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The potential role of computed blood flow in the management of patients with acute coronary syndrome (ACS)

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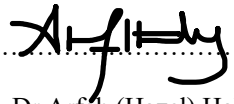
Signature:  Date: 26th February 2022

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ABSTRACT

Background

Acute coronary syndromes (ACS) are one of the leading causes of hospitalization and death. Patients with non-ST elevation ACS (NSTE-ACS) undergo coronary angiography (CAG). However, identifying the lesions which are physiologically significant is difficult based upon CAG alone. Fractional flow reserve (FFR) measured with a pressure wire is used in a few and produces a 25% change in management compared with visual assessment. Virtual (computed) FFR (vFFR), which uses a 3D model of the coronary arteries constructed from the invasive angiogram, and application of the physical laws of fluid flow, has the potential to be used more widely. Its practicability and impact in the acute setting need to be tested.

Hypothesis

vFFR leads to a change in planned treatment in >10% cases compared with angiographic assessment.

Methods

This was a prospective, observational study of patients with NSTE-ACS undergoing coronary angiography. Clinical data, demographics, CAG result and the initial management (medical therapy, PCI, coronary artery bypass grafting (CABG) or multidisciplinary team (MDT)) were recorded. The vFFRs were calculated and the cardiologist was asked for any change in decision. Study meetings were also convened, and their decisions recorded. The primary endpoint was the number of patients in whom management changes.

Results

Two hundred and ninety-four patients were screened, 208 were recruited and 335 vessels were processed. vFFR resulted in an hypothetical change of management in 22% [95% CI: 15% to 25%, $p < 0.001$] and increased the confidence level of the decisions in 126/208 (61%) cases and reduced it in 12/208 (6%). At six months, 6/208 (3%) of patients experienced a MACE; one death, two MIs, two unplanned revascularisations and one bleed.

Conclusion

vFFR is feasible and leads to an hypothetical change in management in 22% of cases. It may have the potential impact to augment simple, angiography-based decision making in ACS.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisors Prof Gunn and Dr Morris for the opportunity to undertake this research project under their supervision. I have thoroughly enjoyed it and have learned a lot in the process. I am most grateful for their endless support and guidance throughout this stage of my postgraduate career and writing this thesis. I have also been privileged to have been able to continue to work alongside Prof Gunn in the cardiac catheter laboratory to maintain my PCI skill from time to time.

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This study would not have been possible without the kind sponsorship from the British Heart Foundation. I thank you once again.

Lastly, thank you to my family and dearest husband, Jack, who have always believed in me, and been there for me in every way. My love and credit also go to my feline and canine companions, Tom, Snow, Max and Leo, who never ceased to cheer me up with their unconditional affections and cuddles.

PUBLICATIONS

1. Virtual (computed) fractional flow reserve (vFFR): future role in acute coronary syndromes. Haley HA, Ghobrial MSA, Morris PD, Gosling B, Williams G, Albaraikan A, Rammohan V, Pederzani G, Lawford PV, Hose DR and Gunn JP. *Front Cardiovasc Med 2021 Oct 22;8:735008.*

2. The new role of diagnostic angiography in coronary physiological assessment. Ghobrial MSA, Haley HA, Gosling B, Lawford PV, Hose DR, Morris PD, Gunn JP. *Heart* 2021;107(10):783-789.

3. Potential role of coronary physiology in treating 'bystander' disease in patients with ST-elevation myocardial infarction. Knight M, Rammohan V, Preston A, Williams G, Ghobrial M, Al Baraikan A, Gosling R, Morris P, Lawford P, Hose R, Storey R, Gunn J. *Heart* 2020;106:A93-A94.

4. Feasibility of coronary angiogram-based computational modelling of fractional flow reserve in everyday [practice. Preston H, Stroud S, Lai K, Gosling R, Morris P, Hose R, Lawford P, Gunn J. *Circulation* 2019;140:A9797.

5. The impact of virtual (computed) fractional flow reserve in the 'real world' management of patients undergoing coronary angiography. The VIRTU-4 study. Ghobrial M, Haley H, Gosling R, Rammohan V, Richardson J, Morgan K, Barmby D, Iqbal J, Krishnamurthy A, Singh R, Conway D, Hall I, Adam Z, Wheeldon N, Grech E, Storey R, Rothman A, Payne G, Tahir N, Smith S, Cooke J, Hunter S, Cartwright N, Siddique S, Briffa N, Al-Mohammad A, O'Toole L, Rogers D, Lawford P, Hose D, Morris P, Gunn J (in submission).

STATEMENT OF CONTRIBUTION

For this study, I contributed towards the ethics application by helping with the writing at preliminary stage. From then on, I have conducted the VIRTU4-ACS study myself. I wrote the standard operating protocol (SOP), the coronary angiogram (CAG) check list including training the radiographers in the cardiac cath lab (CCL). I also wrote the informed consent, designed the data collecting template and set up the site file as well as the data base. I consented and recruited the patients, collected the data, modelled and processed the coronary arteries, interviewed the consultants, presented at multi-disciplinary team (MDT) meetings, conducted the six months telephone calls, analysed the data and wrote up the findings.

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ABBREVIATIONS

ACS	Acute coronary syndrome
AF	Atrial fibrillation/atrial flutter
AHA	American heart association
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AUC	Area under the operating curve
BA	Bland Altman (analysis)
BMS	Bare metal stent
BNP	N-terminal pro B-type natriuretic peptide
CAG	Coronary angiography
CAAS-vFFR	Cardiovascular angiographic analysis system for vessel fractional flow reserve
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCL	Cardiac catheter laboratory
CCS	Chronic coronary syndrome
CCS	Canadian cardiovascular society
CFD	Computational fluid dynamics
CFR	Coronary flow reserve
CMR	Cardiac magnetic resonance
CMVC	Coronary microvascular circulation
CMVR	Coronary microvascular resistance
COMPLETE	Complete revascularisation with multivessel PCI for myocardial infarction (study)
COURAGE	Clinical outcomes utilizing revascularisation and aggressive drug evaluation (study)
COMPARE-ACUTE	Fractional flow reserve-guided multivessel angioplasty in myocardial infarction (study)
COX	Cyclooxygenase
CT	Computed tomography
CTCA	Coronary CT angiography
CT-FFR	CT fractional flow reserve

CVD	Cardiovascular disease
CX	Circumflex artery
DANAMI-3-PRIMULTI	Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (study)
D1	First diagonal artery
D2	Second diagonal artery
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
DFR	Diastolic hyperaemia-free ratio
DJ	Duke jeopardy
DM	Diabetes mellitus
ECG	Electrocardiogram
ESC	European Society of Cardiology
FAME	Fractional flow reserve versus angiography for multivessel evaluation (study)
FAMOUS-NSTEMI	Fractional flow reserve vs. angiography in guiding the management to optimize outcomes in non-ST-segment elevation myocardial infarction study (study)
FAVOR	Angiographic quantitative flow ratio-guided coronary intervention (studies I, II and III)
FDA	Food and drug administration
FFR	Fractional flow reserve
FFR_{sim}	Simplified model of FFR calculation
FLOWER-MI	Multivessel PCI guided by FFR or angiography for MI (study)
GRACE	Global registry of acute coronary events
HIT	Heparin induced thrombocytopenia
HTN	Hypertension
IFR	Instantaneous wave-free ratio
IMR	Index of microcirculatory resistance
IVUS	Intravascular ultrasound
LBBB	Left bundle branch block
LAO	Left anterior oblique

LAD	Left anterior descending (coronary artery)
LDL	Low density lipoprotein
LIMA	Left internal mammary artery
LMS	Left main stem
LMWH	Low molecular weight heparin
LVEDP	Left ventricular end diastolic pressure
LV	Left ventricle
LVH	Left ventricular hypertrophy
MACE	Major adverse cardiovascular event
MCE	Myocardial contrast echocardiography
MDCTA	Multi detector CT coronary angiography
MDT	Multi-disciplinary team
mFFR	Measured fractional flow reserve
MJI	Myocardial jeopardy index
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary artery disease
MRI	Magnetic resonance imaging
MVD	Multivessel disease
NCEPOD	National confidential enquiry into peri-operative deaths
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
NSTE-ACS	Non-ST elevation acute coronary syndrome
NSTEMI	Non-ST elevation myocardial infarction
NYHA	New York Heart Association
OASIS-5	Fifth organization to assess strategies in acute ischaemic syndromes (study)
OCT	Optical coherence tomography
OM	Obtuse marginal artery
OMT	Optimised medical therapy
PA	Posterior-anterior
PCC	Pearson correlation coefficient
PE	Pulmonary embolism

PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
PLV	Posterior left ventricular branch artery
PPP	Positive predicted value
PVD	Peripheral vascular disease
RAO	Right anterior oblique
RCA	Right coronary artery
RCT	Randomised control trial
RFR	Resting full cycle ratio
RIPCORD	Does routine pressure wire assessment influence management strategy at coronary angiography diagnosis of chest pain? (study)
RWMA	Regional wall motion abnormality
SCAD	Spontaneous coronary artery dissection
SPECT	Single photon emission computed tomography
STEMI	ST elevation myocardial infarction
SMCs	Smooth muscle cells
SYNTAX	The Synergy between PCI with Taxus™ (stents) and Cardiac Surgery (study)
TIA	Transient ischaemic attack
TIMI	Thrombolysis in myocardial infarction
TXA2	Thromboxane A2
UA	Unstable angina
UFH	Unfractionated heparin
VFAI	Virtual functional assessment index
vFFR	Virtual fractional flow reserve
QALY	Quality adjusted life year
QCA	Quantitative coronary angiography
QFR	Quantitative flow ratio

1. Background

1.1. Coronary artery disease (CAD)

Cardiovascular disease (CVD) is the leading cause of death worldwide. In 2019, approximately 17.9 million people died from CVD alone, with 85% of the cases being myocardial infarction (MI) and stroke (1). MI is caused by coronary artery disease (CAD) due to underlying atherosclerosis. Atherosclerosis is an inflammatory process which begins as fatty streaks in early life, progressing to fibrous plaques at 15-30 years (2). Following a cascade of pathologies, it leads to the formation of plaques that comprise cholesterol, smooth muscle cells, intercellular matrix, calcium salts and substances found in blood. Plaques can harden and gradually narrow the arteries, resulting in reduction in blood flow to the organs such as the heart (3). They can also become unstable and heal (see below).

1.1.1 Pathophysiology

Atherosclerosis is a result of complex pathological changes which involve endothelial dysfunction, inflammation and thrombosis (4). Following an endothelial cell injury, monocyte cells become activated and form adhesion molecules which later migrate into the arterial intima. Lipids, such as low-density lipoprotein (LDL), bind to endothelial cells and become oxidised. Macrophages which matured from monocytes then transform the oxidised LDL into foam cells which express the pro-coagulant molecule tissue factor. Inflammatory responses are amplified by T helper cells which leads to the death of smooth muscle cells (SMCs) and foam cells. Macrophages continue to promote the recruitment of SMCs by using pro-inflammatory cytokines. SMCs replicate and enhance the dense extracellular matrix which results in a lesion formed by subendothelial plaque consisting of lipid core covered by SMCs and connective tissue fibres (5). Plaque distorts the layers in an artery and altered shear and hydrostatic force may lead to instability, with intramural haemorrhage, erosion and rupture. The content of the ruptured plaques can become exposed to circulating blood resulting in thrombosis, which can occlude arteries, or embolise (6). This phenomenon underlies acute coronary syndrome (ACS). In ST-elevation myocardial infarction (STEMI), atherothrombosis usually causes a total occlusion of the artery, whereas in non-ST-elevation ACS (NSTE-ACS), the artery is only partially occluded.

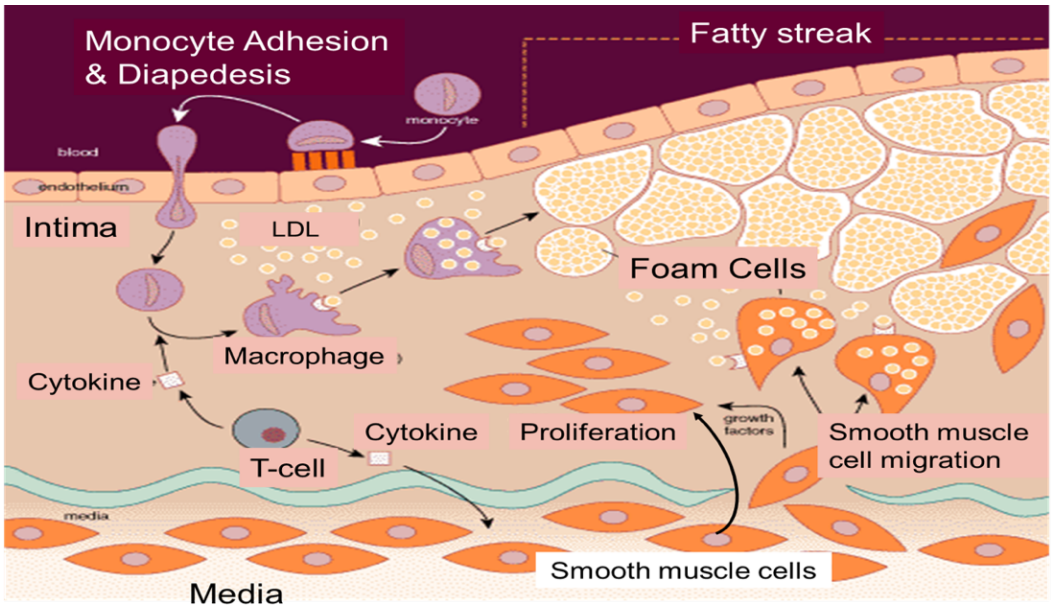


Figure 1 – Endothelial injury triggers monocyte adhesion. Monocytes migrate and differentiate into macrophages. Endothelium becomes loose and permits LDL to enter the intima. Macrophages engulf the LDL and form "foam cells" which subsequently becomes a collection of fatty streaks. T-cells in the intima secrete cytokines and encourage smooth muscle cells (SMC)s to migrate and proliferate with the help of growth factors. (Illustration from https://sphweb.bumc.bu.edu/otlt/MPHmodules/PH/PH709_Heart/PH709_Heart3.html).

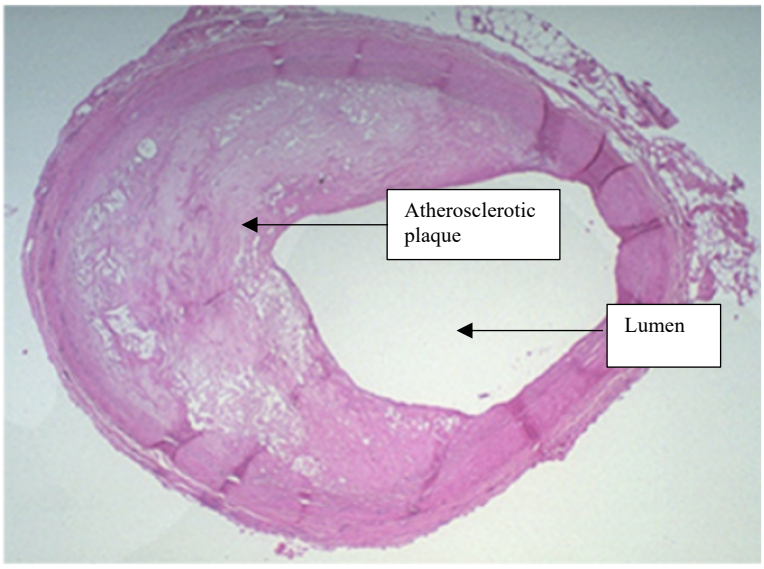


Figure 2 - Cross-section image of an artery. Progressive accumulation of lipid and SMCs in the intima raises the endothelium and become an atherosclerotic plaque which invaded into the lumen of the artery. (Illustration adapted from https://sphweb.bumc.bu.edu/otlt/mph-modules/ph/ph709_heart/ph709_heart3.html)

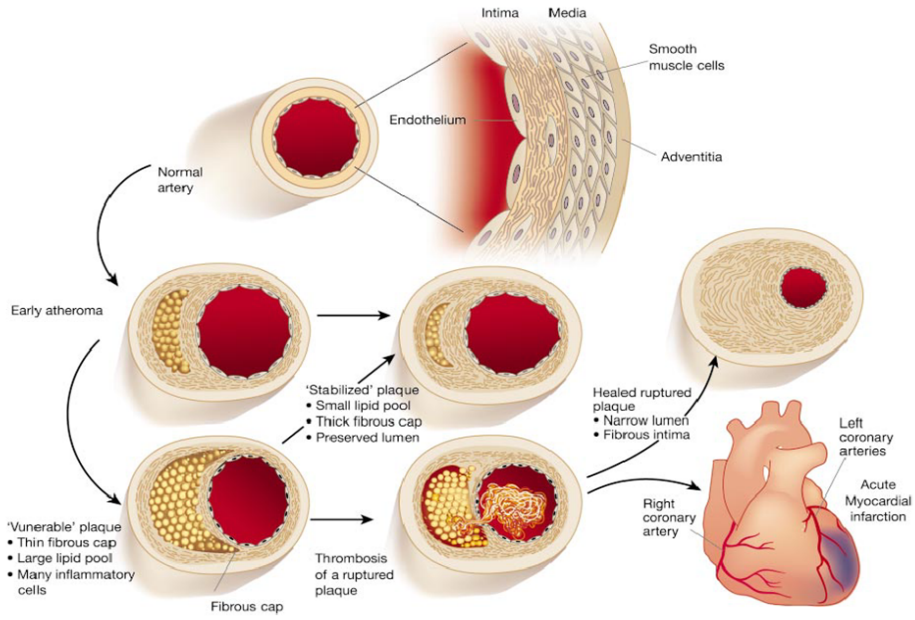


Figure 3 - Formation of thrombosis and ruptured plaque leading to an acute myocardial infarction. (Illustration from Libby, Peter. Nature; London. Vol 420 Iss 6917 (Dec 19-Dec 26, 2002): 868-74).

1.2. Acute coronary syndromes (ACS)

1.3.1 Epidemiology

ACS is one of the leading causes of hospitalization and death in the UK and around the world (7). In 2014-15, the UK national registry recorded 83,842 admissions of acute myocardial infarction (MI) to NHS hospitals in England, Wales and Northern Ireland (8). Of these, STEMI comprises 40.5% and Non-ST-Elevation MI (NSTEMI) 59.5% with the annual incidence for the latter being 3 per 1,000 (9). There is a higher rate of ACS in men than in women below the age of 60 years although, after the age of 75, women represent the majority of patients (10).

1.3.2 Definition

ACS is divided into three main categories; STEMI, NSTEMI, and unstable angina (UA) (11). The term NSTE-ACS is used to include the latter two. Acute MI is defined as evidence of myocardial injury or cardiac cell necrosis alongside acute myocardial ischaemia in the presence of an elevated cardiac troponin in serum plasma. Both STEMI and NSTEMI have some level of cardiomyocyte necrosis which lead to the leak of troponin, a cardiac biomarker measured to diagnose ACS. The universal definition of myocardial infarction defines acute MI as a detection of raised troponin with at least one of the following (12):

1. Ischaemic symptoms e.g., chest pain;
2. New ST-T wave changes or left bundle branch block (LBBB) on a 12 lead ECG;
3. Pathological Q waves on electrocardiogram (ECG);
4. Imaging e.g., echocardiogram (ECHO) demonstrating new or presumed new loss of viable myocardium or regional wall motion abnormality (RWMA);
5. Intracoronary thrombus detected at angiography or autopsy.

Unstable angina (UA) is characterised by the absence of cardiomyocyte necrosis but by myocardial ischaemia at rest. Patients with NSTE-ACS typically present with central crushing chest pain or crescendo angina radiating to the neck or arm with sweating and nausea in some. Nonetheless, the presentation can also be atypical and manifest in non-specific symptoms like shortness of breath, abdominal pain and syncope which are usually more common in women, elderly and patients with co-morbidities such as diabetes and renal disease (13)(14)(15).

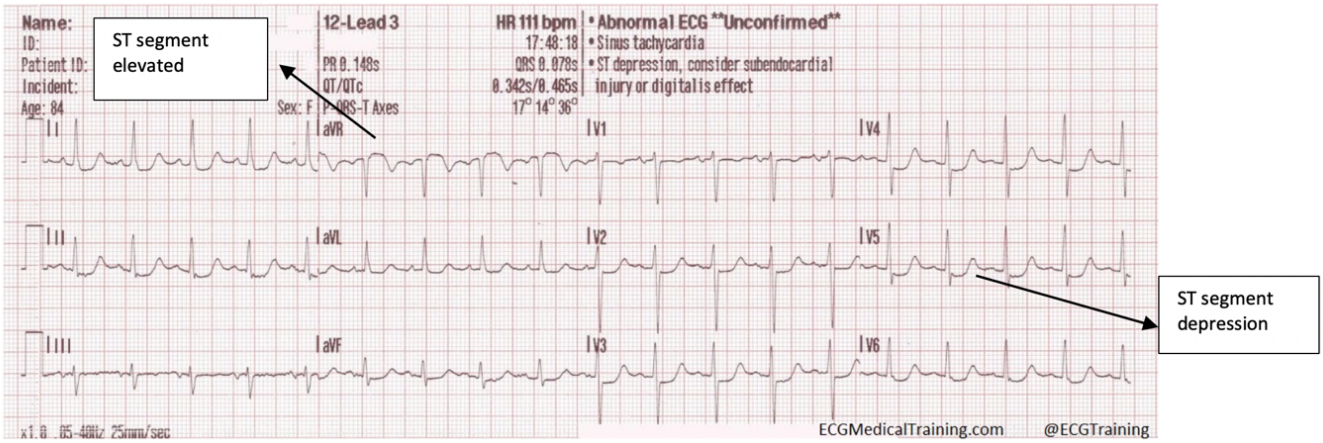


Figure 4- ECG of an acute MI.ST segment is elevated in lead aVR and widespread ST depression in lead I, II, and V2-V6. (Illustration adapted from http://ecgmedicaltraining.com).

1.3.3 Types of MI

MI can be further divided into five categories (see table 1 for summary). Type 1 MI is caused by atherosclerotic plaque rupture or erosion leading distal embolization and reduction in coronary blood flow as well as myocardial necrosis. It also includes coronary embolism, spontaneous coronary artery dissection (SCAD) and coronary vasospasm. Some patients may have underlying CAD, but in 5-10%, women particularly, obstructive CAD may not be evident (see 1.3.4 MINOCA below). Type 2 MI occurs when myocardial necrosis is caused by a mismatch between myocardial oxygen supply and demand like in hypertension, tachy-brady

arrythmias and anaemia. Type 3-5 are MI resulting in deaths without cardiac biomarkers, secondary to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) respectively (16).

MI	Clinical classification
Type 1	Spontaneous MI related to primary thrombotic event
Type 2	Secondary to ischaemic imbalance
Type 3	MI resulting in death without cardiac biomarkers
Type 4a	MI related to PCI procedure
Type 4b	MI related to stent thrombosis
Type 5	MI related to CABG

Table 1 - Summary of different types of MI.

1.3.4 MI with non-obstructive coronary arteries (MINOCA)

MINOCA is clinically acute MI with the absence of obstructive CAD (coronary artery stenosis ≥ 50%) on coronary angiography (CAG) and no other specific cause as alternative diagnosis for the acute presentation (17). It can meet the criteria of either type 1 or type 2 MI. There are various underlying causes of MINOCA, encompassing pulmonary embolism (PE), coronary artery spasm or embolism, anaemia, tachy-brady arrythmias etc, but the latest guidance and consensus have now excluded myocarditis and Takutsubo cardiomyopathy as underlying causes (16). When MINOCA is suspected, further investigation following CAG should be performed. This may be invasively using intravascular ultrasound (IVUS) or optical coherence tomography (OCT) to rule out plaque rupture or dissection. Coronary flow reserve (CFR) (abnormal <2.0) and index of microcirculatory resistance (IMR) (abnormal ≥24) can also be performed to evaluate microvascular dysfunction and coronary vasospasm. The CAG should also be reviewed to rule out any potentially significant CAD missed. Standard left ventricular (LV) functional assessment should be done either using echocardiography (Echo) or ventriculography. Cardiac magnetic resonance (CMR) imaging is also recommended (class 1) to assess evidence of ischaemia, myocarditis or Takutsubo cardiomyopathy in those without obvious underlying cause. Other specific laboratory test such as D-dimer, septic screen, N-terminal pro B-type natriuretic peptide (BNP) are also recommended to assess for PE, heart failure or sepsis. The European Society of Cardiology (ESC) recommends a traffic light algorithm to assist the assessment of suspected MINOCA (see figure 5). Patients with MINOCA should be treated based on the underlying cause but those identified as NSTE-ACS

or MINOCA of unknown cause should be treated in the same way as the standard ACS patients (16).

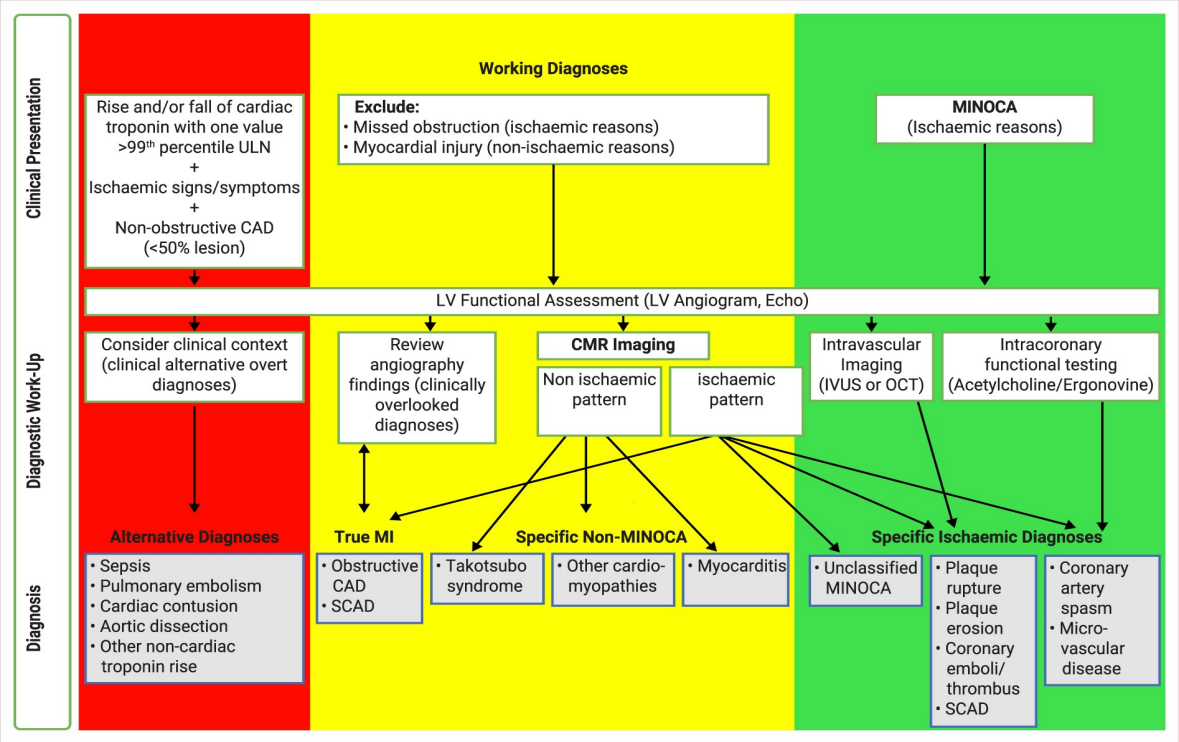


Figure 5 - Diagnostic algorithm for myocardial infarction with MINOCA using a traffic light scheme. Red represents those with Red immediate alternative diagnosis without further additional testing. Yellow represents those with initial working diagnosis that may lead to the final MINOCA diagnosis or alternative diagnoses. Green indicates final MINOCA diagnosis. CAD = coronary artery disease; IVUS = intravascular ultrasound; MINOCA = myocardial infarction with non-obstructive coronary arteries; CMR = cardiac magnetic resonance; Echo = echocardiogram; LV = left ventricular; OCT = optical coherence tomography; SCAD = spontaneous coronary artery dissection. ULN =upper limit of normal. (Illustration from ESC guidance on patients on the management of patients with ACS without persistent ST-segment).

1.4 Treatment of NSTE-ACS

1.4.1 Non-invasive strategy: pharmacotherapy

1.4.1.1 Anti-ischaemia therapy

Immediate general supportive measures for patients with ACS include anti-ischaemic therapy, such as a beta blocker, to reduce myocardial oxygen demand by decreasing heart rate, blood pressure and contractility, or to increase oxygenation to the myocardium by supplying oxygen if the blood saturation is <90% or if there is respiratory distress (18)(19). Coronary and systemic venous vasodilation is achieved by using nitrates and is recommended in patients suffering ongoing ischaemia (19)(16). Several studies have shown the benefit of beta-blockers at reducing in-hospital mortality rate when introduced early (20). On the other hand, in those with vasospastic angina, beta-blockers must be avoided and be treated with calcium channel blockers instead (21). Opiates such as intravenous morphine can also be administered while waiting for angiography, although it may slow intestinal absorption of oral antiplatelet agents (22)(23).

1.4.1.2 Anti-platelet therapy

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is recommended to be initiated as soon as diagnosis of ACS is established, irrespective of the management strategy (24)(25). Aspirin, a cyclooxygenase (COX) inhibitor, which acts by blocking the production of thromboxane A2 (TXA2), is recommended in all patients with ACS, with the loading dose of 300mg followed by 75mg as maintenance long term. In a meta-analysis study of randomised control trials, aspirin administration for up to two years in patients with acute or previous vascular disease or some other predisposing condition, has been shown to reduce major vascular events (26). P2Y12 inhibitors such as clopidogrel, ticagrelor and prasugrel are also advocated in addition to aspirin for 12 months unless there is a high bleeding risk. In NSTEMI patients, Yusuf et al and Mehta et al both demonstrated that treatment with DAPT (aspirin and clopidogrel) resulted in a reduction of recurrent ischaemic events when compared with aspirin alone (27)(28). The current preferred P2Y12 inhibitors of choice are ticagrelor and prasugrel, following the evidence of their superiority in terms of reducing composite endpoint of cardiovascular death, MI or stroke when compared with clopidogrel (29)(30).

1.4.1.3 Anticoagulation therapy

Current guidelines also advise the administration of an anticoagulant along with DAPT in patients with NSTE-ACS (19)(16) from the initial presentation during the course of hospital admission up to coronary angiography (CAG). Anticoagulants act by inhibiting the thrombin pathway, therefore reducing the risk of thrombus formation. Eikeboom et al showed that the combination of antiplatelets with anticoagulation is effective in reducing ischaemic events in NSTE-ACS patients when compared with placebo (non-treated control group) (31). There are several recommended anticoagulants which include fondaparinux, unfractionated heparin (UFH) and low molecular weight heparin (LMWH). Fondaparinux has the most favourable efficacy and safety profile based on evidence thus far. In the OASIS-5 study for example, fondaparinux was shown to be non-inferior to enoxaparin but was associated with 50% fewer in-hospital major bleeds and significantly reduced mortality at 30 days (32). Enoxaparin, a type of LMWH, in comparison with UFH, has a more predictable behaviour and causes fewer side effects such as heparin induced thrombocytopenia (HIT). Two meta-analysis comparing trials involving enoxaparin and UFH in ACS with percutaneous coronary intervention (PCI) demonstrated that enoxaparin is favourable in terms of reduction of the composite end point of death and MI as well as fewer major bleeds (33)(34). UFH is no longer used as a medical therapy in its own right but is employed during PCI for ACS (24).

1.4.2 Invasive strategy; coronary angiography (CAG) in ACS

NSTE-ACS is the most common type of ACS and contributes a large proportion of the patients undergoing PCI. After six months, it carries as higher risk of mortality and morbidity in comparison to STEMI, and therefore requires early risk stratification for the best treatment strategy (35)(36) . The aim of CAG and revascularisation is to relieve symptoms and to improve prognosis. Patients with NSTE-ACS who have evidence of ischaemia and low risk of adverse cardiovascular events (six months mortality prediction of <3%) should be offered CAG according to the National Institute of Health and Care Excellence (NICE) guideline (37). This allows the clinician to establish the diagnosis and identify the culprit lesion(s) to formulate management regarding revascularization (PCI or CABG), and to guide antithrombotic treatments as well as stratify the patient's risk (11). An early invasive strategy (<72 hours) carries a class 1 recommendation in the ESC guidelines, whilst those who are at higher risk, e.g. with dynamic ECG change, high Global Registry of Acute Coronary Events (GRACE) score and rise and fall of cardiac troponin compatible with MI, should have CAG within 24

hours (38)(39). Patients with extremely high risk, eg with recurrent dynamic ST changes or ST-elevation, haemodynamic instability, life threatening arrhythmias and cardiac arrest, or a mechanical complication of MI, should be prioritised for immediate (<2h) invasive CAG (40)(41)(42). Identifying the acute lesions in patients with NSTE-ACS on CAG alone can be challenging because nearly 15% present with an acutely occluded artery, about 60% of occlusions are already collateralised and about 25% of patients have non-obstructive or normal epicardial arteries (43)(44)(45)(46); and, of the remainder, it is frequently unclear whether the angiographic lesion, of which there is often more than one, is flow limiting. A culprit lesion should show at least two features of a ruptured plaque, such as filling defects due to thrombus, plaque ulceration, plaque irregularity, dissection or impaired flow (47)(48)(49). Angiography alone can rarely provide such detail. The pattern of ST depression on the ECG and regional wall motion abnormalities (RWMA) on echocardiography can be useful to help identify the area of culprit lesion (50)(11).

Figure 6 - Standard cardiac catheter laboratory (the author is performing a coronary angiogram).

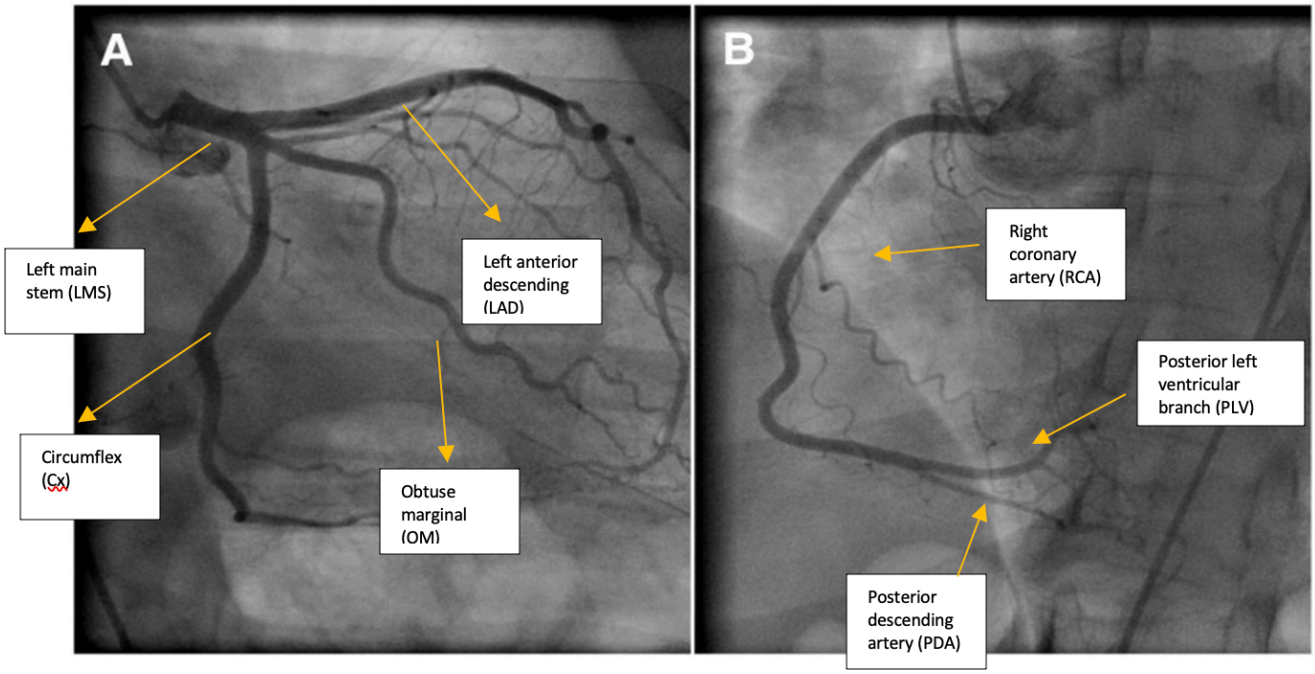


Figure 7 - CAG of normal coronary arteries. **A -** Left coronary artery. **B –** Right coronary artery.

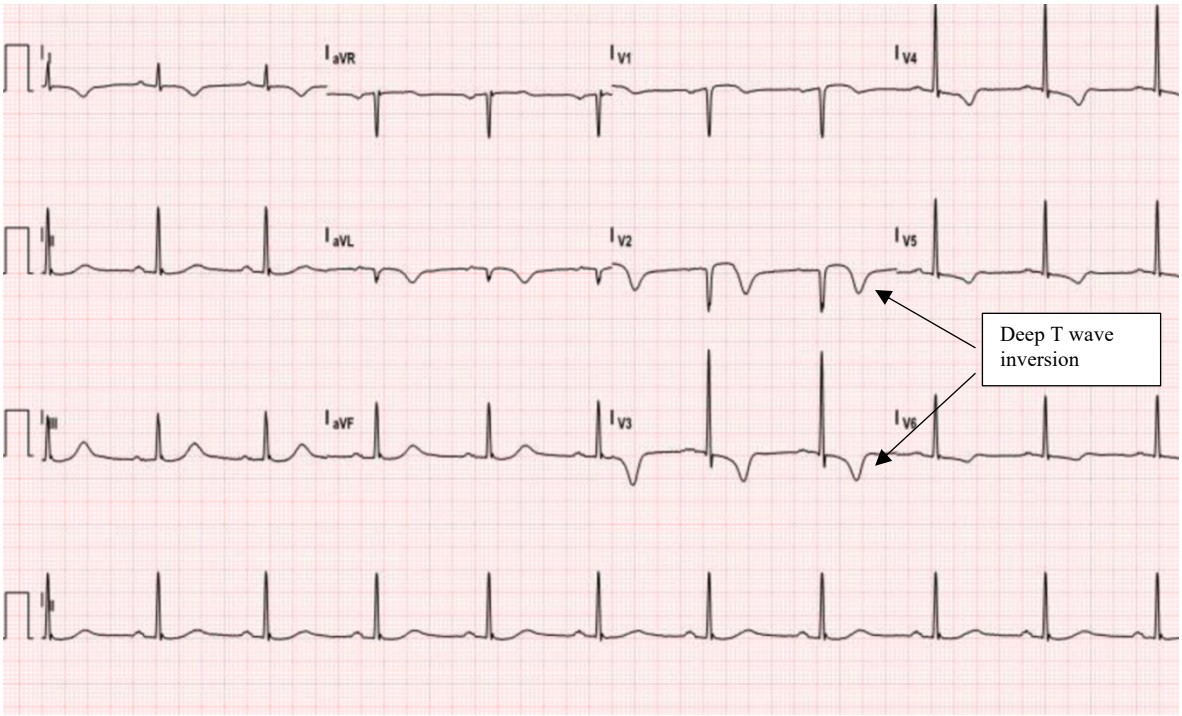


Figure 8 - Wellen's sign on ECG. Deep T wave inversion in the anterior lead V2-V4 associated with ST segment change in V1-V3 suggest a critical stenosis in the left anterior descending artery (LAD).

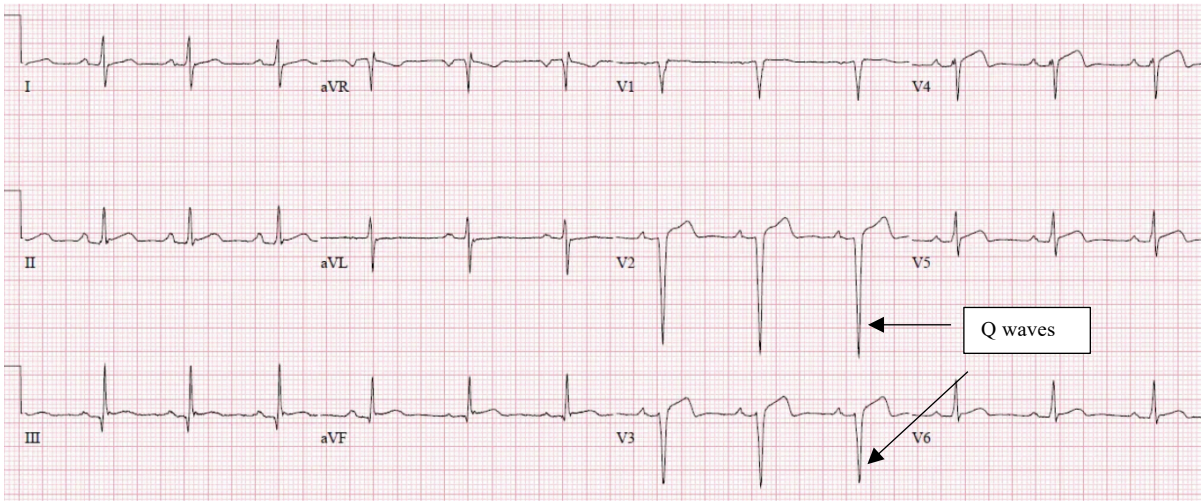


Figure 9 - ECG showing Q waves in V1-V3 suggesting of an old anterior infarction.

1.5 Revascularisation; PCI and CABG

1.5.1 Percutaneous coronary intervention (PCI)

The presence of ischaemia-provoking lesions is a crucial risk factor for an adverse clinical outcome (51)(52), and the revascularization of these lesions have been demonstrated to improve a patient's functional status and outcome (52)(53)(54). PCI with stent implantation in patients with ACS can help minimize the risk of abrupt artery closure and restenosis associated with balloon angioplasty only, with evidence supporting the use of new-generation drug eluting stents (DES) over bare metal stents (BMS) (55)(56)(57)(58). Vascular access for PCI can be obtained via femoral or radial artery although the current recommendation is to use the radial approach whenever possible (24)(59).

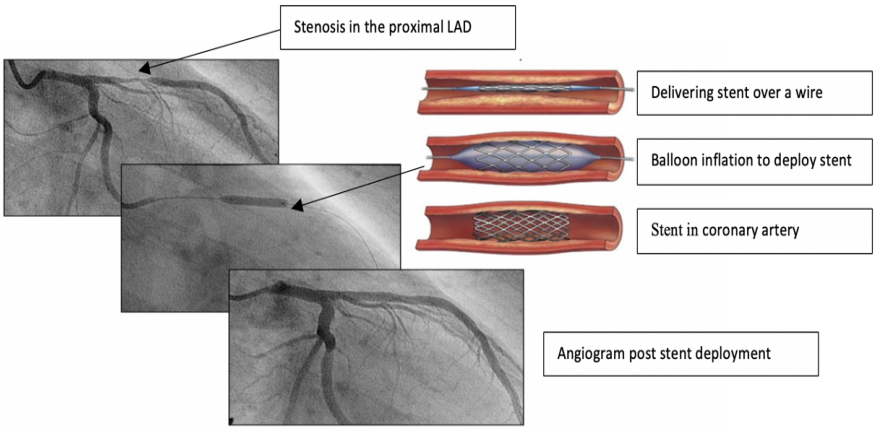


Figure 10- Angiography guided PCI to a stenosed coronary artery (proximal LAD). (Images courtesy of J Gunn).

