The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis (VIRTU-AS)

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Statement of Probity

I, the author, confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of Unfair Means (www.sheffield.ac.uk/ssid/unfair-means). This work has not been previously been presented for an award at this, or any other, university.

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) is a growing treatment modality for severe aortic stenosis, not only in the cohort of patients who would once have been unsuitable for surgical aortic valve replacement (SAVR), but also in lower risk patients. A significant proportion of patients undergoing TAVI have concomitant coronary artery disease. The best way to treat coronary disease in these patients remains contentious. Conventional assessments of ischaemia, such as fractional flow reserve (FFR) and the instantaneous wave-free ratio, are not validated in these patients. A better understanding of coronary physiology in these patients is required to optimise treatment pathways.

Hypotheses: Treatment of severe aortic stenosis with TAVI has long-term haemodynamic benefits with a measurable change in a) absolute coronary blood flow and microvascular function, b) symptoms and indices of coronary and myocardial physiology and c) LV mass.

Aim: To achieve a multi-modality assessment of the changes in coronary blood flow and microvascular function, before and after TAVI, correlating with expected reduction in LV mass.

Methods: Patients awaiting elective TAVI were recruited. Coronary angiography was performed and a pressure wire deployed in all diseased coronary arteries. Hyperaemia was induced and relevant parameters of coronary blood flow (resting full-cycle ratio, FFR, index of microcirculatory resistance and coronary flow reserve) were measured. Lesions associated with a positive FFR (≤0.80) were treated with PCI and the full range of coronary physiology repeated. Absolute coronary flow at rest and hyperaemia was modelled using virtuQ™ computational fluid dynamics software. Quantitative stress perfusion cardiac MRI was also performed to assess left ventricular parameters, global myocardial blood flow and coronary sinus flow. All measurements were repeated 3-6 months after TAVI.

Results: Pre-TAVI physiology data were obtained from 15 patients. Eight patients received PCI. Ten patients had cardiac MRI. Seven patients had post-TAVI physiology and cardiac MRI. The mean age was 81 years and 65% were male. There was a significant improvement in the coronary flow reserve from 1.45 to 2.3 ($P<0.05$) post-TAVI. The FFR increased from 0.87 to 0.89 ($P<0.05$) post-TAVI. There was no change in the index of microcirculatory resistance. There was a 20% reduction in coronary flow at rest from 178mL/min pre- to 146mL/min

(P<0.05) post-TAVI, whilst hyperaemic coronary flow remained stable at a vessel-specific level. However, when myocardial blood flow was analysed using cardiac MRI, there was a 32% reduction in global hyperaemic flow from 554 to 374mL/min (P<0.05) and a 45% reduction in global resting flow from 478 to 265mL/min (P<0.05). The indexed left ventricular mass also regressed from 79g/m^2 to 71g/m^2 (P<0.05) post-TAVI. Coronary sinus flow and myocardial perfusion reserve did not change significantly.

Conclusion: There was a significant improvement in coronary flow reserve following TAVI, evidencing an improvement in the functional capacity of the myocardium to respond to stress. The mechanism for this was a 20% reduction in resting vessel-specific coronary blood flow, and a 45% reduction in global myocardial flow. The unchanged microvascular resistance suggests that resistance was not the reason for this. Rather, after TAVI, a much smaller portion of the microvascular bed is recruited. Resting flow fell due to a less demanding myocardium and regression of the baseline hyperaemic conditions, accompanied by an enhanced ability to respond to stress, and the expected reduction in LV mass.

Table of Contents

List of figures

List of tables

List of acronyms

aCBF	Absolute coronary blood flow
ACT	Activated clotting time
AKI	Acute kidney injury
AI	Artificial intelligence
AR	Aortic regurgitation
AS	Aortic stenosis
AF	Atrial fibrillation
AHA	American heart association
AV	Aortic valve
AVA	Aortic valve area
BAV	Bicuspid aortic valve
BCIS	British cardiovascular intervention society
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BSE	British society of echocardiography
CABG	Coronary artery bypass Grafting
CAD	Coronary artery disease
CBFV	Coronary blood flow velocity
CCL	Cardiac catheter laboratory
CCS	Canadian cardiovascular society
CCT	Cardiac computed tomography
CFD	Computational fluid dynamics
CFR	Coronary flow reserve
CHB	Complete heart block
CKD	Chronic kidney disease
CMR	Cardiac MRI
COPD	Chronic obstructive pulmonary disease
CS	Coronary sinus
CVA	Cerebrovascular accident
DAPT	Dual antiplatelet therapy
DATT	Dual anti-thrombotic therapy

DES	Drug-eluting stent
DICOM	Digital imaging and communications in medicine
DJ	Duke jeopardy score
DOAC	Direct oral anticoagulant
ECG	Electrocardiogram
ESC	European society of cardiology
EACTS	European association for cardiothoracic Surgery
FFR	Fractional flow reserve
GTN	Glyceryl trinitrate
HCM	Hypertrophic cardiomyopathy
HFpEF	Heart failure with preserved ejection fraction
HMR	Hyperaemic microvascular resistance
HRA	Health research authority
ICA	Invasive coronary angiography
iFR	Instantaneous wave-free ratio
IQR	Interquartile range
INR	International normalised ratio
IMBV	Intra-myocardial blood volume
IMR	Index of microcirculatory resistance
IV	Intravenous
LAD	Left anterior descending artery
LCx	Left circumflex artery
LDL	Low density lipoprotein
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEDD	Left ventricular end diastolic diameter
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVOT	Left ventricular outflow tract
MACE	Major adverse cardiovascular events
MASTER	Mechanisms of Excess Risk in Aortic Stenosis
MBF	Myocardial blood flow

