How Will Virtual (Computed) Fractional Flow Reserve (FFR) Impact the Management of Patients with Chronic Coronary Syndromes? The VIRTU-4 CCS Trial

Dr. Mina S A Ghobrial

MBChB (Hons), BMedSci, MRCP (Lon)

Mathematical Modelling in Medicine

Department of Infection, Immunity and Cardiovascular Disease

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Abstract

Background

Fractional flow reserve is the 'gold-standard' method for the measurement of coronary artery stenosis physiological significance. FFR-guided revascularisation has a positive impact on mortality and morbidity. However, FFR is under-used owing to its invasive nature and because of patient and physician factors. Computational fluid dynamics modelling has been validated as method of calculating a virtual (v)FFR without the need for a pressure wire, hyperaemic agents, additional contrast or radiation.

Hypothesis

Disclosure of vFFR in patients with stable angina undergoing elective invasive coronary angiography will result in significant changes in patients' management strategies.

Methods

VIRTUheart™ was applied to patients with stable angina at four hospitals in South Yorkshire. Patients' management plans were classified as optimal medical therapy (OMT), percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG) or more information, based upon the angiogram and again after vFFR disclosure. A management strategy change of 10% or more was considered significant. Changes in cardiologists' confidence levels in their original strategies were also recorded before and after vFFR disclosure.

Results

223 patients were screened and 112 patients were recruited. Median vFFR was 0.83 (IQR 0.15) and calculation time was 15 minutes (IQR 8). vFFR disclosures lead to an observed change in 22.3% (95% CI: ± 8.12%, $p < 0.013$) of patients' management strategies driven by a 39.5% relative increase in patients being reassigned to PCI and or invasive FFR measurement. The mean confidence levels in the original strategy before and after vFFR disclosure were 8.90/10 (SD 1.28) and 9.22/10 (SD 1.39) respectively ($p = 0.026$).

Conclusion

The addition of vFFR to the coronary angiogram has the potential to significantly change management strategies in up to 22.3% of patients providing a detailed and specific 'all-in-one' anatomical and physiological assessment of coronary disease. However vFFR health related outcomes and cost-effectiveness have yet to be determined.

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List of Abbreviations

ACS	Acute coronary syndrome
AUC	Area under the curve
ANOVA	Analysis of variance
BA	Bland-Altman
BMS	Bare metal stent
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CASS	Coronary artery surgery study
CI	Confidence interval
CCS	Chronic coronary syndrome
CE-MARC	Clinical evaluation of magnetic resonance imaging in coronary heart disease
CFD	Computational fluid dynamics
CFR	Coronary flow reserve
CMR	Cardiac magnetic imaging
COMPARE ACUTE	Comparison between FFR guided revascularization versus conventional strategy in acute STEMI patients with multi-vessel disease trial
COURAGE	A randomized multicentre trial to evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total coronary occlusions
CTCA	Computed tomography coronary angiography
CTFFR	Computer tomography derived fractional flow reserve
CTO	Chronic total occlusion
DISCOVER-FLOW	Diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve trial
DEFACTO	Determination of fractional flow reserve by anatomic computed tomographic angiography trial
DEFER	Percutaneous coronary intervention of functionally non-significant stenosis: 5-year follow-up of the DEFER trial
DEFINE-FLAIR	Functional lesion assessment of intermediate stenosis to guide revascularisation trial

DES	Drug eluting stent
DGH	District General Hospital
DHP	Dihydropridine receptor antagonist
DSE	Dobutamine stress echocardiography
ESC	European Society of Cardiology
ETT	Exercise tolerance test
FAME	Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease trial
FAME-2	Fractional flow reserve guided percutaneous coronary intervention plus optimal medical treatment versus optimal medical treatment trial
FAMOUS-NSTEMI	Fractional flow reserve versus angiographically guided management to optimise outcomes in unstable coronary syndromes trial
FFR	Fractional flow reserve
FSI	Fluid structure interaction
ICA	Invasive coronary angiography
ICC	Intra-class correlation coefficient
iFR	Instantaneous wave-free ratio
iFR-SWEDEHEART	Instantaneous wave-free ratio versus fractional flow reserve in patients with stable angina pectoris or acute coronary syndrome. A multicentre, prospective, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry
IM	Intermediate artery
IMR	Index of microcirculatory resistance
INOCA	Ischaemia with no obstructive coronary disease
LAD	Left anterior descending artery
LCx	Left circumflex artery
LMS	Left main stem
MACE	Major adverse cardiovascular events
MDT	Multidisciplinary team
MI	Myocardial infarction
MMM	Mathematical modelling in medicine group

MPS	Myocardial perfusion study
NICE	National Institute for Health and Care Excellence
NPV	Negative predicted value
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
NSTEMI	Non-ST-segment myocardial infarction
NYHA	New York Heart Association classification
NXT	Analysis of coronary blood flow using CT angiography: Next steps trial
ORBITA	Objective randomised blinded investigation with optimal medical therapy of angioplasty in stable angina trial
OMB	Obtuse marginal branch
OMT	Optimal medical therapy
PET	Positron emission tomography
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
PLATFORM	Prospective longitudinal trial of FFR_{CT}: Outcomes and resource impacts trial
POBA	Plain old balloon angioplasty
POST-IT	Portuguese study on the evaluation of FFR guided treatment of coronary disease trial
PPCI	Primary PCI
PPV	Positive predicted value
PROMISE	Prospective multicenter imaging study for evaluation of chest pain trial
PTP	Pre-test probability
QCA	Quantitative coronary angiography
QFR	Quantitative flow ratio
RCA	Right coronary artery
RIPCORD	Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain trial
SCOT-HEART	Scottish computer tomography of the heart trial
SPECT	Single-photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction

SYNTAX	Taxus drug-eluting stent versus coronary artery bypass surgery from the treatment of narrowed arteries trial
TIMI	Thrombolysis in myocardial infarction
vFAI	Virtual functional assessment index
vFFR	Virtual fractional flow reserve

Preface

Contents

Chapter 1: Introduction

1.1 Cardiovascular Disease

1.1.1 Epidemiology and Burden of Disease

Cardiovascular disease is the leading cause of death worldwide. [1] Thirty percent of global mortality is attributable to cardiovascular disease. Before the 1900s, death from infectious disease and malnutrition predominated but, as a result of improved public healthcare and nutrition, life expectancy improved. Increased longevity, the impact of smoking, high-fat content diets and risk factors for chronic disease have resulted in cardiovascular disease and cancer as the leading causes of mortality worldwide. [2]

However in the UK, after 2012, cardiovascular disease was overtaken by cancer as the leading cause of mortality (28% versus 29% respectively). This was true in men but not in women. [3] CHD is the largest component of cardiovascular disease comprising 46% of cardiovascular disease deaths. [3] Mortality from coronary heart disease in the UK in 2021 was 63, 000 deaths, amounting to one in eight of all male and one in thirteen of all female deaths. [3]

In the UK, there is seasonal and geographic variation in cardiovascular mortality, with a tendency towards excess mortality in winter and in Scotland and the North West of the country. [4] Data from the CPRD GOLD database estimates that the almost 2.3 million people are living with coronary heart disease with the lion's share of the prevalence amongst people aged 65 and over. [5] Coronary heart disease is responsible for almost half a million admissions to hospital across the UK, with men twice as likely to be admitted than women, accounting for 3.5% and 1.5% of all inpatient episodes respectively. [3]

Over 100,000 percutaneous coronary interventions are carried out annually in the UK, which is double the number two decades ago. [5] The numbers of coronary artery bypass graft operations have fallen likely reflecting the

advancements in PCI.[5] Data from NHS England reveal that more than £6.8 billion is spent on treating cardiovascular disease. The greatest proportion of that sum is spent on emergency admissions in secondary care and medication prescribing in primary care settings. [5] Coronary heart disease remains a significant burden in the UK with regards to health and economy, despite declining incidence and mortality rates. This. coupled with increased life expectancy, means that there is a growing prevalence of coronary heart disease and increased costs through prescription of secondary prevention medication. [3]

1.1.2 Risk Factors

The concept of cardiovascular risk factors emerged after the initial findings of the Framingham Heart Study in the 1960s. [6,7] Conventional risk factors include smoking, hypertension, hyperlipidaemia, insulin resistance and diabetes, obesity, physical inactivity and family history. However not all coronary events occur in patients with multiple traditional risk factors, in such individuals abnormalities in inflammation, haemostasis and thrombosis constitute prominent risk factors. [7] Reduction in modifiable risk factors is associated with reduction in mortality and morbidity from cardiovascular disease. [8] Therefore identification and modification of risk factors where possible is a sensible and feasible goal in preventing the mortality and morbidity caused through cardiovascular disease. [9]

1.1.3 Pathogenesis of Coronary Artery Disease

Coronary artery disease is a consequence of the build-up of atheroma and subsequent obstruction of coronary arteries. Atherosclerosis is characterized by a chronic proliferative inflammatory response of various dysfunctional cell types. [10] Morphologically, atheromatous deposits are visible in the first two decades of life as fatty streaks within the intimal layer. [10] Damaged and dysfunctional endothelial cells bind circulating oxidized lipoproteins triggering the release of a cascade of pro-inflammatory chemokines and cytokines. [10] Inflammatory cells attracted to the inflammatory milieu are transformed into

foam cells through phagocytosis of the oxidized lipoproteins. This process is propagated in a positive feedback manner leading to plaque formation mediated through increase in the size of lipid deposits and abnormal proliferation and function of smooth muscle cells and fibroblasts.[10] Initially plaque growth is in an outward direction (positive remodelling); into the tunica media, but once 40% of the cross-sectional area of the vessel is reached, the direction of growth expands into the lumen (negative remodelling). [10] As the atherosclerotic plaque matures, its core becomes a highly thrombogenic necrotic lipid-rich pool that is surrounded by a thin and friable fibrous cap as a result of dysregulation of smooth muscle cell apoptosis and over activity of collagenases and extracellular matrix degradation enzymes. [11]

Typically, by the fourth and fifth decades of life, atherosclerotic plaques may reach a size where by they cause obstruction of coronary blood flow resulting in symptoms of myocardial ischaemia. This occurs when the plaque results a luminal cross-sectional area reduction of 75% or a luminal diameter reduction of 50%. [12] Atherosclerotic plaques demonstrate a predilection for bifurcations and proximal portions of the vascular tree. [13] This implies that a haemodynamic factor may contribute to the pathogenesis of plaques. One possible explanation suggests that low shear-stress caused by turbulent blood flow, such as occurs at bifurcations, leads to reduced endothelial nitric oxide production. Nitric oxide is produced by healthy endothelial cells and plays a protective role against the formation of atherosclerotic plaques. [14]

Occlusive coronary disease may arise through progression of the plaque or more commonly through acute rupture or fissuring of the fibrous cap, exposing the highly thrombogenic lipid rich core, triggering platelet activation and aggregation as well as the clotting cascade. [15] Arterial thrombus is composed of an initial white thrombus comprised of the platelet plug and then secondly a red thrombus made up of fibrin, red blood cells and clotting factors. [15] Thrombus formation rapidly propagates along the vessel wall to occlude the coronary artery resulting in myocardial ischaemia and subsequent infarction. This is the principal mechanism of acute coronary syndromes. [15]

1.1.4 Coronary Anatomy

The coronary arteries are the first branches of the aorta. The origins of the left and right coronary arteries arise from the left and right sinus of Valsalva respectively. The course of the right coronary artery follows the right atrioventricular groove and the acute margin of the heart giving off the sino-atrial, conus and a number of acute marginal and right ventricular branches along its course. Towards the crux of the heart, at the point where interventricular and atrioventricular grooves intersect, the right coronary artery branches into the posterior interventricular artery (also known as the posterior descending artery), posterolateral left ventricular branches and the atrioventricular node artery. Septal perforators from the posterior descending artery travel within the interventricular septum to anastomose with those from the anterior interventricular artery (clinically known as the left anterior descending artery).

The left coronary artery courses behind the pulmonary artery as the left main stem where it bifurcates into the left anterior descending and the left circumflex arteries. Rarely, the left main stem is absent and the circumflex and left anterior descending arteries have separate origins from the aorta. In a proportion of individuals the left main stem trifurcates giving rise to the intermediate artery. The first branches of the left anterior descending artery are the septal perforators followed by a number of diagonal braches which course over the anterolateral ventricular surface. The left anterior descending artery terminates at the apex of the heart. The course of the left circumflex artery mirrors that of the right coronary artery. The left circumflex artery follows the left atrioventricular groove and the left margin of the heart branching into obtuse marginal branches that supply the left ventricular free wall. [16]

The dominance of the coronary circulation is defined by which principal coronary artery gives rise to the posterior descending artery. In 85% of individuals the posterior descending artery is supplied by the right coronary artery. A left dominant circulation is one in which the left circumflex gives rise

to the posterior descending artery in approximately 15% of individuals. In a minority of there is a co-dominant system. [16,17]

It is clinically important to divide the coronary arteries into segments to allow for universally standardized localization and reporting of atherosclerotic lesions. Many anatomical and functional classifications exist. One such classification in wide use is the American Heart Association classification that divides the coronary tree into 17 segments. [18]

Dedicated lesion classification and myocardial jeopardy scores exist to predict the difficulty of successful revascularisation and the risk of adverse clinical outcomes following intervention based on lesion morphology and the volume of myocardium at risk. The most contemporary of these, the SYNTAX Score grades the complexity and the pathophysiological burden of coronary artery stenoses. [19]

1.1.5 Coronary Physiology

Basal myocardial oxygen extraction from circulating blood is 75% compared to the whole body average of 25%. Increases in myocardial oxygen demand are primarily met by increased [20] coronary artery blood flow, mediated through coronary blood flow auto-regulation. [20] The main determinants of myocardial oxygen consumption are heart rate, ventricular contractility and systemic systolic arterial blood pressure. [20]

In ventricular systole, coronary blood flow is impeded and the tissue perfusion gradient is away from the subendocardium towards the subepicardial tissues, reflecting the transmitted intraventricular pressure. The relationship is reversed in ventricular diastole. It is because of this pressure dependent relationship that subendocardial tissues are the most vulnerable to ischaemia and infarction. [20]

Coronary autoregulation is the process whereby a constant coronary blood flow is achieved despite fluctuations in aortic or systemic pressure through

modulation of coronary artery vascular tone. The physiological mechanisms governing coronary autoregulation are complex constituting an interplay between circulating systemic vasodilatory mediators, paracrine substrates, systemic neurohumoral signals and local physical factors causing myogenic and flow responses to sheer wall stress. [20]

Coronary reserve is the ability of the coronary circulation to increase blood flow to meet myocardial oxygen demand. In health, the coronary blood flow may increase five-fold from basal levels. Tachycardia, increased myocardial contractility and increased preload along with factors that increase basal oxygen demand such as hypoxia and anaemia result in reduction of coronary reserve. [20]

Stenoses in the epicardial arteries create a fixed resistance to coronary blood flow thereby limiting maximal myocardial perfusion and maximally dilated flow. One of the most important determinants of resistance at any coronary blood flow rate is the cross-sectional area of a stenosis. This is because resistance is inversely proportional to the square of the cross-sectional area. Therefore small changes in area lead to significant disruptions of the pressure-flow relationships. [21,22] Coronary autoregulation maintains a constant coronary blood flow despite stenosis severity at basal conditions through maximal vasodilation, therefore in times of increased myocardial oxygen demand coronary reserve is depleted, triggering the ischaemic cascade. [22,23]

Lesions causing less than 50% luminal diameter reduction are unlikely to be clinically or haemodynamically significant. [22] Lesions that result in 50% to 70% reduction in luminal diameter are borderline with up to 35% of lesions in this category demonstrating blunted hyperaemic responses that are apparent in non-invasive testing or fractional flow reserve testing. [24] Almost all lesions causing 70% to 99% diameter reduction are clinically and haemodynamically significant demonstrating significant disruptions in the hyperaemic response. [25]

1.2 Clinical Consequences of Coronary Artery Disease

1.2.1 Acute Coronary Syndromes

Acute coronary syndromes consist of two distinct clinical entities differentiated by the appearance of the ECG.

1.2.1.1 ST Segment Elevation Myocardial Infarction

Persistent ST-segment elevation measured at the J-point in at least two contiguous leads ≥ 2.5mm in men < 40 years of age or ≥ 2mm in men ≥ 40, or ≥ 1.5mm in women in leads V_{2-3} and/or ≥ 1mm in the other leads on the ECG with acute chest pain of duration greater than 20 minutes is classified as ST-segment elevation myocardial infarction. [26] STEMI usually reflects acute total coronary artery occlusion and requires immediate revascularisation through primary PCI or fibrinolysis if timely PPCI cannot be achieved. [27]

1.2.1.2 Non-ST Segment Elevation Acute Coronary Syndromes

Acute chest pain associated with ST-depression, T-wave flattening or inversion or absence of any significant ECG changes with biochemical evidence of myocardial necrosis is termed NSTEMI. Acute myocardial ischaemia without evidence of myocardial necrosis is defined as unstable angina. The clinical spectrum of NTEACS is broad ranging from asymptomatic individuals to those with refractory angina, electrical or haemodynamic instability, heart failure or cardiac arrest. The amount of myocardium at jeopardy, the presence of malignant ventricular arrhythmias and or heart failure dictate the urgency of coronary angiography and revascularistion, if appropriate. [28]

1.2.2 Chronic Coronary Syndrome

Transition from stable coronary artery disease to unstable or acute coronary syndromes is a continuum with no clear boundary. [29] Stable coronary artery disease results in episodes of reversible myocardial demand-supply mismatch. Triggers are mediated through ischaemia or hypoxia, typically induced by exercise, emotion or other stressors. There are various

mechanisms that underpin the pathophysiology of supply-demand mismatch. These include plaque-related obstruction of epicardial arteries, focal or diffuse vasospasm of normal or diseased arteries, microvascular dysfunction and left ventricular dysfunction. [30]

Chronic coronary syndrome is an umbrella term encompassing a diverse constellation of patients and presentations over various timescales. Common examples include those patients with suspected CAD and 'stable' anginal symptoms, patients with new onset heart failure and suspected CAD as well as asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularisation. Patients with angina and suspected vasospastic or microvascular disease and asymptomatic subjects in whom CAD is incidentally detected are also classified under CCS. [29]

1.2.2.1 Assessment, Diagnosis and Pre-Test Probability

Typical angina is defined as a central retrosternal heaviness or discomfort, which may radiate to the inter-scapular region, to either arm, neck, jaw or teeth, lasting between 1 to 10 minutes that is triggered by exertion and is relieved by rest or nitrates. Typical features may be absent in diabetics and the elderly where breathlessness and autonomic symptoms are more prevalent. [31] The Canadian Cardiovascular Society classification [32] is a four-stage functional grading system to determine the maximal threshold for stable angina. [30]

Decision-making in patients with suspected stable coronary artery disease begins with determination of a patient's pre-test-probability of underlying coronary artery disease and selecting an appropriate investigation. Once the diagnosis has been made, risk stratification for subsequent events and optimal therapy is instituted.

The ability of a diagnostic test to accurately determine the presence of a condition is influenced by the condition's prevalence. When the likelihood of a condition is high, the negative predictive value is low; meaning a large proportion of patients need to be tested to identify a small number of patients without the disease. However when the likelihood is low, a negative test result

can confidently rule out the disease but at the expense of an increased false-positive result rate. Therefore patients at the extremes of likelihood of underlying coronary artery disease, can either be dismissed from diagnostic testing or referred for invasive coronary angiography, assuming that the patient has or does not have obstructive CAD based on clinical evaluation alone. [29]

The pre-test probability of having coronary artery disease is a function of the condition's prevalence and a patient's individual characteristics. Diamond and Forrester [33] proposed using age, sex and nature of symptoms to determine pre-test probability of coronary artery disease. However contemporary data and insights from SCOT-HEART [34] and PROMISE [35] trials suggest that the prevalence of coronary artery disease is lower in reality with a trend for over-estimation of pre-test probability. This in turn drives a low-diagnostic yield for invasive and non-invasive testing. [36] The European Society of Cardiology suggests a non-invasive investigation in those patients with a PTP of >15%. Invasive coronary angiography is reserved for those patients either who have a high burden of ischaemia following the results of their non-invasive investigations or those patients who have a high pre-test probability with significant risk factors, refractory angina and typical angina at low work-loads. [29]

1.2.2.2 Non-invasive Anatomical Testing

1.2.2.2.1 CT Coronary Angiography

The coronary lumen and wall can be visualized with intravenous contrast performed via a coronary CT angiogram. The strength of CTCA lies in its high negative predictive value. Its high accuracy for the detection of obstructive coronary artery disease in low-to-intermediate likelihood patients makes it an ideal test to guide subsequent management [37-39]. CTCA has been shown to halve ischaemic events over a five-year follow-up period [34] and to improve the diagnostic yield of coronary angiography. [40] This is pertinent as up to two-thirds of diagnostic coronary angiograms reveal non-obstructive coronary artery disease. [39] This creates an economic burden and exposes patients to

risks of complications from invasive coronary angiography. [39-41]

Current NICE guidance suggests that CTCA should be considered as the primary non-invasive test in patients with suspected coronary artery disease with typical, atypical or non-cardiac chest pain and ECG changes. [42] This contrasts with the ESC guidance that advocates either a non-invasive test of ischaemia or CTCA to diagnose coronary artery disease. However the ESC recommend taking into account the likelihood of coronary artery disease and the patient factors that influence the performance of the test to guide selection of the initial investigation. [29] Furthermore the PROMISE trial, which randomised 10,003 low to intermediate risk patients with suspected coronary artery disease to either CTCA or non-invasive ischaemia testing demonstrated that there was no difference in major adverse cardiovascular events between an initial anatomical strategy compared to a functional approach. [43]

CTCA is not without its limitations. Several patient factors limit good image acquisition and interpretation. These factors include obesity, irregular heart rate, and inability to follow breath-hold commands or to achieve a heart rate of less than sixty beats per minute. The diagnostic accuracy of CTCA was found to be lower in patients over the age of 75 and in patients with extensive vascular calcification. The availability of high-spec CT scanners may be an important limitation as the use of 64 row-detector-CT scanners or less was associated with a reduction in specificity and sensitivity of the test. Hasse et al. advise caution when performing CTCA in patients with high likelihood of coronary artery disease (pre-test probability >67%), as the negative predictive value of CTCA falls below 85%, increasing the rate of false-negative results. [41] Despite CTCA being a good tool to rule-out haemodynamically significant coronary artery disease, it performed poorly for the identification of coronary lesions that cause ischemia, with 60% specificity and 64% positive predicted value. [44]

1.2.2.3 Non-invasive Myocardial Ischaemia Testing

Functional non-invasive tests make a diagnosis of obstructive coronary disease based upon detection of myocardial ischaemia resulting in detectable ECG changes, regional wall motion abnormalities and/or myocardial perfusion defects through either pharmacological or exercise stress. [29]

1.2.2.3.1 Exercise ECG

Exercise ECG is not recommended to diagnose stable coronary artery disease in patients without known coronary artery disease. [42] Exercise ECG is inferior to diagnostic imaging tests, with limited power to rule-in or rule-out obstructive CAD. [37] It is not suitable for patients with ECG changes that prevent interpretation of the ST-segment, or patients unable to exercise. Rather exercise ECG should be used as a supplementary investigation to help assess exercise tolerance, arrhythmias, blood pressure response to exercise and to risk stratify patients. Recent data clearly demonstrates that the addition of a non-invasive anatomical [34,45] or functional [46,35] test to standard care is superior to exercise ECG alone in guiding further management, prevention and reduction of MI.

1.2.2.3.2 Stress Echocardiography

Exercise or pharmacological stress with intravenous dobutamine can be used to precipitate regional wall motion abnormalities on echocardiography, prior to ST-segment changes on the ECG, in the presence of obstructive coronary artery disease. [29] Zacharias et al. demonstrated that stress echocardiography was more accurate than exercise ECG in detecting obstructive coronary disease as well as more cost effective through reduction of downstream investigations as more patients were reclassified as low risk. [46-48] However poor echocardiographic windows in various patient cohorts and its lack of widespread availability limit the mainstream use of stress echocardiography.

1.2.2.3.3 Single-Photon Emission CT and Positron Emission Tomography

SPECT and PET are non-invasive tests of regional myocardial perfusion using a gamma camera or PET imaging technology and intravenous radio-labelled technetium-99m during either exercise or pharmacologic stress. Defects in tracer perfusion reflect either abnormal regional flow reserve or myocardial scar. Patients with normal stress myocardial perfusion scans have a <1.0% mortality or non-fatal myocardial infarction per year. [49]

The head-to-head prospective PACIFIC trial compared PET, SPECT and CTCA against invasively measured fractional flow reserve. The PACIFIC trial demonstrated that PET had the greatest accuracy in diagnosing haemodynamically significant coronary artery disease. [44] One important limitation of SPECT is that unlike PET, which gives a measure of absolute perfusion, SPECT gives an assessment of relative perfusion. Therefore in cases where “balanced” ischemia is observed such as in triple-vessel or left main disease, a normal study may be presented. [44]

1.2.2.3.4 Cardiac Magnetic Resonance

In the landmark CE-MARC trial [50] stress-perfusion cardiac MRI was shown to be highly accurate in its detection of coronary heart disease, demonstrating its superiority over SPECT with regards to sensitivity and negative predicted values. Multiparametric CMR protocols also allow for a greater yield of information per scan without exposing the patient to ionizing radiation. CMR protocols can also provide detailed assessments of ventricular function, myocardial perfusion and viability as well as coronary anatomy in a single scan. [50]

Stress-perfusion CMR reduced the numbers of unnecessary angiograms compared with execution of national guidelines (7.5% vs 28.8% respectively). Importantly there were no statistically significant differences in major cardiovascular event rates at 12 months. [51]

1.2.2.4 Invasive Coronary Angiography

The first selective coronary angiogram was performed by Sones and Shirley in 1960. [52] Coronary angiography is an invasive procedure in which the coronary arteries are opacified with contrast injected through pre-shaped diagnostic catheters introduced through the peripheral arterial system and selectively intubated into the coronary ostia under fluoroscopic guidance. By 1977 the first coronary intervention, namely coronary angioplasty, was performed with angiographic guidance by Andreas Grüntzig. [53]

Invasive coronary angiography (ICA) is reserved as the initial investigation for patients at very high likelihood of obstructive coronary disease, those with low-effort angina or in patients that have failed medical management with anti-anginal medication. Follow-on ICA to guide revascularisation is performed in patients who have demonstrated high event risk after initial non-invasive testing or in patients with an ACS. [29]

ICA is preferentially performed via the right radial artery, owing to its rapid ambulation time, reduction in hospital stay duration and significant reduction in major bleeding complications compared with femoral artery access. [54] The risk of death, myocardial infarction, or stroke associated with ICA is in the range of 0.1–0.2%. [55]

Luminal stenosis diameter > 50% corresponds to a reduction in coronary flow reserve. [56] Therefore percent diameter stenosis is the current metric used to determine the significance of coronary lesions on angiography and the subsequent need for revascularisation. [56] Both the American and European societies of cardiology have defined a significant lesion requiring revascularisation as those with a 70% diameter stenosis measured in the most severe angiographic projection. [57,58]

1.3 Treatment of CCS

The goals of treatment are to improve symptoms and prognosis by the modification of risk factors and behaviors through the appropriate use of medications and interventions. [29]

1.3.1 General Recommendations

The impact of appropriate lifestyle behaviours upon cardiovascular mortality and morbidity, even correcting for the effects of secondary preventative medication and interventions cannot be emphasized enough. General measures such as smoking cessation, regular moderate-intensity exercise, healthy diet and maintaining a healthy weight have significant impacts on future cardiovascular risk and adverse events. [59] Benefit from lifestyle modifications can be seen as early as 6 months after an index event. [59,60] Compliance with prescribed cardiovascular medications is an important behavior to promote. It is estimated that as much as 9% of cardiovascular events in Europe were caused through poor adherence. [61]

1.3.2 Pharmacological Therapy

The aim of pharmacological treatment is to reduce anginal symptoms and to prevent cardiovascular events. Initial pharmacological management involves one or two regular antianginal medication as well as medications for the prevention of cardiovascular disease. [62] Antianginal medications are tailored to the patient's resting heart rate, blood pressure, risk of drug interactions and comorbidities.

1.3.2.1 Antianginals

Beta-blockers and calcium channel blockers represent the first-line choice of antianginal medications and may be used in combination. [63] The aim with beta-blockers is to reduce resting heart rate in order to reduce myocardial oxygen demand. Beta-blockers have been shown to provide prognostic

benefit in patients with reduced ejection fraction or prior myocardial infarction. [64,65] In contrast, non-DHP calcium channel blockers such as verapamil and diltiazem act to reduce peripheral and effort-induced coronary vasoconstriction. Caution should be advised as this class of calcium channel blocker are both moderately negatively inotropic and chronotropic. Caution should be excercised with their concomitant administration with beta-blockers given the risk of precipitating heart failure or high-grade heart block. [29] Long acting DHP calcium channel blockers such as nifedipine and amlodipine are powerful arterial vasodilators. They are particularly efficacious in hypertensive patients with relatively few side effects. The combination with beta-blockers is particularly efficient, resulting in fewer referrals for invasive coronary angiography and hospitalisations for angina documented in one 24-month follow-up trial. [66]

Where first-line agents are contraindicated, not tolerated or symptoms persist a second-line antianginal can be commenced. Common choices include long-acting nitrates, nicorandil, ranolazine and ivabradine. [29] None of the antianginal medications, except beta-blockers in patients with reduced ejection fraction or previous myocardial infarction, reduce the rates of cardiovascular death or non-fatal myocardial infarction. [67-69]

1.3.2.2 Antiplatelets

Antiplatelet and anticoagulant regimens and their many permutations represent one of the most intensely studied topics in medicine. A comprehensive review of this topic is beyond the scope of this thesis. Suffice it to say that in patients in sinus rhythm with evidence of CAD low-dose aspirin (75-100mg) may be considered for primary prevention in individuals at high-risk of ischaemic events and for the secondary prevention of further ischaemic events. [70] The $P2Y_{12}$ inhibitor class of antiplatelet which includes clopidogrel can be used as monotherapy in situations of aspirin intolerance, previous ischaemic stroke or evidence of peripheral arterial disease. [71] Clopidogrel and aspirin dual therapy is commonly used post-PCI in CCS patients for durations of up to 6 months depending on the patient-specific balance of

ischaemic and bleeding complications. More potent $P2Y_{12}$ inhibitors such as ticagrelor and prasugrel are often reserved for patients with acute coronary syndromes or those elective patients at very high risk of ischaemic complications. [72] Long-term use of these agents especially in patients with prior MI, multivessel disease and diabetes has been shown to reduce the incidence of ischaemic events at the expense of increased non-fatal bleeding rates. [73]

1.3.2.3 Statins and Lipid Lowering Medication

All patients with chronic coronary syndrome should receive a statin. [74,75] It is important to measure total cholesterol, high-density lipoprotein (HDL) and non-HDL levels. Combination therapy with ezetimibe should be considered in patients with suboptimal lipid profiles. Very high-risk individuals should be considered for PCSK9 inhibitor treatment. [29,76]

1.3.3 Revascularisation

Revascularisation by either PCI or CABG reduces myocardial ischaemia in patients with significant coronary artery stenosis reducing the risk of acute MI and cardiovascular death. [29] Numerous meta-analyses comparing a strategy of PCI against medical therapy in patients with CCS have conflicting results. This culminated in the current guideline recommendations that PCI should be reserved for those who have failed optimal medical treatment for control of symptoms or for prognostic benefit in patients with significant left main stem or proximal LAD lesions or multi-vessel disease with abnormal LV function as well as those with greater than 10% ischaemic burden on non-invasive testing, in whom revascularisation is advised upfront. [72]

One meta-analysis of the use of POBA, BMS, DES and OMT in 25,338 stable angina patients yielded no significant differences with regards to cardiovascular mortality or MI rates. [77] However many of the trials do not reflect current practice with third or fourth generation DES, physiology-guided revascularisation or contemporary antiplatelet therapy. One large contemporary meta-analysis of 100 randomised trials showed a signal for an

incremental reduction in death, MI or urgent revascularisation in stable coronary disease patients revascularised with CABG or the new-generation DES over medical therapy alone. [78]

Data from the 3-year follow up of the FAME-2 study suggests a sustained clinical benefit in patients treated with PCI specifically targeting the ischaemia-producing stenoses in addition to optimal medical therapy versus optimal medical therapy alone with regards to significantly lower rates of urgent revascularisation and spontaneous MI (HR: 0.27, 95% CI: 0.18 to 0.41 and HR: 0.62, 95% CI 0.39 to 0.99 respectively). Furthermore this study showed a trend towards improved quality of life, increased exercise capacity and reduction in the number of antianginal medication in the revascularisation group. [79] This signal was corroborated by a patient-level meta-analysis of three randomised control trials of contemporary FFR-guided PCI versus medical management in CCS. The investigators observed a reduction in the composite outcome measure of cardiac death or MI in the FFR-guided PCI group compared with medical therapy alone group (HR: 0.72, 95% CI: 0.54 to 0.96; $p = 0.02$). This difference was primarily driven by a reduced risk of spontaneous MI. [80]

In contrast, the multicenter, randomised and double-blinded ORBITA trial enrolled 230 patients with stable angina, preserved LV function and single vessel coronary artery disease. Patients received consultant-led optimization of medical treatment in a six-week run-in period prior to randomisation to either PCI or ongoing medical therapy. All patients underwent invasive physiological assessment of the coronary lesion in question. Patients were blinded to whether they underwent PCI or physiological measurement only, whereas the physicians were blinded to the results of the physiological measurements. The investigators concluded that there was no significant difference between PCI and optimal medical therapy. [81] However, the small sample size, highly selected sample population with relatively low-level symptoms, short follow-up period (6 weeks) and the lack of adherence to physiological guidance have cast doubts upon the findings of this study. Importantly, one third of the trial population had non-significant coronary artery disease evidenced by normal fractional flow reserve or instantaneous

wave-free ratio measurements. [82,72]

1.4 Invasive Assessment of Myocardial Ischaemia

1.4.1 Is there a need for Fractional Flow Reserve?

In a substantial number of patients undergoing diagnostic coronary angiography, the appearance of coronary lesions leads to diagnostic uncertainty. Firstly, visual estimation of coronary stenosis percent diameter is highly variable, even amongst experienced interventionists. [83-85] Secondly, visual and 2D-QCA of stenosis severity correlates poorly with the degree of inducible ischaemia in the myocardium subtended by the lesion. [86-88] This holds over a wide range of intermediate stenosis diameters (50%-90%). [89] A sub-study of the COURAGE trial demonstrated that only 32% of angiographically severe lesions (>70% diameter stenosis) were truly flow-limiting by intracoronary physiological assessment. [90] With this respect, fractional flow reserve was derived from trans-stenotic pressure gradient measurements, with the aid of an intracoronary pressure wire, as an objective and reproducible measure of stenosis significance. [91] Data from a study of 4086 intermediate coronary stenosis conducted by Toth et al. demonstrated considerable discordance in lesion significance defined as >50% diameter stenosis by visual and 2D-QCA assessment compared with an FFR < 0.80. [92]

1.4.2 Theoretical Basis of FFR

Coronary flow and pressure are related by their relationship with epicardial and myocardial vascular resistance. Factors such as systemic arterial pressure, heart rate, myocardial oxygen demand, contrast injection and coronary vasomotion mean that the resistance in the coronary circulation is dynamic. However, at maximal hyperaemia, vascular resistance is theoretically minimized and remains at a constant. [93,94] Under these conditions, epicardial stenosis severity can be correlated to coronary pressures using trans-stenotic pressure gradients. [91]

FFR represents the maximally achievable flow in a stenotic artery divided by maximum flow expected in the same artery in the absence of that stenosis. [91]

This is in contrast to absolute coronary flow reserve, which is defined as the ratio of maximum flow divided by resting flow [94] and relative CFR, which is the ratio of maximal flow in a stenotic artery to the maximal flow in the adjacent normal arterial distribution. [95] FFR has several advantages over coronary flow measurements as reduced coronary flow reserve can reflect reduced maximal flow, increased basal flow or a combination of the two. FFR can be used in triple vessel disease, as comparison with a normal artery is not required. FFR demonstrates greater reproducibility as it is not reliant on basal flow measurements, which are highly variable and poorly reproducible in vivo. [91] The following is the formula for calculating FFR:

$$FFR = Q_S/Q_N = P_d - P_v/P_a - P_v \approx P_d/P_a$$

Where Q_s is the maximal flow in the stenotic artery, Q_N is the theoretical maximal flow expected in the same artery without a stenosis. P_d is the distal coronary pressure, P_a is the mean arterial pressure and P_v is the central venous pressure. The formula was simplified by removing P_v, sacrificing maximal fidelity to facilitate the widespread use of FFR measurement as a practical clinical tool. [96,91]

1.4.3 Practical Approach to FFR Measurement

From a practical perspective, an appropriate guiding catheter is introduced into the coronary ostium. Aortic pressure is zeroed ensuring that the transducer is at the level of the heart and open to the atmosphere. There are 3 currently available pressure wire systems St Jude Aeris®, Volcano Verrata® and Acist Navvus®. The pressure wire or microcatheter is flushed and zeroed. The pressure wire transducer is then placed at the distal tip of guiding catheter for equalisation with aortic pressure. Before equalisation the catheter must be free of contrast, the introducer needle must be removed and haemostatic valve must be closed for accurate equalisation. [97]

Intracoronary nitroglycerin is administered prior to advancement of the pressure wire to minimize epicardial resistance and coronary spasm. The

pressure wire is then navigated along the coronary artery of interest, with the pressure transducer distal to lesion of interest in the main vessel. A hyperaemic agent is commenced. Intravenous adenosine infusion at a dose of 140 micrograms per kilogram per minute is commonly used as a starting dose. Other agents include regadenoson and papaverine. Once steady state hyperaemia is achieved, the lowest ratio of distal coronary pressure (P_d) to aortic pressure (P_a) is recorded. A normal value is 1.0. Once FFR measurement is complete the pressure wire transducer is returned to the starting position at the tip of the guiding catheter to rule out pressure "drift" or "shift". [97]

Care must be taken to recognise artifacts that may affect FFR measurement such as guide catheter pressure damping, arrhythmia, atrioventricular block, ectopic beats and interaction of the pressure wire and vessel wall in tortuous arteries. [97]

1.4.4 Why is an FFR ≤0.80 a Discriminator of Reversible Ischaemia?

In order to use FFR as a binary value for revascularisation, the chosen value must have adequate statistical and clinical power to clearly differentiate between lesions above that value and those below. This value must be robust, reproducible with low false-positive and false-negative rates. Current guidelines advocate revascularisation in intermediate lesions (40%-90% diameter stenosis) when FFR is less than or equal to 0.80. [98]

In a study of 45 patients, Pijls et al. demonstrated that an FFR of < 0.75 (n = 21) correlated very strongly with a positive non-invasive functional tests such as bicycle exercise testing, dobutamine stress echocardiography or SPECT. Pijls et al. also reported a sensitivity, specificity, PPV, NPV and accuracy of FFR in the identification of reversible ischemia as 88%, 100%, 100%, 88% and 93% respectively. [99]

Further validation work to determine the optimal cut-off value against non-invasive tests of ischaemia consistently showed that there was a range of FFR values; between 0.76 and 0.80, where the specificity for predicting non-

invasive test results was sub-optimal. [100-106] This range of FFR constitutes the “grey-zone” where a holistic approach and clinical judgment are advised to decide whether a lesion is ischaemia-producing or not. Data from a systematic review and meta-analysis exploring the outcomes of deferral against revascularisation in grey-zone FFR patients indicates that revascularisation carries the same overall risk of MACE as deferral (12.54 % versus 11.25%; odds ratio: 1.64 (95% CI: 0.78–3.44) p = 0.19) but with reduced target-lesion revascularisation (9.12% versus 5.78%, odds ratio: 1.85 (95% CI: 1.03–3.33 *p* = 0.04). [107] Further analysis of revascularisation in patients in the grey zone demonstrated that the benefit of revascularisation was at the expense of increased peri-procedural MI which was offset by increased target vessel revascularisation rates in the medically managed controls. [108]

Therefore based upon validated data demonstrating good agreement between positive non-invasive ischaemia testing with FFR < 0.75 and outcome data following PCI in stable patients with FFR ≤ 0.80, the FFR cut-off value for revascularisation was set at ≤ 0.80. [89, 98,109-111]

1.4.5 Relationship between FFR, CFR and Microvascular Resistance

FFR is a function of a dimensionless parameter linking microvascular resistance, aortic pressure and a pressure-loss-coefficient. This pressure-loss-coefficient, described as Euler’s number, reflects pressure loss secondary to wall friction and the degree of blood flow turbulence. [112]

CFR represents the myocardial vasodilator capacity. This is defined as the ratio of maximal hyperemic coronary blood flow to resting coronary blood flow. [93] A CFR less than 2 represents an ischaemia inducing stenosis. [113] FFR and CFR are inter-related through their relationship with microvascular resistance as demonstrated in Figure 1.1 Microvascular resistance can be measured by means of a dual thermistor and pressure-wire. Application of the principles governing thermodilution, pressure and flow, a quantitative assessment of the minimum microcirculatory resistance in a coronary artery territory can be derived. This is defined as the index of myocardial resistance.

(114)

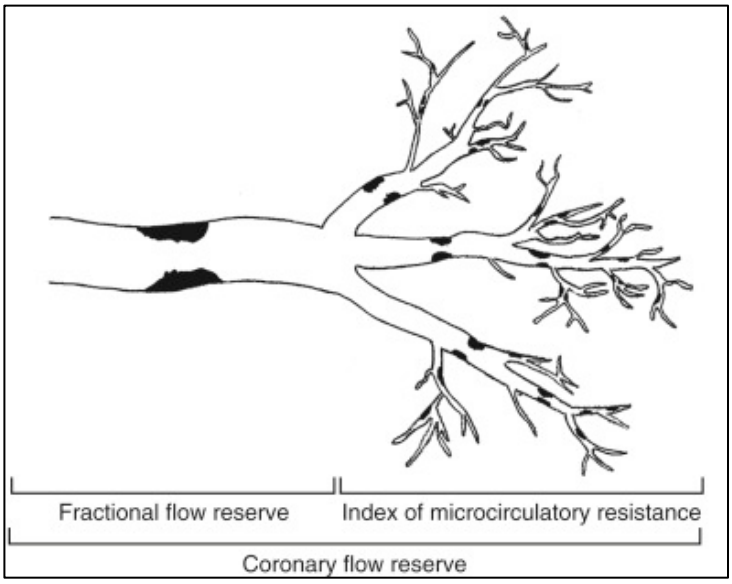

Figure 1.1 Relationship between FFR, IMR and CFR

Ng et al. demonstrated the importance of microvascular resistance, as even in stable patients undergoing elective FFR-guided angioplasty, impaired microvascular function was found to be an independent predictor of peri-procedural myocardial infarction. (115) FFR and CFR measurements are discordant in approximately 30% of intermediate lesions. (112) Microvascular resistance largely accounts for this discordance. The relationship relating CFR to FFR can be described as follows:

$$CFR = 1 + FFR\ (BMR/HMR-1)$$

Where BMR and HMR represent the basal and hyperaemic coronary microvascular resistances respectively. (112)

1.4.6 Impact of FFR on Clinical Practice

Since its introduction in 1993, several landmark clinical trials have used FFR to shape modern day practice. What follows is a summary of the key FFR trials.