1.5.2 Coronary artery bypass graft (CABG)

CABG is open-heart surgery in which bypass grafts using a healthy artery, such as the left internal mammary artery (LIMA, in situ), and veins, most commonly the long saphenous veins, are placed from the aorta to the coronary arteries to bypass blocked or stenosed segments. Traditionally, CABG surgery uses a heart-lung bypass machine to pump and oxygenate the blood while the heart is stopped; however, in off-pump surgery, this is not required (60). Minimally invasive CABG is also possible with a smaller incision to the left side of the sternum, although this technique is not suitable for everyone. A small proportion of NSTE-ACS patients (c10%) may require CABG (61). In about 5% of patients the underlying cause of the ACS is bypass graft failures, and in c10% it is left main stem (LMS) disease (24). Compared with patients undergoing elective CABG, balancing the risk of ischaemia and bleeding in regards to antithrombotic therapy and timing of surgery can be more challenging in ACS patients because there is a higher proportion of elderly patients, females, LMS disease, and heart failure; all of which carries a high surgical risk (62).

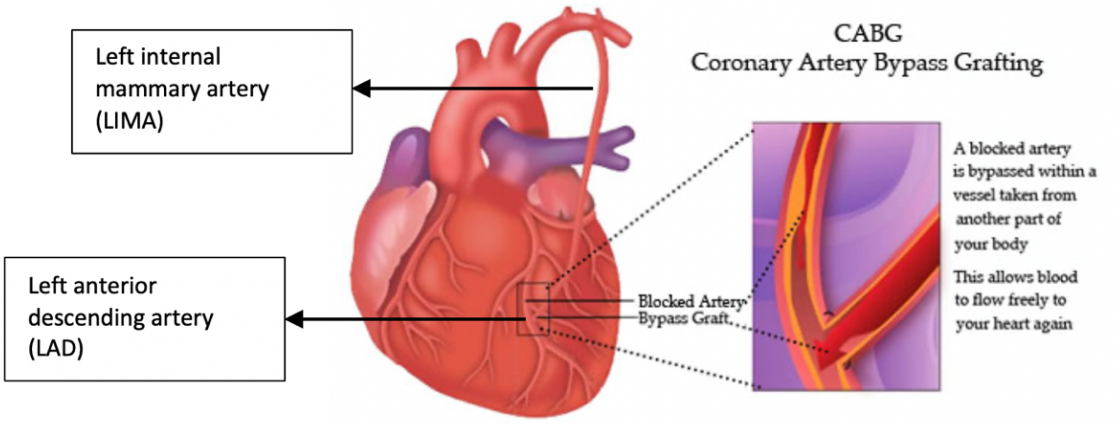


Figure 11 – CABG using LIMA into the LAD. (Illustration adapted from http://www.clinicalexcercise.co.uk).

1.6 PCI and medical treatments in stable coronary artery disease (CAD)

In a study of 558 patients with stable coronary artery disease (CAD) with angina symptoms, initial treatment strategy with revascularisation with either PCI or CABG was shown to be superior to OMT in terms of reducing the rate of death, myocardial infarction or repeat cardiac hospitalisation, but this study was not statistically powered to detect differences in clinical outcome (53). On the contrary, in the COURAGE trial, which studied 2287 patients with myocardial ischaemia, the initial approach of PCI added to optimal medical therapy did not

result in reduction in cardiovascular adverse events when compared to the group who received medical therapy only (63). Another study (ORBITA) investigated the effect of PCI vs placebo procedure on patients with stable angina in addition to six weeks optimal medical therapy. It showed that PCI did not relieve angina symptoms or improve exercise time over and above OMT, although it did resolve ischaemia on stress echocardiography (64). Nevertheless, there are issues to be considered in this study regarding its statistical power, sample size, methodology, patient selection, and result interpretation; therefore any information from it should be used judiciously (65)(66). Lastly, in the latest study of 5179 patients with stable CAD and moderate or severe ischaemia, an initial invasive strategy was not found to be superior to an initial OMT strategy at reducing the risk of cardiovascular events or death. When compared with medical therapy, PCI is thought to provide greater relief from angina symptoms, which usually arise from a functionally significant stenosis. When combined with medical therapy, both CABG and PCI are associated with significantly improved survival compared with medical treatment alone (67). Whilst the earlier evidence may have shown the benefits of the initial revascularization with PCI when compared to optimised medical treatment (OMT) alone in patients with stable CAD, more recent studies have suggested otherwise. Interventionalists make decisions regarding treatment based upon clinical judgment regarding the individual patient and not purely on evidence-based guidance (68). RCTs investigating PCI vs medical treatment in patients with ACS in the early twenty first century led to the current ESC recommendation for treating stable CAD by optimization of medical therapy combined with early invasive management. PCI is recommended, with fractional flow reserve (FFR) guidance especially in those with intermediate lesions on CAG (69).

1.7 Invasive strategy (CAG/PCI) vs medical therapy in ACS

In contrast to patients with stable coronary CAD, a routine initial invasive strategy is superior to a non-invasive approach in patients with ACS. A randomised control trial (RCT) of approximately 2,500 patients with NSTE-ACS investigated the impact of invasive strategy with the aim to revascularise within seven days compared with a selective invasive approach (symptom or ischaemia driven angiography). The study demonstrated the superiority of invasive strategy at reducing major adverse cardiovascular events (MACE) as well as delaying readmissions with ischaemic symptoms by an average of 37 months (70). Furthermore, a few large meta-analyses of RCTs concluded with similar findings. A meta-analysis of approximately 8,000 patients with NSTEMI who had PCI, demonstrated that a routine invasive

approach leads to a lower risk of death as well as fewer re-admissions to hospital for recurrent ACS within two years when compared with those who had non-routine angiography (38). In another, a routine invasive approach led to a reduction in cardiovascular death and myocardial infarction with a more pronounced absolute risk reduction in those at higher vs lower risk (71). Whilst there may not be any more recent evidence, an invasive approach has continued to be proven a successful practice and remains the recommended treatment strategy in patients with ACS (19)(24) (see table 2 below).

1.8 Multi-vessel disease (MVD) and bystander disease

Multivessel CAD is associated with worse outcome compared with single vessel disease (72)(73). It is found in approximately half the patients with STEMI (74), and about 40-60% of NSTE-ACS (75). There is emerging evidence that revascularisation of non-culprit arteries within eight weeks results in a significant survival benefit and improved quality of life compared with culprit-only treatment (76)(77)(78)(79). In a randomised control trial (RCT) of 627 patients with STEMI, complete revascularisation guided by fractional flow reserve (FFR) measurements was shown to reduce risk of future events compared to treating the culprit lesion only (79). Smits et al also described a similar result in a study of 887 STEMI patients with MVD, demonstrating a lower cardiac composite end point and repeat revascularisations in the group who had complete revascularisation (78). Another much larger RCT, COMPLETE, consolidated this finding. In this study, 4,047 patients with STEMI and MVD were randomised to complete-revascularisation vs infarct related artery only and demonstrated that the complete revascularisation resulted in a lower risk of cardiovascular death or new myocardial infarction at three years follow up (80). In patients with NSTE-ACS, a complete revascularisation strategy should be considered, because several studies have shown advantages of early intervention on these lesions when compared with a conservative approach (81)(82). This finding is supported by other trials demonstrating a detrimental prognostic effect of incomplete revascularisation (83)(84)(85). In a large observational cohort study of 37,491 patients with NSTE-ACS, Rathod et al showed that long term mortality was reduced in the group which had complete revascularisation compared with the culprit-only group (86). Although most evidence to date is not from RCTs, the trend is in favour of complete revascularisation in NSTE-ACS patients (see table 2 below).

Evidence for revascularization in patients with NSTE-ACS			
Study	Type of study	N=patients	Outcome
Wallentin et al (82)	FRISC-II invasive randomized controlled trial	2457	An early invasive treatment strategy delayed the occurrence of death or MI compared with a non-invasive strategy.
Poole-Wilson et al (87)	RITA – 3 Randomized controlled trial	1810	An interventional strategy is preferable to a conservative strategy in terms of refractory or severity angina, and with no increased risk of death or MI.
Fox et al (39)	Meta-analysis	5467	A routine invasive strategy reduces long-term rates of cardiovascular death or MI with the largest absolute effect in seen in higher risk patients.
Shishehbor et al (88)	Retrospective observational study	1240	Multivessel intervention was associated with a lower revascularization rate and lower composite end point compared with culprit only stenting.
Rathod et al (86)	Observational cohort study	37491	In NSTEMI patients with MVD, complete coronary revascularization appears to be superior to culprit-only vessel PCI in terms of long-term mortality rates.
Kim et al (89)	Observational, retrospective multicentre study	2872	Multivessel revascularization reduced 3-year MACE compared with culprit only revascularization. .

Table 2 – Table summarizing the evidence for revascularization in patients with NSTE-ACS

1.9 PCI vs CABG in MVD

Treating multivessel CAD with PCI using DES has increased in recent years, although CABG has been the treatment of choice before that. Whilst there are no randomised control trials to address the selection of intervention mode (PCI vs CABG) in patients with ACS in the current era, the ESC has suggested that the revascularisation strategy for patients with stable CAD can be followed in patients with NSTE-ACS patients who have been stabilised (90). Serruys et al, in the SYNTAX study, comparing PCI and CABG in patients with stable CAD, showed that there was lower MACE at one year in the CABG group (91). Current guidelines recommend

that the preferred method of treating multivessel CAD is CABG (90). Nevertheless, recent studies have also indicated that PCI can be performed as an alternative method to CABG in patients with low and intermediate SYNTAX scores; a clinical tool used to grade complexity of coronary artery disease (90)(92). A study has also demonstrated the increase use of PCI over the course of nine years (from 2001-2009) with a decreasing trend of CABG in patients with NSTE-ACS (93). Nonetheless, pursuing complete revascularisation could pose increase risks from PCI, possibly including emergency CABG, especially in patients with complex coronary anatomy. Therefore, it is desirable that these patients are considered carefully and discussed in a multi-disciplinary 'heart team' meeting involving an interventional cardiologist, a cardiac surgeon and other healthcare professionals relevant to the needs of the patient based upon their general condition, age and co-morbidities as well as the number of lesions, their complexity, the quality of the distal vessels and the level of revascularisation required regarding the choice of treatment strategy (PCI or CABG). If PCI is the choice of strategy, intervening on the culprit lesion first is recommended; whereas in cases of multiple non-culprit stenoses, or those which are difficult to assess angiographically, the use of fractional flow reserve (FFR; see below) is advised to aid treatment strategy (94). However, determining which lesions are ischaemia-inducing in patients with multivessel disease can be challenging, and non-invasive stress testing is limited in its ability to localize these lesions and that angiography guidance alone is often insufficient (95). Overall, deciding on a PCI approach that would result in judicious use of stents to achieve relief of ischaemia is a pragmatic approach to improve the clinical outcome as well as health economics.

1.10 Health economics of ACS

ACS leads to significant economic burden because of its high mortality and morbidity. At least 50% of all CVD deaths are secondary to this condition (96). The need to improve and reduce medical and societal expenditure related to this condition is pivotal and should include evaluation of admissions cost as well as treatment strategies encompassing medical management, PCI or CABG. Zhao et al analysed 10,487 ACS patients and demonstrated that the medical cost for medical management was lowest, followed by PCI, CABG being the most expensive at one year follow up (97). Ensuring that the right treatment strategy is selected when treating patients with ACS can potentially lower the overall cost of care by reducing resource utilization. Treatment with CABG, as shown by a few studies, carries the highest cost when compared with conservative and PCI strategies, so assessing and investigating patients with

CAD methodically prior to any decision making will ensure that no unnecessary revascularisation or intervention is done (97)(98). This approach may also reduce the number of repeat revascularisations or re-hospitalisations, and hence the overall cost, in the future. Adoption of a coronary physiology approach using FFR when treating these patients may also contribute not only to an improvement in clinical outcome but also to a total cost reduction (see below). Additionally, new generation drug eluting stents (DES) are now less costly than bare metal stents (BMS) used to be (99). Furthermore, even though an invasive strategy can be costly at the start, in the long term this option can reduce the rates of complications and myocardial infarction in patients with myocardial ischaemia, which may reduce subsequent treatment costs (100).

1.11 Non-invasive ischaemia testing; is there a role in NSTE-ACS?

In patients with NSTE-ACS who are considered to be at low risk for ischaemic events, without the criteria listed above for early or immediate invasive strategy, and no recurrent symptoms, a non-invasive approach can be applied, e.g. with stress electrocardiography or cardiac magnetic resonance (CMR) imaging, before deciding upon angiography (101).

1.11.1 CTCA

Multi detector CT coronary angiography (MDCTA) is excellent at excluding significant CAD with negative predictive values (NPVs) approaching 100% (102). It is a useful tool to risk stratify patients presenting with chest pain with no ECG changes. Functioning as a 'triple rule-out', it can also identify those with other life-threatening causes like acute aortic syndrome or pulmonary embolism (103). In one study of 568 patients with suspected ACS, 84% were identified as low risk and were discharged after CTCA with no adverse cardiac events at 30 days (104). In another study of 368 patients with acute chest pain who underwent CTCA after an inconclusive initial evaluation, showed that 50% of patients were free of CAD and had no ACS (105). This illustrates how early CTCA could improve patient management when used at triage in the emergency department. Current ESC guidelines recommend CTCA as an alternative to invasive CAG in patients with low to intermediate risk of CAD and, when the troponin and ECG are inconclusive, to exclude ACS as class IIa (11). However, the RAPID-CTCA trial of 1748 patients did not demonstrate a benefit of CTCA in reducing death, MI or stent thrombosis in suspected ACS when compared to standard practice (5.8% vs 6.1%; p=0.65) (106). More importantly, not all patients with significant CAD have ACS, thus

achieving an accurate, quick 'rule-in' or 'rule-out' diagnosis in this group is challenging. Sarno et al also demonstrated that only half of the stenoses classified as significant by CTCA are associated with ischaemia (107). CTCA is limited at predicting the haemodynamic significance of a lesion, and its use in the acute setting is less reliable than invasive angiography, which also provides the opportunity to be combined with PCI in a single procedure. CT-FFR, however, can demonstrate ischaemia-provoking lesions by modelling the coronary vasculature and incorporating computational fluid dynamics (CFD) (108) with a diagnostic accuracy of 81% (109)(110). CT-FFR is now recommended as an adjunct to CTCA in stable patients (111). It is limited, however, by the presence of calcification, tachycardia and arrhythmia (112). Other limitations are the availability of CT and, for CT-FFR, cost, and the requirement for off-site processing (up to 24h). In the move towards timely interventional management for the ACS patient, CTCA is, therefore, generally impractical.

1.11.2 Stress tests

Stress echocardiography, using bicycle, treadmill or pharmacological stressors such as dobutamine, is more accurate than an exercise ECG to detect ischaemia and has a sensitivity (80-85%) and specificity (84-86%) but is operator-dependent in comparison to other imaging techniques (113). Compared to exercise ECG testing, stress imaging is preferred in patients with previous PCI or CABG because it is superior at quantifying and localizing ischaemic areas in cases with abnormal resting ECG or when the patient is unable to exercise. Cardiac magnetic resonance imaging (MRI) stress testing is also useful to detect wall motion or perfusion abnormalities. Recent meta-analyses have demonstrated a sensitivity and a specificity of more than 80% in detecting wall motion abnormalities and sensitivity as high as 91% at showing perfusion abnormalities (114). However, there are still limitations for using stress imaging in clinical practice. First, most patients are pain free by the time of investigations; therefore, the demonstration of a perfusion or motion abnormality may be unreliable. Second, myocardial ischaemia may be confined to a small part of the myocardium or sub-endocardium, and so contractility or perfusion abnormalities in this scenario may not be identified (115). Third, it can be challenging to identify the exact ischaemia-causing lesion at CMR imaging. Fourth, a practical limitation is to conduct dynamic tests on patients who have only just been stabilised in hospital; and often the anti-ischaemic therapy is heart rate limiting and can mask the results. Stress tests are therefore rarely used in ACS patients in the acute phase.

1.12 Problems with CAG

Whilst CAG is the final common pathway, and the default investigation for patients with ACS, it has several limitations, in particular in diagnosing 'significant' CAD using coronary angiography alone. First, there are technical factors limiting the quality of the image, such as the position of the x-ray source, the age of the intensifier, variations of contrast concentration and flow, selection of the radiographic projections, the frames recorded and analysed, subject movement and pixilation of the images (116). Second, because it is a 'film' resulting from multiple stationary two-dimensional images, recorded in different projections, lesions in the complex three-dimensional structure of branching coronary arteries can be misinterpreted (117). Third, the percentage stenoses based upon visual interpretation from angiography is subjective and therefore varies from operator to operator. The severity of a lesion is often overestimated, whilst the length is underestimated. White et al described, in a study of 39 patients (44 vessels), that overestimation is as high as 95% in lesions with >60% stenosis, whilst both overestimation and underestimation commonly occur in the lesions with <60% stenosis when compared against the true measurement using coronary physiology (118). In another study that investigated 83 moderate lesions (40%-70% stenosis by visual inspection), the visual estimation demonstrated a poor specificity (45%) and a positive predicted value (PPV) (25%) when compared with FFR. Furthermore, the reviewer's estimation of lesion severity and FFR were concordant in only about 50% of the cases. The study also showed that quantitative coronary angiography (QCA), a technique used to measure the stenosis by tracing the 2D angiogram image, is only reliable in moderate lesions (<60%) or a minimal luminal diameter of more than 1.4mm (119). In summary, CAG assessment is critically dependent upon the quality of the angiographic images; inadequate contrast, insufficient projections, overlapping vessels, excess movement, and lesions located at ostia, branch points and in series pose particular challenges. In addition, it cannot reveal the vulnerability or instability of lesions without the assistance of intravascular imaging, although this is also a limitation of physiological assessment (120).

1.13 Coronary physiology in the cardiac catheter laboratory (CCL): Fractional flow reserve (FFR)

FFR is an invasive technique used in selected cases of cardiac catheterization to determine if a narrowing in a coronary artery impedes blood flow by measuring the pressure difference as a

surrogate for blood flow itself across a stenosis during maximal hyperaemia. This equates to the ratio of the maximum achievable blood flow in the stenotic coronary artery vs the theoretical maximum flow in a normal coronary artery (Pd/Pa):

$$FFR = \frac{Q \text{ with stenosis}}{Q \text{ normal}} = \frac{((P_d - P_v)/R)}{((P_a - P_v)/R)} \approx \frac{P_d}{P_a}$$

Pa: Mean aortic pressure. **Pd:** Hyperaemic coronary pressure distal to the stenosis. **Pv:** Central venous pressure **R:** Resistance

where Pa is mean aortic (proximal) pressure, Pd is pressure distal to the stenosis, Pv is the central venous pressure and R is resistance to flow. FFR approximates the ratio of the distal to proximal pressure, so it can be measured with a pressure-sensitive angioplasty guidewire. It is best calculated during maximum hyperaemia, during which microvascular resistance (MVR) is assumed minimal or constant which can be achieved by an infusion of adenosine (see figure 10).

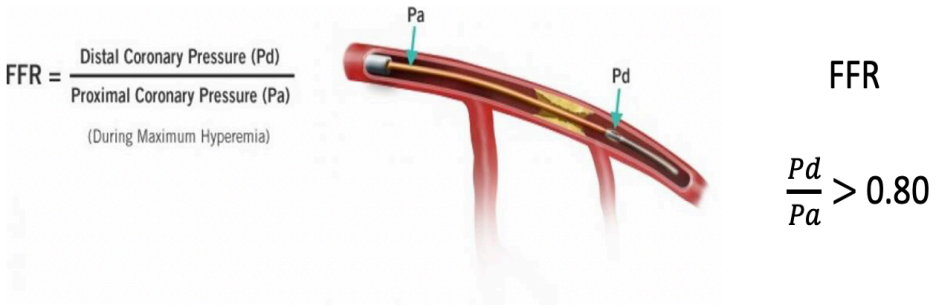


Figure 12 - FFR. The ratio of the distal coronary pressure (Pd) over the proximal coronary pressure (Pa).

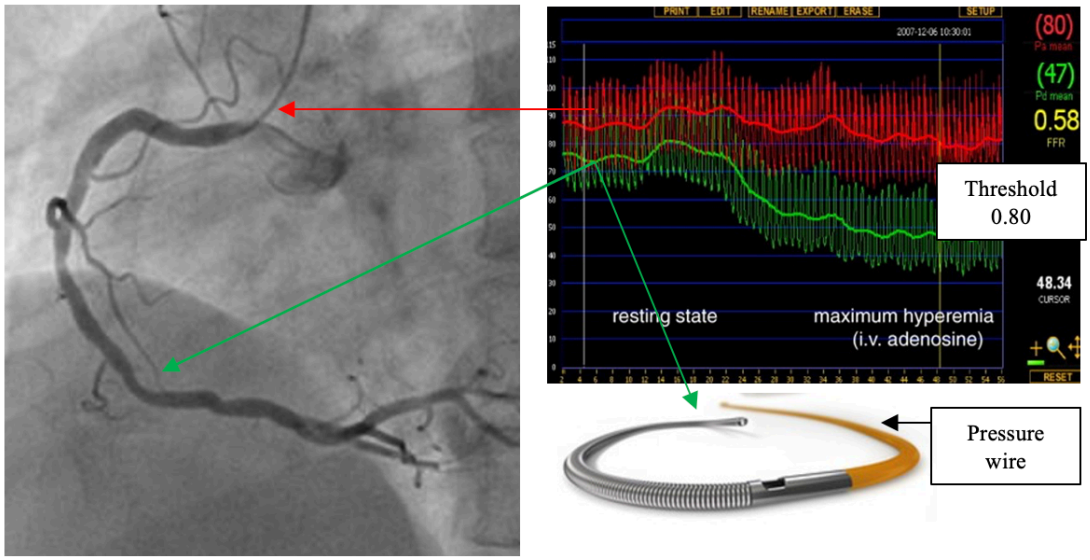


Figure 13 -The application of FFR in the CCL. Red and green arrow represent proximal (Pa) and distal pressure (Pd) respectively. FFR (Pd/Pa) is 0.58 in the RCA. (Images courtesy of J. Gunn).

FFR, or related 'resting' indices such as resting full cycle ratio (RFR) or instantaneous wave-free ratio (iFR), is recommended in arteries with narrowing estimated visually between 50% and 90%, when non-invasive testing is unavailable or inconclusive (121). It requires a pressure wire to be placed into the coronary artery and the use of a vasodilatory agent such as adenosine to achieve maximal hyperaemia, rendering myocardial resistance constant and minimal. During maximal hyperaemia, the ratio between the mean blood pressure distal to the stenosis (p_d) and mean pressure in the aorta (p_a) is recorded and the FFR obtained. The positioning of the wire's pressure sensor is crucial; it must be placed in the main vessel and distal to the lesion that is being investigated. When assessing a sequential stenosis in the same artery, the pressure sensor should be positioned downstream of the most distal lesion, because the presence of the second lesions affects the FFR of the proximal one (122). An FFR of 1.0 is normal whilst a value of <0.80 is the accepted threshold for ischaemia and justifies intervention (123)(124)(125). The resting gradient (Pd/Pa) of <0.80 is sufficient to justify ischaemia and its haemodynamic relevance, therefore proceeding to maximal hyperaemia is not necessary. Physiological guidance, compared with angiography alone, reduces symptom burden, repeat revascularisation and health expenditure at the time of percutaneous coronary intervention (PCI) (126)(52)(125). A hidden 'benefit' of physiological guidance is that, perhaps unfortunately, angiographic precision is not essential.

1.14 Evidence for the utility of FFR

Pijls et al first described the FFR concept in 1993 (127). There are now several clinical trials showing that the use of FFR to guide PCI is beneficial clinically and is cost effective (125)(128)(124)(123)(129). In summary, three large studies have concluded that FFR-guided revascularization in patients with CAD and narrowing of >50% result in better outcomes when compared with angiography guidance alone. In the DEFER trial, 325 patients with a moderate stenosis and scheduled for PCI were studied. The FFR was measured before the planned intervention and, if the FFR was ≥ 0.75, the patients were randomised to deferral (Defer group; n = 91) or performance (Perform group; n = 90) of PCI. If the FFR was <0.75, PCI was performed (Reference group; n = 144). There was no difference in the primary endpoint (freedom from MACE) between the two groups, suggesting that it is safe to treat lesions with FFR >0.75 conservatively (130)(126). In the Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME) trial, 1,005 patients with stable or unstable CAD were randomised to an angiography-only approach or to angiography + FFR-guidance. In the FFR-guided group, PCI was only performed when the FFR was ≤0.80 whilst all stenoses ≥50 % in the angiography-only group were revascularised. The rate of the combined endpoint, and myocardial infarction was lower in the FFR-guided group (131)(132). The FAME 2 trial, in which 882 patients with CAD were randomised to FFR-guided vs angiography-guided revascularization, also demonstrated similar outcomes with a lower rate of the combination of death, myocardial infarction and urgent revascularization in the FFR-guided arm (133)(134). Although the FAME 2 trial did not include patients with NSTE-ACS, it still demonstrated the benefit of FFR-guided approach. Furthermore, in another study of 200 patients with CAD, FFR guided approach was shown to result in a change in management in 26% of the cases. There was also discrepancy in 32% of the patients between the assessment of ischaemic lesions by CAG and FFR-derived stratification. For example, patients who were initially referred for revascularisation were found to have no ischaemia-inducing disease, whilst some who were deemed to have no significant disease turned out to have MVD after FFR measurements (135). Most importantly, overall, the implications of all these studies are profound, and have proven that FFR is a valid concept, and that judging CAD based upon angiography assessment alone is inaccurate in a proportion. The above evidence, however, is derived largely from patients with chronic coronary syndrome (CCS) rather than ACS.

1.15 FFR in NSTE-ACS

In patients with NSTE-ACS, there is usually no functional information on ischaemia because stress testing in this group is not recommended (24)(9). The care of these patients is usually based upon rapid revascularisation, which implies coronary angiography and follow-on PCI. Visual interpretation of the stenoses at angiography is the current standard, and this may be inaccurate for the reasons outlined above, potentially leading to an inappropriate treatment decision (118)(136)(137). FFR guided revascularization could be adopted because some studies have shown its benefit in patients with NSTE-ACS. Whilst the majority of the evidence for FFR is in CCS, there were large NSTE-ACS subsets in some of the seminal studies. In the FAME study, 30% of patients had NSTE-ACS. The two-year rate of major adverse cardiovascular events (MACE) was significantly reduced in the FFR- vs the CAG-guided groups, with no difference between the CCS and NSTE-ACS cohorts (138). Importantly, the study also showed that no MIs occurred in the FFR-guided deferred lesions in the NSTE-ACS cohort at two year follow up (94). A health economics analysis from the study also revealed that FFR-guided PCI improved outcomes and costs at one year when compared with the CAG-guided approach (139). In a 'real-world' observational study of 3,000 patients with ACS, a lower in-hospital mortality was observed for FFR guidance than for a CAG-based approach (1.1 vs 3.1%, $p < 0.01$), and reductions in hospital stay, acute kidney injury (AKI) and bleeding (140). In a study of 350 ACS patients randomised to FFR- vs CAG-guidance, disclosure of the FFR resulted in changed management in 21.6% of cases, reducing the number of unnecessary procedures and downstream unplanned revascularizations (129). A cost-effectiveness assessment disclosed that increased up-front costs (pressure wire use and laboratory time) were more than compensated by later savings in subsequent hospital stay, events and procedures; and there was also a small benefit in quality-adjusted life year (QALYs) (141). In another study of 107 patients with multi-vessel disease and moderate non-culprit lesions, FFR resulted in 76% of patients not being revascularised; and importantly there was no MACE in this group (142). A meta-analysis of the three major RCTs also concluded that FFR guidance in patients with NSTE-ACS led to a reduction in the rate of MI without any difference in death or all-cause mortality and target vessel revascularisation compared with CAG guided approach (143). In a study of 1,983 patients with ACS (n=533) and CCS (n=1450), FFR led to a similarly high percentage of reclassification of treatment in both groups (ACS=38% vs CCS=39%). In the ACS patients, FFR guidance led to a change from revascularization in 70% and medical therapy in 30% to revascularisation in 38% and medical therapy in 62%. There was no

significant difference in MACE (8.0% vs 11.6%; p=0.20) or symptoms (92.3% vs 94.8% angina free; p=0.25) between the reclassified (FFR discordant with CAG) vs the non-reclassified patients (FFR concordant with CAG) groups. FFR-guided deferral to medical therapy in the ACS group was as safe as in the CCS group (MACE 8% vs 8.5%; revascularization 3.8% vs 5.9%; and freedom from angina 93.6% vs 90.2%). Worse outcomes were observed in the six percent of patients in whom FFR was disregarded (144). In a study of 1596 patients of which 301 had ACS (n=449 lesions), deferral of the non-culprit lesion based upon FFR resulted in a MACE 3.8% (ACS) VS 1.6% (CCS), mainly driven by ischaemia-driven revascularisation (2.8% vs 1.1%)(145). Two systematic reviews comparing available data on FFR guidance confirmed this difference, with no significant difference in mortality (146)(147). ESC guidelines propose that FFR can be used in ACS (class IIb) to assist decision-making in non-culprit lesions whose severity is moderate (148), which contrasts with the recommendation to use FFR in intermediate stenoses in CCS (Class I) for patients with multi-vessel disease (MVD)(class IIa) (149).

1.16 Does FFR have a role in STEMI?

FFR has no role in selecting the 'culprit' vessel of ST elevation MI (STEMI), but it may be useful in assessing ‘bystander’ stenoses. In COMPLETE, a study of 4041 STEMI patients with MVD, in which visual, rather than FFR guidance, was used, complete revascularization reduced the risk of cardiovascular deaths, MI and repeat revascularizations from 16.9% to 8.7% at 36 months when compared with a culprit-only-PCI approach; the benefit largely driven by a reduction in unplanned revascularization (80). In COMPARE-ACUTE (885 patients), DANAMI-3-PRIMULTI (627 patients) and FLOWER-MI (1171 patients), an FFR-guided approach, rather than a purely visual one, was used. In COMPARE-ACUTE, the primary outcome (composite of all-cause mortality, non-fatal MI, revascularisations and cerebrovascular events) occurred in 20% of the culprit-only revascularization group vs 8% in the FFR-guided complete revascularization group (P<0.001) (78). In DANAMI-3-PRIMULTI, the equivalent figures were 22% and 13%, respectively (p=0.004) (79). The risk of future cardiovascular events was mainly driven by a 69% reduction in repeat revascularizations. In contrast, in FLOWER-MI, an FFR-guided approach in the non-culprit lesions in STEMI was not found to be superior to an angiography-guided strategy at reducing the risk of death, MI or repeat revascularization at one year. PCI of non-culprit lesions was performed in 66% of patients with the FFR-guided strategy and in 97% with the angiography-guided strategy. The

primary outcome occurred in 5.5% (32 of 586 patients) in the FFR-guided approach vs 4.2% (24 of 577 patients) in the angiographic-guided group (p=0.31) (150). The difference was driven by a non-significant 77% higher risk of MI in patients assigned to the FFR group (18 patients in the FFR guided group vs 10 patients in the angiographic guided group). The study was powered to detect a 37% lower risk of the primary composite outcome, but ultimately generated a wide confidence interval (hazard ratio, 1.32; 95% CI 0.78 to 2.23). In addition, intervention on the non-culprit lesions was encouraged to be performed at index presentation, rather than as a staged procedure. A larger RCT specifically addressing timing may be required. A parallel line of enquiry may be necessary to interrogate the hypothesis that conventional physiological assessment of bystander lesions may be of lesser importance than identifying vulnerable plaques.

1.17 Validity, safety and feasibility of FFR

Despite robust evidence supporting the use of FFR, in practice its use remains low, at less than 10% of PCIs, and in an even smaller proportion of diagnostic angiograms; the majority being in patients with CCS (151)(152). This low uptake in the acute setting may reflect the time and cost associated with deploying a pressure wire. Also, if stenting a borderline lesion is likely to be straightforward, it may be felt that a 'quick fix' is reasonable. This is not, however, a position supported by the evidence. Other reasons for under-use may include complex anatomy, such as tortuosity, angulation, calcification and diffuse disease, in which manipulating a pressure wire might be hazardous. There may also be a lack of awareness of the accumulating evidence in ACS confounded by pressure on the operator to make a swift therapeutic decision in response to situational factors.

1.18 Is FFR reliable in acute MI?

The validity of FFR in an acute MI has been questioned due to the possibility that blunted acute microvascular dysfunction might limit maximal hyperaemia, reducing the apparent physiological significance of a lesion (153). Does this mean that the FFR is 'incorrect'? The value is indeed correct and reflects the current physiology, however the concern is that lesion significance may increase as the microvasculature recovers. Whilst this may be the case in a culprit lesion, in a study of 101 patients undergoing PCI for an acute MI (75 STEMI and 26 NSTEMI), the FFR measurements in 112 non-culprit vessels did not change between the acute

presentation and follow up (154). De Bruyne et al also demonstrated in a study of 57 patients who had recovered from an MI with an average six days previously, FFR measurement of <0.75 is accurate at distinguishing between patients with or without reversible flow when compare with single photon emission scintigraphy (SPECT), with a sensitivity of 82% and specificity of 87%. It also showed that the relationship between the microvascular resistance in the infarcted territory and the viable myocardium was inversely proportioned (155). Similar results were found in a separate study of 38 patients (156). In another study of 1,983 patients, which investigated the use of FFR to guide treatment in ACS in comparison to patients with stable CAD undergoing angiography, the reclassification of the treatment decision in the FFR-guided group for ACS patients was 38%, which was as high as the proportion in the non-ACS group, with no difference in MACE at one year follow-up. It also showed that FFR-guided revascularisation strategy, including deferral to medical treatment, is safe in patients with ACS. Most importantly, the study demonstrated that, in those whose FFR measurements were disregarded, there was a worse outcome when compared with FFR-guided strategy (144). Although these studies were not all large, randomised control trials, they still effectively exhibit the positive impact of integrating FFR in patients with ACS and that it is feasible and indeed safe clinically in order to deliver the appropriate treatment to each individual patient.

1.19 Problems with FFR

FFR is based upon the assumption that the relationship between flow and pressure in healthy and diseased arteries is predictable from a linear relationship. This is not strictly true, because energy is lost through friction in the diseased artery (viscous losses), and there is acceleration of flow at the outlet, producing a curvilinear relationship, which may particularly affect the acute patient (157). The second assumption is that the microvascular resistance in diseased and non-diseased artery is the same. This is not always the case, so it is essential to obtain maximal hyperaemia in order to keep microvascular resistance minimal; although this is not always achievable due to other confounding factors, such as clinical factors, procedural complications and extrinsic influence such as caffeine intake as well as endothelial dysfunction; all of which can affect the accuracy of FFR measurement (158)(159)(160). In patients with left ventricular (LV) dysfunction, the LV end diastolic pressure (LVEDP) is high and this can also affect the FFR calculation. Leonardi et al studied 20 coronary arteries in 17 patients to examine the effect of LVEDP upon FFR and demonstrated that FFR is higher in patients with higher LVEDPs, especially in stenoses with FFR of <0.80. This means that in patients with heart failure, FFR

must be interpreted with caution (161). Uncertainty of the measurement itself is also a feature as described by Petraco et al. The reproducibility of a therapeutic decision is >95% when the FFR is outside the 0.75-0.85 range, but only about 50% when it is close to 0.80 (162). This is of importance in the angiographic 'borderline' lesion, for which the FFR is often also borderline which means that a repeat FFR calculation could change the initial decision for revascularisation. Furthermore, there are no randomised data studying the use of FFR in left main stem (LMS) disease and it is therefore unclear whether the same threshold of 0.80 applies to these patients given the larger area of subtended myocardium. LMS disease also often involves the bifurcation and further disease downstream which interferes with the interpretation of proximal FFR measurements. There are also technical difficulties measuring ostial lesions. Measurement of FFR in serial lesions is also difficult due to the relationship of each narrowing to flow and pressure. De Bruyne et al stated that FFR measurement in each stenosis is possible with the addition of lesion wedge pressure to equation (163). This is not practical in clinical practice, but a steady pull-back can be performed instead to identify any discrete step-up during maximal hyperaemia. Lastly, microvascular dysfunction which can be present in patients with diabetes mellitus (DM), hypertension (HTN), left ventricular hypertrophy (LVH) and cardiomyopathy may also affect FFR assessment. It leads to over-estimation of the FFR and should always be taken into consideration when performing measurement. Measured FFR, therefore, has not achieved routine use in the management of ACS.

1.20 Decision-making in the CCL and in the MDT meeting

Selecting the right treatment for patients with ACS in which the culprit lesion may be uncertain can be difficult, especially in MVD. Adjunct tools such as FFR are useful but are under-used. Moreover, in the CCL, other factors such as time pressure and caseload burden can play an important role and could influence an interventionist to conform to a familiar revascularisation strategy such as PCI. In oncology, the role of the multi-disciplinary team (MDT) meeting has been established; a number of observational studies demonstrating the benefit of MDT to facilitate optimum decision making to deliver a uniform and co-ordinated treatment plan (164)(165)(166). In coronary revascularisation, the British Cardiovascular Intervention Society (BCIS) has reported that this approach is inconsistent and variably implemented, with only 9.5% of complex cases, such as those with MVD, being discussed; and 23.8% of cases that were initially felt unsuitable for PCI being discussed (167). The ESC and AHA guidelines now

recommend a Heart Team MDT approach (with class 1c evidence) to guide the revascularisation strategy of patients with CAD to ensure that best practice is consistently followed (90). This followed reports from the National Confidential Enquiry into Patients Outcome and Death (NCEPOD) in first time isolated CABG, NICE guidelines on ACS, and ESC data on the variability of utilisation of CABG and PCI in different countries (168)(169)(9). Cases discussed should include those with triple vessel disease especially in those with obstruction in the left main stem (LMS) or the proximal segment of its left anterior descending (LAD) branch; particularly cases in which CABG may provide prognostic advantage (170)(171). Heart team MDT meetings should be attended by a general cardiologist, an interventional cardiologist, a cardiac surgeon, and other health care professionals including specialty registrars, junior doctors and nurses. However, it is pragmatically impossible to discuss all patients with NSTE-ACS, because they are so numerous. Nevertheless, for complex cases, it has a useful function to provide guidance, uniformity and best evidence-based treatment to aid revascularisation strategy for individual patients. If such cases are to be discussed, knowing the FFR values in major diseased vessels is an advantage.

1.21 Computed, or 'virtual' FFR (vFFR)

Virtual FFR (vFFR) is a novel technique to compute FFR non-invasively, without the passage of wire, by using computational fluid dynamics (CFD) and a mathematical formula. CFD is a specialised area of mathematics and fluid mechanics that utilizes specific algorithms and equation to simulate and analyse the flow of fluid. It has been used and adapted in many technologies including safety systems, vehicles and aeronautical designs. Solving the Navier-Stokes and conservation equations of mass, momentum and energy is the fundamental key to CFD analyses.

1.21.1 Imaging based FFR

vFFR can be derived from CTCA (FFR-CT). The DISCOVER-FLOW study, in which 159 vessels were studied, was the first major trial using this concept, and demonstrated a high accuracy to diagnose and exclude ischaemic provoking lesions (FFR >0.80 or ≤0.80) (109). Following that, Heartflow®, with an improved version of FFR-CT, diagnostic accuracy of 81%, updated software and refined segmenting and automation tools, obtained U.S Food and Drug administration (FDA) approval and became the first computational tool for blood flow measurement to be applied in clinical practice (110). FFR-CT is now recommended by NICE

as an adjunct to CTCA in diagnosing angina in stable patients with symptoms of chest pain suspected to be of cardiac origin with the aim to reduce the number of unnecessary referrals for angiography (172). It is limited, however, by the same factors as CTCA such as calcifications and cardiac arrythmias. It is not appropriate in ACS, as demonstrated in RAPID CTCA (106).

1.21.2 CAG based FFR and how they differ

vFFR can also be modelled from CAG and, to date, several groups have done so. Each has differing methodology. These include Quantitative Flow Ratio (QFR, Medis, Leiden, Netherlands and Pulse Medical Imaging, China) and Cardiovascular Angiographic Analysis System for Vessel FFR (CAAS-vFFR, Pie medical, Maastricht, Netherlands) based upon 3D quantitative coronary angiography (QCA); FFR_{angio} (Cathworks Ltd, Kfar-Saba, Israel) based upon 3D functional CA mapping with coronary rapid flow analysis; and Virtual Functional Assessment Index (vFAI) and Simplified Model of FFR Calculation (FFR_{sim}) based upon 3D QCA and CFD. QFR, FFR_{angio} and CAAS-vFFR are commercially available, with QFR being the first to obtain CE-mark and FDA approval. VIRTUheart™ is the Sheffield University system, currently confined to research use. It applies 3D pseudo-transient CFD based on the Navies-Stokes equation to perform analysis (173). Whilst the first QFR study was based upon CFD, subsequent studies used faster computation using an algorithm incorporating coefficients from flow data to calculate pressure drops (174). QFR employs a 3D reconstruction and a QCA algorithm without reconstructing side branches (175). The software assumes that the coronary pressure remains constant in a normal coronary artery and that the distal coronary flow velocity is similar to the proximal. Based upon the mean hyperaemic velocities, the software can provide three different computation values: fixed-QFR (fQFR) based upon a flow velocity of 0.35 m/s; contrast-QFR (cQFR) applies Thrombolysis in Myocardial Infarction (TIMI) frame counting analysis at non-hyperaemic conditions; and adenosine-QFR (aQFR) uses intravenous administration of adenosine. FFR_{angio} provides colour-coded vFFR by applying a rapid analysis of flow based upon Poiseuille's law. A 3D coronary tree is generated and applies epipolar ray tracing with mathematical calculation. The software identifies the stenosis automatically by systematic segment, branch and junctional analysis. A user correction is required to correct any axis displacements contributed by movement. The resistance of the coronary arterial network in each segment is estimated by the vessel diameter and length, each vessel flow being based upon the overall impact of the resistance, and the FFR_{angio} value being

calculated as the contribution of each narrowing to the total resistance and flow (176). CAAS-vFFR uses 3D model reconstruction, the vFFR being computed by measuring the pressure drop across a lesion by using simpler physical laws of viscous resistance and separation loss effects in coronary flow behaviour (177). In addition, it incorporates patient's specific aortic pressure with the assumption that the velocity of proximal coronary artery is preserved, along with the maximum hyperaemic blood flow previously determined from clinical data. Table 2 summarizes the various CAG-based FFR techniques.