MI	Myocardial infarction
MJI	Myocardial jeopardy index
mmHg	Millimeters of mercury
MMMXNAT	Mathematical modelling in medicine XNAT
MPR	Myocardial perfusion reserve
MRR	Microvascular resistance reserve
MVO_2	Myocardial oxidative metabolism
MVD	Microvascular coronary disease
MVR	Microvascular resistance
NICOR	National institute for cardiovascular outcomes research
NSTEMI	Non-ST-segment elevation myocardial infarction
NYHA	New York heart association
PACS	Picture archiving and communications system
PET	Positron emission tomography
PCI	Percutaneous coronary intervention
PI	Principle investigator
POLARIS	Pulmonary lung and respiratory imaging Sheffield
PPM	Permanent pacemaker
QCA	Quantitative coronary angiography
QFR	Quantitative flow ratio
RCA	Right coronary artery
REC	Research ethics committee
RFR	Resting full-cycle ratio
RV	Right ventricle
SAPT	Single antiplatelet therapy
SAVR	Surgical aortic valve replacement
SD	Standard deviation
SF-12	Medical outcomes short form 12-point questionnaire
SOC	Standard of care
SR	Stenosis resistance
STH	Sheffield teaching hospitals
SVi	Stroke volume index
TAVI	Transcatheter aortic valve implantation
TAVI-CT	Transcatheter aortic valve implantation computed tomography

TOE	Trans-oesophageal echocardiography
TTE	Transthoracic echocardiography
vFFR	Virtual-FFR
VKA	Vitamin K antagonist
WU	Wood units
2D	Two-dimensional

Chapter 1: Introduction

Aortic stenosis (AS) is a progressive and chronic condition causing significant mortality and morbidity due to narrowing of the major outflow tract of the heart, resulting in a pathological cascade (1). Treatment guidelines for severe AS have expanded over the last 20 years to include transcatheter aortic valve implantation (TAVI) (2). Many patients with AS also have coronary artery disease (CAD); the treatment of concomitant CAD in these patients remains contentious (3). Physiology based treatment of isolated CAD is well validated (4) and guideline-based (5); however, patients with severe AS are excluded from these trials and guidelines (6). The effects of AS on coronary physiology and blood flow are complex and require further elucidation if we are to understand how best to evaluate and manage CAD in this growing cohort of patients (6). This thesis will begin with an overview of AS, our current knowledge, guidelines and treatments, before expanding on the current literature around coronary physiology, AS, microvascular coronary disease (MVD) and computational fluid dynamics (CFD). It will then describe the nature of the question posed by this piece of scientific research and subsequently will outline the hypothesis, objectives and methods used to attempt to answer it. It will finally demonstrate the outcomes and results, followed by discussion and overarching conclusions.

1.0 Aortic valve anatomy

The aortic valve is situated between the left ventricle (LV) and the aorta, and is the main outflow valve of the heart (1) (Figure 1). It has a tri-leaflet structure in the majority of people (Figure 1), although some individuals are born with a bi-leaflet valve (7). The valve leaflets are bowed inwards towards the heart to support antegrade unidirectional flow (Figure 2). When the left ventricle contracts, the pressure within exceeds that of the aorta, and blood flows forward through the aortic valve into the proximal and ascending aorta. The valve's structure allows significant mechanical stress and pressure to be distributed evenly between its three cusps, the aorta, and the surrounding annular ring (Figure 2) (1). These cusps are typically less than 1mm thick and comprise four distinct cellular layers from the aortic side to ventricular aspect as follows: endothelium; fibrosa; spongiosa; and finally ventricularis, which are seen in Figure 2 (1). The valve is attached to a collagenous ring called the annulus, which is in turn attached to the aortic root and left ventricular outflow tract (1).