1.4.6.1 DEFER Trial

The DEFER trial randomised 325 patients scheduled for PCI of intermediate coronary stenoses to PCI versus deferral of PCI as long as the pre-procedure FFR ≥ 0.75 was met. If FFR was < 0.75 then PCI was performed as planned. The 5-year outcome data showed no difference in event-free survival between deferral or intervention (80% and 73%, respectively; p = 0.52) and that the risk of myocardial infarction or death was less than 1% per year and was not reduced by intervention. The investigators concluded that deferral of PCI in lesions with an FFR ≥ 0.75 was safe and that PCI of such lesions was of no prognostic or symptomatic benefit to patients. [96] This effect persisted at very late follow-up (15 years) with no signs of a "catch-up" phenomenon. [116]

1.4.6.2 FAME Trial

The FAME trial investigated the FFR-guided multivessel PCI against angiography-guided PCI. This international multicentre prospective randomised trial enrolled 1005 patients. The cutoff for FFR-guided PCI was an FFR ≤ 0.80. The primary endpoint was a composite of death, non-fatal myocardial infarction and revascularisation at 1 year. The primary endpoint occurred in 18.3% at one year and 22.4% at two years follow-up in the angiography guided revascularisation group compared with 13.2% and 17.9% in the FFR-guided revascularisation group (p = 0.02 and p = 0.08 respectively). [117,118] The investigators concluded that routine use of FFR to guide multivessel PCI resulted in a reduction in the rates of death, MI and repeat revascularisation as composite endpoint. However secondary analyses failed to show statistically significant difference in the individual components of the primary endpoint. For example death occurred in 3.0% of the angiography group compared with 1.8% in the FFR group (p = 0.19), myocardial infarction occurred in 8.7% of the angiography group compared with 5.7% in the FFR group (p = 0.07) and similarly repeat revascularisation was required in 9.5% of the angiography group in contrast to the 6.5% of the FFR group (p = 0.08).Furthermore there was signal for a reduction in the volume of contrast agent and number of stents used per case with an overall

reduction in procedural costs. [117]

1.4.6.3 FAME-2 Trial

The FAME-2 investigators also used an FFR cut-off value of ≤ 0.80 in a study comparing PCI for lesions with an FFR ≤ 0.80 in patients with stable coronary disease in addition to optimal medical treatment versus optimal medical treatment alone. The primary endpoint was a composite of death, MI and urgent revascularisation. This international, multicentre prospective "all-comer" design trial enrolled 1220 patients. However the study was halted early due to a significant difference in the rate of the primary endpoint between groups, largely driven by a high urgent revascularisation rate in the optimal medical management group. The investigators observed the primary endpoint in 4.3% in the PCI group and 12.7% in the optimal medical therapy group ($p < 0.001$). The rate of urgent revascularisation in the PCI group compared to that observed in the medical-therapy group was 1.6% vs. 11.1% ($p < 0.001$). [110]

1.4.6.4 RIPCORD Trial

The RIPCORD trial was a UK multicentre prospective, randomised controlled trial investigating whether incorporating routine FFR measurement at diagnostic angiography in the assessment of stable coronary artery disease would result in a change in management compared to angiographic assessment alone. Primary endpoints were defined as the number of vessels in which there were discrepancies between FFR and angiographically significant disease and the difference in management plan according to the angiogram alone compared with disclosure of the FFR data. A change in management plan in >10% of patients was considered significant. Two hundred and three patients were randomised. There was a change in management plan after FFR data were disclosed in 26% (n = 53) of the study population ($P < 0.001$). Furthermore in 64 cases (32%), the number of vessels considered as significant changed after FFR data were revealed. [119] Out of 81 patients labeled as having no significant coronary stenoses after coronary

angiography alone, 22% had functionally significant lesions with an FFR < 0.80. [119] Importantly 18% of LAD, 13.5% of LCx and 8.5% of RCA PCI indications were incorrect when based on angiography alone. 13% of medically managed patients would have required revascularisation when FFR was disclosed. Conversely the availability of FFR data would have resulted in a 28% reduction in all revascularisations compared to visual assessment alone. Furthermore Curzen et al. demonstrated that there was a reduction in the proportion of patients requiring additional investigations following coronary angiography with FFR at the diagnostic stage. This could translate into more expedient and complete decision-making for patients. However this study was not without limitation. There was a 1.5% complication rate, requiring emergency CABG in one case and emergency PCI in one other patient following vessel dissection. Furthermore the study was not powered to assess clinical outcomes. [119]

In summary this trial demonstrated that availability of coronary physiology had significant implications on the management of patients with stable coronary disease, simultaneously emphasizing the unreliability of visual assessment alone in determining lesion significance in keeping with previous trials' observations. However the inherent risk of performing FFR measurement is non-negligible and may limit its use outside of interventional cardiac catheter laboratories.

1.4.6.5 POST-IT Registry

The POST-IT registry comprised of 918 consecutive stable coronary artery disease patients (1293 lesions) enrolled in a Portuguese multicentre registry. Change in management plan driven by FFR, was assessed at patient and lesion levels. Primary endpoints were major adverse cardiovascular events (death, myocardial infarction and urgent revascularisation) at one year and change in management plan. The investigators reported a mean FFR of 0.81, with an observed 44.2% change in management plan at patient level. One-year MACE was 5.3% in patients in whom all lesions were deferred. In contrast those patients with at least 1 lesion left untreated with an FFR ≤ 0.80 the MACE rate was higher at 7.3% ($p = 0.014$). At the lesion level, there was

a threefold increase in the risk of MACE in those lesions deferred with an FFR ≤ 0.80 (p = 0.012). This was largely driven by unplanned target lesion revascularisation. Much in the same way as RIPCORD, POST-IT demonstrated that the routine use of FFR resulted in a significant management strategy change and that it identifies lesions that can be safely deferred from revascularisation. [120]

1.4.6.6 FAMOUS-NSTEMI Trial

The FAMOUS-NSTEMI investigators randomised 350 patients with NSTEMI in a 1:1 fashion into two groups. All patients had FFR measurement of significant lesions (> 30% stenosis by visual estimation), but in the comparator group the operator was blinded to the FFR result and decision-making was based upon the angiographic information alone. The primary outcome was the between group difference in the proportion of medically managed patients. The investigators observed a 21.6% change in management plan once the FFR was disclosed to operators. The proportion of medically treated patients was higher in the FFR-guided group compared to the angiography group (22.7% vs 13.2%, p = 0.022). One-year analysis demonstrated that the rate of unplanned revascularisation in the FFR-guided group remained lower than the comparator group (79.0% vs 86.8%, p = 0.054). In a similar fashion to RIPCORD [119] and POST-IT, [120] the FAMOUS-NSTEMI investigators concluded that routine FFR measurement in the NSTEMI populations was safe, feasible and resulted in a at least a 20% change in management plan compared to visual assessment of the angiogram alone with overall less angioplasty. [121]

1.4.6.7 COMPARE ACUTE Trial

This prospective multicentre randomised control trial investigated the use of FFR to guide complete revascularisation of non-infarct related arteries in the context of PPCI for STEMI and multivessel disease patients. All patients who were haemodynamically stable received FFR measurements in non-infarct related arteries. Patients randomised to complete revascularisation had at least one coronary stenosis > 50% with an FFR ≤ 0.80 and underwent PCI either at the time of PPCI or as a staged procedure during the index hospital

admission. The primary endpoint was the rate of MACE at 12 months. Planned elective intervention less than 45 days from the date of the PPCI, based upon non-invasive ischaemia testing, symptoms or clinical judgment were not counted as events. A total of 885 patients were enrolled with 295 patients randomised to complete revascularisation with FFR and 590 to treatment of the culprit-only. At 12 months the rate of MACE in the FFR-guided complete-revascularisation group was lower than in the culprit-only group (7.8% vs 20.5% HR 0.35, 95% CI: 0.22 to 0.55, $p < 0.001$). Revascularisation in the infarct-artery only group was the main driver in this difference. Subgroup analysis demonstrated a significantly lower rate of MACE among patients with treated lesions than among patients with untreated lesions with an FFR of 0.80 or less (8.9% vs. 30.7%, $p < 0.001$). [122]

In summary FFR guided revascularisation is safe, feasible and applicable in both stable and acute patients. [123] It is considerably more reliable than visual assessment of the coronary angiogram alone in differentiating between significant lesions. [87,88] Deferral of lesions with FFR ≤ 0.80 is associated with significant adverse events. [120] Lesions can be safely deferred without a subsequent increase in MACE, as long as FFR > 0.80. [96,110,116,118] The routine use of FFR results in clinically significant changes to practice through the reclassification of lesions and the subsequent reduction in revascularisation. [119-121] The cost effectiveness of an FFR-guided strategy has yet to be determined on a large-scale.

1.4.7 Post-PCI FFR

Post-PCI FFR is not routinely performed nor is it mandated especially if the angiogram demonstrates interventional success. However, recent data suggests that post-PCI FFR < 0.86 is associated with worse outcomes. [124] Another study by Kasula et al suggests that the FFR threshold for successful intervention could be as high as 0.91 in patients with acute coronary syndromes. [125] The FFR-REACT trial is a prospective randomised controlled trial that will look to elucidate the reasons for low post-PCI FFR and whether additional IVUS-guided intervention in those with post-PCI FFR < 0.90 could decrease adverse events. [126]

1.4.8 Non-Hyperaemic Pressure Ratios

Despite achievement of maximal hyperaemia, intracoronary resistance fluctuates in a phasic manner throughout the cardiac cycle. Consequently, FFR measurement is averaged over several cardiac cycles. Furthermore, administering the adenosine infusion takes time, judging an adequate hyperaemic response is not always clear and can be unpleasant for patients. Non-hyperaemic assessment of coronary stenoses can be achieved through measures of P_d/P_a in the specific 'wave-free' phase of diastole [Figure 1.2] where resistance is naturally constant and minimal allowing for a linear relationship between pressure and flow, negating the need for a hyperaemic agent. [127] The ADVISE investigators demonstrated that the P_d/P_a ratio in the wave-free period, termed instantaneous wave-free ratio, correlated well with FFR ($r = 0.9$, $p < 0.001$) with excellent diagnostic efficiency at the FFR < 0.80 threshold (ROC-AUC 0.93). The authors reported iFR characteristics of specificity, sensitivity, negative and positive predictive values as 91%, 85%, 85%, and 91%, respectively. [127]

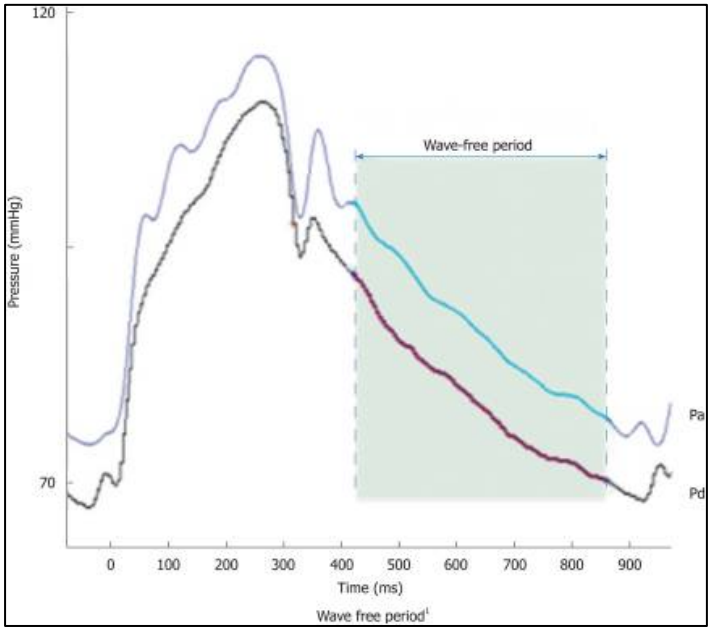

Figure 1.2 Wave-free period

The CLARIFY study sought to compare the ability of iFR and FFR to classify stenosis severity against hyperaemic stenosis resistance (HSR) as a

reference. Their findings demonstrated no significant difference between iFR and FFR. However this study was small in size, n = 51, with only 4 patients having conflicting iFR and FFR lesion classifications. The iFR cutoff used in this study was 0.86. This was in contrast to the ADVISE registry threshold of 0.89 that demonstrated superior agreement with an FFR of < 0.80 in a much larger sample size. [128]

The retrospective, non-randomised RESOLVE study compared the diagnostic accuracy of iFR against the established FFR threshold < 0.80. Analysis of 1593 lesions revealed agreement of iFR with FFR in only 80.4% of cases. The results of the non-randomised VERIFY study were disparaging of iFR reporting an accuracy of 60% in comparison to FFR when an iFR threshold of < 0.80 was used, casting doubt about the accuracy of iFR. [129,130]

1.4.8.1 DEFINE-FLAIR Trial

The DEFINE-FLAIR trial was the first to examine clinical outcomes with the use of iFR. This landmark multicentre, international, prospective, blinded randomised controlled study aimed to prove the non-inferiority of iFR-guided revascularisation to FFR-guided revascularisation. 2492 patients were randomised to either modality in a 1:1 fashion and followed up for one year. The primary endpoint was a composite of death, MI and unplanned revascularisation. The threshold of non-inferiority was 3.4 percentage points. At one year the primary endpoint occurred in 6.8% and 7.0% in the iFR and FFR groups respectively (-0.2% difference, 95% CI: −2.3 to 1.8; p < 0.001 for non-inferiority, HR: 0.95, 95% CI: 0.68 to 1.33 p = 0.78). The authors concluded that iFR was non-inferior to FFR with secondary analyses demonstrating that iFR shortened overall procedure length with better patient tolerability in comparison with FFR. [131]

1.4.8.2 iFR-SWEDEHEART Trial

The iFR-SWEDHEART trial examined the use of iFR in 2037 patients who were eligible for physiology-guided revascularisation. Patients were randomised to either iFR or FFR guidance. This trial was a multicentre, randomised, open-label study with a composite primary endpoint of death, MI or unplanned revascularisation at one year. The non-inferiority margin was

3.2%. The primary endpoint occurred in 6.7% in the iFR group and 6.1% in the FFR group (0.7% difference, 95% CI: −1.5 to 2.8, p = 0.007 for non-inferiority, HR: 1.12, 95% CI: 0.79 to 1.58, p = 0.53). The authors of IFR-SWEDEHEART concluded that iFR-guided revascularisation in stable angina or acute coronary syndrome was non-inferior to an FFR-guided strategy and was also better tolerated by patients. [132]

1.4.9 Limitations of FFR

Despite the significant advantages of FFR over angiographic guidance, FFR is not without its limitations; chiefly its use as a dichotomous value to define revascularisation versus deferral decisions. FFR is a continuous variable with several variable intrinsic physiological inputs reflecting a gradient of risk. [133] Petraco et al. demonstrated that patients outside of the FFR 'grey-zone', (0.75 to 0.85), i.e. those at the extremes of FFR, have a >95% certainty of clinical decision making with the greatest prognostic and symptomatic benefits. However this diagnostic certainty dropped to < 80% when FFR values ranged from 0.77 to 0.83 and to a nadir of 50% certainty at the cut-off value of 0.80; no better than a coin toss. Additionally it was demonstrated that the closer the FFR was to the cut-off value of 0.80, the greater the chance of a change in management when FFR measurement was repeated after 10 minutes. [134] This chance of management change was as high as 20% when FFR was between 0.77 and 0.83. [135]

Diagnostic uncertainty around the ischaemic-threshold is particularly important because current practice does not reflect the severity of lesions assessed in the DEFER, FAME and FAME-2 trials. The mean FFRs in those trials were 0.56, 0.60 and 0.68 respectively correlating with more angiographically severe lesions. [133] In real-world practice FFR is applied to angiographically intermediate lesions with intermediate FFR values that cluster around the cut-off value. [109] Data from a systematic review and meta-analysis exploring the outcomes of deferral against revascularisation in grey-zone FFR patients indicates that revascularisation carries the same overall risk of MACE as deferral (12.54 % versus 11.25%; odds ratio: 1.64 (95% CI: 0.78–3.44) p = 0.19) but with reduced target-lesion revascularisation rates

(9.12% versus 5.78%, odds ratio: 1.85 (95% CI: 1.03–3.33 p = 0.04). [107] However there was signal for increased peri-procedural myocardial infarction in patients receiving revascularisation, offsetting the benefit of revascularisation. [108] Conversely there was an incremental reduction in the overall benefit of PCI in patients that had higher pre-intervention FFR values with a signal for harm. [136] This has clear implications for the interventionist, in that FFR should not be used as a binary tool as a substitute for clinical judgment and experience.

The premise of FFR is that at maximal hyperaemia, a trans-stenotic pressure gradient is representative of coronary blood flow. However this gradient can be misleading in low-flow and high-flow states where a pressure drop across a stenosis may be underestimated or overestimated respectively. [137] The greater the blood-flow the greater the friction and separation losses resulting in an increased pressure gradient whereas in low-flow states the opposite is true. In the latter circumstances, the diminished the pressure gradient translates into an underestimation of the functional severity of a coronary obstruction. [56]

Garcia et al demonstrated that microvascular resistance is as important as epicardial stenoses in determining FFR. [112] Conditions that increase microvascular resistance such as diffuse coronary disease, high left ventricular end diastolic pressure, diabetes mellitus, left ventricular hypertrophy and acute myocardial infarction, increase post-stenotic pressure (P_d). This reduces the pressure gradient across a stenosis resulting in an elevated value of FFR so that a stenosis appears to be less severe. [112,137] The absolute change in FFR in such situations is likely to be small, in the order of 5% or 0.05 in absolute terms. [138] However this becomes especially pertinent in intermediate lesions that are close to the 0.80 cut-off. Microvascular dysfunction can also impair drug-induced coronary vasodilation resulting in a blunted flow response thereby increasing FFR spuriously. [135] Measurement of CFR and IMR are complementary to FFR in these settings, however their use is complex, time consuming and limited outside of research centres.

FFR measurement is also influenced by the amount of subtended myocardium. The size of the perfusion territory directly affects the coronary flow rate and in-turn the pressure gradient across a given stenosis. [139] The larger the mass of myocardium to be perfused, the greater the coronary flow rate and therefore the greater the pressure gradient induced by maximal hyperaemia. [140,141] This likely explains the greater mean FFR values in women compared to age-matched males observed in the FAME study, owing to their smaller heart sizes. [142,143]

Measurement of FFR is more invasive than routine diagnostic coronary angiography. Navigating the pressure-wire into position through coronary stenoses may result in acute vessel closure, intimal dissection, rupture of vulnerable plaque and or coronary perforation necessitating emergent angioplasty or CABG. [97] Therefore performance of FFR measurement is limited to centers where angioplasty is performed routinely. [119] The medications infused to achieve maximal hyperaemia may result in arrhythmias, atrioventricular block or severe bronchospasm in patients with asthma receiving adenosine. The incidence of such complications is uncommon, reported in less than 2% of the major FFR trials. [117-119]

Another limitation is that the majority of landmark FFR trials have excluded patients with left main stem and aorto-ostial disease as well those patients with chronic total occlusions or prior CABG. Small non-randomised studies suggest that the traditional 0.80 cut-off value applies to aorto-ostial lesions [144] and only in left main lesions without significant downstream proximal stenoses of both daughter branches. [145] FFR has also not been validated in the context of diffuse disease or serial stenoses where lesion length was found to be an independent predictor of a positive FFR. [146] In such cases, continuous pullback under hyperaemia can be used to identify the segments of vessel that contribute the most towards the positive FFR result. [97]

The clinical significance of a stenosis in the donor vessel to a chronic totally occluded vessel is likely to be overestimated as collateral vessels reduce P_d

through increased coronary flow. Following successful CTO recanalization a modest increase in the FFR of the donor vessel is observed secondary to reduction in donor vessel coronary flow. [147,148]

FFR is under-used in coronary catheterisation laboratories worldwide. [149] This is despite its well established clinical value in detecting prognostic ischaemia and guiding revascularisation at the time of clinical decision-making, as well as being a class 1a recommended tool in the clinical guidelines for chronic coronary syndromes [29,72] Barriers to the routine use of FFR include the time consuming nature of FFR, availability of equipment and adenosine, patient-discomfort, contraindications, lesion complexity and lack of re-imbursement. [149] There may also be human factors, such as the operator perceiving that their clinical acumen does not require the routine input of invasive physiology.

1.5 Computational Fluid Dynamics

Computational fluid dynamics is a specialist area of mathematics describing fluid motion. CFD modelling has long been established as an indispensable tool in the field of engineering pervading the aerospace and vehicle industries as well as other safety-critical systems. [150] Computers are used to perform calculations required to simulate the complex three-dimensional flow of fluids and their interaction with relevant surfaces defined by pre-specified boundary conditions. Simulation of a desired model is achieved through the solution of continuity and non-linear partial differential equations described by Navier and Stokes, derived from Newton's second law of conservation of mass and momentum. [151] Simplifications of these equations yield the familiar Bernoulli and Poiseuille equations. More recently bioengineers have applied the same technology to cardiovascular medicine to enhance diagnosis and device designs as well as to predict responses to interventions. [152-155]

1.5.1 Fundamentals of Model Construction and Workflow

CFD modelling of the cardiovascular system can be achieved in various levels

of detail and complexity. Zero-order models lump together physiological systems into a single description of the global behavior of a system. Zero-order models typically assume uniform distribution of key variables such as pressure, resistance and flow that vary only as a function of time. Such models generally feature the major cardiovascular components, such as the heart and its valves as well as the subdivisions of the vasculature tree. They are suitable for examination of global distributions of pressure, flow and blood volume [156] as well as modelling the compliance or resistance of arterial walls. [157] One-dimension models are useful in representing wave propagation and reflections that exist with pulsatile flow *in vivo*. They typically allow physiological variables to be simulated as a function of one spatial dimension. [156,158,159] 2D and 3D models simulate physiological variables over a period of time in two and three planes respectively. These models often incorporate lower-order models to define boundary conditions to improve the overall accuracy of a model. [158]

The steps of CFD modelling can be grouped into a workflow. This involves several key steps outlined below and illustrated in Figure 1.3:

1.5.1.1 Clinical Imaging

CFD modelling can be applied to most clinical imaging modalities such as CT, MRI or X-ray angiography as long as they provide adequate image resolution [160] and physiological detail to enable segmentation and data extraction. [161]

1.5.1.2 Segmentation

Segmentation describes the process whereby medical images are reconstructed as digital geometries that define the physical boundaries of the model. Images that are acquired over a cardiac cycle can be used to model anatomical motion. [162]

1.5.1.3 Discretisation

After segmentation, the digital geometry under goes spatial discretisation where by the digital geometry is volume rendered using a finite number of non-overlapping volumetric elements or cells. Temporal discretisation is the division of the simulation into discrete time-steps. The overall accuracy and stability of the simulation are in part related to the refinement of the spatio-temporal discretisation, which is required to capture the haemodynamic behavior of the region of interest. However, excessive refinement increases computational requirement, which in turn prolongs simulation time. [158]

1.5.1.4 Boundary Conditions

Boundary conditions inform the simulation with regards to the physiological conditions at the walls, inlets and outlets of the model over time. Boundary conditions can be individual patient measurements such as blood pressure and heart rate, population-averaged data, assumptions based on physical models or 0D and 1D models incorporated into the 3D CFD model of interest. [158,163]

1.5.1.5 Simulation

A computer programme then incorporates the segmented and discretised model along with the pre-specified boundary conditions using a pre-defined fluid model. The fluid model in this case depicts the physical characteristics of blood such as viscosity, density and its non-Newtonian properties. Simulations can be performed in a steady or transient state. Steady state simulations assume constant initial conditions such as pressure and flow independent of time. This simplifies or removes all together some non-linear terms allowing for faster computational time. Transient simulations are time dependent and require significant computational power and time to converge solutions as millions of non-linear partial differential equations are solved simultaneously and repeatedly for each element at all time points to converge towards a final solution. [158]

1.5.1.6 Post-processing

CFD simulations generate large quantities of pressure and velocity data for each volumetric element over all time-steps. Post processing allows for extraction of useful data. An example is the computation of fractional flow reserve in a stenotic coronary artery [164] [Figure 1.3].

1.5.1.7 Validation

Validation of CFD simulation results against a reference standard is critical in generating confidence in the accuracy and reliability of the technology. An example is the validation of computed (virtual) FFR against invasively measured FFR. [164]

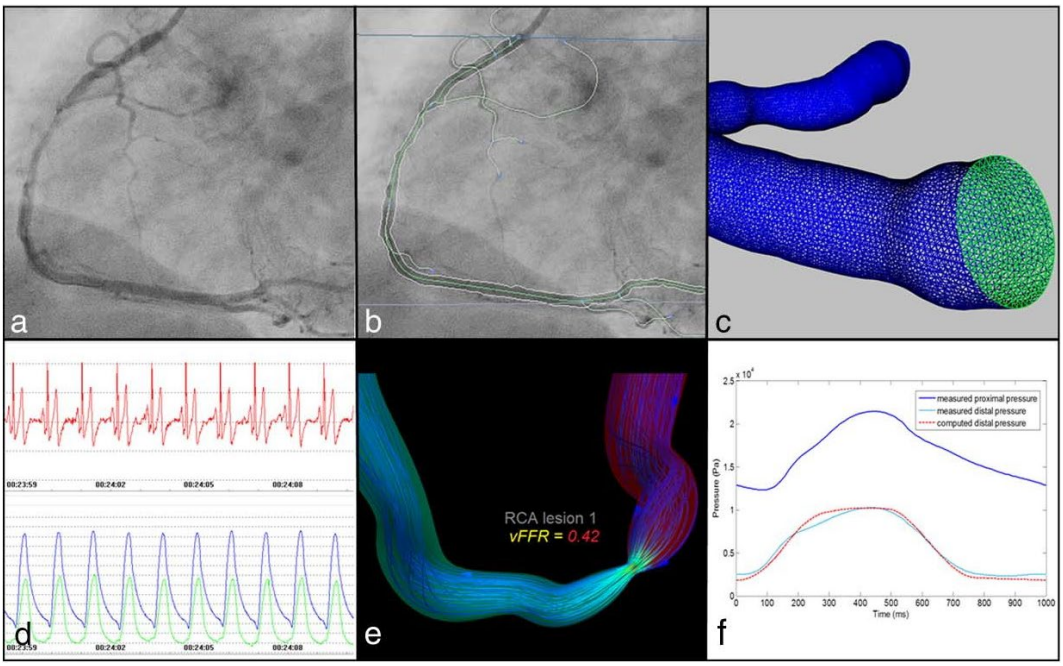

Figure 1.3 Workflow for Simulation of virtual FFR (a) Coronary angiogram of RCA. (b) Segmented coronary angiogram. (c) Discretisation of segmented model. (d) Application of pressure data as boundary conditions. (e) Simulation and post-processing results displaying useful data. (f) Validation of simulation against invasively measured values. Reproduced with permission from Morris et al. [158]

1.5.2 Applications of CFD in Cardiovascular Medicine

1.5.2.1 Prosthetic Heart Valve Function and Design

CFD solvers have been used to model the complex blood flow and haemodynamics experienced by blood cells interacting with bi-leaflet mechanical heart valves. These models have been used to understand the mechanisms whereby these valves fail or cause thromboembolic complications, with the goal of enhancing future design of mechanical valves. [165-167] However current models utilise computationally demanding and time-consuming fluid structure interaction models with little in the way of validation. [168]

1.5.2.2 Aortic Aneurysms and Dissections

Similarly in aortic dissections CFD has been used to simulate the complex flow fields in chronically dissected aortas, providing prognostication and insight into interventional planning. [169-171] CFD in these scenarios allows for truly individualised patient care and simulation of the effects of intervention. [172] However the complex nature of the flow fields created by entry, re-entry and communication channels as well as the dynamic nature of the aortic wall necessitate complex computational simulations requiring more advanced and time-consuming FSI modelling. [173]

1.5.2.3 Stent Design

CFD has been used to integrate angiographic and CT imaging in addition to physiological data to delineate the inverse relationship of neointimal hyperplasia to wall shear stress, a variable that is not directly measureable in vivo. [174,175] Building on this knowledge, future stent designers could model streamlined stent-strut designs to reduce turbulent and recirculation flows that are conducive to poor endothelialisation and thrombosis. [176,177]

1.5.2.4 Ventricular Assist Devices and Congenital Cardiac Disease

Optimisation of pump design and implant location can be achieved through modelling of haemodynamics in the heart and great vessels allowing for personalisation of patient care tailored to an individual's physiology. Similarly CFD modelling of complex congenital heart disease will allow caregivers to assess the effects of surgical and/or implanted devices on the circulatory tree. (178,179)

1.6 Computed (virtual) FFR

The benefits of FFR-guided revascularisation are well documented, yet FFR is used in less than 10% of cases worldwide largely due to procedural and patient factors. (118) CFD modelling is an attractive means of computing virtual FFR, reducing the need for invasive instrumentation. Several models have been developed based upon CT coronary angiography (180) and invasive coronary angiography. (164,181)

1.6.1 Virtual FFR Derived from CT Coronary Angiography

CT coronary angiography provides excellent anatomical evaluation of coronary artery disease at the expense of a high false-positive rate. (182) As explained previously, the relationship between visual stenosis severity and inducible ischaemia is unreliable. CFD modelling has been applied to CTCA to address this problem, effectively creating an "all-in-one test". (183)

In addition to the workflow outlined in previous sections, CTFFR relies upon three key physiological assumptions. The first assumption is that at rest coronary supply and demand are matched, allowing coronary flow to be related to myocardial mass. The second is that microvascular resistance is non-linearly and inversely proportional to vessel size. The third is that at maximal hyperaemia, microvascular resistance is minimal and constant in the presence of normal coronary flow. Together these assumptions are used to

create coupled lumped parameter models that inform boundary conditions of the 3D model. [183]

1.6.1.1 Diagnostic Performance of CTFFR

A summary of the diagnostic performance of CTFFR derived from the landmark clinical trials is outlined in Table 1.1.

1.6.1.1.1 DISCOVER-FLOW Trial

This prospective, multicentre, randomised and blinded trial sought to assess the diagnostic performance of CTFFR against CTCA alone, using invasively measured FFR as a reference. 159 vessels in 103 patients with suspected or known coronary artery disease were analysed. Patients underwent CTCA and ICA. Invasive FFR was measured and CTFFR was computed in a blinded fashion by the HeartFlow Inc. (Redwood City, California) core lab. The threshold for ischaemia for both FFR and CTFFR was 0.80 and an obstructive lesion on CTCA was defined as a lesion causing ≥ 50% diameter stenosis. The position of the distal pressure-wire sensor was recorded to enable calculation of CTFFR at the same point as the invasive FFR. CTFFR analyses required 5 hours per case. The accuracy, sensitivity, specificity, PPV and NPV of CTFFR were 84%, 88%, 83%, 74% and 92% respectively. Similar performance was observed in intermediate stenoses defined as 50-70% diameter stenosis. Good correlation with invasive FFR (r = 0.72) was reported. CTFFR underestimated measured FFR by 0.022 (±0.016). However CTFFR was superior to CTCA alone in discriminating between ischaemic and non-ischaemic lesions, (AUC 0.92 versus AUC 0.72, p = 0.001). The investigators concluded that the power of CTFFR lies in its ability to reduce the false-positive rate of CTCA without additional radiation, medication or contrast, leading to a reduction in overall costs as a better gatekeeper for ICA. [182] However this study is not without its limitations. This study was only powered to assess performance on a per-vessel rather than per-patient level, given its small sample size. This study did not enroll consecutive patients, rather patients already scheduled to undergo ICA who were at low to

intermediate risk. Patients with prior PCI or CABG were excluded and the authors did not describe whether there were any non-evaluable CTCAs for CTFFR calculation as was the case in similar studies.

1.6.1.1.2 DEFACTO Trial

The DEFACTO trial also assessed the diagnostic performance of CTFFR against invasively measured FFR. This prospective international, multicentre trial enrolled 252 patients with suspected coronary artery disease who subsequently underwent CTCA and ICA with calculation of CTFFR and FFR respectively. The primary outcome was achievement of > 70% in the lower boundary of the 95% confidence interval for diagnostic accuracy. [184] This cut off was selected based upon previous studies investigating the diagnostic accuracies of stress imaging demonstrating 70% to be the mid-point of the reported diagnostic accuracies. [185,186] Lumped parameter models were coupled with 3D models to define inlet and outlet boundary conditions. Computation time was 6 hours per case. The investigators reported CTFFR overall diagnostic accuracy of 73% (95% CI: 63% to 78%) falling short of the primary endpoint. Sensitivity, specificity, positive and negative predicted value were 90%, 54%, 67% and 84% respectively. The correlation between CTFFR and invasive FFR was 0.63 with a tendency of CTFFR to underestimate FFR by an average of 0.058. Discrimination of ischaemic lesions, assessed by the area under the receiver-operating curve, showed CTFFR to be superior to CTCA alone (CTFFR c = 0.81 versus CTCA alone c = 0.68, $p < 0.001$). Importantly 11% (n = 31) of screened patients had suboptimal CTCA scans and were excluded, being unsuitable for CFD modelling. Approximately 75% of enrolled patients had excellent scan quality assessed by the blinded HeartFlow Inc. (Redwood City, California) core lab. Although this trial failed to reach the primary endpoint, the authors concluded that CTFFR imparts considerable discriminatory power to identify and exclude ischaemia in low to intermediate risk patients with suspected CAD. However, the low specificity and positive predictive value of CTFFR for ischemia detection, suggests that a substantial rate of false-positive results would persist. [184]

1.6.1.1.3 NXT Trial

The third international and multicentre randomised trial of CTFFR diagnostic accuracy against invasive FFR recruited 254 patients with stable angina without a history of previous revascularisation. The primary outcome of the NXT trial was the diagnostic accuracy on a per-patient level for the discrimination of ischaemia of CTFFR ≤ 0.80 versus CTCA ≥ 50% luminal diameter stenosis using invasively measured FFR ≤ 0.80 as the gold standard. The key differences of this trial compared to its predecessors were enhancement of the CFD modelling processes and more stringent requirements for high CTCA scan quality. 13% (n = 47) of CTCA scans were excluded due to sub-standard image quality. The results of the NXT trial, in keeping with previous studies, reveal that CTFFR has significantly better discriminatory capacity than CTCA for the detection of ischaemia (c = 0.90 versus c = 0.81 p = 0.0008 respectively). In the NXT trial, CTFFR had a diagnostic accuracy of 82% compared with invasively measured FFR. The reported sensitivity, specificity, positive and negative predicted values are 86%, 79%, 65% and 93% respectively. CTFFR correctly reclassified approximately two-thirds of false-positive CTCA patients as true negative patients. The investigators demonstrate the improved specificity of CTFFR and the associated improved false-positive rate compared to previous studies of CTFFR diagnostic accuracy. This means that CTFFR can be a reliable gatekeeper for ICA in an intermediate risk patient cohort without the use of additional radiation, medication or contrast or a second investigation. [180]

	DISCOVER-FLOW [182]	**DEFACTO** [184]	**NXT** [180]
Accuracy	84%	73%	81%
Sensitivity	88%	90%	86%
Specificity	83%	54%	79%
PPV	74%	67%	65%
NPV	92%	84%	93%
AUC	0.92	0.81	0.90
Correlation with FFR	0.72	0.63	0.82
Computation time (hrs)	5	6	1-4

Table 1.1 Summary of diagnostic performance of CTFFR.

1.6.1.2 Impact of CTFFR on Clinical Practice and Outcomes

The PLATFORM trial was a prospective, consecutive cohort study utilising a comparative effectiveness observational design that recruited 584 patients with intermediate pre-test probability of obstructive CAD. The trial addressed the hypotheses that patients with suspected CAD evaluated using CTFFR would have fewer invasive angiograms that showed no obstructive CAD (defined as QCA < 50% or FFR > 0.80) than patients who were evaluated according to current practice. Furthermore the investigators hypothesized both groups would have similarly low rates of major cardiac events. Patients were enrolled in two consecutive cohorts receiving either usual-care testing or CTFFR testing. Each cohort was subdivided into two groups based on the evaluation plan decided upon before enrolment, namely non-invasive testing (any stress-test or CTCA without CTFFR) or ICA. The PLATFORM investigators demonstrated that in patients initially referred for ICA, there were significantly lower rates of non-obstructive CAD in the CTFFR group compared to the ICA group (24 (12%) versus 137 (73%) respectively P < 0.0001). Furthermore there was no difference in clinical events in patients referred for non-invasive testing, between a usual-care and CTFFR-guided strategy at 90 days. The investigators concluded that CTFFR is a safe and feasible alternative to ICA for the investigation of stable coronary artery disease that resulted in significantly lower rates of invasive angiograms without obstructive disease compared to CTCA alone. Importantly the use of CTFFR improved the availability of functional data for those referred for revascularisation (95% CTFFR vs. 55% usual care), allowing compliance with current revascularisation guidelines recommending both anatomic and functional data in decision-making. [72,187]

Retrospective analysis of the PROMISE trial CTCA cohort of patients with post-hoc CTFFR calculation revealed that a CTFFR ≤ 0.80 was a significantly better predictor for revascularisation or MACE than severe stenosis on CTCA (HR: 4.3 [95% CI: 2.4 to 8.9] vs. 2.9 [95% CI: 1.8 to 5.1] p = 0.033). Importantly reserving ICA for patients with a CTFFR ≤ 0.80 could reduce unnecessary ICA by 44% and increase the proportion of ICA leading to

revascularisation by 24%. However in this retrospective analysis 33% of CTCAs were excluded, being sub-optimal for CFD modelling. [188] Similarly a retrospective analysis of the RIPCORD CTCA cohort of patients with post-hoc CTFFR calculation resulted in reclassification of 36% (n = 72) of CTCA patients. This was largely due to discordance between how CTFFR and CTCA classified lesion severity. CTFFR > 0.80 was observed in 29.5% (13 out of 44) vessels originally classified as > 90% by CTCA alone. [189]

1.6.1.3 Limitations of CTFFR

Despite the successes of CTFFR, it is not without its limitations. Factors that reduce image quality of any CTCA scan directly affect the applicability of CFD modelling to compute CTFFR. In the landmark CTFFR clinical trials 11% to 13% of CTCA scans were rejected due to poor image quality that prohibited CFD modelling. [180,182,186] However this figure was as high as 33% in the retrospective PROMISE trial. [188]. Factors such as sub-optimal heart rate, irregular heart rhythm, high BMI, motion and step artifacts significantly affect image quality. [41] Blooming and beam-hardening artifacts secondary to heavy and diffuse coronary calcification lead to overestimation of stenosis severity. One study comparing stenosis severity on CTCA stratified by degree of calcification against ICA as a reference, demonstrated overestimation of stenosis severity in one-third of heavily calcified (Agatston score > 400) lesions. [190] Good image quality with accurate lesion characterization is paramount to the segmentation and discretisation of the CTCA image necessary to compute accurate CFD models. This phenomenon is especially more common in those patients over the age of 75 and those with peripheral arterial disease, which may limit the accuracy of CTFFR, let alone CTCA in this cohort of patients.

A comprehensive systemic review of the diagnostic performance of CTFFR measured against invasive FFR by Cook et al., analysing 908 vessels in 536 patients across five studies, demonstrated that CTFFR was predominantly applied to a low-risk patient population with milder disease than previous landmark trials. For example, the prevalence of intermediate stenoses (50-70% diameter stenosis) from the combined FAME [117] and FAME-2 [110]

studies was 46.8% compared to the 12% observed in the five studies of CTFFR eligible for the systematic review. [191] Furthermore the median invasive FFR in the CTFFR trials was 0.88 in comparison to the DEFER trial with a mean FFR of 0.56. [116] The overall diagnostic accuracy of CTFFR was 81.9%. However an analysis of diagnostic accuracy of CTFFR over various brackets of invasive FFR: < 0.60, 0.60 to 0.70, 0.70 to 0.80, 0.80 to 0.90 and > 0.90 revealed the diagnostic accuracy of CTFFR was 86.4% (95% CI, 78.0%-94.0%), 74.7% (95% CI, 71.9%-77.5%), 46.1% (95% CI, 42.9%-49.3%), 87.3% (95% CI, 85.1%-89.5%) and 97.9% (95% CI, 97.0%-98.8%), respectively. This suggests that in physiologically intermediate stenoses, close to the cut-off threshold for revascularisation, the diagnostic certainty of CTFFR predicting a positive invasive FFR is poor with a slight bias towards underestimation of invasively measured FFR [191]

Currently, the most widely used CFD CTFFR algorithm is proprietary and confidential. Therefore the distal vessel location used to compute CTFFR is not known. The lack in transparency may result in CTFFR values that reflect measurement at positions in vessels that are too distal and/or small to stent compared to FFR values derived from invasive pressure-wire transducers. [191]

1.6.2 Virtual FFR Derived from Invasive Coronary Angiography

When derived from the invasive coronary angiogram, FFR simulation can be computed using CFD modelling [164,181,192], rapid pressure-flow simulation [193] or through solution of mathematical formulae [194,195] deduced by Gould et al. [22,56]

1.6.2.1 Virtual FFR Derived From CFD Modelling

1.6.2.1.1 VIRTU-1 Study

In the first study of its kind, Morris et al applied CFD modelling to compute FFR from invasive rotational coronary angiography in 19 patients with confirmed simple (Type A) lesions undergoing elective PCI in one tertiary centre in the United Kingdom. FFR was invasively measured in any vessel

with a lesion > 50% diameter stenosis by visual estimation. Virtual FFR was subsequently computed using generic downstream boundary conditions at the model outlets, derived from a 0D Windkessel model. The Windkessel model is an electrical analogue of the arterial vasculature, in which the downstream resistance is calculated from pressure and flow throughout the duration of the cardiac cycle. [196] A total of 35 data sets were analysed. Navier-Stokes continuity equations were solved in 3 dimensions in approximately one million volumetric elements. Post processing of the simulation was used to calculate vFFR. The computation time was approximately 24 hours per case. Using FFR < 0.80 as a binary threshold for revascularisation the diagnostic accuracy of vFFR was measured against invasively measured FFR. The overall diagnostic accuracy of vFFR was 97%. Sensitivity, specificity, positive and negative predicted values were 86%, 100%, 100% and 97% respectively. On average, the vFFR values deviated from the invasive FFR by ±0.06 (mean delta = 0.02, SD = 0.08). There was good correlation between vFFR and mFFR (r = 0.84) with good agreement between the two modalities. [164]

The excellent level of accuracy of vFFR reported in this pilot study must be interpreted with caution due to the small sample size and simple pattern of disease analysed. Further limitations of this study are the generic boundary conditions depicting microvascular resistance. A ‘one-size-fits-all’ approach may underestimate FFR in individuals with high microvascular resistance. Rotational angiography is cumbersome to perform and not routinely available. Computation time was 24 hours per case. Although the majority of lesions were type A and visually intermediate, only nine lesions were physiologically intermediate FFR (FFR 0.70 to 0.90). Despite these limitations, this proof of concept study demonstrates that vFFR can be used without additional procedures or inducing hyperaemia to improve patient access to physiology guided decision-making with potential impact on clinical outcomes and cost. [164]

1.6.2.1.2 VIRTU-Fast Study

The VIRTU-Fast study was an observational, analytical, single-centre study computing vFFR using a novel “pseudotransient” protocol. This was validated

against invasive FFR measurement and fully transient CFD analysis. The purpose of this study was to address the two fundamental limitations of CFD modelling, the very long computation time and the factors that determine the accuracy of the modelled coronary geometries and physiological parameters. CFD modelling of pulsatile blood flow requires time-dependent (transient) CFD analysis, which requires complex and time consuming computing. However in reality, calculation of FFR is derived from the mean pressure difference over time. Steady state analysis takes far less computation time than transient CFD analysis, however it was not yet clear whether the transient pressure and flow distributions could be accurately represented by this means of analysis. [197]

Twenty patients with known coronary artery disease awaiting elective PCI were recruited. A total of 73 data sets were generated. Rotational angiography was performed and FFR invasively measured in all lesions > 50% diameter stenosis by visual estimation. Angiograms were then segmented and discretized using 1 to 2 million volumetric elements. Full transient CFD analysis was performed to calculate vFFR in addition to pseudotransient and steady-state CFD analyses to compute vFFR. Pseudotransient vFFR required transient analysis of two compartments of the segmented vessel representing the lesion and the distal microvasculature as a function of nine parameters. Steady-state vFFR was calculated using a single steady flow simulation at mean coronary pressure that only required four parameters. [197] Proximal boundary conditions were the patient-specific pressures from the guiding catheter at the coronary ostium. The outlet of the reconstructed model corresponded to the location of the pressure wire transducer. The outlet physiological boundary conditions characterizing the distal impedance were patient-specific derivations from the guiding catheter and pressure wire pressures. Flow rates of one and three ml/second were used to simulate steady and hyperaemic flow respectively. Pseudotransient CFD simulations took on average four to five minutes, being 500 times faster than full transient CFD analysis.

