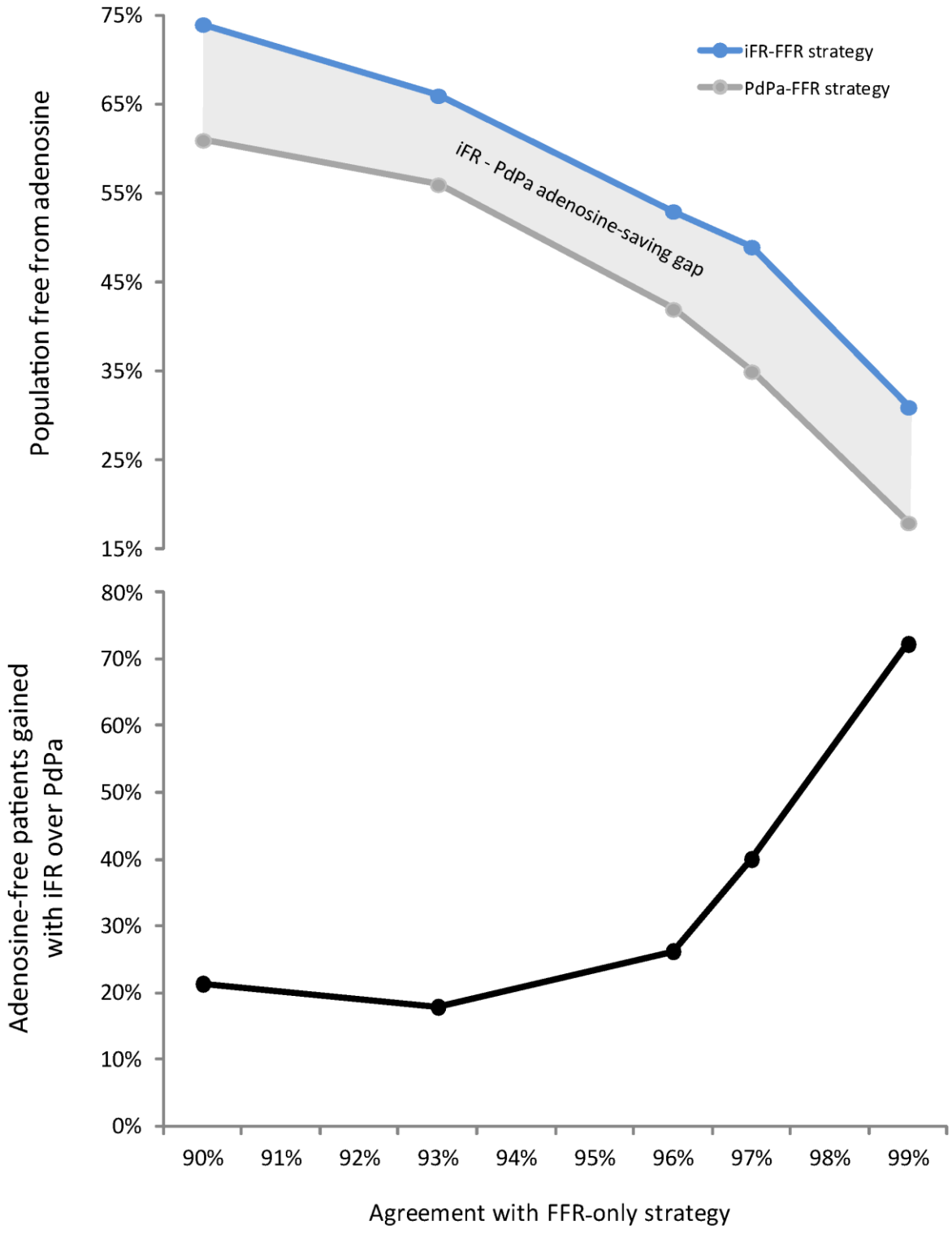


**Figure 5.6: Incremental adenosine-saving benefits of iFR over resting PdPa**

For each level of agreement with an FFR-only strategy, the utilisation of a hybrid iFR-FFR strategy significantly increases the adenosine-free population, when compared to a hybrid PdPa-FFR strategy. The absolute number of patients saved with each strategy is shown in top panel, with the incremental benefit of iFR over PdPa demonstrated in bottom panel.

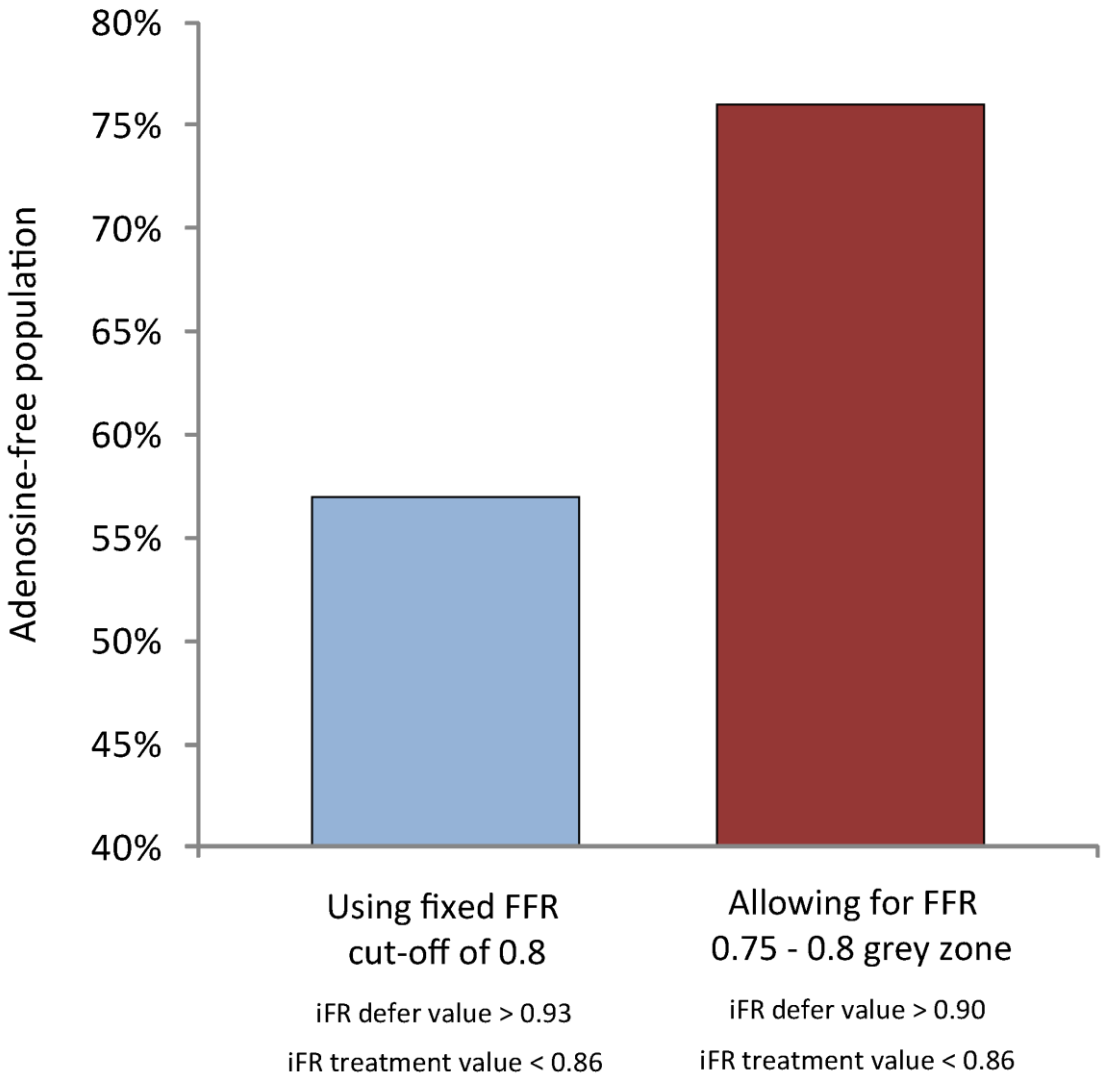


**Figure 5.7: Adenosine-free population increases if FFR grey zone is accounted for**

If the widely acknowledged FFR 0.75 – 0.8 diagnostic grey zone is accounted for, the proportion of patients free of adenosine in a hybrid iFR-FFR strategy would increase to 76%. In this scenario, a deferral iFR value of > 0.90 could be used with a negative predictive value of 94%, maintaining an overall agreement with FFR-only strategy of 95%.

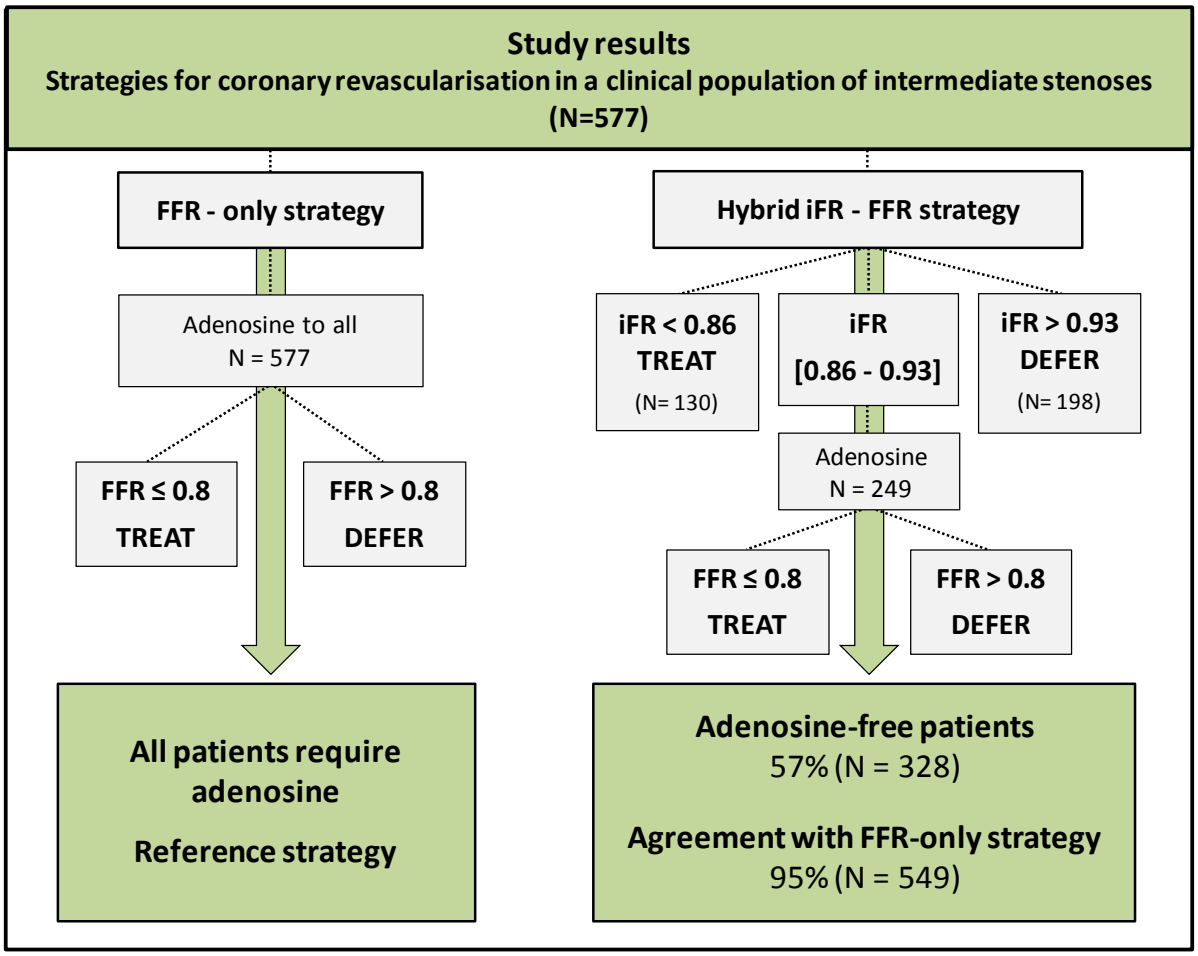


**Figure 5.8: Summary of the predicted results of a hybrid decision-making revascularisation strategy with instantaneous wave-Free Ratio (iFR) and fractional flow reserve (FFR).**