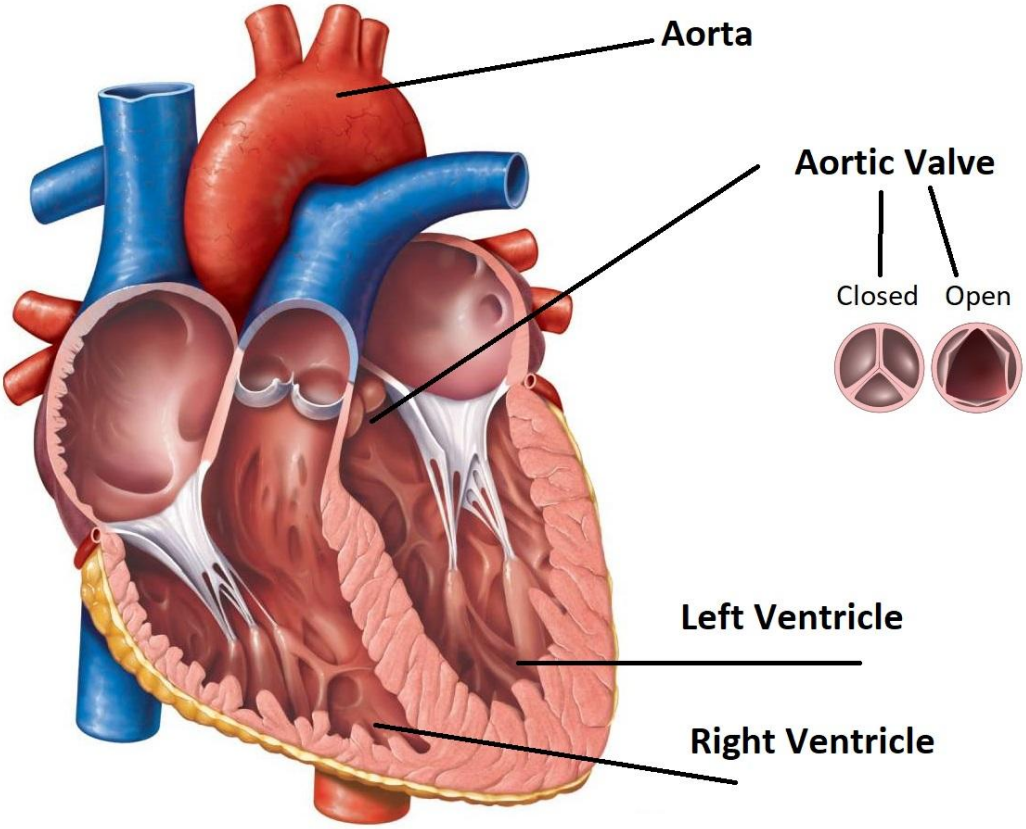


Figure 1. *Diagram of the heart.*

Diagram of the heart, aortic valve and aorta, with cross sectional view through a tri-leaflet aortic valve. Adapted from Wikimedia commons and Clipart Library (public domain).

1.1 Epidemiology of aortic stenosis

The epidemiology of AS varies widely across the world (8). Rheumatic heart disease is the primary driver of mortality and morbidity associated with AS in the developing world (8, 9); Oceania, Sub-Saharan Africa and Southeast Asia are particularly afflicted with a very high prevalence in comparison with developed countries (8). In economically developed countries, fibrocalcific AS is the most common form of valvular heart disease (1). It creates a significant burden of morbidity and mortality and its prevalence increases with age (10), affecting around 2% of people over the age of 60 (11). A meta-analysis of the prevalence of severe AS in the over-75 age group (Osnabrugge et al) analysed databases in 19 European countries and North America (12). A total of seven trials (9,723 subjects) were analysed, demonstrating an

overall prevalence of 12.4% of AS and 3.4% of severe AS in this age group (12). Furthermore, the analysis demonstrated that annually, there may be around 27,000 new patients who become eligible for TAVI in the USA and Europe each year (12). This number is likely to increase further as TAVI becomes offered to younger patients (9). In younger people in developed countries, bicuspid aortic valve (BAV) is the most common congenital heart disease, affecting 0.5-0.8% of the population (9). The mean age for surgical intervention is significantly lower than for fibrocalcific AS, usually necessitating treatment at under 50 years of age (9, 13). Once symptoms begin to develop, invasive treatment is generally recommended (14). Patients with untreated symptomatic severe AS will invariably deteriorate without intervention, and 2-year mortality is 50% (11).

1.2 Pathophysiology of aortic stenosis

Aortic stenosis is characterised by progressive narrowing of the aortic valve orifice (Figure 2), resulting in raised left ventricular pressures and hypertrophy in order to maintain cardiac output (2). This physiological response to progressive AS is eventually exhausted, resulting in heart failure and death (2). The pathophysiology and sequelae of AS are multi-faceted (15), beginning with disease of the valve itself, and ending with consequent effects on the myocardium and circulation (2, 10). The historically accepted paradigm of AS as a progressive condition associated with rheumatic fever and the degenerative “wear and tear” effect of ageing, as first described by Mönckeberg in 1904 (2), has shifted in recent decades (10). In 2007, Aikawa et al first described the complex inflammatory and osteogenic processes that lead to irreversible valvular calcification (16). The development and subsequent progression of fibrocalcific AS can be divided into two distinct pathological phases: initiation and propagation (10, 11). An initiation phase is characterised by endothelial injury from mechanical and shear stress (Figure 2), resulting in lipid deposition and oxidisation. This in turn creates a pro-inflammatory environment within the valve tissue, and is followed by deposition of macrophages, T-lymphocytes and mast cells (10, 11). This process is similar to that seen in atherosclerotic cardiovascular disease. Indeed, patients with AS and CAD disease share many risk factors including hypertension, renal failure, and metabolic syndrome, although targeted medical therapies with proven efficacy in CAD have not translated into patients with AS (15). A propagation phase follows, and is characterised by inflammation-driven collagen deposition and osteogenic activity within the valvular interstitial tissues (16,

17). Pathological skeletal bone develops within the diseased aortic valve, generated by myofibroblasts and osteoblasts within the valvular interstitial tissues (15, 16). Once calcium deposition becomes established, it propagates further calcium formation (10). This feedback loop is the primary driver of progressive AS in the propagation phase (10).

When considering patients with a BAV, mechanical stress as the origin of endothelial injury and the subsequent fibrocalcific cascade can be illustrated. The bi-leaflet valve structure results in inefficient distribution of mechanical and shear stress on the valve and its surrounding structures (1), leading to the development of severe AS, and a requirement for intervention several decades earlier than those with tri-leaflet valves (13).