Pseudotransient and single steady-state vFFR demonstrated 100% accuracy, sensitivity, specificity, positive and negative predictive values for diagnosis of

functional lesion significance (FFR < 0.80). Agreement between measured FFR and vFFR derived from both pseudotransient and steady-state analysis were high, the majority of which fell in the clinically important FFR range of 0.70 to 0.90. Subsequent sensitivity analysis determined that characterization of coronary microvascular resistance was the key determinant of the variability in CFD output, accounting for 59.1% of variation. The influence of microvascular resistance was further demonstrated through the application of a generic value (derived from the mean resistances of the studied population) at the distal boundary of the model. This resulted in greater quantitative and diagnostic error. [197]

Morris et al concluded that steady-state CFD analysis could accurately simulate transient pressure and flow distributions from full transient CFD simulations at a fraction of the computational power and processing time. Importantly the accuracy of the CFD model is influenced less by the geometry of the lesion but rather by the accurate characterization of the distal coronary microvascular resistance. Tuning the model parameters with regards to microvascular resistance on an individual basis now represents the single greatest challenge to overcome in CFD modelling. [197]

Tröbs et al utilised CFD to retrospectively calculate angiography-based FFR in 73 patients with stable coronary artery disease. Good correlation with invasive FFR was reported (r = 0.85). Diagnostic accuracy reached 90%. The limits of agreement tested by the Bland-Altman method were high (0.0082 with an SD of −0.117 to 0.134). However the model only catered for a maximum of 1 side branch and interobserver variability was introduced due to manual correction of automatically detected vessel contours. [198]

Similarly Papafaklis et al used 3D-QCA in conjunction with CFD modelling in 139 vessels with physiologically intermediate stenoses as assessed by invasively measured FFR. A stenosis-specific pressure gradient was used to derive the virtual functional assessment index (vFAI) as measure of stenosis severity. The diagnostic accuracy of vFAI to predict invasive FFR reached 88%. [192]

1.6.2.2 Mathematically Derived Virtual FFR

Historically 2D-QCA of percent diameter stenosis has been shown to have only modest correlation with physiological indexes of myocardial ischaemia. [199] However a recent study suggests that visual estimation may be more accurate than 2D-QCA. [87] Recent advancements in technology have demonstrated greater accuracy and correlation with invasive FFR using 3D-QCA compared with 2D-QCA. This is largely due to the elimination of overlapping segments and foreshortening of vessels as well as better characterisation of eccentric lesions. [200]

Tu et al. developed a method of FFR computation by combining 3D-QCA and Thrombolysis in Myocardial Infarction (TIMI) frame counting of contrast media. [181] Initial computation of FFR by this method utilised CFD modelling however in subsequent iterations, mathematical modelling was used to derive a physiological index describing fractional flow reserve termed the quantitative flow ratio. [194,195] QFR utilises 3D-QCA to reconstruct the vessel of interest and then simulates contrast flow over time through the modelled vessel at baseline and hyperemic angiographic projections using TIMI frame count to determine mean volumetric flow rates. This informs some of the boundary conditions for the CFD simulation. However this method requires induction of hyperaemia and can be biased by manual contrast injection rate and timing. [181]

In contrast to CFD modelling, in which accurate coronary microvascular resistance parameters are paramount to the accuracy of the model simulation, the mathematical derivation of QFR relies upon the geometry of the segmented vessel from 3D-QCA and several assumptions. The mathematical model firstly assumes that coronary pressure is constant in normal coronary arteries and that the degree of pressure drop is determined by flow through the stenosis geometry, described by simplified fluid dynamic equations. [56,93,94] Secondly, it assumes 3D-QCA stenosis geometry is accurately determined by sizing relative to the healthy lumen as if there was no stenosis. The third assumption is that coronary flow velocity is preserved distally relative to the proximal flow velocity. This takes into account the reduction in

mass flow rate due to the tapering of the vessel and the presence of side branches. Based upon this assumption mass flow rate throughout the vessel can be determined by the mean flow velocity and the vessel sizing from 3D-QCA at any location. [194] However, the method of FFR computation appears to make little difference to the sensitivity and specificity of FFR according to a meta-analysis of the diagnostic performance angiographically-derived FFR. [201]

1.6.2.3 FFR Derived From Rapid Pressure-Flow Simulation

Kornowski et al developed FFR_{angio}. This is a novel method of mapping the physiology of the coronary tree based on a 3D representation of the coronary arteries and rapid flow analysis derived from a 0D model that can assess FFR. [202] Rapid flow analysis incorporates the patients' haemodynamic parameters alongside classification of the dynamic characteristics of the vessels. Coronary stenoses are converted into resistances in a 0D model. Vessel resistance can be inferred based on its length and diameter, applying Poiseuille and Bernoulli equations. Microvascular resistance is estimated according to scaling laws derived from three important relationships between the length and volume of the coronary tree, the lumen diameter and blood flow rate and thirdly the diameter and length of the vessel and its branches. [203] FFR is then calculated as the ratio of hyperemic flow in the stenotic vessel compared to that in a normal vessel.

1.6.3 Diagnostic Accuracy of Angiography-derived FFR

As can be discerned from Table 1.2, there are several computational methods of deriving FFR from the base coronary angiogram. Generally speaking virtually computed FFR is accurate compared with invasively measured FFR in the discrimination of ischaemia causing stenoses defined by the FFR cut-off value of 0.80. Collet et al. conducted a meta-analysis and systematic review of 13 studies (1842 vessels) that compared angiography-derived FFR against invasively measured FFR using 0.80 as the threshold of lesion significance. A variety of methods of FFR calculation were included in the analyses including, CFD simulation, mathematical modelling and rapid-flow analysis. The primary

outcome was pooled sensitivity and specificity of angiographically derived FFR. [201] The pooled sensitivity and specificity of angiography-derived FFR for the detection of a functionally significant stenosis was 89% (95% CI: 83% to 94%) and 90% (95% CI: 88% to 92%) respectively. The pooled discriminatory ability using the binary FFR cut-off of 0.80 was 84%. Bivariate meta-regression analyses demonstrated no significant difference in the sensitivity and specificity of FFR derived from CFD simulation or mathematical modelling or by online or offline analyses. [201] Pooled lesion-specific analysis was performed in 80% of vessels (n = 1478). The mean invasively measured FFR was 0.82 ±0.11. The mean angiographically derived FFR was 0.82 ±0.11. The mean difference was -0.003 with limits of agreement between 0.13 and -0.13. By utilising a zone of uncertainty between vFFR values of 0.77 and 0.86, angiographically derived FFR achieved 94% sensitivity and 95% specificity. [201] One study reported that utilising a zone of uncertainty, invasive pressure wire measurement of FFR could have been avoided in 64% of cases with 95% accuracy. [195] This could translate into a potentially more cost effective and safer means for invasive FFR measurement. [201]

	Software	Accuracy	Sensitivity	Specificity	PPV	NPV	AUC	Number of Patients	Correlation with FFR	BA Limits of Agreement
Morris et al [164]	vFFR	97%	86%	100%	100%	97%	*	19	0.84	FFR ± 0.16
Trobs et al [198]	FFR_{angio}	90%	79%	94%	85%	92%	0.93	73	0.85	FFR ± 0.13
Tu et al [181]	QFR	88%	78%	93%	82%	91%	0.93	68	0.81	FFR ± 0.13
Papafaklis et al [192]	vFAI	88%	90%	86%	80%	94%	0.92	120	0.78	*
Pellicano et al [204]	FFR_{angio}	93%	88%	95%	22+	0.12+	0.97	184	0.90	FFR ± 0.10
Kornowski et al [193]	FFR_{angio}	94%	88%	98%	*	*	*	88	0.90	FFR ± 0.10
Xu et al [205]	QFR	92%	95%	92%	86%	97%	0.96	308	0.86	FFR ± 0.13
Yazaki et al [206]	QFR	89%	89%	88%	74%	95%	0.93	142	0.80	FFR ± 0.10
Westra et al [207]	QFR	83%	77%	86%	75%	87%	0.86	172	0.70	FFR ± 0.12
Fearon et al [208]	FFR_{angio}	92%	94%	91%	89%	95%	0.80	301	0.80	FFR ± 0.13
Omori et al [209]	FFR_{angio}	92%	92%	92%	*	*	0.92	50	0.83	FFR ± 0.14
Stahli et al [210]	QFR	93%	75%	98%	89%	94%	0.86	436	0.82	FFR ± 0.07
Li et al [211]	caFFR	96%	90%	99%	97%	95%	0.98	328	0.89	FFR ± 0.10

Table 1.2 A summary of the major trials reporting the diagnostic performance of angiographically-derived FFR. **+** likelihood ratio reported. ***** not reported. **caFFR** (FlashAngio Rainmed Ltd, China), **FFR_{angio}** (CathWorks, Israel) **QFR®** (QAngio XA Medis Medical Imaging Systems, NL), **vFAI** (CAAS 3D-QCA, Pie Medical Imaging,NL), **vFFR** (VIRTUheart™, University of Sheffield, UK)

1.6.4 Comparing Angiographically-derived FFR and CTFFR in the FFR Grey Zone

The diagnostic accuracy of angiographically derived FFR, much like CTFFR is at its lowest around the physiologically ambiguous FFR cut-off point of 0.80. The international, prospective and observational FAVOR II study, in which 329 patients were enrolled, reported that the accuracy of angiographically-derived FFR was 71.3% between FFR values of 0.75 and 0.84 in patients with stable coronary artery disease undergoing invasive FFR measurement. [195] This is in contrast to CTFFR, which demonstrated an overall diagnostic accuracy of 46.1% for FFR values between 0.70 and 0.80. [191] The statistical method of comparison is important. Often in the literature, correlation coefficients are quoted when comparing angiographically-derived FFR or CTFFR to invasively measured FFR. This can be misleading if solely relied upon, because correlation only describes the strength of linear association between the two measurements. However correlation gives no insight on whether there is agreement between the two measures. [212] For example if angiographically-derived FFR or CTFFR measurement was consistently half of the invasively measured FFR, then the two measures would show no agreement but perfect correlation. The reported overall correlation of CTFFR and angiographically-derived FFR with measured FFR is reported as 0.73 [191] and 0.81 [201] respectively. A better method is to use the Bland-Altman method, which allows for a visual appreciation of the association between the difference in measurements and the magnitude of FFR. [213]

Figure 1.4 demonstrates the Bland-Altman plots from CTFFR and angiographically-derived FFR systematic reviews. [191,201] It can be seen that there is mean net bias for underestimation of FFR through CTCA with greater variability when compared to ICA. The CTFFR bias is −0.029 with 95% limits of agreement ranging from −0.212 to 0.155 where as the angiographically-derived FFR bias is 0.003 with 95% limits of agreement ranging from -0.137 to 0.137. Secondly, there is significantly greater scatter about the mean difference with CTFFR in the clinically important range of FFR values between 0.70 and 0.80 when compared to angiographically-derived FFR.

The improvement in diagnostic accuracy with angiographically-derived FFR compared to CTFFR could be explained by the greater image resolution afforded by ICA and the inherent limitations associated with CTCA in patients with calcific disease, irregular heart rhythms, tachycardia and motion artifacts. [164] Utilising a zone of uncertainty in which diagnostic accuracy is ≥95% or greater for a given measurement of computed FFR, a smaller zone of uncertainty would be achieved with angiographically-derived FFR compared to CTFFR (0.77 to 0.86 versus 0.53 to 0.93 respectively). [191,201] This is could translate into more efficient use of invasive fractional flow reserve measurement in clinical practice as virtual measures of FFR become more common place, permitting triage of some cases that otherwise would require invasive FFR.

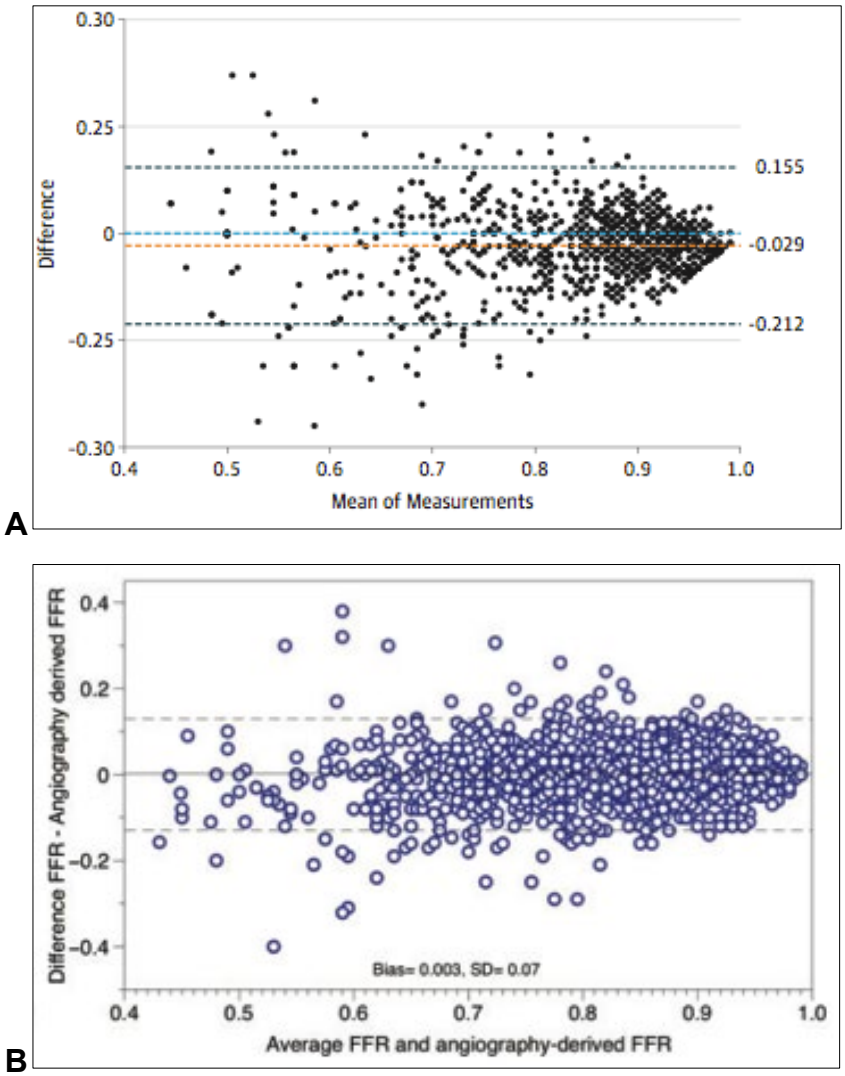

Figure 1.4 Systematic review Bland-Altman plots for agreement of invasively measured FFR against **[A]** CTFFR and **[B]** angiographically derived FFR. Reproduced with permission from Cook et al [161] and Collet et al. [171]

1.7 Rationale of Proposed Study

Prior to the introduction of the NICE guideline for chest pain of recent onset in 2016, [42] which recommended that CTCA should be offered as the first-line investigation for the investigation of stable chest pain, the annual rate of CTCA was estimated at around 42,300 per year. To fully implement this guideline it is estimated that an average 8-fold increase in service provision to reach 350,000 scans per year is required. [214] About 250,000 diagnostic coronary angiograms were carried out in the United Kingdom between 2017 and 2018. This figure has been steady for the past half-decade. [215] It is likely that this number may increase given the non-negligible false-positive rate associated with CTCA extrapolated from the SCOT-HEART trial. [34] Coupled with the considerable evidence base for physiology-guided revascularisation and the advent of well-established technology to facilitate non-invasive or minimally invasive estimation of coronary lesion significance, large prospective multicenter randomised clinical trials are necessary to clarify the clinical and economic outcomes of such ‘all-in one’ means of investigation of CAD. The VIRTU-4 trial is a virtual pilot study to inform the design and execution of such trials in the future.

1.8 Hypothesis

Virtual fractional flow reserve will significantly impact the management strategy of patients with chronic coronary syndromes.

The null hypothesis for this project states that: Virtual FFR will not result in a significant change in the management plans of patients with chronic coronary syndromes undergoing invasive coronary angiography.

1.9 Aims and Objectives

The primary aim of the VIRTU-4 CCS trial is to record whether disclosing vFFR data in elective coronary angiography of stable angina patients would result in a significant change in management strategy. This will be achieved through the following objectives:

- VIRTUheart^{TM} software will be applied to elective patients undergoing coronary angiography recruited from four district general hospitals.
- The initial management strategy of the treating cardiologist will be recorded. vFFR will then be calculated and disclosed only when the initial management strategy has been confirmed. Any hypothetical changes in management strategy will then be recorded.
- Heart Team MDTs will be convened at a later date and each patient will be discussed. A consensus management strategy based upon the angiogram will be documented. Virtual FFR will then be disclosed any changes in strategy will be recorded.
- Telephone follow-up at six months of participants will be carried out to ascertain the actual management strategy implemented, the occurrence of any adverse events.

Chapter 2: Methods

2.1 Study Design and Outline

The VIRTU-4 CCS trial outline is summarized in Figure 2.1.

VIRTU-4 CCS was a 'virtual' cohort, observational study. Patients with symptomatic suspected coronary artery disease were identified at Doncaster, Chesterfield, Rotherham and Barnsley district general hospitals by their respective local cardiology teams between February 2020 and September 2021. These patients were scheduled to undergo elective coronary angiography for stable angina. Prior non-invasive anatomical or functional testing was not a prerequisite for enrollment. A modelled vFFR <0.80 in a vessel was the indication for (virtual) revascularisation. This criterion was based upon a synthesis of the RIPCORD [119] and FAMOUS-NSTEMI [121] studies that employed invasively measured FFR. Written consent was obtained and baseline clinical data were recorded. The treating cardiologists and radiographers were instructed about the key steps to perform optimal coronary angiography for vFFR processing prior to each session. The angiograms were then anonymised and loaded in DICOM ® (Digital Imaging and Communications in Medicine) format into the VIRTUheart™ workflow on the study laptop in the catheterisation laboratory. Any problems in processing the angiograms; in particular, suitability for the segmentation step were also recorded as well as calculation time. Consenting patients had their actual management strategies formulated by the treating cardiologist in the usual manner; on the basis of the clinical picture and the angiogram. The initial management strategy of the treating cardiologist at vessel and patient level were recorded as well as their confidence in their chosen management strategy. Only after documentation of the proposed management strategy was the vFFR data disclosed to the treating cardiologist, with the question of whether the vFFR data would hypothetically change their recommended management strategy and or their confidence level in their proposed strategy. The Heart Team, consisting of an interventional cardiologist, a non-interventionist and a surgeon, were convened remotely at a later date. They

were presented with patients' angiograms and background clinical information. The Heart Team made hypothetical management strategies based on this information. Similarly once strategies were agreed upon, the vFFR data was disclosed and any changes in strategy or confidence level were recorded. Patients were then contacted by telephone at 6 months to determine clinical outcomes and the actual treatment delivered.

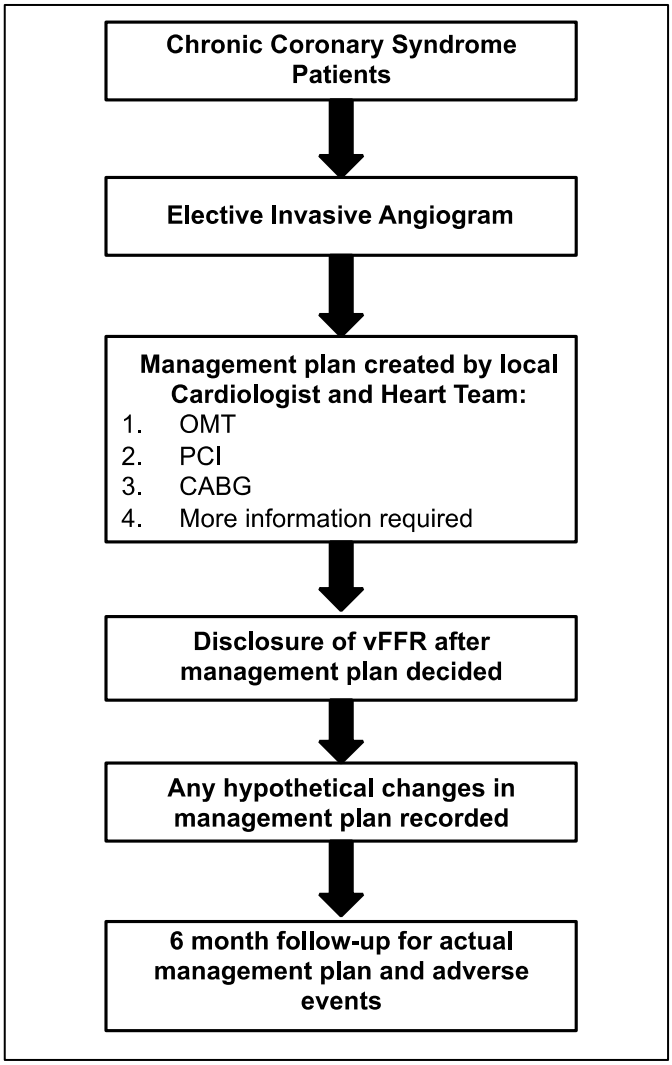

Figure 2.1 VIRTU-4 CCS Study Flowchart

2.2 Sample Size and Sampling Technique

The number of participants required was similar to RIPCORD [(119)], given the similarities in study design and primary end-point. In RIPCORD, invasive FFR disclosure resulted in a change in management strategy of 26% in a sample of 200 patients. In the VIRTU-4 CCS trial, 206 participants would provide 85%

power (two-sided α = 0.05) to reject the null hypothesis. It was anticipated that a proportion of patients would be excluded based on anatomical findings such as unobstructed coronary arteries or left main stem disease that would only be discerned upon completion of the coronary angiogram. Therefore it was estimated that enrolling about 250 patients prior to the angiogram would be sufficient to achieve 206 patients to complete the study. These numbers were thought to be readily achievable because approximately 5000 angiograms are performed across South Yorkshire per year.

The VIRTU-4 trial was an observational cohort study. The cohorts were comprised of the elective CCS patients and the inpatient ACS patients. Each cohort aimed to recruit 206 patients. There was no randomisation. Recruitment commenced in February 2020 in the CCS arm and will continue over a two-year period. Recruitment rate was to be evenly spread across each of the four hospitals over the two-year period.

2.3 Ethics and Regulatory Approval

The VIRTU-4 trial was designed to safely and efficiently determine whether a novel technology might have the potential to improve patient care. It had already been shown that invasive FFR effects such an improvement and this study sought to address the question of whether a virtual FFR, which does not require instrumentation of the patient, could achieve the same end without any of the risks. The potential clinical gain from the study would, therefore, be considerable.

The main ethical issue was to protect the patient's personal information because this was a data-only study. The VIRTUheart^{TM} tool was an experimental tool without MHRA approval or a CE mark. This was emphasized to participating cardiologists so as not to influence actual patient management. All participants had the standard of care expected and delivered by their regular clinical teams. Their dignity was maintained at all times. They were not direct beneficiaries of this research, except to receive the satisfaction of knowing that this work may improve the care offered to

future patients, if the VIRTUheart™ system gains regulatory approval. An approval was issued from the Research Ethics Committee (HRA and Health and Care Research Wales. REC reference: 19/NW/0580, IRAS ID: 270127) for the study protocol (version 1.0), consent form (version 4) and patient information sheet (version 5).

2.4 Consent

The clinical research fellow identified suitable patients on the day of their elective coronary angiogram through examination of each patients clinical notes and clinic letters. Permission was granted after local trust approval via means of a research passport and NHS-to-NHS letter of access. The clinical research fellow then gained written patient consent after supplying them with the patient information sheet [see Appendix A]. A copy of the consent form will be retained. Patients lacking capacity or those requiring and interpreter were not included in the study.

2.5 Eligibility Criteria

Much like the RIPCORD study [119], patients with suspected obstructive coronary artery disease meriting coronary angiography, as determined by a provisional diagnosis of angina by their treating cardiologist, were eligible for enrollment in to the VIRTU-4 CCS study. There was no requirement to demonstrate ischaemia prior to angiography through non-invasive testing.

2.6 Angiographic Inclusion Criteria

Patients with CCS who were over the age of 18, with one or more diseased major vessels of >2.25mm diameter, with one or more lesion >30% diameter stenosis assessed visually, were eligible for recruitment.

2.7 Exclusion Criteria

Exclusion criteria were serum creatinine >180 µmol/L, uncontrolled ischaemia, haemodynamic instability, acute coronary syndrome, prior CABG surgery,

severe valvular disease, intolerance to antiplatelet drugs, ineligibility for revascularisation, life-threatening comorbidity or failure to consent. Exclusion criteria for calculation of vFFR are diffuse disease, chronic total occlusion as the only lesion, left main stem disease, completely normal coronary arteries, coronary artery stenosis > 90% diameter stenosis and inadequate angiographic images for modelling.

2.8 Primary Endpoint

The primary endpoint was the percentage change in management plans based on the angiogram after vFFR disclosure. This was selected to demonstrate that in a similar way to previous studies, physiological data would result in significant changes in management strategy of patients with stable CAD in routine practice. A strategy change was defined as a change of strategy between OMT, PCI, CABG or 'more information' [Figure 3].

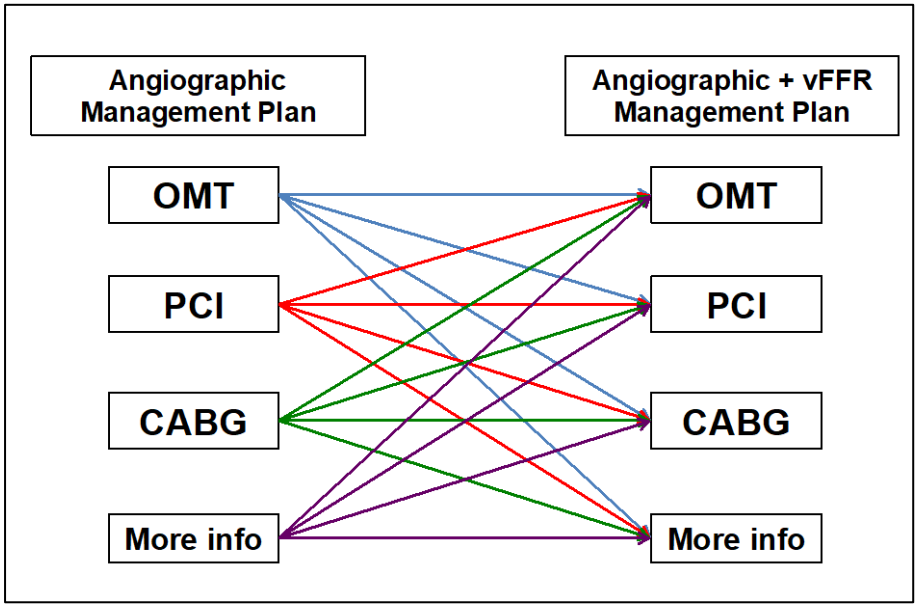

Figure 2.2 Definition of Overall Management Strategy Change.

2.9 Secondary Endpoints

1. The feasibility of running the vFFR workflows on non-specialist angiograms.
2. An assessment of the intra-observer and inter-observer variability of vFFR measurement.
3. Comparison of VIRTUheart™ vFFR against the commercially available CAAS-vFFR (Pie Medical Imaging) and QFR® (Medis Medical Imaging) platforms.
4. An assessment of how vFFR affects cardiologists' confidence levels in their chosen management strategy.
5. Collection of data for a subsequent health economic analysis at a later date.

2.10 Recruitment Sites

Four sites with experienced operators proficient in diagnostic coronary angiography were chosen to recruit patients, namely Doncaster and Bassetlaw Teaching Hospitals Foundation Trust, Barnsley Hospital NHS Foundation Trust, The Rotherham NHS Foundation Trust and Chesterfield Royal Hospital NHS Foundation Trust. These sites do not perform coronary intervention including pressure-wire measurements. Any invasive work beyond diagnostic angiography is referred to a central tertiary centre; Sheffield Teaching Hospitals.

2.10.1 Doncaster and Bassetlaw Teaching Hospitals Foundation Trust

Doncaster Royal Infirmary has two multifunctional angiography suites. Siemens provides both the fluoroscopy apparatus (Artis Zee C-arm) and the cardiac physiology monitoring system (Sensis Vibe).

2.10.2 The Rotherham NHS Foundation Trust

Rotherham Hospital has one dedicated cardiac angiography suite. Philips provides both the fluoroscopy apparatus (Azurion Clarity Q) and the cardiac physiology monitoring system (Xper Information Management System).

2.10.3 Barnsley Hospital NHS Foundation Trust

Barnsley hospital has a single multifunctional interventional radiology suite. Toshiba provides the fluoroscopy apparatus (Ultimax Fluoroscopy System) however GE provides the cardiac physiology monitoring system (Mac-lab™ version 6.9.6.) Following refurbishment of their angiography suite, these two different systems were integrated to allow for an ECG signal to be recorded on the DICOM files, which is a prerequisite for the VIRTUheart™ software.

2.10.4 Chesterfield Royal Hospital NHS Foundation Trust

This site was not operational at the commencement of the VIRTU-4 CCS trial. Currently two different manufacturers provide the fluoroscopy and cardiac physiology equipment. These two systems do not communicate meaning an ECG signal is not present on the DICOM file. This information is a prerequisite for the VIRTUheart™ software. To circumvent this problem, a software-modification to the segmentation tool was made to allow case processing without the need for an ECG signal, accepting a reduction in model accuracy.

2.11 Invasive Coronary Angiography

Invasive coronary angiography was performed according to each district general hospitals' local policies and practices. Arterial access was either via the right radial or right femoral approach. Five and four French diagnostic catheters were used. Contrast was delivered by manual injection. It is important to note that each district hospital has different angiographic equipment, often catering for other radiological interventions.

2.12 Catheterisation Laboratory Standard Operating Procedure

Standard operating procedures for coronary angiography and conducting the study in the catheterization laboratory can be found in Appendix A. Angiographic image quality is paramount to accurate vessel segmentation and discretisation. The VIRTU-1 investigators demonstrated that up to 50% of coronary angiograms could not be used for CFD modelling. Common reasons included, too much vessel overlap, foreshortening, inadequate opacification and too much table movement. However with coaching this number fell to around 20%. [216] With this in mind, guidelines for optimal coronary angiography have been created to aid those performing angiography. The key principle was to capture the lesion in the artery of interest in two orthogonal views at least 30^{o} apart with no or minimal overlapping vessels without panning over at least 4 cardiac cycles.

2.13 Virtual FFR Computation

Patients with lesions of 30-90% visual diameter stenosis in vessels 2.25mm or greater were eligible for vFFR calculation. Anonymised angiograms were burned on to CDs in Digital Imaging and Communications in Medicine (DICOM) format and then processed immediately using the study laptop on which the VIRTUheart™ software was installed.

VIRTUheart™ version 2.0 which incorporates Ansys Fluent™ (a CFD solver software) was used to perform model simulations. The solver conducted pseudotransient simulations to converge several million non-linear Navier-Stokes continuity equations from two steady-state analyses simulating resting and hyperaemic coronary flows at 1ml/second and 3ml/second respectively. Virtual FFR was then calculated from post-processing of the simulation.

What follows is a description of the steps to calculate a vFFR value using the VIRTUheart™ software.

1. Two cine runs displaying the lesion of interest ≥ 30 degrees apart in any direction are selected.

2. End-diastole is identified in each run. This when the coronary arteries have the least motion and the coronary lumen margins are at their clearest.
3. The software is then informed of the catheter size as a sense check of the distance information contained in the DICOM tags. The DICOM distance information is the primary mode of size calibration.
4. An identical point is selected on both of the cine runs. This can be a bifurcation point or the site of maximal stenosis.
5. The vessel centre-line is automatically defined following placement of markers to indicate the start and the end of the segment of interest. The vessel diameter is also defined in a similar way. As much of the vessel should be segmented. The model should start in a healthy portion of vessel and the minimum model length should be at least 10 times the minimum stenosis diameter.
6. An automated lumen edge tracing is generated in a few seconds. The operator then has a chance to review and amend this as necessary.
7. Steps 5 and 6 are repeated for the second cine run.
8. Once the operator is satisfied with the lumen margin tracing, a virtual 3D vessel segmentation and mesh is created.
9. Boundary conditions are inputted to inform the parameters of the model. These are as follows:
    a. The patient's mean arterial pressure, which defines the inlet boundary.
    b. A personalised outlet boundary condition defining microvascular resistance. The clinical parameters used to inform this distal boundary condition are mentioned in Table 2.1.
    c. A generic population averaged outlet boundary condition can also be applied using the constant: 8.721E9.
10. Having been informed of the boundary conditions, the model simulation takes a few minutes to complete. At this point a proximal and distal marker can be placed any where along the length of the model to give the FFR between those points. [Figure 2.3]

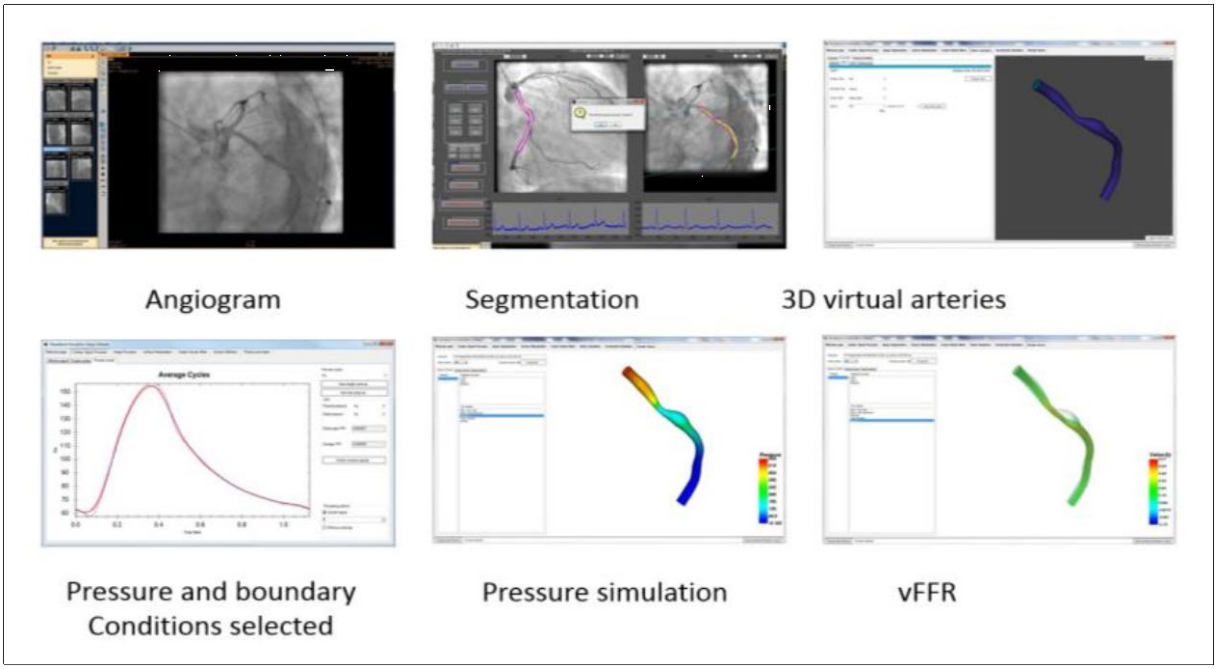

Figure 2.3 VIRTUheart™ workflow.

Vessel
LAD
LCx or Intermediate
RCA
Duke Score
Myocardial Jeopardy Index
Diastolic Blood Pressure (mmHg)
Patient weight (Kg)
Heart Rate (bpm)
ACEi/ARB Prescription
Presence of Hyperlipidaemia
Presence of COPD
Clinical Frailty Score
Haematocrit
QTc duration (ms)
Left Ventricular Hypertrophy Sokolov-Lyon Criteria (mm)
New York Risk Score (%)

Table 2.1. Clinical Parameters Modulating the Distal Boundary Condition.

2.14 Data Collection

What follows is a list of the individual data points divided into broad categories that were collected for each participant over the course of the VIRTU-4 CCS trial. Data entry was made on an Excel spreadsheet.

Generic Demographics

All participants dates of birth, age in years, gender, angiography date and contact telephone numbers were recorded.

Past Medical History

All participants had their diagnosis of hypertension, diabetes mellitus, hypercholesterolaemia, smoking status and previous myocardial infarction documented.

Medications and Investigations

Information about serum creatinine, number of regularly prescribed antianginals (apart from PRN sublingual GTN spray), current prescription of antiplatelet, statin, ACEi/ARB or MRA, previous echocardiogram and left ventricular function was recorded. The modality and findings of previous non-invasive tests was also recorded.

Clinical Scores

Four clinical scores were recorded for all participants. These were the New York Heart Association (NYHA) Classification [217], Clinical Frailty Scale [218], SYNTAX Score I [219] and EQ-5D-5L Score [220] at baseline and at 6 months follow-up. [Appendix A]

Output variables

The output variables recorded were percent diameter stenosis in each main coronary artery (assessed visually), vFFR values, vFFR calculation time in minutes, a proportion of cases processed with CAAS-vFFR and QFR®, a proportion of cases with vFFR results processed by a second operator, mortality at 6 months, unscheduled hospitalisations or GP visits at 6 months, any additional investigations, any complications of coronary angiography and any reasons for failure to generate a vFFR result for any given case or vessel.

2.15 Treating Cardiologists' Decision Making

Having completed the ICA, the treating cardiologist was asked to give a visual percent diameter stenosis for each main coronary artery and or lesion. The treating cardiologist then formulated a management strategy in the usual manner. This strategy was recorded as one of the following options:

1. **Optimal Medical Therapy** – which may involve modification of antianginal and preventative medications.
2. **Revascularisation with PCI** – the number of vessels proposed for PCI was recorded.
3. **Revascularisation with CABG** – the number of proposed bypass grafts was recorded.
4. **More Information Needed** – Additional information in the form of invasive or non-invasive ischaemia testing, viability testing and/or further anatomical or structural imaging. Repeat coronary angiography and non-cardiac investigations were also included in this category.

Only hypothetical management strategy changes were recorded. There were no actual changes in patients' management strategies following vFFR disclosure, as VIRTUheart™ is not currently MHRA approved or CE-marked for clinical use.

2.15.1 Confidence Levels

Once the management strategy had been formerly documented, the cardiologist was asked to rate their confidence in their chosen strategy on a scale of 1 to 10 (10 being extremely confident). The vFFR was then disclosed to the treating cardiologist. Any hypothetical change in management strategy was documented as above. The treating cardiologist was asked to rate their confidence in their initial strategy again after vFFR disclosure.

2.16 Heart Team's Decision Making

The VIRTU-4 trial Heart Teams consisted of an interventional cardiologist, a non-interventional cardiologist and a cardiothoracic surgeon. The Heart Team was convened virtually to adhere with social distancing and for the convenience of the participating consultants. Each patient's pertinent clinical information and coronary angiogram was presented to the Heart Team using a PowerPoint presentation and dedicated DICOM player to ensure the quality of the angiogram was correctly conveyed. Heart Team hypothetical management strategies and confidence levels were recorded before and after vFFR disclosure on a dedicated proforma [Appendix A] in a similar way to the treating cardiologists at the DGHs.

2.17 Data Protection and Storage

Data handling in our study conformed to the Data Protection Act 2018, which is the UK's implementation of the General Data Protection Regulation (GDPR). All study personnel followed the data protection principles described in that Act. All patient data was: used fairly, lawfully and transparently; used for specified, explicit purposes, as described here; used in a way that is adequate, relevant and limited to only what is necessary; accurate; kept for no longer than is necessary; handled in securely, with protection against unlawful or unauthorised processing, access, loss, destruction or damage.

Specifically, for this study, the clinical research fellow used an encrypted, dedicated laptop computer. Each patient has a unique study number that is

linked with his or her clinical records. Limited contact information was also securely kept on file until the 6-month telephone follow-up was complete. The data was uploaded to the dedicated ArQ database located in the Department of Infection, Immunity and Cardiovascular Disease. This database was purpose built by the Sheffield Teaching Hospitals Department of Scientific Computing to serve clinical studies. It complies with all necessary governance. The data is therefore maintained using encrypted digital files within password protected folders and storage media. Access was confined to the VIRTU-4 research team for quality control, audit, and analysis. Subsequent data analysis was conducted in the Department of Infection, Immunity and Cardiovascular Disease in the University of Sheffield. In accordance with Sheffield Hospital Trust policy. The anonymised data will be stored for 15 years. The Principle Investigator, Professor Gunn, is the data custodian.

2.18 Statistical Methods

Statistical analysis was conducted using IBM® SPSS® version 26. Categorical variables were presented as counts and percentages. Normal distribution was assessed using the Shapiro-Wilk test and visual assessment of histograms. Normally distributed continuous variables were summarized using the means and standard deviations. Non-normally distributed data was reported using medians and interquartile ranges. Histograms and box-plots was displayed for continuous variables in Appendix B.

Data from the RIPCORD study [119] suggested that invasive FFR changes management in 26% of patients. Given the similarities between VIRTU-4 CCS and RIPCORD, we considered a change of <10% as non-clinically significant. The number of patients required in this study (p) to detect a difference in management plan after disclosure of vFFR was determined using the formula: $\hat{p} \pm 1.96 \text{ sqrt } (\hat{p}(1-\hat{p})/n)$. This gives sample size of around 200 with 95% confidence intervals of 15% to 25% for this effect size.

The primary and secondary outcomes were compared using McNemar-Bowker, χ^2 and paired t-tests as appropriate with a two-sided P value < 0.05

considered as being significant. Differences in treating cardiologists' and the Heart Team's confidence levels before after vFFR disclosure was assessed using a one-way repeated measures ANOVA. Comparison of VIRTUheart™, CAAS-vFFR (Pie Medical Imaging) and QFR® (Medis Medical Imaging) was carried out using Pearson's correlation coefficient and Bland-Altman plots with associated 95% limits of agreement. Inter-observer and intra-observer variability was assessed using the intra-class correlation co-efficient with two-way mixed and one-way random models respectively.

2.19 Follow-up Data Collection

Follow-up data for participants was obtained by means of telephone consultations at a minimum of six months. The telephone call was used to ascertain the actual treatment carried out, a repeat EQ-5D-5L questionnaire and whether there were any additional investigations and unscheduled hospitalisations or GP visits. In addition to telephone consultations, each recruitment site's clinical coding department was contacted to determine the mortality rates and the clinical codes for any unscheduled hospitalisations for any enrolled patients that were not contactable.

Chapter 3: Results

3.1 Study Demographics

A total of 223 patients were prospectively screened for the VIRTU-4 CCS clinical trial over a 19-month period across 4 participating sites [Figure 3.1]. 112 patients were eligible for inclusion. The baseline demographics of the study population are displayed in Table 3.1. Continuous variables such as age and SYNTAX I score were tested for normality and displayed using histograms and boxplots (Appendix 6.2). Figure 3.1 illustrates recruitment by participating hospital. Figure 3.2 illustrates the reasons behind the screen failure rate.