Coronary angiography based FFR technique					
CAG-based FFR technique	**Company**	**Mathematical solution**	**Angiographic projections required**	**CAG angle requirement**	**Key scientific reference**
vFFR (VIRTUheart^{TM})	University of Sheffield	3D pseudotransient CFD based on Navier-Stokes equation	≥ 2 orthogonal images for each vessel	≥ 30 degrees	Morris et al (173) Gosling et al (178)
QFR	Medis, Leiden, Netherlands and Pulse Medical Imaging, China	Analytical equations based on laws of Bernoulli and Poiseuille. Empiric flow velocity (fQFR), TIMI frame counting-derived contrast velocity at baseline (cQFR) and under hyperaemia (aQFR)	≥ 2 orthogonal images for each vessel	≥ 25 degrees	Tu et al (179) Westra et al (180) Xu et al (181) Stahli et al (182)
FFR_{angio}	Cathworks Ltd, Kfar-Saba, Israel	Simple analytical equations based on Bernoulli and Poiseuille	≥ 2 orthogonal images for each vessel	≥ 30 degrees	Pellicano et al (183) Fearon et al (176) Omori et al (184)
CAAS-vFFR	Pie medical, Maastricht, The Netherlands	Simple analytical equations based on Bernoulli and Poiseuille	≥ 2 orthogonal images for each vessel	≥ 30 degrees	Masdjedi et al (185)
caFFR (FLASH FFR)	Rainmed Ltd, Suzhou, China	CFD based on post angiography TIMI frame counting of flow velocity	≥ 2 orthogonal images for each vessel	≥ 30 degrees	Li et al (186)
vFAI	Pie medical, Maastricht, The Netherlands	3D-QCA and steady state CFD	≥ 2 orthogonal images for each vessel	≥ 30 degrees	Papafaklis et al (187)

Table 3 – Table summarising CAG-based FFR software. CAG, Coronary angiography; 3D, Three dimensional; QCA, Quantitative coronary angiography; VIRTUheart^{TM}, (University of Sheffield); QFR, Quantitative flow ratio (Medis, Leiden, Netherlands and Pulse Medical Imaging, China); FFRangio, 3D functional coronary angiography mapping with coronary flow analysis (Cathworks Ltd, Kfar-Saba, Israel); CAAS-vFFR, Cardiovascular Angiographic Analysis System (Pie medical, Maastricht, The Netherlands);caFFR, Coronary-angiography based FFR (FLASH software); vFAI, Virtual Functional Assessment Index. (Reproduced with permission from Haley et al)

1.21.3 Evidence for virtual coronary physiology in ACS?

The VIRTUheart^{TM} system was firstly used in VIRTU1 study in which 19 patients undergoing elective PCI had their measured FFR (mFFR) and vFFR values compared. There were 35 FFR measurements, ischaemic inducing lesions stented and underwent a repeat angiography and the FFR repeated. The software demonstrated an accuracy of 97%, sensitivity of 86%, and a positive and negative predicted value of 100% and 97% respectively to distinguish haemodynamically significant lesions (FFR <0.80). The study also showed that vFFR reliably calculated mFFR to within ± 0.06. Tu et al, using the QFR (quantitative flow ratio) system based upon 3D quantitative coronary angiography (QCA), conducted vFFR in 73 cases with accuracy of 88.3% in different flow models (Medis, Leiden, the Netherlands) (179). In the FAVOR China II study of 308 patients, QFR accuracy was approximately 90% (188). Another model is the virtual functional assessment index (vFAI), developed by Papafaklis et al; the average of the computed pressure ratio between distal and proximal vessel over a steady state CFD analysis (187). Whilst this technique can produce a rapid result with similar accuracy to the QFR technique, it omits the factor of coronary microvascular resistance (CMV). Pellicano et al also validated a technique developed by Cathworks Ltd (FFR_{angio}) in a study of 184 patients with CAD. There was high concordance between FFR_{angio} and invasive FFR, with a calculation time of minutes (183). Additionally, in a study of 301 patients with CAD, FFR_{angio} was shown to have a high diagnostic accuracy (87%) in lesions with FFR range of 0.75-0.85 which reflects the type of stenosis usually interrogated in real world setting (176). A sub-analysis from that study also demonstrated that FFR_{angio} is more accurate than other established FFR indices like instantaneous wave-free ratio (IFR) and diastolic hyperaemia-free ratio (DFR) (189). Most recently, a CE marked vFFR technique derived from 3D-QCA, the Cardiovascular Angiographic Analysis System for vessel FFR (CAAS-vFFR) was shown to demonstrate a linear correlation with mFFR in lesions with FFR ≤0.80 with a low inter-observer variability (190). Table 3 summarizes the accuracy of these systems vs FFR in patients with ACS.

Summary of angiography based virtual FFR trials involving patients with ACS															
Study	**Software**	**Methods**	**Average processing time (min)**	**Total no of patients**	**ACS**	**NSTEMI**	**UA**	**Accuracy (%)**	**Correlation with FFR**	**BA agreement with FFR**	**Sen (%)**	**Spec (%)**	**PPV (%)**	**NPV (%)**	**AUC (%)**
Li et al (186)	caFFR	Prospective, multi-centre, single-arm study	4.5 ± 1.5	328	275	-	275	95.7	0.89	± 0.10	90.4	98.6	97.2	95	0.98
Trobs et al (191)	FFR_{angio}	Retrospective analysis	n/a	73	22	4	18	90	0.85	± 0.13	79	94	85	92	0.93
Fearon et al (176)	FFR_{angio}	Prospective, multi-centre, observational study	2.7	382	126	28	98	93	0.80	± 0.14	93.5	91.2	89	94	0.94
Omori et al (184)	FFR_{angio}	Prospective, single-centre, single-arm study	9.6 ± 3.4	50	22	7	15	92.3	0.83	± 0.14	92.4	92.4	n/a	n/a	0.92
Pellicano et al (183)	FFR_{angio}	Prospective, multi-centre, observational study	n/a	199	55	21	34	93	0.88	± 0.10	88	95	n/a	n/a	0.80
Masdjedi et al (185)	CAAS-vFFR	Retrospective, single-centre, observational study	n/a	100	40	26	14	n/a	0.89	± 0.07	97	74	85	89	0.93
Tu et al (179)	QFR	Prospective observational study	<10	68	9	-	9	88	0.81	± 0.11	78	93	82	91	0.93
Xu et al (188)	QFR	Prospective, multi-centre, observational study	n/a	308	66	-	66	92.7	0.86	± 0.10	94.6	91.7	85.5	97.1	0.96
Westra et al (192)	QFR	Prospective, observational investigator-initiated study	5	272	6	*	*	86.8	0.83	± 0.12	86.5	86.9	76.4	93	0.92
Stahli et al (182)	QFR	Single centre, retrospective study	n/a	436	123	18	105	93.4	0.82	± 0.08	75	97.8	89.3	94.2	0.86
Papafaklis et al (187)	vFAI	Retrospective Study	n/a	120	41	8	33	90.4	0.78	± 0.18	86.2	87.8	79.9	93.8	91.9

Table 4 - Table summarising the evidence of vFFR in ACS. *not specified; n/a, not reported; BA, Bland-Altman; Sen, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating curve. caFFR, Coronary-angiography based FFR (FLASH software); FFRangio, 3D functional coronary angiography mapping with coronary flow analysis (Cathworks Ltd, Kfar-Saba, Israel); CAAS-vFFR, Cardiovascular Angiographic Analysis System (Pie medical, Maastricht, The Netherlands); QFR, Quantitative flow ratio (Medis, Leiden, Netherlands and Pulse Medical Imaging, China); vFAI, Virtual Functional Assessment Index. (Reproduced with permission from Haley et al).

1.22 VIRTUheart™

1.22.1 What is it, and how does it work?

The Sheffield University team developed VIRTUheart™, a software suite which uses CFD technology and computes vFFR based upon invasive coronary angiography. It has now been refined with the introduction of personalised boundary conditions and other parameters to increase its diagnostic accuracy to 90% for detecting ischaemic lesions (FFR ≤0.80), with computing time of less than four minutes (193)(178)(173). This is the vFFR system which I used in my project.

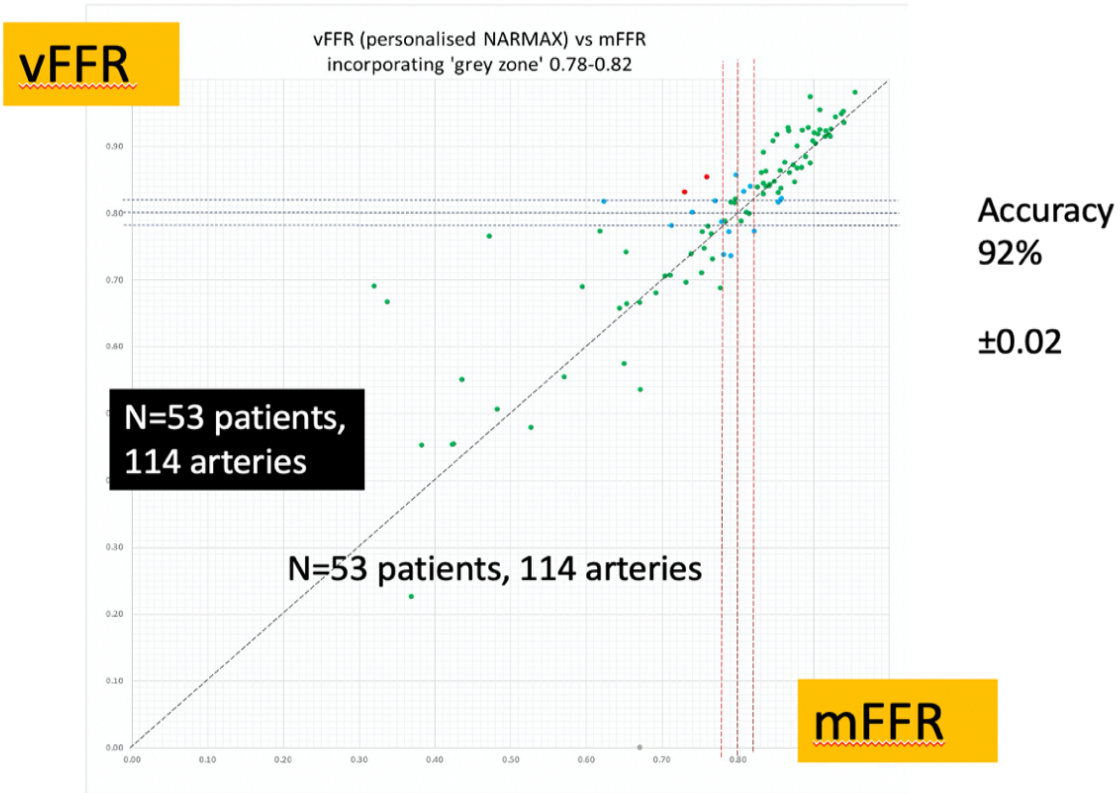


Figure 14- Accuracy of virtual FFR (vFFR) vs measured FFR (mFFR) from the VIRTU1 study (173).

1.22.2 Boundary conditions

Boundary conditions are the physical conditions at the inlet, outlet and arterial walls. They can significantly affect the vFFR calculations and the accuracy of the software. The boundaries are determined before a CFD analysis can be completed. For coronary artery modelling, proximal aortic pressure is deemed as the inlet boundary whilst the vessel wall is constructed as a rigid

wall. The distal boundary (outlet) is set by the coronary microvascular resistance (CMVR) (see figure 12). CMVR is more difficult to be determined as it varies in individuals, especially those who have co-morbidities such as heart failure, diabetes, LVH, and hypertension. A generic resistance value of (8.721e^9 Pa/m^3s^{-1}) can be used to run the simulation; a figure which was obtained from the early study. More recently, the team has shown that personalized distal boundary conditions could improve the accuracy of vFFR calculation. This includes inputting clinical details such as patient's weight, heart rate, diastolic blood pressure (dBP) and frailty score along with two specific scoring of the coronary arteries; The Myocardial Jeopardy Index (MJI) and Duke Jeopardy (DJ) scores. The DJ score is a combination assessment of stenosis severity and location which includes six arteries: the left anterior descending artery (LAD), proximal first perforator, first diagonal (D1), circumflex (Cx), dominant obtuse marginal branch (OM), and posterior descending artery (PDA). Wherever a lesion that is ≥ 75% is proximal to one of these arteries, two points are given. The score is the total of all of the arteries scored. The MJI estimates the amount of myocardium at risk based on the location of the coronary artery stenosis. All vessels are scored. Each vessel is assigned a score of zero to three depending on how large the artery is and the overall distance from base to apex of the heart, with three being the largest area supplied and so forth. The score is then calculated as the ratio of each stenosis divided by the overall score given to all the arteries in total.

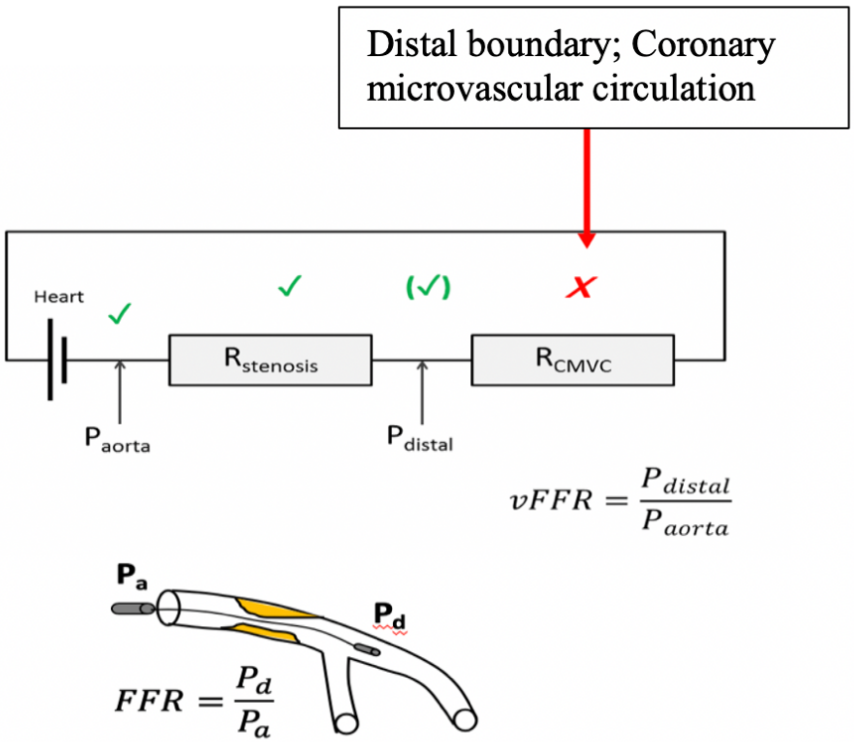


Figure 15 - Coronary microvascular circulation (CMVC) influence on the distal boundary and vFFR result. Personal parameterisation of the distal boundary condition increases the accuracy of vFFR measurement.

1.22.3 VIRTUheart™: how to use it?

The first step in computing vFFR is acquiring a good quality CAG; good opacification, minimal magnification, no panning, minimal vessel overlaps, at least two clear orthogonal planes at least 30 degrees apart and a clear ECG trace to identify end-diastolic frames. No panning is crucial because any table movements could affect the segmentation and construction of the artery. A 3D reconstruction of the coronary anatomy can then be created offline once the arteries are segmented which are then discretised into a number of volumetric elements. Boundary conditions are then applied. The modelled system is then generated and processed through the CFD software to calculate the vFFR. The steps are summarised below and shown in greater detail in the Methods below.

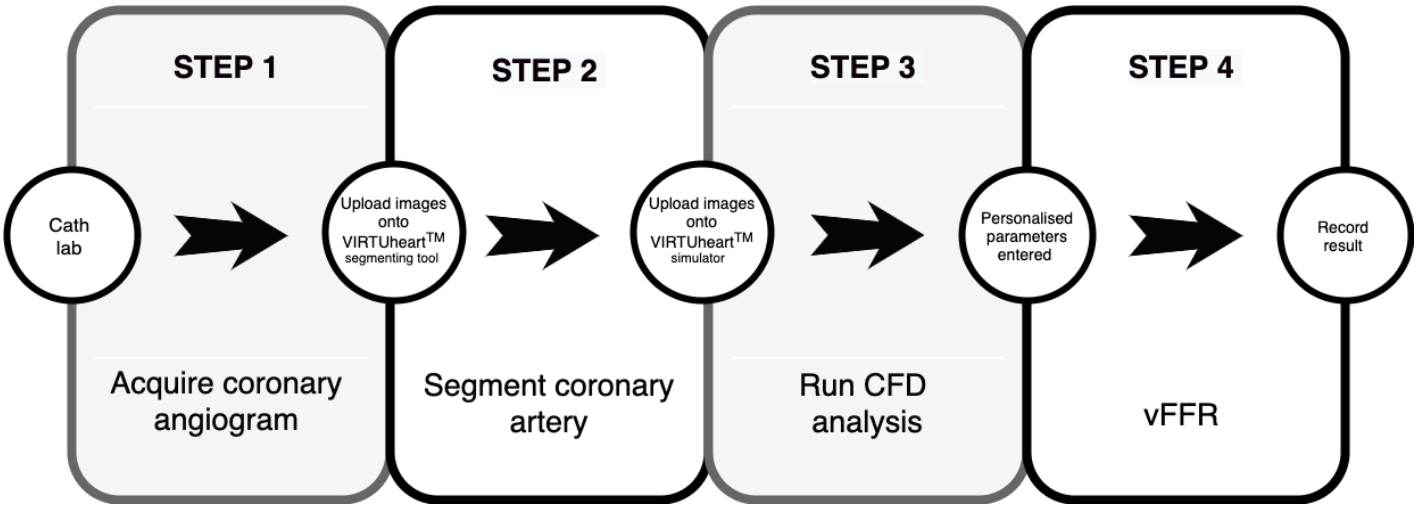


Figure 16 - Summary of steps for vFFR calculation using the VIRTUheart™ software. (Reproduced with permission from Haley et al).

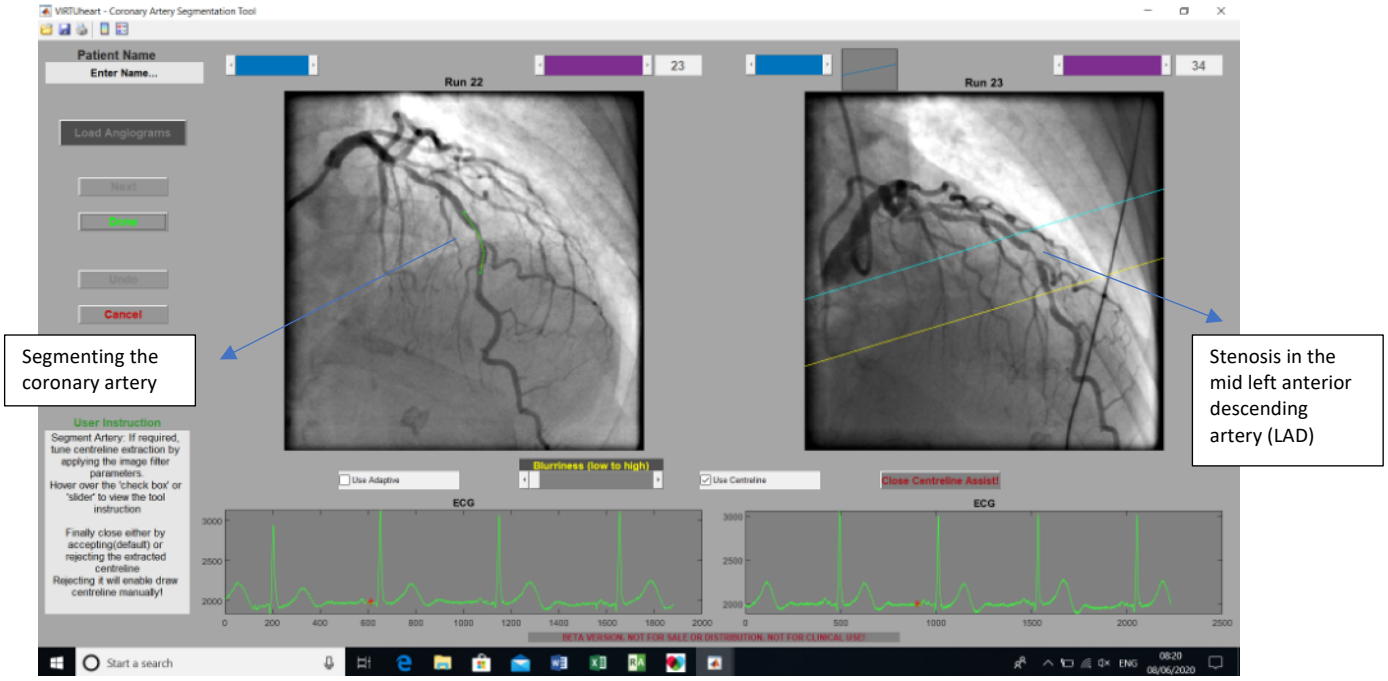


Figure 17 - Step 2. Segmenting the coronary artery using the coronary artery segmentation tool in the VIRTUheart™ software.

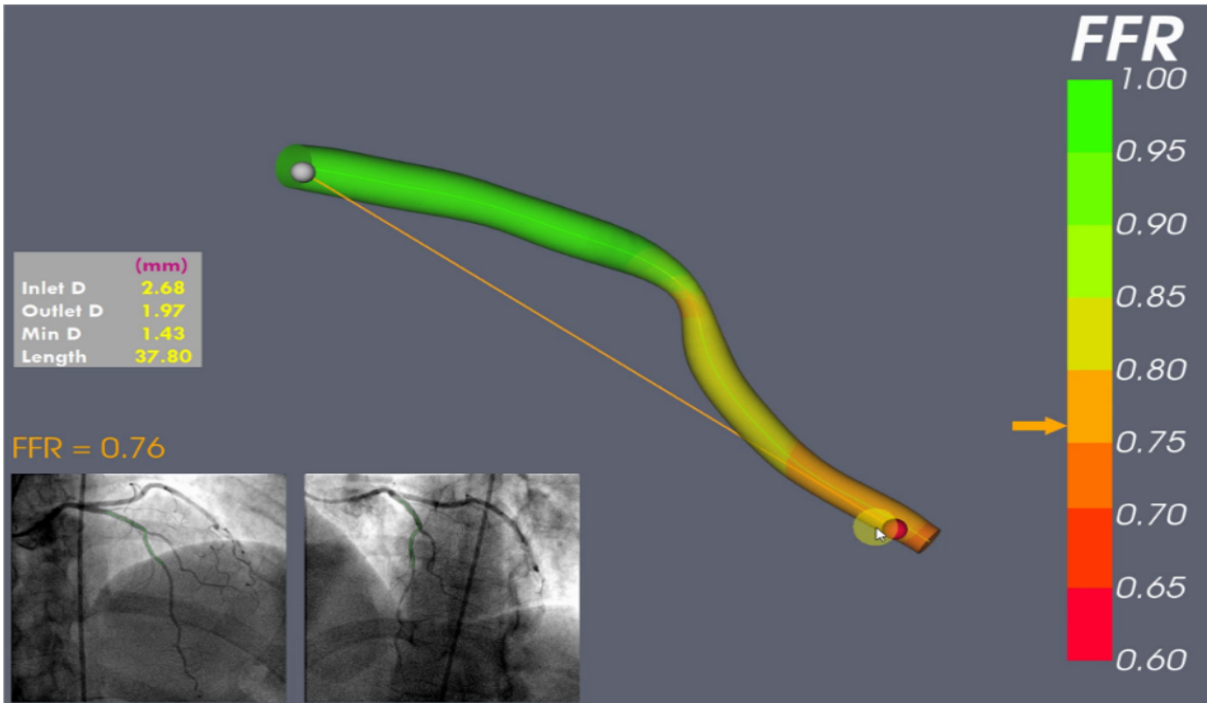


Figure 18 - Step 3. vFFR result post CFD simulation showing the measurement of 0.76.

1.23 Pros and cons of vFFR

vFFR is fast and could be made available for every angiographic procedure to guide decision making. Without the need for inserting a pressure guidewire, it could theoretically be used by non-interventional cardiologists before the decision to refer for intervention. It is efficient and does not require any pharmacologic hyperaemia. In addition, the 3-D model of the coronary arteries can assist the estimation of vessel dimensions and selection of stent size (183). There is also an option to provide virtual coronary intervention by placing virtual stents and ultimately predict anatomic and physiological outcomes prior to invasively intervening on any vessel (178). It has several limitations, however. Poor CAG images or overlapped segments can hamper the process. In addition, the distal outlet boundary condition is proximal to the CMV circulation, and a fundamental assumption of CMV function (maximal dilatation) is made to compute pressure from flow. But the degree of CMV response to hyperaemia varies from person to person, which is why personalisation of this parameter is so important in vFFR. VIRTUheart™ can be used with a standardised or personalised parameterisation (193). Work continues on ways to improve the estimation of the boundary conditions. Training is, however, essential, both for the CAG operator and the image processor. Lal et al showed that there is a substantial difference in vFFR modelling between trained and untrained operators due to errors in the 3-D vessel construction. Importantly, the study showed that expert vFFR processing can

lead to a change in the revascularisation decision in 37% cases (194). However, with some simple improvements in technique, the suitability of angiograms for modelling can be improved from about 50% to about 80% , based upon a study of 200 CAGs performed by trained and untrained operators (195). The trained operators followed the simple steps outlined in 1.21.3.

1.24 Next steps for VIRTUheart™

The feasibility and impact of using vFFR in the CCL in an acute setting is as yet untested, and was addressed in this study, VIRTU4-ACS.

1.25 Hypothesis and aims

The hypothesis for this study was that vFFR will change the management of patients with ACS in more than 10% of cases compared with traditional visual assessment of the CAG.

In this study I aimed to identify patients who have suffered ACS and were undergoing CAG at the Northern General Hospital (NGH), Sheffield. Standard CAG based upon the VIRTU4-ACS protocol were performed, the angiogram result was recorded, and the images downloaded onto the software to be processed for vFFRs. I recorded the initial treatment decision of the Cardiologist, based upon the CAG. The vFFR was revealed to the cardiologist, asking them how it *would* change their proposed management and the confidence in that original clinical decision. I also aimed to investigate the potential implications of such a change.

2. Methods

2.1. Study design

VIRTU4-ACS was a single cohort, prospective, observational study. It was a 'virtual' trial of angiogram vs vFFR. vFFR was not used to actually change patient management (the software was not yet approved by the MHRA) but was designed to determine its likely impact. The target sample size was 206 patients. The study was performed in the cardiac catheter laboratory (CCL) of Sheffield Teaching Hospitals at NGH immediately after the CAG was performed. I used the VIRTUheart™ software to calculate the vFFRs of diseased vessels in patients with NSTE-ACS undergoing CAG and recorded any changes in the treatment decision. The study design was based upon that of RIPCORD, which was a study of measured FFR vs angiogram-based management (135). The difference here was that the FFR was computed, not measured with a wire. As in RIPCORD, I investigated what difference the vFFR would make to the normal plan of management based upon the angiogram. The study was originally planned to be conducted from January 2020 to December 2021, but recruitment was extended to March 2022 due to the COVID-19 pandemic.

2.2. Ethics

This study was approved by a national ethics committee (IRAS 270127 / STH 20595 / REC 19/NW/0580*) (see appendix).* All patients recruited were dealt with face-to-face. They were given information leaflets and provided written, informed consent on arrival to hospital prior to undergoing CAG to allow enough time for questioning and consideration. They were also informed about the follow up phone at six months. VIRTU4-ACS was a virtual study and had no impact upon patient care. Permission was granted to allow patients' data to be anonymised and processed.

2.3. Power and sample size

Because this study design mimicked RIPCORD, the number of subjects required was similar. In that study, it was 200, and FFR disclosure resulted in a change in treatment between medical therapy, PCI or CABG in 26%. But this study investigated patients with ACS. In FAMOUS (also FFR in ACS), treatment changed in 22%. Allowing for a lower threshold of treatment with vFFR, 206 subjects were estimated to provide 85% power at 5% two-sided significance

to reject a change in treatment of 10% when the true rate is 17%; i.e. we would have needed to see 35 changes to reject the hypothesis that vFFR changed the decision in 10% or less. From the evidence cited above, it was estimated that a change in management would occur in 20% of patients, and we asserted that a change of <10% would not be deemed important. The number of patients required in this study was directed by p, the proportion of cases in which the decision is different after the intervention compared with before. The 95% confidence intervals for p are derived from the formula:

$$\hat{p} \pm 1.96 \sqrt{(\hat{p}(1-\hat{p})/n)}.$$

[where $\hat{p}$ is the proportion in a sample; in this case 0.20]

2.4. Patient selection

Adult (≥18 years) patients with ACS undergoing CAG at NGH were screened for the study with the aim to recruit 206 patients. Patients were excluded if they had a previous history of CABG, severe kidney disease (creatinine >180µmol/l), severe valve disease, intolerance to anti-platelet drugs, severe frailty or life-threatening co-morbidities and if they were unable to consent due to language barrier. Arteries with narrowing of more than 30%, or less than 90%, and a diameter of at least 2.25mm, were included. Patients with a normal CAG, a chronic total occlusion (CTO) as the only lesion, severe diffuse disease, left main stem or ostial disease were excluded from the study *(see SOP pathway in appendix).*

2.5. Standard operating procedure

Patients' clinical data, demographics, CAG result and the initial treatment were recorded on a standardized proforma. CAG was done either via radial or femoral approach. Post CAG, the cardiologists were asked to identify and grade the stenosis of any stentable or graftable arteries (≥ 2.25mm) which had >30% stenosis and stated their initial management plan of either PCI, CABG, OMT or MDT referral. The arteries were then modelled *in silico* and the vFFR was calculated. A modelled vFFR <0.80 in a vessel was taken as an indication for (virtual) revascularisation. The result was shown to the cardiologist and any change in decision was recorded. Their confidence level of the initial decision made on a scale of 1-10, and any changes post vFFR were also logged. Most interview with the cardiologists were done face to face on the same day post vFFR calculation. When there has been a delay in processing the vFFRs, they were contacted via email using the questionnaire in the same format in order to

maintain standard. A Heart Team MDT study meeting was separately convened, involving a general cardiologist, an interventional cardiologist and a cardiac surgeon to record their decisions in order to introduce a second level of consistency in the decision-making. Ten percent of my cases were checked by a colleague for external validation. In addition, for internal validation, I re-processed 10% of the cases in random order. The primary outcome for this study was the proportion of cases with a treatment decision change after vFFR calculation. At six months, a follow up telephone call was conducted to collect secondary outcomes to examine the potential for change in clinical outcomes, the CCL time and key aspects of health economics such as length of hospital stay, waiting time and other events or complications. Clinical frailty using the Rockwood Score and quality of life using the (EQ-5D-5L) questionnaire were completed for patients at baseline and repeated at six months follow up to assess for any change. Figure 17 summarizes the recruitment workflow and standard operating procedure.

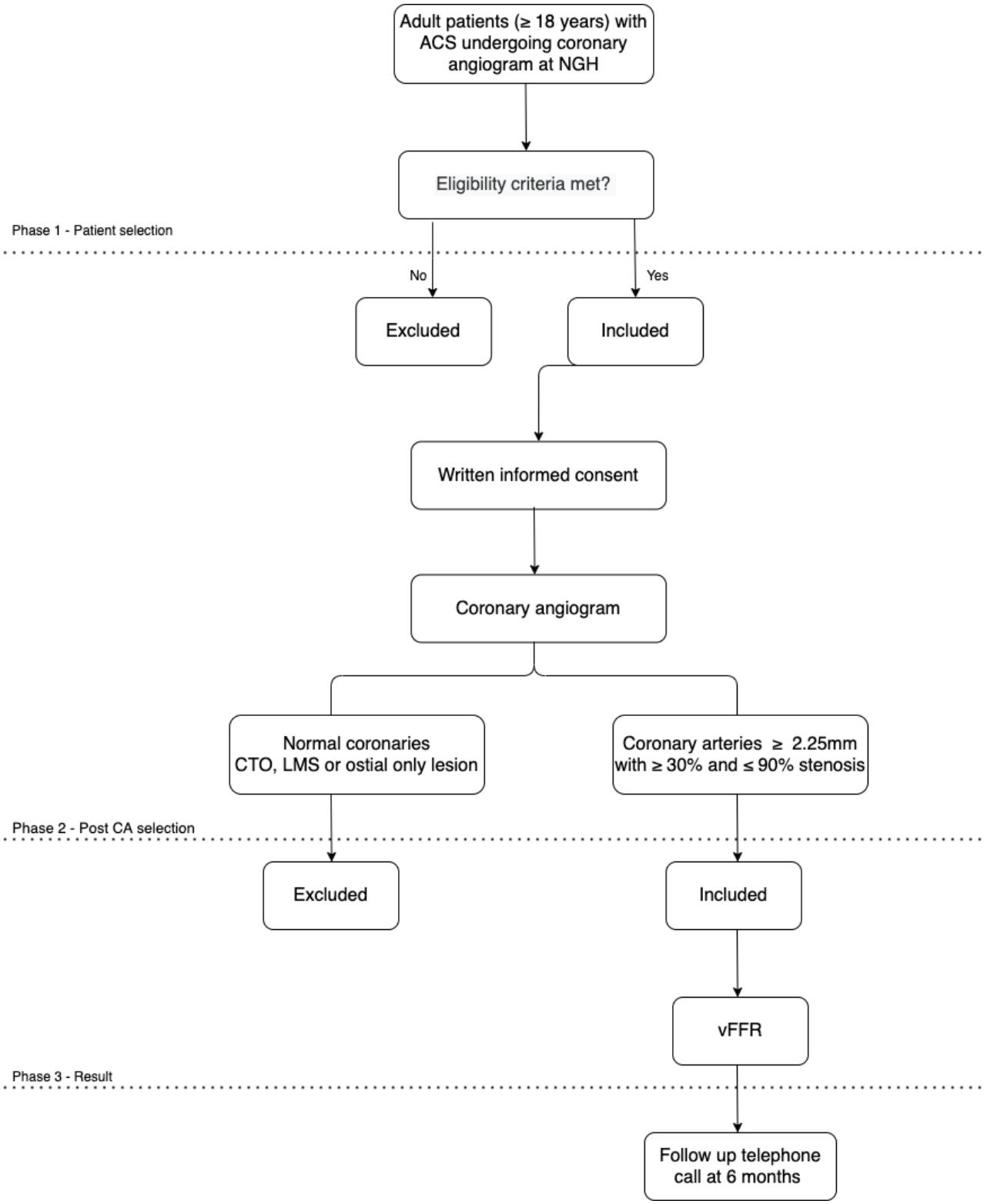


Figure 19 - VIRTU4-ACS recruitment workflow

2.5.1. Clinical data

ECG changes (ischaemic or non-ischaemic), peak troponin rise (<5 fold of the upper limit of the normal range, >5 but < 10-fold of the upper limit of the normal range, or > 10 times above the normal range), weight, height, heart rate (HR), body mass index (BMI) and creatinine level were recorded for all participants. Past medical history including diabetes (DM), atrial fibrillation or flutter (AF), previous strokes or transient ischaemic attacks (TIA), peripheral vascular disease (PVD), previous PCI, previous MI, treated hypertension (HTN), treated high cholesterol, and smoking status prior to admission were recorded. Left ventricular (LV) function was documented when the data was available. Treatments with LMWH, DAPT, anticoagulant, statin, beta-blockers, calcium channel blockers, nitrate or other additional anti anginal therapy were also noted.

2.5.2. Clinical scores

Clinical risk scores were recorded at baseline, including the Global Registry of Acute Coronary Events (GRACE) score for six-month prediction of mortality from admission, Killip score (quantification of severity of heart failure and prediction of 30-day mortality in NSTEMI), the Rockwood scale for clinical frailty, the Canadian Cardiovascular Society (CCS) angina classification, the New York Heart Failure Association (NYHA), and the EQ-5D-5L for health-related quality of life (see appendix). The EQ-5D-5L was also repeated at six months follow-up.

2.6. Modelling protocol

The CAG was recorded using a standardized protocol optimal for modelling purposes. For the left coronary artery, six positions are required encompassing postero-anterior (PA) caudal, right anterior oblique (RAO) caudal, RAO cranial, PA cranial, left anterior oblique (LAO) cranial and LAO caudal whilst the right coronary artery requires an LAO, LAO cranial, PA cranial and an RAO angle to ensure that two orthogonal planes of 30 degree apart were obtained in order to model a selected artery *(see appendix for CAG).* In both, images were selected with minimal vessel overlap, no or minimal magnification to ensure the images are acquired in one full screen, with no panning of the arteries. The injection of the contrast was firm to achieve a good opacification of the coronary arteries with acquisition of at least three cardiac cycles in order to attain a suitable end diastolic frame for coronary artery segmentation.

For an appreciation of the best angiographic views for different arterial segments, see figures 18-20).

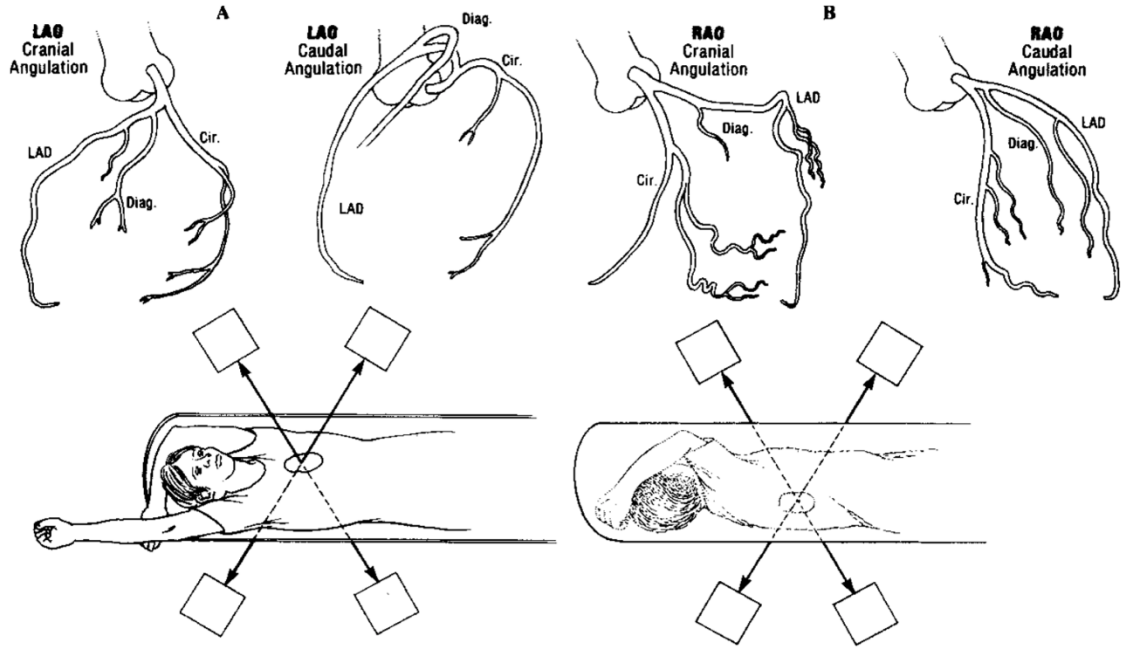


Figure 20 - Coronary angiography projection views of LAO cranial, LAO caudal, RAO cranial and RAO caudal of the coronary artery. (Illustration from http://semanticscholar.org).

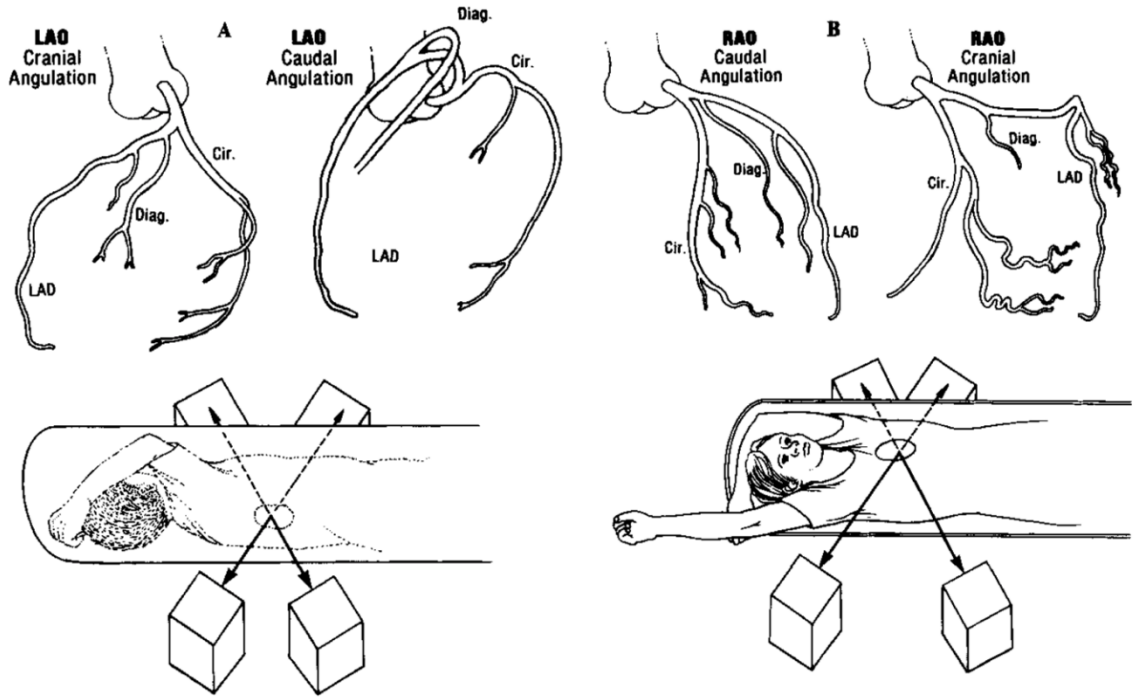


Figure 21 - Coronary angiography projection views of LAO cranial, LAO caudal, RAO caudal and RAO cranial of the coronary artery.(Illustration from http://semanticscholar.org).

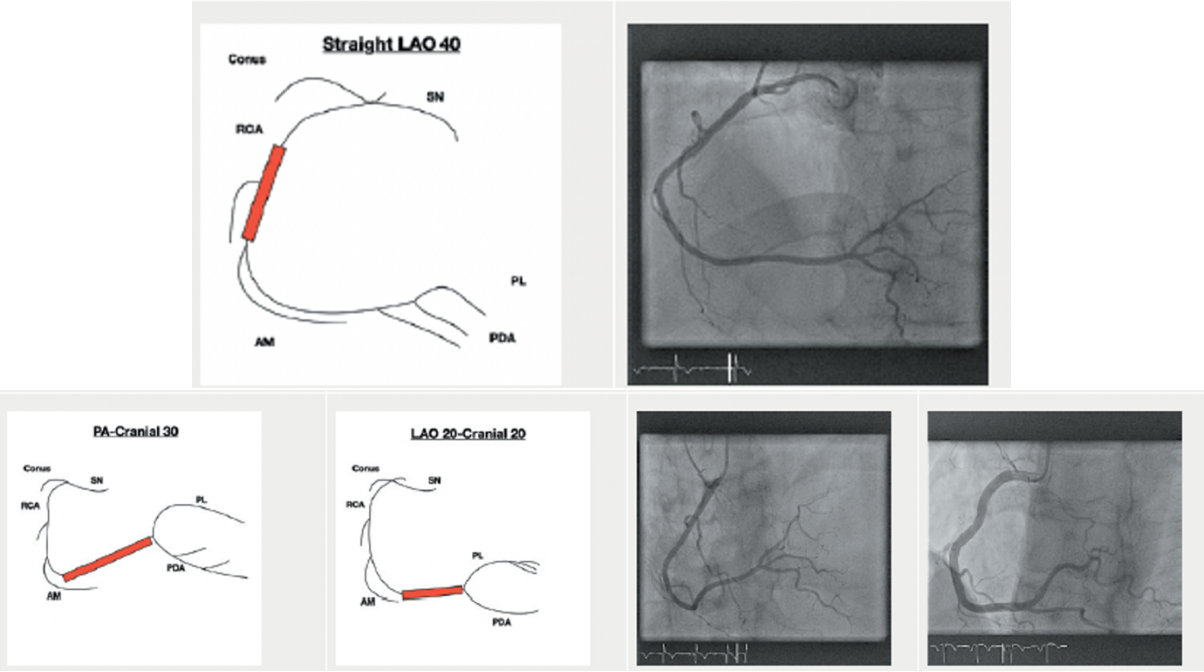


Figure 22 - Coronary angiography projection views of LAO, PA cranial and LAO cranial of the right coronary artery.

2.6.1. Data protection and handling of the CAG images

CAG images were automatically transferred into the NGH radiology server (IMPAX), as a standard hospital policy. I transferred and uploaded all of the images post CAG into another secured database, (XNAT), created by the scientific computing department at Sheffield University especially for clinical studies like VIRTU-4, which specifically require storage and access to imaging and physiology data. All patients had a unique study identifier identification and were anonymized. From XNAT, I was able to download the CAG images into an encrypted laptop to process in the VIRTUheart^{TM} software on site. Some cases were processed securely off-site only when there was a delay in the image transfer between the servers due to internal error. All data were used lawfully complying with the Data Protection Act 2018. Only authorized users were given access to the database to maintain quality control and protected data analysis. The storage of the anonymized database conforms to the standard research governance and will be stored for up to 15 years.