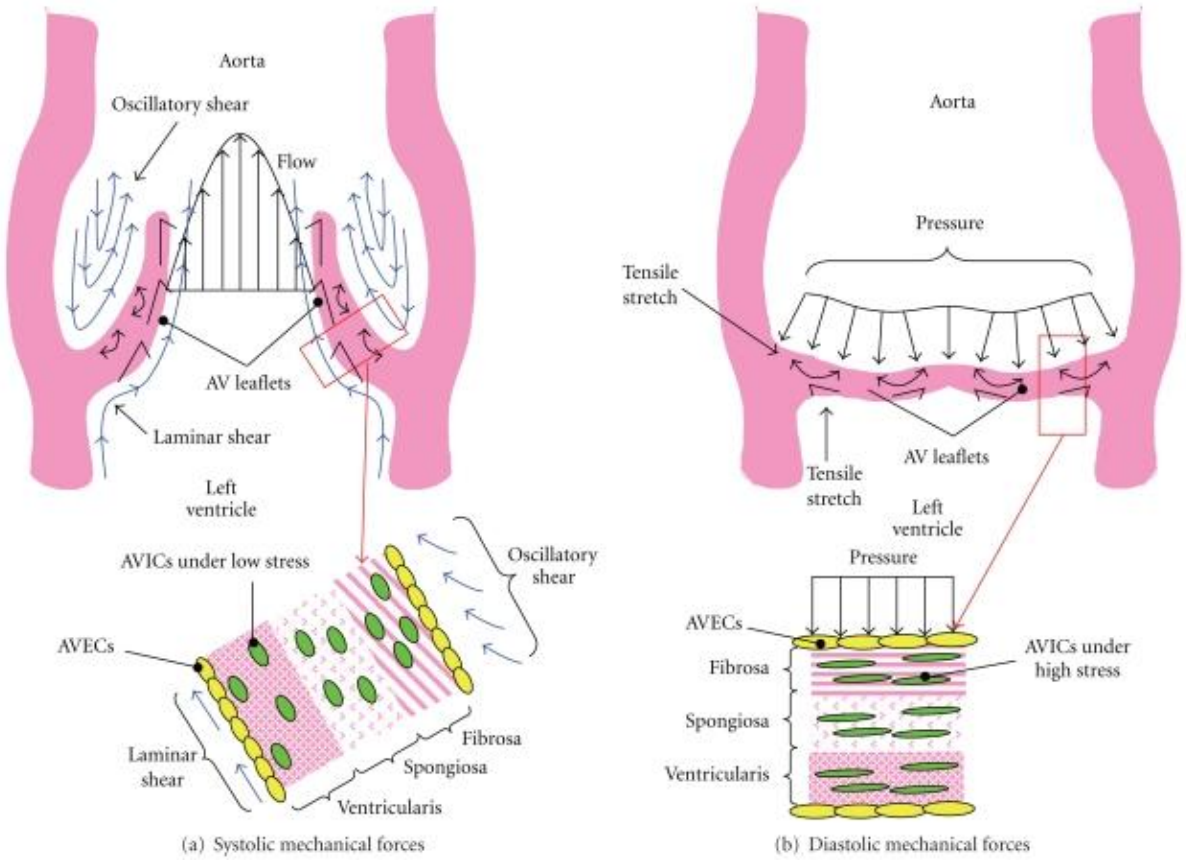


Figure 2. *Diagram of the haemodynamic effects at the aortic root.*

The haemodynamic effects at the aortic root and cellular architecture of the aortic valve. AVEC: aortic valvular endothelial cells; AVIC; aortic valvular interstitial cells. Reproduced with permission from Balachandran et al 2011 (18).

Progressive narrowing of the aortic valve orifice (Figure 2) consequently results in a cascade of adaptive and maladaptive processes within the myocardium and microvasculature (19). There is an adaptive increase in LV mass resulting from hypertrophy of myocytes and peri-myocytic fibrosis (19), in order to generate greater power and overcome the restricted outflow tract (20). The resultant left ventricular hypertrophy (LVH) is in turn associated with a series of maladaptive processes in the myocardium, microvasculature and coronary arteries (21). Ultimately, this leads to adverse LV remodeling, heart failure and death (1).

Sex-related differences in the myocardial response to AS are well recognised and have implications for disease progression and treatment. Women typically develop concentric LVH and have smaller LV cavity size, increased relative LV wall thickness, and preserved ejection fraction, while men are more likely to develop eccentric LV remodelling and have larger LV volumes with LV impairment (22, 23). These patterns arise from differing biological mechanisms, including sex-specific variations in myocyte hypertrophy, extracellular matrix expansion, and fibrotic signalling (24). Women may demonstrate lower levels of myocardial fibrosis, which may influence symptom burden and response to intervention (24). Long-term outcomes after TAVI also differ by sex and some evidence suggests that women, despite often being older and having higher procedural risk, tend to experience better survival, lower stroke rates, and have more favourable reverse remodelling compared to men (25, 26). These differences demonstrate the need for sex-specific considerations in patients with severe AS.

1.3 Treatment of aortic stenosis

Current guidelines recommend treatment of aortic stenosis when the valve lesion is “severe” and there is evidence of LV decompensation, whether demonstrated echocardiographically, or clinically with the development of symptoms (14). Symptoms of severe AS include shortness of breath, angina, syncope, and in heart failure; cardiac arrest and death. The only

definitive treatment of AS is mechanical relief of the outflow tract obstruction. In the United Kingdom, patients with aortic stenosis are broadly treated according to the European Society of Cardiology (ESC) and European Association for Cardiothoracic Surgery (EACTS) guidance for valvular heart disease (14).

1.3.1 Echocardiographic evaluation of aortic stenosis

The mainstay of diagnosis and surveillance of AS is echocardiography, which also provides data on LV function, calcification, aortic morphology and other co-existing valvular pathologies (14). ESC guidelines recommend the routine use of echocardiographically derived mean pressure gradient across the aortic valve (mmHg), peak transvalvular flow velocity ((V_{max}) in m/s) and aortic valve area ((AVA) in cm^2) to diagnose and quantitatively assess AS (14). If there is LV failure, LVH or significant hypertension, these parameters may be unreliable and other parameters or imaging modalities, such as stress testing, may be required to aid diagnosis (14). In LV failure, reduced systolic function leads to lower transvalvular flow, which can cause underestimation of AS severity due to diminished velocity and gradient despite severe valve obstruction (27). In significant LVH or hypertension, increased myocardial stiffness and high left ventricular end diastolic pressure (LVEDP) affects LV filling and afterload, which can modify flow dynamics and mask the true severity of AS (28). These altered haemodynamic states can complicate the interpretation of standard Doppler measurements used to diagnose severe AS. Hence, additional imaging modalities such as low-dose dobutamine stress echocardiography can unmask true AS severity by augmenting forward transvalvular flow and evaluating contractile reserve (29).