Number of Patients Recruited	112
Male	(83) 74.1%
Age (Mean ± SD)	65.3 (± 9.1) years
SYNTAX score (Median ± IQR)	10 (± 13.8)
Diabetes Mellitus	(40) 35.7%
Hypertension	(60) 53.6%
Hypercholesterolaemia	(63) 56.3%
Smoking	(20) 17.9%
Previous Myocardial Infarction	(23) 20.5%
Mean Serum Creatinine	82μmol/L
Clinical Frailty Score	
Very Fit	(46) 41.1%
Well	(43) 38.4%
Managing Well	(13) 11.6%
Vulnerable	(6) 5.4%
Mildly Frail	(3) 2.7%
Moderately Frail	(1) 0.9%
NYHA Status	
Class I	(59) 52.7%
Class II	(39) 34.8%
Class III	(14) 12.5%
Medications	
Antiplatelet	(106) 95.0%
Statin	(103) 92.0%
ACEi/ARB	(67) 59.8%
MRA	(9) 8.0%
Number of Antianginals	
0	(6) 5.4%
1	(39) 34.8%
2	(38) 33.9%
3	(24) 21.4%
4	(5) 4.5%
Echocardiogram Performed	(75) 67.0%
Non-invasive Test Performed	(66) 58.9%
Myocardial Perfusion Study	(35) 53.1%
CTCA	(17) 25.8%
Exercise Tolerance Test	(11) 16.7%
Dobutamine Stress Echocardiogram	(2) 3.0%
Perfusion CMR	(1) 1.5%

Table 3.1 Study population demographics

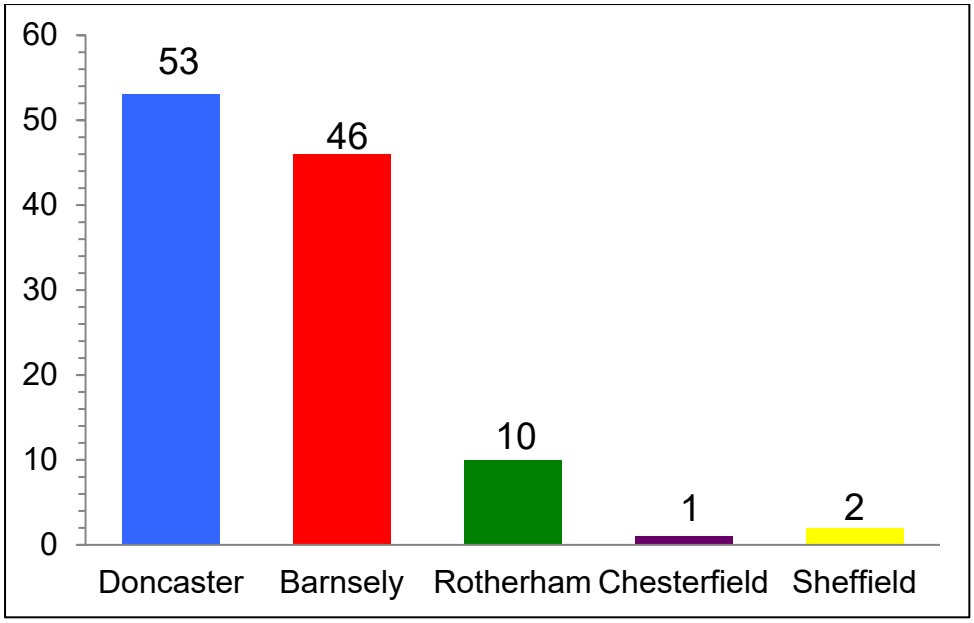

Figure 3.1 Recruitment by hospital. N = 112.

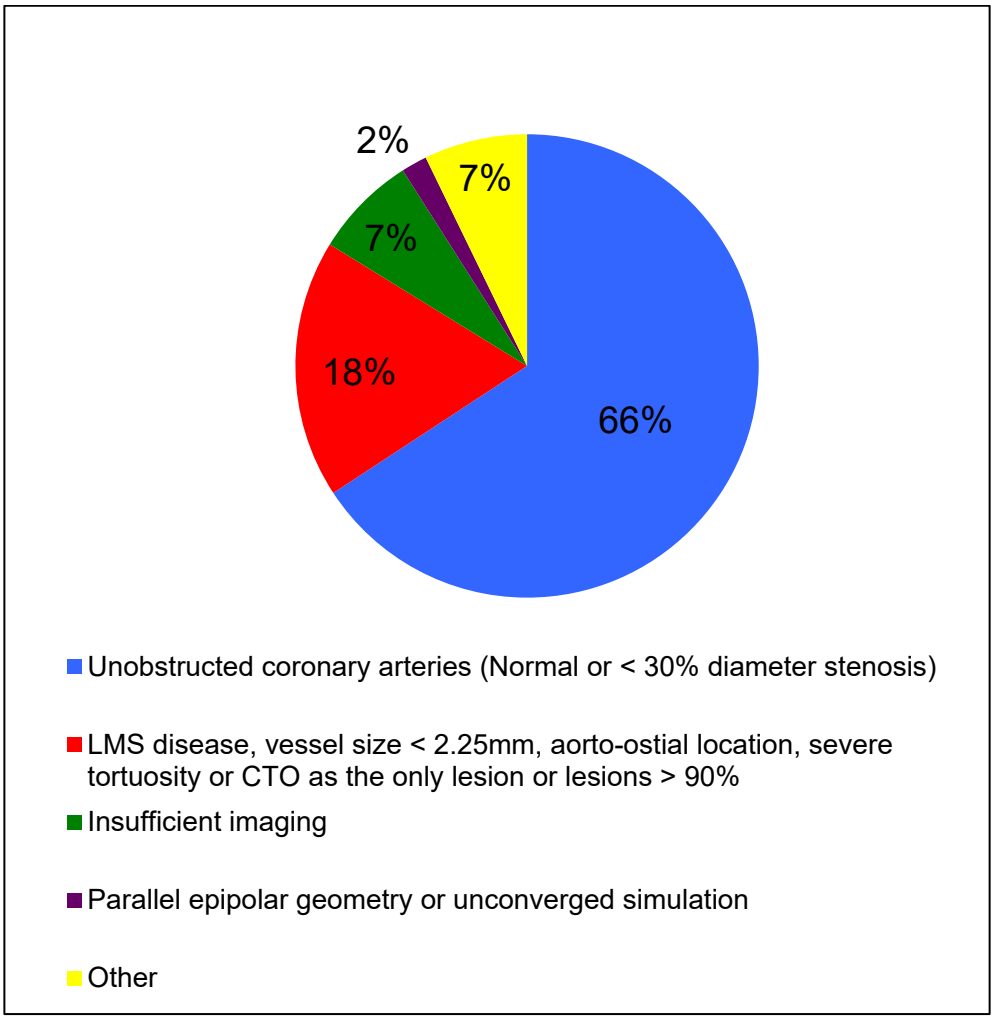

Figure 3.2 Screen failure reasons. Other includes cancelled or abandoned procedures. N = 111

3.2 Extent and Reclassification of CAD

All patients that were eligible for angiographic inclusion were classified as no-significant disease, 1VD, 2VD or 3VD. The mean number of angiographically significantly diseased vessels was 1.23 and 1.55 at the DGH and Heart Team assessments respectively. Virtual FFR disclosures lead to a reclassification of 50.0% (N = 56) and 56.3% (N = 63) of patients to predominantly 1VD and no-significant coronary disease at the DGH and Heart Team assessments respectively. After vFFR disclosures, the mean number of significantly diseased vessels dropped to 0.73 and 0.71 ($p < 0.001$) at the DGH and Heart Team assessments respectively [Tables 3.2 and 3.3]. The changes in the proportion of patients according to their extent of significant vessel disease before and after vFFR disclosure are illustrated in Figures 3.3 and 3.4.

District General Hospitals		Extent of Significant CAD After vFFR Disclosure				
		0VD	1VD	2VD	3VD	Totals
Extent of Angiographically Significant CAD	0VD	27	6	0	0	33
	1VD	12	25	3	1	41
	2VD	7	10	2	1	20
	3VD	1	11	4	2	18
	Totals	47*	52*	9*	4	112

Table 3.2 Cross-tabulation of angiographic extent of CAD by vFFR at the district general hospitals. (McNemar-Bowker test, $p < 0.001$). *These numbers differ from those presented in Table 3.3 as 12 vessels were reprocessed prior to the Heart Team meeting.

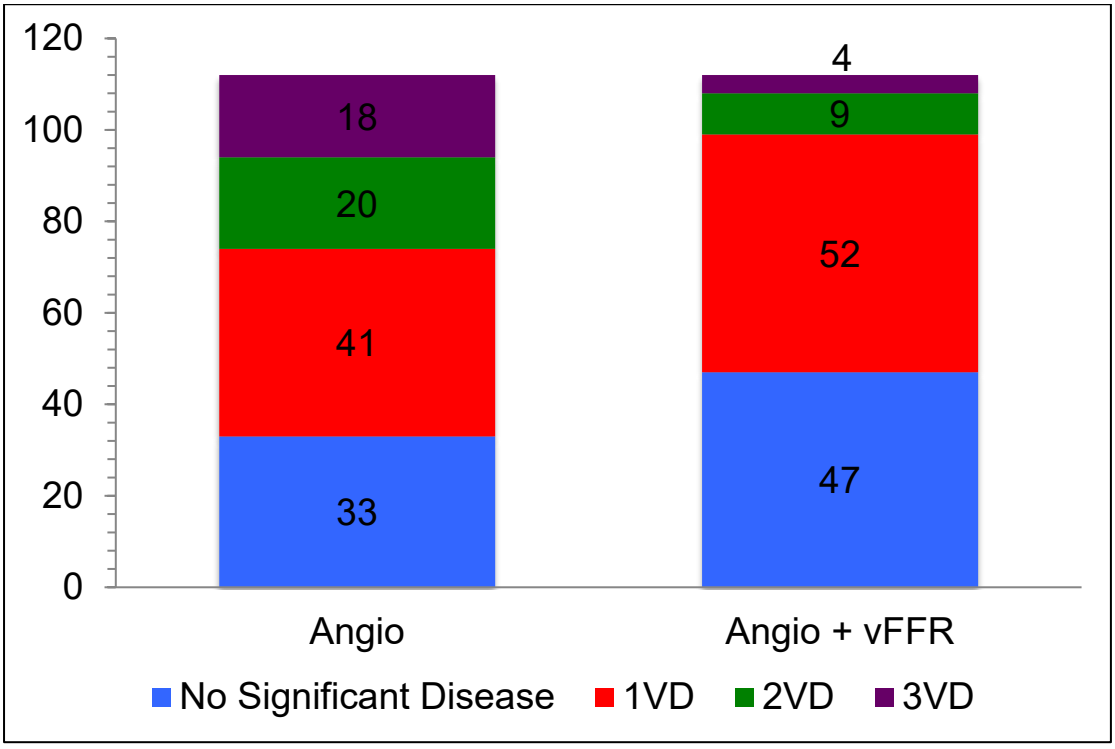

Figure 3.3 Proportion of patients according to their extent of significant coronary disease before and after vFFR disclosure at the District General Hospitals.

Heart Team MDT		Extent of Significant CAD After vFFR Disclosure				
		0VD	1VD	2VD	3VD	Totals
Extent of Angiographically Significant CAD	0VD	15	1	0	0	16
	1VD	12	26	1	0	39
	2VD	14	18	4	0	36
	3VD	4	13	0	4	21
	Totals	45*	58*	5*	4	112

Table 3.3 Cross-tabulation of angiographic extent of CAD by vFFR at the Heart Team level. (McNemar test, $p < 0.001$). *These numbers differ from those presented in Table 3.2 as 12 vessels were reprocessed prior to the Heart Team meeting.

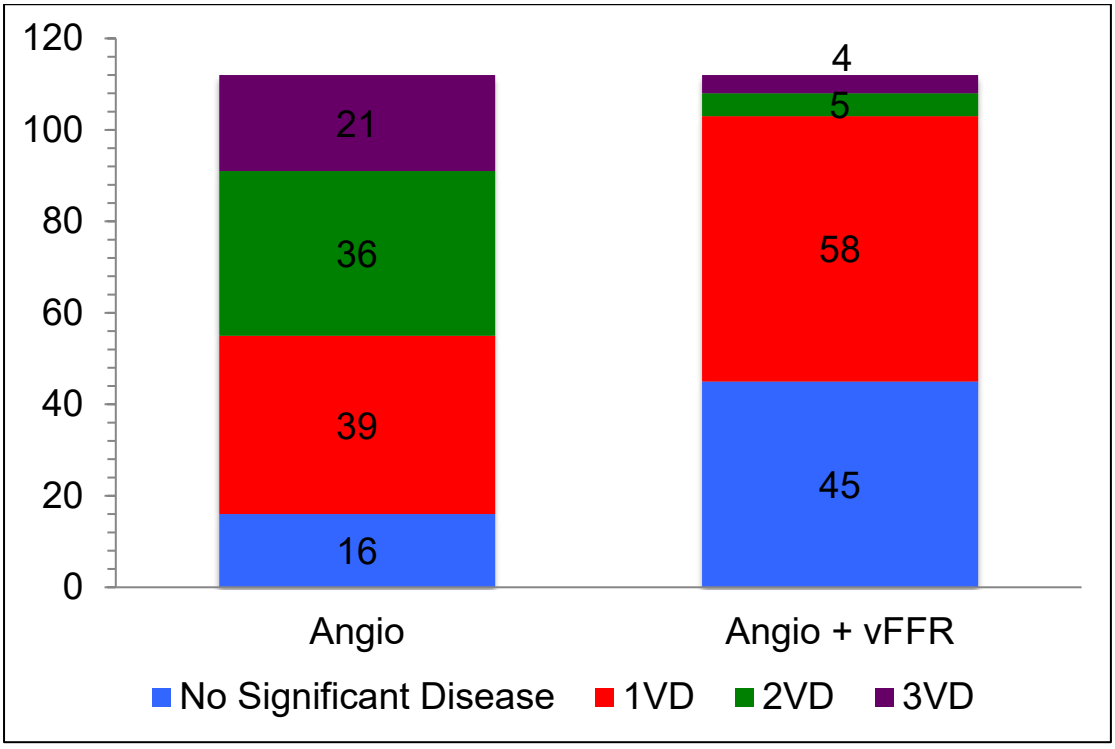

Figure 3.4 Proportion of patients according to their extent of significant coronary disease before and after vFFR disclosure at the Heart Team MDT.

3.3 Visual Stenosis Severity and Functional Significance

The treating DGH cardiologists' visual estimation of lesion severity was grouped into mild (30-50%), moderate (51-70%) and severe (71-90%) categories and cross-tabulated with vFFR as a dichotomous variable set at 0.80 [Table 3.4] as well as plotted against their corresponding vFFRs [Figure 3.5]. This data corroborates the findings of the RIPCORD trial which demonstrates the poor relationship between visual stenosis severity and functional significance.

Diameter Stenosis	vFFR ≤ 0.80	vFFR > 0.80
30-50%	15	54
51-70%	17	17
71-90%	33	14

Table 3.4 Cross-tabulation of stenosis severity by vFFR as a binary variable set at 0.80.

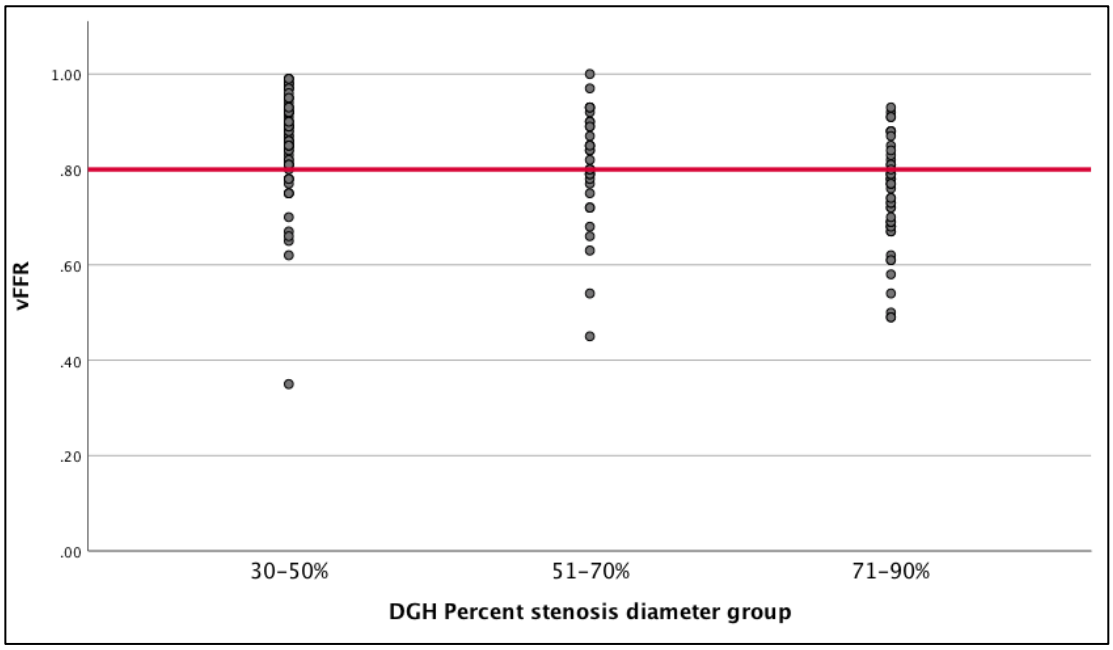

Figure 3.5 Scatter plot of visual stenosis severity against vFFR**.** The red line at 0.80 denotes the ischaemic threshold below which revascularisation should be considered. N = 150

3.4 Primary Outcome

The primary endpoint was the hypothetical percentage change in overall patient management strategy after vFFR disclosure.

3.4.1 DGH Cardiologists' Management Strategies

In a sample size of 112 patients a statistically and clinically significant change in overall management plan was observed in 22.3% (n = 25) of patients (95% CI: ± 8.12%, p = 0.013) after vFFR disclosure at the DGH level. Figure 3.6 illustrates the proportion of management strategies before and after vFFR disclosure. Figure 3.7 illustrates how these management strategies changed.

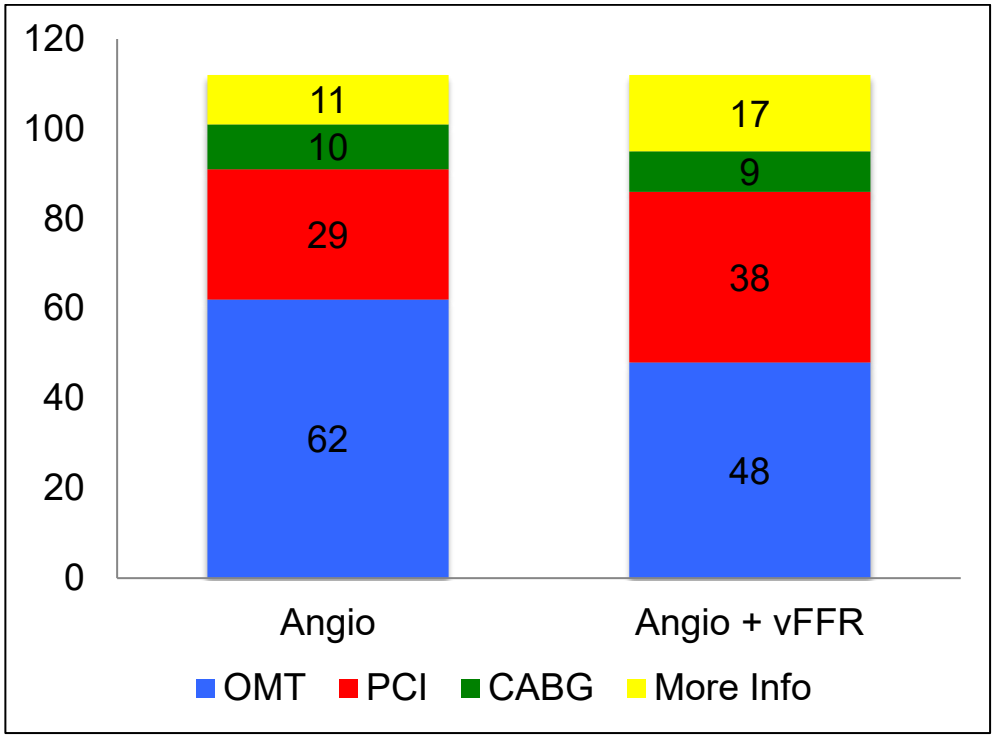

Figure 3.6 Hypothetical DGH management strategy changes after vFFR disclosure.

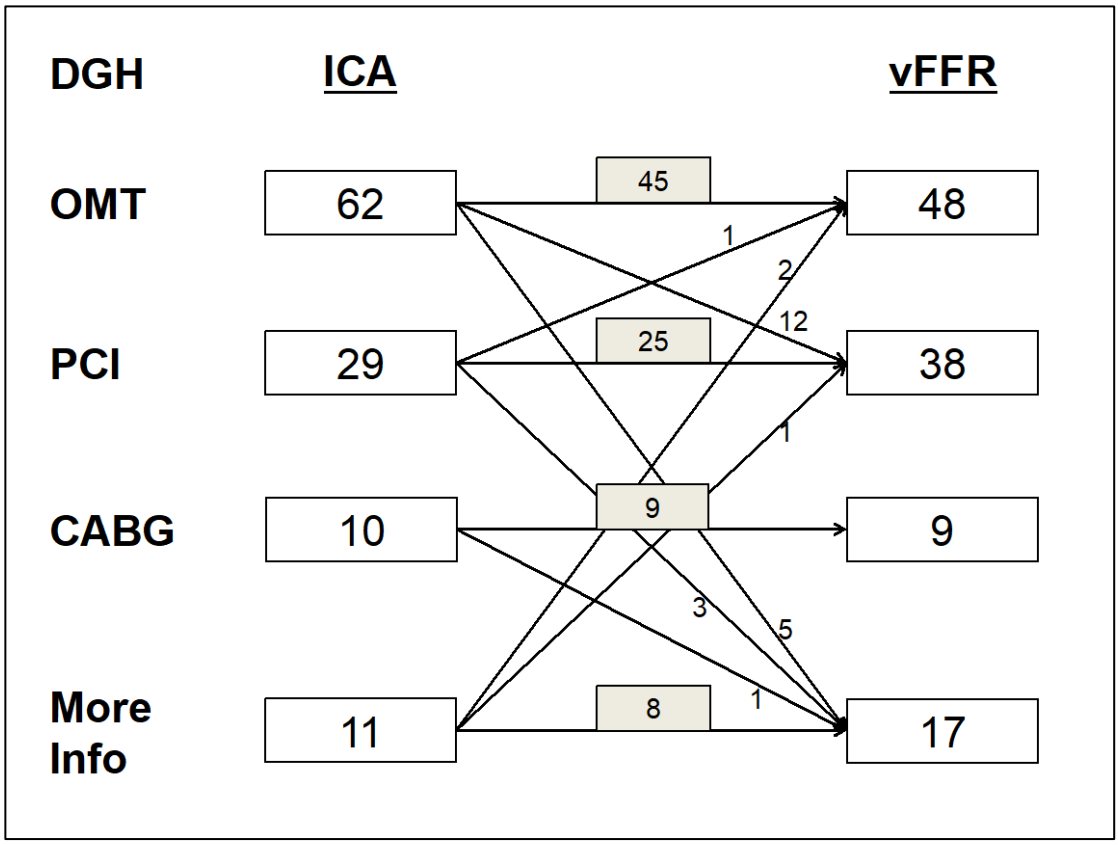

Figure 3.7 Diagram of Hypothetical DGH management strategy changes after vFFR disclosure. CABG coronary artery bypass graft surgery, **DGH** district general hospital, **ICA** invasive coronary angiography, **OMT** optimal medical therapy, **PCI** percutaneous coronary intervention.

3.4.1.1 Impact of vFFR on Hypothetical Invasive FFR Referrals from DGHs

The increase in the number of strategies changed to the 'more information' category after vFFR disclosure is a result of an increase in the rate of referrals for invasive FFR as a stand-alone test (4 to 7 patients) or in addition to PCI of other vessels (5 to 8 patients). This data suggests a relative increase in the use of invasive FFR by 67% (p = 0.001). The number of non-invasive test remained unchanged [Figure 3.8]

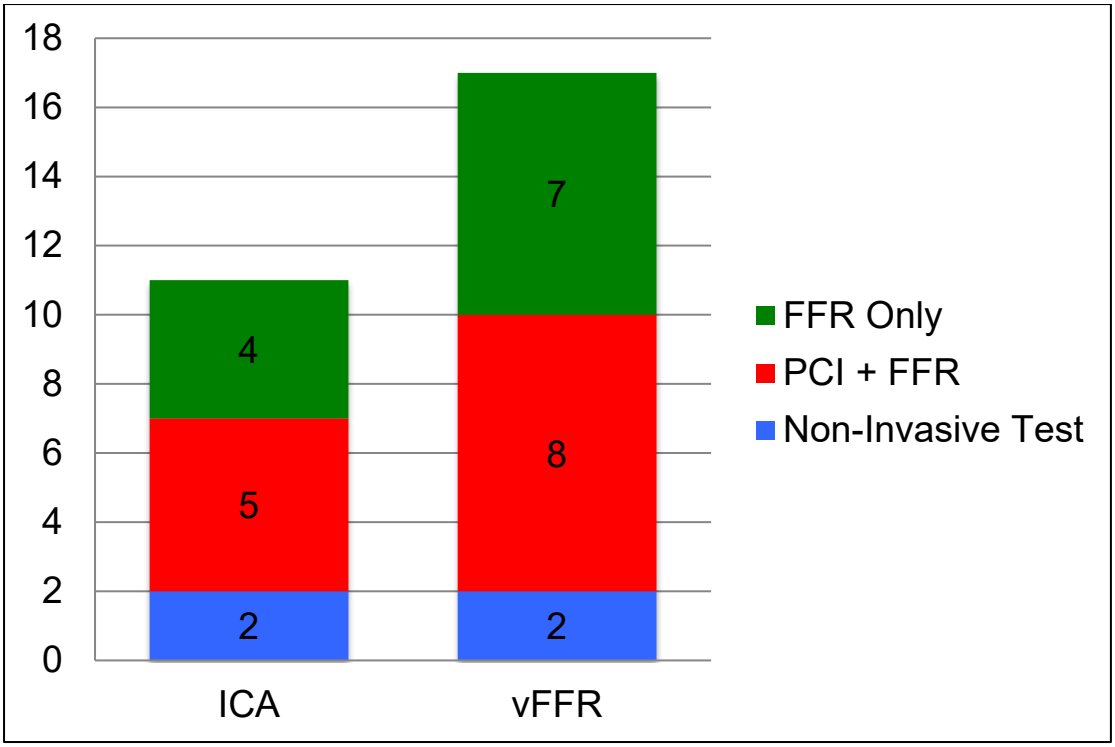

Figure 3.8 Impact of vFFR on hypothetical invasive FFR referrals from DGHs.

3.4.2 Heart Team's Management Strategies

In a sample size of 112 patients a non-statistically significant change in overall management plan was observed in 17.9% (n = 20) of patients (95% CI: ± 8.12%, p = 0.269) after vFFR disclosure at the Heart Team MDT assessment. The lower bound 95% confidence interval lies below the 10% change cut-off that was predetermined for clinical significance. Figure 3.9 illustrates the proportion of management strategies before and after vFFR disclosure. Figure 3.10 illustrates how these management strategies changed.

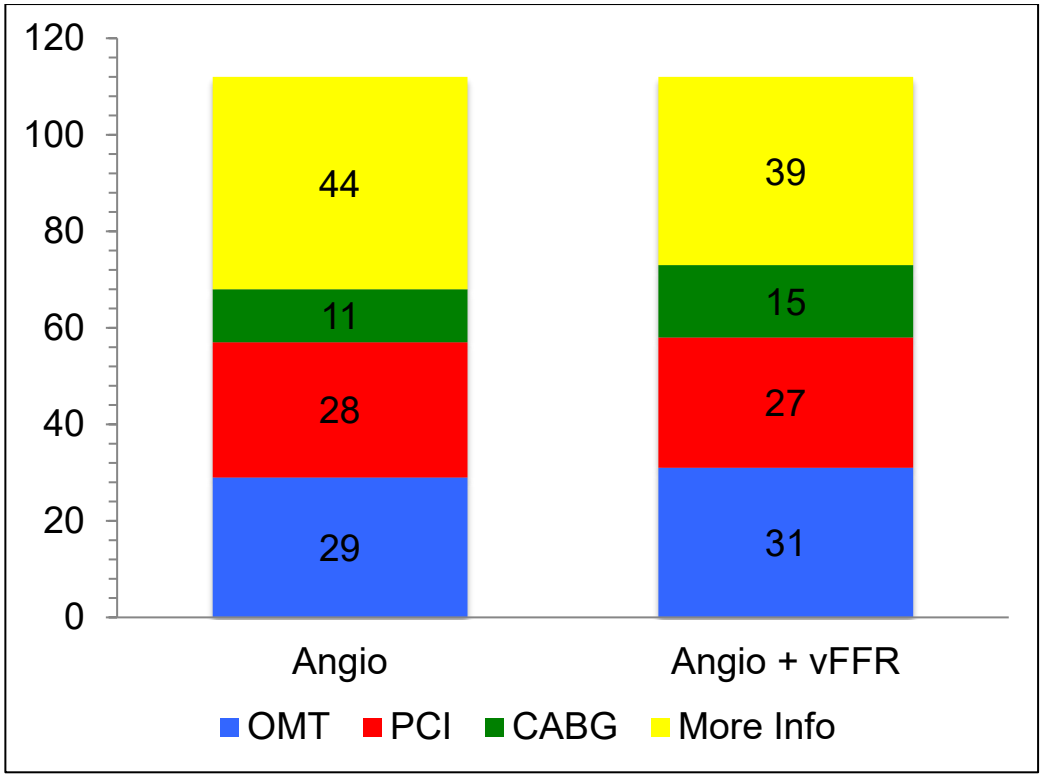

Figure 3.9 Hypothetical Heart Team management strategy changes after vFFR disclosure.

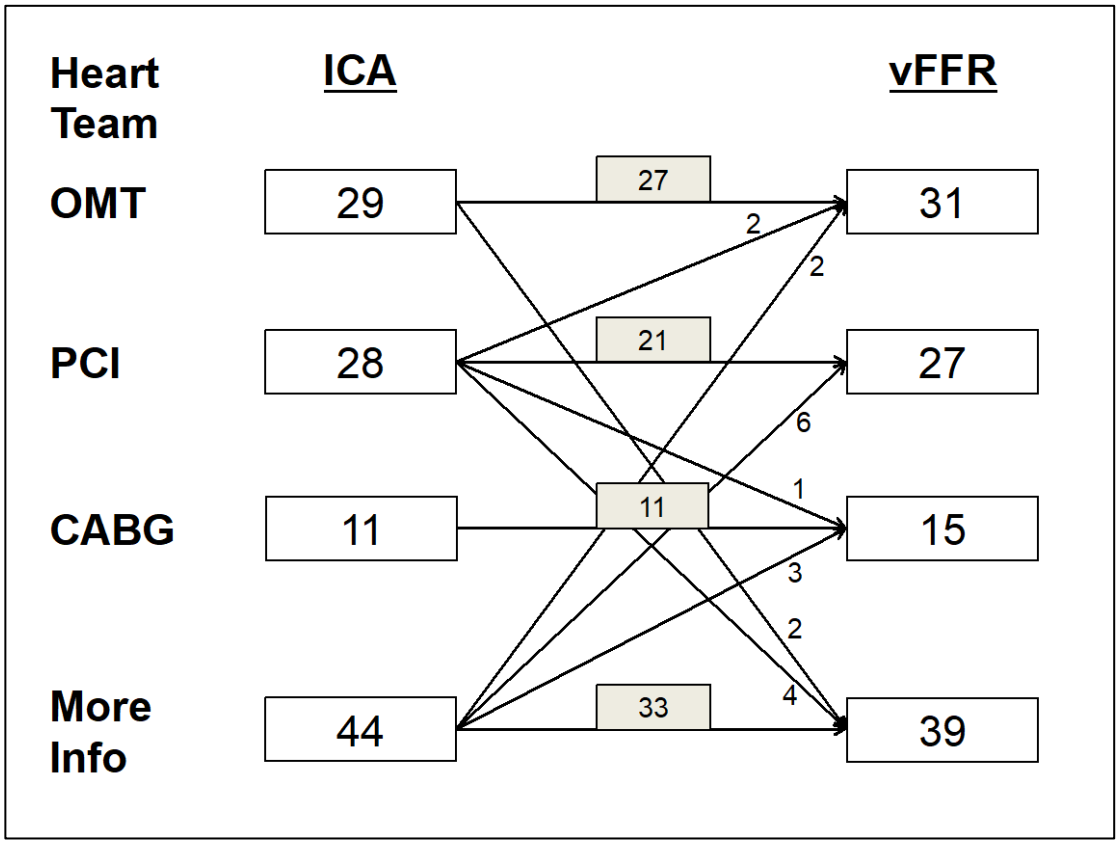

Figure 3.10 Diagram of Hypothetical Heart Team management strategy changes after vFFR disclosure. **CABG** coronary artery bypass graft surgery, **ICA** invasive coronary angiography, **OMT** optimal medical therapy, **PCI** percutaneous coronary intervention.

3.4.2.1 Hypothetical Impact of vFFR on Invasive FFR Referrals from the Heart Team

There appeared to be little impact on use of invasive FFR after vFFR disclosure as the rate of invasive FFR usage as a stand-alone test or in addition to definite PCI of another vessel was already high at the Heart Team assessment [Figure 3.11]. There was almost a 4-fold increase in the baseline rate of invasive FFR usage in the Heart Team assessments when compared to that of the DGH cardiologists.

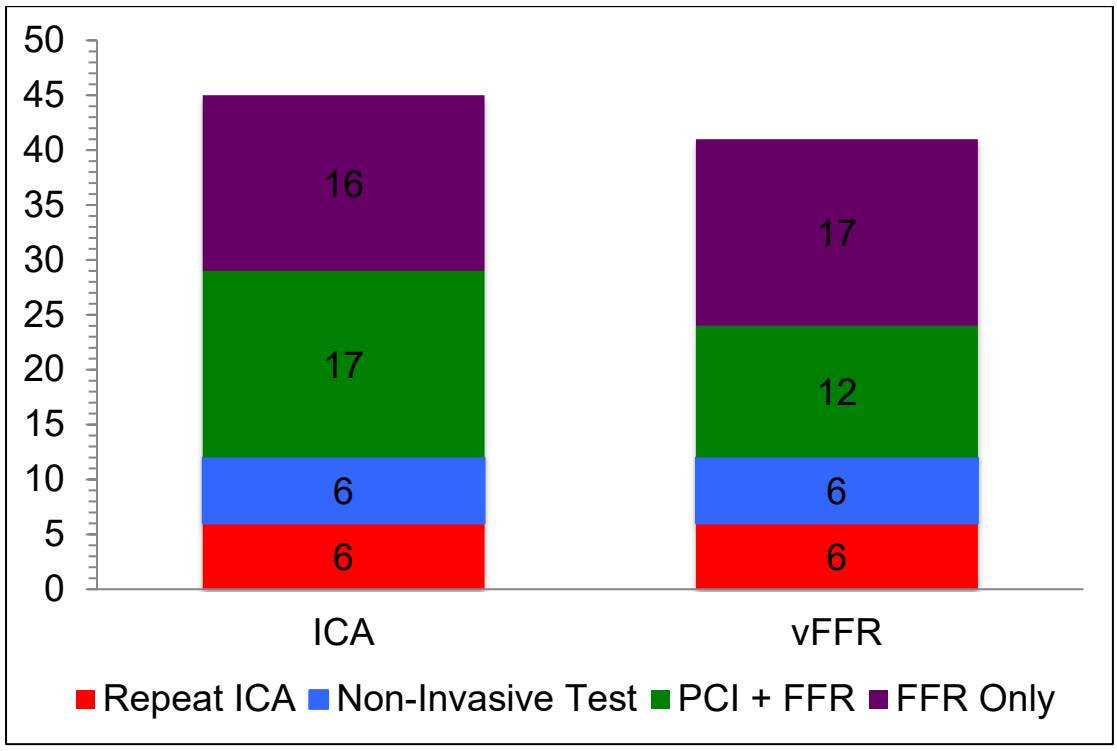

Figure 3.11 Hypothetical Impact of vFFR on invasive FFR referrals from the Heart Team.

3.5 Secondary Outcomes

3.5.1 VIRTUheart™ Analysis and Feasibility

A total of 150 vessels in 112 patients were processed with VIRTUheart™ [Table 3.5]. As an experimental academic tool, VIRTUheart™ was constantly being refined. Two iterations of the VIRTUheart™ software were used to generate vFFR results. An additional modification was made to the segmentation tool to allow for processing of angiograms without the need for an ECG DICOM tag at the expense of diagnostic accuracy. The ECG signal is required to accurately determine end-diastole to allow for correct frame selection for the segmentation step of the CFD workflow.

3.5.2 VIRTUheart™ Failure Rate

VIRTUheart™ failure rate as consequence of software failure was (n = 6) 5.4%. Two patients were not recruited due failure to generate a vFFR result as consequence of software failure. At the vessel level, there were four patients enrolled that had two-vessel disease that was eligible for modelling, in which a vFFR result could not be generated for one of the vessels due to software failures. VIRTUheart™ failure as a result of inadequate imaging was (n = 8) 7.1%. The overall VIRTUheart™ failure rate was therefore 12.5%.

Median vFFR	0.83 (IQR 0.15)
Median calculation time	15 mins (IQR 8 mins)
Mean visual stenosis severity	60% (SD 19%)
Proportion of vessels generated	
LAD	(72) 48%
LCx	(30) 20%
RCA	(33) 22%
Diagonals	(5) 3.3%
OMB	(6) 4.0%
PDA	(2) 1.3%
IM	(2) 1.3%

Table 3.5 Summary of vFFR analysis. N = 150.

3.5.3 Angiographic Quality

All angiograms were assessed by the Heart Team for their diagnostic quality. Angiograms were rated as good, satisfactory or poor. A good angiogram is one that had good co-axial engagement of the catheter with sufficient injection of contrast to fully opacify the vessel over several cardiac cycles. All coronary arteries should be engaged and imaged. There should be good positioning of the gantry and appropriate magnification so that excessive table movement is avoided. Supplemental views should be obtained when standard views do not clearly demonstrate the lesion of interest in at least two orthogonal views. Fluoroscopy settings should be augmented for patients with high-BMI and collimation applied to reduce flair caused by inclusion of the lung fields. A satisfactory angiogram is one which includes some but not all of the aforementioned characteristics. A poor angiogram is one that lacks most of the above and or is insufficient to make a confident clinical decision. Figure 3.12 illustrates the proportions of good, satisfactory and poor angiograms in the current cohort. The majority of diagnostic angiograms were of adequate quality to give a clinical decision. However 17.0% were considered poor with six (5.4%) angiograms being so poor that the consensus Heart Team management strategy was for repeat invasive coronary angiography.

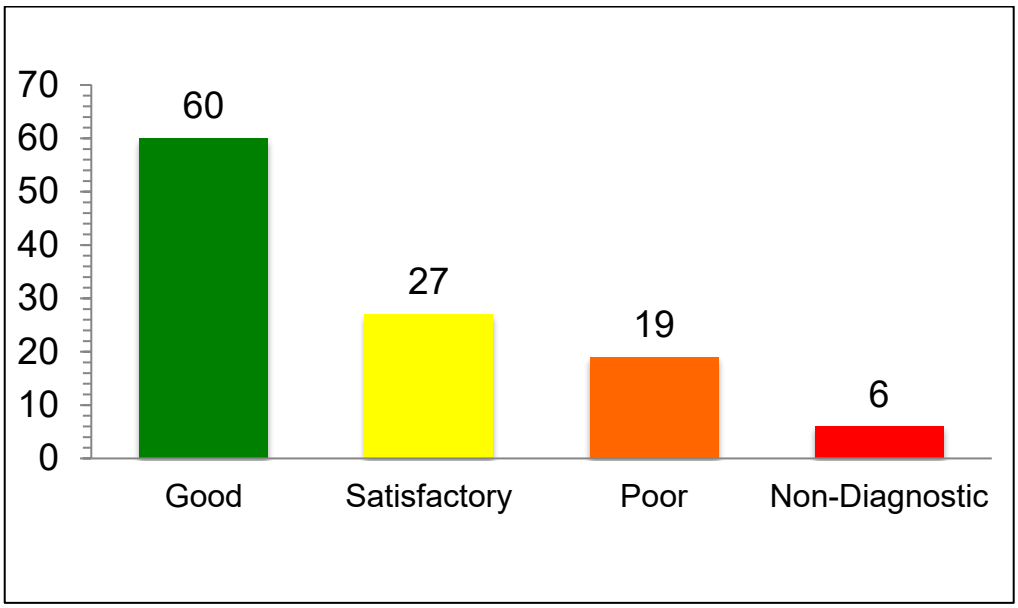

Figure 3.12 Diagnostic Quality of VIRTU-4 CCS Angiograms. N = 112.

3.5.4 Intra-observer Variability

Intra-observer variability was calculated using ICC and Pearson's correlation coefficient after 20 patients were randomly selected for re-processing. Both generic and personalised boundary conditions were assessed [Table 3.6].

Generic vFFR	Mean vFFR	SD
Operator 1	0.77	0.15
Operator 1 Repeat	0.82	0.08
R	0.69	
ICC	0.75	
Personalised vFFR		
Operator 1	0.71	0.15
Operator 1 Repeat	0.82	0.10
R	0.62	
ICC	0.73	

Table 3.6 Intra-observer variability using generic and personalised boundary conditions. **ICC** intraclass correlation coefficient, **SD** standard deviation and **R** Pearson's correlation coefficient.

Table 3.6 demonstrates that there is strong agreement [221] and moderate correlation [222] when vFFR is re-processed by the same experienced operator.

3.5.5. Inter-observer Variability

Inter-observer variability was calculated using ICC and Pearson's correlation coefficient after 20 patients were randomly selected for re-processing by two experienced operators. Both generic and personalised boundary conditions were assessed [Table 3.7].

Generic vFFR	Mean vFFR	SD
Operator 1	0.82	0.08
Operator 2	0.77	0.11
R	0.66	
ICC	0.79	
Personalised vFFR		
Operator 1	0.82	0.10
Operator 2	0.74	0.11
R	0.63	
ICC	0.77	

Table 3.7 Inter-observer variability using generic and personalised boundary conditions. **ICC** intraclass correlation coefficient, **SD** standard deviation and **R** Pearson's correlation coefficient.

Similarly table 3.6 demonstrates both strong-to-very strong inter-observer agreement [221] and moderate correlation [222] of vFFR when the same vessels are analysed by two experienced operators. It can also be seen that there is only a negligible reduction in agreement and correlation as a result of the increased variance caused by personalizing the outlet boundary condition. Operator 2 could not model one vessel so the analysis was conducted with 19 patients. The degree of discordance between operators when using 0.80 as the threshold for revascularisation was 3 out of 19 cases. This data suggest

that vFFRs generated by VIRTUheart™ are reproducible in the hands of experienced operators.

3.5.6 Initial Strategy Confidence Levels

The treating cardiologist and the Heart team were asked to rate their confidence level in their chosen management strategy based on the angiogram on a scale from one to ten. Once vFFR data was computed and disclosed, they were asked to rate their confidence level in their original management strategy.

The null hypothesis states that vFFR disclosure will not result in any significant changes in treating cardiologists' or the Heart Team's confidence levels. This was assessed using a one-way repeated measures ANOVA and Wilks' Lambda.