2.6.2. VIRTUheart™ workflow for vFFR calculation

VIRTUheart™ vFFR calculation can be summarized as having three phases. The first is to acquire suitable angiographic images for modelling as described above. Second, the coronary artery of interest is segmented using the segmenting tool on the software. Two images which are at least 30 degree apart and ideally at end diastolic frame are selected for this process. Here, the catheter size is entered, two reference point identifying the same spot on each image is marked, centreline is drawn, and the vessel outline is traced. Manual correction is used to smoothen and perfect the outlining. The cumulative effect of all these steps will generate the 3D construction of the segmented artery which are then saved. The saved 3D mesh is uploaded onto the CFD simulator afterwards for vFFR processing. The detailed step-by-step segmentation is demonstrated below (figure 21-29).

Figure 23 - Step 1. Two images of the LAD (>30 degrees apart) are selected at end diastole.

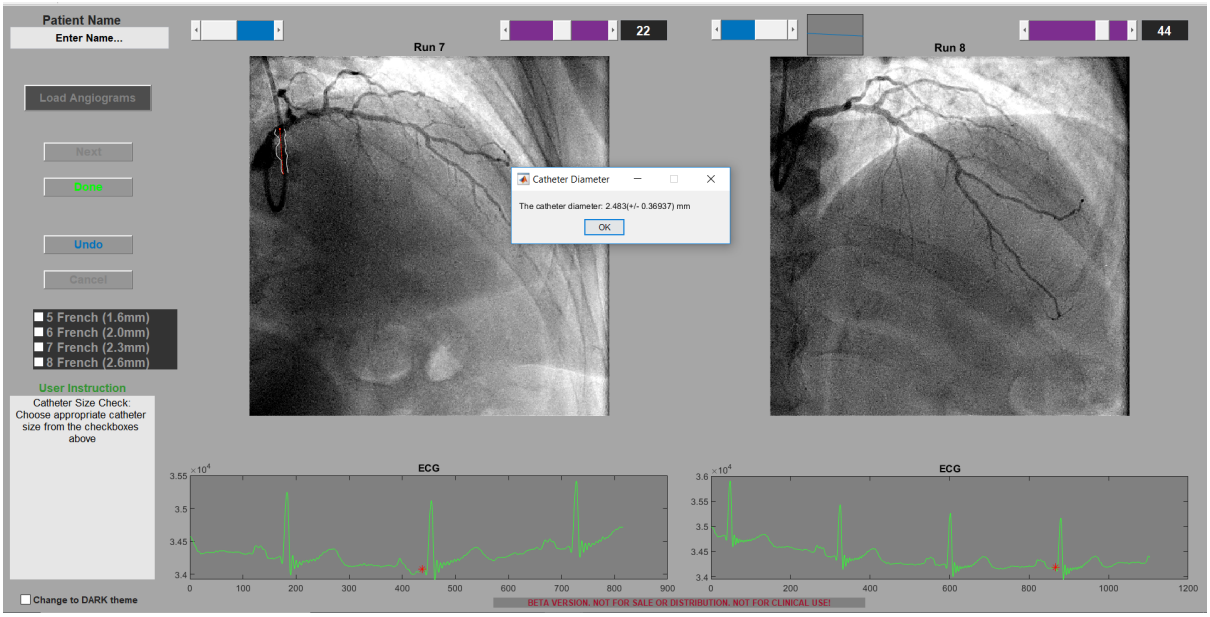


Figure 24 - Step 2. Two points are placed along the catheter to determine the diameter of the catheter.

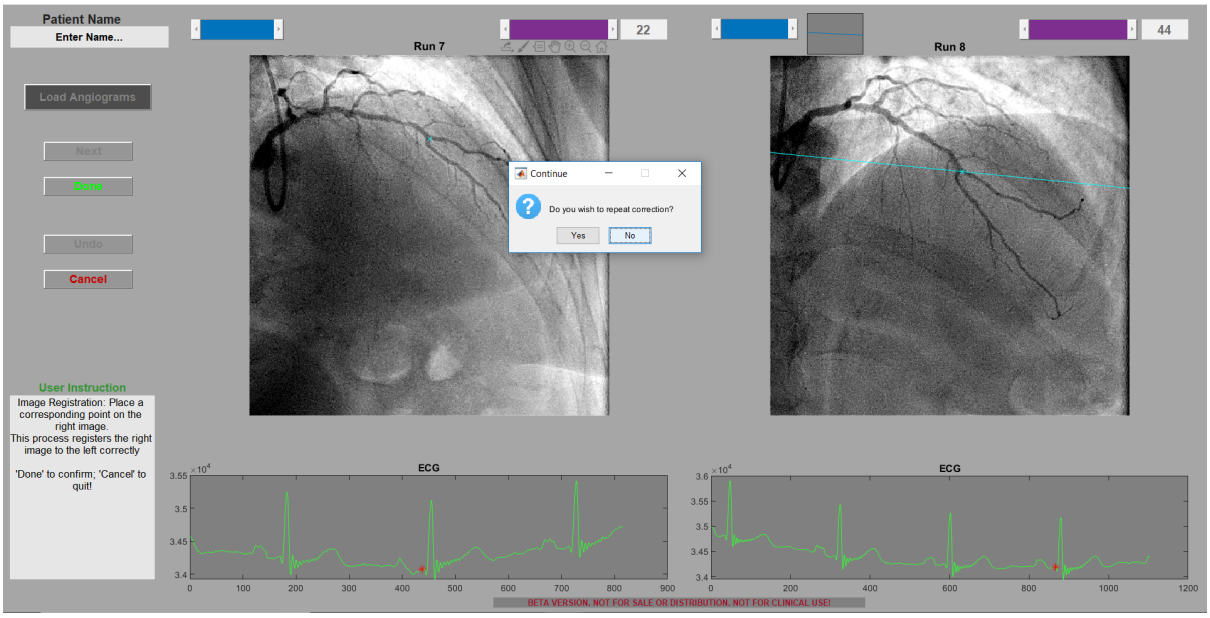


Figure 25 - Step 3. Two similar points are placed on both images as reference.

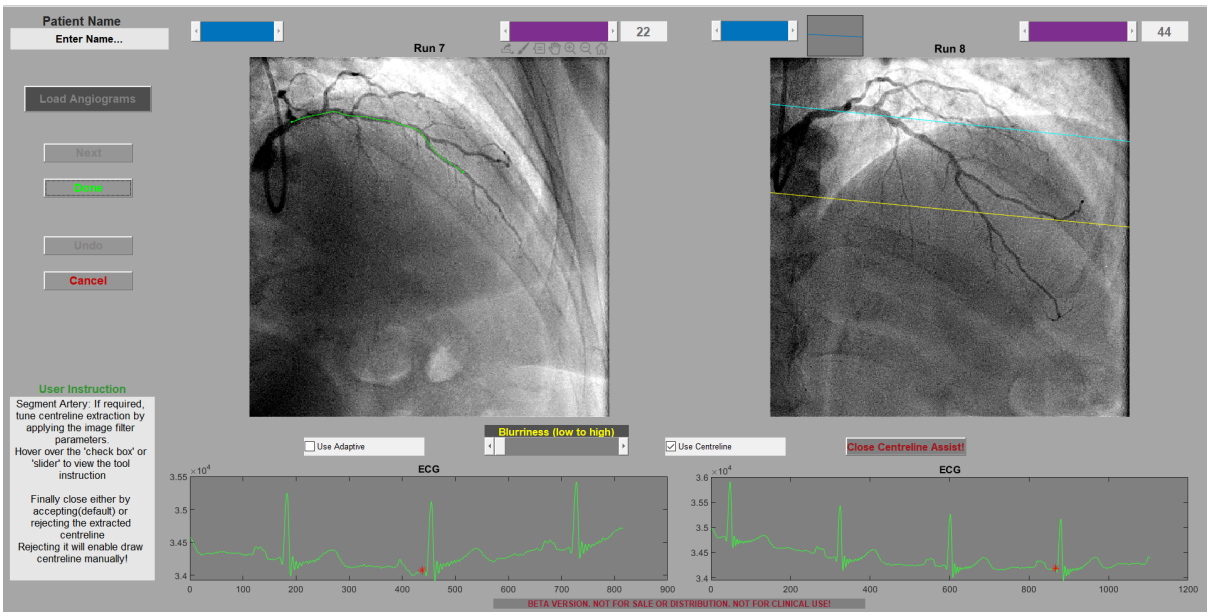


Figure 26 - Step 4. Centreline is drawn in the left image along the artery.

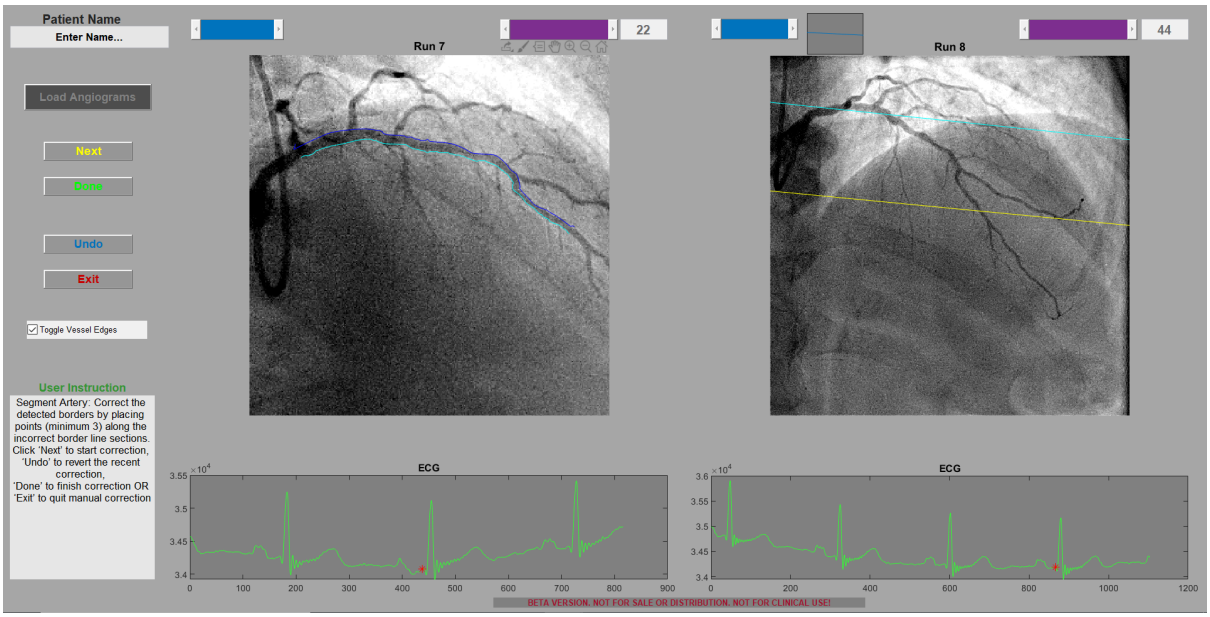


Figure 27 - Step 5. The edges of the artery are traced and manually corrected.

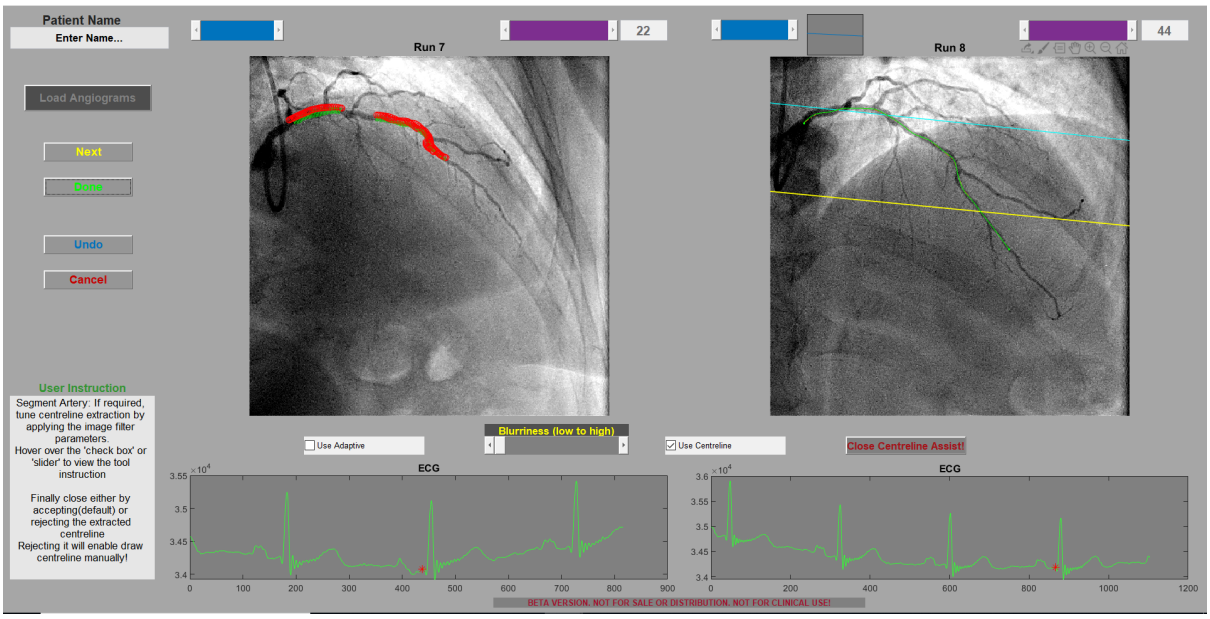


Figure 28- Step 6. Similar steps are repeated on the right image with the centreline in the right image placed before the blue and beyond the yellow epipolar lines.

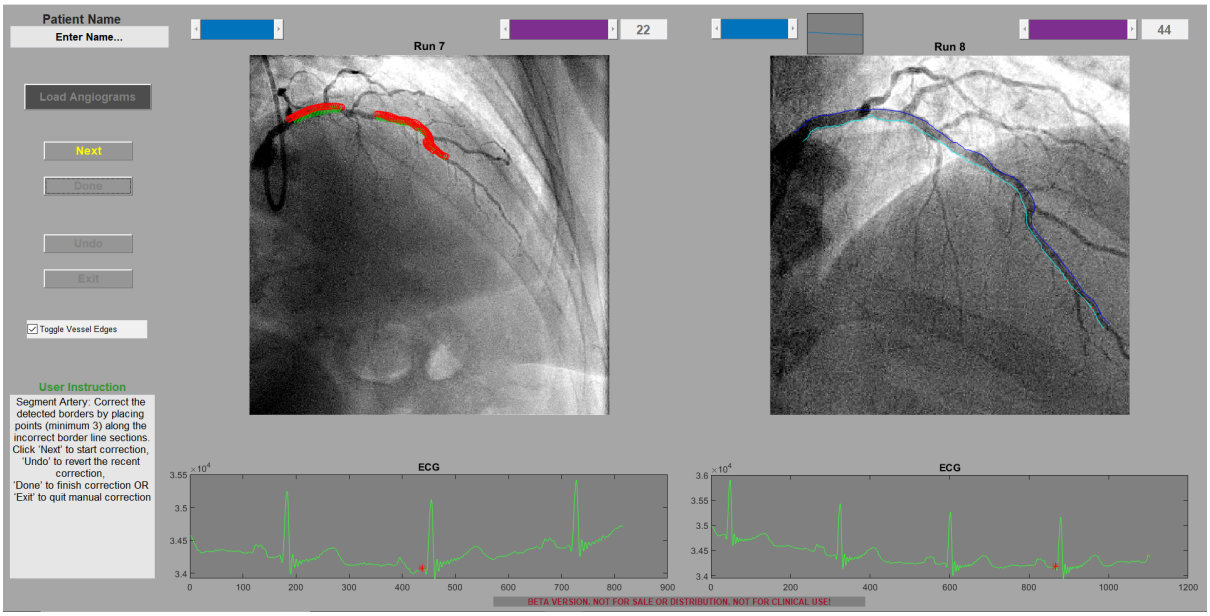


Figure 29 - Step 7. The artery is traced and corrected manually on the right image.

Figure 30 - Step 8. The segmented arteries from the images are ready to be constructed into a 3D model.

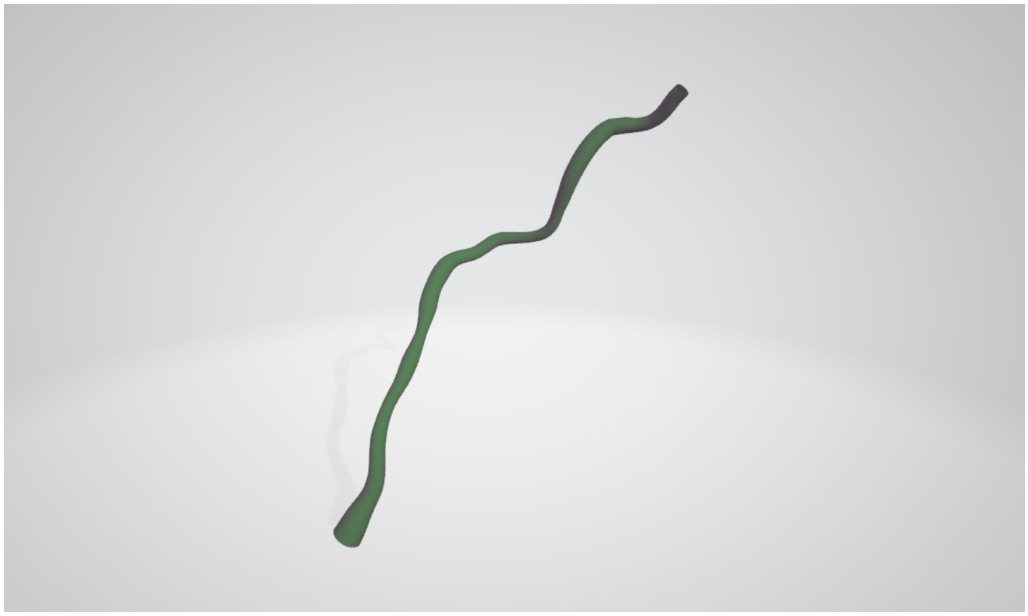


Figure 31 - Step 9. The generated 3D reconstruction of the LAD.

Third, the reconstructed 3D segment is uploaded into the CFD software to calculate the vFFR. In this section a standardised myocardial resistance ($8.721e^{9}$) or a personalised parameter generated by incorporating the patient's weight, heart rate, diastolic blood pressure, MJI, DJ, and frailty score can be used. The latter is used to improve the accuracy of the result obtained. This process is shown below (figure 30-32).

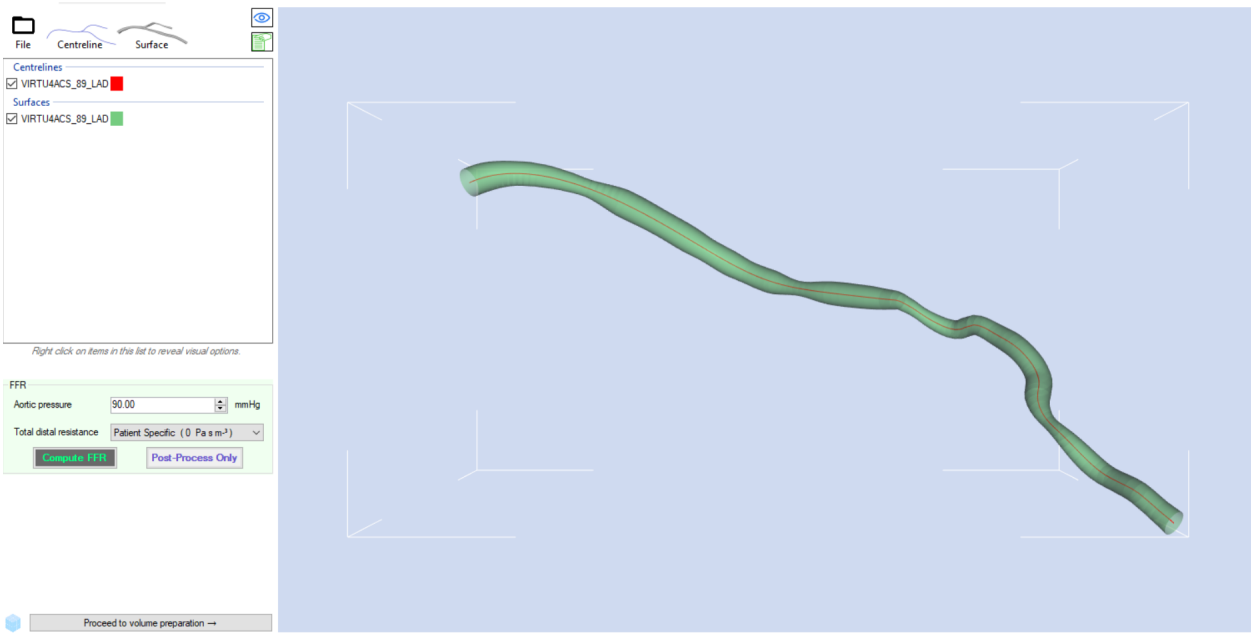


Figure 32- Step 10. The 3D model of the LAD is loaded onto the CFD simulation software.

Figure 33 - Step 9. Personalized parameter is entered to improve accuracy of vFFR calculation.

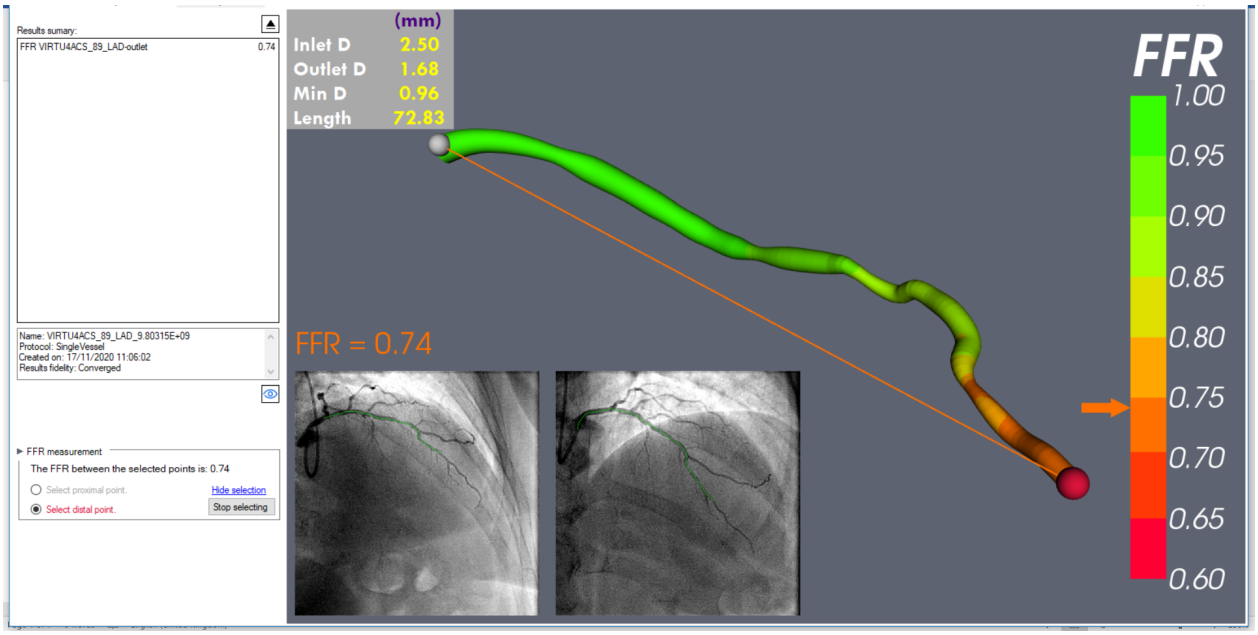


Figure 34 - Step 9. Post CFD analysis. vFFR of the LAD of 0.74.

A unique feature of the VIRTUheart™ software is the flexibility to calculate vFFR between any chosen points along the artery after the model has been generated. To do this, the user can mark the proximal and distal point in between which the vFFR is required, as demonstrated below. Moreover, from the pre-calculated inlet, outlet and minimum diameter of the vessel a percentage stenosis can be generated as well. These aspects are shown below (figure 33 and 34).

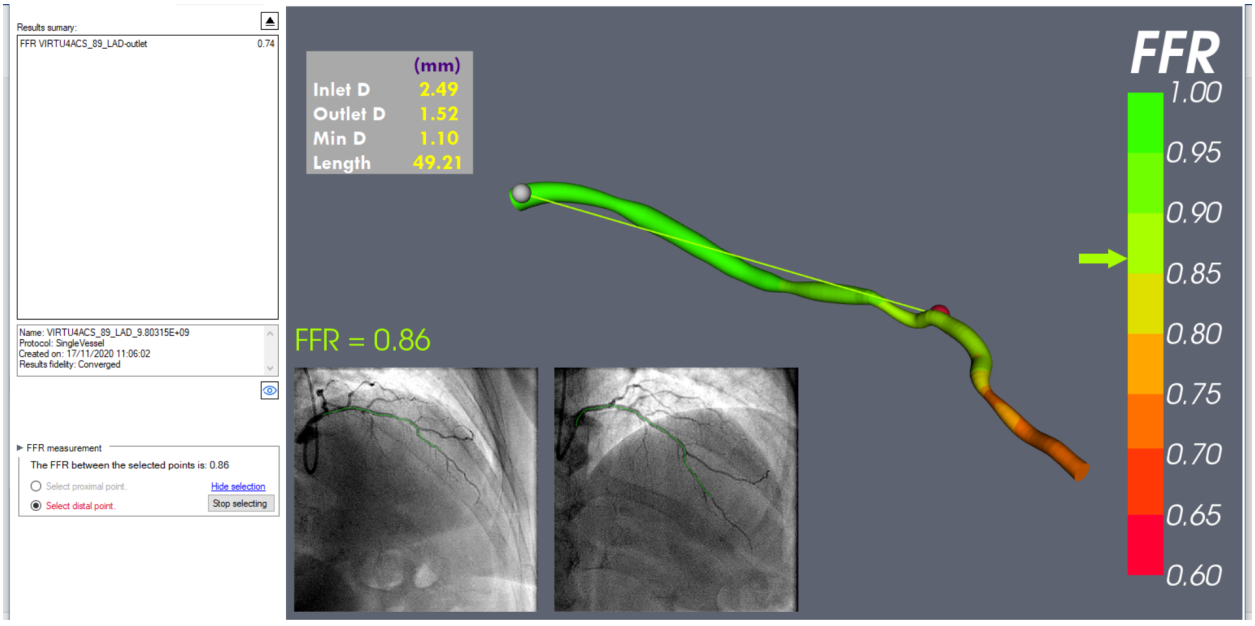


Figure 35 - Example 1. Post CFD analysis. VFFR of the chosen LAD segment of 0.86.

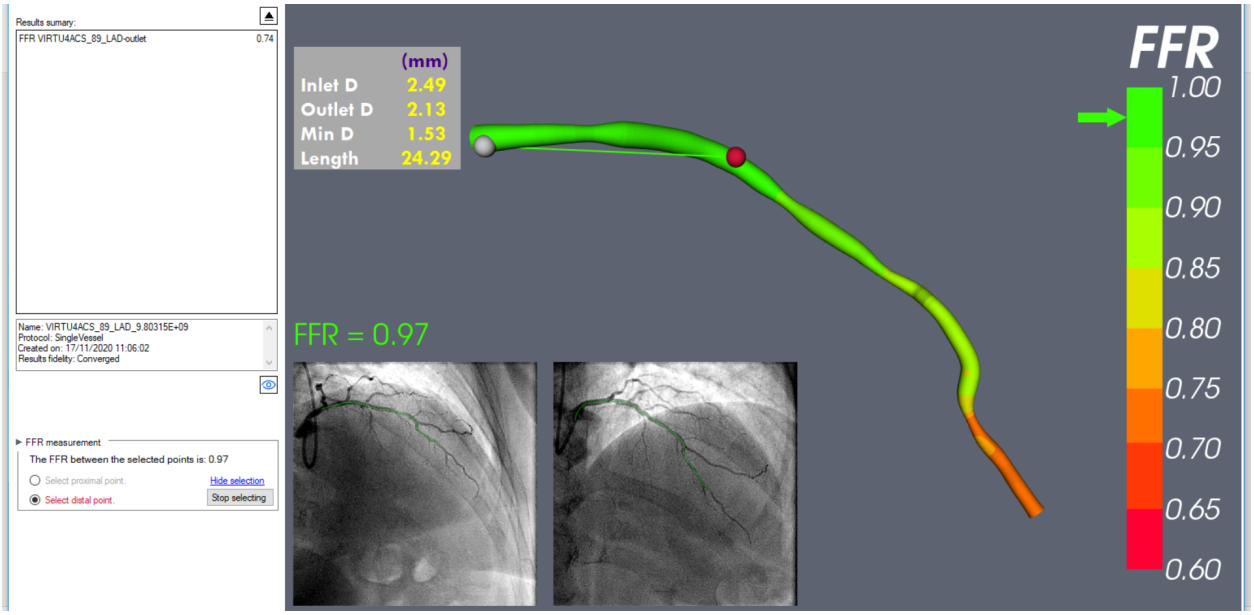


Figure 36 - Example 2. Post CFD analysis. vFFR of the proximal segment of the LAD of 0.97.

2.7. Treatment plans

A standardized proforma was used to record treatment plans pre- and post-vFFR calculation *(see appendix for VIRTU4-ACS treatment proforma).* This was divided into five options comprising of OMT, PCI, FFR guided PCI, referral for CABG and discussion in an MDT. Details regarding any of the treatments could be added in the space provided. The CAG quality was recorded as good, average or poor. The confidence level for the treatment decision or the revascularisation strategy was recorded using a scale of one to ten. Similarly, any change in the treatment plan and the confidence level after vFFR calculation was recorded.

2.8. MDT meeting protocol

Study MDTs were convened to provide consistency of decision making. They comprised of a general cardiologist, an interventional cardiologist and a cardiac surgeon. Cases were re-discussed, and their initial management plan treatment were recorded. This was conducted in sessions of about 10 cases at a time. The MDT members were presented with the patient's clinical data, ECG and the CAG images. Each specialist was also asked to grade the CAG quality (good, average or poor) and the percentage of stenosis of any diseased arteries (>30% stenosis) from visual estimation. They then decide on the initial treatment plan of either OMT, PCI, FFR, CABG or if more information is required. Their confidence level from a scale of 1-

10 for the initial decision made was also recorded (*see workflow below)*. They were then presented with the vFFR result of the processed arteries. Similar questions were asked after revealing the vFFR result and any change towards treatment plan and confidence level were recorded once again. When general consensus was not reached, a majority decision was used instead. When there was equipoise in the decision between the three specialists, the interventionist's decision was used as the primary choice.

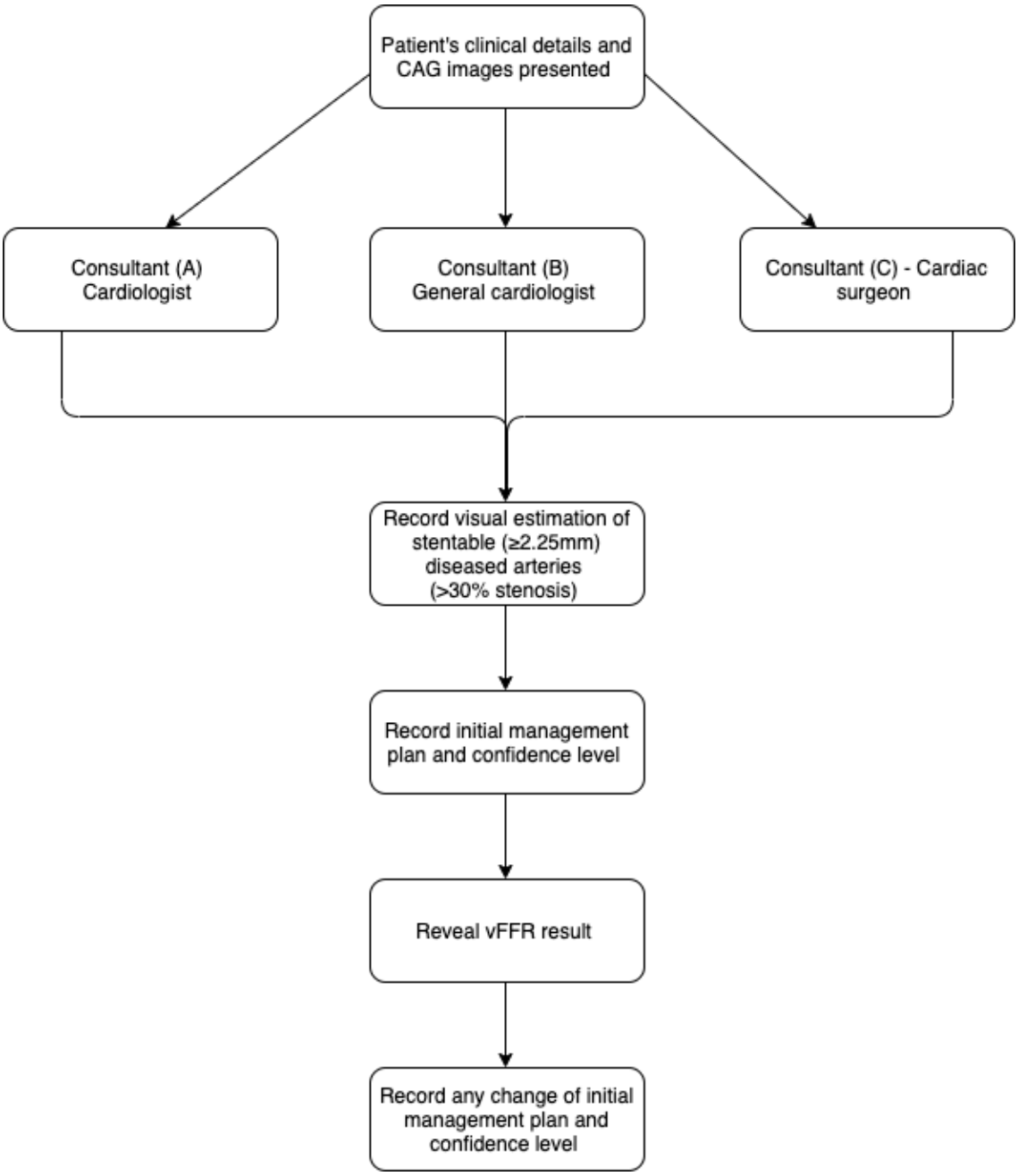


Figure 37 - MDT workflow**.**

2.9. Clinical outcomes

The primary endpoint was the number of patients in whom management changed. The secondary outcomes were MDT outcomes and clinical events at six months, ascertained with national statistics, hospital records and telephone follow-up. Relevant events included death, hospital admissions and repeat revascularisation, MI, angina, CVA, major bleed, or any important related events. Three different sub-analyses were be performed; first, to examine any change in the confidence level of the treatment decision; second, the inter- and intra-observer variability at calculating the vFFRs; and third, a validation between vFFR and mFFR.

2.9.1. Inter and intra-observer variability

To assess variability, inter- and intra-observer analysis were performed for vFFR calculation and the treatment decision. The vFFR measurements were re-calculated by me as well as by a secondary research investigator in 10% of the cases. A Pearson correlation coefficient (PCC) and Bland Altman (BA) analysis were used.

2.9.2. Sub-analysis of vFFR against mFFR

In 10% of the cases, an offline vFFR validation study against mFFR was also performed. A PCC and BA analysis were used.

2.10. Statistics

The primary and secondary outcomes were compared using Fisher exact tests, X^2 and paired t-tests, as appropriate, with a P value <0.05 considered as significant. Continuous variables were presented as means and standard deviations or medians and quartile ranges, as appropriate. Categorical variables were presented in counts and percentages. Sub-analysis for inter, intra-observer and mFFR vs vFFR were compared using PCC and BA analysis.

2.11. Health economics

From the data collected, in this study, a further analysis will be performed to investigate the potential benefit of vFFR with regards to health economics. This analysis is beyond the scope of the present study, but the necessary data were collected. These included the clinical events listed above, augmented by length of hospital stay, the angiogram and PCI time, the vFFR

computing time, waiting times, the number of stents used, change in quality of life and most importantly, the documented changes that vFFR would have made. A collaboration with a health economist (Dr Thaison Tong) assisted in identifying the correct methodology.

3. Results

3.1. Patients: screening, enrolment, angiography and processing vFFRs

From August 2020 to September 2021, 292 patients were screened and recruited into the study. After CAG, a total of 208 were included in the study, whilst 84 patients were excluded based on the study protocol. The breakdown is shown below (table 4).

Cases excluded from the study

Reasons for exclusion	Number (n)	Percentage (%)
Normal coronaries or <30% diseased only	37	13
All or single lesion >90% including CTO	22	8
Ostial RCA and no other suitable lesions in the left coronary arteries	4	1
Severe LMS stenosis with no other suitable lesions	14	5
Lesion in a small artery (2.25mm) only	2	1
Poor images, difficult anatomy or overlapped vessels	5	2
Total	84	30

Table 5 - Summary of excluded cases.

All 208 patients had at least one artery processable for vFFR. A total of 335 vessels were successfully processed for vFFR. Twenty of 355 vessels (5.6%) failed to process due to the

lesions being too severe (>90%), or other technical errors. The former led to a 'non-convergence errors. See consort diagram below (figure 36).

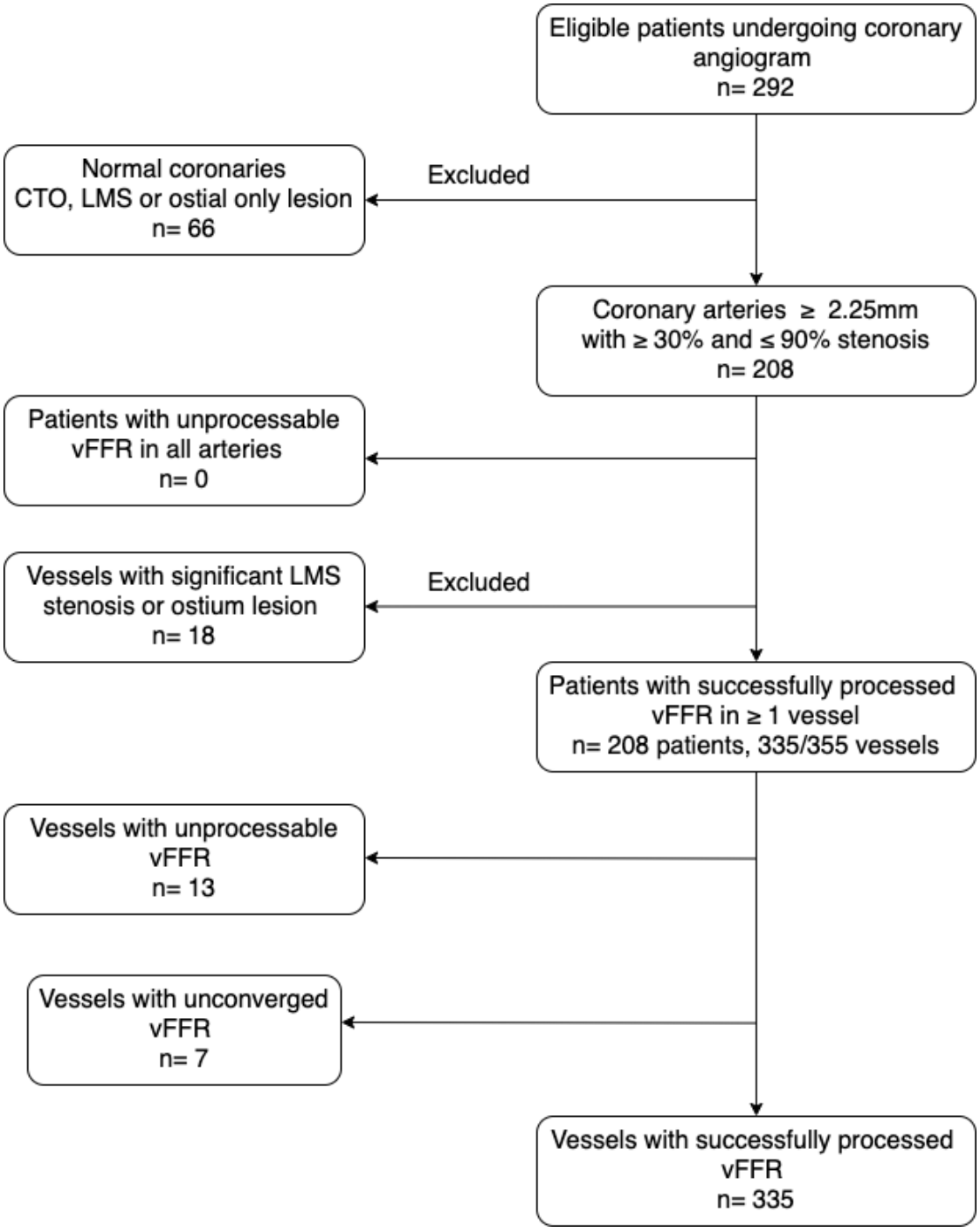


Figure 38 – Summary of the vFFR procedural outcomes.

3.2. Clinical characteristics (processed patients)

All patients who were recruited had their clinical characteristics and demographic recorded prior to undergoing CAG. Echocardiogram data was available in 35% (72 out of 208) patients. This is summarized below (table 5).

Baseline and clinical characteristics	**n=208**
Clinical	
Age	65±12
Male sex *n (%)*	150 (72)
Female *n (%)*	58 (28)
Heart rate b.p.m	68±11
ECG evidence of ischaemia at presentation *n (%)*	139 (67)
Peak troponin before the procedure	
Less 5 upper limit of normal or zero *n (%)*	27 (13)
More than 5 upper limit of normal *n (%)*	47 (23)
More than 10 upper limit of normal *n (%)*	134 (64)
*GRACE score for death or myocardial infarction at 6 months	108±25
Patients with GRACE score for death or myocardial infarction of >140 *n (%)*	20 (10)
Killip Score	
I	208
II	0
III	0
IV	0
Diabetes mellitus *n (%)*	54 (26)
History of atrial fibrillation or flutter *n (%)*	27 (13)
History of stroke or TIA *n (%)*	9 (4)
Previous myocardial infarction *n (%)*	36 (17)
Previous percutaneous intervention *n (%)*	39 (19)
History of treated hypertension *n (%)*	127 (61)
History of treated hypercholesterolaemia *n (%)*	126 (61)
History of smoking *n (%)*	
Current	68 (33)
Former (stopped > 3 months)	61 (29)
Never	79 (38)

Angina Canadian Cardiovascular Society (CCS) class at presentation *n (%)*	
I	148 (71)
II	55 (26)
III	5 (2)
IV	0
New York Heart Association (NYHA) functional class at presentation *n (%)*	
I	32 (15)
II	155 (75)
III	21 (10)
IV	0
Left ventricular function on echo at presentation *n (%)*	
Normal	38 (18)
Mildly impaired	16 (8)
Moderately impaired	13 (6)
Severely impaired	6 (3)
Frailty (Rockwood score) class classification *n (%)*	
Well (1-3)	173 (83)
Vulnerable (4-5)	35 (17)
Frail (6-9)	0
Health-related quality of life EQ-5DL score	67±14
Medication at procedure *n (%)*	
Aspirin	208 (100)
P2Y12 inhibitor	208 (100)
Ticagrelor or Prasugrel	196 (94)
Clopidogrel	12 (6)
Warfarin	1 (<1)
Direct oral anticoagulant (DOAC)	11 (5)
Statin	207 (100)
Beta-blocker	200 (96)
Calcium channel blocker	28 (13)
Isosorbide mononitrate	25 (12)
Nicorandil	0
Intravenous nitrate	208 (100)
Low molecular weight heparin	208 (100)

Table 6 – Patients' demographics and clinical characteristics. Mean ± SD or median (inter-quartile range) for normal and non-normally distributed data, respectively. (*Estimates mortality rate from admission up to 6 months for patients with ACS; [low risk (1-108) probability of death in hospital <1%, intermediate (109-140) probability of death in hospital 1-3%, high (141-372) probability of death in hospital >3%]).

3.3. Procedure characteristics

Procedure characteristics and findings after CAG are summarised and presented in the table below (table 6).