# 6 The baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve

## 6.1 Introduction

Three decades of research have repeatedly demonstrated the diagnostic and prognostic values of coronary flow reserve (CFR) in patients with coronary artery disease (CAD). Whether measured invasively or non-invasively, CFR has been shown to be able to identify patients with myocardial blood flow impairment, predict prognosis and stratify which lesions may benefit from revascularisation[9, 32, 66-70].

In the cardiac catheterisation laboratory, however, CFR has largely been replaced by a pressure-only measurement, fractional flow reserve (FFR), as the most common invasive tool to guide coronary revascularisation. FFR uses a ratio between distal coronary and aortic *pressures* under conditions of maximal hyperaemia[42] to *estimate* the relative *flow* reduction caused by a stenosis. The development of pressure-only FFR has undoubtedly facilitated the clinical application of invasive physiology and its role as a decision-making tool is supported by large clinical trials[13-15]. There remain, however, 30% of cases in which information derived from pressure FFR conflicts with direct measurement of underlying coronary flow reserve (CFR)[35-37]. These diagnostic disagreements are known not to be a result of measurement error but instead represent true biological differences between CFR and FFR: because both indices rely on the achievement of maximal coronary flow for their calculation, for any given stenosis their values move in opposite directions when hyperaemic flow increases[35, 36] (Figure 6.1).

The instantaneous wave-free ratio (iFR) has recently been proposed as an index which uses pressure-only recordings to identify physiologically significant stenoses[38]. Because iFR does not intend to estimate maximal myocardial blood

flow with pressure, it differs from FFR as it does not require pharmacological induction of hyperaemia for its calculation. Although early studies have reported a close relationship between iFR and FFR[38, 39, 58, 71], it is not known which pressure-only index agrees more closely with the true flow reserve CFR.

In this study we performed the first comparison between pressure indices iFR and FFR against coronary flow velocity reserve (CFVR) in patients undergoing invasive functional assessment of coronary artery disease. We sought to evaluate whether iFR, by avoiding hyperaemia, would agree more closely with underlying CFVR. If confirmed, this would provide further physiological validation for iFR as a vasodilator-free index of coronary disease severity.

## 6.2 Methods

### 6.2.1 Study sample

This study included 216 stenoses from 186 patients scheduled for coronary angiography or percutaneous coronary intervention at the Academic Medical Centre, Amsterdam, the Netherlands, and Imperial College, London, United Kingdom. The sample from Amsterdam included 141 stenoses from two sub-studies: one sub-sample of 56 lesions in which pressure and flow was measured simultaneously, collected between November 2001 and January 2012. The other includes 85 stenoses with non-simultaneous measurements of pressure and flow, from the BSR study dataset[51], with data collected from April 1997 and September 2006. The sample from Imperial College consisted of 75 stenoses, all collected from 2010 to 2013, as part of the ADVISE study and subsequent studies from the group. Exclusion criteria were restricted to significant valvular pathology and prior coronary artery bypass graft surgery. The local ethical review boards approved the respective study protocols, and all subjects gave written informed consent.

### 6.2.2 Cardiac catheterization and hemodynamic recording

Cardiac catheterization was performed according to standard practice. 5000iu unfractionated intravenous heparin was given at the start of the procedure together with 300mcg-600mcg of intracoronary GTN Invasive physiological data was acquired after diagnostic angiography. In 131 stenoses pressure and flow velocity were measured simultaneously with a 0.014inch combined pressure and Doppler sensor-tipped wire (ComboWire® XT, Volcano Corporation, San Diego,

CA). In the remaining 85 lesions pressure and flow were measured sequentially with separate pressure and flow wires. Distal and proximal pressures were normalised at the tip of the catheter. Measurements were performed during baseline conditions and during hyperaemia, induced by either intravenous infusion in 75 cases (140μg/kg/min), or intracoronary bolus injection (20-60μg) of adenosine in the remaining 141 stenoses.

### 6.2.3 Hemodynamic data analysis

Data (EKG, pressure and flow velocity) was extracted from a digital archive (ComboMap® or personal computer). Pressure drift was identified either by returning the pressure sensor to the catheter tip at the end of the procedure or by means of pressure drop-flow velocity curves, using the zero-flow pressure intercept as a measure of drift. Hemodynamic data analysis was performed off-line using a custom software package in MatLab (Mathworks Inc., Natick, Mass). Pressure and flow data acquired simultaneously were aligned as previously described[72]. The diastolic iFR window was identified using fully automated algorithms acting over EKG-gated, time-aligned pressure traces, as described previously[38]. Quantitative coronary angiography (QCA) was performed off-line in appropriate consoles.

### 6.2.4 Definition of physiological indices

Pa = Proximal (aortic) pressure (mmHg)

Pd = Distal (coronary) pressure (mmHg)

Fractional Flow Reserve (FFR) = $\frac{Pd}{Pa}$ at whole-cycle hyperaemia

Instantaneous wave-Free Ratio (iFR) = $\frac{Pd}{Pa}$ at baseline iFR window

Instantaneous wave-Free Ratio during adenosine administration (iFRa) = $\frac{Pd}{Pa}$ at hyperaemic iFR window

Baseline Flow = Mean baseline whole-cycle coronary flow velocity (cm/s)

Flow $_{FFR}$ = Mean whole-cycle coronary flow velocity at stable hyperaemia (cm/s)

Flow $_{iFR}$ = Mean coronary flow velocity during the baseline iFR window (mid-diastole) (cm/s)*

Coronary flow velocity reserve (CFVR) ** = $\frac{Whole-cycle\ hyperaemic\ flow\ velocity}{Whole-cycle\ baseline\ flow\ velocity}$

Hyperaemic Stenosis Resistance (HSR) = $\frac{Whole-cycle\ hyperaemic\ pressure\ gradient\ (mmHg)}{Whole-cycle\ hyperaemic\ flow\ velocity\ (\frac{cm}{s})}$

* Only calculated in stenoses in which pressure and flow velocity were measured simultaneously (N=131).

** *Coronary flow velocity reserve* (CFVR) refers to indices using a ratio of flow velocities (invasive Doppler and non-invasive stress echocardiography) and *coronary flow reserve* (CFR) refers to measures of underlying flow rate (Positron Emission Tomography and invasive thermo-dilution).

### 6.2.5 Statistical Analysis

Statistical analysis was performed using Stata 13.1, (Statacorp, USA). Data are expressed as mean ± standard deviation (SD), unless stated otherwise. Correlations between pressure-only indices and CFVR were assessed by calculation of the Pearson's correlation coefficient rho (ρ) by Greiner's relation using the *somersd* routine in Stata, since this is more robust to outliers and can take account of clustering of data within patients[73]. Receiver-operating-characteristics (ROC) curves were constructed for each pressure-only index against CFVR as the reference standard, using multiple CFVR cut-offs (1.7, 2.0, 2.5 and 3.0). The areas under the ROC curve (ROCAUC) were compared using *somersd* to calculate Harrel's c. An additional comparison of ROC curves was made with the comproc routine in Stata which uses percentile values derived from the empirical distribution of the test measure among controls with a

correction for ties and taking account of clustering[74]. A Wald test for comparisons based on bootstrap standard errors (1000 replications) was performed, but as this analysis gave almost identical values to *somersd* these results have not been presented below. The classification agreement (and sensitivity, specificity, negative predictive value and positive predictive value) between pressure only indices (iFR and FFR) and CFVR was calculated using ROC-derived cut-offs (highest sum of sensitivity and specificity for a CFVR of 2.0) and using clinically established cut-offs (CFVR 2.0[67]; FFR 0.80[13, 14]; and the equivalent iFR cut-off of 0.90[75]). When evaluating the underlying haemodynamics of large baseline-hyperaemic pressure disagreements, we used an FFR cut-off of 0.75 for significance, as this has been demonstrated to be the optimal ischaemic FFR cut-off across multiple studies[25, 76]. Comparison of means was performed using Student's t-test. A p value of $< 0.05$ was considered statistically significant.

## 6.3 Results

### 6.3.1 Sample characteristics

The 216 stenoses (186 patients) demonstrated unimodally distributed iFR, FFR and CFVR values. Mean FFR was 0.74 ± 0.17, mean iFR was 0.81 ± 0.21 and mean CFVR was 2.1 ± 0.77. Mean diameter stenosis was 56 ± 16%. The majority of patients included in this study presented with stable symptoms (98%), with 52% demonstrating single-vessel disease. 56% of all stenoses evaluated were in the left anterior descending (LAD) coronary artery. Angiographic and demographic characteristics are summarised in Table 6-1.

### 6.3.2 Diagnostic agreement between pressure-only indices and CFVR

iFR showed a stronger correlation with underlying CFVR (iFR-CFVR ρ=0.68 [0.60, 0.76]) than did FFR (FFR-CFVR ρ=0.50 [0.39, 0.62]) ($p<0.001$ for comparison). Across the entire range of functional stenosis severities, iFR was found to be in closer diagnostic agreement with CFVR than FFR (iFR $ROC_{AUC}$ 0.82 [CI 0.76 – 0.88] versus FFR $ROC_{AUC}$ 0.72 [CI 0.65 – 0.79], $p < 0.001$, for a CFVR of 2) (Figure 6.2). This was particularly evident within the intermediate 0.60 - 0.90 FFR range (iFR $ROC_{AUC}$ 0.78 [CI 0.69 – 0.86] versus FFR $ROC_{AUC}$ 0.59 [CI 0.48 – 0.69], $p < 0.001$, for a CFVR of 2). iFR also demonstrated better diagnostic discrimination over baseline Pd/Pa (Pd/Pa $ROC_{AUC}$ 0.78 [0.72 - 0.85], p=0.004). The better agreement of iFR with CFVR was found for different CFVR cut-offs (Table 6-2). The iFR cut-off value with the highest diagnostic accuracy to identify stenosis with a CFVR < 2 was 0.85. Although iFR values were significantly lower when measured at hyperaemia (iFRa) (mean iFRa 0.63 ± 0.22

versus mean iFR 0.81 ± 0.21 and mean FFR 0.74 ± 0.17, p<0.001), the agreement between iFRa and CFVR was significantly worse than baseline iFR (iFR $ROC_{AUC}$ 0.82 [CI 0.76 – 0.88] versus iFRa $ROC_{AUC}$ 0.74 [CI 0.68 – 0.81], p<0.001).