3.5.6.1 DGH Cardiologists' Confidence Levels

The mean confidence levels in the original strategy based on the angiogram alone and after vFFR disclosure were 8.90 (SD 1.28) and 9.22 (SD 1.39) respectively with p-value of 0.026. This suggests that vFFR improves confidence in DGH cardiologists' decision-making.

Further sub-analysis showed an increase in confidence levels in 34.8% (39 decisions), a decrease in 16.1% (18 decisions) and remained unchanged in 49.1% (55 decisions). There was a mean increase in confidence level by 1.26 points and a mean decrease of 0.5 points when vFFR was concordant and discordant with the initial management strategies respectively.

3.5.6.2 Heart Team's Confidence Levels

For each patient presented to the Heart Team, the average confidence levels of its three members were assessed before and after vFFR disclosure. The mean confidence levels in original strategy based on the angiogram alone and after vFFR disclosure were 7.80 (SD 0.93) and 7.93 (SD 1.11) respectively

with p-value of 0.113. This suggests that vFFR does not have a significant effect on confidence levels in consensus clinical decision making in a MDT setting.

3.5.7 Comparisons of VIRTUheart™, CAAS-vFFR and QFR®

Sixty patients' angiograms (71 vessels), selected at random, were processed with CAAS-vFFR (Pie Medical Imaging) and QFR® (Medis Medical Imaging). Table 3.8 provides a summary of the baseline characteristics of the comparison data. Normally distributed data are reported as mean and standard deviation and non-normally distributed data are reported as median and interquartile range [Appendix B].

Platform (Variant)	**Median (IQR)/Mean (SD)**
VIRTUheart™-vFFR (Generic)	0.82 (IQR 0.20)
VIRTUheart™-vFFR (Personalised)	0.79 (IQR 0.18)
CAAS-vFFR	0.73 (IQR 0.27)
QFR® (Fixed Flow)	0.69 (SD 0.19)
QFR® (Contrast Vessel)	0.74 (SD 0.17)
Vessel	
LAD	(40) 56.3%
RCA	(13) 18.3%
LCx	(12) 16.9%
OMB	(3) 4.2%
Diagnonal	(1) 1.4%
PDA	(1) 1.4%
IM	(1) 1.4%
Mean Processing Time	
VIRTUheart™ (Personalised)	15 minutes
CAAS-vFFR	4 minutes
QFR® (Contrast Vessel)	3.5 minutes

Table 3.8 Baseline VIRTUheart™, CAAS and QFR® characteristics.

3.5.7.1 VIRTUheart^{TM} (Personalised) vs CAAS-vFFR

The correlation between personalised vFFR and CAAS-vFFR [Figure 3.13] was weak-to-moderate (r = 0.35, p = 0.03). The proportion of diagnostic discordance between the two methods was 22.5% (n = 16). This was the proportion of results in the upper left and lower right quadrants of the correlation plot. The mean difference in vFFR illustrated by the BA-plot [Figure 3.14] was -0.08 with 95% limits of agreement ±0.35 (green lines). Linear regression analysis was statistically significant (p = 0.005) implying there was a difference in the performance of the two platforms across the range of vFFR values. This is also known as proportional bias. Figure 3.14 suggests that there is more consistent agreement around the clinically important threshold of 0.80, illustrated as greater clustering around the mean at this point.

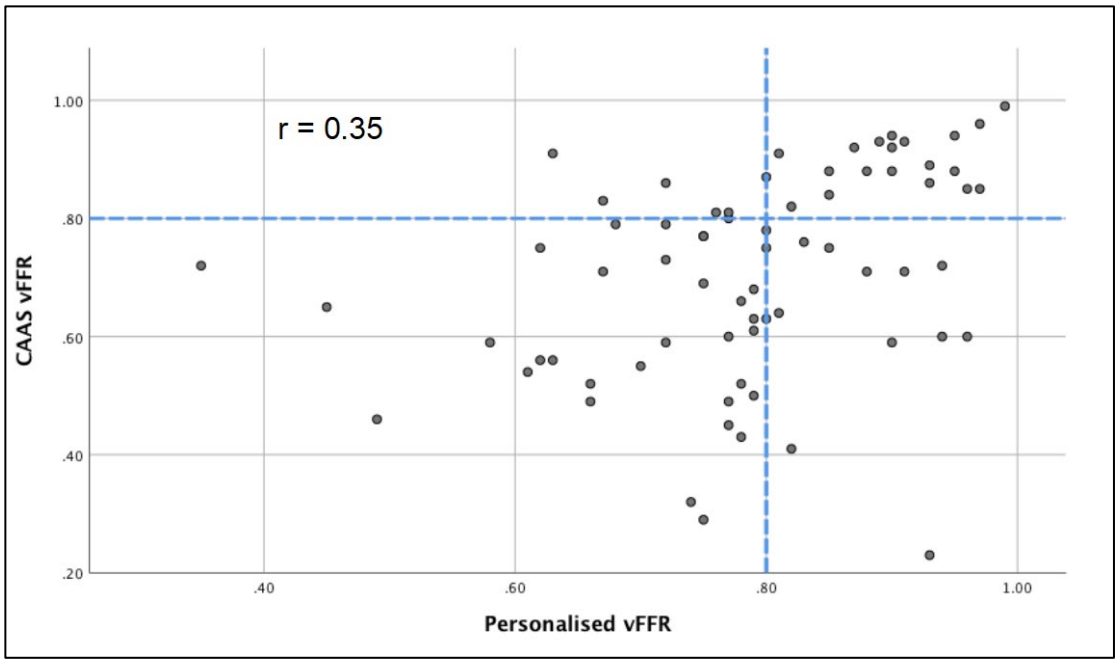

Figure 3.13 Correlation of personalised VIRTUheart^{TM}-vFFR and CAAS-vFFR. Dashed blue lines at 0.80 represent the treatment threshold.

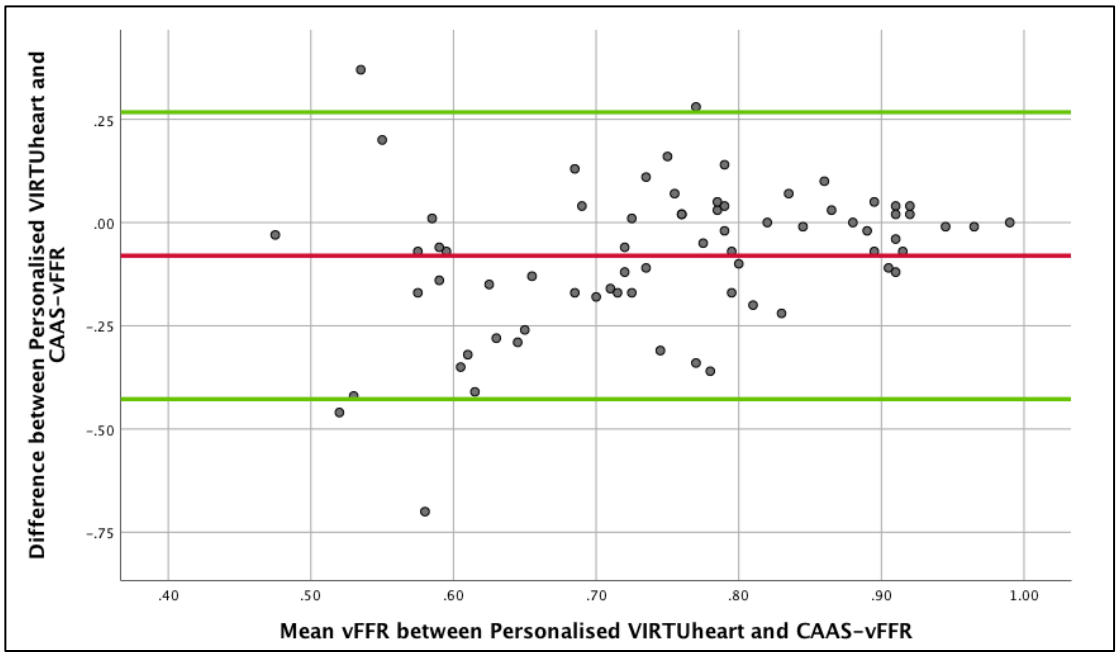

Figure 3.14 Bland-Altman plot of the mean differences against the means of vFFRs between personalised VIRTUheart™ and CAAS-vFFR. The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.7.2 VIRTUheart™ (Personalised) vs QFR® (Contrast Vessel)

The correlation between personalised vFFR and QFR® (Contrast Vessel) [Figure 3.15] was moderate (r = 0.44, p = 0.001). The proportion of diagnostic discordance between the two methods was 21.1% (n = 15). The mean difference in vFFR illustrated by the BA-plot [Figure 3.16] was -0.05 with 95% limits of agreement ±0.31. Linear regression analysis was statistically significant (p = 0.014) confirming the presence of proportional bias with increasing vFFR values.

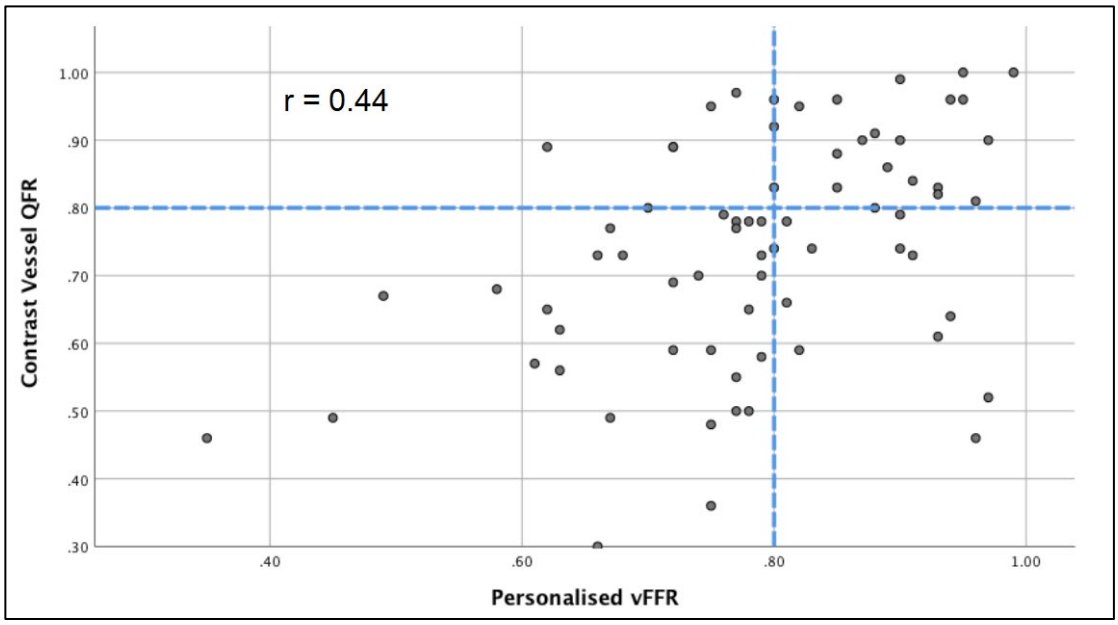

Figure 3.15 Correlation of personalised VIRTUheart™-vFFR and QFR® (Contrast Vessel). Dashed blue lines at 0.80 represent the treatment threshold.

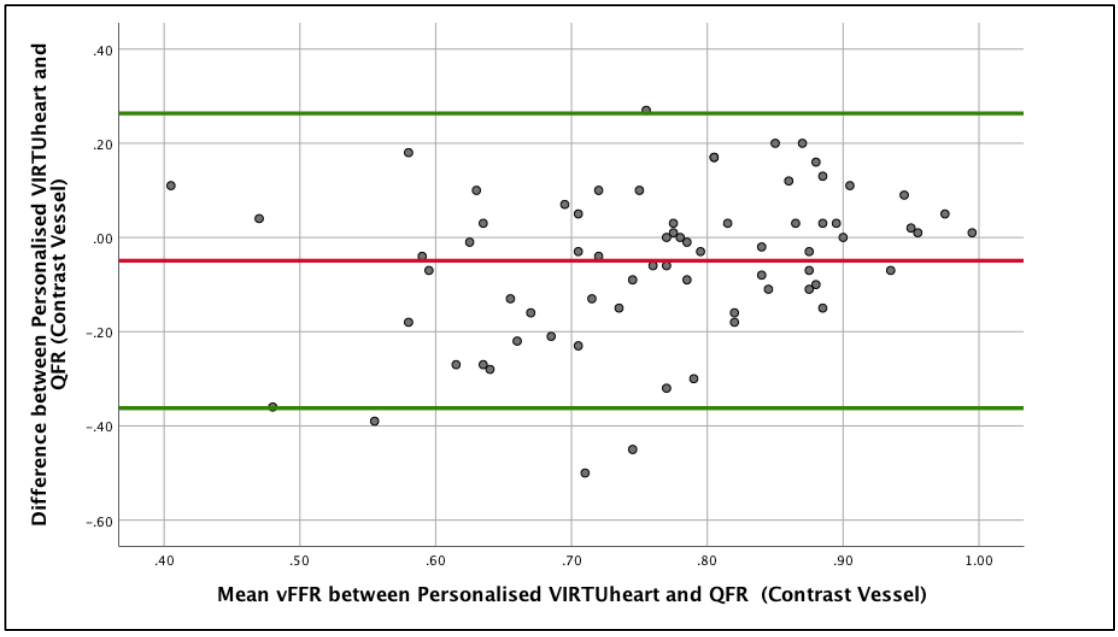

Figure 3.16 Bland-Altman plot of the mean differences against the means of vFFRs between personalised VIRTUheart™ and QFR® (Contrast Vessel). The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.7.3 VIRTUheart™ (Personalised) vs QFR® (Fixed Flow)

The correlation between personalised vFFR and QFR® (Fixed Flow) [Figure 3.17] was moderate (r = 0.44, p = 0.001). The proportion of diagnostic discordance between the two methods was 28.2% (n = 20). The mean difference in vFFR illustrated by the BA-plot [Figure 3.18] was -0.09 with 95% limits of agreement ±0.35. Linear regression analysis was statistically significant (p = 0.001) confirming the presence of proportional bias with increasing vFFR values.

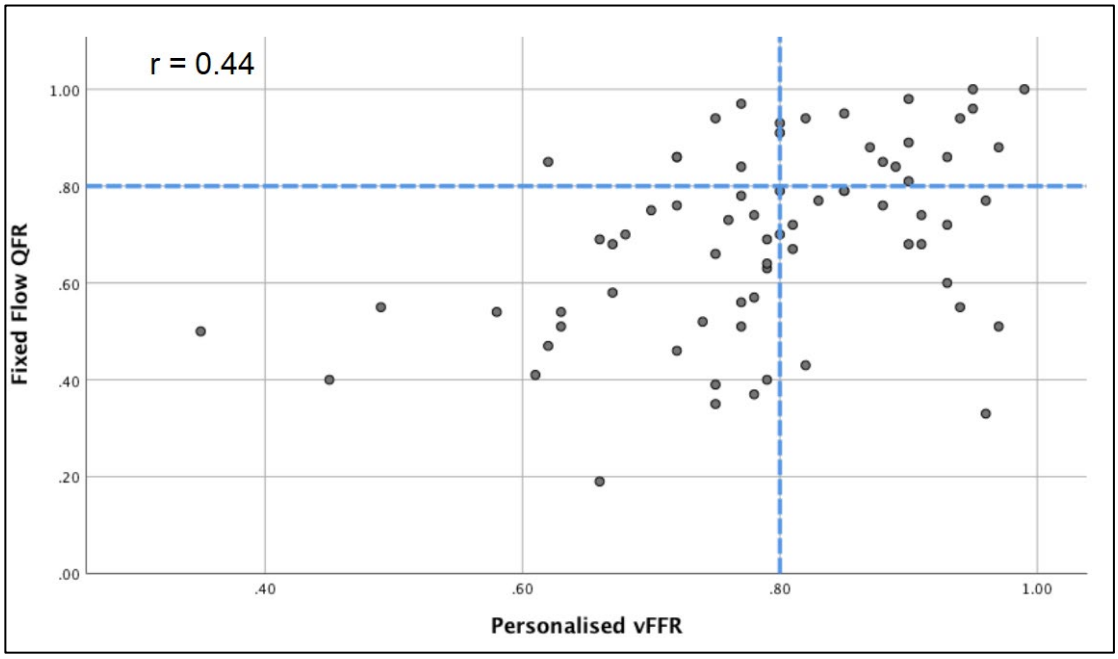

Figure 3.17 Correlation of personalised VIRTUheart™-vFFR and QFR® (Fixed Flow). Dashed blue lines at 0.80 represent the treatment threshold.

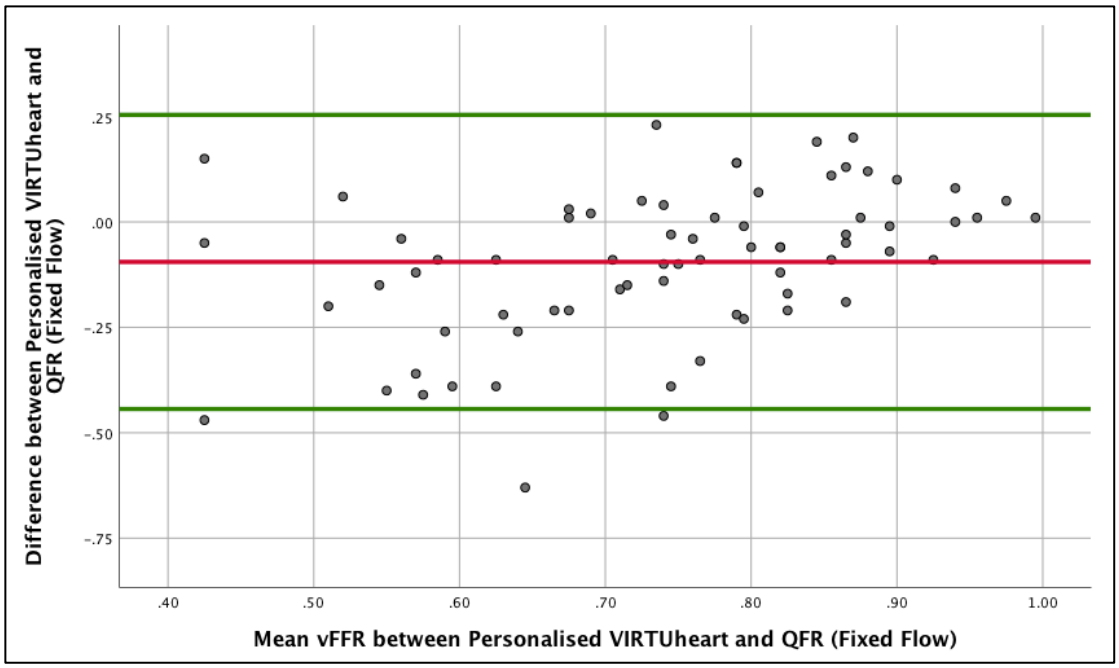

Figure 3.18 Bland-Altman plot of the mean differences against the means of vFFRs between personalised VIRTUheart™ and QFR® (Fixed Flow). The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.7.4 VIRTUheart™ (Generic) vs CAAS-vFFR

The correlation between generic vFFR and CAAS-vFFR [Figure 3.19] was moderate (r = 0.45, p = 0.001). The proportion of diagnostic discordance between the two methods was 25.4% (n = 18). The mean difference in vFFR illustrated by the BA-plot [Figure 3.20] was -0.09 with 95% limits of agreement ±0.32. Linear regression analysis was statistically significant (p = 0.04) confirming the presence of proportional bias with increasing vFFR values.

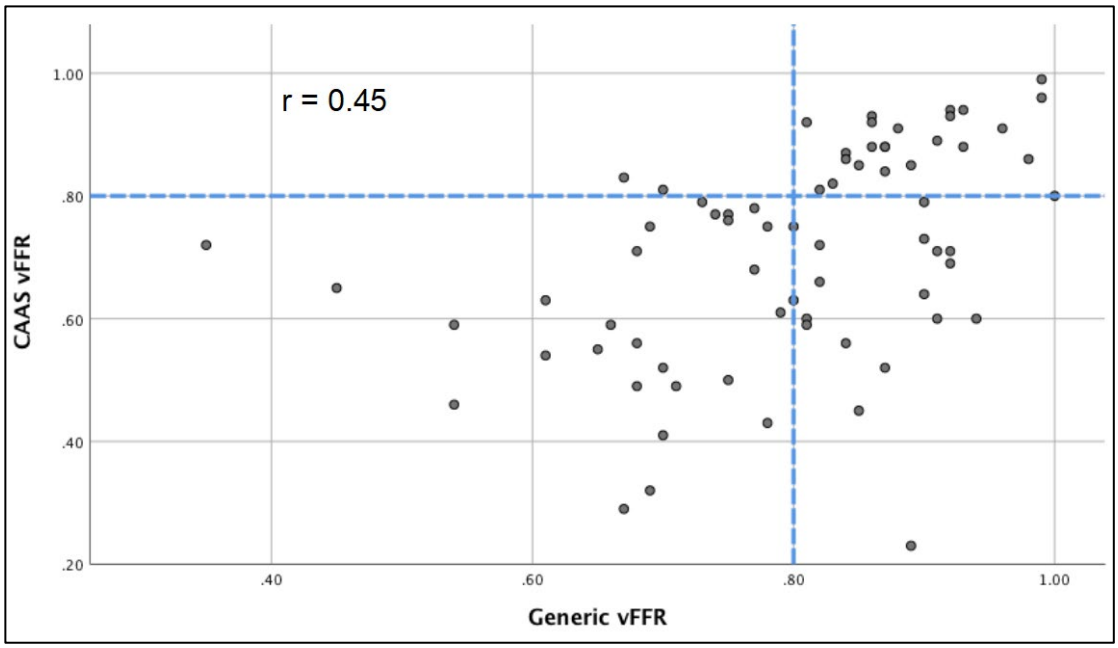

Figure 3.19 Correlation of generic VIRTUheart^{TM}-vFFR and CAAS-vFFR. Dashed blue lines at 0.80 represent the treatment threshold.

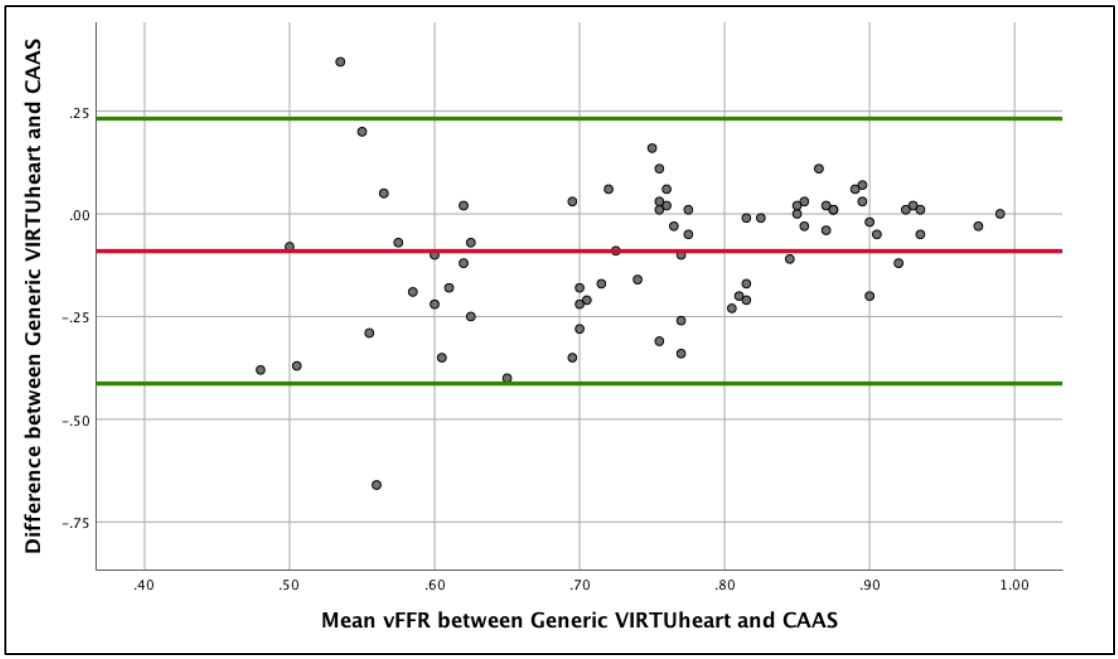

Figure 3.20 Bland-Altman plot of the mean differences against the means of vFFRs between personalised VIRTUheart^{TM} and CAAS-vFFR. The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.7.5 VIRTUheart™ (Generic) vs QFR® (Fixed Flow)

The correlation between generic vFFR and QFR® (Fixed Flow) [Figure 3.21] was weak (r = 0.32, p = 0.07). The proportion of diagnostic discordance between the two methods was 39.4% (n = 28). The mean difference in vFFR illustrated by the BA-plot [Figure 3.22] was +0.11 with 95% limits of agreement ±0.38. Linear regression analysis was statistically significant (p < 0.001) confirming the presence of proportional bias with increasing vFFR values.

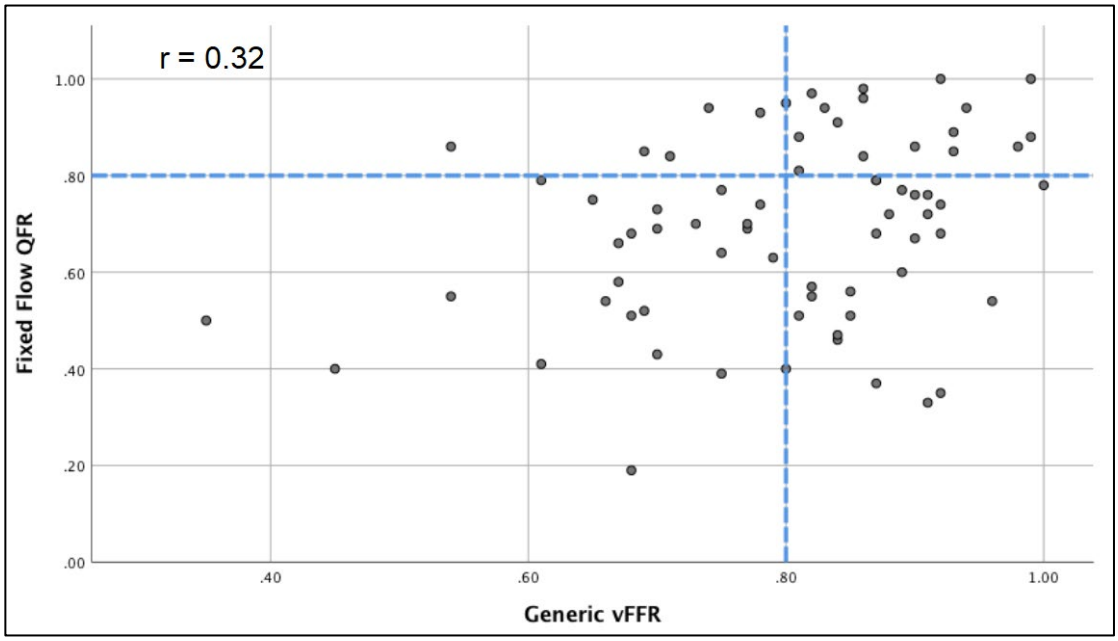

Figure 3.21 Correlation of generic VIRTUheart™-vFFR and QFR® (Fixed Flow). Dashed blue lines at 0.80 represent the treatment threshold.

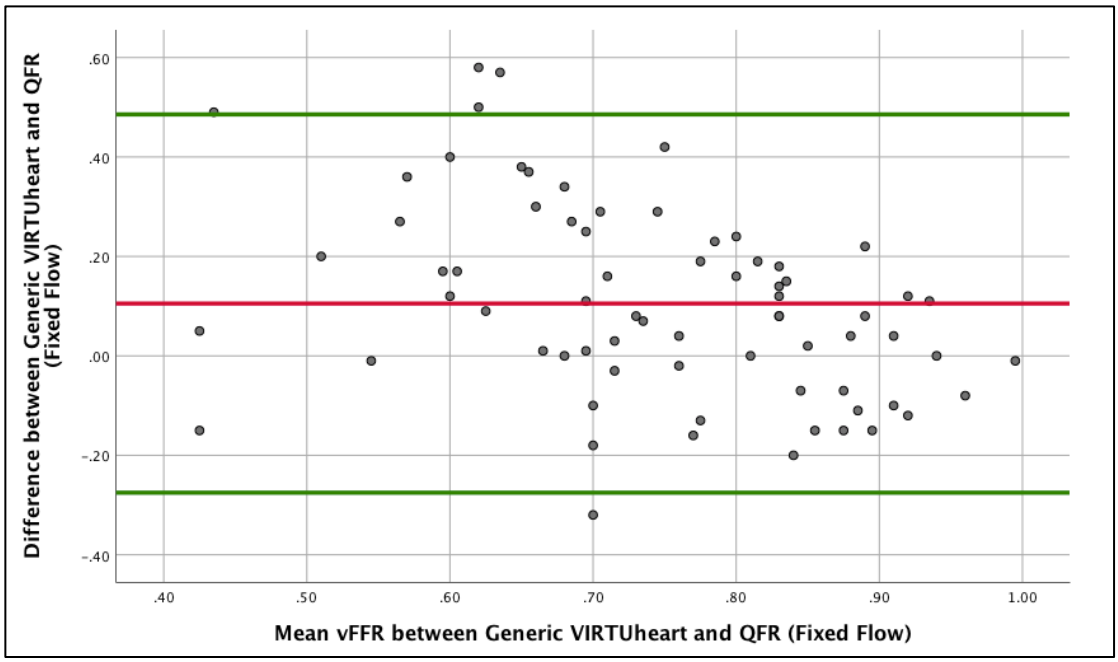

Figure 3.22 Bland-Altman plot of the mean differences against the means of vFFRs between personalised VIRTUheart™ and QFR® (Fixed Flow). The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.7.6 CAAS-vFFR vs QFR® (Contrast Vessel)

The correlation between CAAS-vFFR and QFR® (Contrast Vessel) [Figure 3.23] was moderate to strong (r = 0.48, p = 0.001). The proportion of diagnostic discordance between the two methods was 19.7% (n = 14). The mean difference in vFFR illustrated by the BA-plot [Figure 3.24] was -0.03 with 95% limits of agreement ±0.34. Linear regression analysis was statistically non-significant (p = 0.646) implying the two tests performed consistently across the range of vFFR values.

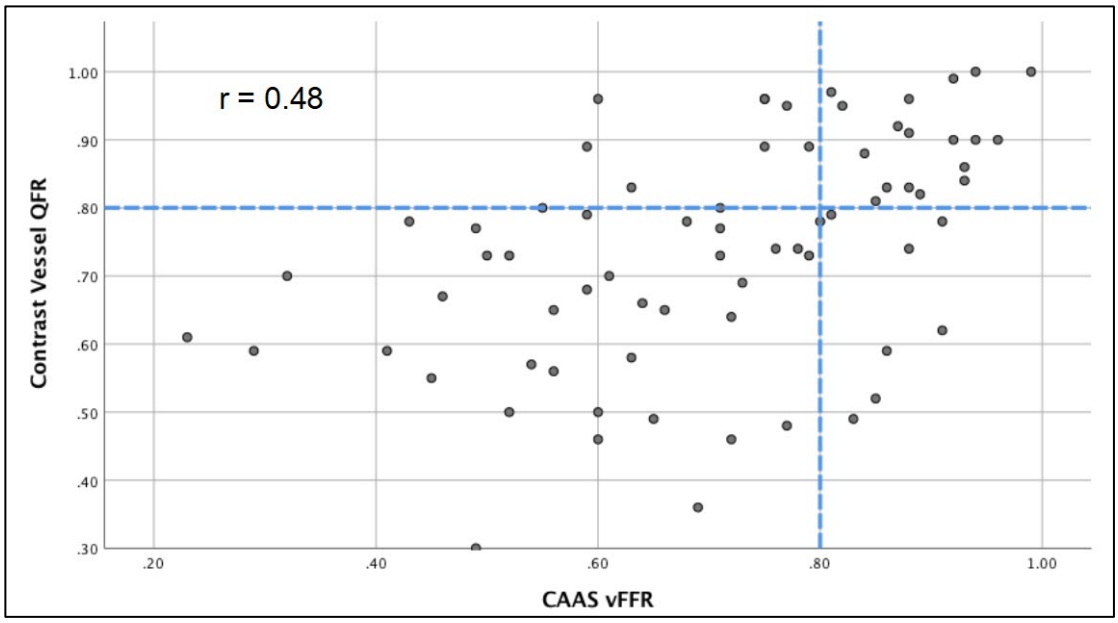

Figure 3.23 Correlation of CAAS-vFFR and QFR® (Contrast Vessel). Dashed blue lines at 0.80 represent the treatment threshold.

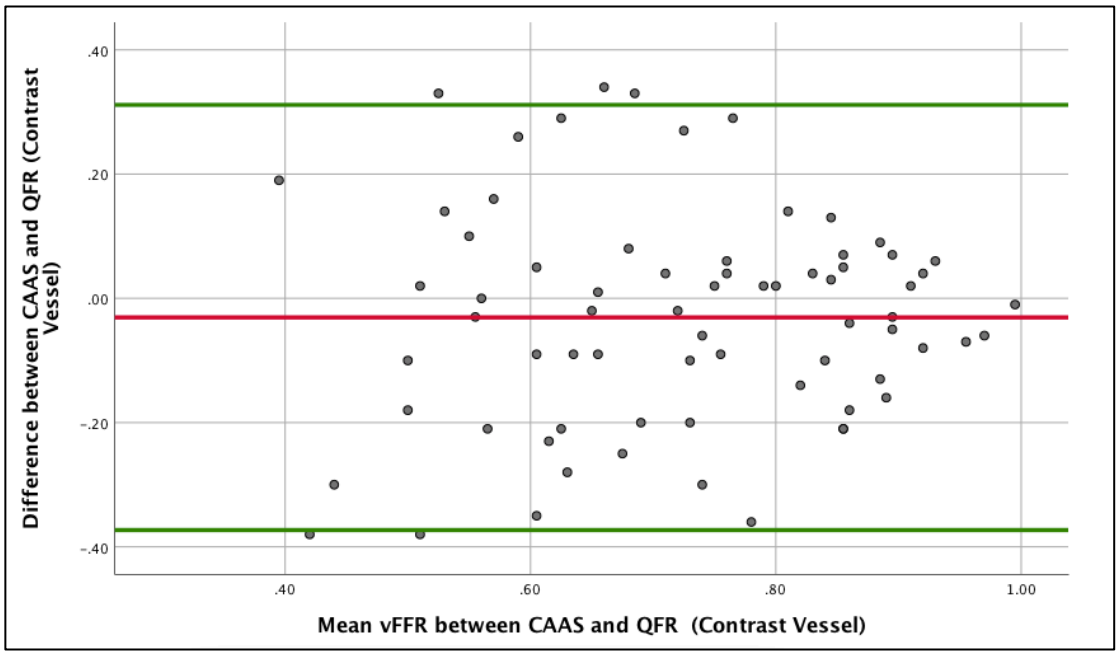

Figure 3.24 Bland-Altman plot of the mean differences against the means of vFFRs between CAAS-vFFR and QFR® (Contrast Vessel). The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.7.7 CAAS-vFFR vs QFR® (Fixed Flow)

The correlation between CAAS-vFFR and QFR® (Fixed Flow) [Figure 3.25] was moderate-to-strong (r = 0.49, p = 0.001). The proportion of diagnostic discordance between the two methods was 19.7% (n = 14). The mean

difference in vFFR illustrated by the BA-plot [Figure 3.26] was +0.01 with 95% limits of agreement ±0.36. Linear regression analysis was statistically non-significant (p = 0.398) implying the two tests performed consistently across the range of vFFR values.

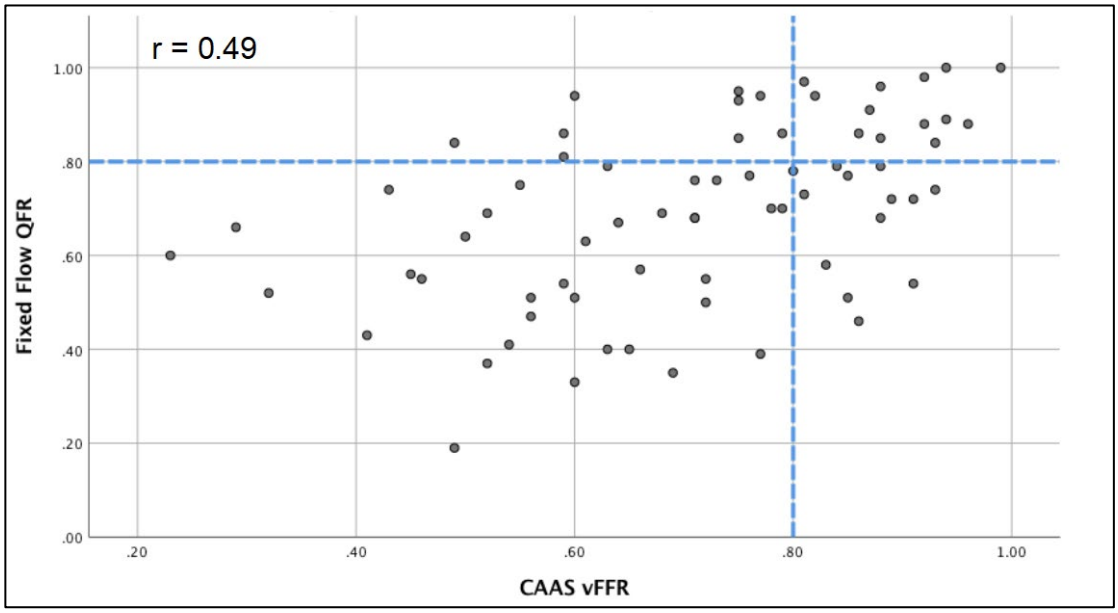

Figure 3.25 Correlation of CAAS-vFFR and QFR® (Fixed Flow). Dashed blue lines at 0.80 represent the treatment threshold.

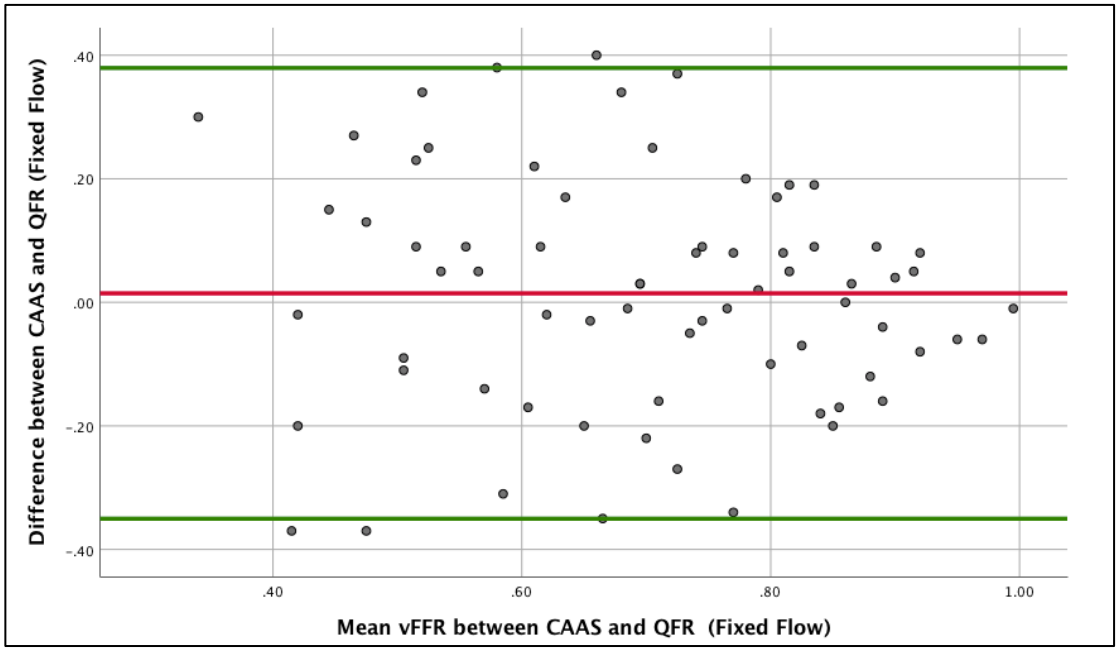

Figure 3.26 Bland-Altman plot of the mean differences against the means of vFFRs between personalised CAAS-vFFR and QFR® (Fixed Flow). The red line represents the mean difference and the green lines represent the 95% limits of agreement.

3.5.8 Summary of Comparisons

Overall correlation between the platforms ranged from weak to moderately strong. CAAS-vFFR and QFR® appear to have better agreement and consistency across all ranges of vFFR result compared with VIRTUheart™. On average CAAS-vFFR and QFR® are four times faster than VIRTUheart™ However, the limits of agreement when comparing the different platforms are very wide, ranging from ±0.31 to ±0.38. A difference of 0.31 in vFFR is highly likely to result in significant changes in management strategy within the same patient when different platforms are applied. This is illustrated in the high rate of diagnostic discordance ranging from 19.7% to 39.4% when using 0.80 as a dichotomous threshold. Most of the outlying results occurred well below the clinically significant threshold of 0.80. Agreement and correlation appeared to deteriorate when there was less patient personalisation. Caution needs to be exercised when interpreting these data as there were no invasive FFR measurements to act as a gold-standard reference. This is because all angiograms were obtained from non-interventional catheterisation laboratories. Table 3.9 provides a summary of the various software comparisons.

Software Comparison	Mean Difference	95% limits of agreement	Linear Regression	Correlation Coefficient	Discordance
vFFRp and CAAS	-0.08	±0.35	p = 0.005*	r = 0.35**	22.5%
vFFRp and QFR-CV	-0.05	±0.31	p = 0.014*	r = 0.44**	19.7%
vFFRg and CAAS	-0.09	±0.32	p = 0.04*	r = 0.45**	25.4%
vFFRg and QFR-FF	0.11	±0.38	p < 0.001*	r = 0.32**	39.4%
QFR-CV and CAAS	-0.03	±0.34	p = 0.646	r = 0.48**	19.7%
QFR-FF and CAAS	0.01	±0.36	p =0.398	r = 0.49**	29.6%
QFR-FF and vFFRp	-0.09	±0.35	p < 0.001*	r = 0.44**	28.2%

Table 3.9 Summary of software comparisons. **vFFRp** (VIRTUheart™ Personalised), **vFFRg** (VIRTUheart™ Generic), **QFR-CV** (Contrast Vessel QFR), **QFR-FF** (Fixed Flow QFR) and **CAAS** (CAAS-vFFR). **Discordance** = proportion of vessels where platforms differ on clinical significance using 0.80 as the threshold for ischaemia. ***** A value of $p < 0.05$ denotes the presence of proportional bias, denoting differing strength of agreement across the range of vFFR. ** All values have $p < 0.05$ denoting a significant correlation co-efficient.

3.6 VIRTU-4 CCS Follow-up

Fifty-five out of 83 (66.3%) patients were successfully contacted for telephone consultations during the course of the follow-up phase. The median time to follow-up to the nearest month was six months.

3.6.1 Actual Management Strategy Implemented at 6 months

There were two patients out of the 55 contactable patients who had a different management plan at follow-up. The first patient was initially managed with optimal medical therapy but was referred for PCI as a result of hospitalisation for a troponin-negative chest pain episode and a GP visit for antianginal medications up-titration prior to that. Angiographically, this patient had a severe stenosis (90%) of a large obtuse marginal branch (OMB). VIRTUheart^{TM} was unable to converge a solution to give a vFFR for this vessel. However, secondary analyses with CAAS and QFR platforms demonstrated a highly positive vFFR (0.58 and 0.73 respectively). One could speculate that vFFR-guided decision-making could have prevented hospital and GP visits in this case. However given this was a prognostically non-significant side branch lesion along with the increased technical risks incurred with side branch intervention that involves a disease-free main vessel, an initial conservative approach in such lesions is justifiable and common practice. The second patient was managed medically and had an elective surgical aortic valve replacement for symptomatic severe aortic stenosis as his valvular heart disease progressed during the course of follow-up.