Procedure characteristics and findings	N=208
Procedure	
Average time from index episode of MI to the invasive CAG, *n=days*	5±2
Average time for coronary angiogram only, *min*	46±12
Average time for coronary angiogram and PCI or ± FFR , *min*	91±39
Procedure characteristics	
Radial artery access	197 (95)
Femoral artery access	11 (5)
Procedure time *(including angiography and PCI), min*	78±39
Stents	
Total number of stents	223
Average number of stents per patient	1.6
Angiographic findings, *n(%)*	
Total number of lesions with a stenosis ≥ 30% diameter	462 (55)
Total number of lesions with a stenosis ≥ 50% diameter	380 (45)
Patients with at least one lesion ≥ 50% severity	193 (93)
Lesion characteristic based upon visual interpretation at angiography, *n(%)*	
>30-49% stenosis	70 (14)
>50-69% stenosis	115 (26)
>70-90% stenosis	170 (36)
>90% stenosis	86 (20)
Total occlusion	20 (4)
Arteries with at least one significant lesion *n(%)* *An angiographically significant artery was defined as an artery with one or more lesions ≥70% of the reference vessel diameter*	
0	32 (14)
1	86 (41)
2	63 (30)
3	26 (13)
4	1 (<1)

Patients with at least one lesion >50% severity in the proximal or mid left anterior descending artery, *n (%)*	134 (27)
Invasive treatment strategy	
1VPCI	101 (48)
2VPCI	30 (14)
3VPCI	3 (1)
FFR	25 (12)
1VPCI+FFR	4 (2)
2VPCI+FFR	2 (1)

Table 7 - Procedure characteristics. A diseased artery was defined as an epicardial artery with one or more lesions ≥30% of the reference vessel diameter and amenable to PCI or CABG. An angiographically significant artery was defined as an artery with one or more lesions ≥70% of the reference vessel diameter. 1VPCI, one vessel PCI; 2VPCI, two vessel PCI; 3VPCI, three vessel PCI; FFR, Fractional flow reserve; 1VPCI+FFR, 1VPCI with an additional FFR to another vessel; two vessel PCI with an additional FFR to another vessel. Mean ± SD or median (inter-quartile range) for normal and non-normally distributed data, respectively.

3.4. vFFRs processed: vessels and values

VFFR computation was processed in 355 vessels with a 94% (335 out of 355 vessels) success rate. All patients included had at least one successful artery processed for vFFR. When the there was a delay in processing the arteries on the same day due to internal radiology error, the cases were processed off site as soon as images were available to upload. The interventionalists were then questioned using the same standardised proforma via email to maintain consistency. There were 148 haemodynamically significant vessels (vFFR <0.80) and 187 non-significant vessels (vFFR ≥0.80). The vFFR processing and findings are summarized below (table 8).

vFFR findings	
Average vFFR processing time per case, *mins*	18±10
Average vFFR processing time per vessel, *mins*	11±3
Lesions successfully measured for vFFR number/total number *(%)*	335/355 (94)
Number of physiologically significant (vFFR <0.80) (% of all lesions)	148/335 (44)
Arteries with ≥1 physiologically significant (vFFR <0.80) lesion, *n (%)*	
0	95 (28)
1	80 (24)
2	31 (9)
≥3	2 (1)
vFFRs processed	
LAD	138 (41)
CX	58 (17)
OM	13 (4)
D1	28 (8)
D2	4 (1)
Intermediate	3 (1)
RCA	79 (24)
PDA	8 (2)
PLV	4 (1)
Patients with ≥1 physiologically significant (vFFR <0.8) lesion, *n (%)*	113/208 (54)
Patients with ≥1 physiologically significant (vFFR <0.8) lesion, in the proximal or mid left anterior descending artery, *n (%)*	76/208 (37)
Mean vFFR in lesions with vFFR <0.80	0.65
Mean vFFR in lesions with vFFR ≥0.80	0.89

Table 8 - vFFR findings. LAD, Left anterior descending artery; CX, Circumflex artery; OM, Obtuse marginal artery; D1, First diagonal artery; D2, Second diagonal artery; Ix, Intermediate artery; RCA, Right coronary artery; PDA, Posterior descending artery; PLV, Posterior left ventricular branch artery. Mean ± SD or median (inter-quartile range) for normal and non-normally distributed data, respectively.

3.5. How did the visual stenosis severity compare with vFFR?

The severity of stenoses were visually graded by the interventionalist immediately post CAG. This was divided into mild (30 - 49%), moderate (50 - 69%), severe (70 – 90%), and extremely severe (>90%). Extremely severe lesions (>90%) were not processed for vFFR as per study protocol. The rest of the categories were tabulated and plotted against the vFFR result (see table 8 and figure 37).

Stenosis (%)	vFFR <0.8	vFFR ≥0.8	Total
30-49	3	58	61
50-69	32	83	115
70-90	123	36	159
Total	158	177	335

Table 9 – Relationship of the stenosis severity graded visually with the lesion's haemodynamic significance based on vFFR.

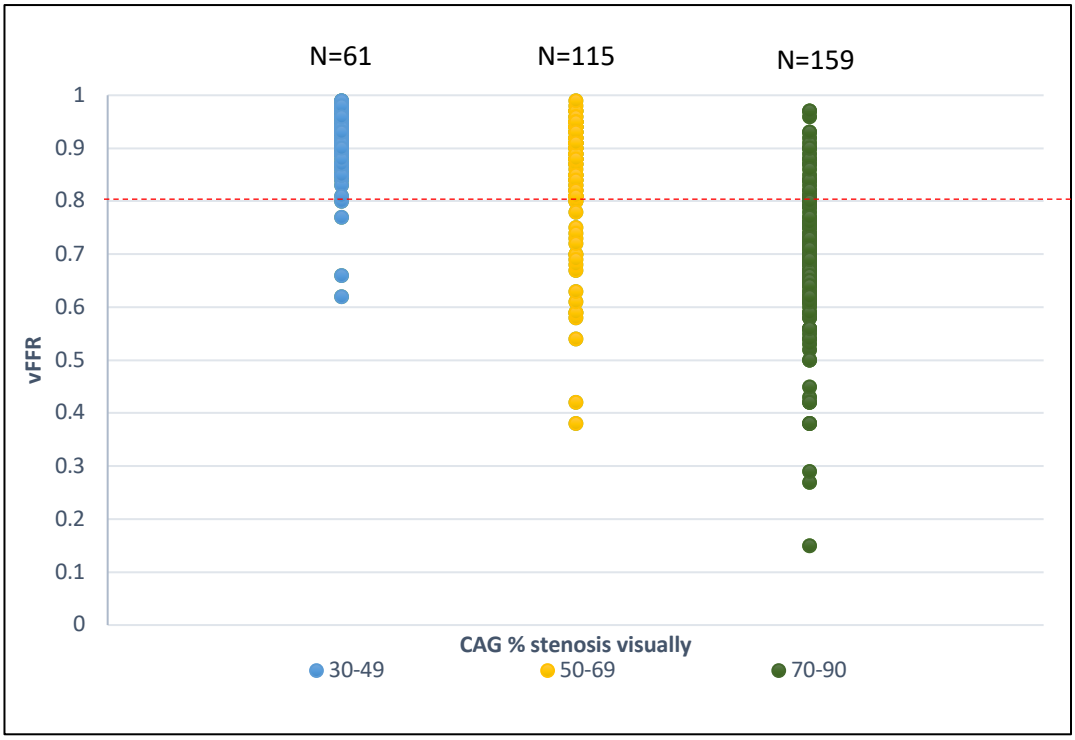


Figure 39 – Scatter plot of CAG % stenosis severity vs vFFR measurement. vFFR measurements below 0.80 (dotted red line) is the reference point of which revascularization is recommended.

3.6. Actual treatment given vs initial treatment plan

Fifteen cardiologists (interventionists) were involved in this study. After CAG, 165 patients were planned to have at least one vessel PCI (± FFR), 32 to have OMT and seven CABG. Four patients were referred for MDT. Those who were initially planned for PCI underwent their treatment as planned, apart from two minor changes during the procedures, in which intended two vessel PCI was changed to single vessel PCI. The first of these was a change from PCI to RCA and LAD to PCI to RCA only, with the bystander LAD procedure being abandoned, due to a peri-procedural TIA. In the second of these, the operator felt that the LAD was too small and diffusely diseased to undergo PCI after guide catheter engagement and opted for PCI to RCA only. In one case, PCI to RCA was unsuccessful because the wire was unable to cross the lesion, so the patient was treated with OMT in the first instance and planned for repeat PCI as a complex case should he remain symptomatic. Two of the four patients referred for MDT underwent CABG with three grafts, whilst the other two had a complex multivessel PCI to LAD, CX and OM. In both, the LAD was deemed ungraftable alongside issues with frailty. All seven patients who were referred for CABG had the surgery as planned. Two patients from the OMT group had left ventriculography which demonstrated apical ballooning suggestive of Takutsubo cardiomyopathy. Most patients who were transferred from district hospitals for CAG were repatriated to back to their respective hospital on the same day. In those with non-obstructive CAD (<30% stenosis) treated with OMT, further investigations such as LV function assessment, CMR or specific laboratory test to rule out other causes and underlying MINOCA were recommended to be undertaken locally.

3.7. vFFR: impact upon treatment plans

3.7.1. Change in management

After the vFFRs were revealed, there was an hypothetical change in management in 46/208 patients (22%) [95% CI: 15% to 25%, p <0.001]. Figure 38 illustrates the distribution of change in management pre and post vFFR. The change between the extent of significant CAD angiographically and post vFFR is shown below (table 9).

Extent of angiographically significant CAD		Extent of significant CAD post vFFR					
		0VD	1VD	2VD	3VD	4VD	**Total**
	0VD	31	1	0	0	0	32
	1VD	4	59	22	1	0	86
	2VD	0	4	52	6	1	63
	3VD	0	0	2	24	0	26
	4VD	0	0	0	0	1	1
	Total	35	64	76	31	2	**208**

Table 10 – Extent of significant CAD angiographically and post vFFR reclassification, n=208.

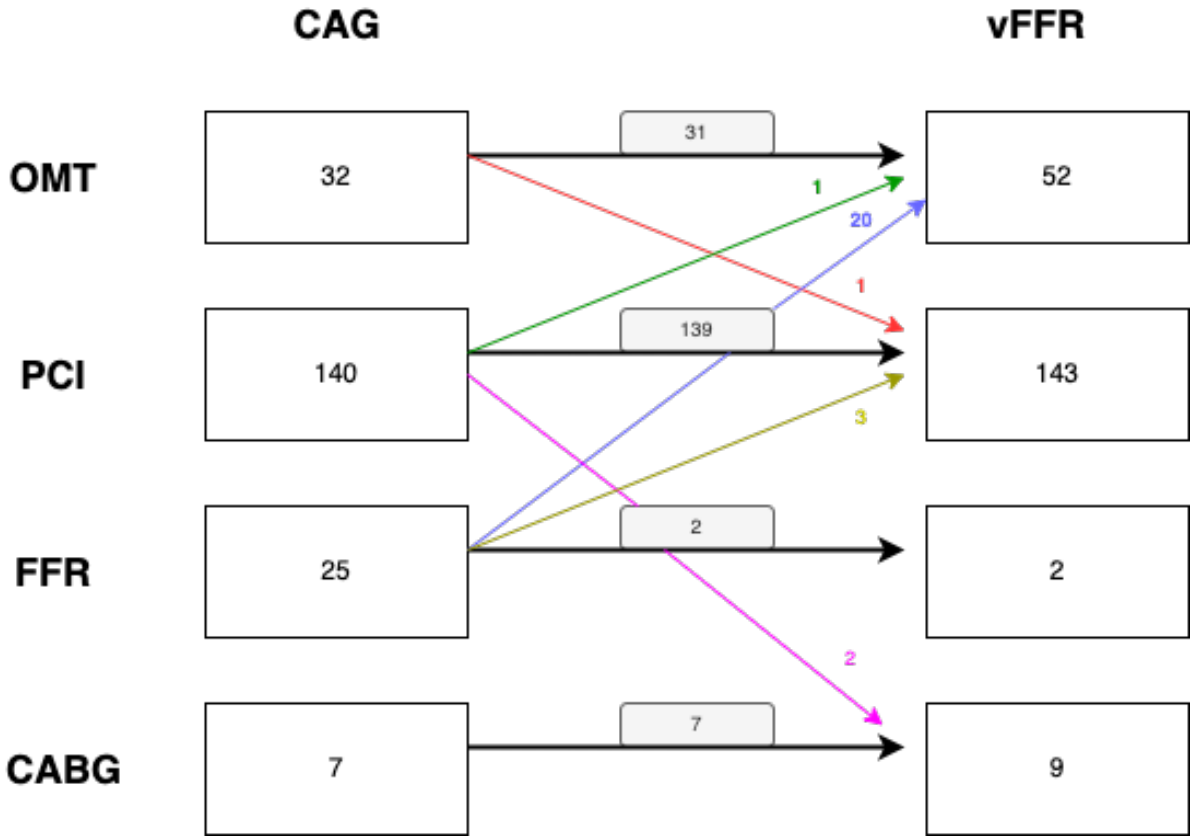


Figure 40 - Distribution of treatment pre and post vFFR. A change occurred in 46/208 patients (22%); p <0.001. Out of the 46, 18 changes occurred within the PCI group (10 had an additional intervention with PCI/FFR to another vessel whilst 8 had less intervention with PCI/FFR to another vessel). 1change occurred within the CABG group (FFR to a vessel was eliminated).

Table 10 and 11 summarized the distribution of treatment plans after CAG and following vFFR recommendation. In 184 cases (88%) there was agreement between the pre vFFR and post vFFR treatment plan. In further detail, there were six patients who were initially referred for at least one vessel PCI with an additional FFR to another vessel post CAG. After vFFR calculation, a 5 would have hypothetically had their original FFR plan omitted. In those with hypothetical changed in management, vFFR calculation only increased the number of additional vessels intervened upon by 7% (12/165 patients: 10 for PCI or FFR, 2 for CABG) only. Overall, the use of vFFR showed a trend of reduction in PCIs and increased in referral to OMTs. In 146/208 (70%) patients whereby vFFR did not impact the management, 89 were simple one vessel PCI and 30 were multivessel PCI.

	Post vFFR				
Post CAG	OMT	PCI	CABG	MDT	***Total***
OMT	31	1	0	0	32
PCI	21	142	2	0	165
CABG	0	0	7	0	7
MDT	0	0	0	4	4
Total	52	143	9	4	**208**

Table 11 – Breakdown of treatment plan post CAG compared with post vFFR of all cases, n = 208. Six PCIs included FFR with PCI and 25 included FFR without PCI.

	Post vFFR		
Post CAG	OMT	PCI	***Total***
OMT	31	1	32
PCI	21	142	163
Total	52	143	**195**

Table 12 - Summarized table for treatment plan post CAG compared with post vFFR recommendation excluding CABG and MDT cases which were statistically non-calculable, n = 195; p <0.001 by Fisher exact test.

	Post vFFR							
Post CAG	OMT	-FFR/PCI*	PCI	+PCI/FFR*	FFR	CABG	MDT	***Total***
OMT	31	0	0	0	1	0	0	32
PCI	1	3	118	10	0	2	0	134
PCI+FFR*	0	5	0	0	1	0	0	6
FFR	20	0	2	0	3	0	0	25
CABG	0	0	0	0	0	7	0	7
MDT	0	0	0	0	0	0	4	4
Total	52	8	120	10	5	9	4	**208**

Figure 41 - Full breakdown of distribution of treatment change pre and post vFFR. *PCI+FFR - At least 1 vessel PCI and FFR to another vessel ; -FFR/PCI - Less FFR or PCI to a vessel ; +PCI/FFR - Additional FFR or PCI to another vessel, N=208.

3.7.2. Concordance

Concordance between post vFFR and initial treatment decision was marginally higher in the non-significant lesions vs significant lesions (74% vs 70%; p= 0.73). In those vessels with vFFR <0.80, 103/148 (70%) were concordant; whilst 45/148 (30%) were discordant with the initial decision. In those vessels with vFFR ≥ 0.80, 138/187 (74%) were concordant, whilst 49/187 (26%) were discordant with the treatment decision. Details are shown in the following consort diagram (figure 39).

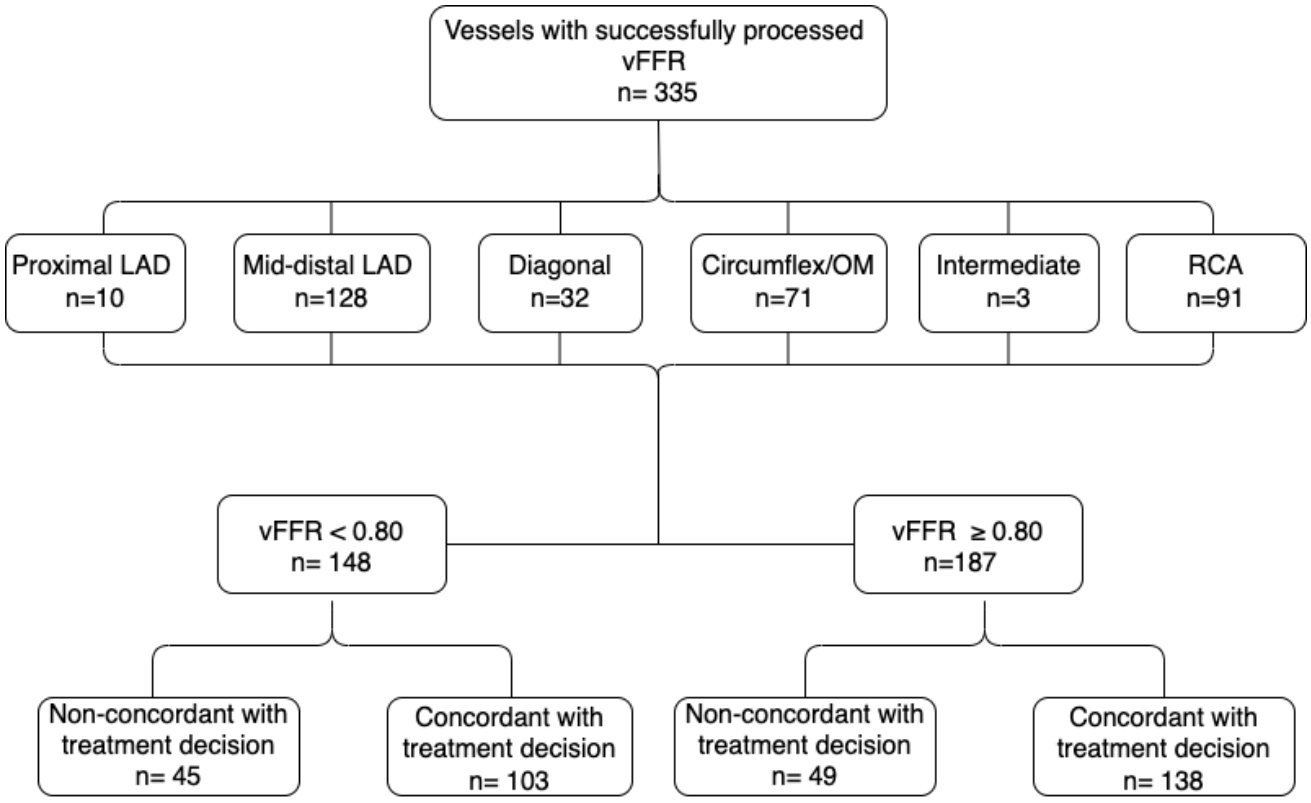


Figure 42 – Consort diagram on all vessels successfully processed for vFFR, n=335.

3.8. Operator confidence

The average operators' confidence levels pre vFFR and post vFFR were 8 (SD 1) and 9 (SD 1) respectively, ($p < 0.004$). vFFR calculation led to an increase of confidence in 126/208 (61%) of cases whilst in 12/208 (6%), the confidence level was reduced. Of those who had an increased confidence level, 106/126 (84%) were recommended to have an invasive strategy with either PCI or FFR. Those with reduced confidence were associated with discordance of treatment with the initial plan after vFFR (ie vFFR ≥ 0.80 with planned PCI, or vFFR <0.8 with medical OMT). In 70/208 (33%) cases, vFFR calculation did not affect the decision and therefore the confidence level remained unchanged. This was usually in cases in which there was either a severe culprit lesion (>90% stenosis) with no bystander disease or clear-cut, non-obstructive lesions in which patients were recommended to have OMT with possible consideration of MINOCA.

3.9. Inter-observer and intra-observer variability

To investigate the variability of the measured vFFRs, inter-observer and intra-observer analysis were performed. I re-processed 10% of the cases. I conducted the repeat measurements blinded to the initial result to reduce bias. The specific personalization parameters, MJI and DJ scores were also recalculated. PCC was used to analyse the result. I found there was a good correlation between my initial vFFR measurements and my repeat measurements (R=0.96) (figure 40). BA analysis showed a mean difference (bias) of 0.01 (±0.01) (figure 41).

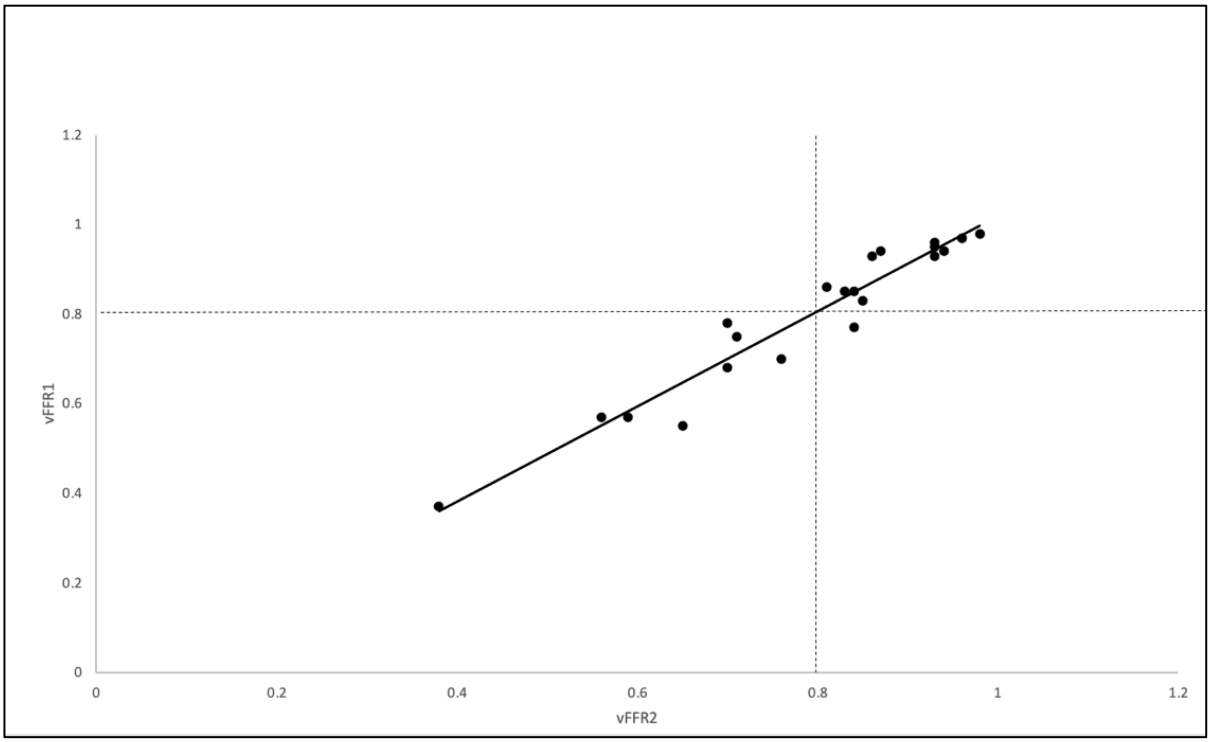


Figure 43 - Correlation between vFFR1 (initial vFFR) and vFFR2 (repeated vFFR). R=0.96. 0.80 represents the ischaemic threshold.

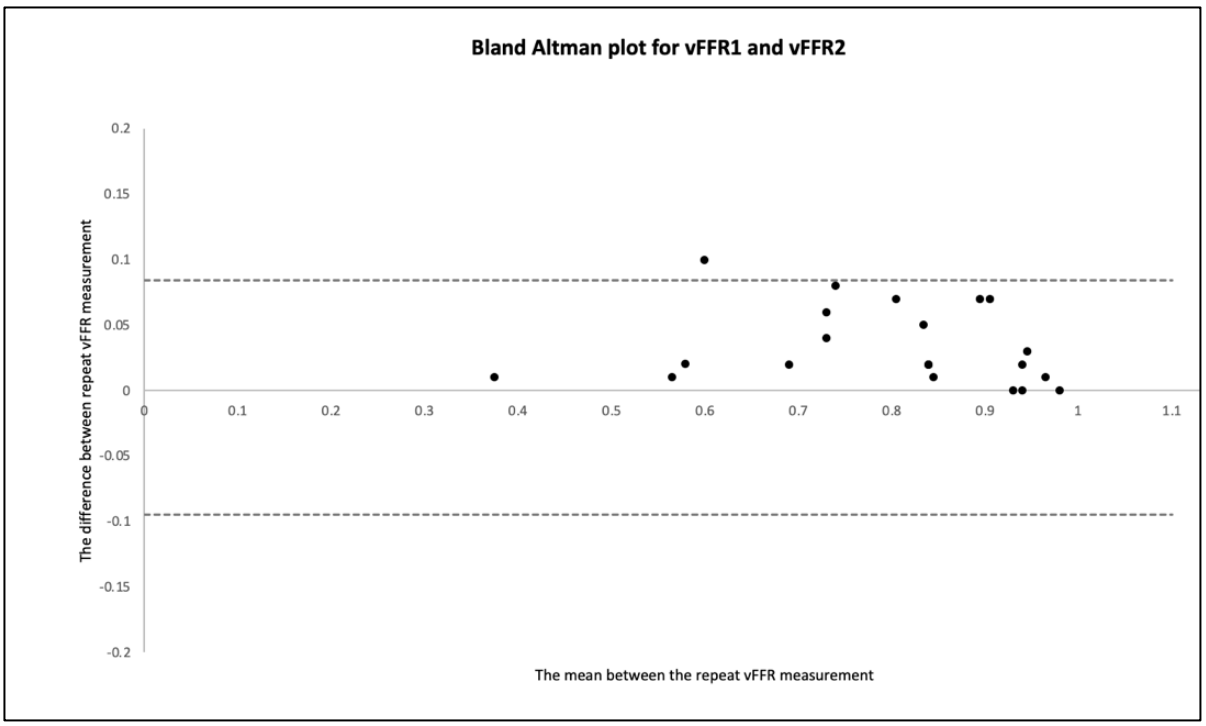


Figure 44 - Bland Altman plot for the difference between the vFFR measurements with a mean difference of 0.01 (±0.01) and limits of agreement from -0.09 and 0.08 (1.96 SD dotted lines).

For the inter-observer analysis, another expert user was invited to re-process 10% of the cases. The expert was blinded to the initial vFFR calculation and the MJI and DJs scores were also re-calculated. The same correlation analysis was performed on these results and demonstrated a correlation of R=0.90 (figure 42) and a BA analysis showed a mean difference (bias) of 0.03 (±0.03) (figure 43).

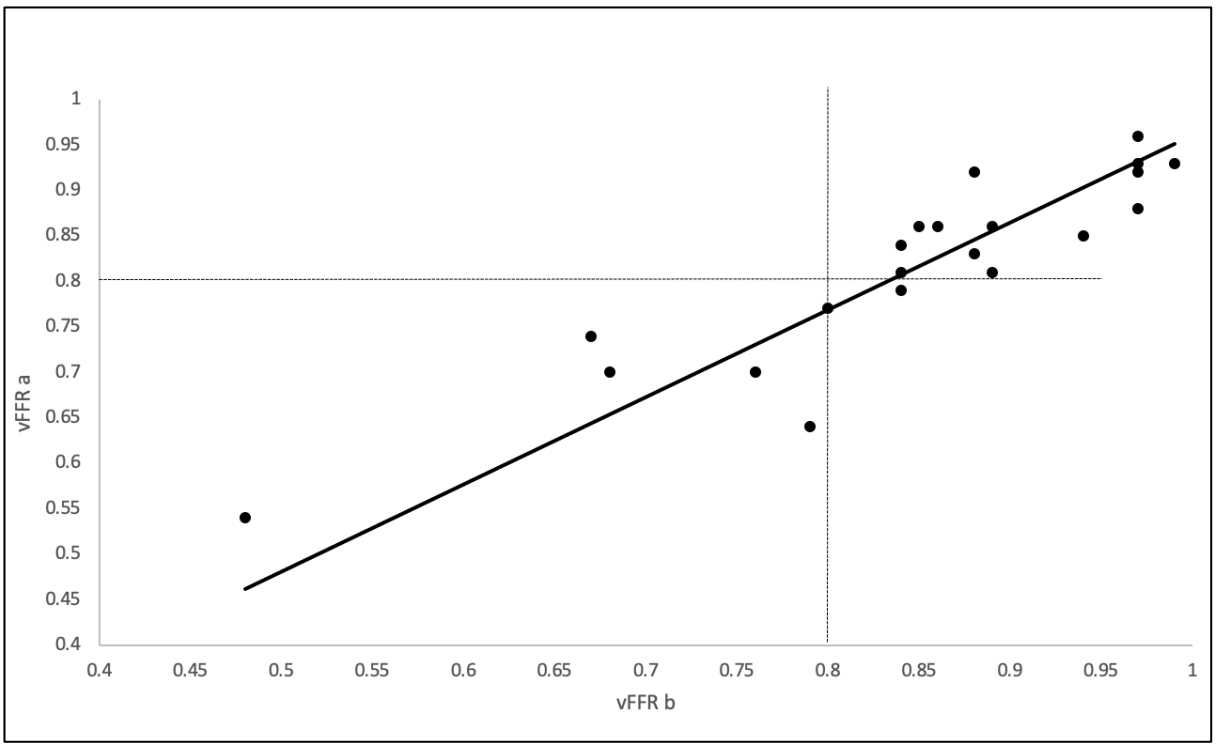


Figure 45 - Correlation between vFFRa (second expert user) and vFFRb (primary investigator). R=0.90. 0.80 represents the ischaemic threshold.

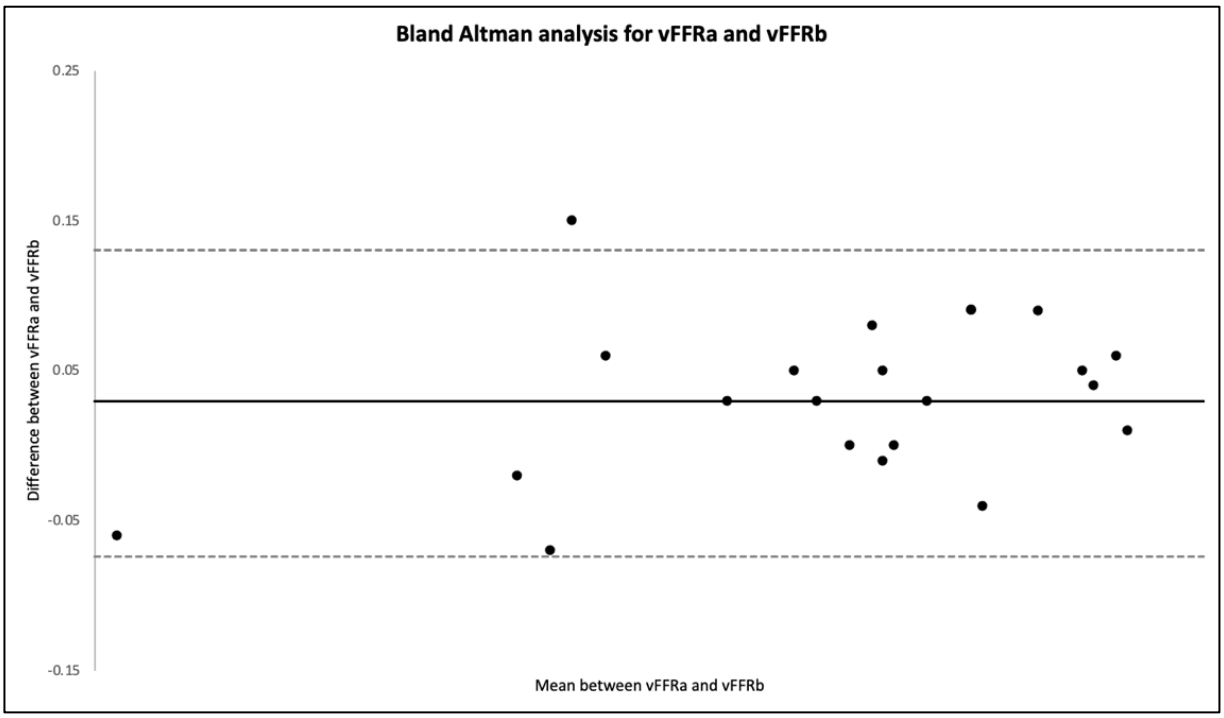


Figure 46 - Bland Altman plot for the difference between vFFRa and vFFRb with a mean difference of 0.03 (±0.03) and limits of agreement from -0.07 and 0.13 (1.96 SD dotted lines).

3.10. Sub-analysis validating vFFR against mFFR

In 33/208 (16%) of cases, mFFRs were performed for clinical reasons, allowing the vFFRs to be compared with the mFFRs. The mean vFFR was 0.85 (SD 0.08) and mean mFFR was 0.86 (SD 0.08). The accuracy, sensitivity, specificity, PPV and NPV were 94%, 83%, 96%, 83% and 96% respectively, and the ROC-curve AUC was 0.95 (95% CI: 0.85 to 1.00) (figure 44). There was a good correlation between vFFR and mFFR (R=0.86) (figure 45). BA analysis showed a mean difference of 0.01 (±0.01) (figure 46).

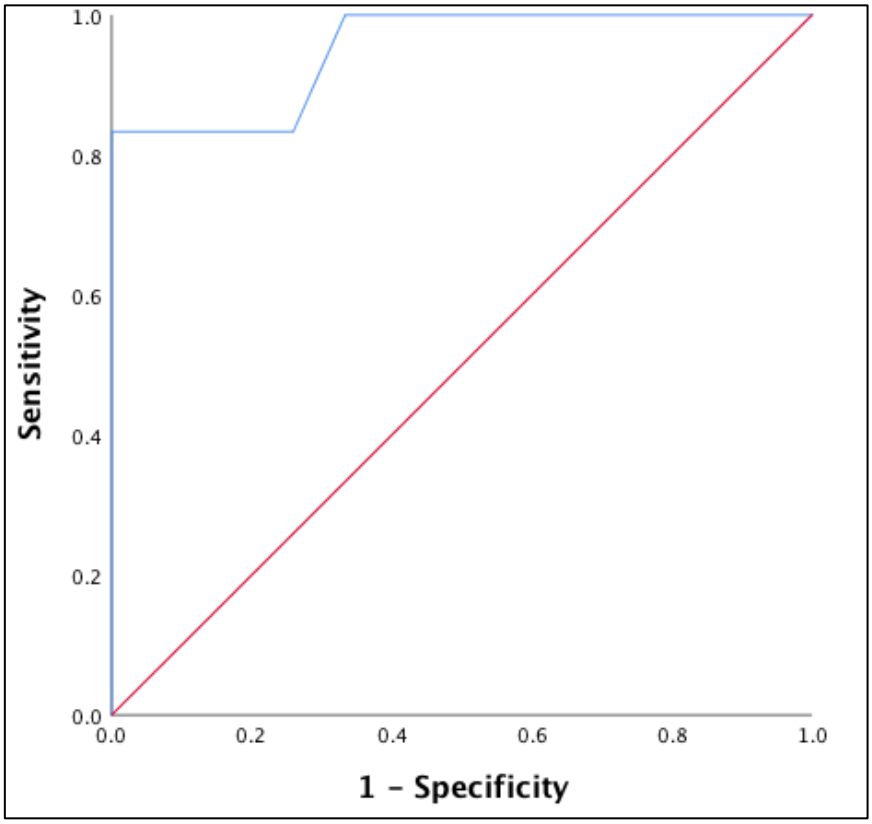


Figure 47 - ROC curve of vFFR compared to mFFR. AUC 0.95.

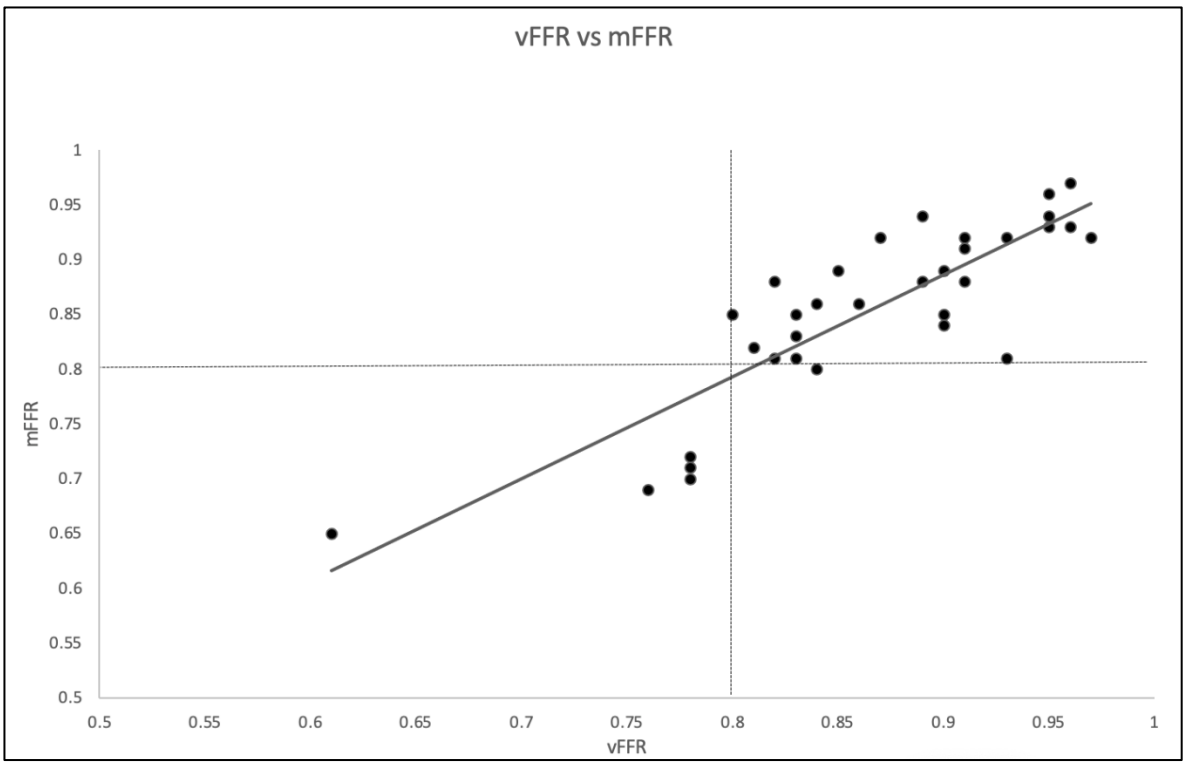


Figure 48 - Correlation between vFFR and mFFR. R=0.86. 0.80 represents the ischaemic threshold.

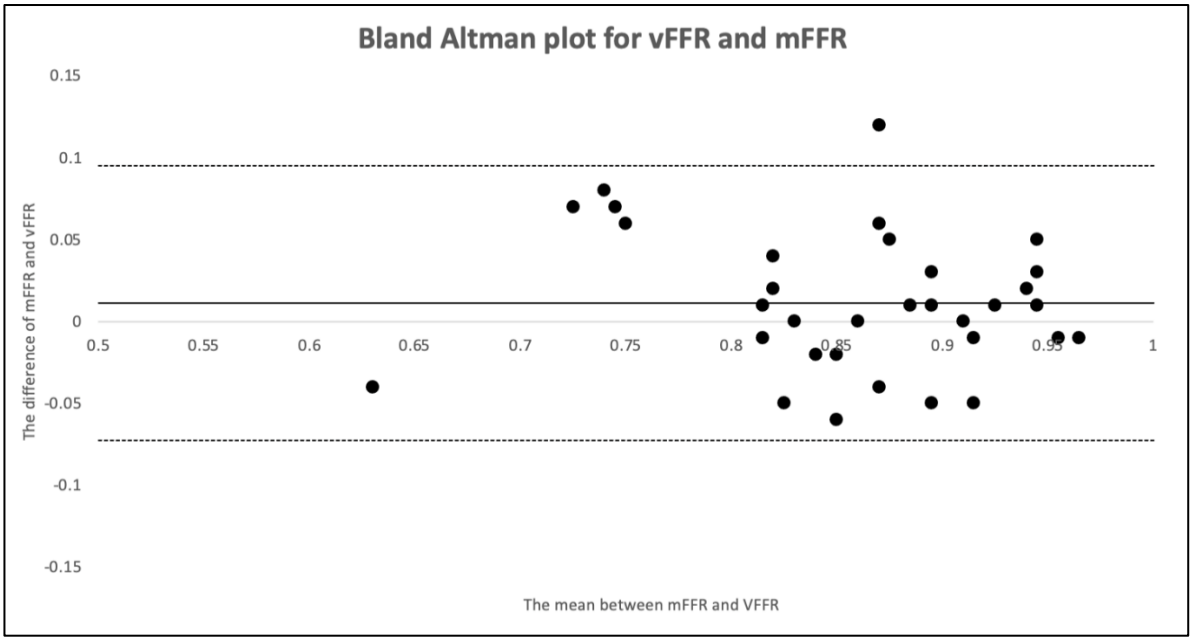


Figure 49 - Bland Altman plot for the difference between vFFR and mFFR with a mean difference of 0.01 (±0.01) and limits of agreement from -0.07 to 0.1 (1.96 SD dotted lines).

3.11. Study MDT outcomes

Eleven MDTs were convened. A total of 101 cases were discussed with an average of nine cases per meeting. At the MDT, 71% of the angiogram images were categorized as good, 27% as average and 2% poor in quality (see figure 47). vFFR hypothetically led to a change in management in 34/101 (34%) of cases [95% CI: 12% to 28%, p <0.001]. No change of decision was observed in 67/101 (66%) cases. Out of those in which management changed, 23/34 (68%) patients were from PCI to OMT, reducing the total number of PCI by 31%. Confidence level in the decision made increased in 45% (45 out of 101 cases), did not change in 53/101 (52%) and was reduced in 3/101 (3%) of cases. The breakdown of treatment plans and changes are shown in table 12 and 13.

	Post vFFR			
Post CAG	OMT	PCI	CABG	***Total***
OMT	14	1	0	15
PCI	23	51	0	74
CABG	0	0	12	12
Total	37	52	12	**101**

Table 13 - Distribution of treatment change between post CAG and post vFFR at the MDT level, n = 101.

	Post vFFR		
Post CAG	OMT	PCI	***Total***
OMT	14	1	15
PCI	23	51	74
Total	37	52	**89**

Table 14 – Distribution of treatment plan and changes between post CAG and post vFFR group, excluding CABG cases which were statistically non-calculable, n = 89; p <0.001 by Fisher exact test.

3.12. Secondary outcomes

All 208 patients were followed up for MACE (see figure 48 and table 14). Six of 208 (3%) of experienced a MACE; one death, two MIs, two unplanned revascularisations and one

intracerebral bleed. The death was in a patient who had CABG. The unplanned revascularizations were due to continued angina arising from diseased arteries which were not treated at first presentation. One of the two MIs was triggered by sepsis due to chest infection, and the other was caused by in-stent thrombosis secondary to non-compliance of DAPT. A six month follow up phone call was undertaken in 143 patients to record other clinical events. Three patients who were initially referred for MDT were excluded for further analysis because the interventionists were encouraged to decide on either PCI, OMT, or CABG as their final plan. Overall, there were 33 hospital admissions. Of those, 10 were visits to A&E only. The breakdown for clinical events resulting in either hospital or A&E visits are summarized below (table 15). The seven admissions for chest pain required observation, investigation and medication up-titration. Treatment concordance and discordance following vFFR in those followed up for clinical events excluding those initially referred for MDT is shown below (table 16). Ninety-six patients were in touch with their GPs either by phone consultation, home visit or appointment at the surgery. Most of these were routine checks, medication reviews or minor medical issues.