### 6.3.3 Pressure-indices and discrimination between stenoses with normal and abnormal CFVR

Mean CFVR of stenoses with iFR value > 0.9 was 2.51 ± 0.7, whilst mean CFVR of stenoses with an iFR ≤ 0.9 was 1.69 ± 0.6 ($p<0.001$). A lower iFR value of ≤ 0.85 identified a subgroup of stenoses with a particularly low CFVR (mean CFVR of 1.44 ± 0.44 with a positive predictive value to identify stenoses with CFVR of less than 2.0 and 2.5 of 83% and 99%, respectively).

Diagnostic discrimination was not improved by adenosine administration and FFR calculation (Figure 6.3). For instance, amongst stenoses with iFR ≤ 0.9, those with FFR > 0.8 still had a mean CFVR < 2. Also, amongst stenoses with iFR > 0.9 a low FFR result paradoxically identified lesions with an even higher CFVR.

### 6.3.4 Magnitude of coronary flow velocities during baseline and hyperaemia

$Flow_{FFR}$ was significantly higher than $flow_{iFR}$ in mild stenoses, when FFR > 0.75 (mean $flow_{FFR}$ 42.3 ± 22.8 cm/s versus mean $flow_{iFR}$ 26.1 ± 15.5 cm/s, $p < 0.001$, Figure 4). However, amongst FFR-significant lesions (≤ 0.75), $flow_{iFR}$ and $flow_{FFR}$ were not significantly different (mean $flow_{FFR}$ 25.8 ± 13.7 cm/s versus mean $flow_{iFR}$ 21.5 ± 11.7 cm/s, $p = 0.13$, Figure 6.4). Both $flow_{FFR}$ and $flow_{iFR}$ were significantly higher than whole-cycle baseline flow ($flow_{Pd/Pa}$) across the whole spectrum of FFR values ($flow_{Pd/Pa}$ 16.8 ± 8.4 cm/s in lesions with FFR ≤ 0.75; and $flow_{Pd/Pa}$ 19.8 ± 8.4 in lesions with FFR > 0.75, $p<0.001$ for comparisons with $iFR_{flow}$ and $FFR_{flow}$).

Magnitudes of hyperaemic flow velocities were not different between intracoronary (IC) and intravenous (IV) adenosine administration. Amongst mild stenoses (with FFR > 0.8) mean $flow_{FFR\ IV}$ was 42.5 ± 21.6 cm/s versus mean

$flow_{FFR\ IC}$ 44.5 ± 21.1 cm/s (p=0.61). Amongst functionally severe stenoses (FFR<0.6), mean $flow_{FFR\ IV}$ was 20.8 ± 11.6 cm/s versus mean $flow_{FFR\ IC}$ 21.9 ± 12 cm/s (p=0.82). Amongst intermediate lesions (FFR 0.6-0.9) mean $flow_{FFR\ IV}$ was 38.6 ± 15.3 cm/s versus mean $flow_{FFR\ IC}$ 39.9 ± 20.1 cm/s (p=0.70).

### 6.3.5 Prevalence and mechanisms behind large trans-stenotic gradients only present at hyperaemia

High iFR values (iFR >0.90) which, following adenosine administration, demonstrated a significant drop in FFR (FFR ≤ 0.75) were observed only in 4.1% of cases (Figure 6.5).

Amongst stenoses with FFR values ≤ 0.75, the difference between iFR and FFR values was primarily driven by the magnitude of trans-stenotic flow velocity, with larger numerical differences being associated with significantly higher CFVR values (Figure 6.5). Analysis of absolute flow velocities in this subgroup of stenoses (FFR ≤ 0.75 and iFR > 0.9) revealed that the high value of CFVR was caused by higher than average hyperaemic flow velocities with normal values of baseline flow (Table 6-3). Furthermore, the magnitudes of hyperaemic coronary flow velocities in this subgroup were similar to the ones observed in unobstructed lesions, with FFR > 0.80 (Table 6-3). The underlying flow profile of stenoses with large gradients only present during hyperaemia are similar to those of FFR-negative vessels, with high hyperaemic flow velocity and higher than average CFVR. Examples of such cases are presented in Figure 6.

Therefore, amongst stenoses showing a definite abnormal FFR result (≤ 0.75), two distinct groups existed with respect to the underlying CFVR value: those with abnormal iFR (≤ 0.9), in which CFVR values were also abnormal and those with normal iFR (>0.9), which demonstrated significantly higher hyperaemic flow and CFVR values (Table 6-3).

## 6.4 Discussion

In this study we have found that (1) iFR provides better pressure-derived diagnostic agreement with CFVR than FFR; (2) the diagnostic conflicts between pressure-only indices and CFVR is at least partly caused by the induction of hyperaemia, as iFR loses its better classification agreement with CFVR when calculated during adenosine administration (iFRa); (3) $flow_{FFR}$ is higher than $flow_{iFR}$ only in physiologically mild stenoses, when FFR > 0.75 and (4) large drops from high iFR values to low FFR values are driven by high CFVR and high magnitudes of hyperaemic flow.

### 6.4.1 iFR – FFR disagreements: comparison with another flow based index

The classification agreement between iFR and FFR has already been extensively evaluated in over 2000 stenoses[38, 49, 58, 75] . Multiple studies consistently showed the iFR-FFR classification match to be 80 - 90%; similar to the agreement reported between different invasive and non-invasive functional tests[17, 26, 51, 66, 77-79]. However, direct comparisons between iFR and FFR are of limited value because when disagreements occur it is not possible to infer which index correctly identifies flow-limiting stenoses. Simultaneous iFR and FFR comparisons against independent discriminators are essential to assess the diagnostic performance of both indices. In the present study, therefore, by evaluating iFR and FFR against CFVR, an established and extensively studied flow-based index, we provide further evidence to support iFR as an index capable of detecting flow-limiting coronary disease (Figure 6.2 and Table 6-2). The closer diagnostic agreement between iFR and CFVR was observed for different CFVR cut-offs and particularly marked within intermediate FFR values (Table 6-2), which suggests our results are not driven by the extremes of disease

severity. Our findings are similar to those of the CLARIFY study[39] and a study by van de Hoef et al.[71], both of which found that iFR was non-inferior to FFR to detect ischaemia using invasive flow and myocardial perfusion imaging, respectively. Also, the present study identified 0.85 as the iFR cut-off with the maximal accuracy to identify flow-limiting stenoses by CFVR, value similar to 0.86 reported in CLARIFY[39].

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### 6.4.2 Adenosine does not significantly increase coronary flow in patients with obstructive CAD

Whilst early FFR experiments elegantly demonstrated that hyperaemic flow is significantly higher than baseline flow in healthy young animals with normal coronary arteries[23] and in healthy young human subjects[35], we found that adenosine does not invariably increase coronary flow in patients with CAD (Figure 6.4). Previous studies have indeed suggested that direct extrapolation of coronary haemodynamic findings cannot be made from animals or healthy subjects to patients with vascular risk factors, coronary artery disease and varying degrees of microvascular dysfunction. Uren et al demonstrated with PET that in patients with CAD hyperaemic flow is on average only higher than baseline whole-cycle flow in lesions with less than 50% diameter stenosis[80]. Similar results were recently reported by Sen et al in the CLARIFY study, which showed that FFR hyperaemic distal coronary resistance is only significantly lower than baseline iFR resistance in vessels without flow-limiting disease[39]. Finally, a large variability in microcirculatory resistance measured with thermo-dilution has recently been demonstrated in coronary vessels with intermediate stenoses[81] supporting the idea that an inconsistent inter-patient response to adenosine is

one of the main responsible for the variable magnitudes of hyperaemic flow achieved during FFR calculation[39]. In agreement with these studies, we found that hyperaemic $flow_{FFR}$ is on average only higher than the baseline $flow_{iFR}$ in patients with FFR > 0.75. Therefore, in patients undergoing invasive functional assessment of coronary disease in clinical practice, adenosine administration (IV or IC) only significantly increases coronary flow above baseline diastole in non-obstructing, FFR-negative stenoses. In the remaining clinically relevant significant lesions, the baseline diastolic flow of auto-regulatory vasodilatation appears to suffice[82].

### 6.4.3 Pressure-flow diagnostic conflicts

Our study also contributes to our understanding of the mechanisms behind pressure-flow diagnostic conflicts[83]. Induction of maximal hyperaemia is a pre-requisite for the calculation of *both* FFR and CFVR[30]. However, as their values move in opposite directions when hyperaemic flow increases (Figure 6.1) for any given stenosis and fixed baseline flow, an improvement in hyperaemic flow would paradoxically lead to a "worse" FFR result (and vice-versa). Therefore, because the individual response to adenosine has been shown to vary significantly amongst patients with CAD[35, 36, 39], diagnostic disagreements between pressure indices and CFVR are expected to occur if both are measured during hyperaemia. Our results support this concept, as we found that the closer relationship between iFR and CFVR is lost when iFR is measured during adenosine administration (iFRa), suggesting the hyperaemic response itself (and not the utilisation of whole-cycle physiology) is the most likely cause of conflicts between pressure indices and CFVR.

It is already acknowledged that conditions which restrict hyperaemic flow (severe ventricular hypertrophy, increased left ventricular pressures and microvascular obstruction) can make FFR values artificially higher and challenging to interpret clinically[84, 85]. Our findings also help to clarify the physiological mechanisms behind the other discordant group. In a small proportion of stenoses, ischaemic FFR values (≤ 0.75) may be generated by high hyperaemic flow rates and higher than average CFVR (Table 6-3 and Figure 6.5 and Figure 6.6). Specifically, the generation of large hyperaemic gradients in stenoses with normal iFR values (> 0.9), identify a particular subgroup of patients with high CFVR (Figure 6.1, mechanism 2 and Figure 6.3). These lesions demonstrate, on average, magnitudes of hyperaemic flow velocities equal to what is observed in stenoses with FFR > 0.80, both significantly higher than flow velocities seen in the overall population of FFR significant lesions (≤ 0.75) (Figure 6.3). Also, these cases have been shown to have five year outcome similar to vessels with concordant FFR and CVFR results (FFR>0.75, CVFR>2.0)[32]. Although uncommon (less than 5% of cases in this cohort), this phenomenon has been previously described in studies using PET[35], Doppler[36] and thermodilution-derived CFR[81].