3.6.2 EQ-5D-5L Questionnaire

The baseline and 6-month mean EQ-5D-5L scores were 66.6 and 63.9 respectively. There was a reduction in EQ-5D-5L score in (29/55) 52.7% of patients. Twenty-four out 29 (82.8%) of these patients were managed medically or still waiting to undergo elective PCI. There was no change in EQ-5D-5L score in 10.9% (6/55) of patients. There was an increase in EQ-5D-5L score in 36.4% (20/55) of patients. Only three out of 20 patients reported overall improvement in EQ-5D-5L after PCI with one patient's score improving

following SAVR after severe AS was discovered at a later date. Sixteen patients were managed medically or still waiting for elective PCI.

3.6.3 Adverse Events

An adverse event in VIRTU-4 CCS was defined as all cause mortality, any unscheduled hospitalisation or GP visit. The mortality rate for this cohort was 0%. Unscheduled hospitalisations and GP visits are outlined in table 3.10. A cross-tabulation of initial management strategy against adverse outcomes (stratified by vFFR) [Table 3.11] did not show any statistically significant differences between groups. Similarly cross-tabulation of adverse events by vFFR < 0.80 [Table 3.12] did not yield any statistically significant differences, although the results showed a trend towards significance.

Hospitalisations	**Frequency**
Chest pain	5
NSTEMI	1
Acute heart failure	1
PR bleeding	1
Pneumonia	1
Hydronephrosis	1
GP Visits	
Worsening Angina	5
Fatigue	2
Breathlessness	1
Palpitations	1
Muscle aches	1
Hypertension	1

Table 3.10 Summary of unscheduled hospitalisations and GP visits. Two patients had more than one adverse event.

Initial Management Strategy	vFFR ≤ 0.80		vFFR > 0.80	
	No Adverse Events	Adverse Events	No Adverse Events	Adverse Events
OMT	9	6*	14	2
Revascularisation	3	2	2	1
a/w PCI or CABG	7	7*	1	1

Table 3.11 Cross-tabulation of management strategy against adverse events stratified by vFFR (X^2 (8, N = 55) = 8.633, p = 0.195).

	vFFR ≤ 0.80	vFFR > 0.80
Adverse Events	15	4
No Adverse Events	9	17

Table 3.12 Cross-tabulation of adverse outcome by vFFR at the treatment threshold of 0.80 (X^2 (1, N = 55) = 3.608, p = 0.057).

3.6.4 Complications of Invasive Coronary Angiography

The complication rate of diagnostic angiography in this study was 1.8% (N = 2). The first complication was the precipitation of acute heart failure with pulmonary oedema post-angiography in a patient with severe left ventricular impairment. This patient required admission and treatment for several days. The second complication was a grade II right forearm haematoma that lead to an accident and emergency visit to assess swelling and paraestheia.

Chapter 4: Discussion

4.1 Summary of Results

The availability of vFFR resulted in a hypothetical 22.3% (95% CI: 14.18% to 30.42%, p = 0.013) change in the management plan of patients undergoing diagnostic coronary angiography for suspected coronary artery disease. This was primarily driven by a 39.5% relative increase in patients being reassigned to percutaneous coronary intervention and further investigation with invasive FFR. At the Heart Team assessment the availability of vFFR resulted in a non-statistically significant hypothetical 17.9% (95% CI: 9.78% to 26.02%, p = 0.269) change in the management plans. At the vessel level 21.7% of mild (30-50% diameter stenosis) lesions were re-classified as physiologically significant (vFFR ≤ 0.80) and 29.8% of severe (71-90% diameter stenosis) lesions were reclassified as physiologically insignificant (vFFR > 0.80). After disclosure of vFFR the confidence levels in the original strategy increased from 8.90 to 9.22 (p = 0.026) in the treating district general cardiologists. However at Heart Team assessment there was no significant difference in average case confidence levels after vFFR disclosure (7.80 to 7.93 respectively, p = 0.113). The median computation time was 15 minutes (IQR 8 minutes). Of the patients screened who fulfilled all clinical and anatomic eligibility criteria, 7% (n = 8) were unsuitable for vFFR calculation due to poor image acquisition. The intra-observer and inter-observer agreement of vFFR calculation was strong (ICC 0.73 and 0.77 respectively) and the rate of discordance between operators was low (3 out of 19 patients). Although the study did not recruit the prerequisite number of participants and was therefore underpowered, the trends suggested by the data are contrary with findings in the literature. [119,194]

4.2 The Impact of the COVID-19 Pandemic

The global COVID-19 pandemic caused significant disruption to healthcare provision and research activities culminating in suboptimal patient recruitment. The UK national lockdown in March 2020 resulted in complete cessation of

research activity and all elective diagnostic angiography in the South Yorkshire region for 5 months. Upon resumption of elective diagnostic coronary angiography at participating sites, social distancing measures, reduced staffing levels through self-isolation or shielding meant resumption of procedural lists at less than half capacity. It was only by late-March that procedural volume was almost at pre-pandemic levels at some participating sites. Subsequent national lockdowns have caused further disruption to recruitment with some participating sites prohibiting all research activity during this period. Due to the significant backlog of patients awaiting invasive angiography, the initial case mix was altered to prioritise patients with severe valvular heart disease or those who were deemed to have suspected severe prognostic coronary artery disease. The case mix was further affected by the recent ESC guidance [223] recommending early (<24hrs) angiography in patients with ACS, resulting a reduction in the number elective patients at any given list in some of our participating sites. The fourth participating site, Chesterfield Royal Hospital, did not recruit its first patient until May 2021 due to a delay in refurbishment of their catheterization laboratory. This was in effort to reduce the long waiting-list times for diagnostic angiography in their region.

The COVID-19 pandemic resulted in a shift in consultation style with more patients undergoing telephone consultations. There may have been more emphasis on antianginal medication prescribing and optimisation in the lockdown period, which in turn may have resulted in deferral of invasive investigation secondary to improvement in symptoms in a proportion of patients with obstructive CAD. The proportion of patients on 2 or more antianginal medication in VIRTU-4 was 59.8% in contrast to 18.9% observed in a study of over 300,000 elective PCI procedures. [224] This is more in keeping with the ORBITA trial in which the mean number of antianginals was 3 per patient. [81] Conversely the COVID-19 pandemic may have lead to increased numbers of low-probability-of-CAD patients with normal coronary arteries being referred for invasive coronary angiography as a result of increased waiting-list times for non-invasive functional tests (SPECT/ETT or CTCA) at a regional level, that would have otherwise been screened out. This

may account for the high proportion of normal coronary angiograms (66%) observed in VIRTU-4 CCS.

Furthermore there was the inevitable consequence of increased NHS waiting-times for elective angioplasty procedures at interventional centres. This was observed in the current study with some patients waiting over 18 months for PCI whilst others sought out private healthcare provision to circumvent the long waiting-times. It unclear if the COVID-19 pandemic had an impact on the cardiovascular outcomes of this cohort of patients as this study was not adequately powered or designed to discern this.

4.3 Insights from VIRTU-4 CCS

4.3.1 First-line Investigations for Suspected Obstructive CAD

The VIRTU-4 CCS trial suggests that the first-line test for suspected obstructive coronary artery disease in the South Yorkshire district general hospitals is a an invasive coronary angiogram (41.1%) followed by myocardial perfusion studies (31.3%). The NICE recommendation of CTCA as a first-line investigation accounted for only 15.2% tests. Furthermore ETT, which is no-longer recommend as a first-line test accounted for almost 10% of investigations in this cohort. [42] At present there would have to be a 8-fold increase in the number of CTCAs to meet the current recommendations. [34] Any changes to service provision to be compliant with current recommendations will be slow to implement and heavily influenced by cost, training, staffing and the perceived impact on existing services. As with CTCA, coronary angiography, is purely an anatomical test and the non-invasive adjuncts of CTFFR and vFFR respectively could potentially streamline any further functional investigations and expedite patient management strategies with no additional radiation or contrast, minimal additional cost and may lead to improvement in the quality of CT scanning and invasive coronary angiography.

4.3.2 Optimal Medical Therapy Prescribing

Optimal medical therapy is defined by NICE as 1 or 2 antianginal medications as necessary plus drugs for the secondary prevention of cardiovascular disease. [62] The VIRTU4-CCS trial demonstrates that there is robust optimal medical therapy prescribing in the region. This is evidenced by the excellent rate of appropriate antiplatelet and statin prescribing (95.5% and 92.0% respectively). Similarly in patients with documented left ventricular systolic dysfunction on echocardiography (N = 22) an angiotensin converting enzyme inhibitor or angiotensin receptor blocker was appropriately prescribed in 95.5% of patients. With regards to antianginal prescribing, approximately 67% of patients were on 1 or 2 antianginal medications at the time of diagnostic angiography.

4.3.3 Extent of Significant CAD

The VIRTU-4 CCS trial enrolled unselected consecutive patients undergoing elective diagnostic coronary angiography from a pooled list of patients with suspected obstructive CAD. This pool of patients was consisted of either referrals from a specialist nurse-led rapid access chest pain clinics or routine outpatient clinic appointments. Patients with at least one visually assessed 30-90% stenosis in a vessel of at least 2.25mm diameter were included. The mean number of significantly diseased vessels was 1.23, with a median SYNTAX I score of 10 (IQR 13.8) reflecting the ‘real-world’ case mix of non-obstructive disease or one vessel disease with relatively few left main stem and or triple vessel disease patients. However, the disclosures of vFFR lead to a significant reclassification of the extent of significant coronary disease in up to 50% of patients. The mean number of significantly diseased vessels dropped to 0.73 ($p < 0.001$). This is due to a reclassification in the number of patients originally labeled as triple or two-vessel disease based on angiographic assessment to one-vessel disease or no-significant disease after vFFR disclosure.

4.3.4 Follow-up and Outcomes

The number of patients followed up so far is relatively small (N = 55). There were 16 patients still waiting for elective PCI, of those patients who had a vFFR < 0.80, seven had unscheduled hospitalisations or GP visits compared to one patient with a vFFR > 0.80. Thirty-one patients were conservatively managed. Similarly six patients with a vFFR < 0.80 had unscheduled hospitalisations or GP visits compared to two patients who had a vFFR > 0.80. Cross-tabulations failed to show any statistically difference in the occurrence of adverse events when stratified by management strategy or by vFFR < 0.80, however the trend was becoming more positive in the latter, in keeping with the findings of DEFER and FAME-2. [96,110]

4.4 What is the Role of Ischaemia-Guided Revascularisation in CCS?

The availability of vFFR lead to a hypothetical 22.3% change in management plans in patients with stable angina undergoing diagnostic coronary angiography in non-interventional catheterisation laboratories. The magnitude of change is largely in keeping with contemporary trials of a similar nature. [119-121] However where some these trials have predominantly reported an overall reduction in revascularisation procedures, the present study suggests a hypothetical increase in the proportion of patients referred for PCI and or invasive pressure-wire assessment who had previously been medically managed and found to have at least one vFFR< 0.80 [Figure 3.11]. This strategy change was in the context of an observed coronary artery disease burden reclassification rate of 50.0% (N = 56) to predominately single-vessel and non-obstructive coronary disease after the disclosure of vFFR data [Figure 3.7]. This suggests that the visual estimation of stenosis functional severity is inaccurate with a tendency for the underestimation severity in ‘mild’ lesions. As much as 21.7% of ‘mild’ lesions were found to be functionally significant [Figure 3.8 and Table 3.4] and it is roughly by this margin that management strategies changed in the present study. Historically, such lesions were the driving factor for unplanned revascularisation and late adverse events in the positive findings of FFR-guided intervention studies. [119-123] Importantly prior physician experience, unfamiliarity with FFR and

skepticism surrounding the diagnostic accuracy of vFFR may weigh heavily in the decision-making process. Therefore vFFR results may appear counter-intuitive to some cardiologists resulting in incorrect deferral of revascularisation in some patients and accounting for some of the medically managed patients with a vFFR < 0.80. Conversely, the reclassification of the majority of patients to single-vessel disease after vFFR disclosure may have encouraged general cardiologists to refer for targeted single-vessel PCI or invasive FFR compared to a trial of optimal medical therapy in patients with functionally ambiguous multivessel disease. There are many reasons that may account for these observations and behaviours. To understand these reasons an appreciation of the complexities of clinical-decision making in CCS, which is underpinned by decades of conflicting trial data must be unraveled. There are two principle paradigms of clinical decision-making, these are the significance of ischaemia and the benefit of revascularisation in the chronic coronary syndrome patient's symptoms and prognosis.

Early clinical trials examining outcomes of optimal medical therapy versus an initial revascularisation strategy in patients with stable angina demonstrated superiority of CABG over PCI and OMT in patients with multivessel disease and in those with isolated proximal LAD disease with respect to the incidence of myocardial infarction, cardiovascular death, repeat revascularisations and freedom from angina. [225,226] This was in contrast to the CASS trial, which examined over 1300 patients over 10 years and found no advantage of surgical revascularisation over OMT in the survival of stable angina patients. [227] Further conflicting data arose from the COURAGE trial, which randomised 2287 stable angina patients with significant angina who had at least one epicardial stenosis and objective evidence of ischaemia to either revascularisation or OMT. The findings of this trial demonstrated no benefit of revascularisation over OMT-alone for a composite end-point of cardiovascular death, stroke, myocardial infarction or hospitalization for acute coronary syndromes after an initial 3 year follow up period [228]. There was no catch-up phenomenon after 15 years of follow up. [229] Similarly in diabetic patients with stable angina there appeared to be no survival advantage with the addition of revascularisation to optimal medical therapy. [230] Several meta-analyses and systematic reviews also found no survival benefit with revascularisation over

OMT-alone in stable angina. [231-233] However one systematic review reported greater symptomatic relief and exercise capacity with revascularisation compared with optimal medical therapy. [231] From an anatomical perspective, there is a clear signal for the prognostic benefit of an initial revascularisation strategy over medical therapy in specific subsets of patients, such as those with significant left main stem [234] or proximal LAD stenoses [225] and those with both with multivessel disease and severe left ventricular systolic impairment. [235]

The relationship between ischaemia and outcomes in stable angina is less clear-cut in the literature and can be dichotomized through the use of invasive and non-invasive physiological testing in clinical trials. Prior to the invasive FFR trials namely, DEFER, FAME and FAME 2, that have established FFR as the gold-standard test for ischaemia, ETT and myocardial perfusion imaging were, and still are (owing to their wide-spread availability), the non-invasive functional tests utlisied in clinical trials to detect ischaemia. One study comparing concordance between SPECT and FFR in the detection of ischaemia in patients with multivessel coronary artery disease demonstrated that SPECT underestimated ischaemia in 36% and overestimated ischaemia in 22% of patients. [236] Several meta-analyses conducted since have demonstrated that SPECT is, at best only moderately accurate compared to FFR, with ETT-alone performing far worse as a discriminator of ischaemia. [237-239]

The ISCHAEMIA trial enrolled 5179 patients and demonstrated no benefit of an initial revascularisation strategy in addition to OMT over OMT-alone in patients with chronic coronary syndrome with evidence of moderate-to-severe ischaemia on non-invasive functional testing. However those with refractory angina gained the greatest symptom relief and improvements in quality of life with revascularisation. There was also a signal for harm with revascularisation through increased peri-procedural myocardial infarctions. [240] This is in contrast to the findings of a commonly cited single-centre observational study of 10,627 patients in which a survival benefit was found in those patients who demonstrated a greater than 10% ischemic burden on SPECT who underwent an initial revascularisation strategy compared to those who did not. [241]

However the observational and retrospective nature of this study, coupled with treatment selection bias and inherently different patient groups caused by unbalanced confounding factors make the generalisability of this study limited. The ISCHAEMIA trial was underpowered due to under-recruitment and subsequently relied on greater inclusion of less sensitive stand-alone exercise testing (in up to 25% of the study population) to determine the presence of ischaemia. Furthermore 14% of randomised patients had less ischaemia than pre-specified in the inclusion criteria and 78% of randomised patients had no angina or monthly angina only. The ISCHAEMIA trial also excluded those with LV impairment, left main stem disease, severely symptomatic patients despite maximal OMT and those with NYHA class III or IV heart failure. Importantly, under-recruitment to this trial lead to a change in the pre-specified primary end-points to include more subjective variables such as hospitalisation for heart failure and unstable angina, which may undermine the validity and reliability of the study especially as this study was not blinded. Despite its limitations, the ISCHAEMIA trial adds weight to the safety of optimal medical therapy in young, male patients without left main stem disease or LV impairment who have moderate-to-severe ischaemia on the most widely available non-invasive functional testing.

Proponents of revascularisation in chronic coronary syndromes often cite the FAME 2 trial. This trial set out to examine the impact of revascularisation in addition to optimal medical therapy versus optimal medical therapy alone in patients with stable angina who had documented angiographic disease and an FFR ≤ 0.80. The trial aimed to recruit 1632 patients (roughly 816 patients in each group) but was terminated after recruitment of 888 patients due to a highly significant difference in primary endpoint in favour of the PCI group. The difference in primary end-point was driven by high rates of urgent revascularisation in the conservative group (11.1% versus 1.6%, $p < 0.001$). The rates of death and MI were the same in both arms of the trial. The findings of this trial advocate the use of FFR-guided PCI to reduce the rate of urgent revascularisations in patients with stable CAD. Secondary analyses suggest that patients who had the greatest ischaemia (FFR < 0.65) derived the greatest benefit and symptom relief from revascularisation. [110] The five-year follow-up of FAME 2 demonstrated the maintained benefit of PCI over

OMT-alone with respect to urgent revascularisations (6.3% versus 21.6%) with no difference in mortality or myocardial infarction. [79] FAME 2 is criticized for its use of a relatively soft-endpoint as urgent revascularisation. In this trial, it was defined as admission to hospital with increasing or persistent chest pains with or without ECG and or cardiac biomarkers. Fifty-two percent of patients requiring urgent revascualrisation in the conservative arm of the trial were diagnosed on clinical features alone without ECG or cardiac biomarker elevations. Given that randomisation to FAME 2 was non-blinded, there is concern that intervention during the follow-up period may have been biased against the conservative arm of the trial. Both FAME 2 and ISCHAEMIA demonstrated a reduction in spontaneous myocardial infarctions in the intervention groups offset by increased rates of peri-procedural myocardial infarctions. [79,240] Similar findings regarding a reduction in the risk-benefit ratio with PCI was described in the 'grey-zone' FFR studies. These studies suggest that in borderline ischaemia the benefits of PCI are offset by procedural complications and peri-procedural myocardial infarctions. [107,108,133]

A contemporary meta-analysis reported an incremental reduction in death and myocardial infarction in those patients revascularisaed with the latest generation DES and surgical techniques over medical therapy alone. [78] This signal was corroborated by another patient-level meta-analysis of 2400 patients who underwent FFR-guided revascularisation. This meta-analysis demonstrated a reduction in death and myocardial infarction over a median of 33 months (HR 0.74, 95% CI: 0.56 - 0.989). [80]

The largest obstacle in demonstrating a prognostic benefit for revascularisation in a randomised controlled trial of chronic coronary syndromes management strategy is the rarity of the primary endpoints, death, stroke and myocardial infarction. At national levels cardiovascular mortality rates ranges from 0.9% to 1.2% and was 1% in patients with a positive exercise test. [242-244] Myocardial infarction rates are similarly rare with reported rates between 1.0% and 2.6% reported in population-based studies. [245] To adequately power, conduct and finance a prospective randomised controlled trial to accurately determine a true treatment effect would be practically and financially unviable requiring several tens of thousands of

patients followed up over several decades. To put things in perspective, the ISCHAEMIA trial was the largest study of its kind to date, requiring over $100 million to finance, which enrolled 5179 patients over a median follow-up of 3.2 years. [240]

On a biological level, chronic ischaemia results in various adaptive changes across the entire coronary circulation, from the epicardial vessels to the microvasculature and myocardium. These changes may contribute to the disparity between an initial revascularisation strategy and prognostic outcomes in patients with stable angina that demonstrate ischaemia. This may also highlight the deficiencies of currently available tests of ischaemia to accurately characterize the complex interplay of the various vascular compartments that constitute the coronary circulation in its entirety. [246] The coronary circulation is an anastomotic circulation. Chronic ischaemia promotes the development of collateral circulations between different coronary artery territories to limit the impact of flow-limiting epicardial stenoses. [247] On a cellular level, chronic ischaemia may result in protective myocardial metabolic responses such as ischaemic pre-conditioning and myocardial hibernation to mitigate against recurrent ischaemic episodes and infarction. [248,249] To contrast with ACS patients who have no time for any adaptive changes to occur, an initial and prompt revascularisation strategy has become in no uncertain terms the gold-standard management. [72]

The RIPCORD 2 trial, an open-label, prospective, randomised trial enrolled 1100 patients with stable angina and at least one stenosis of greater than 30% diameter in any epicardial vessel amenable to PCI or CABG in 17 UK centres. Patients were randomised to either angiography only or angiography and systematic FFR guided decision-making at the time of diagnostic catheterisation. The investigators demonstrated that systematic FFR measurment in all amenable coronary arteries was cost neutral and resulted in no difference in management plans, quality of life, angina status or length of hospital stay. The secondary outcomes of myocardial infarction, stroke, death or urgent revascularisation were no different between the two groups. However a management plan was in place immediately after catherisation in 98% of patients in the FFR group compared to an additional follow-on

investigation required in 14.7% of patients in the angiography alone group. [250] Although this is an equivocal trial, FFR is seldom performed in this way at an early point in the diagnostic pathway of stable angina patients. The true benefit of FFR likely lies in the assessment of the intermediate lesion at the revascularisation stage of which vFFR could represent a useful gatekeeper.

4.5 Decision Making in CCS: The Role of the Heart Team

Cardiologists making management decisions in the context of chronic coronary syndromes are faced with decades worth of conflicting data to assimilate alongside their own 'real-world' experiences in order to distil the information to the individual patient who has their own unique comorbidities and expectations. Here in lies the skill and nuances of applying acumen to evidence-based practice. Convening a multidisciplinary Heart Team can help share the decision-making process when considering whether or not to intervene, with what modality and in what time frame especially in increasingly more complex patients. [251] The use of Heart Teams in the decision-making process for CAD has gained class 1C recommendations in both the American and European guidelines despite the lack of robust data, as their effectiveness is yet to be determined. [57,72] The advantages of a Heart Team are facilitation of a treatment plan and shared decision-making in complex and increasingly co-morbid patients, which may ultimately represent a source of safety from medico-legal repercussions that are becoming increasingly more prevalent in contemporary practice. [252] Despite this, Heart Teams are used to various degrees in different institutions, sometimes just to comply with departmental audit tick-box exercises. There are several barriers and questions to address to create an effective Heart Team. For example, there is considerable logistical effort required to convene Heart Teams in a manner that balances the commitments of consultants and the provision of treatment recommendations to patients in a timely matter. The dynamics in Heart Teams are likely to be highly variable based on the experiences and preferences of the consultants and the local resources at their disposal. How are the decisions made? Is there a consensus or do the most senior participants dictate the decisions? How is clinical equipoise circumvented? Perhaps most importantly, how is decision-making shared with patients and

their families? [253] One study investigating the consistency and implementation of Heart Team decisions in a tertiary-centre demonstrated that Heart Team decisions were reproducible 80% of the time and that further information from additional functional investigations resulted in deferral and delay of decisions in up to 27% of cases. [254] Another single-centre US study of 180 patients demonstrated that Heart Team decision-making was safe resulting in outcomes in keeping with national standards. [255]

Data from the present study suggest that there are significant differences between individual general cardiologists and the Heart Team with respect to their initial management strategies and their confidences in those strategies. The difference in decision-making between the Heart Team and the treating cardiologist likely reflects the differing levels of expertise, knowledge and investigations available to the Heart Team. For example, the rate of recommendation for invasive FFR measurement as an initial strategy was almost four times higher in the Heart Team setting when compared to the individual cardiologist. Unsurprisingly, the disclosure of vFFR did not significantly alter the rate of invasive FFR usage in the Heart Team compared to the individual general cardiologist, where invasive FFR recommendation increased by 66.7% relative to pre-vFFR disclosure levels. The combined acumen and experience found in the Heart Team is considerably different to that of the individual general cardiologist. For example, a cardiothoracic surgeon in the Heart Team would not routinely be faced with making management decisions in patients with single-vessel disease, but may be very confident in deciding a revascularisation strategy for a complex multivessel disease patient where a generalist would most commonly defer to an MDT for a definitive management strategy. Factors such as prior extensive experience managing a wide spectrum of patients with stable angina, familiarity with FFR and skepticism surrounding the diagnostic accuracy of vFFR weighed heavily in the decision-making process at the Heart Team assessment. It may be these factors that lead to the non-significant management change observed in this group (17.9% change in management plans) especially when faced with conflicting vFFR data.

There are often other variables that add to the complexity of clinical decision-making. One of these increasingly recognised factors is patient frailty. Frailty is defined as '*a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes'.* [256] Frailty is a separate entity apart from comorbidity and disability, with a complex interplay between the physiological changes of aging and disease that ultimately leads to disability. [256] Practically, factors that constitute frailty can be objectively assessed by the presence of reduced activity, weakness, shrinking secondary to sarcopenia or unintentional weight loss and poor endurance or slowness. The risk of procedural complications and the incidence of adverse events such as acute kidney injury or major bleeding coupled with a perceived lack of efficacy from intervention may deter clinicians following an interventional strategy when treating elderly and frail patients. [257] For example, frailty was found to be the greatest predictor of major bleeding post-PCI independent of age. [258] Despite the advances in PCI and antiplatelet regimens, a treatment paradox exists whereby the patients with the most to gain; the elderly and frail are the least likely to receive the benefits of these advancements. [259] The current study had a mean patient age of 65.3 years with 91% of patients scoring well to very fit on the clinical frailty scale and therefore was not designed nor powered to examine the effects of frailty, age and comorbidities on clinical decision making CCS.

In summary, clinical decision-making in CCS is not always straightforward and is fraught with conflicting data as a result of the wealth of literature. The decision-making process is not necessarily simplified at the Heart Team level as the disparities between trial data and 'real-world' practice become more contentious. As things stand there is clear prognostic benefit for revascularisation in patients with left main stem disease, proximal left anterior descending artery disease and multivessel disease with significant left ventricular impairment. There is more contentious evidence for the prognostic benefit of revascularisation in patients that demonstrate ischaemia, with the greatest treatment effect observed in those who are most ischaemic and symptomatic despite maximal medical therapy.

4.6 The Place of Invasive Coronary Angiography in CCS

Since Sones and Shirley performed the first selective coronary angiogram in 1960 [52], invasive coronary angiography has been the gold-standard test for the diagnosis of obstructive CAD. In the UK, invasive coronary angiography is reserved for those patients who have a high pre-test probability of CAD, those with refractory or low-effort angina and in those with significant findings on non-invasive testing. [28] Otherwise, CT coronary angiography should be offered as the first-line investigation for the investigation of stable chest pain. [42] According to current activity in the UK, this would require on average an eight-fold increase in national service provision. [34] Approximately 250,000 ICAs, including about 40,000 in non-interventional cardiac catheter laboratories, are carried out in the UK per annum, a consistent figure in recent years. [215] The impact of CTCA upon this figure is as yet unclear. Some have suggested that the rise in popularity, accuracy and accessibility of CTCA may signal the death knell for ICA [260] yet national audit data reveal a slow increase in numbers. [215] The main limitation of ICA is its invasive nature. However radial artery access, small diameter catheters and improved contrast media and fluoroscopy technology have reduced the complication rate to negligible levels. Its main diagnostic deficiencies include its anatomical rather than functional nature, a poor relationship between stenosis severity and blood flow, the subjectivity of visual interpretation particularly in intermediate (30-70%) stenoses [261] and technical inadequacies, such as poor vessel opacification and lesion assessment. Nevertheless, ICA remains the final common pathway for revascularisation and treatment planning, and is a pre-requisite for valve surgery and other major interventions such as organ transplantation. Figure 4.1 illustrates the major milestones in the evolution of the coronary angiogram. Table 4.1 outlines a comparison of contemporary invasive and CT coronary angiography.

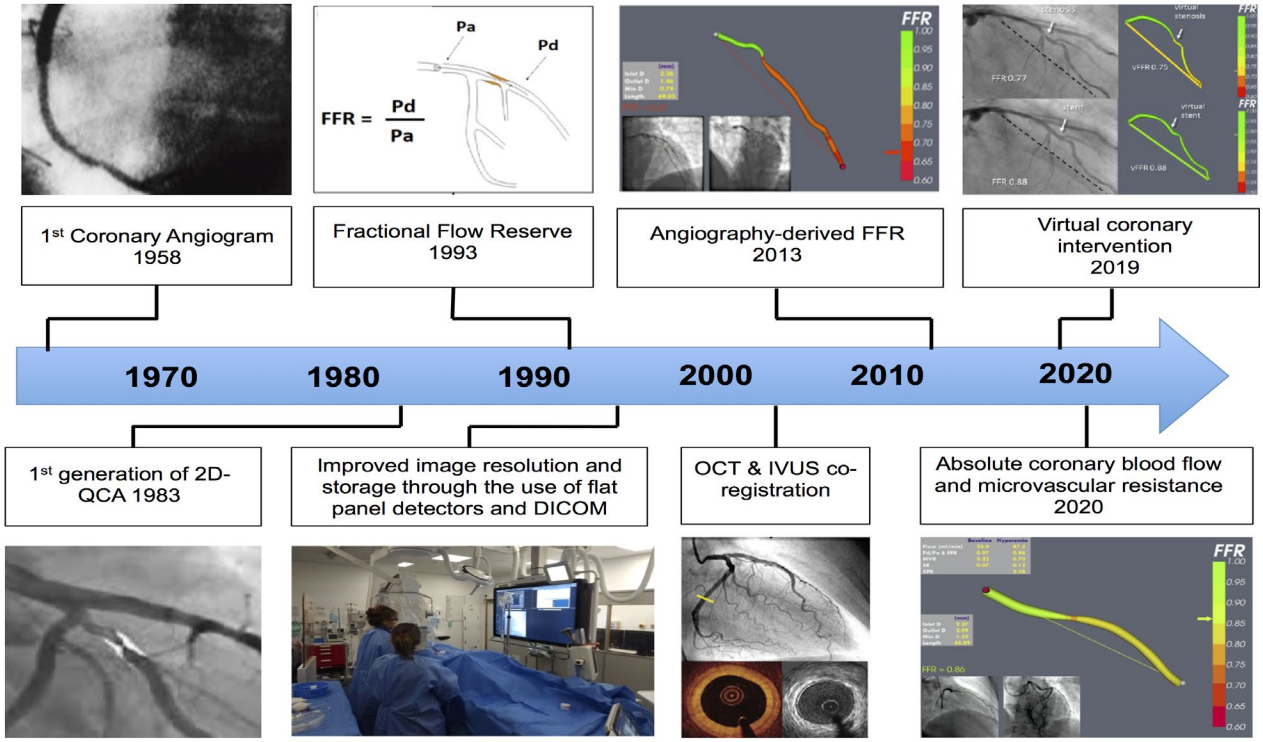

Figure 4.1: Milestones in the history of diagnostic coronary angiography. **QCA** quantitative coronary angiography, **FFR** fractional flow reserve, **Pa** aortic pressure, **Pd** pressure distal to stenosis, **OCT** optical coherence tomography, **IVUS** intravascular ultrasound. Reproduced with permission from Ghobrial et al. [262]

Factor	CT Coronary Angiography	Invasive Coronary Angiography
Invasiveness	Non-invasive	Invasive
Cost	£305	£2000
Radiation dose	2-5mSv	2-12mSv
Contrast dose	50-120ml	13-90ml
Spatial resolution	0.50mm	0.16mm
Temporal resolution	83-153ms	1-10ms
Sensitivity for obstructive CAD	High	Gold-standard investigation
Specificity for obstructive CAD	Low to moderate	Gold-standard investigation
Patient limiting factors	Calcification	Severe frailty
	Tachycardia/ irregular heart rhythm	Low eGFR
	Low eGFR	
Other limiting factors	Intolerance of rate-limiting medication	Intolerance of hyperaemia inducing medication
	Motion artifacts	
Physiological adjuncts	FFRCT	Invasive FFR/iFR/CFR
		CAG-FFR
Complication rate	Contrast induced anaphylaxis <1%	Arterial access site complications (radial) 0.2%
	Contrast induced nephropathy 3%	Major adverse events (MI 0.05%, CVA 0.07%,
	Side-effects related to rate limiting	Death 0.08%)
	medications uncommon	Contrast induced anaphylaxis <1%
		Contrast induced nephropathy 3%

Table 4.1: A comparison of CT coronary angiography with invasive coronary angiography. Reproduced with permission from Ghobrial et al. [262]

The latest ESC chronic coronary syndrome guidance mandates invasive functional assessment to evaluate stenoses before consideration of revascularisation, unless very high grade (>90%) with class 1B recommendation. [263] In the UK alone over 40,000 ICAs are performed in 60 non-interventional cardiac catheterisation laboratories by those not trained in intervention or the management of the complications of coronary instrumentation. [215] Shifting this workload to interventional centres would stretch the national service beyond financial and operational capacity factoring in the additional procedural costs, duration and complications that would result. Furthermore it is unclear how the latest recommendation for ACS patients to undergo invasive angiography within 24 hours [264] (a far cry from current 'real-world' practice) would alter case-mix at interventional sites, potentially prolonging waiting list times for elective procedures. Virtual FFR offers an attractive solution to this problem.

4.7 The Contribution of vFFR

The possible future contribution of vFFR, or any other angiographically-derived FFR, can be discerned to some extent by examining the effect CTFFR has had on clinical practice to date. As described in the literature CTFFR has boasted improved sensitivity, specificity and diagnostic accuracy over CTCA alone in ruling-out patients with low-to-intermediate suspicion of obstructive coronary artery disease leading to an overall reduction in the number of unnecessary invasive coronary angiograms. [182] Despite it's variability in diagnostic accuracy and the limitations of 'real-world' CTCA acquisition, CTFFR has gained NICE approval as a result of its non-invasive nature and an anticipated cost-saving of £9.4million by 2022 by avoiding unnecessary invasive investigations. [265] This strategy was further strengthened by the findings of the ISCHAEMIA trial, which suggests that once significant LMS disease has been ruled out, a conservative strategy can be safely adopted even in the presence of moderate ischaemia. Therefore CTFFR is ideally poised to offer a robust 'one-stop-shop' for the low-to-intermediate probability population.

Similarly, vFFR represents an ideal all-in-one test for patients being assessed for revascularisation; particularly for those triaged directly for ICA. Virtual FFR could provide enhanced and rapid decision-making while the patient is on the table. Its great advantage is that it can provide a preliminary physiological assessment in any ICA, including in non-tertiary centres, without the need of a wire, an interventionist, extra equipment or expense. This represents a substantially increased potential compared with the present situation. In the UK, of the annual 250,000 ICAs, only about 13,000 include pressure wire assessment, all of which are in interventional catheterisation labs; and, of the 100,000 PCIs performed, only 10,000 involve pressure wire assessment. [215] Therefore, invasive physiology is deployed in only 6-7% of all patients assessed and treated. The availability of vFFR is likely to considerably increase the availability of coronary physiology, wherever an ICA can be performed, with a reduction in subsequent non-invasive tests of ischaemia, delays and potentially further visits to the catheterisation lab. However, the VIRTU-4 CCS trial suggests that there may be an increase in the number of deferred management plans as vFFR lead to a need for more invasive physiological data (n = 9 pre-vFFR versus n = 15 post vFFR disclosure). If performed in an interventional catheterisation lab, vFFR can justify proceeding to PCI immediately but, importantly, deferring it in others. The software licences for vFFR means the per-patient price will likely be low and, being software-based, can be integrated into existing catheterisation labs relatively simply. Virtual FFR may also enable advanced treatment planning by simulating the physiological effects of virtual stent deployment. This, in turn, could help operators to achieve optimal physiological benefit, whilst minimising the length of stent deployed. [266] Ultimately, the CFD methods behind vFFR may also enable quantification of absolute (volumetric) blood flow and other parameters such as microvascular resistance, providing a more comprehensive coronary physiological assessment. [267] In the future, IVUS and OCT, co-registered with ICA may augment anatomical reconstruction and this may improve vFFR accuracy.

Virtual FFR has a potentially important contribution to make in patients with multivessel disease being considered for CABG who arguably have the

greatest need for physiological assessment. [268] However, very few receive invasive physiological assessment prior to CABG as referral for surgery is often based upon a coronary angiogram performed in a non-interventional centre. Further guidance with invasive FFR would therefore require a second procedure at an interventional catheterisation lab or a non-invasive functional test resulting in further delays for the patient, and is therefore rarely done. Without FFR, if two vessels need grafting, the third being angiographically borderline, the surgeon may feel obliged to apply a graft which, if the lesion is physiologically insignificant, may lead to an unnecessarily long operation, a wasted conduit, and occlusion due to competitive flow. Anatomical triple vessel disease, 'mandating' CABG, when subjected to physiological assessment, may be converted to physiological two- or even one-vessel disease, adequately treated by PCI. This was observed in the current study as 34.2% of three and two-vessel disease patients remained so after vFFR disclosure. This was also described in a sub-analysis of the SYNTAX II trial in which only 37.2% patients remained as having triple vessel disease after invasive physiological assessment. [269] This group of patients may derive particular benefit from vFFR. Although clinical trials comparing physiology-guided CABG with angiography-guided CABG have not shown clear benefit of physiological guidance, these trials included small numbers of patients, and it seems counterintuitive to graft a vessel with non-flow limiting disease. [270]

4.8 Where Could vFFR Fit into Future Guidelines?

Current UK guidelines advocate CTCA as the first-line investigation for suspected obstructive coronary disease. Functional tests of ischaemia are recommended in cases in which there is uncertainty about the findings of CTCA. [62] Functional tests can also be first-line investigations in symptomatic patients with confirmed CAD. ICA is currently only recommended as a third-line investigation. Pre-test stratification according to the likelihood of significant CAD often over-estimates risk and has fallen out of current national guidance. European guidance supports the use of ICA for patients who have a high pre-test probability of CAD with significant risk factors and refractory angina or typical angina at low work-loads; [263] a pathway which retains some

popularity for many UK cardiologists. Given the characteristics of CTCA and ICA [Table 4.1] and the variability of locally available investigations, Figure 4.2 outlines a modified algorithm for the diagnosis of obstructive CAD incorporating virtual coronary physiology. In this framework, the role of ICA is strengthened. Instead of some patients at medium and higher risk requiring both a non-invasive test and ICA, they could have a stand-alone vFFR providing a detailed and appropriate plan for revascularisation in a time-efficient manner.

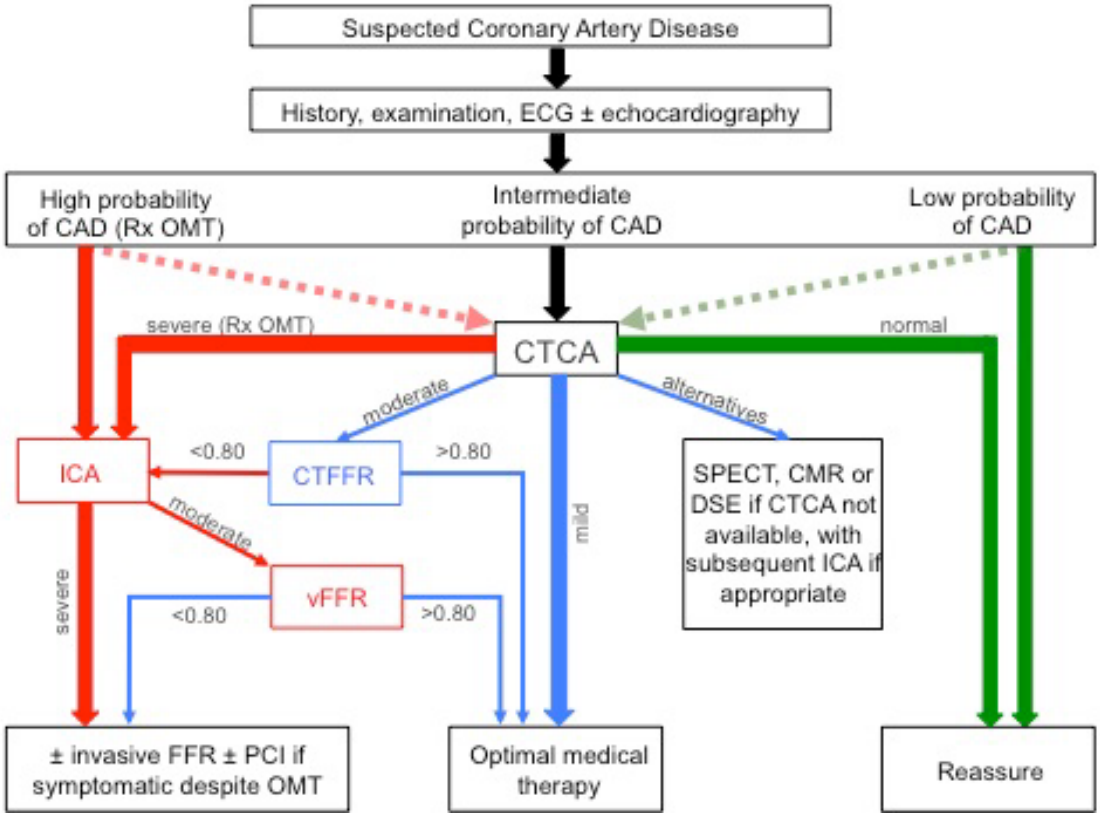

Figure 4.2: Proposed algorithm for the incorporation of vFFR and CTFFR in the assessment of patients with suspected chronic coronary syndromes. Reproduced with permission from Ghobrial et al. [262]

4.9 How Could vFFR Impact Decision-making Confidence in CCS?

The VIRTU-4 CCS study demonstrated a change in management plans in 22.3% of cases and that cardiologist confidence levels in their management plans generally increased after vFFR disclosure (mean confidence level pre- and post-vFFR disclosure: 8.90 vs 9.22 p = 0.026). Rather intuitively cardiologists' confidence levels increased when the vFFR result agreed with

their management plans, but did not decrease significantly when vFFR was discordant with the consultants' management plan. Similarly, Gosling et al demonstrated that the use of vFFR and an associated virtual coronary intervention tool lead to a change in interventional cardiologist's management strategies in up to 27% of cases with and overall increase in confidence level. [271] However, the relationship between physician confidence and strength of therapeutic decision-making is not well characterized. One study examining diagnostic accuracy and confidence in diagnostic accuracy of 118 general internists suggests that physicians may be overconfident in their decision making in more challenging cases and subsequently less likely to request additional investigations or to re-consider their management strategies. [272]

The VIRTU-4 CCS study demonstrates that when vFFR data was discordant with the initial management strategy, cardiologist confidence was not significantly reduced (mean DGH cardiologist confidence level reduction 0.5 points). Where as when vFFR data was concordant with management strategy there was a mean increase in confidence by 1.26 points, more than two and half times the magnitude in the increase in confidence level providing positive reinforcement to decision-making. This may reflect basic human psychology where people tend to trust in their instincts and past experiences when faced with conflicting information. This is especially true with novel technologies such as vFFR where cardiologists were unfamiliar with it's diagnostic accuracy compared to invasive FFR, it's lack of outcome data and feeling that the coronary anatomy has been misrepresented at the segmentation step. The Heart Team deemed approximately 17.0% and 6% of study angiograms as poor or completely non-diagnostic respectively. Despite the poor quality of these angiograms, a 3D-model could be synthesized and a vFFR result was calculated. This raised concern that such vFFR results could be extrapolating the ambiguity from non-diagnostic angiograms and that cardiologists, who are less informed about the limitations of vFFR, are making potentially erroneous management decisions based on these data.