Four broad categories of AS are defined by the EACTS and ESC guidelines (14). The following describe the echocardiographic categorisation of the four subtypes (14).

1. High gradient AS. Defined as a mean transvalvular gradient of >40mmHg, peak V_{max} of >4.0 m/s and AVA of <1.0 cm^2. These parameters confirm severe aortic stenosis regardless of haemodynamic conditions.

2. Low flow, low gradient AS with low LV ejection fraction (LVEF). Defined as a mean transvalvular gradient of <40mmHg, AVA <1.0 cm^2, LVEF <50% and stroke volume index (SVi) <35mL/m^2. Dobutamine stress echocardiography is recommended to identify and differentiate between severe and pseudo-severe AS.

3. Low flow, low gradient AS with normal LVEF. Defined as a mean transvalvular gradient of <40mmHg, AVA <1.0 cm^2, LVEF >50% and stroke volume index (SVi) of <35mL/m^2. Careful assessment is required in these cases to ensure that the values obtained are accurate and, in some cases, cardiac computed tomography (CCT) is useful to determine calcific burden, in Agatston units. Severe AS is highly likely when the Agatston score at CCT is >3000 in men and >1600 in women.

4. Normal flow, normal gradient AS with normal LVEF. Defined as a mean transvalvular gradient of <40mmHg, AVA <1.0 cm^2, LVEF >50% and stroke volume index (SVi) >35mL/m^2. Further assessment of these patients is required and in most cases the AS is not truly severe (14).

Figure 3 shows echocardiographic images from a study patient with severe AS, including measurements of the parameters noted above to quantify severity. Note the severely stenosed aortic valve orifice and heavy calcium burden. There is also significant adaptive LVH with a subsequently reduced LV cavity size.

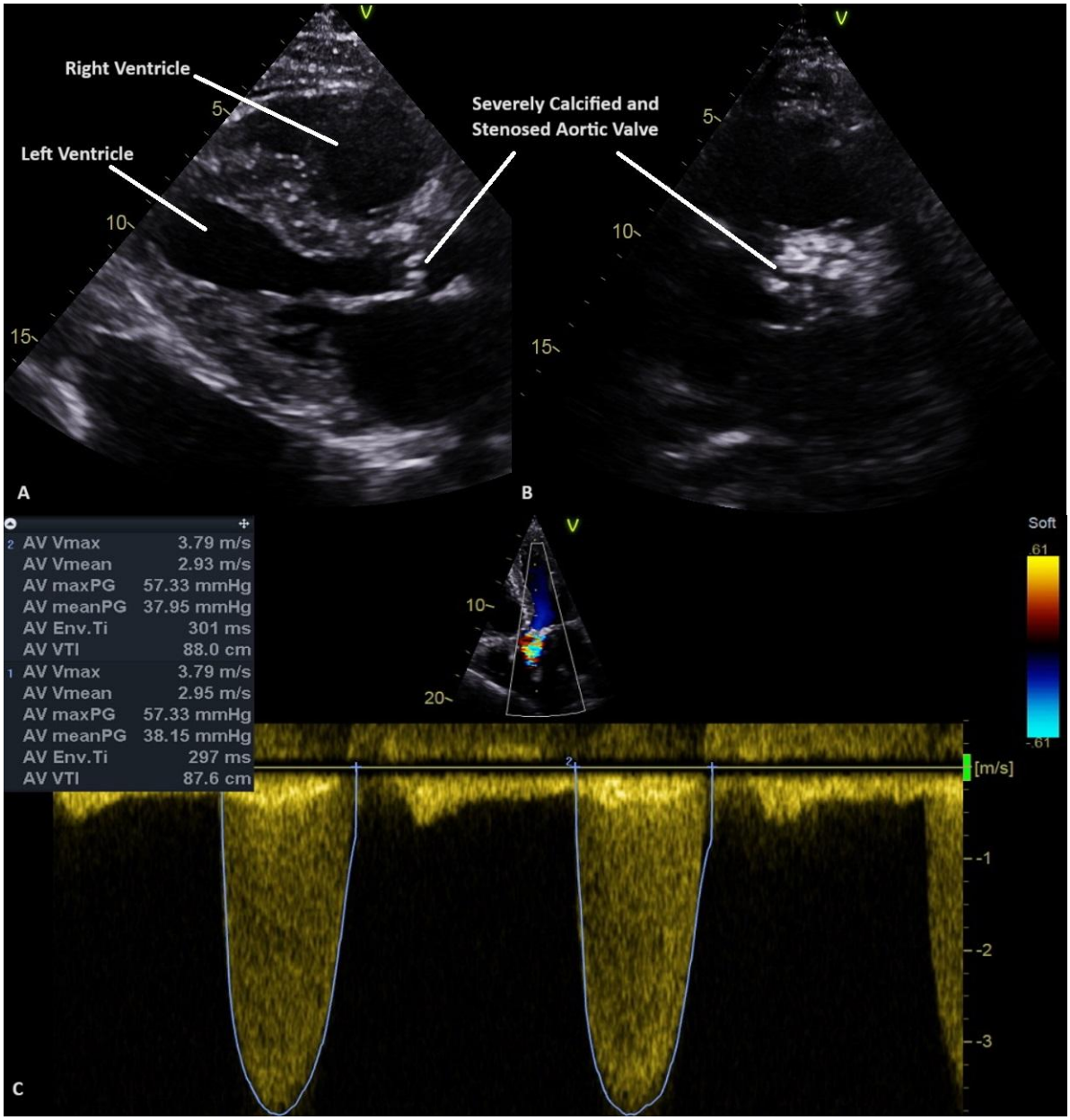


Figure 3. *Echocardiogram images of a study patient with severe AS.*

3**A**; Parasternal long-axis view demonstrating a tiny valve orifice and LVH. 3**B**; Parasternal short-axis view demonstrating heavy calcification of the valve cusps with small AVA. 3**C**; Measuring the parameters of severity using Doppler echocardiography. Images used with permission.