The concept that a large coronary pressure gradient only present during hyperaemia is a result of high CFVRs has previously been identified and explored by independent groups. Akasaka et al and MacCarthy et al have independently demonstrated that a good correlation with CFVR can be obtained from pressure alone, by measuring the changes in pressure gradients, from baseline to hyperaemia[86]. Indeed, Johnson et al, using data derived from a large PET dataset[35, 83], specifically warned against the universal application of a fixed FFR cut-off of 0.75-0.8 to detect ischaemia in all patients, as this threshold could

vary depending on the inter-individual variability of CFVR and the extent of microvascular disease in any given population. Therefore, stenoses with a large discrepancy between high iFR and low FFR values represent, on average, a sub-group of lesions with high CFVR in which hyperaemic coronary flow is not significantly limited. In such cases, care should be taken when interpreting the low FFR values as evidence of ischaemia. Randomised clinical trials need to be performed to prospectively evaluate outcomes in such subgroup of stenoses.

### 6.5 Clinical implications

Utilisation of invasive functional evaluation of coronary disease has significantly increased with the development of FFR, largely because of the simplification brought by use of pressure-only methods. However, adoption of FFR remains low (6-8%)[33, 60]. The reasons are multi-factorial and include difficult access to adenosine in some geographies and concerns over increased procedural time and costs, particularly in patients with 3-vessel disease[33]. Therefore, the demonstration that iFR, a pressure-only index which does not require adenosine, has a close association with underlying CFVR, is supportive of its potential future role as a tool to guide decision-making in CAD. By eliminating the need for hyperaemia, iFR could make coronary functional assessment simpler and deliver the known benefits of physiology-guided revascularisation to many more patients with CAD. Clinical trials will evaluate the impact of iFR-guided decisions on clinical outcomes. The FLAIR study will prospectively compare iFR and FFR-guided strategies in 2500 patients with stable coronary artery disease.

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### 6.6 Limitations

Our study has limitations. Firstly, our analysis was performed retrospectively in previously recorded haemodynamic traces. However, our study represents the largest comparison of pressure-only indices against invasive flow in patients with CAD, meticulously recorded in centres dedicated to the measurement of coronary haemodynamics.

This study used CFVR as a reference comparison, an index which, despite its established diagnostic and prognostic value in coronary disease, is not widely used in the catheterisation laboratory for clinical decision-making. For the interrogation of intermediate stenoses, CFVR has been largely replaced by a simple pressure ratio (FFR), because of its easier applicability and demonstrated superiority over angiography[13, 14]. Clinical application of invasive CFVR is now largely limited to evaluation of coronary microvascular function[42] and scientific research. These practical aspects of CFVR utilisation, however, do not diminish its biological value as flow-based discriminator, especially when measurements are performed by experienced operators in high-volume centres which participated in this study. Both FFR and CFVR have demonstrated to be useful to guide revascularisation, with similar rates of MACE[42], and equal ability to detect myocardial ischaemia in the presence of coronary stenoses[51, 77]. Also, iFR and FFR were obtained from the same haemodynamic trace in which CFVR was measured. Therefore, technical limitations to CFVR should equally affect its relationship with both iFR and FFR. Finally, although a CFVR value of 2.0 is the most widely accepted cut-off and the majority of our analysis is based on such value, we have also performed comparisons with multiple CFVR cut-offs to reduce the potential bias of choosing a single dichotomous cut-off for the reference test.

We used a ratio of flow velocities to calculate flow reserve, which assumes the cross-sectional area of the vessel is maintained from baseline to hyperaemia. This is achieved by the administration of intracoronary GTN at the start of the recordings. Significant changes in underlying flow rate are unlikely to occur as a result of changes in vessel diameter during adenosine administration[23].

Different adenosine routes (intravenous versus intracoronary) and doses were used to induce coronary hyperaemia. Although this might be seen as a potential limitation, it better reflects the real-world utilisation of FFR in clinical practice, making our results directly applicable to patients with CAD. Although larger doses of intracoronary adenosine can be used, the dose used in this study (20-60mcg) achieved the same magnitude of hyperaemic flow velocity as 140mcg/Kg/min of intravenous adenosine infusion, regime used in FAME and FAME II. Also, recent large clinical cohorts have shown the clinical benefits of FFR when utilising such lower doses in clinical populations[87]. A more detailed discussion on the optimal dose of vasodilators to achieve maximal coronary hyperaemia has recently been provided by van de Hoef et al[76].

We performed a specific ROC analysis on the performances of iFR and FFR against CFVR in the intermediate 0.6 - 0.9 FFR range. Whether such narrower range of FFR values represents a particularly important sub-group of lesions is debatable, considering that cardiac events are lower in this region when compared to more severe stenoses[13, 87]. Because recent reports suggested that such intermediate range is important[88], our analysis aimed to demonstrate that the diagnostic agreement between iFR and CFVR was maintained when FFR values fell between 0.6 and 0.9. However, we did not perform any correlation

analysis in such restricted range, as this can artificially lower the relationship between any two tests.

A word of caution is important when using pressure indices as an estimation of underlying coronary flow. Although different in many physiological aspects, both iFR and FFR use a trans-coronary ratio of *pressures* as a means of *estimating* the underlying reduction in coronary *flow*. Whilst this pressure-only approach facilitates clinical application of physiology in the catheterisation laboratory, it should not be seen as a biological equivalent of direct measurement of coronary flow.

Finally, the demonstration that, when compared to FFR, iFR has a closer relationship with underlying CFVR should not be interpreted as *superiority* of one index over another. In studies of coronary physiology and ischaemic heart disease, all inter-test comparisons are limited by the lack of a true gold standard for the detection of myocardial ischaemia. Although extensively validated as a measure of myocardial perfusion, CFVR is only *one* of several available methods to measure it and is currently not the most commonly used tool in the catheterisation laboratory. Therefore, our findings cannot infer any clinical benefits of iFR over FFR in clinical decision-making. We have simply demonstrated a close diagnostic agreement between iFR and underlying coronary flow, which helps its validation as a potential test to detect flow-limiting stenoses. Our findings help to set the physiological foundations for future studies with clinical outcomes, which will evaluate the merits of iFR as a clinical decision-making tool.

## 6.7 Conclusion

When compared to FFR, iFR agrees more closely with underlying coronary flow reserve, a strong predictor of events in patients with coronary artery disease. Because it does not require the induction of hyperaemia for its calculation, iFR may simplify functional evaluation of coronary stenoses and enable expansion of physiology-guided revascularisation to many more patients with coronary artery disease.

## 6.8 Tables

**Table 6-1: Demographic and angiographic data**

| | |
|---|---|
| Number of stenoses (patients) | 216 (186) |
| Age, yrs | 61±11 |
| Male % | 75 |
| Co-morbidities, % | |
| Hypertension | 47 |
| Hypercholesterolaemia | 73 |
| Smoking history | 44 |
| Diabetes | 22 |
| Chronic renal disease | 2 |
| Severe LV dysfunction (EF<30%) | 1 |
| Clinical presentation, % | |
| Stable angina | 98 |
| Unstable angina | 2 |
| Coronary anatomy, % | |
| Single vessel CAD | 52 |
| Multivessel CAD | 48 |
| LAD | 56 |
| LCx | 18 |
| RCA | 24 |
| Other | 2 |
| Proximal vessel | 35 |
| Diameter stenosis, % ± SD | 56 ± 16 |
| Adenosine route, % | |
| Intravenous | 35 |
| Intracoronary | 65 |

EF = Ejection Fraction; CAD = Coronary artery disease; LAD = Left anterior descending artery; LCx = Left circumflex artery; RCA = Right coronary artery; SD = Standard deviation of the mean.
Smoking history includes current and previous cigarette smoking.

**Table 6-2: Diagnostic agreement between pressure-only indices and different cut-offs of coronary flow velocity reserve**

| CFVR Cut-off | Whole sample (186 patients, 216 observations) | | | 0.6 - 0.9 FFR range (113 patients; 129 observations) | | |
|---|---|---|---|---|---|---|
| | iFR AUC | FFR AUC | p value | iFR AUC | FFR AUC | p value |
| 1.7 | 0.89 [0.84, 0.93] | 0.80 [0.73,0.87] | <0.001 | 0.86 [0.79,0.93] | 0.67 [0.56, 0.77] | <0.001 |
| 2.0 | 0.82 [0.76, 0.88] | 0.72 [0.65, 0.79] | <0.001 | 0.78 [0.69, 0.86] | 0.59 [0.48, 0.69] | <0.001 |
| 2.5 | 0.79 [0.74, 0.85] | 0.71 [0.64, 0.78] | 0.002 | 0.74 [0.65,0.83] | 0.55 [0.45, 0.66] | <0.001 |
| 3.0 | 0.77 [0.70, 0.84] | 0.69 [0.59, 0.79] | 0.057 | 0.76 [0.67, 0.86] | 0.54 [0.42, 0.67] | <0.001 |

CFVR = coronary flow velocity reserve; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; AUC = area under the ROC curve

**Table 6-3: Underlying coronary flow in different sub-groups of stenoses**

| Flow parameters | Stenoses with iFR ≤ 0.9 and FFR ≤ 0.75 (concordant group, gradient present at baseline *and* hyperaemia) | | Stenoses with iFR > 0.9 and FFR ≤ 0.75 (discordant group, gradient only present at hyperaemia) | Overall stenoses with FFR > 0.80 (reference group, unobstructed arteries) |
|---|---|---|---|---|
| Hyperaemic CFV (cm/s) | 24.9 ± 13.4 | p = 0.016 ⟷ | 44.7 ± 19.6 | 43.6 ± 21.3 |
| CFVR | 1.59 ± 0.58 | p < 0.001 ⟷ | 2.80 ± 0.54 | 2.40 ± 0.74 |