Interestingly the present study demonstrates that mean confidence levels in initial management strategies were higher in the district general cardiologists

compared to their counterparts in the Heart Team, both before and after vFFR disclosure (mean confidence level DGH vs Heart Team respectively: 8.90 vs 7.80 pre-vFFR disclosure, $p < 0.001$ and 9.22 vs 7.93 post-vFFR disclosure, $p < 0.001$). This could be explained by the Dunning-Kruger paradox. This describes how increasing experience and knowledge leads to a reduction in confidence given the greater appreciation of the complexities and factors involved before a definitive conclusion or decision can be reached surrounding a subject. [273] This is not to say that general cardiologists are not competent to make these kinds of decisions, but rather they act as gatekeepers to streamline referral and expedite treatment for more complex patients and patterns of coronary disease that would benefit from the MDT process. In reality the process of MDT referral varies from region to region. In some centres there is reliance on voluntary referral to a central tertiary-centre MDT for selected patients and in other regions MDT discussion is mandated for any patient under consideration for revascularisation irrespective of the modality.

4.10 How Practical is vFFR?

The VIRTU-4 CCS trial was conducted in catheterisation laboratories across 4 district general hospitals in South Yorkshire. Participating centres differed with regards to their fluoroscopy, physiology-monitoring equipment and reporting systems reflecting the multipurpose usage of some of these catheterisation laboratories. In some laboratories these systems were not interconnected. This could potentially represent a barrier to integrating a vFFR software as an ECG signal is required to accurately identify end-diastole. For the purpose of this study, a stand-alone version of VIRTUheart^{TM}, loaded on to the study laptop computer was used to carry out vFFR analysis. This was reliant on CD or DVD copies of the angiograms being created. However this technology is rather antiquated compared with current practice that uses secure online-digital transfer platforms that are the standard of image transfer across institutions around the country. At some centres it was possible to create the CD or DVD directly from the fluoroscopy hardware in the catheterisation lab with minimal delay compared to other centres where this process required a

hand-written request that was queued by a PACS officer meaning the disk wasn't available until after an hour or so in some instances.

The mean processing time per vessel was 15 minutes with 21.3% of cases requiring more than one vessel to be processed. The mean turn-around time between finishing one angiogram and starting the next procedure was around 20 minutes. This meant that the vast majority of single-vessel vFFR models were finished in this turnaround time, being available for integration into the patients management plans, if performed by an experienced vFFR operator.

Poor characterization of coronary microvascular resistance is the main determinant of error in vFFR analysis. [197] To mitigate against this, a degree of patient-specific personalisation was used to better inform the CFD model of the individual's microvascular resistance. The key components of this step required an in-depth understanding of two separate myocardial jeopardy indices, the Duke jeopardy score [274] and the BARI myocardial jeopardy index [275] as well as having an understanding frailty scoring [218]. This additional layer of complexity will lead to a steeper learning curve and lengthen the overall case processing time, which may not be pragmatic for everyday clinical usage. However it is important to consider that in its current form, VIRTUheart™ is a detailed research tool that has yet to be commercialised. Therefore the ideal vFFR platform should be easily integrated into existing catheterisation laboratories with real-time image transfer and have more sophisticated automation to mitigate against user inexperience in the key steps such as image frame selection, model segmentation whilst incorporating simplified personalisation in a user-friendly interface.

4.11 What are the Limitations of vFFR?

Virtual FFR is particularly dependent upon the quality of the angiographic images. This is because coronary angiography is essentially a series of 2D images that need to be converted into a 3D computational model. Even a straight tube with a simple stenosis needs two 2D images, at least 30 degrees apart, to derive a reasonably accurate 3D model. Thus, lesions located at

bifurcations, or overlapped by vessels, at the arterial ostium or in the left main artery, pose particular challenges. As with a simple diagnostic ICA, poor catheter engagement, inadequate artery opacification with contrast, excessive 'panning', movement (patient, respiratory or cardiac), magnification or 'coning' that obscures or cuts off parts of the vessel are problematic. Therefore, as many as 80% of ICAs are unsuitable for analysis; but with some simple improvements in angiographic technique [Appendix A], this figure can be substantially reduced. (216) The VIRTU-4 CCS trial demonstrated that through the use of a standardised coronary angiogram acquisition protocol optimised for vFFR application only 7% of coronary angiograms were completely inadequate to generate a vFFR model. The ability to generate a vFFR from a poor quality angiogram may lead to erroneous decision-making. This point was raised at during the Heart Team assessments, where 5.6% of ICAs were deemed of too poor quality to make a confident clinical decision and more information in the form of repeat invasive angiography was recommended. Therefore, just because a vFFR model can be generated from these angiograms, it could be entirely misleading. This reinforces the need for standardised angiography and local quality-control audits. Indeed centres that have adopted vFFR, often report improvement in the quality of angiography when working with an acquisition protocol suited for vFFR analysis. A level of skill in image processing is also required, with knowledge of coronary anatomy and training in using the software, particularly at the segmentation step. (276) In most centres, this is likely to be the domain of the radiographer. The main scientific limitation and challenge in these models is that of variability in the resistance of the coronary microvascular bed. Not only is this the dominant influence of coronary blood flow, and FFR, but it is also the single largest contributor to error in vFFR. (197) Because MVR is unknown, models rely upon assumptions that do not apply in all patients, such as those with prior MI, diabetes or LVH. (158)

Despite an overall diagnostic accuracy of > 90% when compared to invasive FFR, the error margins of vFFR are more in keeping with those of CTFRR. The 95% limits of agreement for vFFR are ±0.14. (201) This raises the question of whether this accurate enough to guide treatment especially near the

treatment threshold of 0.80? [277] One study suggests that by utilising a zone of uncertainty between vFFR values of 0.77 and 0.86, angiographically derived FFR achieved 94% sensitivity and 95% specificity. [201] This would have resulted in avoidance of unnecessary invasive FFR measurement in 64% of cases with 95% accuracy. [195] This is important as the current trial suggests that vFFR could lead to an increase in invasive FFR referrals from district general cardiologists to corroborate virtual measurements.

In the current study inter-observer variability between two expert vFFR operators assessed with ICC was 0.79 (r = 0.66) indicating a very strong agreement and moderate correlation between operators. [221] There were only 3 out of 19 vFFRs what were discordant between operators. The ICC and correlation co-efficient between expert operators dropped slightly (ICC = 0.77, r = 0.63) when comparing personalised vFFR. This likely reflects an inevitable additional degree of variance incurred when undertaking personalisation. Therefore there may be a signal for a trade-off between increased diagnostic accuracy through personalisation and model reproducibility. Intra-observer ICC was lower than expected (ICC = 0.75 generic vFFR and ICC = 0.73 personalised vFFR) likely reflecting the presence of a learning curve at the beginning of the trial and upgrades to the VIRTUheart^{TM} software throughout recruitment. However the accuracy and reproducibility of vFFR has yet to be determined outside of expert academic core-laboratories. Lal et al. demonstrated that there is a clear learning-curve in the use of vFFR in their study comparing expert and novice vFFR operators in 199 patients (231 vessels). There was significant variability and only moderate agreement between novice operators resulting in a reclassification rate of 27% between treatment allocations (revascularisation versus optimal medical management). In contrast the reclassification rate was only 10% in the expert vFFR operator cohort. This clearly highlights the need for robust training and quality assurance as operator experience plays a crucial role the quality of results and treatment allocation. [278]

4.12 How does VIRTUheart™ compare to CAAS-vFFR and QFR®?

The purely academic VIRTUheart™ tool utilises pseudotransient CFD simulations informed by patient-specific microvascular resistances to calculate vFFR. This computation takes on average four to five minutes (apart from the time required for segmentation and personalisation). This is in contrast to the commercially available CAAS-vFFR platform which calculates vFFR instantaneously based on a pressure-drop calculation derived from physical scaling laws, the formulae described by Gould et al [93], as well assumptions about preserved hyperaemic flow in the proximal vessel of interest. The only personalisation afforded to the model is the patient's aortic blood pressure. [279] Similarly QFR® utilises 3D-QCA and fixed hyperaemic flow velocity (derived from invasive FFR measurements) to calculate FFR through the use of rapid CFD modeling. QFR® assumes that trans-stenotic pressure gradients are a function of stenosis geometry and the fluid dynamic principles described previously. QFR® also assumes constant coronary pressure in the epicardial vessels as well as preserved coronary flow velocity in the distal vessel under examination. Furthermore QFR® assumes stenosis geometry can be inferred from healthy vessel lumen diameters as a reference. These in turn are derived from the 3D-QCA reconstructions. Additional personalisation can be achieved through the use of TIMI frame counting of contrast media as it first reaches the start and end of the reconstructed portions of the vessel. [181,194,195] Despite the differences in computation methodology, it has been demonstrated that these platforms correlate well with invasive FFR measurements with acceptable agreement and accuracy [201,279]. However it is important to note that these studies have been conducted in core-laboratories by the experts and pioneers of virtual coronary physiology, without any direct head-to-head comparisons.

Without the gold-standard reference of invasive FFR measurements, it is not possible to do a head-to-head comparison between VIRTUheart™, CAAS-vFFR and QFR®. An example of their respective outputs is illustrated below.

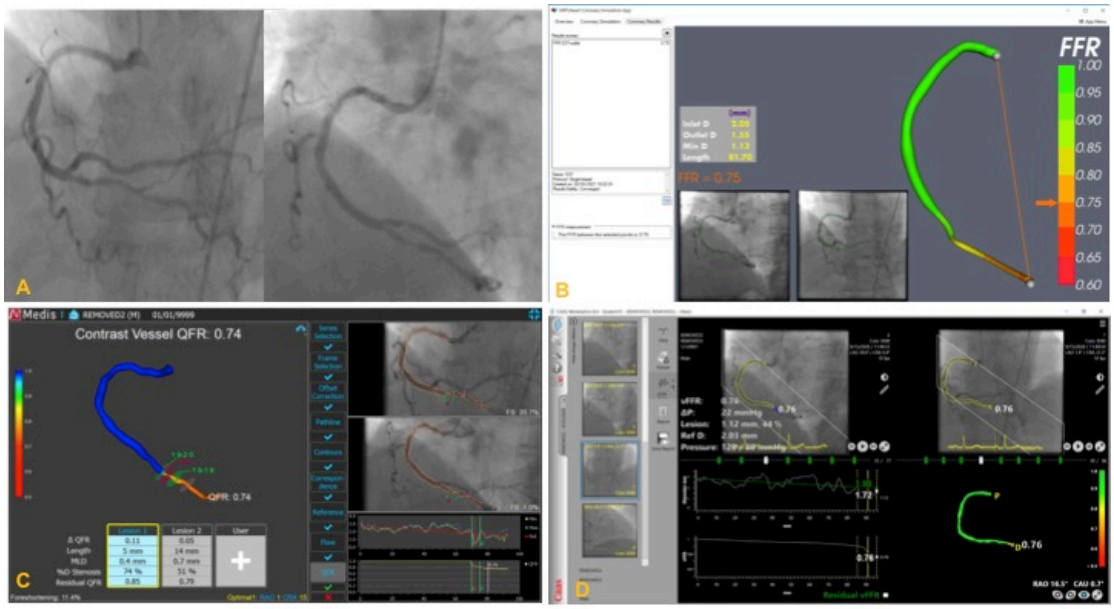

Figure 4.3 Visual output of VIRTUheart™, CAAS-vFFR and QFR® **[A]** Intermediate distal RCA stenosis in two orthogonal views. **[B]** VIRTUheart™ output with vFFR of 0.75. **[C]** Contrast Vessel QFR® output with vFFR of 0.74. **[D]** CAAS-vFFR output with vFFR of 0.76.

A sub-study of the VIRTU-4 CCS trial examined the performance of all three vFFR platforms in 71 vessels. The left anterior descending artery comprised 56% of analyses. The mean computation time per vessel was significantly different between the three platforms (14 mins VIRTUheart™, 4 mins CAAS-vFFR and 3.5 mins QFR®). Severe vessel tortuosity and lesions > 90% diameter stenosis were not consistently processable by VIRTUheart™. These anatomical factors were readily processable by the CAAS and QFR® systems. VIRTUheart™ is primarily a research tool and as of yet lacks some of the user-friendliness resulting from commercialisation of the other two platforms; specifically, the ability to modify the common image point, as well as being able to review and modify the 3D-reconstruction at any point during the modeling process. Furthermore the personalisation feature of VIRTUheart™ is much more complicated and time-consuming involving the calculation of two separate myocardial jeopardy indices as well as the input of other variables, which may not be routinely collected in clinical practice.

Overall this sub-analysis indicates that there is weak to moderate agreement between the various permutations of the three platforms. Adjusting for the expected variance in personalisation by using generic boundary conditions for

VIRTUheart™ and Fixed Flow-QFR®, there appeared to be little effect in reducing the limits of agreement between platforms and resulted in increased discordant vFFR values. The magnitude of the limits of agreement are clinically significant, as even at their lowest, a ±0.31 difference will result in vastly different management decisions between different platforms, unless the lesion is obviously very flow limiting in which case a physiological assessment would seldom be necessary. There appears to be proportional bias in the performance of VIRTUheart™ evidenced by greater clustering of values around the mean difference around the clinically important 0.80 threshold. This implies that there is more consistency around this vFFR value. Discordance between platforms was significant ranging from 19.7% to 39.4%. Greater discordance was observed with the use of generic boundary conditions. However these findings need to be interpreted with caution, as there was no comparison with invasive FFR, there was limited operator experience with the CAAS-vFFR and QFR® platforms compared to VIRTUheart™. Furthermore this was only a single-centre, single-observer experience in a limited sample size.

4.13 VIRTU-4 CCS Study Limitations

4.13.1 Design

The VIRTU-4 trial is primarily a hypothetical observational cohort study with prospectively collected data that looked to examine the potential impact vFFR could have on the management of patients with coronary artery disease. The study is not designed nor powered to detect clinically important differences in outcomes. Furthermore the VIRTUheart™ software is not yet MHRA approved for clinical use and so, apart from informing the design of future trials, the findings of the current trial cannot be translated into clinical practice because there have been no actual changes in patients' management plans as a result of vFFR disclosure. Furthermore this trial was conducted without invasive FFR as a reference gold-standard test to validate vFFR in 'real-world' diagnostic coronary angiograms.

4.13.2 Sample size

The main limitation of VIRTU-4 CCS is that it did not recruit the prerequisite number of participants and so its findings may be underpowered. The reasons behind this are multifactorial. First there was significant and prolonged disruption to all non-COVID-19 related clinical research activities in the NHS in the wake of the COVID-19 pandemic. The effect this has had on elective clinical service provision across the NHS has been outlined previously. Second it was assumed that screening around 250 patients would be required to recruited 206 patients. This may hold true for the ACS population however screening data from VIRTU-4 CCS reveals the ratio of screened to recruited patients was more in the order of 2:1. This was primarily due to the finding of unobstructed coronary arteries at angiography, in keeping with findings described in the wider literature [280] and the non-guideline based approach to diagnostic testing observed in this cohort. However the VIRTU-4 CCS trial is a pilot study that will inform the design of future outcome-based randomised control trials comparing angiography-alone versus vFFR in addition to angiography. The initial sample calculation required a sample size of 206 patients to achieve a 95% CI of ±5% to detect a mean change of 20% in management plans of patients undergoing angiography. In the VIRTU-4 CCS trial a 22.3% change in management plans in 112 patients at the DGH level was observed, giving a wider 95% CI of 14.2% to 30.4%. However at the Heart Team level the observed change was smaller (17.9%, 95% CI: 9.78% to 26.0%, p = 0.269) giving rise to a 95% confidence interval that included the cut-off of < 10% management change implying no clinical significance. Perhaps with a greater sample size the proportion of management change at the Heart Team level would have reached significance.

4.13.3 Study Population

The study population in the VIRTU-4 CCS trial was not truly representative of the regional population of South Yorkshire. This trial was conducted across 4 district general hospitals across South Yorkshire that would aim to recruit around 40 patients per year over two years. Over-recruitment from one site

would be avoided if possible. Given there was only one recruiting clinical research fellow for VIRTU-4 CCS and many of the participating sites had angiography lists that coincided on the same two or three days of the week, the research fellow had to carefully plan which lists to attend to maximize recruitment. Factors such as differing case volumes at each site, heterogeneous case mixes (often including ad-hoc pacing and ACS angiography at some sites) and an overall reduced number of patients on any given procedural list (to comply with social distancing rules in recovery areas) had to be considered when selecting a list to recruit from. As a result the trial population was significantly skewed with over recruitment from some sites to in order to recruit the maximum number of patients to the trial. For example in a similar time frame, the research fellow recruited 53 and 10 patients from Doncaster royal infirmary and Rotherham hospital respectively. Therefore the trial population may not reflect the true nature of coronary artery disease in this region as recruitment was unintentionally biased towards the more deprived and ill-health-burdened areas of South Yorkshire. [281] Four patients were screened at Sheffield Teaching Hospital, two of which were suitable for enrollment. This was in effort to boost recruitment during the national lockdown period at the beginning of 2021. This site was initially planned just for VIRTU-4 ACS trial recruitment.

In keeping with invasive FFR trials, the VIRTU-4 trial excluded patients with prior CABG, aorto-ostial and LMS lesions as well as those with severe (>90%) stenoses and severe diffuse coronary artery disease. This is a result the lack of validation data in these disease patterns and their effects on microvascular resistance. This is particularly pertinent for vFFR, which can only make generalised assumptions about microvascular resistance, compared to invasive FFR measurement that intrinsically incorporates these effects. [277]

4.13.4 Protocol

My presence as a senior interventional clinical research fellow during the angiography and vFFR disclosure stages could have been a source of bias at the time of management strategy formulation and confidence level rating,

especially when the treating cardiologists were non-interventionists. Perhaps an automated digital questionnaire with vFFR data only disclosed upon completion of the initial management strategy page, could be remotely passed on to the treating consultant after the case to avoid this type of bias in the future. The VIRTUheart^{TM} software underwent several upgrades to its segmentation tool during the course of recruitment. This could represent a source of inaccuracy in cases that were processed with earlier versions of the segmentation tool. The segmentation step occasionally required parts of the 3D reconstruction to be cut-off. Often a different CFD solver would simulate vFFR for these cases. This could have introduced another layer of variance.

A deviation from the protocol when calculating intra-observer variability was carried out to avoid practice-bias. A random proportion of cases (approximately 20%) were re-processed towards the end of recruitment to mitigate against this. Coronary angiograms along with their corresponding clinical information were displayed to the Heart Team to assess any changes in management plan after vFFR disclosure. Virtual FFRs were calculated beforehand based on the treating district general cardiologists' interpretation of the coronary angiogram. Therefore, there may be some cases and or vessels that were not processed, in which the Heart Team may have thought contained lesions that met the inclusion criteria but would have been otherwise discounted by the treating cardiologist. Similarly there may have been vessels that the Heart Team may have thought too small or lesions less than 30% diameter stenosis to be included in the study. Perhaps 2D-QCA could be used in the future to standardise angiographic inclusion criteria.

4.13.5 Follow-up and Outcomes

The waiting list times for elective PCI has significantly increased as a result of the disruption to clinical service caused by the COVID-19 pandemic with cardiac waiting lists predicted to return to pre-pandemic levels in 2026. [282] Unsurprisingly, all patients referred for PCI that were recruited prior to the national lockdowns, were still awaiting elective PCI at 6 months follow-up. Table 3.9 appears to suggest a trend towards significance with increasingly

more adverse events observed with vFFR < 0.80. However, the VIRTU-4 CCS trial was not designed nor powered to detect these differences in outcomes but may inform the design of prospective randomised trials on this subject. The COVID-19 lockdowns may have also resulted in bias when conducting the follow-up EQ-5D-5L questionnaires. It is well documented that the national lockdowns have led to deterioration in mental health and wellbeing [283], which could have resulted in worsening of EQ-5D-5L scores. Paradoxically the national lockdowns may have improved angina symptoms in some patients through the lack of physical exercise and exertion, which may have led to increases EQ-5D-5L scores apart from the treatment effect of optimised antianginal prescribing and or revascularisation.

4.14 What Does VIRTU-4 CCS Add to the Literature?

The most recent NICE guidance has not recommended the use angiographically-derived FFR in patients with stable angina owing to a lack of evidence regarding its clinical and cost effectiveness. [284] More specifically there is a lack of data on how these technologies could effect decision-making for revascularisation, their ease of use and failure rates in clinical practice. The VIRTU-4 CCS trial indicates that when applied in diagnostic-only catheterisation laboratories, vFFR is likely to lead to an increase in the proportion of patients referred for revascularisation with an associated increase in referrals for invasive FFR measurement. Similarly, in a retrospective study that applied QFR® to patients from the IRIS-FFR registry, [285] QFR® lead to an increased revascularisation rate compared to invasive FFR (42% versus 40%) without any improvement in MACE. [286] However prospective mortality and morbidity data is still lacking for all angiographically-derived FFR platforms.

The signal for an increase in the invasive FFR referral rate from non-interventional centres observed in VIRTU-4 CCS is an important one. The implications of this may translate into overall reduced cost effectiveness and unnecessary exposure of patients to procedural risk as a second invasive angiogram with pressure-wire assessment at an interventional catheterisation

laboratory becomes necessary. This was confirmed to be the least cost effective strategy in a non-interventional setting according to an extensive health economics simulation commissioned by NICE for its recommendations on angiographically-derived FFR. [286] However through the use of a zone of uncertainty for QFR® values between 0.78 and 0.84, Westra et al demonstrated in their retrospective analysis that 64% of invasive FFR measurements could be avoided. [195] This metric could not be calculated for the VIRTU-4 CCS cohort because there was no validation against invasive FFR measurements to derive sensitivity and specificity data.

The VIRTU-4 CCS trial sheds light on the test failure rate of angiographically-derived FFR when prospectively applied to real-world angiograms performed in non-interventional centres. The use of a standardised angiography protocol optimised for the application of vFFR lead to a test failure rate of 12.5%. This was largely comprised of software failures and poor quality imaging prohibiting further processing. This corroborates the findings of prospective QFR® and CAAS diagnostic accuracy studies where a median exclusion rate of 17% of angiograms was observed. [286]

The VIRTU-4 trial is a pilot study that will inform the design of a UK-based randomised control trial to formally investigate the outcome measures, quality of life, clinical and cost effectiveness of vFFR against invasive FFR and alternative diagnostic tests in contemporary NHS practice as recommended by NICE. At present the randomised clinical non-inferiority trial FAVOR III, is in the process of recruiting 2000 patients across Europe and Japan to investigate whether a QFR®-based diagnostic strategy will result in non-inferior 12-month clinical outcomes compared with the standard pressure-wire assessment of patients with stable angina. [287]

4.15 Future Research

Future work will likely involve comparative head-to-head analyses of the diagnostic performance of VIRTUheart™, QFR® and CAAS-vFFR platforms against invasively measured FFR. Angiographically-derived FFR can also be

applied retrospectively to landmark revascularisation clinical trials that lacked coronary physiology, to examine if the recommendations would have been affected through the use of physiology-guided revascularisation. At an institutional level, future work will involve refinement of microvascular resistance characterisation through machine learning as well as working on algorithms to improve segmentation and CFD simulations to better simulate the complex flow patterns arising at bifurcations, vessel tapering and excessive tortuosity.

At its essence, FFR is a surrogate for coronary flow reserve reduction. The advent of CFD simulation in the coronary circulation along with integration of routine acquired pressure-wire data from interventional catherterisation laboratories can be use to predict absolute coronary flow and microvascular resistance. [267] This may help to discriminate between epicardial disease and microvascular dysfunction without the need for additional catheters, wires or infusions. Validation and refinement of this technology is likely to prove invaluable for the future assessment of the increasingly recognised INOCA patient. These patients are a heterogeneous group with elevated baseline risk that often incur similar costs to patients with obstructive coronary disease through recurrent hospitalisations and repeated investigations. [288]

4.16 Final Conclusions

The addition of virtual fractional flow reserve to a standard coronary angiogram provides a robust an ‘all-in-one’ anatomical and physiological assessment of coronary artery disease. The lack of requirement for a pressure wire makes this technology feasible in the purely diagnostic cardiac catheterisation laboratory, providing the benefits of physiological guidance to a far greater number of patients with coronary artery disease than at present receive it. vFFR could help guide decisions about revascularisation, streamline management, be a useful gatekeeper to the interventional laboratory and triage patients and lesions for direct, invasive measurements of FFR and similar indices. The present study demonstrates a 22.3% hypothetical change in management plans with the use of vFFR in a district general hospital setting. However vFFR is highly dependent on optimal

coronary angiography and its performance has yet to be determined by non-expert users. Finally data pertaining to outcomes, cost-effectiveness and its non-inferiority compared to existing alternative functional tests are still lacking and represent the subject of future research.

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Chapter 6: Appendices

6.1 Appendix A

VIRTU-4 Chronic Coronary Syndrome Trial Standard Operating Procedure

Inclusion Criteria:

- Age > 18
- Suspected or known coronary artery disease
- Epicardial stenosis ≥ 30% in any vessel ≥ 2.25mm

Exclusion Criteria:

- No consent (including non-English speaking)
- Creatinine > 180mmol/L
- Severe comorbidities
- Severe valvular heart disease
- Acute coronary syndrome
- Patient anatomy unsuitable for revascularisation
- Prior CABG
- Chronic Total Occlusion (CTO) as the only lesion
- Severe diffuse disease
- Left main and ostial disease
- Normal coronary angiogram

Threshold for Ischaemia: vFFR ≤ 0.80

1. Eligible patients identified and supplied with patient information sheet.
2. Consent patients for study participation prior to angiogram.
3. Brief cath lab team on angiography protocol for VIRTU-4.
4. Consultant performs coronary angiogram and records treatment plan.
5. Coronary angiogram and ECG data anonymised and loaded into the VIRTUheart™ workflow on study laptop in the cath lab as DICOM files.
6. Virtual FFR calculated and disclosed to consultant cardiologist after treatment plan recorded.
7. Any hypothetical change to management plan that would have occurred after disclosure of vFFR is recorded.
8. Patient demographics, clinical data and processing difficulties recorded
9. Record patient participation in VIRTU-4 in patient medical notes.
10. Angiograms re-processed offline centrally and second set of vFFRs calculated and used in subsequent Heart Team MDTs in a similar fashion to steps 4 to 7.
11. All anonymised data uploaded to central ARQ database.
12. 6-month follow-up conducted via telephone interview and remote interrogation of medical records.

Angiography Protocol for the VIRTU-4 CCS Trial

The following outlines general measures to ensure the VIRTUheart™ Software can be successfully applied to coronary angiograms.

The key objective is to the capture the lesion in the artery of interest in two orthogonal views at least 30° apart with no or minimal overlapping vessels without panning over 4 cardiac cycles.

This can be achieved through the following general measures:

1. Centre the image before acquiring
2. No magnification (+1 mag if small patient)
3. No panning
4. Increase dose if obese patient
5. Good catheter engagement
6. Decent contrast injection
7. Acquisition over at least 4 cardiac cycles

Suggested RCA views:

1. LAO cranial
2. AP cranial
3. RAO cranial

Suggested LCA views:

1. AP caudal
2. RAO caudal
3. RAO cranial
4. AP cranial
5. LAO cranial
6. LAO caudal - super spider. As much caudal as possible.

The University Of Sheffield.

VIRTUheart™

Patient information sheet

How will virtual (computed) fractional flow reserve (vFFR) impact the management of coronary artery disease? (VIRTU-4)

Principal Investigator: Professor Julian Gunn, Consultant Cardiologist
Northern General Hospital, Sheffield and the University of Sheffield

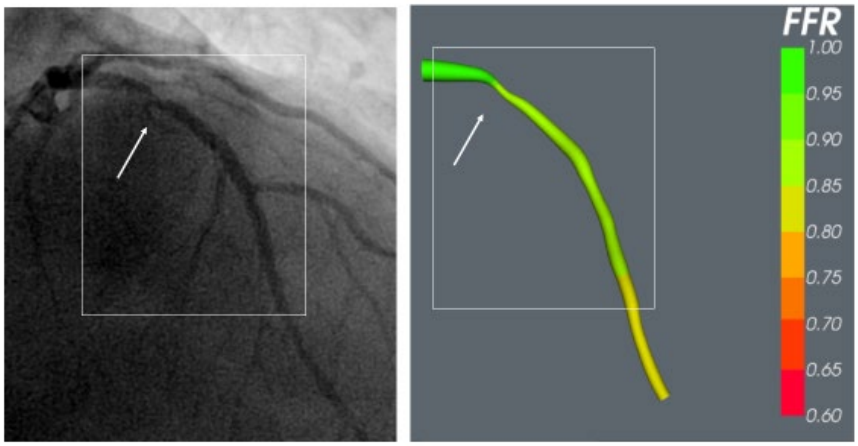
An invitation to take part in medical research

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it will involve. This information sheet will help you in making the decision. Please take your time to read the following information and, if you wish, discuss it with friends, relatives or your doctor. If anything is not clear, or if you would like more information, please contact Professor Julian Gunn on 07778 652500 or ask the Research Doctor who gave it to you.

What is the purpose of the study?

You are about to have a coronary angiogram (Xray pictures of the arteries in your heart). This will reveal if there are any narrowings or blockages in the arteries in your heart. The pictures look something like the one on the left below. The arrow is pointing at a narrowing in one of the coronary arteries. As you can imagine, this can restrict blood flow to the artery downstream and this can cause chest pain or breathlessness. But how badly is the blood flow reduced? It's hard for the doctor to tell.

Coronary angiogram | Our model of the artery



So we have developed a software system (computer model, shown on the right) that uses the images, makes some calculations, and tell us how restricted the blood flow is. It displays the blood flow in colour, as in the example on the right. If treatment is needed, the artery is shown in orange or red. This makes it easier to make the right recommendation, which might be a stent, for instance. This one is green. No stent is required!

Why have I been selected?
It is time to see if this software might be useful for patients. If you agree to take part, we will try out the software and ***see if it might help***. When your angiogram is completed, and the consultant has made plans for your treatment, we will create the model for your artery, like the one above. We will then show the pictures to your doctor and ***ask if that <u>might</u> change his or her recommendations for your treatment***. He or she will not be allowed to change your treatment because the model is not yet approved for use in the NHS. (We will need to do more research before we know whether it would be safe and effective). In 6 months' time, we will contact you to see how you are and what treatment you have had since the angiogram.

What do I have to do?
Nothing. We simply request permission to ***use your angiogram images and some information about your health*** for this research, and to contact you in 6 months' time to see how you are getting on.

Do I have to take part?
No. Taking part is entirely voluntary. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. If you prefer not to take part, you do not have to give a reason and this will not affect the standard of care you receive.

What will happen to me if I take part?
This study won't affect you at all. Your care will continue in the usual way, unaffected by this new technology. This is because this study is designed to ask a 'what if' question: ***if*** the doctors were to use this new software, and not just their normal methods of assessment, how much ***would*** your treatment be changed? It's a hypothetical question. We won't actually change your treatment. If it turns out at the end of this study that a lot of patients would have their treatment changed, our next study will be to actually use it to make those real decisions. But for the time being, nothing will change.

Can I withdraw?
Yes, at any time, and you don't have to explain why. Withdrawal will not affect your care in any way. Any identifiable information you have given will be destroyed, but we may use non-identifiable data collected up to the time of your withdrawal.

What will happen to my clinical information?
Your data will be held securely on a computer kept at the University of Sheffield. No-one other than the study team will have access to it. It will be anonymised, identified only by a number known to the team.

The University of Sheffield, with whom this hospital works, is the 'sponsor' for this study. This means that the Hospital will hold all your clinical information, and the University will act as the controller of your anonymised study data. They will keep the anonymised information about you safe and secure for 15 years after the study has finished. Your rights to access, change or move this information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we already obtained; but this should not affect you because your identity will have been removed from the data. To safeguard your rights, we will not use personally-identifiable information for the study. You can find out more about how we use your information at https://www.sheffield.ac.uk/govern/data-protection/privacy/general

The hospital will keep your name, NHS number and contact details confidential and will not pass this information to the University. You can find out more about how the hospital uses your information at https://www.sheffieldclinicalresearch.org/for-patients-public/how-is-your-information-handled-in-research/. We will only use this information as needed, to contact you about the research study via the hospital, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from the University of Sheffield and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The University of Sheffield will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

How will this study benefit patients?
If the results of this study are promising, our next study will test whether the software against the traditional methods to see how patient care ***actually*** changes. This sort of research has the potential to help doctors improve their decision making for patients like you in the future. This could make treatments safer, less invasive, and cheaper.

Who has reviewed this study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by scientists and doctors appointed by the British Heart Foundation when they awarded us the research grant. It has also been approved by a panel of ex-patients at Sheffield, who have read the protocol, and this information sheet.

Expenses and payments
There are no extra expenses for you, and you won't have to do anything special for the study, or attend any other appointments. So there is no payment I am afraid!

What are the alternatives for diagnosis or treatment?

Your diagnosis and treatment will not be affected by this study. Participation in this study will not alter how you are assessed or treated.

What are the possible disadvantages and risks of taking part?

There will be no new drugs or techniques used as part of this study. All the experimentation is being done afterwards on a computer and will not affect you or expose you to risk.

Ionising radiation (X rays)

You will not receive any more X rays than anyone else having an angiogram.

What are the side effects of any treatment received when taking part?

There are no new drugs or treatments involved in this study, so you won't have any unusual side effects.

What happens when the research study stops?

Your treatment and follow-up will continue as before. We will hope to publish the results in a scientific journal which will allow specialists all over the world to understand how to treat their patients more effectively. The data that is obtained as part of this study may be used in future projects to assist with the further development in this area.

What will happen to the results of the research study?

The results will be published in a scientific journal. It will not be possible to identify you in any such publication or report arising from this study. If you would like a copy of the research report, we can send this to you (please feel free to contact Professor Gunn in due course on J.Gunn@Sheffield.ac.uk). We will use the information gained in this study to help design a big trial of the technology with more patients. If that is positive, then we will roll out the technology throughout the NHS to help benefit patients like you.

What if I wish to complain about the way in which this study has been conducted?

If you have a concern about any aspect of the study, please contact the Chief Investigator, Professor Gunn on 0114 2714953 or the email above. If you remain unhappy and wish to make a formal complaint about any aspect of the study, or how you have been treated during the study, you can do this by contacting Professor Chris Newman, Dean of the Medical School, University of Sheffield, Beech Hill Road Sheffield S10 2RX (C.Newman@sheffield.ac.uk; 0114 271 3194).

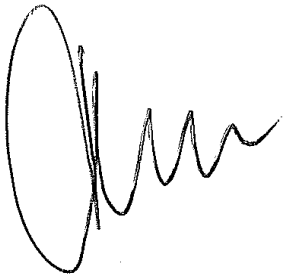
If I have any later questions, whom do I contact?

Please contact the Research Doctor whom you net today, or Professor Gunn. He is based at the University of Sheffield and also at the Northern General Hospital, Sheffield. His email is above, and his secretary is on 0114 271 4953.

What do I do now?

Ask any questions that occur to you. Our Research Fellow will be able to help. If you are happy, we will then ask you to sign the consent form for the study.

Thank you.



Professor Julian Gunn
Professor of Interventional Cardiology, University of Sheffield
Hon. Consultant Cardiologist, Sheffield Teaching Hospitals NHS Foundation Trust

Study Number: STH 20595 IRAS Number: 270127

Patient Identification Number for this trial: ☐

CONSENT FORM
How will virtual (computed) fractional flow reserve (vFFR) impact the management of coronary artery disease? (VIRTU-4)
Professor Julian Gunn

		Please initial box
1.	I confirm that I have read and understand the information sheet dated 14.08.19 (V4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust or University where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4.	I agree to take part in this study	☐

Name of Patient	Date	Signature

Name & Job Title of Person Taking Consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) for medical notes

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

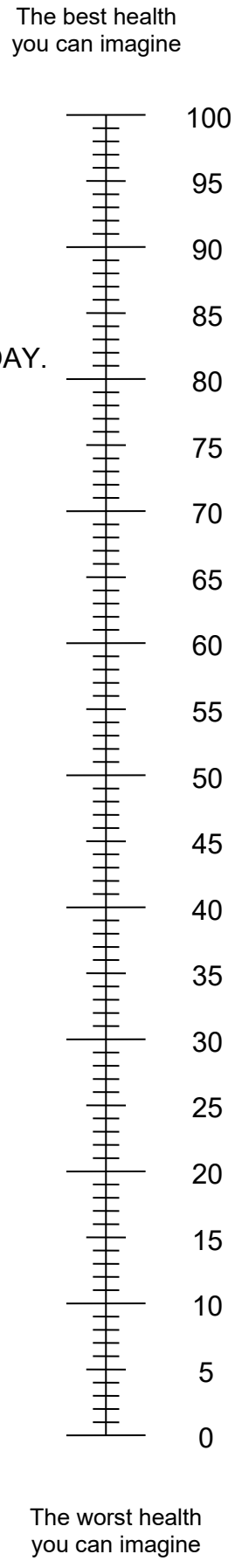
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



1. **Very fit** – Robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age.

2. **Well** – Without active disease, but less fit than people in category 1.

3. **Well with treated comorbid disease** – Disease symptoms are well controlled compared to those in category 4.

4. **Apparently vulnerable** – Although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms.

5. **Mildly frail** - With limited dependence on others for instrumental activities of daily living.

6. **Moderately frail** – Help is need with both instrumental and non-instrumental activities of daily living.

7. **Severely frail** – Completely dependent on others for activities of daily living or terminally ill.

Clinical Frailty Scale adapted from Rockwood et al.

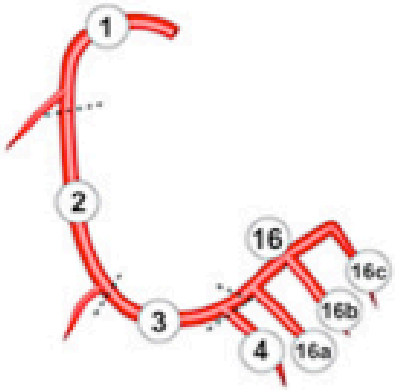
Class I	No limitations to ordinary physical activity
Class II	Slight limitation to ordinary physical activity. Ordinary activity results in breathlessness, palpitations or fatigue.
Class III	Marked limitation to ordinary physical activity. Less than ordinary activity results in breathlessness, palpitations or fatigue.
Class IV	Symptoms at rest or on minimal exertion.

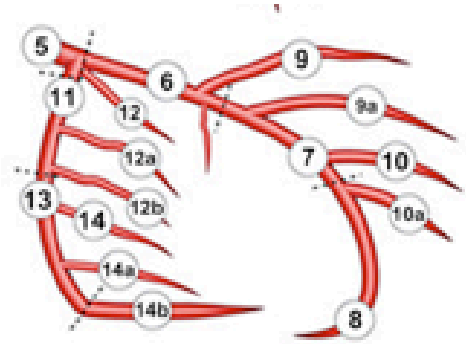
New York Heart Association Classification

VIRTU-4 Chronic Coronary Syndrome Heart Team Proforma

Patient ID: **Date:**

What is the diameter stenosis of each vessel?





Overall Quality of Angiogram: **Poor** ☐ **Adequate** ☐ **Good** ☐

What is the initial management plan?

1. **Optimal medical management** ☐
2. **PCI**
   - LAD (D1) ☐
   - LCx (OM/Ramus) ☐
   - RCA (PLVB) ☐
   - ± FFR ☐
3. **CABG** ☐
   - How many grafts? .....
4. **More information** ☐
   - Please specify below:

.....

.....

Confidence level:

1 2 3 4 5 6 7 8 9 10

What is the management plan with vFFR data?

1. **Optimal medical management** ☐
2. **PCI**
   - LAD (D1) ☐
   - LCx (OM/Ramus) ☐
   - RCA (PLVB) ☐
   - ± FFR ☐
3. **CABG** ☐
   - How many grafts? .....
4. **More information** ☐
   - Please specify below:

.....

.....