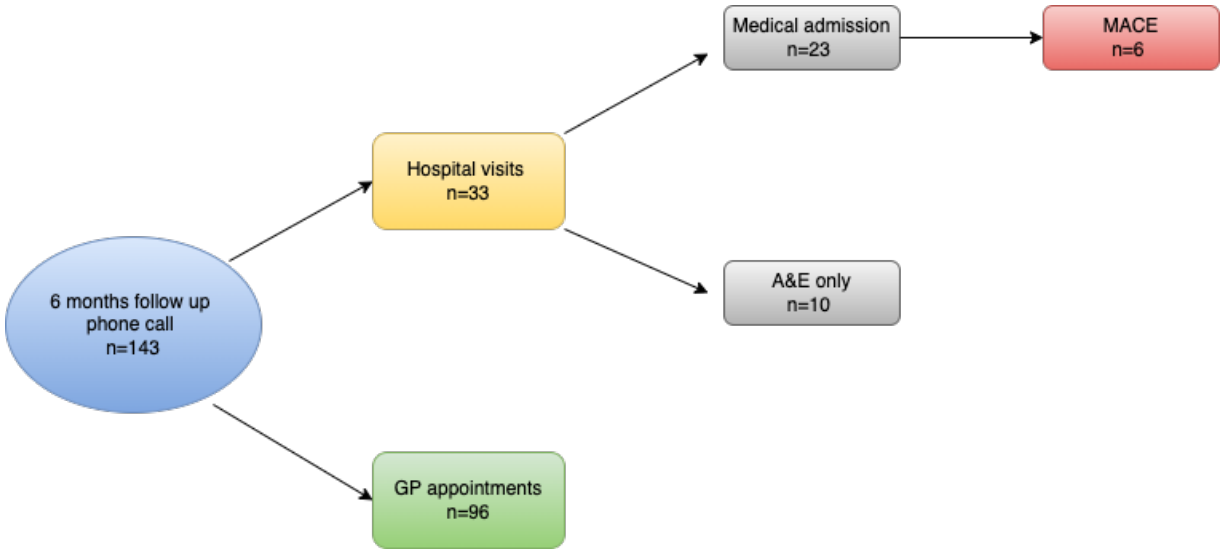


Figure 50 - Consort diagram summarizing the secondary outcome at 6 months; total number of patients followed up for MACE, n=208; total number of patients followed up by phone call for all other clinical events, n=143.

	Details	n (%)
MACE	Death	1 (<1)
	MI	2 (1)
	Unplanned revascularisation	2 (<1)
	Intracerebral bleed	1 (<1)
	Total	**6 (3)**

Table 15 – Summary for causes of MACE; n=208.

	Hospital admissions	**n (%)**	**A&E admissions**	**n (%)**
Clinical events	MI	2 (1)	M/S Chest pain	6 (3)
	Angina	7 (3)	Palpitations	2 (1)
	Bleed (Intracranial)	1 (<1)	Dizziness	1 (<1)
	Unclassified chest pain	2 (1)	Other	2 (<1)
	Infection/sepsis	3 (1)		
	Anaemia	1 (<1)		
	AF	2 (1)		
	Diabetes	1 (<1)		
	Bladder/urinary issues	1 (<1)		
	Fall/Collapse	2 (1)		
	Diverticulitis	1 (<1)		
	Total	**23**		**10**

Table 16 – Breakdown of clinical events based on hospital or A&E admissions at 6 months follow up; n=143.

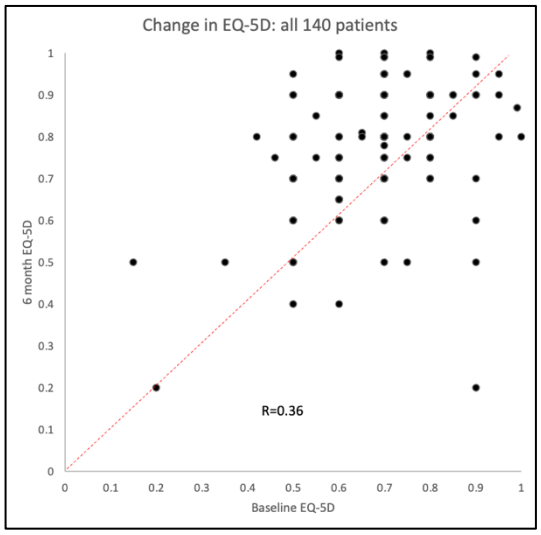
		Concordant	Discordant	**Total**
Clinical events	Yes	23	8	31
	No	89	20	109
	Total	112	28	140

Table 17 - Summary of treatment concordance and discordance following vFFR in the patients followed up for clinical events, n=140; p=0.45 by Fisher exact test.

3.13. Quality of life

A repeat EQ-5D score was also performed for comparison from baseline. At six months follow up, 99/140 (70%) of patients had increased in quality of life. There was no change in 23/140 (16%) and a reduction was seen in 20/140 (14%) of patients (see table 17 and 18). Treatment with PCI, OMT and CABG, all resulted in a statistically significant increase in EQ-5D score. The relationship between treatment concordance and change of EQ-5D score is shown in table 19 and 20. The breakdown of treatment and the change of EQ-5D score at 6 months are shown in table 21. Out of those with changed of management, vFFR led to increase in EQ-5D score in 15/26 (59%) of patients.

A



B

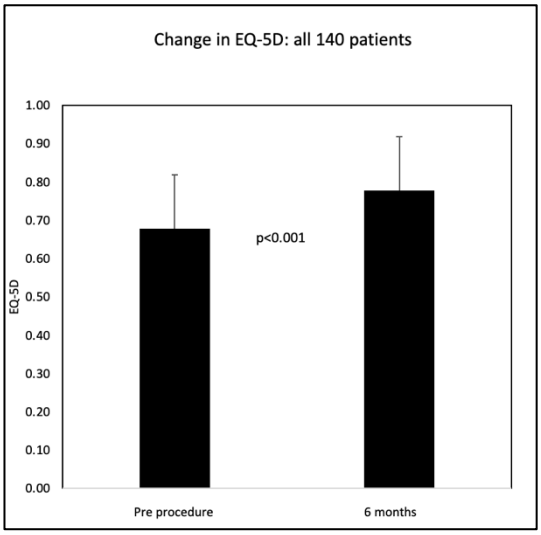
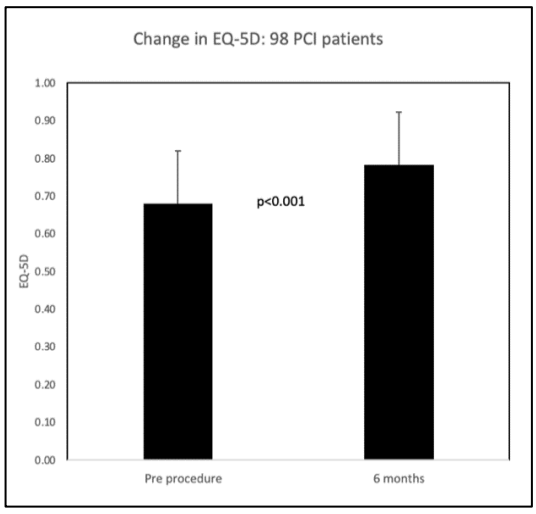
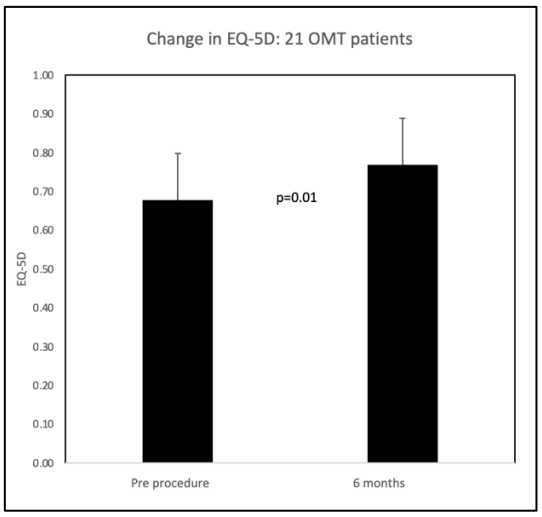


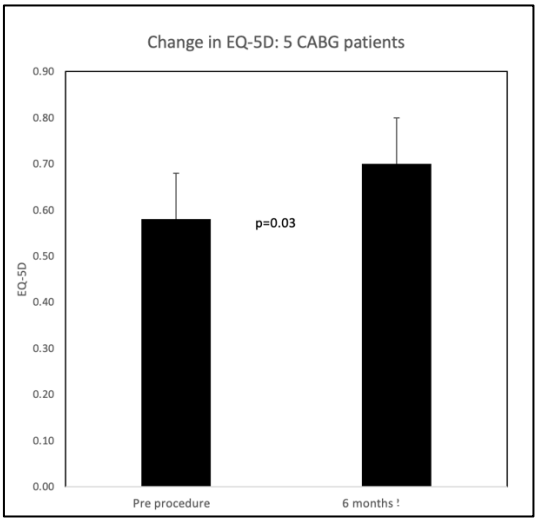
Table 18 – A) EQ-5D score at baseline and 6 months, n=140; R=0.36. B) Change in EQ-5D score at baseline and 6 months; p<0.001 by paired t-test.

A



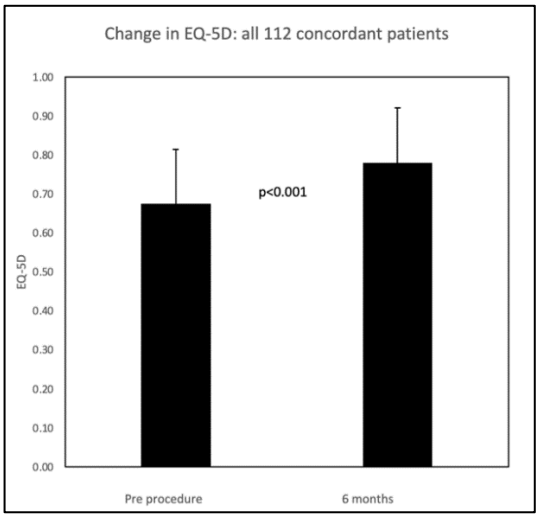
B



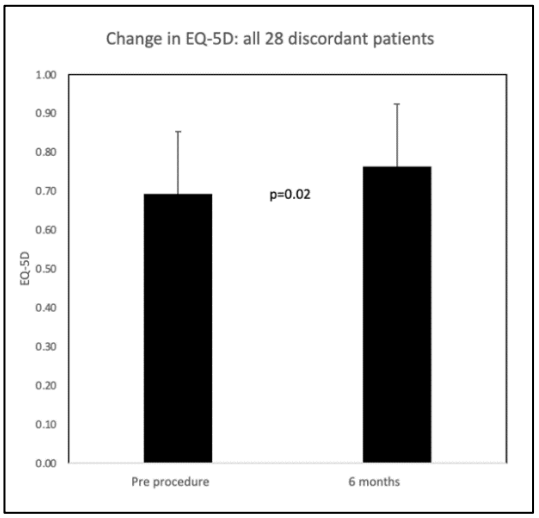


C

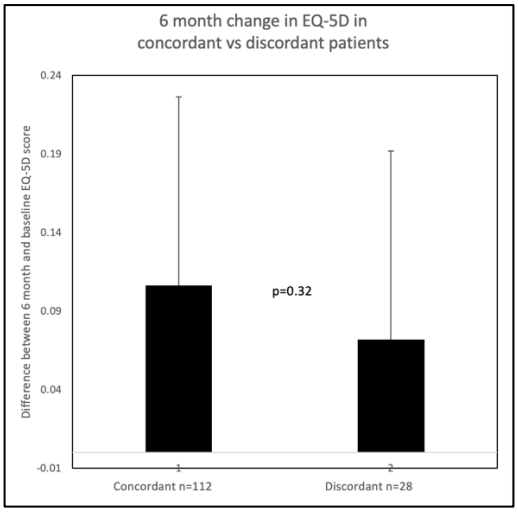
Table 19 – Change of EQ-5D score for PCI baseline and at 6 months for each treatment. A) PCI patients B) OMT patients C) CABG patients; n=140.



A



B



C

Table 20 – Change of EQ-5D in A) concordant; n=112, p<0.001 and in B) discordant; n=28 patients, p=0.02 by paired t-test. C) Difference between 6 month and baseline EQ-5D score in these patients, p=0.32.

Treatment	Patients n (%)	EQ-5D score	Patients n (%)
Change from FFR to OMT	9 (62)	Increased	15 (58)
Additional vessel FFR/PCI *(existing planned PCI)*	4 (25)		
Change from PCI to CABG	2 (13)		
Change from FFR to OMT	2 (33)	Decreased	6 (22)
Additional vessel FFR/PCI	3 (50)		
Less vessel FFR/PCI *(existing planned PCI)*	1 (17)		
Change from FFR to OMT	4 (80)	Unchanged	5 (19)
Additional vessel FFR/PCI *(existing planned PCI)*	1 (20)		

Table 21 – Distribution of change in EQ-5D score at 6 months of all 140 followed up patients whose hypothetical treatment changed following vFFR.

3.14. Health economics: preliminary findings

Out of 208 patients, 165 were treated with PCI with or without measured FFR. A total number of 223 stents were used with an average of 1.6 stents per patient. The use of vFFR would have reduced the average total number of stents by 18% (42/223 stents). Moreover, vFFR led to a lack of requirement for mFFR in 25/31 (80%) cases. There were seven patients referred for CABG with an average inpatient waiting time of 35 (SD 28) days. MACE is summarized in the consort diagram above (figure 48). Average waiting time for inpatient CAG from index presentation was 5 (SD 2) days. The average procedural time for CAG only was 46 (SD 12) min, and for PCI ± FFR 91 (SD 39) mins. The average computing time for vFFR was 18 (SD 10) mins per case and 11 (SD 3) mins per vessel.

4. Discussion

4.1. Summary of results

In this study, VIRTU4-ACS, I have shown that applying vFFR is feasible in 'real time' in the CCL in the management of patients with NSTE-ACS. This novel tool was successfully applied in 208/208 (100%) cases and 335/355 (94%) vessels. vFFR was not processable in 20/355 (5.6%) vessels. The application of vFFR resulted in an hypothetical change of management in 46/208 (22%) [CI 15% to 25%; p <0.001]. The main hypothetical change was largely secondary to patients being changed to OMT from PCI in 21/208 (10%). At the MDT level, vFFR triggered an hypothetical change of management in 34/101 (34%) [95% CI: 12% to 28%, p <0.001]. vFFR increased the confidence level of the decisions made in 126/208 (61%) and reduced it in 12/208 (6%) cases; the average increase in confidence being 1/10 per case (p< 0.004). At six months, 6/208 (3%) patients experienced MACE; one death, two MIs, two unplanned revascularisations, and one intracerebral bleed.

4.2. How did this study compare to other relevant clinical trials?

The large discrepancy between haemodynamically significant lesions assessed physiologically, compared to visually, supports the findings of existing studies of measured FFR. My study demonstrated an hypothetical change of management in 22% of patients with an overall increase in operator confidence. This is in keeping with a study of 'virtual stenting' by Gosling et al, which also led to an hypothetical change of management in 27% as well as an increased confidence in the decision made (196). The 22% change of management in this study is identical to the change after measured FFR in ACS seen in FAMOUS-NSTEMI . My study also showed that hypothetically, a higher proportion of patients were treated with OMT after vFFR was revealed, compared with before; 52/208 (25%) vs 32/208 (15%). Again, this finding is in keeping with FAMOUS-NSTEMI, [40 (22.7%) vs. 23 (13.2%)] (129). This also accords with the trend seen in other trials such as RIPCORD, in CCS (135). This is relevant because physiology guidance supports the intervention of haemodynamically significant lesions only and can reduce the incidence of adverse events by at least 30% (131). A recent study of 3847 patients (1213 ACS patients) performed a head-to-head comparison of treatment guided by QFR vs CAG. There were fewer MIs and ischaemia-driven revascularisations in the QFR-guided group when compared with the CAG-guided group [hazard ratio 0.65; (95% CI 0.51 to

0.93); p=0.0004]. At one year, the primary endpoint, encompassing death from any cause, MI and ischaemia-driven revascularisation, occurred in 110 (5.8%) vs 167 (8.8%) in the QFR-guided vs the CAG-guided group (197). The use of vFFR in the management of patients with ACS could improve clinical outcomes by achieving a more limited use of PCI, relieving significant ischaemia in the same way as mFFR but with less risk. Of course, this depends upon the accuracy of vFFR when compared to mFFR. This was at a high level in my sub-study. But it may be a limiting factor in the 'real world'. The clinical application of vFFR in patients with ACS should still be subjected to more studies in the future to evaluate how the various types of software will compare to FFR-guided or CAG-guided approach in managing these patients. Nonetheless, the evidence of its feasibility so far is encouraging. This study also suggests that CAG-based vFFR could improve patients' clinical outcomes.

4.3. Changes in treatment plans

In this study, 136 patients had moderate MVD (>50% stenosis). Of these, 101 patients were treated with a single vessel PCI (culprit lesion only), omitting any bystander diseases. Out of the 101 patients, vFFR revealed 27/101 (27%) cases with haemodynamically significant bystander disease (vFFR <0.80). The reason for leaving the significant bystander diseases alone was usually because of treating culprit lesions only. This may be explained by 'real world' practice not being based, in ACS, upon physiology alone, but anatomical and practical features, such as safety, accessibility, tortuosity, calcification, importance of the lesion, etc. The perception that the plaque may be vulnerable may be relevant. Nonetheless, when discussed informally, most interventionalists involved in this study agreed that the use of vFFR as an adjunct tool during CAG may be useful to guide future treatment if the patient remains symptomatic. This study also demonstrated that, in 29/208 (14%) of patients, unnecessary invasive procedures with either FFR or PCI could have hypothetically been avoided by using vFFR guidance. In the case of the patient who was originally planned to undergo PCI to RCA and an FFR guided approach to the LAD, who suffered a TIA during the procedure, the initial FFR plan to treat the LAD was abandoned, and the vFFR in LAD was negative (0.81). The interventionist agreed that this would have led him to leave the LAD untreated. In another case with a negative vFFR, a coronary angioplasty guidewire was trapped behind a stent and was not able to be pulled out easily. It was eventually rectified but became an extended procedure which could have become catastrophic. Two patients had angina within six months of the procedure when a lesion was not treated. They subsequently underwent elective PCIs. One was

initially treated medically. In this case, the vFFR was positive (0.77); in the other the vFFR was (0.83). Both of these patients may have benefited from an FFR guided approach at presentation. In the latter, although vFFR was negative, due to the potential of slight variation when repeating vFFR measurements, an invasive FFR may help to consolidate the result and decision. In another case with severe LMS stenosis and a 51-69% stenosis in the RCA, the interventionist decided to measure the FFR in the RCA. If the RCA was positive, then the patient would have been referred for CABG; and, if negative, undergone PCI. FFR in the RCA was 0.83 and the patient was referred for CABG. vFFR for the RCA was 0.85, in keeping with the measured FFR result. Perhaps this shows that the FFR result, whether measured or virtual, is not the ultimate arbiter of treatment for some cardiologists. But vFFR would have hypothetically avoided the risk of manipulating a guide catheter and wire into the RCA.

4.4. Confidence in decision making

This study demonstrated that the use of vFFR hypothetically increased the confidence of decision making in 126/208 (61%) of patients. In most cases, it reassured the operator of their initial treatment decision, because the vFFR accorded with the lesion appearing significant visually especially if an FFR guided approach was chosen to treat those with moderate stenoses. A reduction of confidence was seen in 12/208 (6%), and was generally associated with cases in which a lesion was thought to be non-significant visually but turned out to be significant based upon vFFR. This does not mean that the use of vFFR confers a negative impact on a patient's treatment, but could generate reasonable doubt about their initial decision. In simpler cases, with one clear culprit, which can be easily treated with one vessel PCI, or in cases with mild CAD disease only, the operator remained neutral to the application of vFFR, and it did not affect the operator's confidence. Additionally, the high agreement rate of vFFR when compared with mFFR also often strengthened the operator's confidence in their decision. All of the operators involved in this study also stated that they would adopt the use of vFFR should it become an approved clinical tool in the future.

4.5. Potential impact of vFFR upon treatment decision

A major attraction of vFFR for patients with ACS is that it can be used at the time of invasive management in a 'one-stop shop', in which coronary anatomy can be revealed alongside lesion-specific ischaemia testing. This is both time- and cost- efficient. It could be particularly useful

in the common situation of multi-vessel, multi-lesion disease, when the culprit is frequently not angiographically obvious. Limited data support intervention for non-culprit lesions (129)(80)(78)(79) but, in the 'real world' and, FFR guidance being rarely used (198). vFFR would provide an opportunity to select lesions requiring intervention without instrumentation and, perhaps more importantly, eliminating those that do not (see figure 50-52). This may be particularly important in apparent triple vessel disease, in which bypass surgery could be avoided. Additionally, even if the vFFR positive lesions are not intervened upon at ACS presentation, the information itself may be extremely useful in guiding future treatments should a patient remain symptomatic. The greatest advantage is that vFFR could bring the advantage of coronary physiology to many more patients with ACS than at present. Finally, recent CFD-based modelling innovations are able to predict microvascular resistance which is known to be of prognostic significance in ACS (199).

4.6. Individual vs collective decision making: Cardiologist and MDT

In both the original clinical situation and the study MDT, there was a trend towards conservative management, with fewer PCIs when the physiology guided approach was used. This corroborates previous studies which showed that a PCI plan based upon visual assessment alone may often overestimate the need for intervention. Interestingly, in my 101 MDT cases, more patients were hypothetically referred for CABG when compared with the individual decision of 208 patients (12/101 vs 7/208). This may because of the presence of the cardiac surgeon and a general cardiologist, allowing for a more systematic and holistic decision, without any bias towards PCI treatment. Equally, it could be because this is the 'true' result, reflecting consistent decision making by the practised study team. I also found that, in the initial individual decision, four patients were referred for MDT. In these cases, a vFFR could have contributed to an immediate MDT, reducing the waiting time for a potential CABG or a complex multivessel PCI, which may benefit not only the patients but also health economics.

4.7. Intra- and inter- observer analysis

As shown in the PCC and BA analyses, both the intra- and inter-observer analysis demonstrated a good correlation and agreement between the vFFRs measured. In a previous study, our group has shown that the accuracy of vFFR is dependent upon training of an expert user, and accuracy is much less without this training (194).

4.8. VFFR validation against mFFR

Although this study was not designed nor powered specifically to validate vFFR against mFFR, in the 33/208 (16%) of the cases which had mFFR measured, there was a strong correlation (R=0.86) and agreement between vFFR and mFFR. This, and the accuracy of 94%, corroborates findings from previous studies which showed accuracy of >90% for the VIRTUheart^{TM} software (173)(178).

4.9. Is VIRTUheartTM really feasible in real time?

VIRTU4-ACS was the first study in which VIRTUheart^{TM} software was used in 'real time' patient management. It showed that the integration of this software into assisting treatment planning for patients who have suffered ACS and are undergoing CAG is feasible. In most cases I was able to download the CAG images and upload it for processing at the same sitting before interviewing the interventionist regarding their treatment decision post vFFR calculation. However, I was also faced with technical errors, such as failure to upload the images on the same day which led to delay in processing the cases on site. In that situation, I processed the cases offline and offsite as soon as the images were uploaded and emailed the consultants with the results using the standard questionnaires. I found this method efficient and usually obtained a reply the same day. In fact, this method was less intrusive to the interventionists who were sometimes preoccupied with other cases following a VIRTU4-ACS study case. This allowed them to reply in their own time. If VIRTUheart^{TM} software were to be integrated into the CCL radiography system, vFFR processing would be quicker, without a need for downloading and images prior to vFFR calculation. The processing time would also be reduced and a vFFR measurement obtained swiftly and during the CAG itself. This would be an attractive prospect when compared with mFFR which, apart from being invasive, carrying a risk, and expensive my actually be slower than integrated vFFR.

4.10. How can vFFR be applied in real life?

A potential algorithm for the invasive management of ACS, incorporating vFFR, is shown in Figure 50.

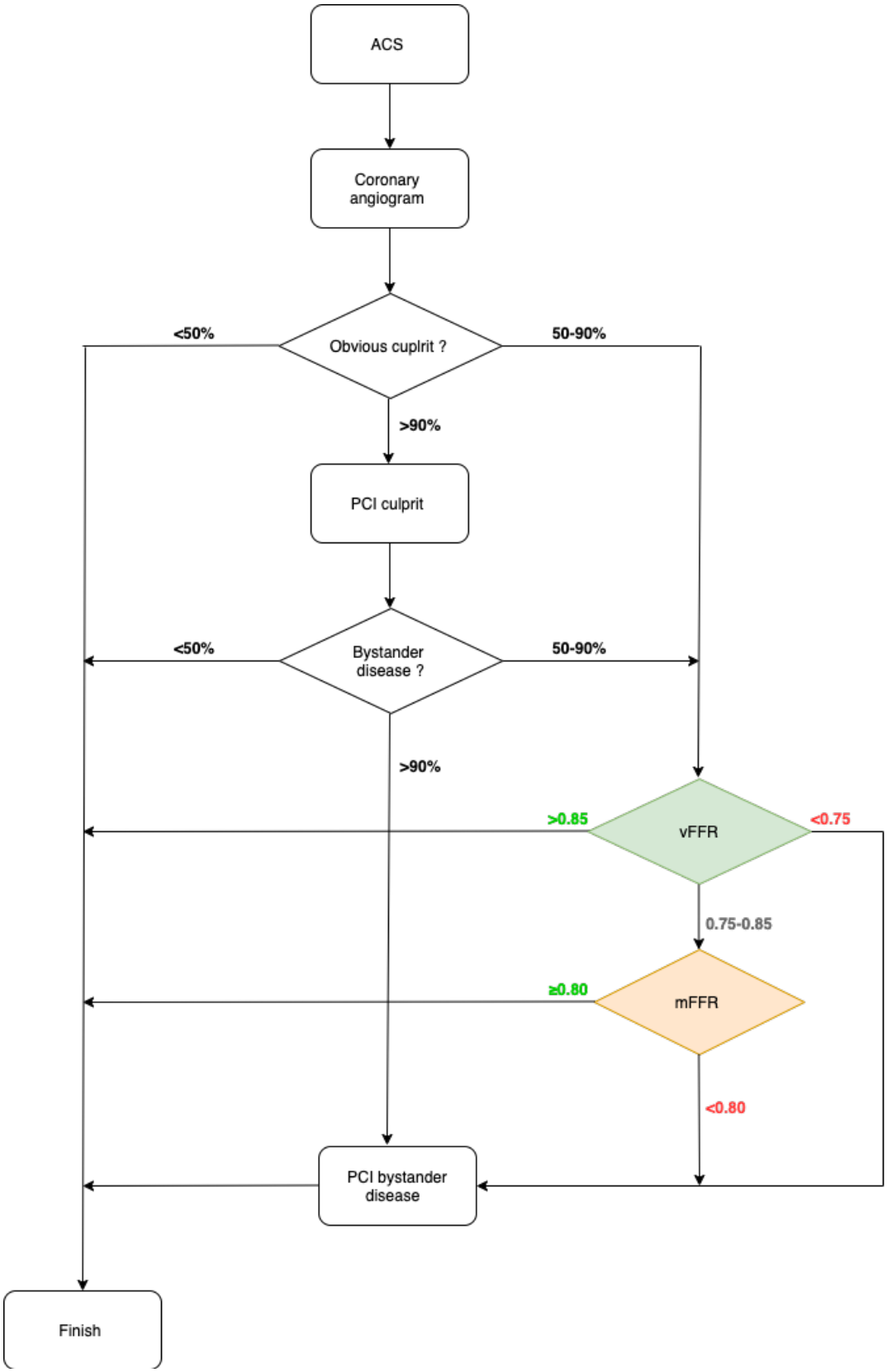


Figure 51 - Proposed algorithm for the use of vFFR in the management of patients with NSTE-ACS. Reproduced with permission from Haley et al.

Examples of vFFR application in patients with ACS are shown below (figure 51-53).

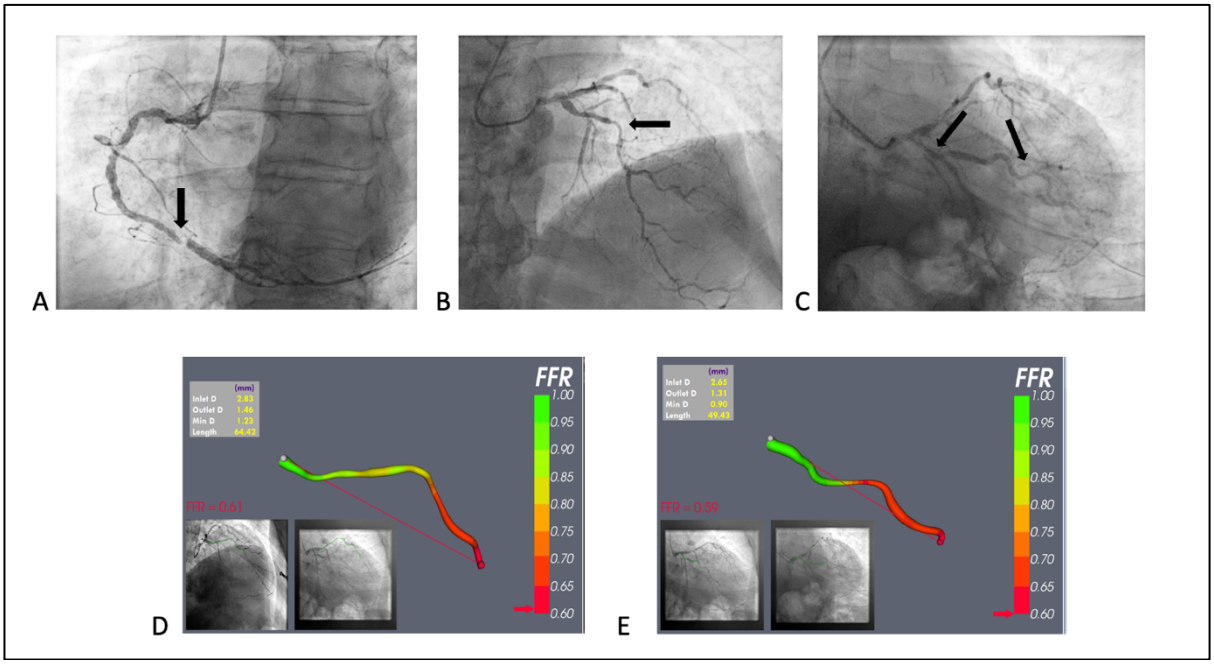


Figure 52 - vFFR use in NSTE-ACS; case 1. A) Severe RCA stenosis, judged to be the 'culprit', and not requiring vFFR; B) mid-LAD stenosis; C) stenosis in the marginal branch D) vFFR model of the LAD lesion; and E) vFFR model of the marginal lesion. Reproduced with permission from Haley et al.

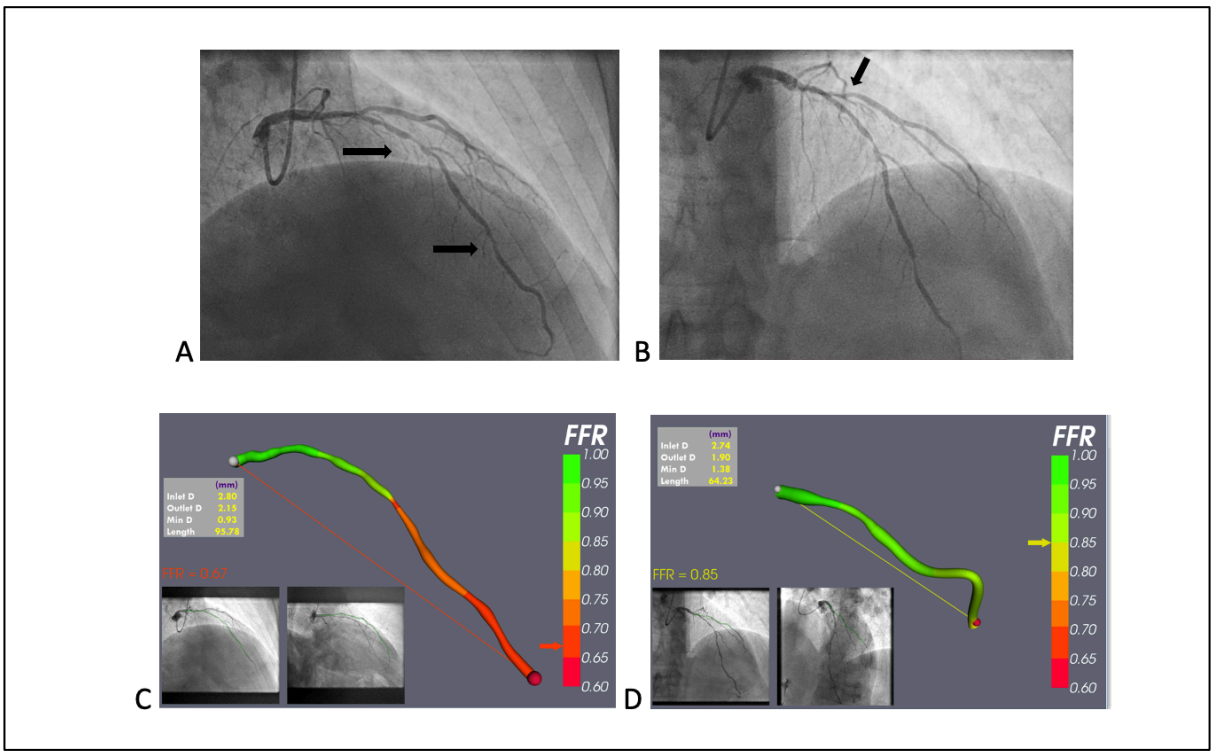


Figure 53 - vFFR use in NSTE-ACS; case 2. A) Probable culprit LAD stenosis; B) Probable bystander ostial diagonal stenosis C) vFFR model of the LAD lesion D) vFFR model of the D1 lesion. Reproduced with permission from Haley et al.

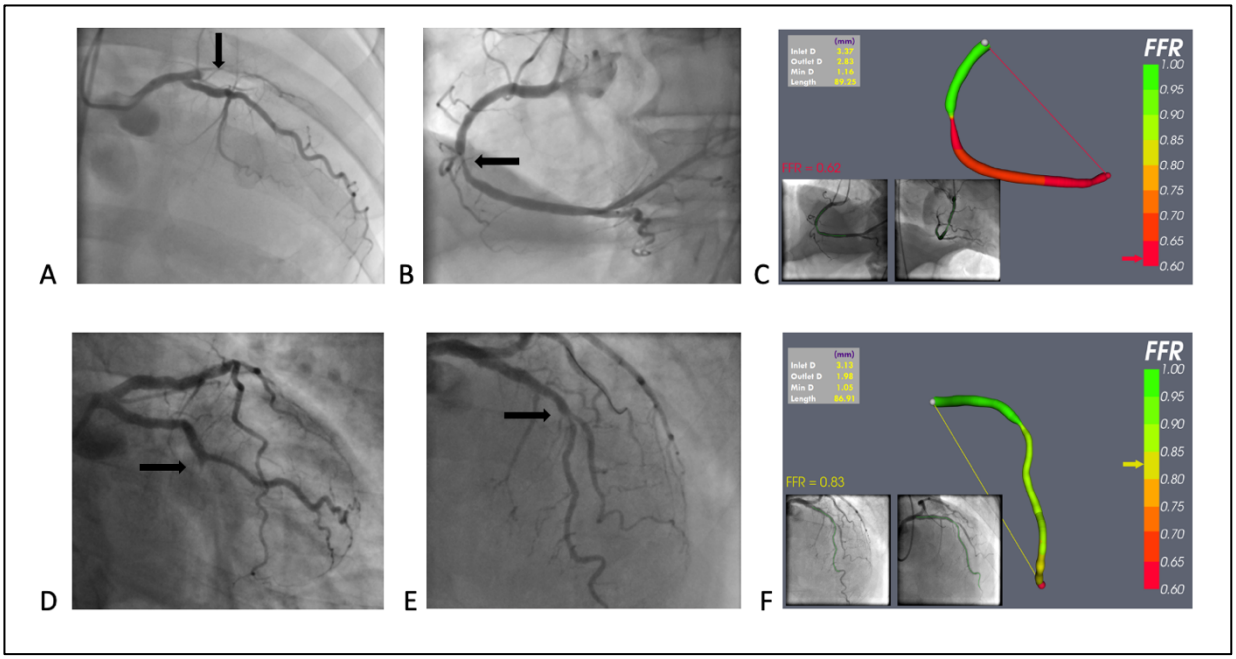


Figure 54 - VFFR use in STEMI. A-C) A case of anterior STEMI: A) occluded proximal LAD; B) mid RCA non-culprit stenosis; and C) vFFR model of the RCA lesion. D-F) A case of infero-lateral STEMI: D) occluded mid Cx; E) non-culprit mid-LAD stenosis. Reproduced with permission from Haley et al.

In all three cases, vFFR was successfully applied in the bystander disease which may provide guidance for the ultimate revascularisation strategy. This technology could also be useful when discussing cases in the MDT setting as vFFR can be applied there and then. Ultimately, with the advantage of vFFR being quick and less invasive, a physiology-guided strategy could be implemented quite simply when treating patients with ACS, be it NSTE-ACS or even STEMI.

4.11. Potential impact upon health economics

The use of vFFR theoretically led to a reduction in the number of PCIs, the typical cost of which is £1815 to £7507 depending on the complexity of the cases and the total number of stents used. It hypothetically led to an increased number of patients being managed with OMT (32 to 52 /208), the more cost-effective treatment in comparison to PCI or CABG. The main contribution may have been the avoidance of mFFR, which would have saved an average of £600 per pressure wire. vFFR can also easily be incorporated in MDT discussions. The additional information which it provides might not only assists team members to instigate optimal management for patients but also could potentially reduce referral waiting time for complex PCI procedure or CABG by avoiding other tests of ischaemia. The cost of vFFR, once installed, on a patient-by-patient basis, is likely to be trivial. This contrasts with FFR_{CT}, for example, which costs £750 per study.

4.12. Potential impact upon quality of life

Although this study was not powered nor designed to evaluate the impact of vFFR upon the change of quality of life, it demonstrated that its deployment may have resulted in a better treatment strategy as evident by the increased in EQ-5D score in 16/27 (59%) patients who had changed of treatment (nine from PCI to OMT, four for additional vessel PCI/FFR, two from PCI to CABG) at six months follow up. Additionally, as discussed above, vFFR could have led to a reduction in MACE by saving two patients from a repeat revascularisation, had vFFR been used as a guidance at presentation. Even though the number of patients referred for CABG was hypothetically increased post vFFR (from 7 to 9/208) and may increase the cost slightly, if balanced overall, with the total reduction of PCIs and repeat admissions, the use of vFFR may still be cost effective. A larger study with a complete health economic analysis will be performed in order to assess the full impact of vFFR application in the management of patients with ACS. The preliminary findings of this study may be a strong platform to encourage future studies to look into this aspect in a more complete form.

4.13. What are the advantages of vFFR?

vFFR is fast. Computation time used to be the limiting factor, but now takes only minutes. The main time-limiting factor is manual image correction prior to the CFD step. The whole process can now be done in 'real time' in the acute CCL while the patient is on the table. It does not require a pressure wire or pharmacologic hyperaemia. In addition, the 3D anatomical model can assist with treatment planning, selection of stent size and 'virtual coronary intervention' together with an estimate of post-stent FFR (183)(178)(196). The same modelling technique can also predict the local haemodynamic consequence of a particular stenting strategy (200). Deploying vFFR does not supplant measured (m)FFR; if a lesion is equivocal at both angiography and vFFR, a pressure wire can still provide ultimate accuracy. There are, though, a few situations in which vFFR might actually be superior to mFFR. The first is serial lesions. Although a pressure wire ‘pullback’ can provide some clues as to the relative significance of serial lesions, it is not infallible. In contrast, vFFR can reveal the FFR at each lesion simply by excluding the other lesion and modelling the lesion in question as if the other were not present. Of course, it can also model both together too. The second situation is when lesion complexity would make passing a pressure wire undesirable or hazardous. Another advantage is that vFFR can be used in any CCL without interventional capability. Also, the cost on a per-patient basis

is likely to be low, because the business model for most commercially available systems is based upon an institutional licence.

4.14. What are the disadvantages of vFFR ?

Whilst the final coloured image appears seductive, its validity is mainly dependent upon good angiographic images, which require meticulous technique. Lesions at ostia, and at or close to the left main or a bifurcation, are difficult to model. In practice, in most CCLs, the radiographer is the most suitable professional to run the software but, even so, thorough training and practice is important. Casual users are considerably less accurate and consistent than regular users, largely due to errors in the 3D reconstruction; expert re-analysis of their models revealing errors that can lead to a change in the treatment decision in 37% cases (194). Although up to 50% of 'standard' angiograms are unsuitable for processing, with a few simple improvements this proportion can be increased to 80% (195). This limitation is unfortunate, because it is the antithesis of measured FFR, where a scrupulous angiogram is less important. In addition, the distal outlet boundary condition is proximal to the CMV circulation, and a fundamental assumption of CMV function (maximal dilatation) is made to compute pressure from flow. The degree of CMV response to hyperaemia varies from person to person, which is why personalisation of this parameter is so important in vFFR. Also, very severe stenoses are difficult to model because the width of the lumen is less than a pixel, although in practice the likelihood is that such a lesion is physiologically significant. Finally, physiological measurement of all kinds is of most use in the assessment of angiographically intermediate lesions. So, however small the error on a vFFR system is, and it is usually at least ±0.10, if the vFFR is calculated to be 0.75-0.85, doubt will remain, and a measured value may be required. There is a further uncertainty, which also applies to measured FFR, which is that the physiological significance of a lesion, particularly in the acute patient, may not correlate with the presence of vulnerable plaque (201)(202)(203), probably explaining why long term outcomes are worse in ACS compared with CCS, even with physiological guidance. vFFR, therefore, whilst being an improvement over current management, is unlikely to provide a complete treatment strategy.

4.15. Technical issues encountered with VIRTUheart™

The success of segmenting an artery for vFFR calculation relies upon good quality CAG images. In some cases, however, images may still be poor due patient factors such as body habitus and obesity. In this situation, it is important to get a balance between an increased x-ray dose and adequate images. Occasionally, patients also have difficult anatomy and vessel overlap. My role in the CCL was often to advise the best angle to minimize overlap, although sometimes this issue could still not be rectified fully. Good catheter engagement and contrast injection are also essential to ensure good opacification of the artery for edge tracing during the segmenting process. Nevertheless, in some cases in which the operator finds difficulty to engage the coronary artery, this can be a significant limitation. Another common technical difficulty with this tool is the epipolar lines. When the centreline is not drawn adequately above the first epipolar line (blue) and beyond the second epipolar line (yellow), the 3D reconstruction of the segmented artery will fail (see figure 54). This can be improved by marking the reference point elsewhere in a trial-and-error manner to find the best spot and solution for this issue, although in rare cases, it may be futile. The automatic edge tracing function can occasionally become impaired and appear erratic (see figure 55). This is due to a condition where, for a certain part of the segment, the edges could not be traced as there is no well-defined gradient change which will be inconspicuous to the human eye but the processed image and pixel level in the code background will lack this information. This phenomenon depends upon the position of the centreline points placed by the user in combination with the local curvature of the vessel segment under consideration. Additionally, if two of the images chosen are too foreshortened or may occasionally lack centreline points correspondence, despite being 30 degrees apart, an error of segmentation can occur. The algorithm cannot resolve or locate the corresponding points from one view onto the other. Table movement and the compensation that is performed in the image registration step can contribute to the lack of correspondence, leading to interpolation error in the radii interpretation, which is an average from the 3D centreline reconstructed from the two views; the segmented artery will form a bell-shaped distal end and will not run on the CFD simulator (see figure 56 and 57). Lastly, if the lesion in the artery is very significant (>90% stenosis), the vFFR will fail to compute and result in a non-converged error, producing a non-processable simulation resulting in a ‘leopard skin’ appearance on the vessel (see figure 58). Although the vFFR is not generated in this situation, it is acceptable to deem the artery as haemodynamically significant. The research

team continues to strive to fix these technical errors to produce reliable and user-friendly software.