CFV = Coronary flow velocity; CFVR = Coronary flow velocity reserve

## 6.9 Figures

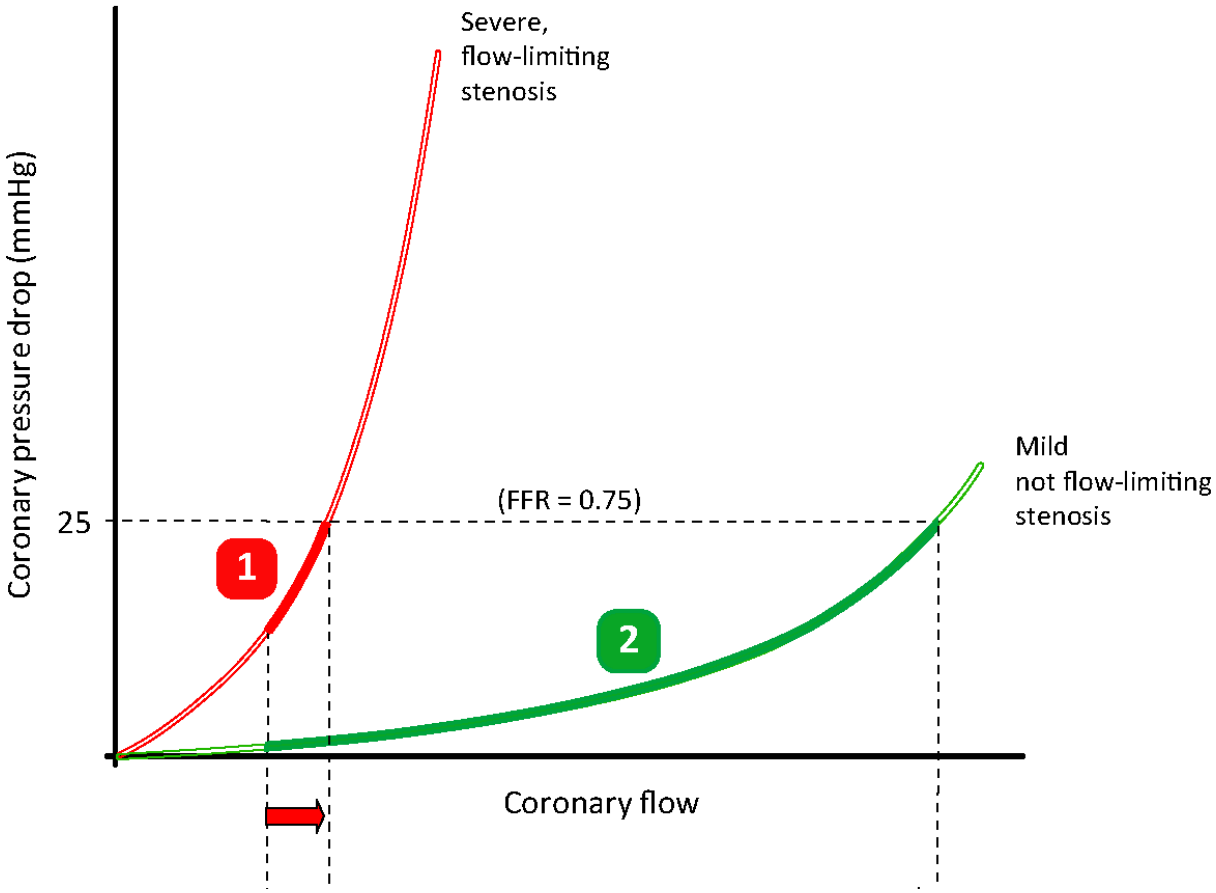
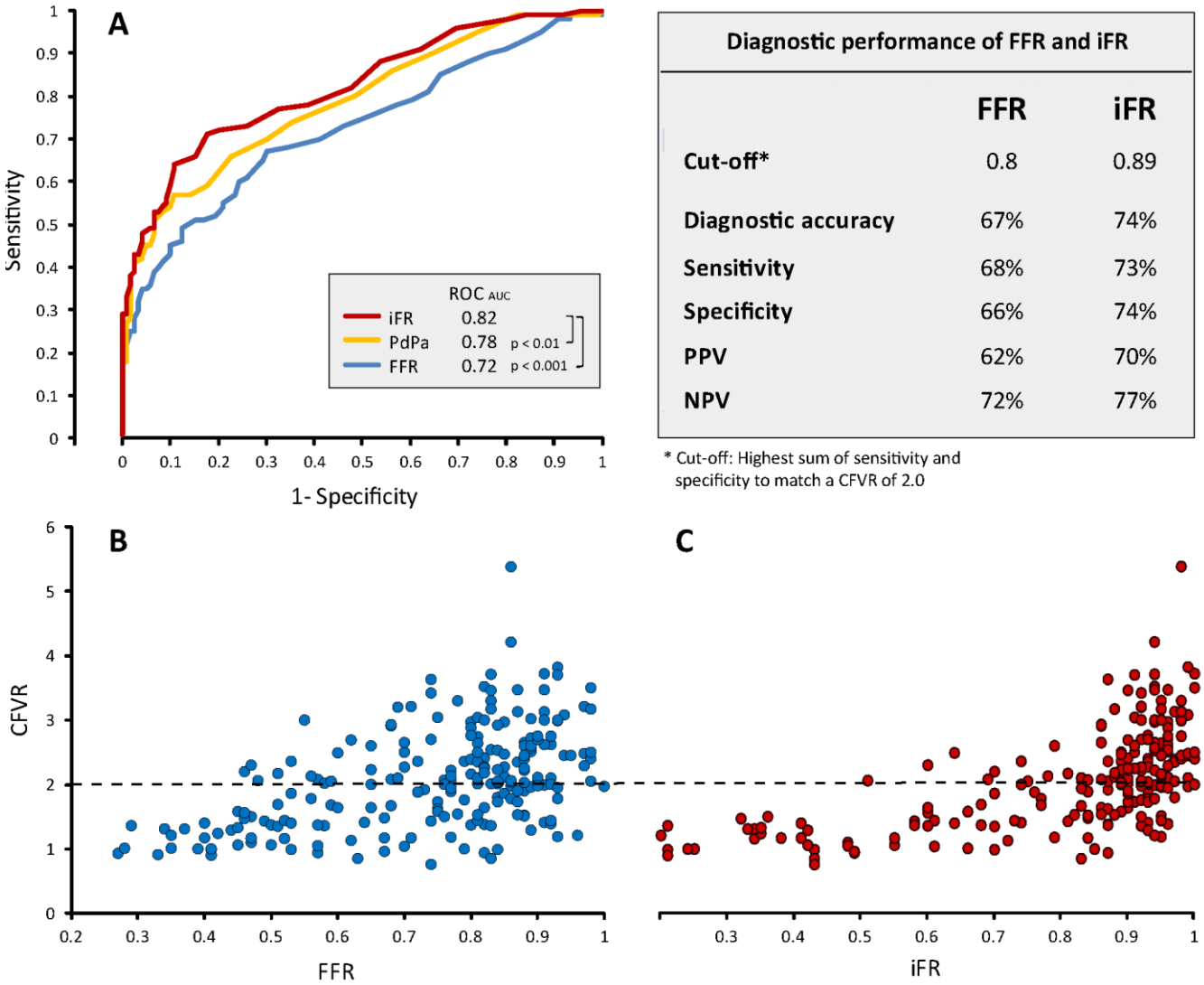



**Figure 6.1: How can a low FFR value be generated?**

Schematic representation of the relationship between pressure gradient and flow across a coronary stenosis. The same FFR value (in this example 0.75, equivalent to a pressure drop of 25mmHg) can be generated via two different mechanisms. In (1), even a small magnitude of hyperaemic flow is sufficient to generate a 25mmHg drop in a severe, flow-limiting lesion. In (2), much higher hyperaemic flow rates are needed for the same 25mmHg to be created in a mild stenosis. Stenosis (1) is very likely causative of myocardial ischaemia, whilst stenosis (2) is by definition not significantly flow-limiting, despite displaying the same FFR classification.




| Diagnostic performance of FFR and iFR | | |
|---|---|---|
| | **FFR** | **iFR** |
| **Cut-off*** | 0.8 | 0.89 |
| **Diagnostic accuracy** | 67% | 74% |
| **Sensitivity** | 68% | 73% |
| **Specificity** | 66% | 74% |
| **PPV** | 62% | 70% |
| **NPV** | 72% | 77% |

* Cut-off: Highest sum of sensitivity and specificity to match a CFVR of 2.0

**Figure 6.2: Diagnostic performance of pressure-only indices against coronary flow reserve**

(A) When compared to fractional flow reserve (FFR), instantaneous wave-free ratio (iFR) has better diagnostic agreement with coronary flow velocity reserve (CFVR). Scatter plots between FFR and CFVR (B) and between iFR and CFVR (C) are shown, with the dashed horizontal line demarcating a CFVR cut-off of 2.0.

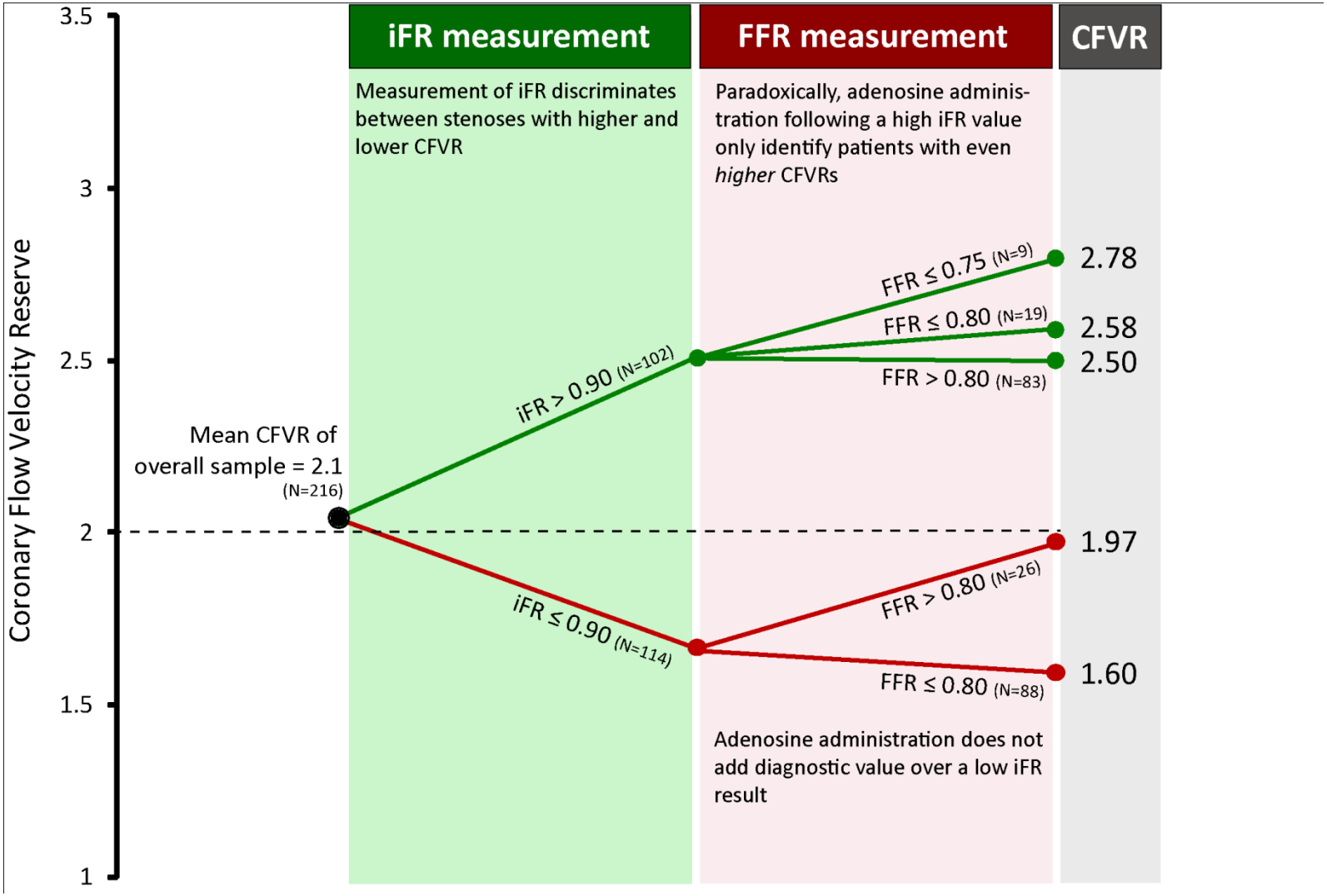



**Figure 6.3: Measurement of iFR and FFR for the identification of stenoses with abnormal CFVR**

iFR measurement identifies lesions with low underlying CFVR (green panel). Adenosine administration and FFR calculation adds no discrimination over baseline iFR results (red panel)