Confidence level:

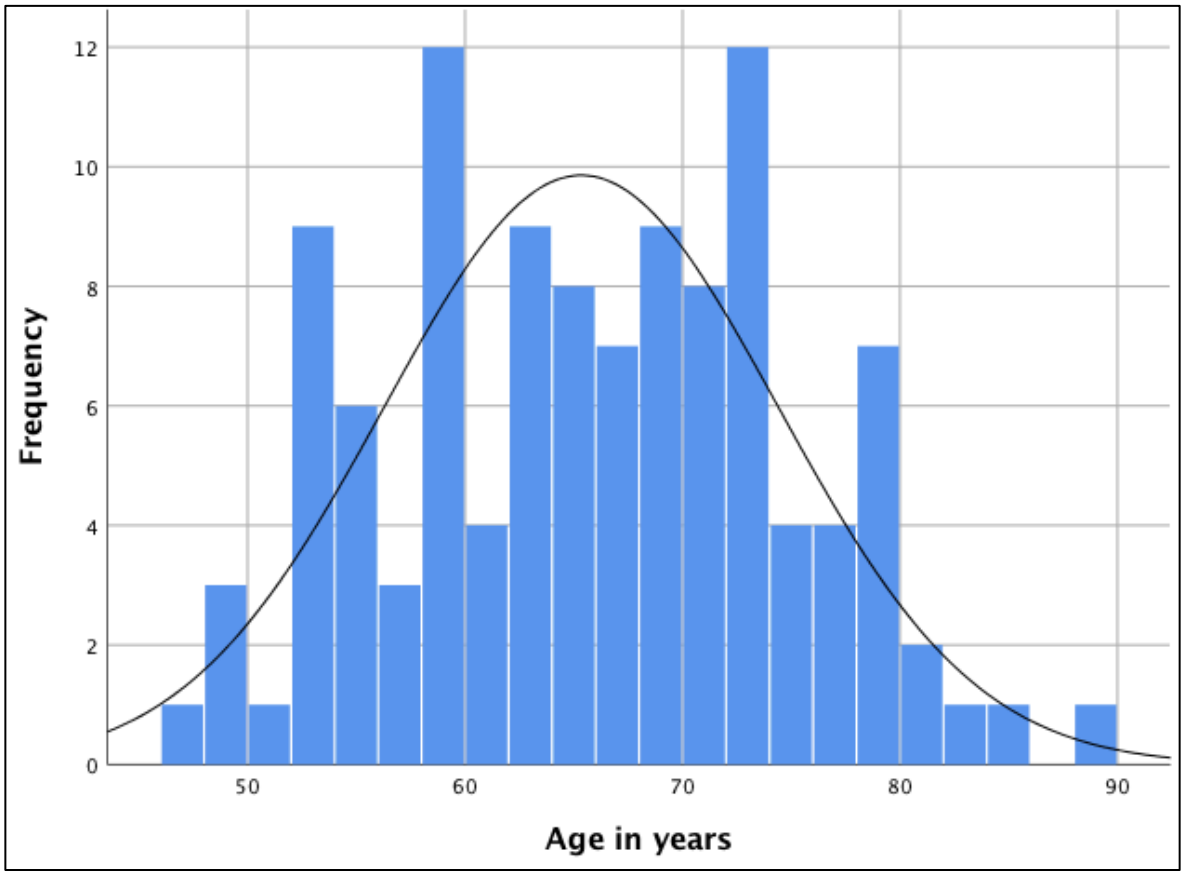
1 2 3 4 5 6 7 8 9 10

6.2 Appendix B

Variable: Age in years

Shapiro-Wilk test: p = 0.168

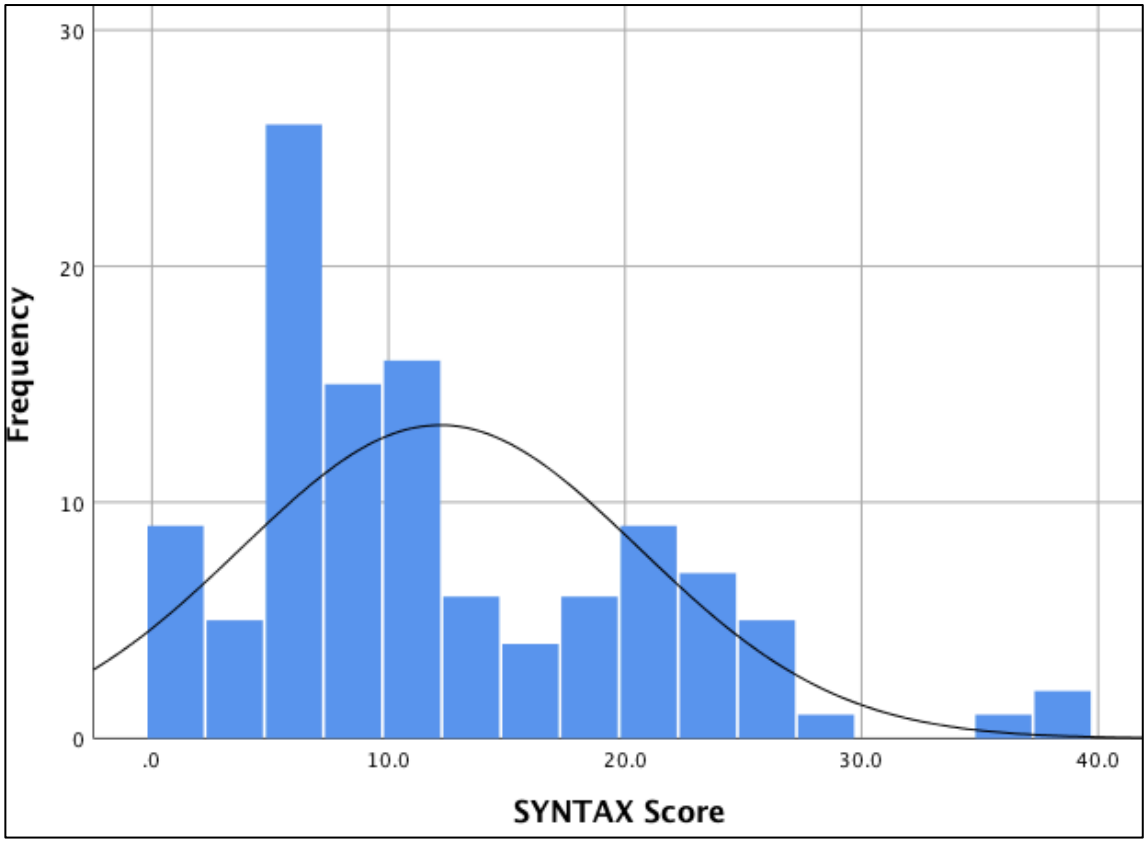
Mean 65.3 (SD 9.1)

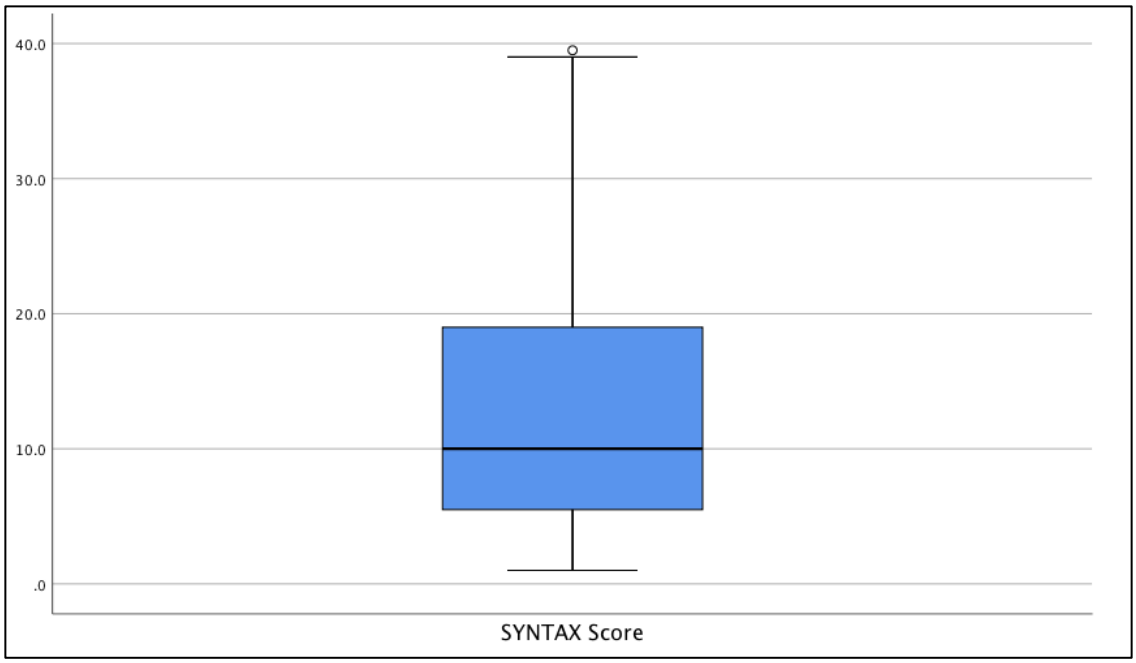


Variable: SYNTAX Score

Shapiro-Wilk test: $p < 0.001$

Median 10 (IQR 13.8)

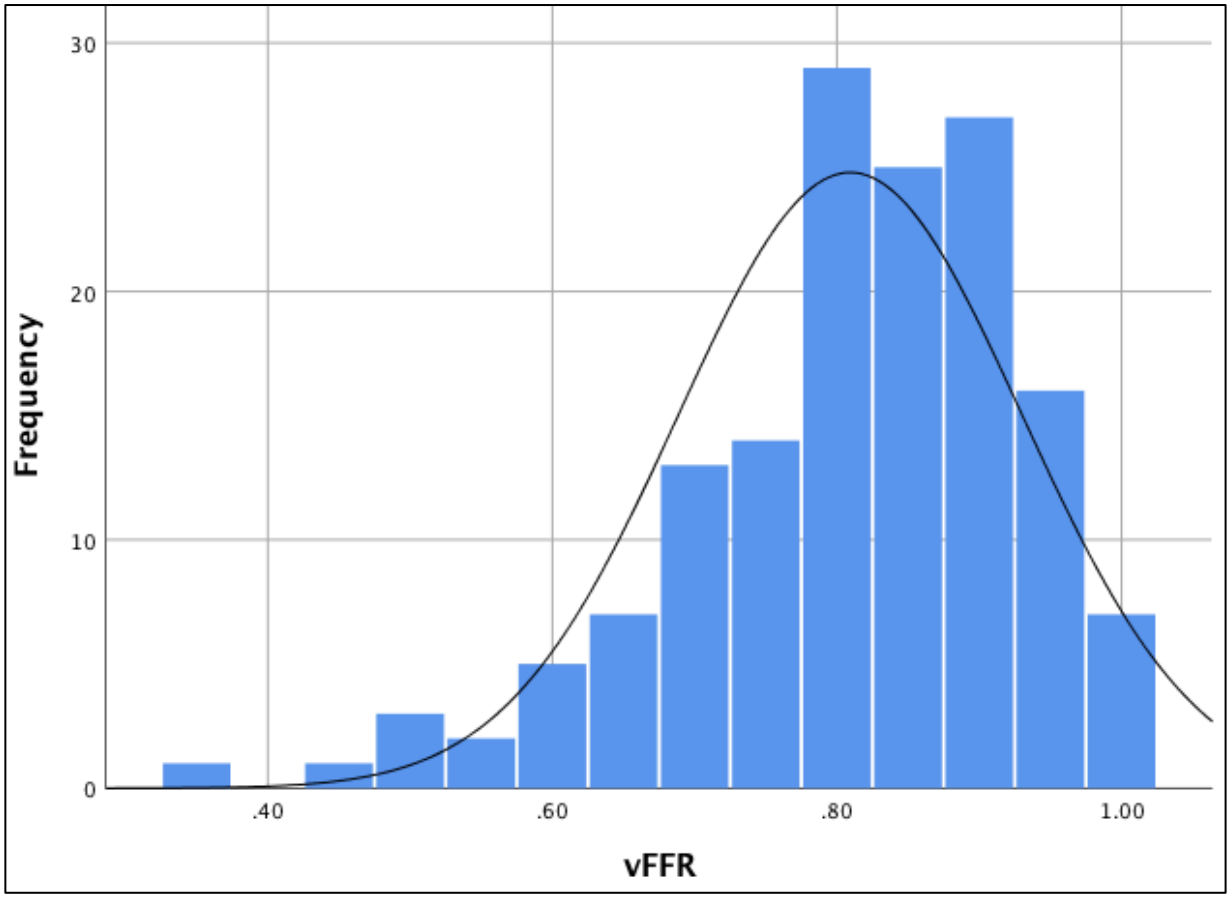


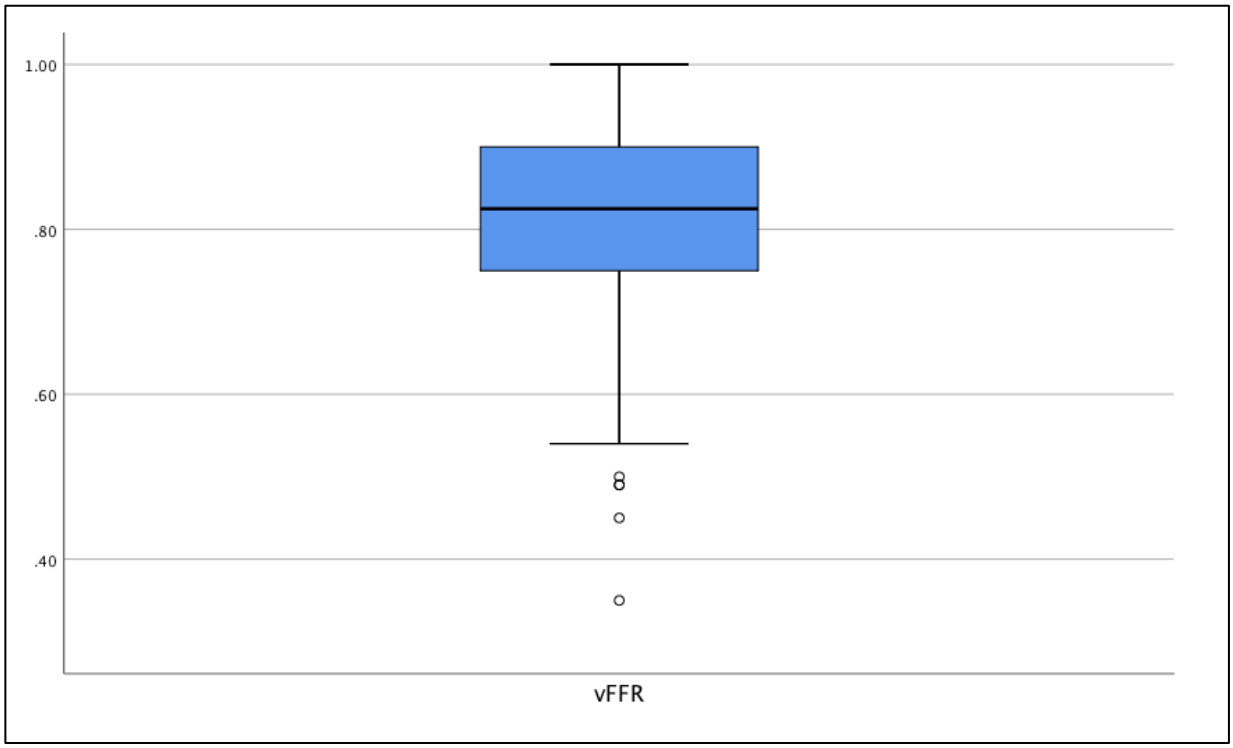


Variable: vFFR

Shapiro-Wilk test: $p < 0.001$

Median 0.83 (IQR 0.15)

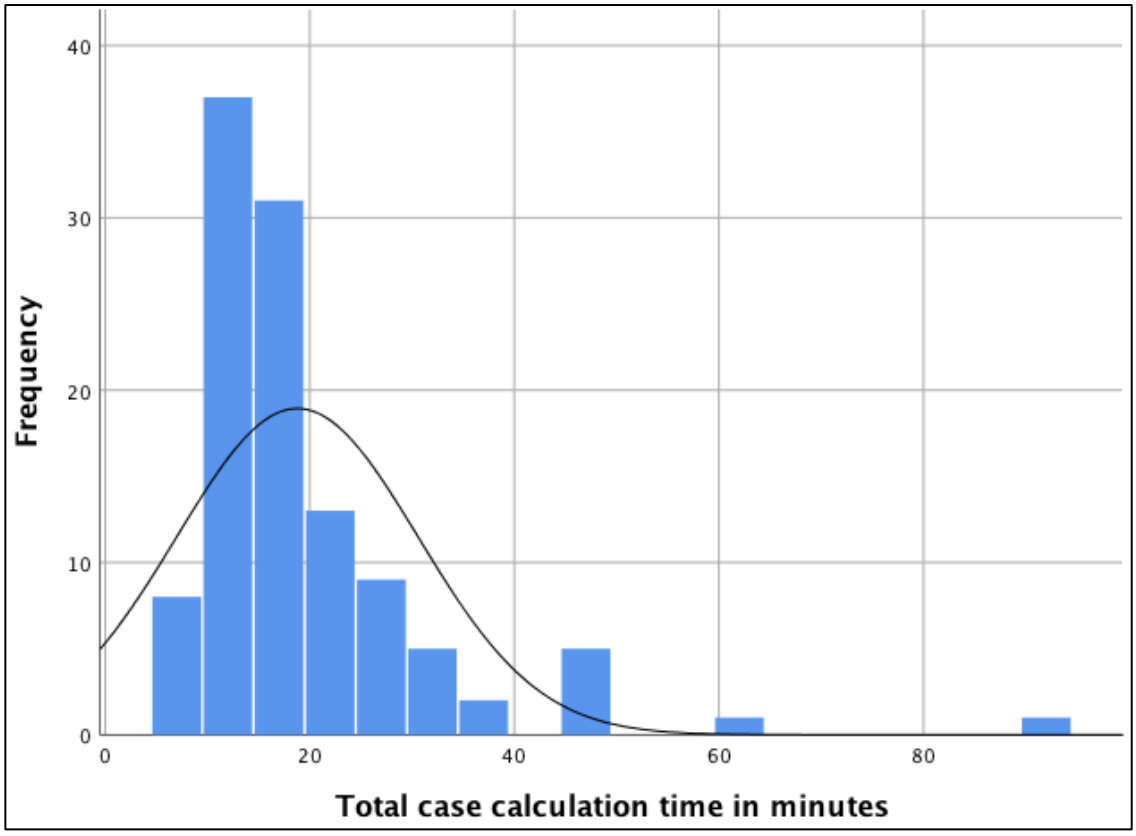


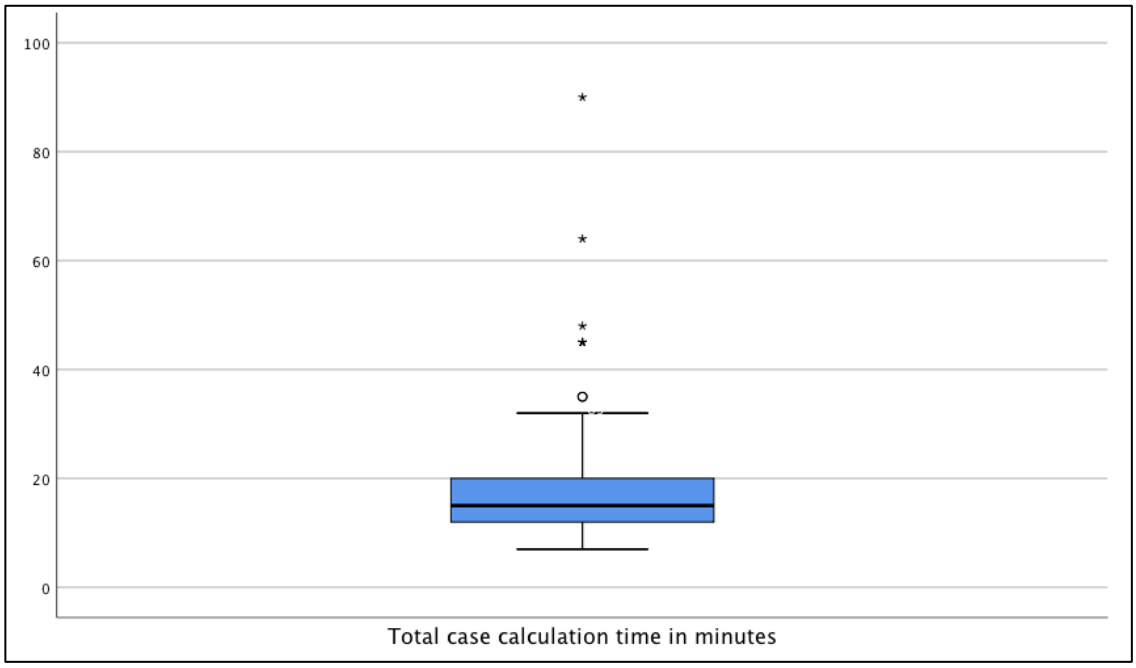


Variable: vFFR calculation time (minutes)

Shapiro-Wilk test: $p < 0.001$

Median 15 (IQR 8)

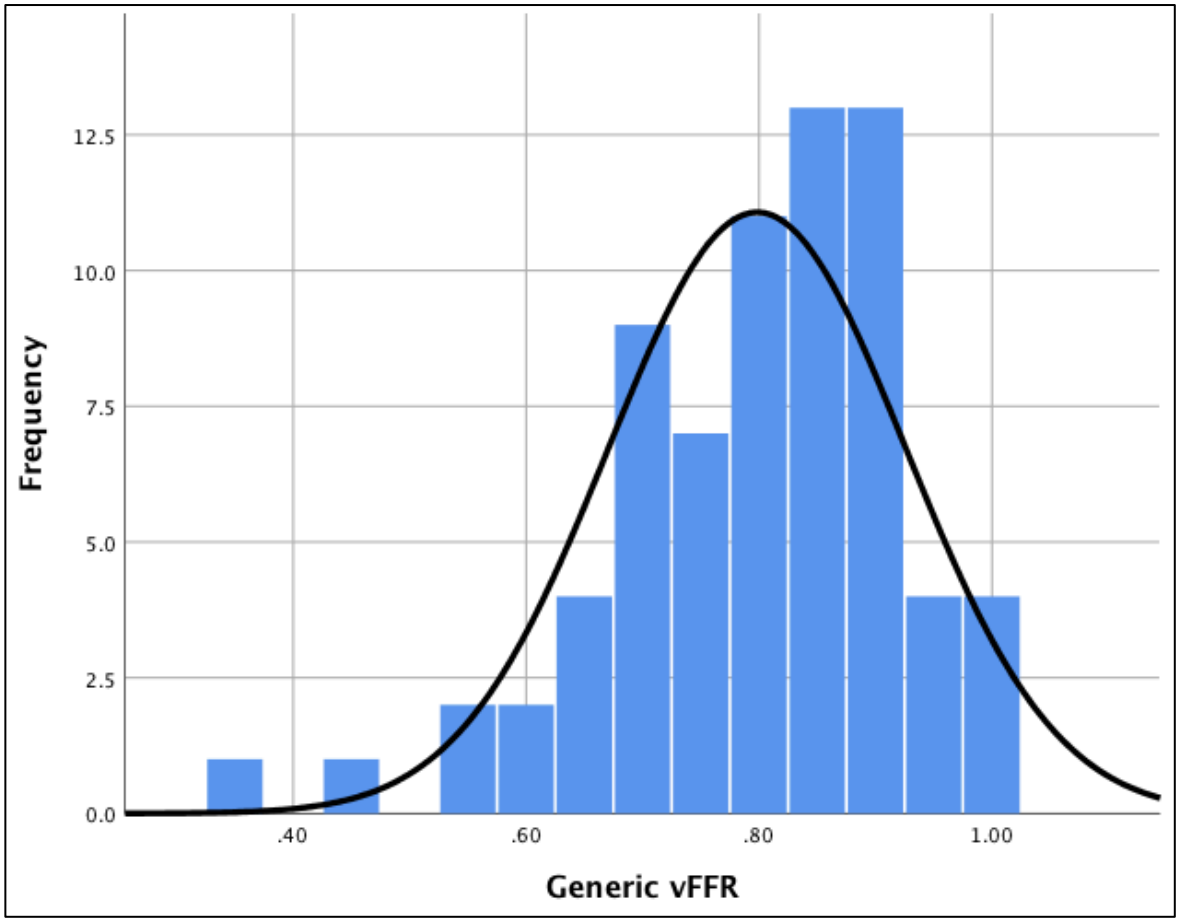


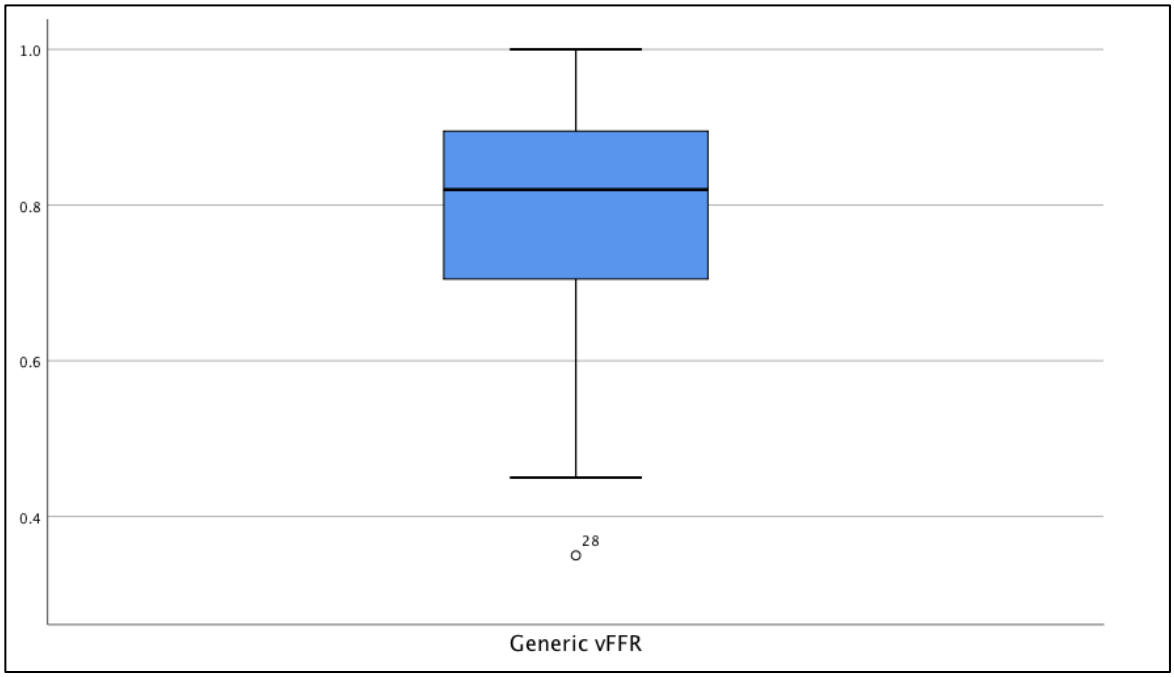


Variable: VIRTUheart™ (Generic)

Shapiro-Wilk test: p = 0.02

Median 0.82 (IQR 0.20)

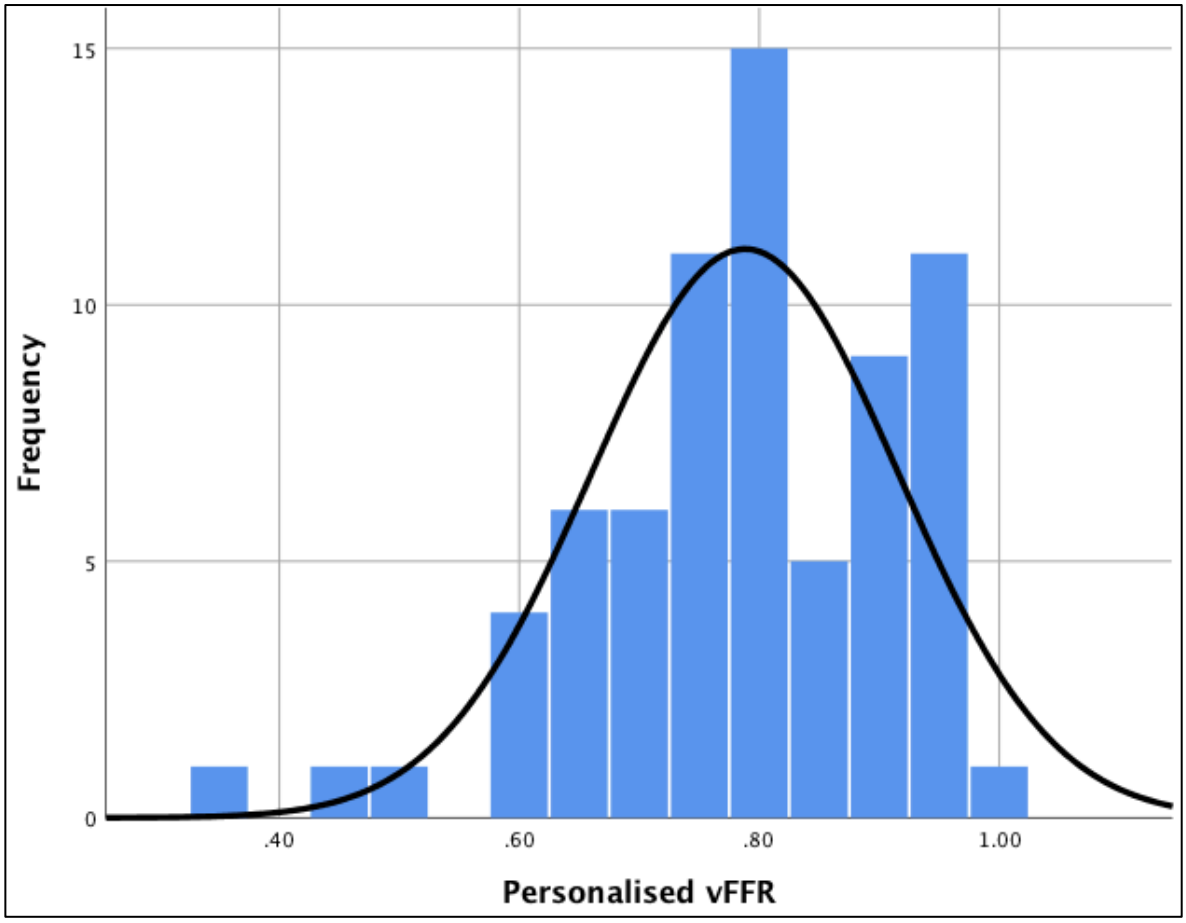


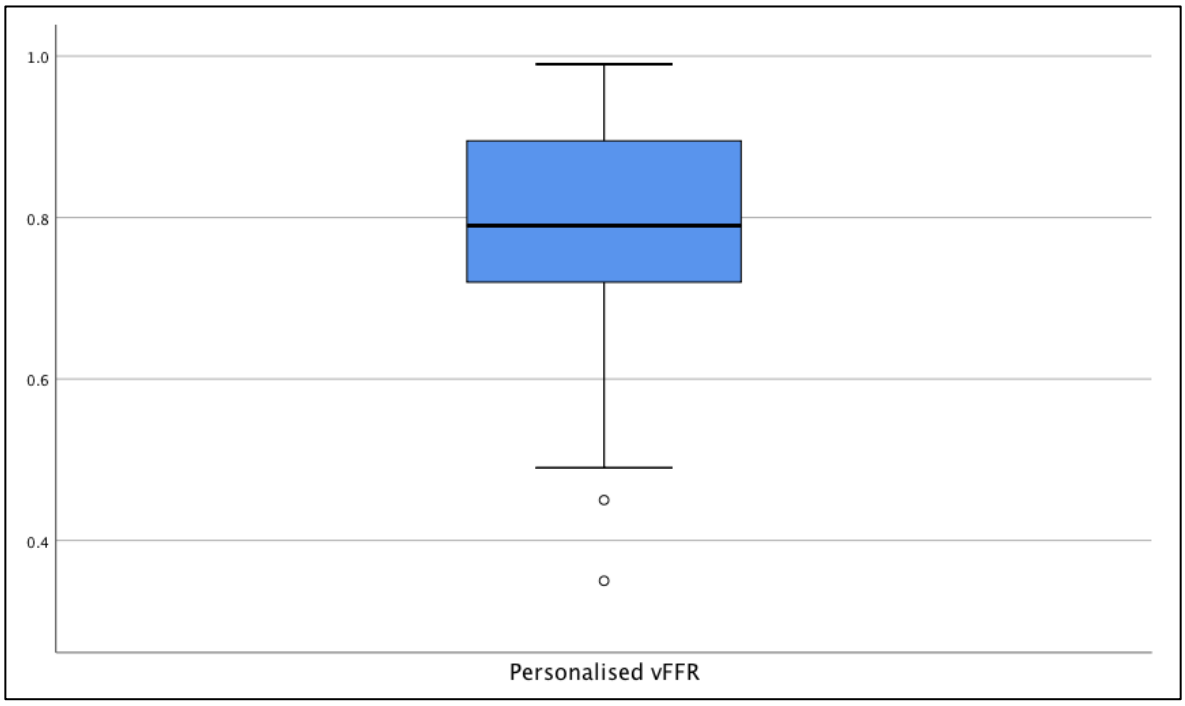


Variable: VIRTUheart™ (Personalised)

Shapiro-Wilk test: p = 0.04

Median 0.79 (IQR 0.18)

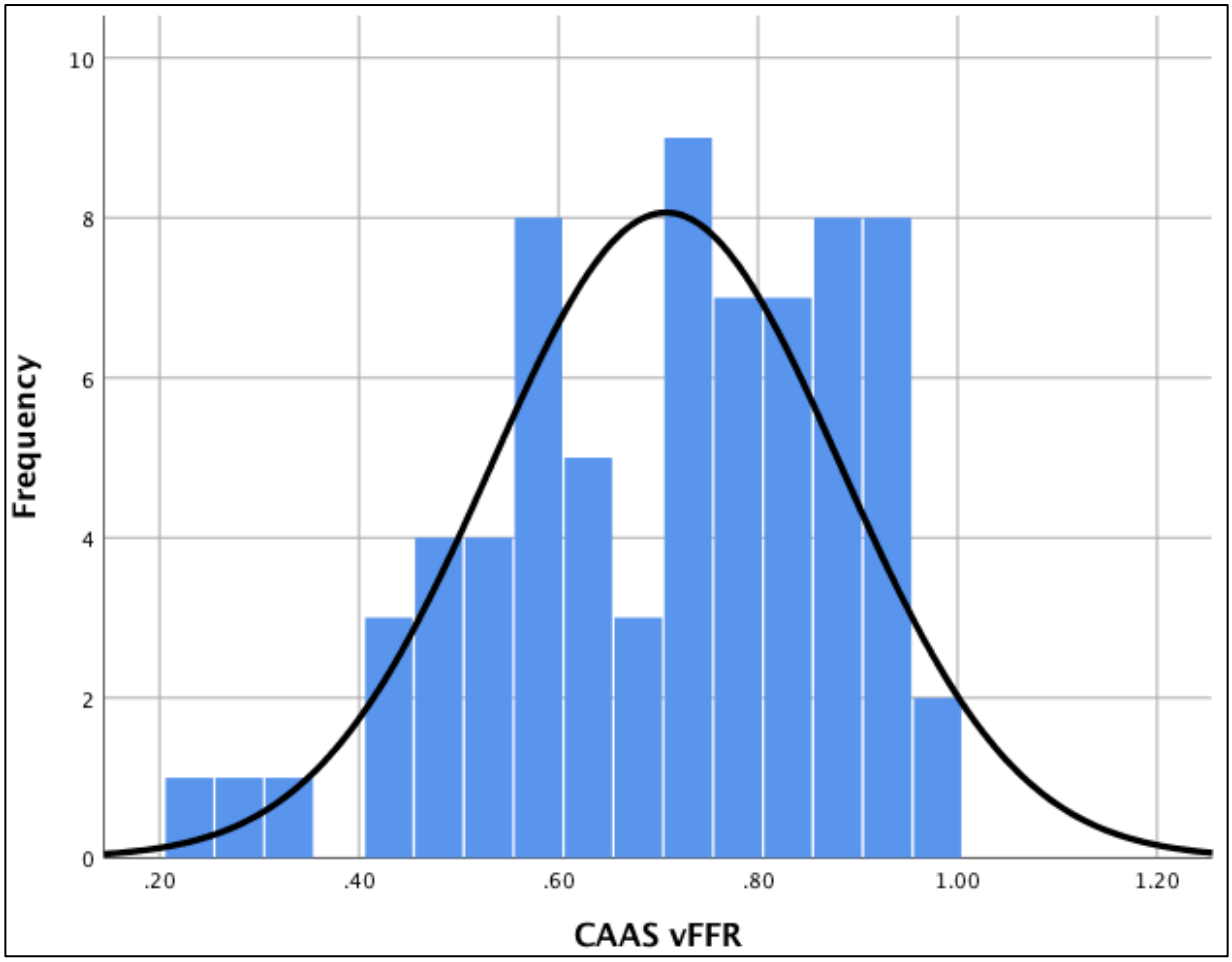


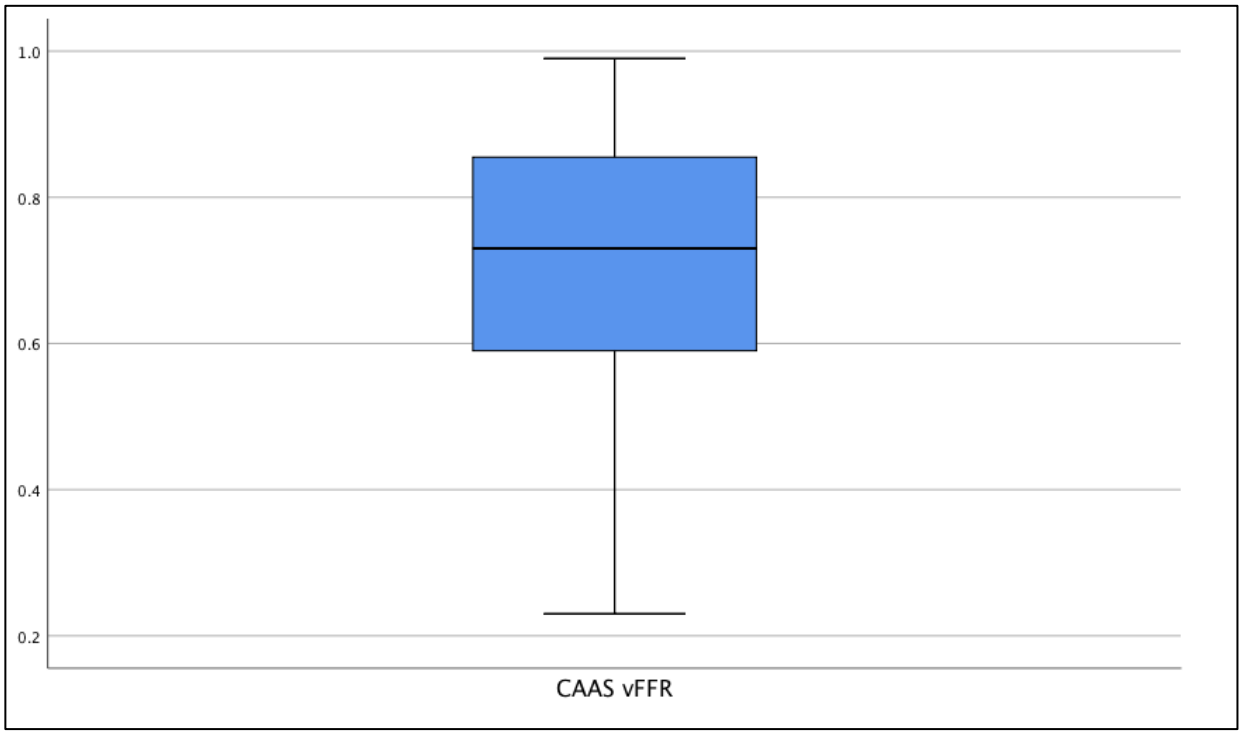


Variable: CAAS-vFFR

Shapiro-Wilk test: p = 0.02

Median 0.73 (IQR 0.27)

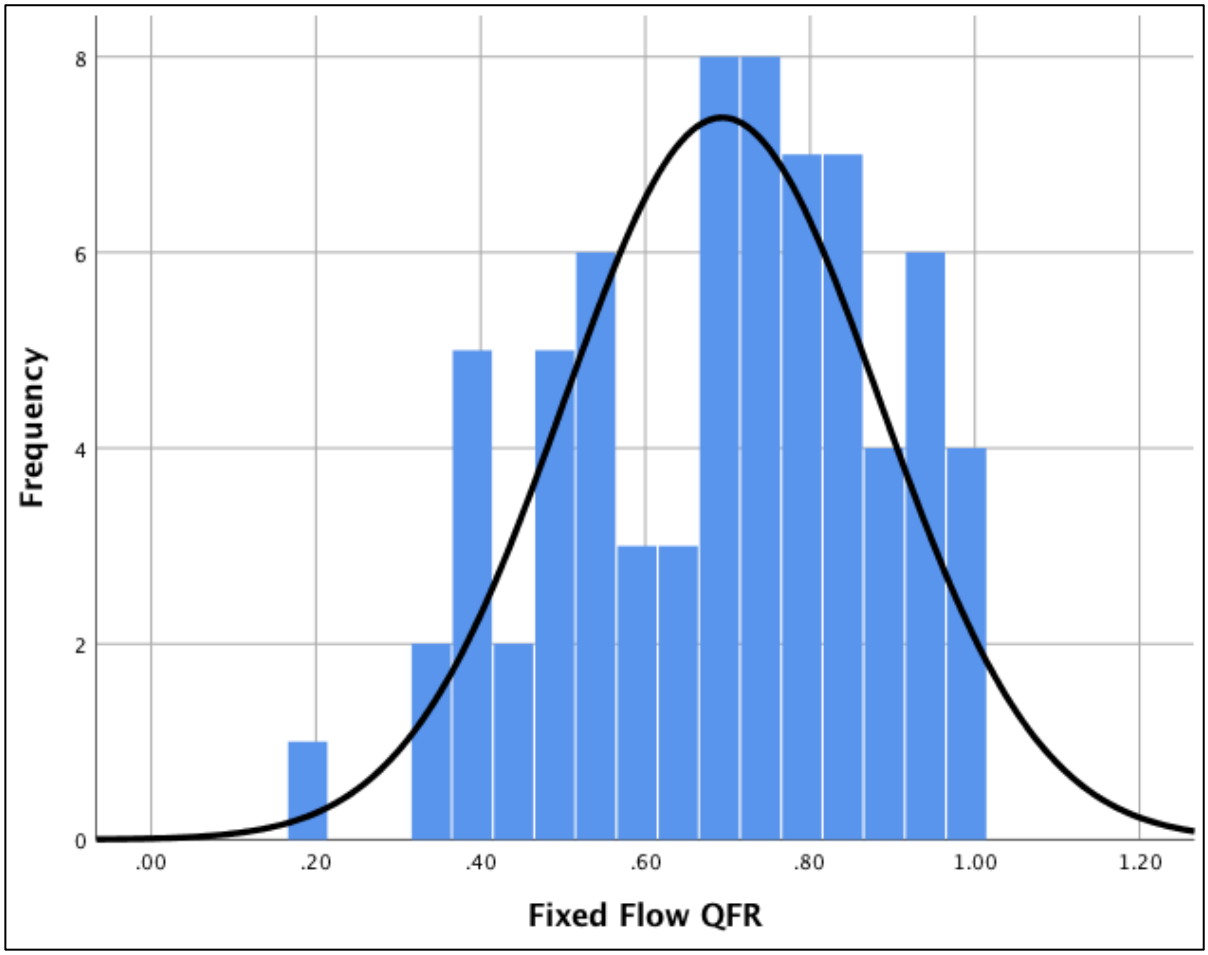


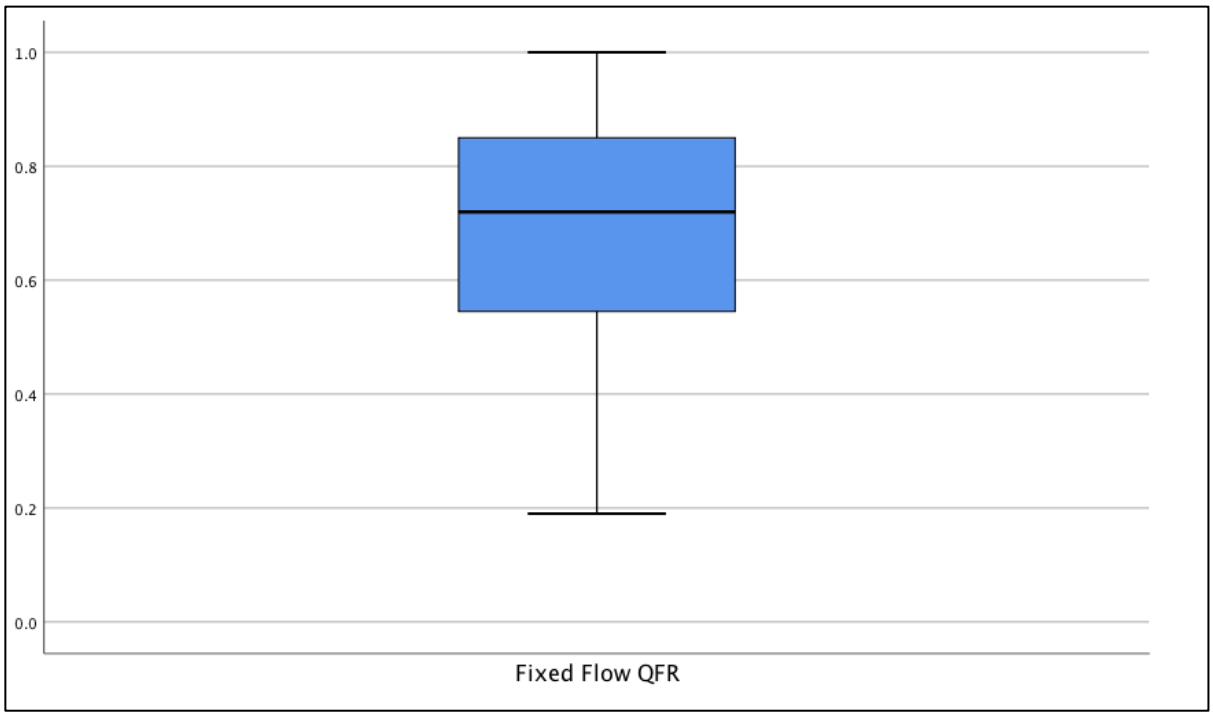


Variable: QFR® (Fixed Flow)

Shapiro-Wilk test: p = 0.07

Mean 0.69 (SD 0.19)





Variable: QFR® (Contrast Vessel)

Shapiro-Wilk test: p = 0.06

Mean 0.74 (SD 0.17)