1.3.2 Patient selection

It is recommended that all patients are discussed at a "Heart Team" meeting in order to optimise outcomes (14). The decision to treat (or not) should consider the clinical need for treatment, benefits (or otherwise) to quality of life, expected survival and risk of complications (14). Patients are also risk stratified at the Heart Team meeting according to their EuroSCORE II (30) and Society of Thoracic Surgeons risk calculator score (31). Pre-existing co-morbidities should be explored, and where possible, optimised before invasive treatment is undertaken. Chronic health conditions such as chronic obstructive pulmonary diseases (COPD), chronic kidney disease (CKD) and prior cerebrovascular ischaemic events (CVA) confer a negative prognosis. Patients with a number of life-limiting conditions and significant frailty are not likely to benefit from invasive treatment and in such cases, intervention should be avoided (14). Furthermore, where life expectancy is deemed to be below one year from life shortening illnesses such as malignancy, intervention on the aortic valve should be avoided (14).

1.3.3 Treatment selection

When severe AS begins to cause symptoms, early treatment is recommended to avoid further LV decompensation and irreversible sequelae. In severe AS without apparent symptoms, it is recommended to exercise patients in a clinical setting (14). In truly asymptomatic patients with severe AS, a plan of watchful waiting is suggested with prompt intervention at the onset of symptoms (14). The Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis trial randomised 145 patients with very severe AS (defined as V_{max} of >4.5m/s, AVA of <0.74cm^2 or mean transvalvular gradient of >50mmHg) to a watch and wait approach or to surgical intervention within two months of randomisation (32). Kang et al found that there was significant reduction in the primary end point of death during or within 30-days of intervention with surgical aortic valve replacement (SAVR) compared with observation (1% vs 15%; P=0.003) (32). The patient cohort in this study was a relatively young one with a median age of 64 years and few comorbidities (32) and therefore the data may not easily be applied to real-world systems. The EARLY-TAVR trial (ClinicalTrials.gov Identifier: NCT03042104) is currently ongoing and has randomised patients to early TAVI or a watchful waiting approach (33). The EACTS/ESC guidance recommends SAVR and TAVI as largely complementary

treatment options for patients who qualify for valve intervention (14). Figure 4 shows the EACTS/ESC treatment algorithm for patients with severe AS.