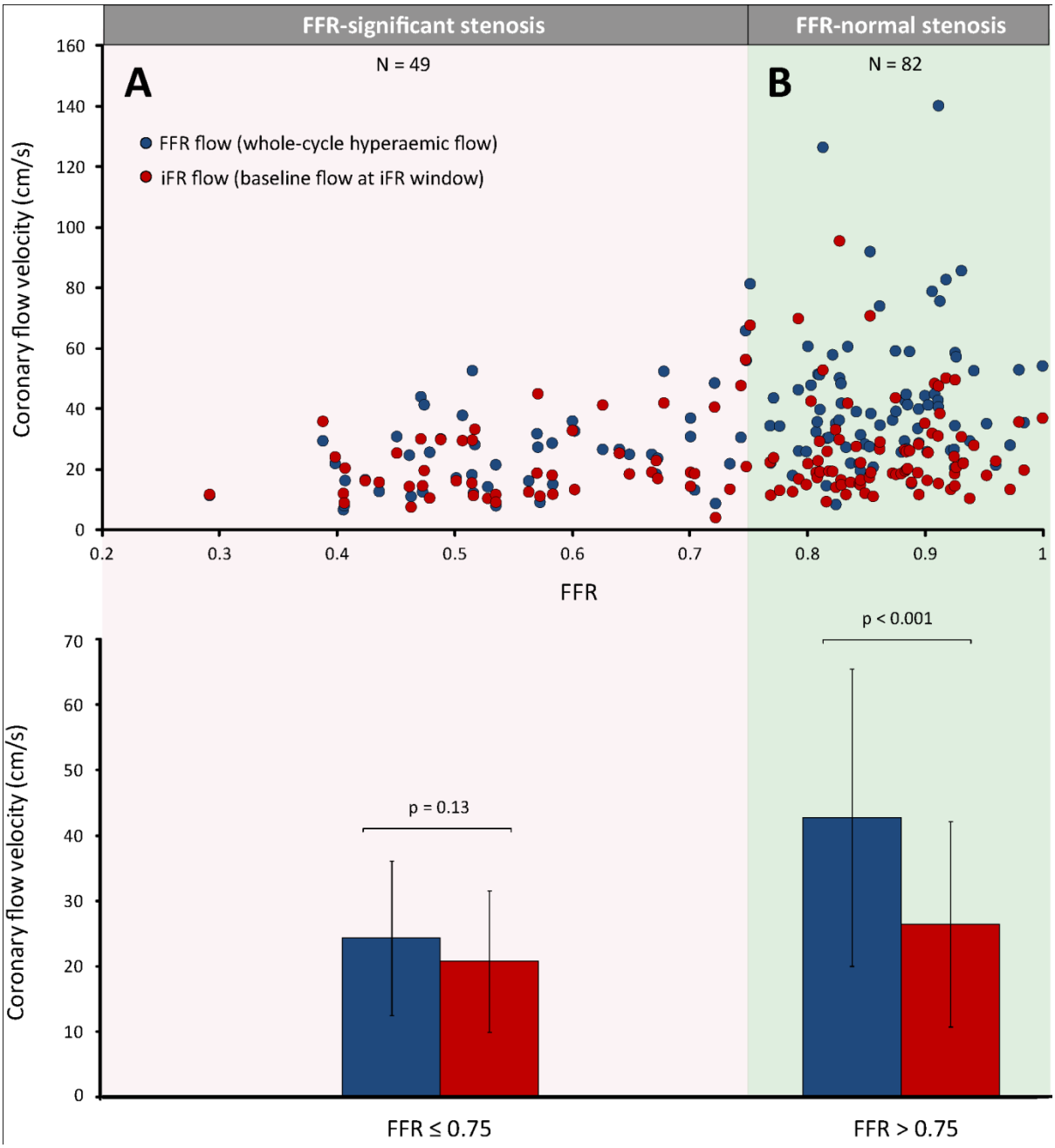



**Figure 6.4: Effects of adenosine on coronary flow in patients with coronary disease**

Adenosine-induced augmentation of coronary flow is variable across the spectrum of disease severity (top panel, scatter plot). Whole-cycle hyperaemic flow (FFR flow) is not higher than baseline mid-diastolic wave-free flow (iFR flow) in functionally ischaemia-inducing stenoses, when FFR ≤ 0.75 (A). FFR flow becomes higher than iFR flow only in mild, FFR-negative lesions (B).

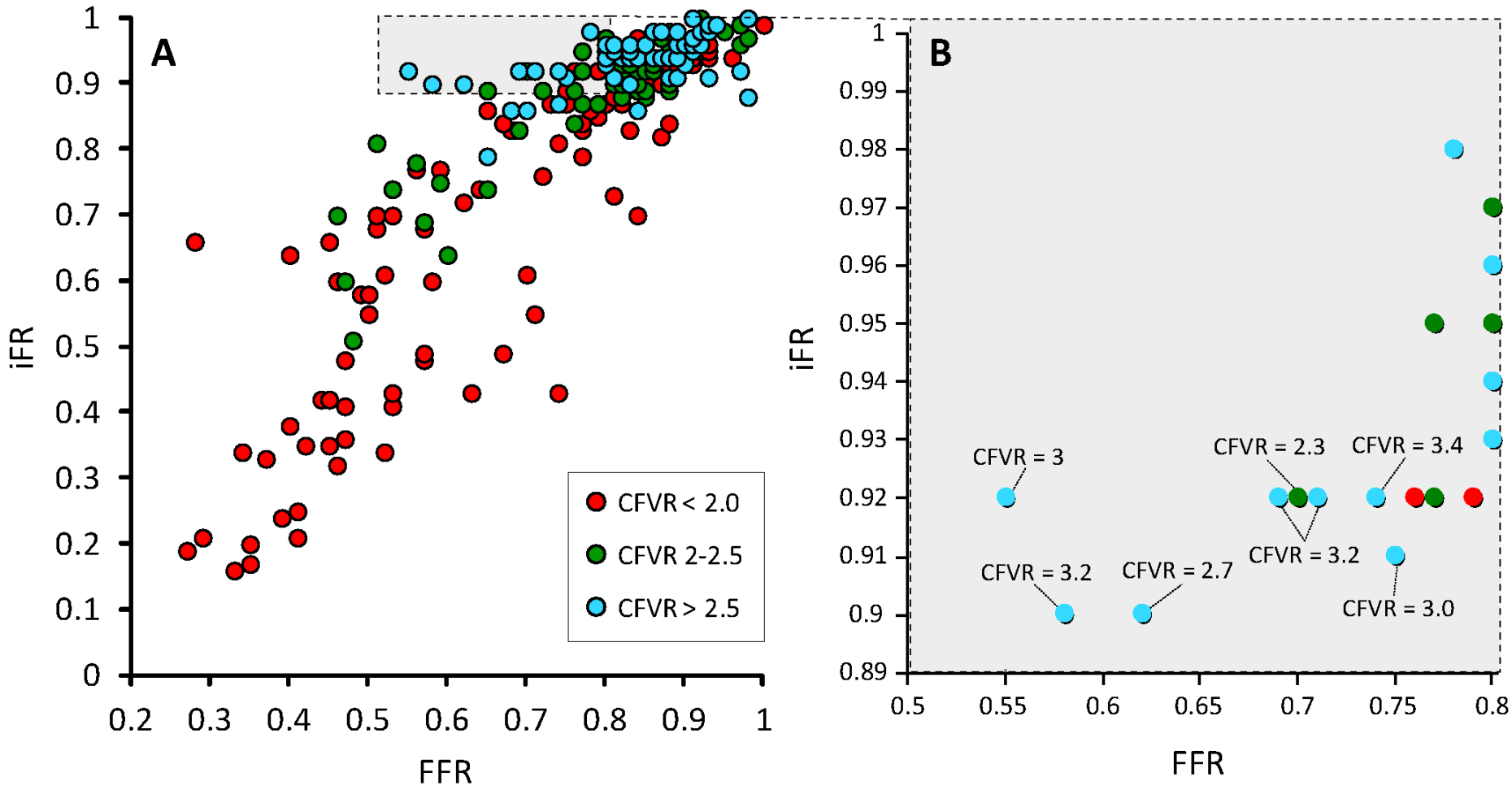



**Figure 6.5: Scatter plot between iFR and FFR, with colour-coded CFVR**

High iFR values are associated with high magnitudes of coronary flow velocity reserve (CFVR) (A). The sub-group of lesions with high iFR values *and* significantly low FFR values (FFR ≤ 0.75) demonstrate, on average, particularly high CFVR (grey box, B).