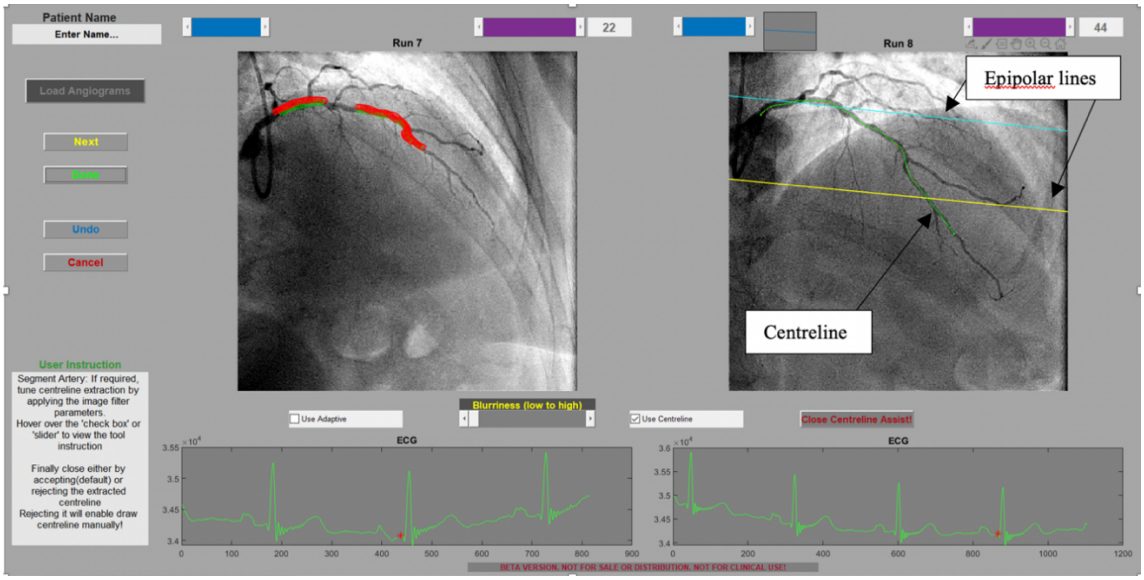


Figure 55 – Drawing of the centreline. It has to start before the first epipolar line (blue) and ends beyond the second epipolar line (yellow) for the segmentation process to accept the vessel registration and proceed to the next step.

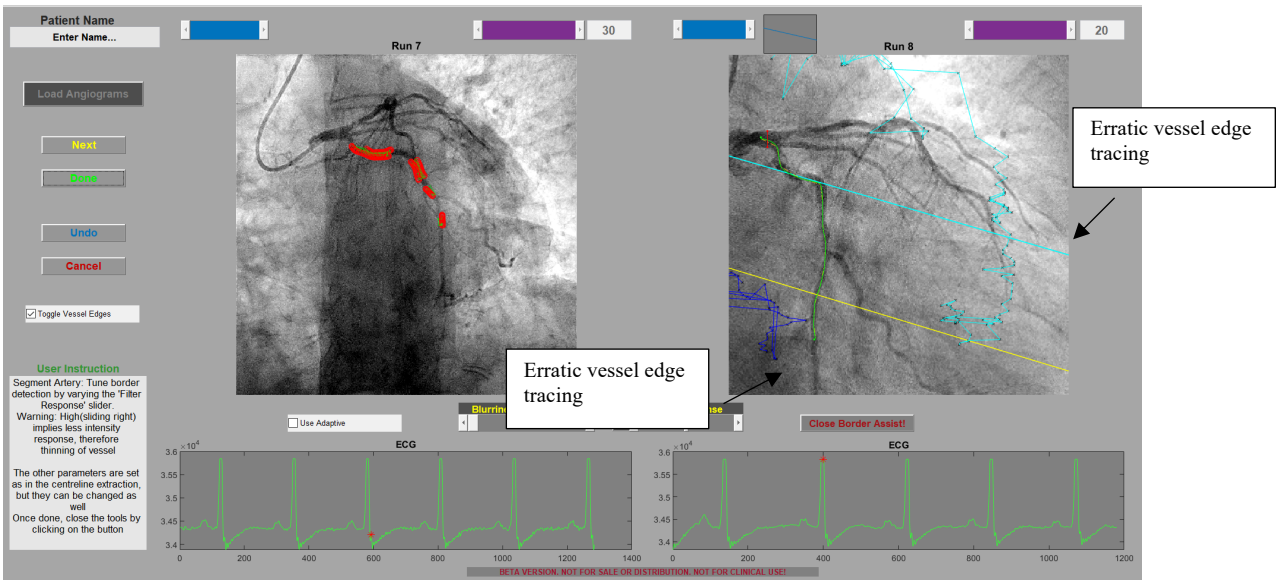


Figure 56 - Erratic vessel edge tracing error.

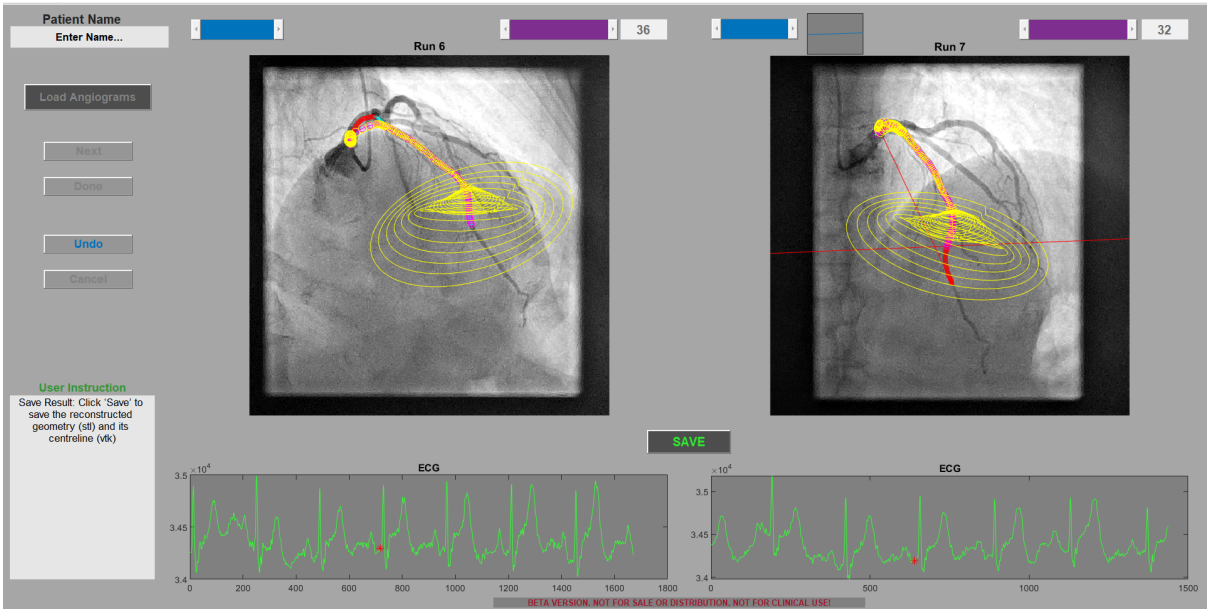


Figure 57 - Bell shape error during segmentation.

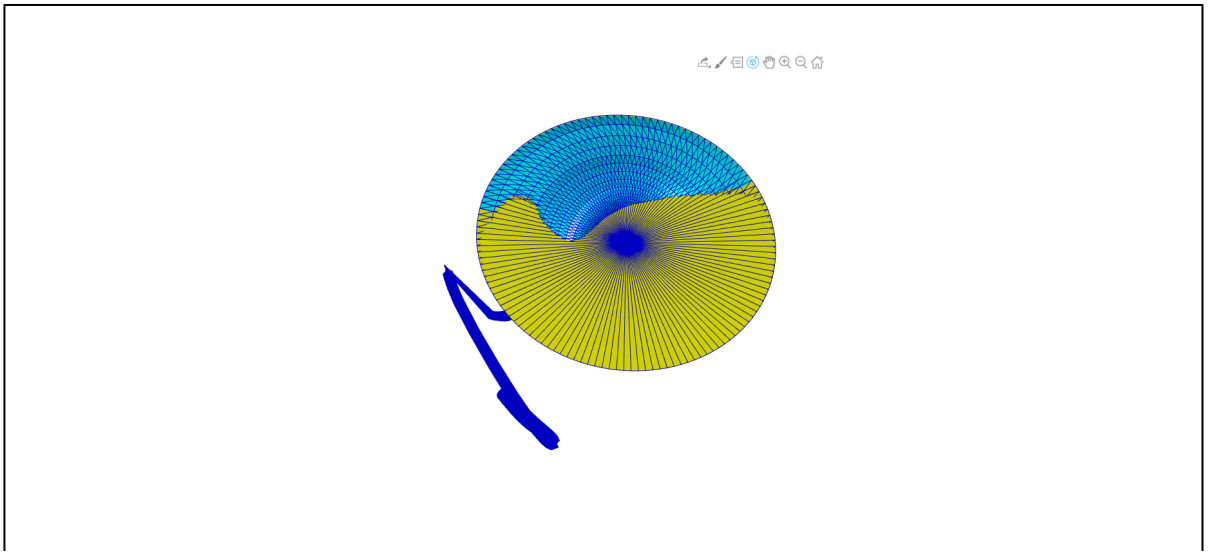


Figure 58 - 3D reconstruction of a vessel following a bell-shaped error.

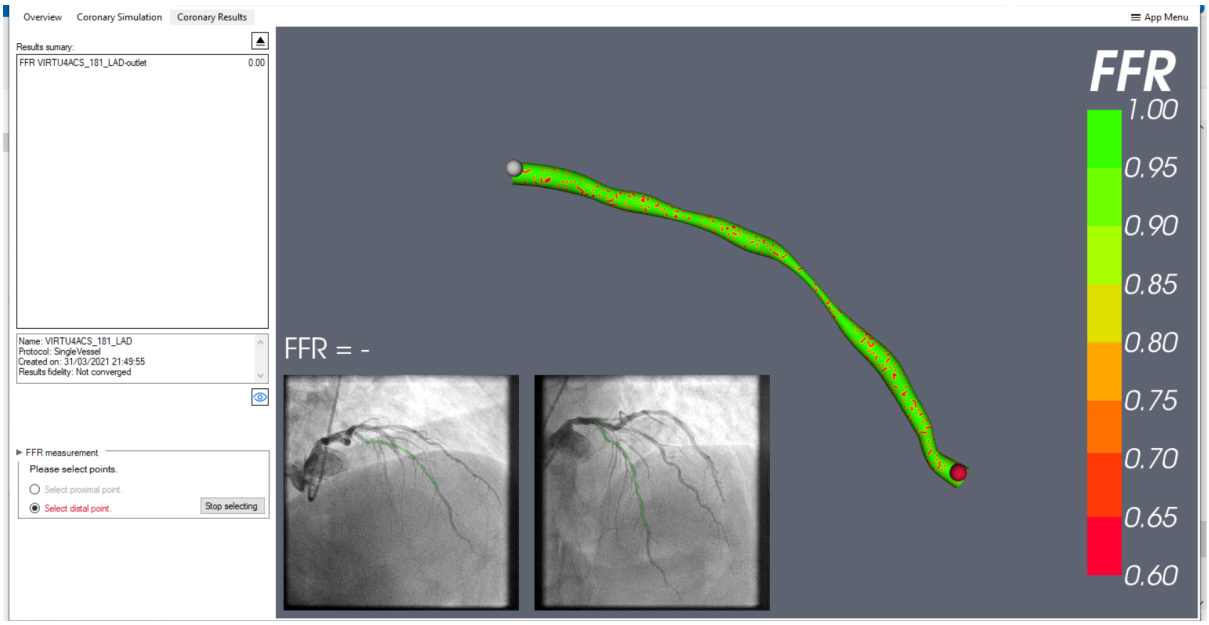


Figure 59 - Non-convergence error of a severely stenosed lesion (leopard skin appearance).

4.16. Reflections and future studies

Reflecting 'real world' practice, the rate of treatment of bystander disease in this study was low [27/101 (27%) of patients], but vFFR was hypothetically demonstrated to have a potentially significant impact to guide PCI treatments either at *de novo* presentation or in the future. By reducing unnecessary invasive procedures, risks and adverse events may be avoided. Even if a bystander lesion is not intervened upon at presentation, the vFFR measurement will be useful to guide future treatments should a patient remain symptomatic. All of these results could influence and may encourage more studies to be undertaken in which vFFR is clinically applied in a larger ACS population. FAVOR III China, a multi-centre RCT of 3860 patients (1213 ACS patients), has shown that a QFR-guided approach led to an improvement in clinical outcome when compared with CAG-guided approach (197). My study has demonstrated that the integration of vFFR into standard management of ACS is feasible and may have benefits. Three approaches are possible for the future. The first would be simply to assume that the benefits seen in the trials of measured FFR are directly transferrable to vFFR, and therefore employ vFFR routinely. However, in the light of the limitations of vFFR outlined here, this assumption may be optimistic. The second would be to interrogate existing data derived from studies employing angiographic guidance, generating post-hoc vFFRs, and re-evaluating outcomes in accordance with vFFR. Because vFFR requires optimal angiographic images, however, many cases would be excluded using this approach; and it would be subject to the

limitations of retrospective studies. The third would be to undertake more prospective, randomised, controlled trials of vFFR- vs CAG- guidance with clinical and health economic endpoints. Work should continue within each vFFR techniques' developers to improve its accuracy and accountancy of CMV resistance in order to improve personalisation the CFD simulation to each individual and/or specific population. This study may be used to generate pilot data to construct a follow-on study focusing on health economics and quality of life. The next step is to compare the head-to-head impact of the various vFFR techniques with CAG-guided or FFR-guided approach in this population. Ultimately, endorsement in clinical guidelines will be required.

4.17. Possible impact of vFFR

vFFR could be the solution to the limited FFR-guided practice in the CCL. In addition to improvement in treatment planning, a benefit of vFFR will be to increase the use of physiological guidance. In the UK, for example, this could be from <20,000 patients who undergo FFR or IFR at the moment, to the 250,000 who undergo CAG. Currently the former groups are all in interventional CCLs. Of the 100,000 PCIs, the equivalent figure is approximately 10,000. So, of all patients being assessed or treated for CAD, invasive physiology is deployed in only 6-7% (198). When vFFR technology becomes available in routine clinical practice and CCL in the future, it may provide greater impact in the way we approach patients with CAD. Whichever approach is adopted, this technology is here to stay.

4.18. What are the limitations of the study?

The first limitation of this study is that it is only hypothetical and did not truly affect the patient's management. Therefore, it cannot be used to assess clinical outcomes. Second, the fact that the study is virtual, may have affected the Cardiologists' decisions. Third, this study excluded prior CABG, severe LMS or ostial lesions, extremely severe lesions (>90%) as well as severe diffuse disease. Therefore, it did not represent those with these conditions. Fourth, it was unknown how it might have been affected by the CMV resistance when compared with mFFR. Fifth, some lesions which were originally deemed <30% and therefore excluded from vFFR computation in the first stage, were re-classified as >30% at MDT level, or vice versa. This may have introduced some inconsistency and would have benefited from a more objective approach of classifying the stenosis in both settings. Sixth, COVID-19 delayed the start of

recruitment by six months. However, because ACS cases were still abundant during the pandemic, I was still able to reach the sample target within the time limit.

5.0. Final summary

In this study, I have shown that vFFR is feasible in a 'real world' cardiac catheter laboratory treating patients with NSTE-ACS, and it hypothetically led to a change in management in 22% of patients. Although vFFR requires meticulous CAG and software training, the less invasive requirements may be more enticing when compared with mFFR which is currently under-used for cost and logistic reasons. The use of vFFR increases operator's confidence. vFFR can be usefully incorporated into MDTs and could positively impact health economics and quality of life. Whilst not all ACS patients may benefit from vFFR, it can be applied to intermediate lesions to aid PCI strategy at presentation or in the future. The next step is to apply vFFR in the real world's clinical setting in order to evaluate its impact on patient's outcome, quality of life and health economic.

REFERENCES

1. Cardiovascular diseases (CVDs) [Internet]. [cited 2020 Feb 5]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

2. Libby P. Inflammation in atherosclerosis. Nature. 2002 Dec;420(6917):868–74.

3. Atherosclerosis | National Heart, Lung, and Blood Institute (NHLBI) [Internet]. [cited 2020 Feb 5]. Available from: https://www.nhlbi.nih.gov/health-topics/atherosclerosis

4. Zaman AG, Helft G, Worthley SG, Badimon JJ. The role of plaque rupture and thrombosis in coronary artery disease. Atherosclerosis. 2000 Apr;149(2):251–66.

5. M A, Ks Y. Pathogenesis of Atherosclerosis A Review. Med Clin Rev [Internet]. 2016 [cited 2020 Feb 5];2(3). Available from: http://medical-clinical-reviews.imedpub.com/pathogenesis-of-atherosclerosisa-review.php?aid=11373

6. Jonason T, Bergström R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand. 1987;221(3):253–60.

7. Moran AE, Tzong KY, Forouzanfar MH, Rothy GA, Mensah GA, Ezzati M, et al. Variations in ischemic heart disease burden by age, country, and income: the Global Burden of Diseases, Injuries, and Risk Factors 2010 study. Glob Heart. 2014 Mar;9(1):91–9.

8. The National Institute for Cardiovascular Outcomes Research (NICOR) | Myocardial Ischaemia/MINAP (Heart Attack audit) [Internet]. [cited 2020 Feb 6]. Available from: https://www.nicor.org.uk/national-cardiac-audit-programme/myocardial-ischaemia-minap-heart-attack-audit/

9. Overview | Unstable angina and NSTEMI: early management | Guidance | NICE [Internet]. NICE; [cited 2020 Mar 10]. Available from: https://www.nice.org.uk/guidance/CG94

10. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst-Ludwig A, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Eur Heart J. 2016 Jan 1;37(1):24–34.

11. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevationTask Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14;37(3):267–315.

12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012 Oct;33(20):2551–67.

13. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. Eur Heart J. 2011 Dec 2;32(24):3107–14.

14. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, et al. Sex-Specific Chest Pain Characteristics in the Early Diagnosis of Acute Myocardial Infarction. JAMA Intern Med. 2014 Feb 1;174(2):241.

15. Canto JG, Fincher C, Kiefe CI, Allison JJ, Li Q, Funkhouser E, et al. Atypical presentations among medicare beneficiaries with unstable angina pectoris. Am J Cardiol. 2002 Aug;90(3):248–53.

16. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289–367.

17. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, et al. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. Circulation [Internet]. 2019 Apr 30 [cited 2022 Jan 11];139(18). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000670

18. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction. Circulation. 2015 Jun 16;131(24):2143–50.

19. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Dec 23;64(24):e139–228.

20. Yusuf S, Wittes J, Friedman L. Overview of Results of Randomized Clinical Trials in Heart Disease: I. Treatments Following Myocardial Infarction. JAMA. 1988 Oct 14;260(14):2088–93.

21. Yasue H, Takizawa A, Nagao M, Nishida S, Horie M, Kubota J, et al. Long-term prognosis for patients with variant angina and influential factors. Circulation. 1988 Jul;78(1):1–9.

22. Silvain J, Storey R, Cayla G, Esteve JB, Dillinger JG, Vicaut E, et al. Impact of morphine administration on ticareglor-induced platelet inhibition in ST-Elevation myocardial infarction patients treated by primary PCI : Results from the private-atlantic study. J Am Coll Cardiol. 2015 Mar;65(10):A15.

23. Thomas M, Morton A, Hossain R, Chen B, Luo L, Shahari NN, et al. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. Thromb Haemost. 2016 Jan;116(07):96–102.

24. Authors/Task Force Members, Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment

elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Dec 1;32(23):2999–3054.

25. Bellemain-Appaix A, Brieger D, Beygui F, Silvain J, Pena A, Cayla G, et al. New P2Y12Inhibitors Versus Clopidogrel in Percutaneous Coronary Intervention. J Am Coll Cardiol. 2010 Nov;56(19):1542–51.

26. Collaboration AT. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71–86.

27. CURE trial investigators. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. N Engl J Med. 2001 Aug 16;345(7):494–502.

28. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. The Lancet. 2001 Aug;358(9281):527–33.

29. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2009 Sep 10;361(11):1045–57.

30. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2007 Nov 15;357(20):2001–15.

31. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. The Lancet. 2000 Jun;355(9219):1936–42.

32. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) investigators and committees. Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. N Engl J Med. 2006 Apr 6;354(14):1464–76.

33. Silvain J, Beygui F, Barthelemy O, Pollack C, Cohen M, Zeymer U, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2012 Feb 13;344(feb03 1):e553–e553.

34. Murphy SA, Gibson CM, Morrow DA, Van de Werf F, Menown IB, Goodman SG, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007 Jul 19;28(17):2077–86.

35. Ren L, Ye H, Wang P, Cui Y, Cao S, Lv S. Comparison of long-term mortality of acute ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome patients after percutaneous coronary intervention. Int J Clin Exp Med. 2014 Dec 15;7(12):5588–92.

36. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). Eur Heart J. 2006 Dec 7;28(12):1409–17.

37. Early management of unstable angina and NSTEMI - NICE Pathways [Internet]. [cited 2020 Mar 5]. Available from: https://pathways.nice.org.uk/pathways/chest-pain/early-management-of-unstable-angina-and-nstemi#content=view-node%3Anodes-when-to-offer-coronary-angiography

38. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of Early Invasive Therapy in Acute Coronary Syndromes. J Am Coll Cardiol. 2006 Oct;48(7):1319–25.

39. Fox KAA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JGP, et al. Long-Term Outcome of a Routine Versus Selective Invasive Strategy in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome. J Am Coll Cardiol. 2010 Jun;55(22):2435–45.

40. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al. Early versus Delayed Invasive Intervention in Acute Coronary Syndromes. N Engl J Med. 2009 May 21;360(21):2165–75.

41. Katritsis DG, Siontis GCM, Kastrati A, van't Hof AWJ, Neumann FJ, Siontis KCM, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. Eur Heart J. 2011 Jan;32(1):32–40.

42. Navarese EP, Gurbel PA, Andreotti F, Tantry U, Jeong YH, Kozinski M, et al. Optimal Timing of Coronary Invasive Strategy in Non–ST-Segment Elevation Acute Coronary Syndromes: A Systematic Review and Meta-analysis. Ann Intern Med. 2013 Feb 19;158(4):261.

43. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the Vulnerable Plaque. J Am Coll Cardiol. 2006 Apr;47(8):C13–8.

44. Kastrati A, Neumann FJ, Schulz S, Massberg S, Byrne RA, Ferenc M, et al. Abciximab and Heparin versus Bivalirudin for Non–ST-Elevation Myocardial Infarction. N Engl J Med. 2011 Nov 24;365(21):1980–9.

45. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al. Early versus Delayed Invasive Intervention in Acute Coronary Syndromes. N Engl J Med. 2009 May 21;360(21):2165–75.

46. Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, et al. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). Eur Heart J. 2012 Aug;33(16):2035–43.

47. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ. Revisiting the culprit lesion in non–Q-wave myocardial infarction. J Am Coll Cardiol. 2002 May;39(9):1456–63.

48. Ambrose JA, Winters SL, Stern A, Eng A, Teichholz LE, Gorlin R, et al. Angiographie morphology and the pathogenesis of unstable angina pectoris. J Am Coll Cardiol. 1985 Mar;5(3):609–16.

49. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple Complex Coronary Plaques in Patients with Acute Myocardial Infarction. N Engl J Med. 2000 Sep 28;343(13):915–22.

50. Sgarbossa EB, Birnbaum Y, Parrillo JE. Electrocardiographic diagnosis of acute myocardial infarction: Current concepts for the clinician. Am Heart J. 2001 Apr;141(4):507–17.

51. Beller GA, Zaret BL. Contributions of Nuclear Cardiology to Diagnosis and Prognosis of Patients With Coronary Artery Disease. Circulation. 2000 Mar 28;101(12):1465–78.

52. Shaw LJ, Berman DS, Maron DJ, Mancini GBJ, Hayes SW, Hartigan PM, et al. Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden: Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear Substudy. Circulation. 2008 Mar 11;117(10):1283–91.

53. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) Study Two-Year Follow-up: Outcomes of Patients Randomized to Initial Strategies of Medical Therapy Versus Revascularization. Circulation. 1997 Apr 15;95(8):2037–43.

54. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, et al. Effects of Percutaneous Coronary Interventions in Silent Ischemia After Myocardial Infarction: The SWISSI II Randomized Controlled Trial. JAMA. 2007 May 9;297(18):1985.

55. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, et al. Coronary Angioplasty with or without Stent Implantation for Acute Myocardial Infarction. N Engl J Med. 1999 Dec 23;341(26):1949–56.

56. Räber L, Kelbæk H, Ostojic M, Baumbach A, Heg D, Tüller D, et al. Effect of Biolimus-Eluting Stents With Biodegradable Polymer vs Bare-Metal Stents on Cardiovascular Events Among Patients With Acute Myocardial Infarction: The COMFORTABLE AMI Randomized Trial. JAMA. 2012 Aug 22;308(8):777.

57. Sabate M, Cequier A, Iñiguez A, Serra A, Hernandez-Antolin R, Mainar V, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. The Lancet. 2012 Oct;380(9852):1482–90.

58. Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, et al. Two-Year Outcomes After First- or Second-Generation Drug-Eluting or Bare-Metal Stent Implantation in All-Comer Patients Undergoing Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2014 Jan;7(1):20–8.

59. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. The Lancet. 2015 Jun;385(9986):2465–76.

60. Cardiac Surgery - Coronary Artery Bypass Grafting (CABG) [Internet]. [cited 2020 Jun 28]. Available from: https://cardiacsurgery.ucsf.edu/conditions--procedures/coronary-artery-bypass-grafting-(cabg).aspx

61. Ranasinghe I, Alprandi-Costa B, Chow V, Elliott JM, Waites J, Counsell JT, et al. Risk Stratification in the Setting of Non-ST Elevation Acute Coronary Syndromes 1999-2007. Am J Cardiol. 2011 Sep;108(5):617–24.

62. Fukui T, Tabata M, Morita S, Takanashi S. Early and long-term outcomes of coronary artery bypass grafting in patients with acute coronary syndrome versus stable angina pectoris. J Thorac Cardiovasc Surg. 2013 Jun;145(6):1577-1583.e1.

63. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. N Engl J Med. 2007 Apr 12;356(15):1503–16.

64. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. The Lancet. 2018 Jan;391(10115):31–40.

65. Jackson M, Freeman Hospital, High Heaton, Newcastle-Upon-Tyne, UK, Zaman A, Freeman Hospital, High Heaton, Newcastle-Upon-Tyne, UK. ORBITA: What Goes Around, Comes Around… Or Does It? Interv Cardiol Rev. 2018;13(3):135.

66. Bhatt DL, Kumbhani DJ. Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina [Internet]. American College of Cardiology. [cited 2020 Jun 24]. Available from: http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2fclinical-trials%2f2017%2f11%2f02%2f08%2f26%2forbita

67. Jeremias A, Kaul S, Rosengart TK, Gruberg L, Brown DL. The Impact of Revascularization on Mortality in Patients with Nonacute Coronary Artery Disease. Am J Med. 2009 Feb;122(2):152–61.

68. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med. 2020 Apr 9;382(15):1395–407.

69. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromesThe Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2020 Jan 14;41(3):407–77.

70. Wallentin L, Lindhagen L, Ärnström E, Husted S, Janzon M, Johnsen SP, et al. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. The Lancet. 2016 Oct;388(10054):1903–11.

71. Fox KAA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JGP, et al. Long-Term Outcome of a Routine Versus Selective Invasive Strategy in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome. J Am Coll Cardiol. 2010 Jun;55(22):2435–45.

72. Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, et al. Extent, Location, and Clinical Significance of Non–Infarct-Related Coronary Artery Disease Among Patients With ST-Elevation Myocardial Infarction. JAMA. 2014 Nov 19;312(19):2019.

73. Toma M, Buller CE, Westerhout CM, Fu Y, O'Neill WW, Holmes DR, et al. Non-culprit coronary artery percutaneous coronary intervention during acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. Eur Heart J. 2010 Jul 2;31(14):1701–7.

74. Desperak P, Hawranek M, Gąsior P, Desperak A, Lekston A, Gąsior M. Long-term outcomes of patients with multivessel coronary artery disease presenting non-ST-segment elevation acute coronary syndromes. Cardiol J. 2019;26(2):157–68.

75. Gąsior P, Desperak P, Gierlaszyńska K, Hawranek M, Gierlotka M, Gąsior M, et al. Percutaneous coronary intervention in treatment of multivessel coronary artery disease in patients with non-ST-segment elevation acute coronary syndrome. Adv Interv Cardiol. 2013;2:136–45.

76. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol. 2015 Mar 17;65(10):963–72.

77. Jang JS, Spertus JA, Arnold SV, Shafiq A, Grodzinsky A, Fendler TJ, et al. Impact of Multivessel Revascularization on Health Status Outcomes in Patients with ST-Elevation Myocardial Infarction and Multivessel Coronary Disease. J Am Coll Cardiol. 2015 Nov 10;66(19):2104–13.

78. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, et al. Fractional Flow Reserve–Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med. 2017 Mar 30;376(13):1234–44.

79. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. The Lancet. 2015 Aug;386(9994):665–71.

80. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019 Oct 10;381(15):1411–21.

81. Fox K, Poole-Wilson P, Henderson R, Clayton T, Chamberlain D, Shaw T, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-

elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. The Lancet. 2002 Sep;360(9335):743–51.

82. Wallentin L, Lagerqvist B, Husted S, Kontny F, Ståhle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. The Lancet. 2000 Jul;356(9223):9–16.

83. Généreux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, et al. Quantification and Impact of Untreated Coronary Artery Disease After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2012 Jun;59(24):2165–74.

84. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, et al. Quantification of Incomplete Revascularization and its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score. Circulation. 2013 Jul 9;128(2):141–51.

85. Curtis JP, Schreiner G, Wang Y, Chen J, Spertus JA, Rumsfeld JS, et al. All-Cause Readmission and Repeat Revascularization After Percutaneous Coronary Intervention in a Cohort of Medicare Patients. J Am Coll Cardiol. 2009 Sep;54(10):903–7.

86. Rathod KS, Koganti S, Jain AK, Astroulakis Z, Lim P, Rakhit R, et al. Complete Versus Culprit-Only Lesion Intervention in Patients With Acute Coronary Syndromes. J Am Coll Cardiol. 2018 Oct;72(17):1989–99.

87. Poole-Wilson PA. Interventional versus conservative treatment in acute non-ST elevation coronary syndrome: time course of patient management and disease events over one year in the RITA 3 trial. Heart. 2006 May 15;92(10):1473–9.

88. Shishehbor MH, Lauer MS, Singh IM, Chew DP, Karha J, Brener SJ, et al. In Unstable Angina or Non–ST-Segment Acute Coronary Syndrome, Should Patients With Multivessel Coronary Artery Disease Undergo Multivessel or Culprit-Only Stenting? J Am Coll Cardiol. 2007 Feb;49(8):849–54.

89. Kim MC, Hyun JY, Ahn Y, Bae S, Hyun DY, Cho KH, et al. Optimal Revascularization Strategy in Non–ST-Segment–Elevation Myocardial Infarction With Multivessel Coronary Artery Disease: Culprit-Only Versus One-Stage Versus Multistage Revascularization. J Am Heart Assoc. 2020 Aug 4;9(15):e016575.

90. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2010 Oct 2;31(20):2501–55.

91. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. N Engl J Med. 2009 Mar 5;360(10):961–72.

92. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Ettinger SM, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart

Association Task Force on Practice Guidelines. Circulation. 2011 May 10;123(18):2022–60.

93. Mårtensson S, Gyrd-Hansen D, Prescott E, Andersen PK, Zwisler ADO, Osler M. Trends in time to invasive examination and treatment from 2001 to 2009 in patients admitted first time with non-ST elevation myocardial infarction or unstable angina in Denmark. BMJ Open. 2014 Jan;4(1):e004052.

94. Sels JWEM, Tonino PAL, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, et al. Fractional Flow Reserve in Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction. JACC Cardiovasc Interv. 2011 Nov;4(11):1183–9.

95. Lima RSL, Watson DD, Goode AR, Siadaty MS, Ragosta M, Beller GA, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. J Am Coll Cardiol. 2003 Jul;42(1):64–70.

96. Kolansky D. Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. Am J Manag Care 200915S36-S41. 2009;15:S36–41.

97. Zhao Z, Winget M. Economic burden of illness of acute coronary syndromes: medical and productivity costs. BMC Health Serv Res. 2011 Dec;11(1):35.

98. Stenvall H, Tierala I, Räsänen P, Laine M, Sintonen H, Roine RP. Long-term clinical outcomes, health-related quality of life, and costs in different treatment modalities of stable coronary artery disease. Eur Heart J - Qual Care Clin Outcomes. 2017 Jan;3(1):74–82.

99. Ferko N, Ferrante G, Hasegawa JT, Schikorr T, Soleas IM, Hernandez JB, et al. Cost-effectiveness of percutaneous coronary intervention with cobalt-chromium everolimus eluting stents versus bare metal stents: Results from a patient level meta-analysis of randomized trials: Cost-Effectiveness of PCI With Co-Cr EES. Catheter Cardiovasc Interv. 2017 May;89(6):994–1002.

100. Janzon M. Cost-effectiveness of an invasive strategy in unstable coronary artery disease. Results from the FRISC II invasive trial. Eur Heart J. 2002 Jan 1;23(1):31–40.

101. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, et al. Testing of Low-Risk Patients Presenting to the Emergency Department With Chest Pain: A Scientific Statement From the American Heart Association. Circulation. 2010 Oct 26;122(17):1756–76.

102. Roobottom C, Mitchell G, Iyengar S. The role of non-invasive imaging in patients with suspected acute coronary syndrome. Br J Radiol. 2011 Dec;84(special_issue_3):S269–79.

103. Beigel R, Oieru D, Goitein O, Chouraqui P, Konen E, Shamiss A, et al. Usefulness of Routine Use of Multidetector Coronary Computed Tomography in the "Fast Track" Evaluation of Patients With Acute Chest Pain. Am J Cardiol. 2009 Jun;103(11):1481–6.

104. Hollander JE, Chang AM, Shofer FS, McCusker CM, Baxt WG, Litt HI. Coronary Computed Tomographic Angiography for Rapid Discharge of Low-Risk Patients With Potential Acute Coronary Syndromes. Ann Emerg Med. 2009 Mar;53(3):295–304.

105. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, et al. Coronary Computed Tomography Angiography for Early Triage of Patients With Acute Chest Pain. J Am Coll Cardiol. 2009 May;53(18):1642–50.

106. Gray AJ, Roobottom C, Smith JE, Goodacre S, Oatey K, O'Brien R, et al. The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) — a multicentre parallel-group randomised trial to compare early computerised tomography coronary angiography versus standard care in patients presenting with suspected or confirmed acute coronary syndrome: study protocol for a randomised controlled trial. Trials. 2016 Dec;17(1):579.

107. Sarno G, Decraemer I, Vanhoenacker PK, De Bruyne B, Hamilos M, Cuisset T, et al. On the Inappropriateness of Noninvasive Multidetector Computed Tomography Coronary Angiography to Trigger Coronary Revascularization. JACC Cardiovasc Interv. 2009 Jun;2(6):550–7.

108. Taylor CA, Fonte TA, Min JK. Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve. J Am Coll Cardiol. 2013 Jun;61(22):2233–41.

109. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, et al. Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms. J Am Coll Cardiol. 2011 Nov;58(19):1989–97.

110. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic Performance of Noninvasive Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography in Suspected Coronary Artery Disease. J Am Coll Cardiol. 2014 Apr;63(12):1145–55.

111. CT coronary angiography with HeartFlow®: a user's perspective. Br J Cardiol [Internet]. 2019 [cited 2020 Oct 2]; Available from: https://bjcardio.co.uk/2019/09/ct-coronary-angiography-with-heartflow-a-users-perspective/

112. Morris PD, Curzen N, Gunn JP. Angiography-Derived Fractional Flow Reserve: More or Less Physiology? J Am Heart Assoc [Internet]. 2020 Mar 17 [cited 2021 Jul 1];9(6). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.119.015586

113. Members AF. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006 Mar 16;27(11):1341–81.

114. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic Performance of Stress Cardiac Magnetic Resonance Imaging in the Detection of Coronary Artery Disease. J Am Coll Cardiol. 2007 Oct;50(14):1343–53.

115. Th Wackers FJ. Chest pain in the emergency department: role of cardiac imaging. Heart. 2009 Jun 15;95(12):1023–30.

116. Katritsis D, Webb-Peploe M. Limitations of coronary angiography: An underestimated problem? Clin Cardiol. 1991;14(1):20–4.

117. Green N. Three-dimensional vascular angiography. Curr Probl Cardiol. 2004 Mar;29(3):104–42.

118. White CW, Wright CB, Doty DB, Hiratza LF, Eastham CL, Harrison DG, et al. Does Visual Interpretation of the Coronary Arteriogram Predict the Physiologic Importance of a Coronary Stenosis? N Engl J Med. 1984 Mar 29;310(13):819–24.

119. Fischer JJ, Samady H, McPherson JA, Sarembock IJ, Powers ER, Gimple LW, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. Am J Cardiol. 2002 Aug;90(3):210–5.

120. Alexander Y, Osto E, Schmidt-Trucksäss A, Shechter M, Trifunovic D, Duncker DJ, et al. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. Cardiovasc Res. 2021 Jan 1;117(1):29–42.

121. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014 Oct 1;35(37):2541–619.

122. Achenbach S, Department of Cardiology, Friedrich-Alexander University (FAU) Erlangen-Nuremberg, Germany, Rudolph T, Department of Internal Medicine 3, University Hospital, Cologne, Germany, Rieber J, Heart Centre, Municipal Hospitals of Munich, Munich, Germany, et al. Performing and Interpreting Fractional Flow Reserve Measurements in Clinical Practice: An Expert Consensus Document. Interv Cardiol Rev. 2017;12(02):97.

123. Pijls NHJ, de Bruyne B, Peels K, van der Voort PH, Bonnier HJRM, Bartunek J, et al. Measurement of Fractional Flow Reserve to Assess the Functional Severity of Coronary-Artery Stenoses. N Engl J Med. 1996 Jun 27;334(26):1703–8.

124. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, et al. Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention in Patients With Multivessel Coronary Artery Disease. J Am Coll Cardiol. 2010 Jul;56(3):177–84.

125. De Bruyne B, Fearon WF, Pijls NHJ, Barbato E, Tonino P, Piroth Z, et al. Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease. N Engl J Med. 2014 Sep 25;371(13):1208–17.

126. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J. 2015 Dec 1;36(45):3182–8.

127. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation. 1993 Apr;87(4):1354–67.

128. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease. N Engl J Med. 2012 Sep 13;367(11):991–1001.

129. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS–NSTEMI randomized trial. Eur Heart J. 2015 Jan 7;36(2):100–11.

130. Pijls NHJ, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis. J Am Coll Cardiol. 2007 May;49(21):2105–11.

131. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van `t Veer M, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. N Engl J Med. 2009 Jan 15;360(3):213–24.

132. van Nunen LX, Zimmermann FM, Tonino PAL, Barbato E, Baumbach A, Engstrøm T, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. The Lancet. 2015 Nov;386(10006):1853–60.

133. De Bruyne B, Fearon WF, Pijls NHJ, Barbato E, Tonino P, Piroth Z, et al. Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease. N Engl J Med. 2014 Sep 25;371(13):1208–17.

134. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018 Jul 19;379(3):250–9.

135. Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, et al. Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?: The RIPCORD Study. Circ Cardiovasc Interv. 2014 Apr;7(2):248–55.

136. Selby JV, Fireman BH, Lundstrom RJ, Swain BE, Truman AF, Wong CC, et al. Variation among Hospitals in Coronary-Angiography Practices and Outcomes after Myocardial Infarction in a Large Health Maintenance Organization. N Engl J Med. 1996 Dec 19;335(25):1888–96.

137. Botman KJ, Pijls NHJ, Bech JW, Aarnoudse W, Peels K, van Straten B, et al. Percutaneous coronary intervention or bypass surgery in multivessel disease? A tailored approach based on coronary pressure measurement. Catheter Cardiovasc Interv. 2004 Oct;63(2):184–91.

138. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, et al. Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary

Intervention in Patients With Multivessel Coronary Artery Disease: 2-Year Follow-Up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) Study. J Am Coll Cardiol. 2010 Jul 13;56(3):177–84.

139. Fearon WF, Bornschein B, Tonino PAL, Gothe RM, Bruyne BD, Pijls NHJ, et al. Economic Evaluation of Fractional Flow Reserve–Guided Percutaneous Coronary Intervention in Patients With Multivessel Disease. Circulation. 2010 Dec 14;122(24):2545–50.

140. Omran J, Enezate T, Abdullah O, Al-Dadah A, Walters D, Patel M, et al. Outcomes of fractional flow reserve-guided percutaneous coronary interventions in patients with acute coronary syndrome. Catheter Cardiovasc Interv. 2019 Nov 29;ccd.28611.

141. Nam J, Briggs A, Layland J, Oldroyd KG, Curzen N, Sood A, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. Cost Eff Resour Alloc. 2015 Dec;13(1):19.

142. Lopez-Palop R, Carrillo P, Torres F, Lozano I, Frutos A, Avanzas P, et al. Resultados del empleo de la reserva fraccional de flujo en la valoración de lesiones no causales en el síndrome coronario agudo. Rev Esp Cardiol. 2012 Feb;65(2):164–70.

143. Briasoulis A, Palla M, Mostafa A, Afonso L, Grines C. Fractional flow-guided management in patients with acute coronary syndromes: A systematic review and meta-analysis. Int J Cardiol. 2015 May 6;187:334–7.

144. Van Belle E, Baptista SB, Raposo L, Henderson J, Rioufol G, Santos L, et al. Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes: PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries - Implementation of FFR [Fractional Flow Reserve] in Routine Practice). Circ Cardiovasc Interv [Internet]. 2017 Jun [cited 2020 Jun 17];10(6). Available from: https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.116.004296

145. Lee JM, Choi KH, Koo BK, Shin ES, Nam CW, Doh JH, et al. Prognosis of deferred non-culprit lesions according to fractional flow reserve in patients with acute coronary syndrome. EuroIntervention. 2017 Oct;13(9):e1112–9.

146. Martins JL, Afreixo V, Santos J, Gonçalves L. Fractional Flow Reserve-Guided Strategy in Acute Coronary Syndrome. A Systematic Review and Meta-Analysis. Arq Bras Cardiol [Internet]. 2018 [cited 2021 Jan 19]; Available from: https://www.scielo.br/scielo.php?pid=S0066-782X2018005013109&script=sci_arttext

147. Liou KP, Ooi SYM, Hoole SP, West NEJ. Fractional flow reserve in acute coronary syndrome: a meta-analysis and systematic review. Open Heart. 2019 Jan;6(1):e000934.

148. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020 Aug 29;ehaa575.

149. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87–165.

150. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, et al. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. N Engl J Med. 2021 Jul 22;385(4):297–308.

151. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary Patterns of Fractional Flow Reserve and Intravascular Ultrasound Use Among Patients Undergoing Percutaneous Coronary Intervention in the United States. J Am Coll Cardiol. 2012 Dec;60(22):2337–9.

152. Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, et al. Revascularization Decisions in Patients With Stable Angina and Intermediate Lesions: Results of the International Survey on Interventional Strategy. Circ Cardiovasc Interv. 2014 Dec;7(6):751–9.

153. Pijls NHJ, Tanaka N, Fearon WF. Functional assessment of coronary stenoses: can we live without it? Eur Heart J. 2013 May 2;34(18):1335–44.

154. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional Flow Reserve for the Assessment of Nonculprit Coronary Artery Stenoses in Patients With Acute Myocardial Infarction. JACC Cardiovasc Interv. 2010 Dec;3(12):1274–81.

155. De Bruyne B, Pijls NHJ, Bartunek J, Kulecki K, Bech JW, De Winter H, et al. Fractional Flow Reserve in Patients With Prior Myocardial Infarction. Circulation. 2001 Jul 10;104(2):157–62.

156. Samady H, Lepper W, Powers ER, Wei K, Ragosta M, Bishop GG, et al. Fractional Flow Reserve of Infarct-Related Arteries Identifies Reversible Defects on Noninvasive Myocardial Perfusion Imaging Early After Myocardial Infarction. J Am Coll Cardiol. 2006 Jun;47(11):2187–93.

157. van de Hoef TP, Nolte F, Rolandi MC, Piek JJ, van den Wijngaard JPHM, Spaan JAE, et al. Coronary pressure-flow relations as basis for the understanding of coronary physiology. J Mol Cell Cardiol. 2012 Apr;52(4):786–93.

158. Briceno N, Lumley M, Perera D. Fractional flow reserve: conundrums, controversies and challenges. Interv Cardiol. 2015 Dec;7(6):543–52.

159. Vranckx P, Cutlip DE, McFadden EP, Kern MJ, Mehran R, Muller O. Coronary Pressure–Derived Fractional Flow Reserve Measurements: Recommendations for Standardization, Recording, and Reporting as a Core Laboratory Technique. Proposals for Integration in Clinical Trials. Circ Cardiovasc Interv. 2012 Apr;5(2):312–7.

160. Matsumuto, Hidenari, Nakatsuma, Kenji, shimada, thoshihiko. Effect of Caffeine on Intravenous Adenosine-Induced Hyperemia in Fractional Flow Reserve Measurement [Internet]. Journal of Invasive Cardiology. [cited 2020 Jun 7]. Available from: https://www.invasivecardiology.com/articles/effect-caffeine-intravenous-adenosine-induced-hyperemia-fractional-flow-reserve-measurement

161. Leonardi RA, Townsend JC, Patel CA, Wolf BJ, Todoran TM, Fernandes VL, et al. Left ventricular end-diastolic pressure affects measurement of fractional flow reserve. Cardiovasc Revasc Med. 2013 Jul;14(4):218–22.

162. Petraco R, Sen S, Nijjer S, Echavarria-Pinto M, Escaned J, Francis DP, et al. Fractional Flow Reserve–Guided Revascularization. JACC Cardiovasc Interv. 2013 Mar;6(3):222–5.

163. De Bruyne B, Pijls NHJ, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-Derived Fractional Flow Reserve to Assess Serial Epicardial Stenoses: Theoretical Basis and Animal Validation. Circulation. 2000 Apr 18;101(15):1840–7.

164. Kesson EM, Allardice GM, George WD, Burns HJG, Morrison DS. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. BMJ. 2012 Apr 26;344(apr26 1):e2718–e2718.

165. van Hagen P, Spaander MCW, van der Gaast A, van Rij CM, Tilanus HW, van Lanschot JJB, et al. Impact of a multidisciplinary tumour board meeting for upper-GI malignancies on clinical decision making: a prospective cohort study. Int J Clin Oncol. 2013 Apr;18(2):214–9.

166. Ray-Coquard I, Thiesse P, Ranchère-Vince D, Chauvin F, Bobin JY, Sunyach MP, et al. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. Ann Oncol Off J Eur Soc Med Oncol. 2004 Feb;15(2):307–15.

167. Norell, M, Luckraz H, Buch M, James R, Cooper C, Fisher M, et al. The Heart Team [Internet]. BCIS. [cited 2020 Jun 23]. Available from: https://www.bcis.org.uk/resources/bcis-guidance-documents/the-heart-team/

168. Head SJ, Kaul S, Mack MJ, Serruys PW, Taggart DP, Holmes DR, et al. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. Eur Heart J. 2013 Aug 2;34(32):2510–8.

169. CABG_summary.pdf [Internet]. [cited 2020 Jun 18]. Available from: https://www.ncepod.org.uk/2008report2/Downloads/CABG_summary.pdf

170. Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI), Authors/Task Force Members, Wijns W, Kolh P, Danchin N, Di Mario C, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2010 Oct 2;31(20):2501–55.

171. Writing Committee Members, Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011 Dec 6;124(23):2610–42.

172. 1 Recommendations | HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography | Guidance | NICE [Internet]. NICE; [cited 2020 May 11]. Available from: https://www.nice.org.uk/guidance/mtg32/chapter/1-Recommendations

173. Morris PD, Ryan D, Morton AC, Lycett R, Lawford PV, Hose DR, et al. Virtual Fractional Flow Reserve From Coronary Angiography: Modeling the Significance of Coronary Lesions. JACC Cardiovasc Interv. 2013 Feb;6(2):149–57.

174. Tu S, Barbato E, Köszegi Z, Yang J, Sun Z, Holm NR, et al. Fractional Flow Reserve Calculation From 3-Dimensional Quantitative Coronary Angiography and TIMI Frame Count: A Fast Computer Model to Quantify the Functional Significance of Moderately Obstructed Coronary Arteries. JACC Cardiovasc Interv. 2014 Jul 1;7(7):768–77.

175. Tu S, Xu L, Ligthart J, Xu B, Witberg K, Sun Z, et al. In vivo comparison of arterial lumen dimensions assessed by co-registered three-dimensional (3D) quantitative coronary angiography, intravascular ultrasound and optical coherence tomography. Int J Cardiovasc Imaging. 2012 Aug;28(6):1315–27.

176. Fearon WF, Achenbach S, Engstrom T, Assali A, Shlofmitz R, Jeremias A, et al. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. Circulation. 2019 Jan 22;139(4):477–84.

177. Gould KLMD, Kelley KORN, Bolson ELMS. Experimental Validation of Quantitative Coronary Arteriography for Determining Pressure-Flow Characteristics of Coronary Stenosis. Circulation. 1982 Nov;66(5):930–7.

178. Gosling RC, Morris PD, Silva Soto DA, Lawford PV, Hose DR, Gunn JP. Virtual Coronary Intervention. JACC Cardiovasc Imaging. 2019 May;12(5):865–72.

179. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography. JACC Cardiovasc Interv. 2016 Oct;9(19):2024–35.

180. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc. 2018 Jul 17;7(14).

181. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol. 2017 Dec;70(25):3077–87.

182. Stähli BE, Erbay A, Steiner J, Klotsche J, Mochmann HC, Skurk C, et al. Comparison of resting distal to aortic coronary pressure with angiography-based quantitative flow ratio. Int J Cardiol. 2019 Mar 15;279:12–7.

183. Pellicano M, Lavi I, De Bruyne B, Vaknin-Assa H, Assali A, Valtzer O, et al. Validation Study of Image-Based Fractional Flow Reserve During Coronary Angiography. Circ Cardiovasc Interv [Internet]. 2017 Sep [cited 2020 May 11];10(9). Available from: https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.116.005259

184. Omori H, Witberg G, Kawase Y, Tanigaki T, Okamoto S, Hirata T, et al. Angiogram based fractional flow reserve in patients with dual/triple vessel coronary artery disease. Int J Cardiol. 2019 May;283:17–22.

185. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, et al. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. EuroIntervention. 2020 Sep;16(7):591–9.

186. Li J, Gong Y, Wang W, Yang Q, Liu B, Lu Y, et al. Accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR. Cardiovasc Res. 2020 Jun 1;116(7):1349–56.

187. Papafaklis MI, Muramatsu T, Ishibashi Y, Lakkas LS, Nakatani S, Bourantas CV, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire – fractional flow reserve. EuroIntervention. 2014 Sep;10(5):574–83.

188. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol. 2017 Dec;70(25):3077–87.

189. Johnson Nils P., Matsumura Mitsuaki, Achenbach Stephan, Engstrom Thomas, Assali Abid, Jeremias Allen, et al. Angiography-Derived Fractional Flow Reserve Versus Invasive Nonhyperemic Pressure Ratios. J Am Coll Cardiol. 2019 Jun 25;73(24):3232–3.

190. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, et al. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. EuroIntervention. 2020 Sep;16(7):591–9.

191. Tröbs M, Achenbach S, Röther J, Redel T, Scheuering M, Winneberger D, et al. Comparison of Fractional Flow Reserve Based on Computational Fluid Dynamics Modeling Using Coronary Angiographic Vessel Morphology Versus Invasively Measured Fractional Flow Reserve. Am J Cardiol. 2016 Jan 1;117(1):29–35.

192. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc [Internet]. 2018 Jul 17 [cited 2021 Jan 19];7(14). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.118.009603

193. Morris PD, van de Vosse FN, Lawford PV, Hose DR, Gunn JP. "Virtual" (Computed) Fractional Flow Reserve. JACC Cardiovasc Interv. 2015 Jul;8(8):1009–17.

194. Lal K, Gunn J, Morris P, Gosling R, Lawford P, Hose R, et al. 17 Computational modelling of fractional flow reserve from coronary angiography: expert training required. In: Imaging [Internet]. BMJ Publishing Group Ltd and British Cardiovascular Society; 2019 [cited 2020 Jun 16]. p. A15–6. Available from: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2019-BCS.16

195. Preston, H, Stroud, S, Lai, K, Gosling, R, Morris, P, Hose, D.R, et al. Abstract 9797: Feasibility of Coronary Angiogram-based Computational Modelling of Fractional Flow Reserve in Everyday Practice | Circulation.

196. Gosling DRC, Adam Z, Barmby DS, Iqbal J, Morgan KP, Richardson JD, et al. The Impact of Virtual Fractional Flow Reserve and Virtual Coronary Intervention Upon Treatment Decisions in the Cardiac Catheter Laboratory. Can J Cardiol. 2021 Jun;S0828282X21003019.

197. Xu B, Tu S, Song L, Jin Z, Yu B, Fu G, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. The Lancet. 2021 Dec;398(10317):2149–59.

198. Ludman, Peter. BCIS Audit of adult cardiovascular interventions performed from 1st of April 2018 to 31st if March 2019. BCIS Audit Rep 2018-2019 [Internet]. 2019 May 5; Available from: https://www.bcis.org.uk/education/bcis-audit-report-2018-19/

199. Morris PD, Gosling R, Zwierzak I, Evans H, Aubiniere-Robb L, Czechowicz K, et al. A novel method for measuring absolute coronary blood flow and microvascular resistance in patients with ischaemic heart disease. Cardiovasc Res. 2021 May 25;117(6):1567–77.

200. Morris PD, Iqbal J, Chiastra C, Wu W, Migliavacca F, Gunn JP. Simultaneous kissing stents to treat unprotected left main stem coronary artery bifurcation disease; stent expansion, vessel injury, hemodynamics, tissue healing, restenosis, and repeat revascularization. Catheter Cardiovasc Interv. 2018 Nov 15;92(6):E381–92.

201. Xie Y, Mintz GS, Yang J, Doi H, Iñiguez A, Dangas GD, et al. Clinical Outcome of Nonculprit Plaque Ruptures in Patients With Acute Coronary Syndrome in the PROSPECT Study. JACC Cardiovasc Imaging. 2014 Apr;7(4):397–405.

202. Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, et al. Association Between IVUS Findings and Adverse Outcomes in Patients With Coronary Artery Disease. JACC Cardiovasc Imaging. 2011 Aug;4(8):894–901.

203. Bom MJ, van der Heijden DJ, Kedhi E, van der Heyden J, Meuwissen M, Knaapen P, et al. Early Detection and Treatment of the Vulnerable Coronary Plaque: Can We Prevent Acute Coronary Syndromes? Circ Cardiovasc Imaging [Internet]. 2017 May [cited 2021 Jan 23];10(5). Available from: https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.116.005973

APPENDIX

I. Standard operating procedure

VIRTU4–ACS standard operating protocol

Does the virtual FFR (vFFR) have the potential to change management of patients with acute coronary syndrome?

Inclusion Criteria

1. Age ≥ 18
2. Patients admitted to NGH or (treat and return) with Acute Coronary Syndrome
3. Arteries with ≥30% but less than 90% stenosis and suitable for stenting (≥ 2.25mm)

Exclusion Criteria

1. Age ≤ 18
2. Unable to consent due to language barrier
3. Patients with stable coronary artery disease in a non-acute presentation
4. Severe co-morbidities and frailty
5. Renal impairment > 180mmol/l
6. Prior CABG
7. Chronic Total Occlusion (CTO) as the only lesion
8. Severe diffuse disease
9. Left main and ostial disease
10. Normal coronary angiogram

Threshold for Ischaemia: vFFR ≤ 0.80

Checklist

1. Identify eligible patients and supply them with patient information sheet
2. Consent patients as per guideline
3. Brief lab team including consultant and radiographers prior to starting the case
4. Ensure angiogram captured are suitable for modelling and that they meet standard requirements
5. Enter patient's data on VIRTU4 ACS spread sheet during each case (Demographics, Clinical data etc)
6. Record Consultants' decision on patient's management after angiogram is taken
7. Upload angiogram images (DICOM format) onto lap top/storage drive/CD for processing on VIRTUheart™ workflow
8. Segment coronary artery as per study criteria, run coronary simulation and compute vFFR
9. Reveal the result of virtual vFFR to the consultant and record how his/her management would change
10. Record patient's participation for the study in medical notes
11. Re-process angiograms offline centrally and calculate second set of vFFRs as per previous steps
12. Present second set of vFFRs at Heart MDTs and record outcome in similar fashion to previous steps
13. Upload all anonymised data to central ARQ database.
14. Conduct telephone interview and remote interrogation of medical records at 6-month and complete VIRTU4 ACS spread sheet

PI: Prof Gunn. Date: 19/01/2020. STH 20595

II. vFFR Angiography protocol

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

The University Of Sheffield.

British Heart Foundation

Angiography Protocol for the VIRTU-4 ACS study – NGH

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
2. LAO cranial
3. RAO cranial
4. PA cranial (if extra image needed)

Suggested LCA views: *(At least 5 views)*

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

Dr Hazel Haley

PI: Prof Gunn. Date: 19/01/2020. STH 20595

III. Proforma for data collection sheet

VIRTUheart

British Heart Foundation

The University Of Sheffield.

VIRTU-4 ACS Proforma

Patient ID: VIRTU4ACS_ **Hospital No :** **Date :**

Interventionalist : **SPR :**

Patient location : NGH ☐ DRI ☐ BGH ☐ RGH ☐ CRI ☐

Diagnosis : ACS ☐ CCS ☐

Angiogram quality : Good ☐ Average ☐ Poor ☐

Dominance : Right ☐ Left ☐

Syntax Score :

Vessels with significant disease (stenosis of ≥30% and ≤ 90% and ≥ 2.25mm in diameter)

		% of stenosis visually	Culprit Vessel (Please tick)
LAD	Proximal		
	Mid		
	Distal		
Diagonal	1		
	2		
Intermediate			
Circumflex	Proximal		
	Distal		
Obtuse Marginal	1		
	2		
	3		
RCA	Proximal		
	Mid		
	Distal		
	PLV		
	PDA		
Others			

Initial plan pre vFFR :

Medical therapy ☐

PCI ☐

Details : _____

FFR ☐

Details : _____

CABG ☐

Details : _____

MDT ☐

Details : _____

Confidence level:

1 2 3 4 5 6 7 8 9 10

vFFR of artery/lesion modelled

LESION	Myocardial Jeopardy	Duke Jeopardy	vFFR

Would this change your initial management plan?

Yes ☐

How ? _____

No ☐

Reason ? _____

VIRTUheart

British Heart Foundation

The University Of Sheffield.

Any change of plan post vFFR :

Medical therapy ☐

PCI ☐

Details : _____

FFR ☐

Details : _____

CABG ☐

Details : _____

MDT ☐

Details : _____

Confidence level:

1 2 3 4 5 6 7 8 9 10

Any special issues :

Would you use vFFR if it is integrated into the cath lab in the future ?

Yes ☐ No ☐

IV. Intra-observer analysis

Intra-observer analysis (vFFR 1 vs vFFR 2)				
	Ha	**Hb**	**Difference**	**Mean**
LAD	0.56	0.57	0.01	0.565
RCA	0.93	0.95	0.02	0.94
RCA	0.71	0.75	0.04	0.73
LAD	0.81	0.86	0.05	0.835
D1	0.86	0.93	0.07	0.895
LAD	0.7	0.68	0.02	0.69
CX	0.87	0.94	0.07	0.905
LAD	0.94	0.94	0	0.94
OM	0.84	0.85	0.01	0.845
LAD	0.38	0.37	0.01	0.375
LAD	0.85	0.83	0.02	0.84
LAD	0.76	0.7	0.06	0.73
RCA	0.96	0.97	0.01	0.965
RCA	0.98	0.98	0	0.98
LAD	0.65	0.55	0.1	0.6
CX	0.93	0.93	0	0.93
OM	0.59	0.57	0.02	0.58
LAD	0.84	0.77	0.07	0.805
LAD	0.7	0.78	0.08	0.74
D1	0.83	0.85	0.02	0.84
RCA	0.93	0.96	0.03	0.945

	Correlation	0.96477347		
		96%		
Bias	0.03380952	0	-0.0945	Lower LOA
Stand Dev	0.03007926	1.1	-0.0945	
Lower LOA	-0.0251458	0	0.084069	Upper LOA
Upper LOA	0.09276487	1.1	0.084069	
		0	-0.00523	Bias
		1.1	-0.00523	

V. Inter-observer analysis

Interobserver analysis (vFFR a vs vFFR b)				
	vFFR a	**vFFR b**	**Difference**	**Mean**
LAD	0.84	0.81	0.03	0.825
RCA	0.97	0.92	0.05	0.945
RCA	0.97	0.88	0.09	0.925
IX	0.89	0.81	0.08	0.85
LAD	0.68	0.7	-0.02	0.69
RCA	0.84	0.84	0	0.84
LAD	0.85	0.86	-0.01	0.855
RCA	0.99	0.93	0.06	0.96
LAD	0.79	0.64	0.15	0.715
LAD	0.86	0.86	0	0.86
RCA	0.97	0.96	0.01	0.965
LAD	0.94	0.85	0.09	0.895
D1	0.67	0.74	-0.07	0.705
RCA	0.97	0.93	0.04	0.95
LAD	0.48	0.54	-0.06	0.51
RCA	0.8	0.77	0.03	0.785
CX	0.76	0.7	0.06	0.73
LAD	0.88	0.92	-0.04	0.9
LAD	0.89	0.86	0.03	0.875
RCA	0.84	0.79	0.05	0.815
D1	0.88	0.83	0.05	0.855

R=0.90 Correlation of 90%	Bias	0.02952381	
	Stan Dev	0.05314849	
	Lower LOA	-0.0746472	
	Uppper LOA	0.13369485	
	0.5	-0.074	Lower LOA
	1	-0.074	
	0.5	0.13	Upper LOA
	1	0.13	
	0.5	0.0295	Bias
	1	0.0295	

VI. vFFR vs mFFR sub-analysis

Sub-analysis : vFFR validation				
mFFR	**vFFR**	**Difference**	**Mean**	
0.86	0.86	0	0.86	
0.78	0.71	0.07	0.745	
0.95	0.96	-0.01	0.955	
0.81	0.82	-0.01	0.815	
0.95	0.93	0.02	0.94	
0.82	0.81	0.01	0.815	
0.84	0.8	0.04	0.82	
0.96	0.93	0.03	0.945	
0.87	0.92	-0.05	0.895	
0.91	0.88	0.03	0.895	
0.76	0.69	0.07	0.725	
0.78	0.72	0.06	0.75	
0.93	0.81	0.12	0.87	
0.95	0.94	0.01	0.945	
0.82	0.88	-0.06	0.85	
0.61	0.65	-0.04	0.63	
0.9	0.89	0.01	0.895	
0.84	0.86	-0.02	0.85	
0.93	0.92	0.01	0.925	
0.89	0.94	-0.05	0.915	
0.91	0.91	0	0.91	
0.78	0.7	0.08	0.74	
0.97	0.92	0.05	0.945	
0.8	0.85	-0.05	0.825	
0.96	0.97	-0.01	0.965	
0.85	0.89	-0.04	0.87	
0.83	0.85	-0.02	0.84	
0.89	0.88	0.01	0.885	
0.91	0.92	-0.01	0.915	
0.83	0.81	0.02	0.82	
0.83	0.83	0	0.83	
0.9	0.85	0.05	0.875	
0.9	0.84	0.06	0.87	
0.86424242	0.85272727	0.01151515	0.85848485	
	0.8629938	0.5	-0.07238	Lower LOA
Correlation	86%	1	-0.07238	
		0.5	0.095	Upper LOA
Bias	0.01	1	0.095	
Stand Dev	0.0425782	0.5	0.011515	Bias
Lower LOA	-0.0734533	1	0.011515	
Upper LOA	0.09345327			

VII. EQ-5D questionnaire

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

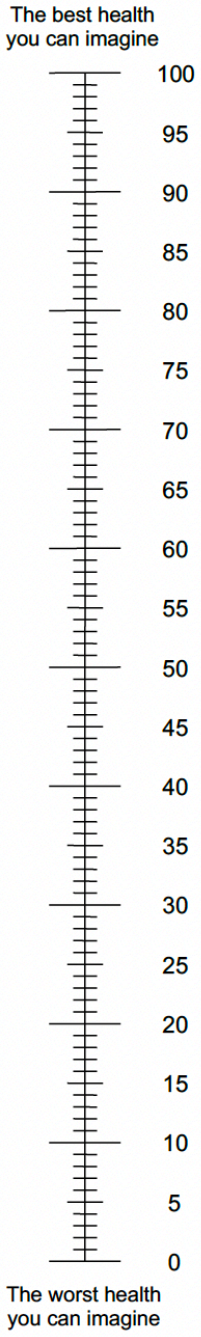
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

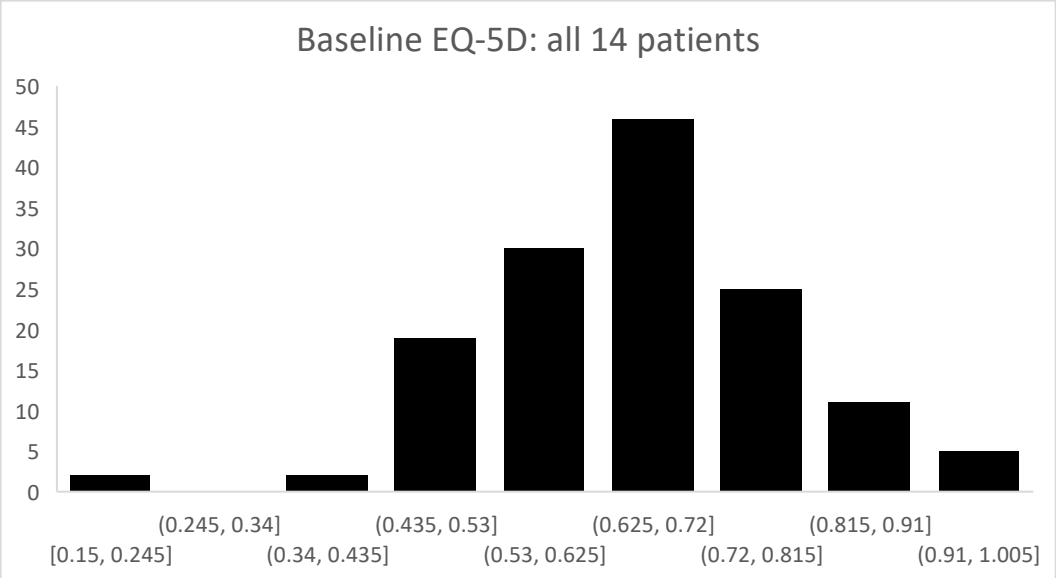
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

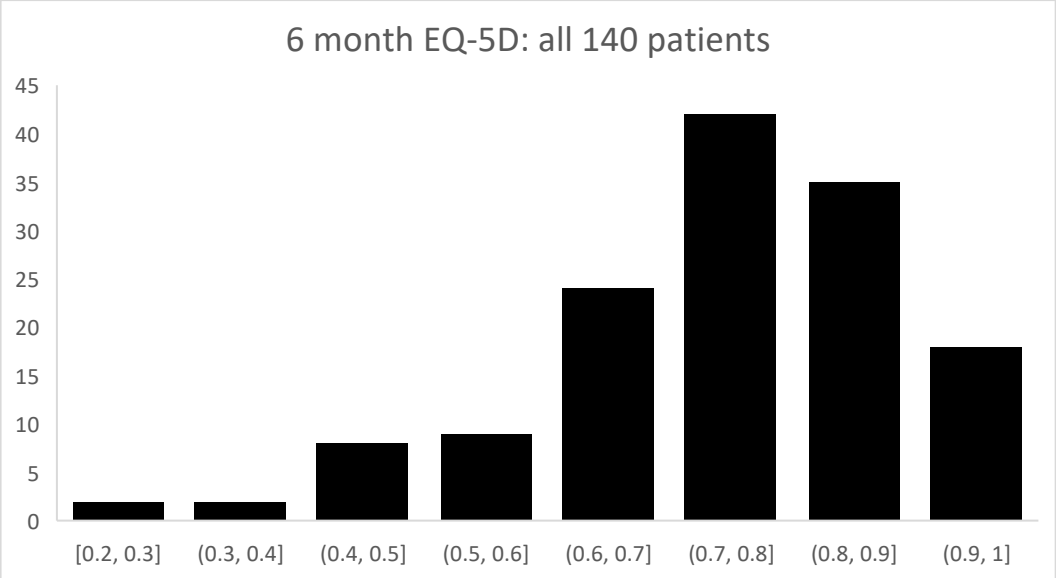
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the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

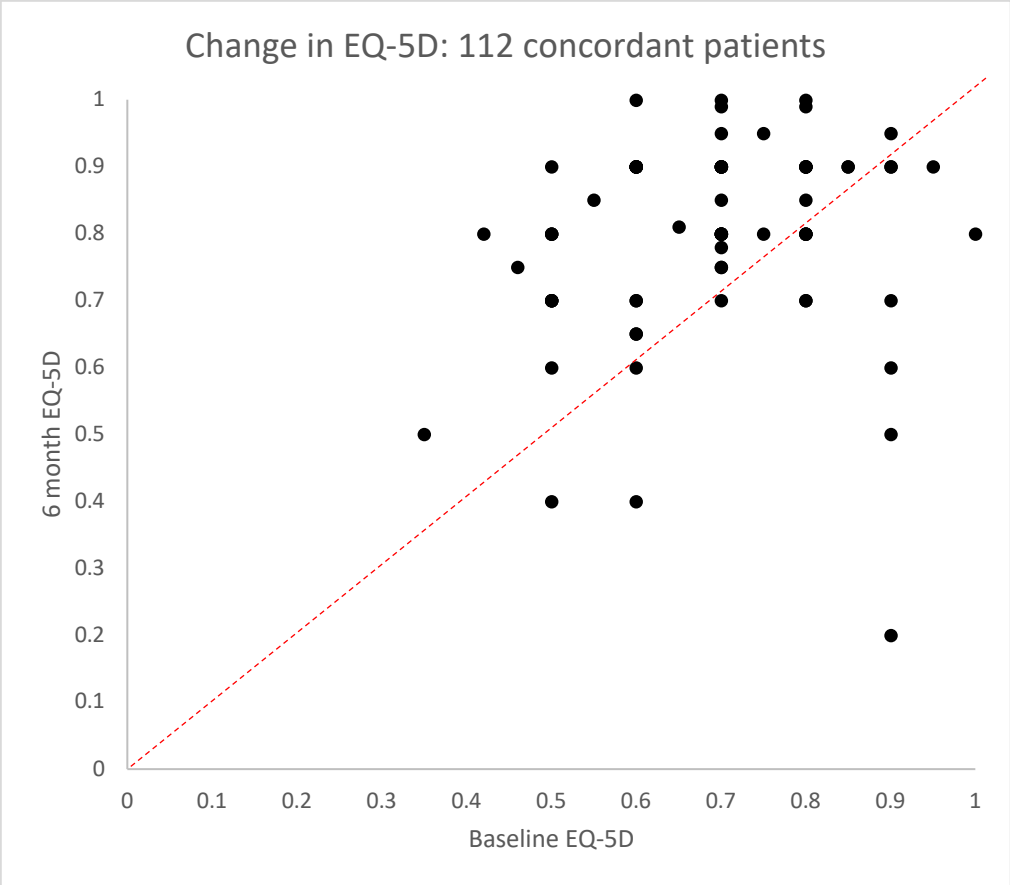
YOUR HEALTH TODAY = ☐

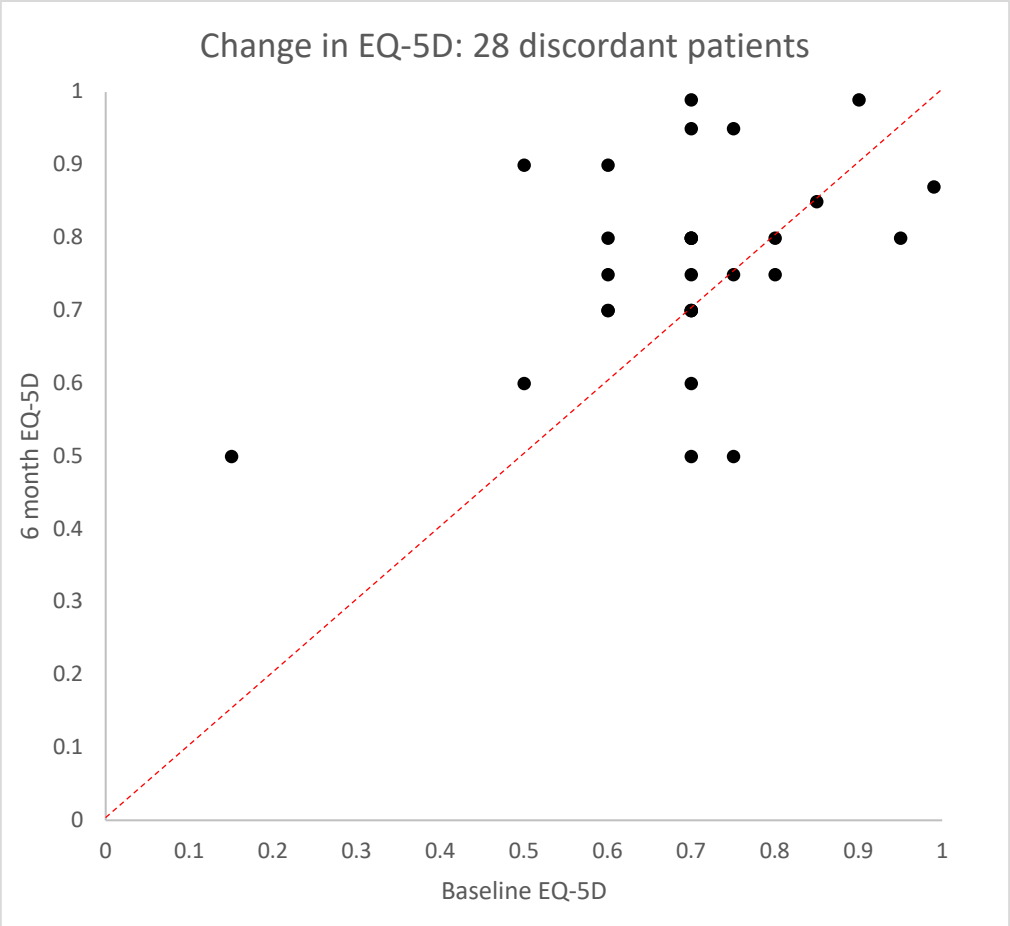


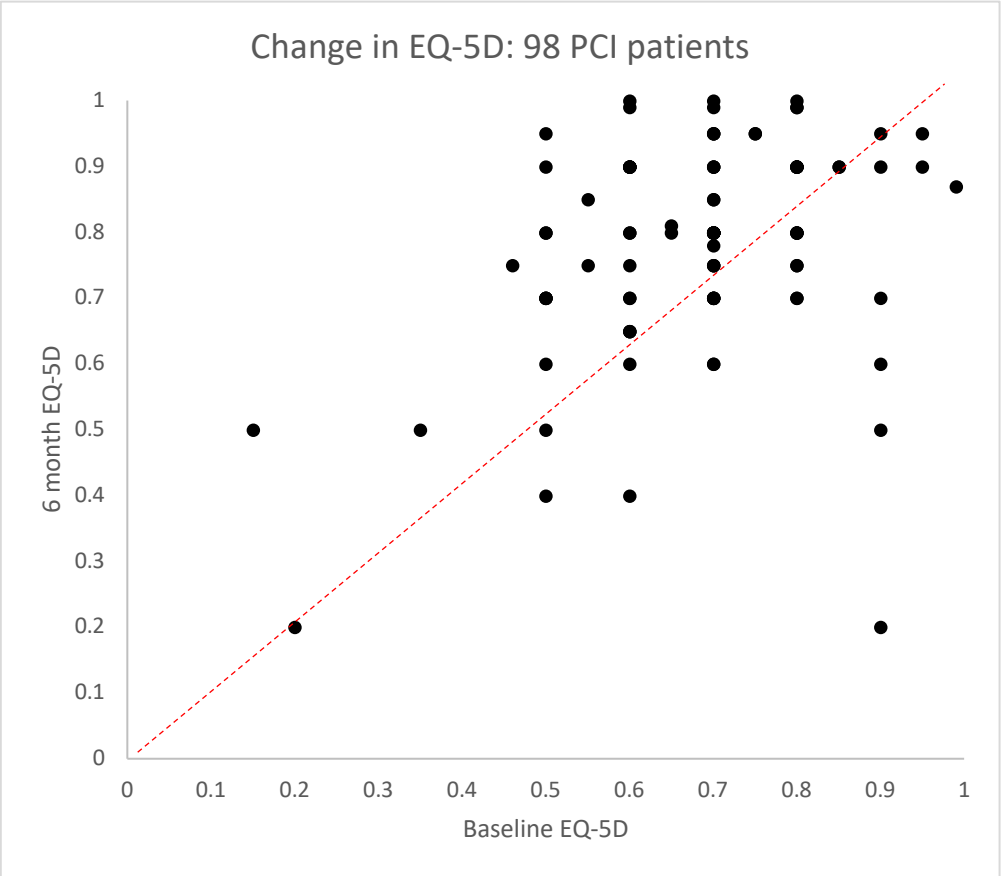
VIII. EQ-5D analysis

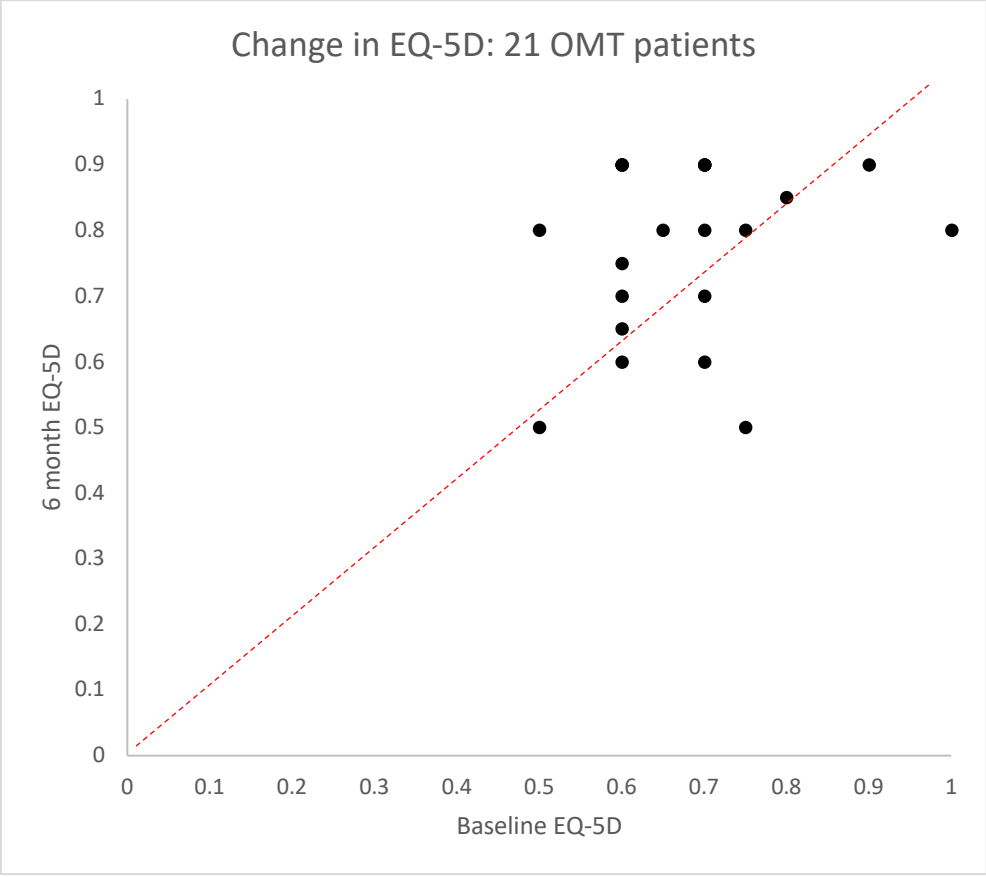





Change in EQ-5D: 112 concordant patients
6 month EQ-5D
Baseline EQ-5D
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

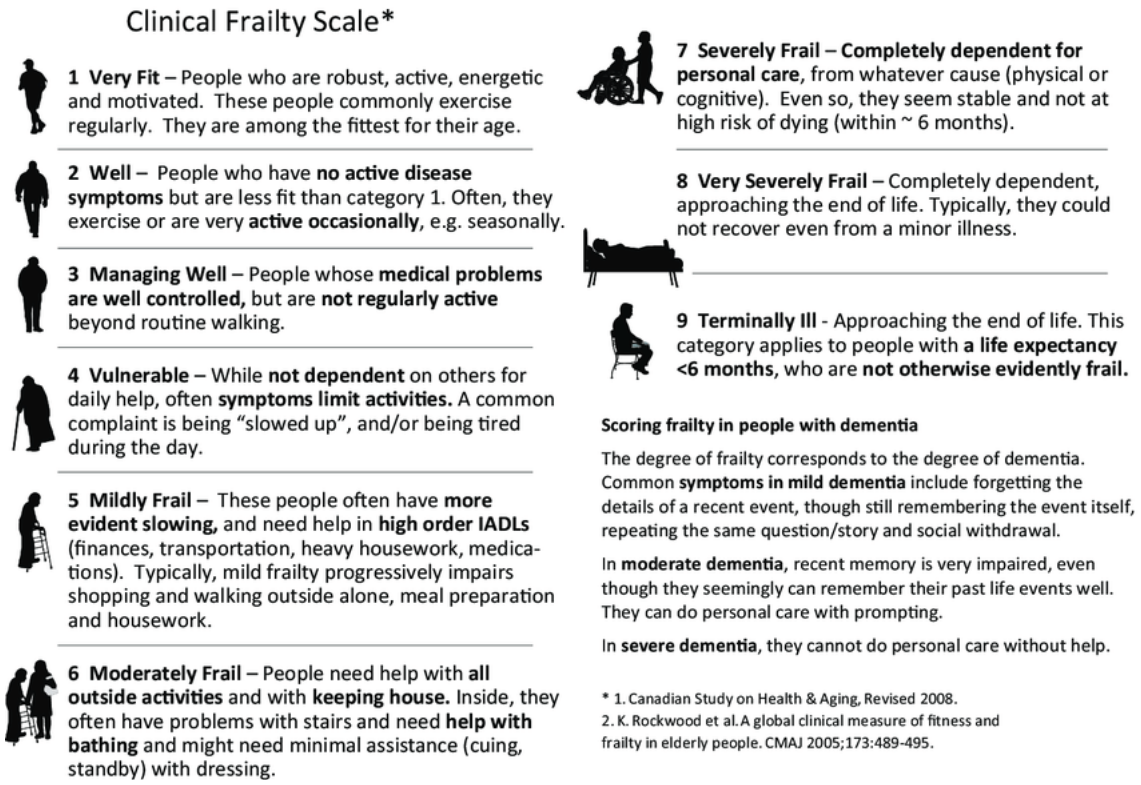

Change in EQ-5D: 28 discordant patients
6 month EQ-5D
Baseline EQ-5D
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1


Change in EQ-5D: 98 PCI patients
6 month EQ-5D
Baseline EQ-5D
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1


Change in EQ-5D: 21 OMT patients
6 month EQ-5D
Baseline EQ-5D
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

IX. Clinical scores

1. *Rockwood clinical frailty scale*



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house.** Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail – Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

V.II. Canadian Cardiovascular Society (CCS) angina classification

Class	Description
I	No angina with ordinary activity. Strenuous activity may cause symptoms
II	Angina causes slight limitation on ordinary physical activity
III	Angina causes marked limitation on ordinary physical activity
IV	Angina occurs with any physical activity and may be present at rest

V.III. New York Heart Association (NYHA) HF classification

Class	Description
I	No symptoms* with ordinary activity. Normal functional status.
II	Mild symptoms* on ordinary physical activity.
III	Moderate symptoms* with less than normal physical activity. Marked limitation of functional status.
IV	Severe symptoms* and with features of heart failure with mild physical activity and even at rest. Severely limitation of functional status.

*Symptoms of dyspnoea, fatigue, palpitations, angina, and/or syncope.

X. Ethics approval

NHS
Health Research Authority
North West - Greater Manchester Central Research Ethics Committee
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8021

01 October 2019

Professor Julian Gunn
OU141, Medical School
Beech Hill Rd
Sheffield
S10 2RX

Dear Professor Gunn

Study title:	**How will virtual (computed) fractional flow reserve (vFFR) impact the management of coronary artery disease? VIRTU 4**
REC reference:	**19/NW/0580**
IRAS project ID:	**270127**

The Proportionate Review Sub-committee of the North West - Greater Manchester Central Research Ethics Committee reviewed the above application on 16 September 2019.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Registration is a legal requirement for clinical trials of investigational medicinal products (CTIMPs), except for phase I trials in healthy volunteers (these must still register as a condition of the REC favourable opinion).

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We routinely audit applications for compliance with these conditions.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_13092019]		13 September 2019
IRAS Application Form XML file [IRAS_Form_13092019]		13 September 2019
IRAS Checklist XML [Checklist_13092019]		13 September 2019
Letter from funder		
Letters of invitation to participant	3.0	10 September 2019
Participant consent form	4	14 August 2019
Participant information sheet (PIS)	4	14 August 2019
Research protocol or project proposal	1.0	06 September 2019
Summary CV for Chief Investigator (CI) [Gunn2page]		08 August 2019
Summary, synopsis or diagram (flowchart) of protocol in non technical language [CVPPPlaySummary]		08 August 2019

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

With the Committee's best wishes for the success of this project.

19/NW/0580	**Please quote this number on all correspondence**

Yours sincerely

pp

Dr Peter Klimiuk
Alternate Vice Chair

Email: nrescommittee.northwest-gmcentral@nhs.net

Copy to: Mrs Lindsay Unwin

North West - Greater Manchester Central Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 16 September 2019

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Peter Klimiuk	Consultant Rheumatologist	Yes	
Mr Rodney Lighton	Retired Software Engineer	Yes	
Dr Alexander Mathioudakis	NIHR ACF ST4 in Respiratory Medicine and Honorary Lecturer in Infection, Immunity and Respiratory Medicine	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Anna Bannister	Approvals Specialist