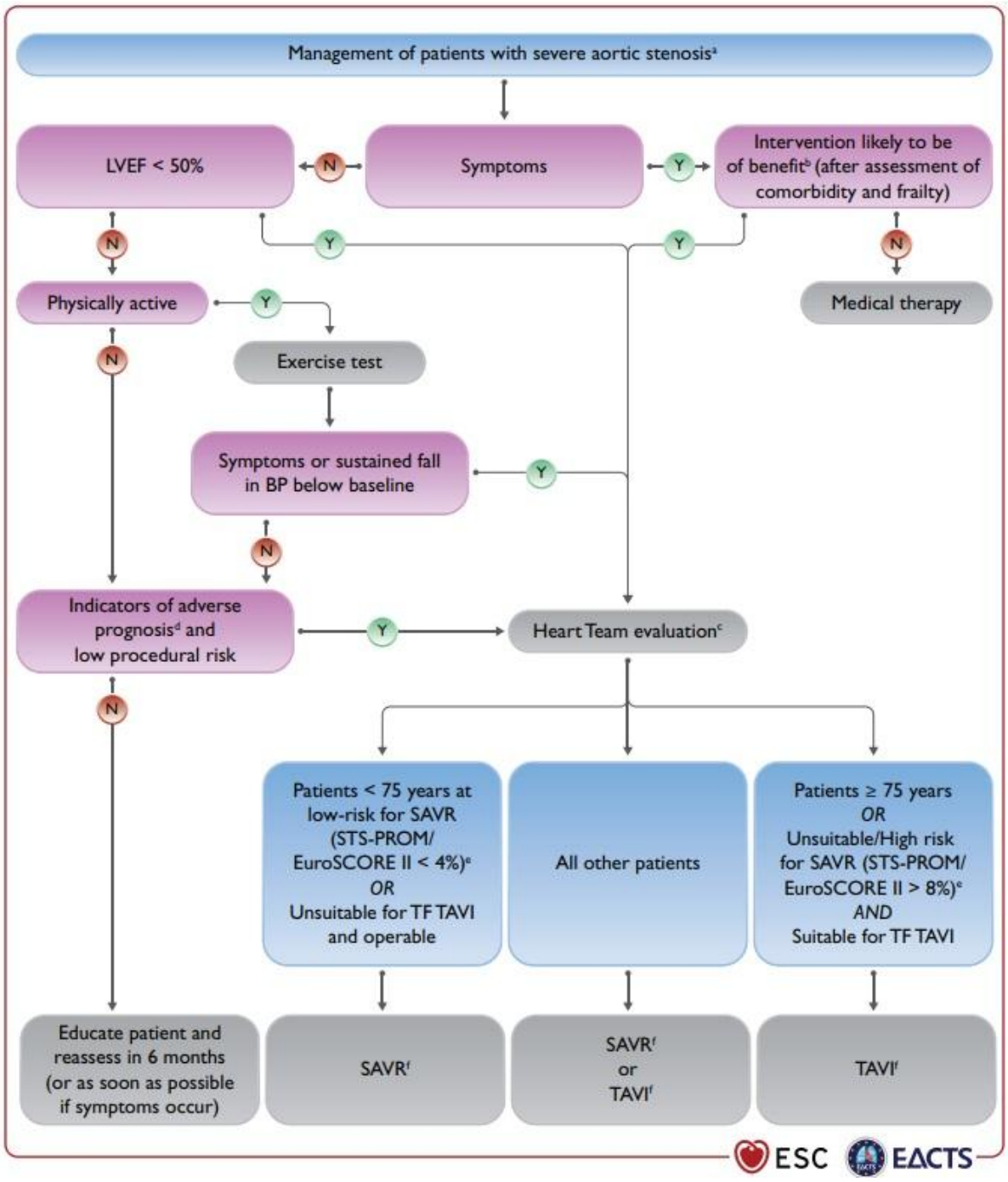


Figure 4. *EACTS/ESC treatment algorithm for patients with severe AS.*

Reproduced with permission from The European Heart Journal, Oxford University Press (14).

1.3.4 Medical therapy

There are currently no medical therapies which halt or reverse the progression of AS (10, 11). The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial was a randomised controlled trial which investigated hyperlipidaemia as a risk factor in the progression of severe AS (34). 1873 patients were randomised to receive high-intensity statin therapy (Simvastatin 40mg) alongside Ezetimibe 10mg or placebo (34). Despite achieving a mean reduction of 53.8% in serum low-density lipoprotein (LDL) cholesterol in the treatment group, there was no reduction in the composite end points of aortic valve related or ischaemic events in patients with AS (34). The rate of AS progression was similar between the groups, as was overall mortality (34). The findings of the SEAS trial were similar to those of the SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) trial (35). The SALTIRE group assigned 27 patients to Atorvastatin 80mg and 78 patients to placebo, and once again, despite noting a statistically significant reduction in LDL-cholesterol in the treatment arm, found no difference in the rate of AS progression (35). A meta-analysis of 2344 patients by Teo et al confirmed the general consensus that lipid lowering therapy currently has no efficacy in slowing the progression of AS and should not be used as such (36). Medicines used for the treatment of osteoporosis, such as bisphosphonates and monoclonal antibodies, which aim to target specific points along the inflammatory and osteogenic pathway, are currently being studied and results of ongoing trials are pending (11). The SALTIRE-II (Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis) trial is currently underway and will randomise 150 patients to either Denosumab, Alendronic acid or a placebo and assess the progression of AS severity and valvular calcification (ClinicalTrials.gov Identifier: NCT02132026 (37)).

The PROGRESSA study, a prospective cohort study by Tastet et al, demonstrated that poor control of systolic blood pressure (BP) was independently associated with accelerated AS progression (38). Patients with higher systolic BP exhibited faster increases in aortic valve calcification and stenosis over time, suggesting that hypertension exacerbates valvular degeneration through increased mechanical stress and adverse vascular remodeling (38). These findings highlight the importance of optimising BP control in patients with AS, not only to reduce cardiovascular risk but also potentially to slow the progression of valvular disease.

1.3.5 Surgical aortic valve replacement

Surgical aortic valve replacement (SAVR) has been the mainstay of treatment of AS since the first operation in 1960 (39). It is a form of "open heart surgery" and performed under general anaesthetic with the patient ventilated and placed on cardiopulmonary bypass. SAVR can be performed using either a metallic or bioprosthetic valve prosthesis. The decision is based on a number of surgical and patient factors which are described in the European Society of Cardiology and European Association for Cardiothoracic Surgery guidance for valvular heart disease (14). The performance and efficacy of SAVR for the treatment of severe AS is widely accepted and established (14, 40).

1.3.6 Transcatheter aortic valve implantation

TAVI is a minimally invasive, percutaneous method of implanting a prosthetic aortic valve for the treatment of AS. TAVI has a class I recommendation in the ESC/EACTS guidance for the treatment of severe AS and multiple vascular approaches are validated including trans-femoral, trans-subclavian, trans-carotid and trans-apical (14). Figure 5 shows the X-ray images of a successful TAVI procedure in a study patient. The first TAVI case was performed by Alain Cribier in 2002 on a patient with severe AS due to BAV, who was unsuitable for SAVR (41). TAVI has since grown into a well-validated, guideline-based, and widely adopted method for the treatment of severe AS, although, it is used rarely in patients with BAV (7, 14).

TAVI is less frequently used in patients with BAV due to several anatomical and procedural challenges (42). BAV is characterized by heterogeneous valve morphology with asymmetric leaflets and calcification, leading to irregular valve geometry which can complicate optimal prosthesis sizing and deployment (43). These anatomical factors increase the risk of procedural complications such as paravalvular leak, valve malposition, and aortic root injury (43). BAV patients are often younger with fewer comorbidities and thus often better candidates for SAVR and this remains the gold standard treatment (44).