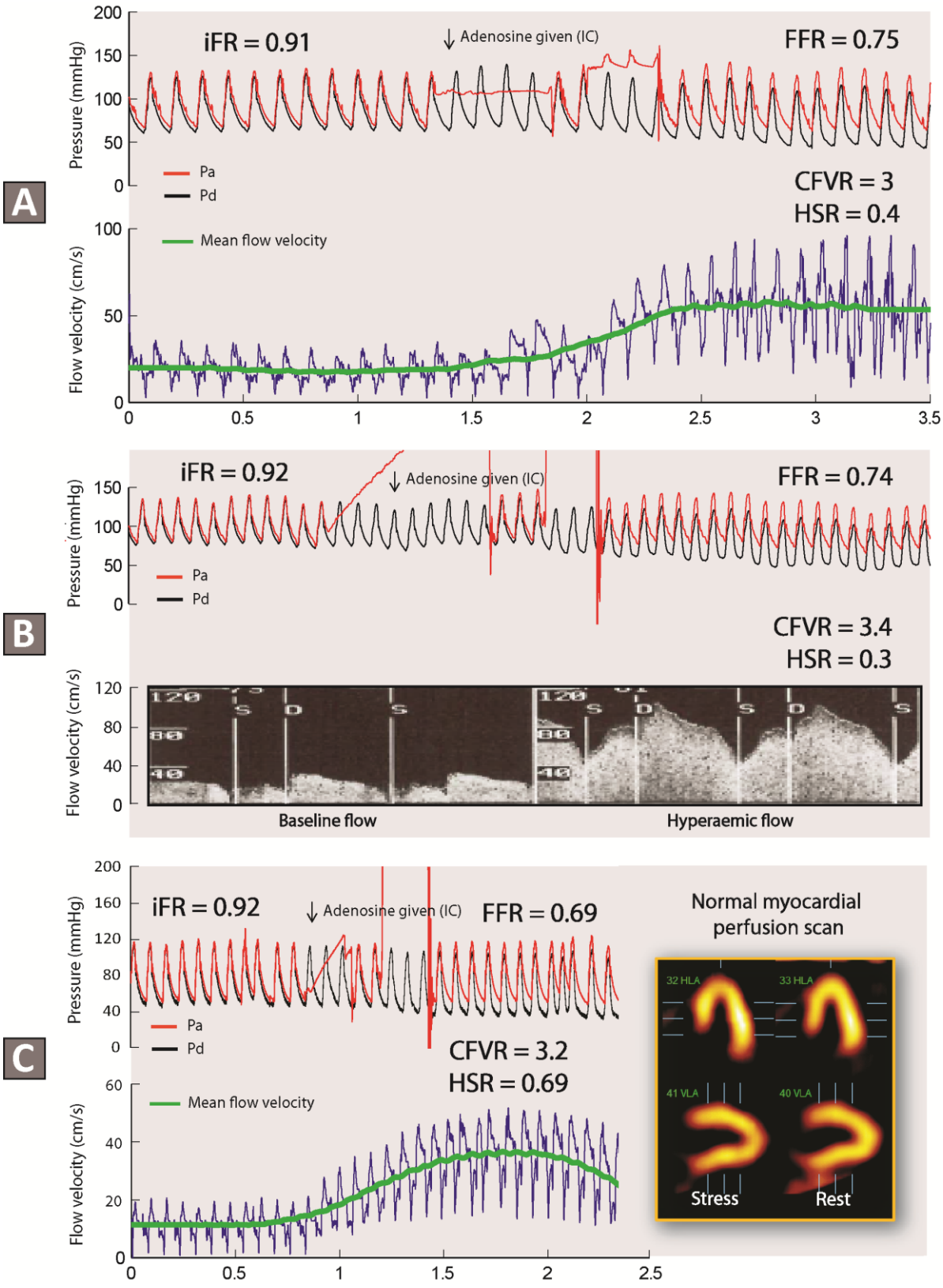



**Figure 6.6: Examples of cases in which low FFR values are generated by high magnitudes of hyperaemic flow**

In all three cases, baseline instantaneous wave-free ratio (iFR), coronary flow velocity reserve (CFVR) and hyperaemic stenosis resistance index (HSR, another flow-based index of disease severity) were normal, indicating a mild, not flow-limiting stenosis. In (C) a SPECT myocardial perfusion scan also confirms the absence of myocardial ischaemia. These lesions should not be considered causative of ischaemia, despite their low FFR value.

# 7 Synthesis

In this thesis I have extended the validation of iFR as an index of coronary stenosis severity, by further exploring its clinical relationship with FFR and by studying its underlying haemodynamics and its relation to coronary flow reserve.

## 7.1 iFR, FFR and stenosis classification

Expanding on the initial analysis presented on the ADVISE study, I have evaluated the classification agreement between iFR and FFR in a large clinical sample of 339 coronary stenoses. This analysis demonstrated that in patients with CAD undergoing invasive functional assessment of coronary lesions, iFR and FFR agreement in stenosis classification is high (80%), to a magnitude compared to the agreement between repeated FFR measurements (86%). In clinical practice therefore, iFR agrees with FFR 94% as well as FFR agrees with itself in repeated measurements. Also, in this initial study I demonstrated the large influence the distribution of disease severity of the underlying sample can have in the agreement between iFR and FFR and between repeated FFR measurements. This is extremely relevant because early validation studies and clinical trials are commonly performed in samples with a *case-control* fashion of disease distribution, and therefore yield higher magnitudes of classification agreement between methods. Clinical samples, on the other hand, are predominantly formed by intermediate values of FFR, straddling its cut-off, which results in lower magnitudes of agreement between tests (iFR and FFR) and between repeated measurements of the reference standard (FFR).

## 7.2 The concept of the V-test: a sample independent statistical measure of accuracy

In chapter 3 I sought to establish the classification agreement (accuracy) between iFR and FFR and compare it to the agreement between repeated FFR measurements in different samples. However, direct comparisons between accuracies derived from different studies are invalid because the distribution of underlying disease severity affects the relationship between tests. To circumvent this limitation I have developed a new sample-independent statistical approach to the calculation of diagnostic accuracy, the V-Test, presented in details in chapter 4. Using a simple conceptual model of disease (the diagnosis of hypercholesterolaemia) and data generated using statistical software I demonstrated how values of diagnostic accuracy are largely influenced by the distribution of underlying disease severity. Finally, I presented a simple solution: the V-test, a methodology which adjusts the values of accuracy according to the underlying distribution of values. Although the concept of the V-test was initially used to better understand the relationship between iFR and FFR, it can be applied to any direct comparison between two methods of clinical measurement, in which values of classification agreement (accuracy) are being evaluated.

## 7.3 Vasodilator-sparing potential of a hybrid iFR - FFR decision-making approach

FFR utilisation is supported by trials with clinical outcomes, but its low adoption is partly caused by its dependence on the induction of hyperaemia and the need for vasodilator administration. iFR is a novel vasodilator-free index which has close agreement with FFR but no trial evidence to support its use as a sole guide to clinical decisions. In chapter 5 I presented the idea of a hybrid decision-making strategy, in

which both iFR and FFR are used together in a common diagnostic pathway. This hybrid approach permits the benefits of both techniques to be immediately applied to patients: the safety and prognostic implications of a high agreement with FFR classification of lesions (95%) and a significant reduction (57%) in the need for vasodilator administration. In practice, it means that a 3 vessel physiological assessment can be performed with adenosine only being given to one interrogation. Whilst we wait for the results of clinical outcome trials which will evaluate the merits of iFR on its own, the hybrid iFR-FFR approach allows the benefits of physiological interrogation to be expanded to more patients with CAD.

### 7.4 iFR and its closer relationship with underlying coronary flow reserve

In the final study of this thesis, I have explored the relationship between pressure indices iFR and FFR with underlying coronary flow reserve (CFR). Several important physiological observations can be drawn from this study, relevant to the clinical utilisation of physiological indices. Firstly, when iFR and FFR disagree in the classification of stenosis, iFR has a closer relationship to underlying CFR. This is important because it provides indirect insights into the safety of iFR utilisation, as CFR provides the most robust prognostic discrimination on the risk of major cardiac events, including death, myocardial infarction and the need for urgent revascularisation. Secondly, a detailed analysis of phasic coronary flow supported the previous findings of CLARIFY: adenosine can only significantly increase coronary flow above baseline diastole (iFR diastolic window) in mild, FFR-negative stenoses. This finding challenges the need for adenosine administration during physiological interrogation, as baseline diastolic flow appears to provide sufficient hyperaemia. Finally, I demonstrated that large numerical disagreements between iFR and FFR

are driven by high magnitudes of hyperaemic flow and high CFR. Therefore, in the majority of cases in which iFR is very high and FFR very low, stenoses do not appear to be truly flow-limiting, which questions the gold standard status of FFR as a marker of myocardial ischaemia and flow limitation. This study provides further physiological justification on the need for outcome trials to evaluate the role of iFR as a sole guide to coronary revascularisation.

# 8 Conclusion

Across different samples of disease severity distribution, iFR demonstrates a close diagnostic relationship with FFR, with most disagreements in lesion classification occurring close to their cut-offs.

Large numerical disagreements between iFR and FFR are driven by high magnitudes of coronary flow and higher than average CFR. iFR, therefore, has a closer relationship with underlying coronary flow reserve, which provides insight into the safety of its future application as a sole guide to clinical decisions.

Until outcome trials evaluate the merits of iFR as an independent clinical tool, iFR and FFR can be used together in hybrid decision-making strategy, which could immediately spare a large proportion of patients from the need of vasodilator, whilst maintaining the safety of FFR classification of lesions.

### 8.1 Future directions

This thesis simply extended the initial validation work on the development of iFR. Therefore, there are still several unexplored areas from which further studies can develop upon. Broadly, this work was performed in patients with stable coronary disease without haemodynamic disturbances or significant valvular disease. An important and under explored area of research is the use of invasive physiology in conditions of haemodynamic fluctuations, such as acute coronary syndromes, cardiogenic shock and severe valvular disease. The role of pressure-only resting indices such as iFR and hyperaemic indices such as FFR will need to be investigated in such scenarios together with the benefits of measuring flow over pressure-only assessment.

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# 10 Publications arising from this thesis

## 10.1 Peer-reviewed papers

1. **Petraco R**, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA... 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 Jul 1. pii: CIRCINTERVENTIONS [Epub ahead of print]

2. **Petraco, R**., Escaned, J., Nijjer, S., Sen, S., Echavarria-Pinto, M., Francis, D. P., . . . Davies, J. E. (2014). Reply: Fractional flow reserve: A good or a gold standard?. *JACC: Cardiovascular Interventions*, *7*(2), 228-229.

3. Echavarría-Pinto, M., Gonzalo, N., Ibañez, B., **Petraco, R**., Jimenez-Quevedo, P., Sen, S., . . . Escaned, J. (2014). Low coronary microcirculatory resistance associated with profound hypotension during intravenous adenosine infusion: implications for the functional assessment of coronary stenoses.. *Circ Cardiovasc Interv*, *7*(1), 35-42.

4. **Petraco, R.**, Escaned, J., Sen, S., Nijjer, S., Francis, D. P., & Davies, J. E. (2013). How high can "accuracy" be for iFR (or IVUS, or SPECT or OCT...) if using fractional flow reserve as the gold standard? RESPONSE. *EUROINTERVENTION*, *9*(6), 770-772.

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9. **Petraco, R.**, Escaned, J., Francis, D. P., & Davies, J. E. (2013). Challenging the need for hyperaemia REPLY. *EUROINTERVENTION*, *9*(1), 167-168.

10. **Petraco, R.**, Sen, S., Nijjer, S., Escaned, J., & Davies, J. E. (2013). Baseline coronary pressures, instant wave-free ratio (iFR) and Pd/Pa: making the most of available information REPLY. *EUROINTERVENTION*, *9*(1), 170-172.

11. **Petraco, R.**, Sen, S., Nijjer, S., & Davies, J. E. (2013). How would I treat?. *EuroIntervention*, *9*(1), 160-161.

12. Sen, S., Nijjer, S., **Petraco, R.**, Malik, I. S., Francis, D. P., & Davies, J. (2013). Instantaneous wave-free ratio: Numerically different, but diagnostically superior to FFR? Is lower always better?. *Journal of the American College of Cardiology*, *62*(6), 566.

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21. **Petraco, R.**, Escaned, J., Sen, S., Nijjer, S., Asrress, K. N., Echavania-Pinto, M., . . . Davies, J. E. (2013). Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. *EUROINTERVENTION*, *9*(1), 91-101.

22. Sen, S., Escaned, J., Malik, I. S., Mikhail, G. W., Foale, R. A., Mila, R., **Petraco R.**, . . . Davies, J. E. (2012). 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. *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY*, *59*(15), 1392-1402.

23. **Petraco, R.**, & Davies, J. E. (2011). Flow limitation in coronary artery disease.. *Am J Cardiol*, *108*(11), 1687.

## 10.2 Abstracts and oral presentations

1. **Petraco, R.**, Sen, S., Nijjer, S. S., Escaned, J., Francis, D. P., & Davies, J. E. (2013). FFR-GUIDED CORONARY REVASCULARISATION: IMPLICATIONS OF ITS BIOLOGICAL VARIABILITY ON CLINICAL DECISIONS. In *HEART* Vol. 99 (pp. 2 pages).
2. Sen, S., Nijjer, S. S., **Petraco, R.**, Foale, R. A., Malik, I. S., Mikhail, G. W., . . . Davies, J. E. (2013). FRACTIONAL FLOW RESERVE AND THE INSTANT WAVE-FREE RATIO HAVE EQUIVALENT AGREEMENT WITH FLOW BASED INDICES ACROSS THE ENTIRE SPECTRUM OF STENOSIS SEVERITY RESULTS OF THE CLARIFY STUDY RESULTS OF CLARIFY. In *HEART* Vol. 99 (pp. A35).
3. Sen, S., Nijjer, S. S., **Petraco, R.**, Foale, R. A., Malik, I. S., Mikhail, G. W., . . . Davies, J. E. (2013). THE TRANS-STENOTIC PRESSURE GRADIENT DURING THE DIASTOLIC WAVE-FREE PERIOD IS PROPORTIONAL TO FLOW: THE PHYSIOLOGICAL BASIS OF THE INSTANT-WAVE-FREE RATIO. In *HEART* Vol. 99 (pp. 1 page).
4. Nijjer, S. S., Eshtehardi, P., Corban, M. T., Mekonnen, G., Gogas, B., McDaniel, M. C., **Petraco, R.**, Samady, H. (2013). RELIABILITY OF RESTING CORONARY HAEMODYNAMICS WHEN REPEATED AFTER 6 MONTHS. In *HEART* Vol. 99 (pp. 1 page).
5. Nijjer, S. S. S., Sen, S., **Petraco, R.**, Cuculi, F., Broyd, C., Foale, R. A., . . . Davies, J. E. (2013). INSTANTANEOUS WAVE-FREE RATIO (IFR) CAN DETECT IMPROVEMENT IN CORONARY STENOSIS SEVERITY AFTER PERCUTANEOUS INTERVENTION. In *HEART* Vol. 99 (pp. A37).
6. Kousera, C. A., Nijjer, S. S., Torii, R., **Petraco, R.**, Sen, S., Foin, N., . . . Davies, J. E. (2013). Patient-specific Coronary Stenoses Can Be Modeled Using a Combination of Optical Coherence Tomography and Flow Velocities to Accurately Predict Hyperaemic Pressure Gradients. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 62 (pp. B186).
7. **Petraco, R**., Janssens, L., van Belle, E., Hellig, F., Mates, M., Haine, S., . . . Davies, J. E. (2013). Real-time utilisation of instant wave-free ratio (iFR) is feasible when performed by clinicians: results of the ADVISE in-practice, an international, multi-centre evaluation of iFR in clinical practice. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 62 (pp. B189).
8. **Petraco, R.**, van de Hoef, T. P., Nijjer, S. S., Sen, S., Meuwissen, M., Foale, R. A., . . . Davies, J. E. (2013). Identification of stenoses with high underlying coronary flow reserve from pressure-only measurements using baseline instant wave-free ratio (iFR) and hyperaemic fractional flow reserve (FFR). In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 62 (pp. B190).
9. Nijjer, S. S., van de Hoef, T. P., **Petraco, R.**, Sen, S., Meuwissen, M., Foale, R. A., . . . Davies, J. E. (2013). Mean Hyperemic Flow is Not Increased Following Adenosine Administration in Physiologically Significant Lesions. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 62 (pp. B188).

10. van de Hoef, T. P., **Petraco, R.**, van Lavieren, M. A., Nijjer, S. S., Sen, S., Henriques, J. P., . . . Piek, J. (2013). Diagnostic accuracy of basal stenosis resistance index (BSR) is higher than that of instantaneous wave-free ratio (iFR): validation of basal stenosis resistance index in an independent cohort of simultaneous pressure and flow measurements. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 62 (pp. B193).

11. Kousera, C. A., Nijjer, S. S., Torii, R., **Petraco, R.**, Sen, S., Foin, N., . . . Davies, J. E. (2013). Optical Coherence Tomography can be combined with angiography to create highly accurate patient-specific models of human coronary anatomy in a rapid automated manner. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 62 (pp. B195).

12. Tarkin, J., Nijjer, S., Sen, S., **Petraco, R.**, Mayet, J., Echavarria Pinto, M., . . . Davies, J. (2013). The haemodynamic response to intravenous adenosine and its impact on fractional flow reserve: results of the AFFECTS (Adenosine For the Functional assEssment of Coronary sTenosis Severity) study. In *EUROPEAN HEART JOURNAL* Vol. 34 (pp. 514).

13. **Petraco, R.**, Park, J. J., Sen, S., Nijjer, S., Malik, I., Pinto, M. E., . . . Davies, J. (2013). Hybrid IFR-FFR Decision-Making Strategy: Implications for Enhancing Universal Adoption of Physiology-Guided Coronary Revascularization.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 54B).

14. **Petraco, R.**, Sen, S., Nijjer, S., Echavarria-Pinto, M., Escaned, J., Francis, D., . . . Davies, J. (2013). Implications of The Biological Variability of Fractional Flow Reserve on Coronary Revascularization Decisions.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 51B).

15. Sen, S., **Petraco, R.**, Nijjer, S., Malik, I., Mikhail, G., Foale, R., . . . Davies, J. (2013). The Instant Wave-free Ratio, a Vasodilator Free Index; Provides Lower Microvascular Resistance Than That During Adenosine Mediated Fractional Flow Reserve in a Significant Proportion of Patients.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 101B).

16. Nijjer, S. S., Sen, S., **Petraco, R.**, Cuculi, F., Broyd, C., Foin, N., . . . Davies, J. E. (2013). Instantaneous Wave-free Ratio Can Assess Improvement in Coronary Haemodynamics After Percutaneous Intervention.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 100B).

17. **Petraco, R.**, Van de Hoef, T. P., Nijjer, S., Sen, S., Meuwissen, M., Escaned, J., . . . Piek, J. (2013). Safety and Prognostic Value of Baseline Hemodynamic Indices of Coronary Disease Severity: Insights from an Estimated Agreement of Stenosis Classification with Fractional Flow Reserve in The DEFER and FAME Studies.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 53B).

18. Sen, S., **Petraco, R.**, Nijjer, S., Malik, I., Foale, R., Mikhail, G., . . . Davies, J. (2013). The Trans-stenotic Pressure Gradient During the Diastolic Wave-free Period Is Proportional to Flow: the Physiological Basis of the Instant-wave-free Ratio.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 100B).

19. Nijjer, S. S., Eshtehardi, P., Corban, M. T., Mekonnen, G., Gogas, B., McDaniel, M. C., **Petraco R.**, . . . Samady, H. (2013). Resting Coronary Haemodynamics are Stable and Reproducible When Retested After 6 Months in Patients with Non-obstructive Coronary Artery Disease.. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 101B).

20. Sen, S., Nijjer, S., **Petraco, R.**, Malik, I., Foale, R., Mikhail, G., . . . Davies, J. (2013). The Effect of Adenosine on Coronary Microvascular Resistance Is More Consistent During the Diastolic Wave-free Period: Should We Continue to Use the Complete Cardiac Cycle for Stenosis Assessment?. In *AMERICAN JOURNAL OF CARDIOLOGY* Vol. 111 (pp. 100B-101B).

21. Sen, S., Asrress, K., **Petraco, R.**, Nijjer, S., Broyd, C., Foin, N., . . . Davies, J. (2012). Does Adenosine Administration Improve Diagnostic Classification Of The Instantaneous Wave-Free Ratio (iFR)?. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 60 (pp. B69).

22. Foin, N., Sen, S., **Petraco, R.**, Torii, R., Nijjer, S., Xu, Y. X., . . . Davies, J. (2012). Investigation of Fractional Flow Reserve Correlation with Direct Anatomical Parameters Using a Percutaneous Model of Coronary Artery Stenosis. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 60 (pp. B67). Miami, FL: ELSEVIER SCIENCE INC.

23. Sen, S., **Petraco, R.**, Nijjer, S., Foin, N., Broyd, C., Foale, R., . . . Davies, J. (2012). The Diastolic Wave-Free Period Is The Most Suitable Period In The Cardiac Cycle For The Assessment Of A Coronary Stenosis: Implications For The Accurate Calculation Of The Instantaneous Wave-Free Ratio (iFR). In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 60 (pp. B68).

24. Sen, S., Nijjer, S., **Petraco, R.**, Asrress, K., Broyd, C., Foin, N., . . . Davies, J. (2012). The Instantaneous Wave-Free Ratio (iFR) and Fractional Flow Reserve (FFR) Have Equivalent Diagnostic Categorisation When Compared To Flow Based Indices. In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 60 (pp. B68-B69).

25. Sen, S., Nijjer, S., **Petraco, R.**, Broyd, C., Foin, N., Malik, I., . . . Davies, J. (2012). STABILITY OF THE DIASTOLIC WAVE-FREE PERIOD AFTER PHARAMOCOLOGICAL PROVOCATION, AND DURING HAEMODYNAMIC PERTURBATIONS: IMPLICATIONS FOR THE CLINICAL APPLICABILITY OF THE INSTANTANEOUS WAVE-FREE RATIO (IFR). In *JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY* Vol. 59 (pp. E1437). Chicago, IL: ELSEVIER SCIENCE INC.

# 11 Awards

Imperial College Charity Research Grant, Sep 2010

Clinical Research Training Fellowship, British Heart Foundation, Sep 2011

Late Break Clinical Trial, EuroPCR meeting 2012

> **Petraco R**, Escaned, J., Sen, S., Nijjer, S., Asrress, K. N., Echavania-Pinto, M., . . . Davies JE. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry.

Eurointervention journal most cited papers in 2013

> **Petraco, R.**, Escaned, J., Sen, S., Nijjer, S., Asrress, K. N., Echavania-Pinto, M., . . . Davies, J. E. (2013). Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. *EUROINTERVENTION*, *9*(1), 91-101.
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> **Petraco, R.**, Park, J. J., Sen, S., Nijjer, S. S., Malik, I. S., Echavarria-Pinto, M., . . . Davies, J. E. (2013). Hybrid EFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. *EUROINTERVENTION*, *8*(10), 1157-1165.

Best abstract, TCTAP meeting, South Korea, 2013

> **Petraco, R.**, Park, J. J., Sen, S., Nijjer, S., Malik, I., Pinto, M. E., . . . Davies, J. (2013). Hybrid IFR-FFR Decision-Making Strategy: Implications for Enhancing Universal Adoption of Physiology-Guided Coronary Revascularization.
>
> **Petraco, R.**, Sen, S., Nijjer, S., Echavarria-Pinto, M., Escaned, J., Francis, D., . . . Davies, J. (2013). Implications of The Biological Variability of Fractional Flow Reserve on Coronary Revascularization Decisions.