The number of TAVI procedures performed in the UK since 2007 have increased significantly, and according to latest British Cardiac Intervention Society (BCIS) and National Institute for Cardiovascular Outcomes Research (NICOR) data, 7601 procedures were performed in 2021-22, outstripping SAVR numbers (45). The mean age is 80.8 years and indications include native valve AS and bioprosthetic valve or TAVI failure (45). Conscious sedation (93.3%), rather than

general anaesthetic, is the primary mode of anaesthetic (45). The benefit of this approach with respect to lower intra-procedural risk and reduced hospital stay is clear. The vast majority (93%) are performed via the percutaneous trans-femoral approach, and around 5% are performed via the surgical (cut-down) trans-femoral approach, the rest are trans-subclavian and trans-apical (45). Cerebral protection devices are used in 12.9% and the average length of hospital stay is five days for elective cases (45).

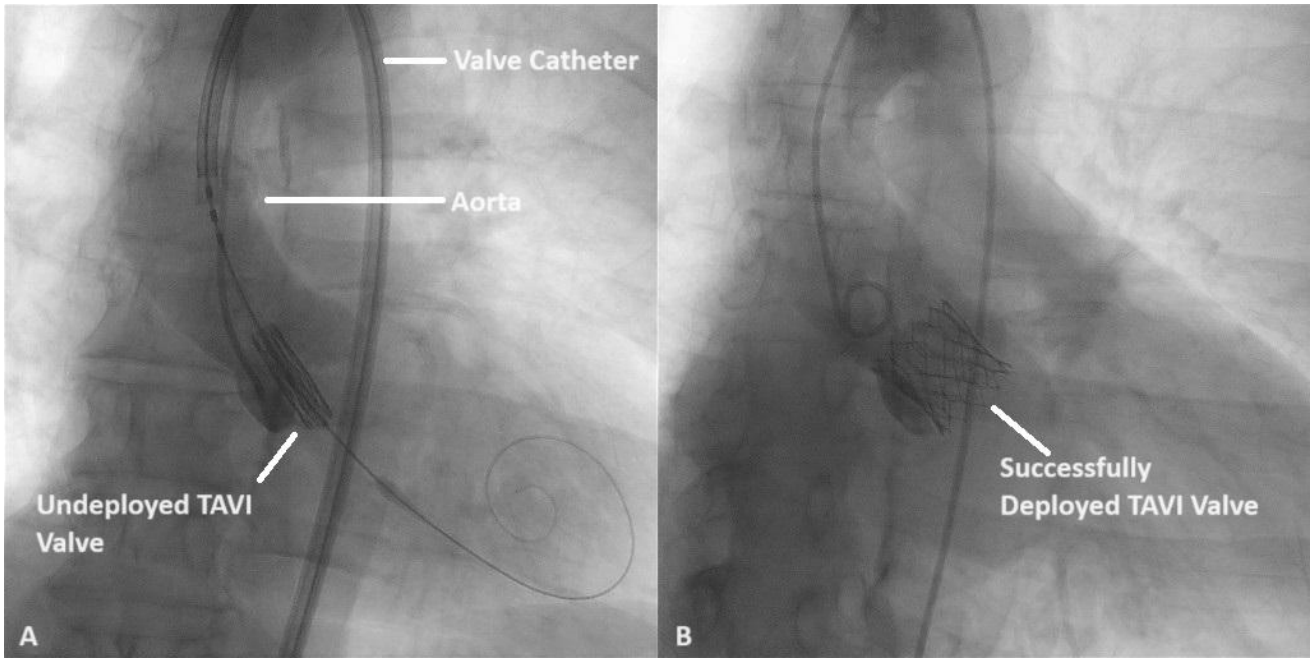


Figure 5. *Successful TAVI procedure.*

TAVI procedure via the femoral artery with a balloon expanded Edwards Sapien Valve. 5**A**; The valve is passed through a large-bore catheter and sited across the aortic valve orifice. 5**B**; The valve has been successfully deployed and there is good antegrade flow across the LV outflow tract.

1.3.6.1 Pre-procedural TAVI planning

Patients considered for TAVI require a series of work-up investigations to ensure suitability and safety (14). All patients require a pre-procedural contrast enhanced TAVI-CT scan in order to delineate the cardiac and aortic anatomy, as well as to plan a safe vascular access route and valve sizing (46-48). Figure 6 demonstrates images from a TAVI-CT in a study patient. Important anatomical information required from the TAVI-CT include:

1. Aortic valve morphology, size and calcium burden to guide valve type and size (47, 48).
2. Left ventricular outflow tract (LVOT) and AV annulus diameter, area and calcium burden. Higher calcific burden increases the risk of annular rupture, iatrogenic conduction disease and para-valvular leak (49).
3. Sinotubular junction, sinus of Valsalva and ascending aorta diameter (48).
4. Coronary ostia height. Low coronary ostia carry higher risk of occlusion at valve implantation and careful valve selection is required to avoid this potentially catastrophic complication (46, 48).
5. Vascular access routes. Ileo-femoral artery size, patency, calcific burden and tortuosity can make trans-femoral TAVI challenging and may mandate the use of an alternative vascular route, or make safe TAVI implantation impossible (46, 48).

Coronary angiography to delineate coronary anatomy prior to TAVI is considered an essential work-up investigation in EACTS/ESC guidance in order to revascularise co-existing severe CAD prior to TAVI, as engaging coronary ostia post-TAVI may be challenging (14). The rationale for treating co-existing CAD is the subject of this thesis and will be described in more detail in subsequent chapters. Electrocardiogram (ECG) monitoring is also a key pre-, intra- and post-procedural investigation due to the high risk of developing conduction disease, owing to the proximity of the atrioventricular node to the aortic root (50). Co-existing conduction disease, including right or left bundle branch block increases the risk of intra-procedural complete heart block (CHB) and may be an indication for pre-procedural permanent pacemaker (PPM) insertion to mitigate for this (50). Intra-procedural temporary pacing may be required in cases where PPM insertion has been deferred (50).

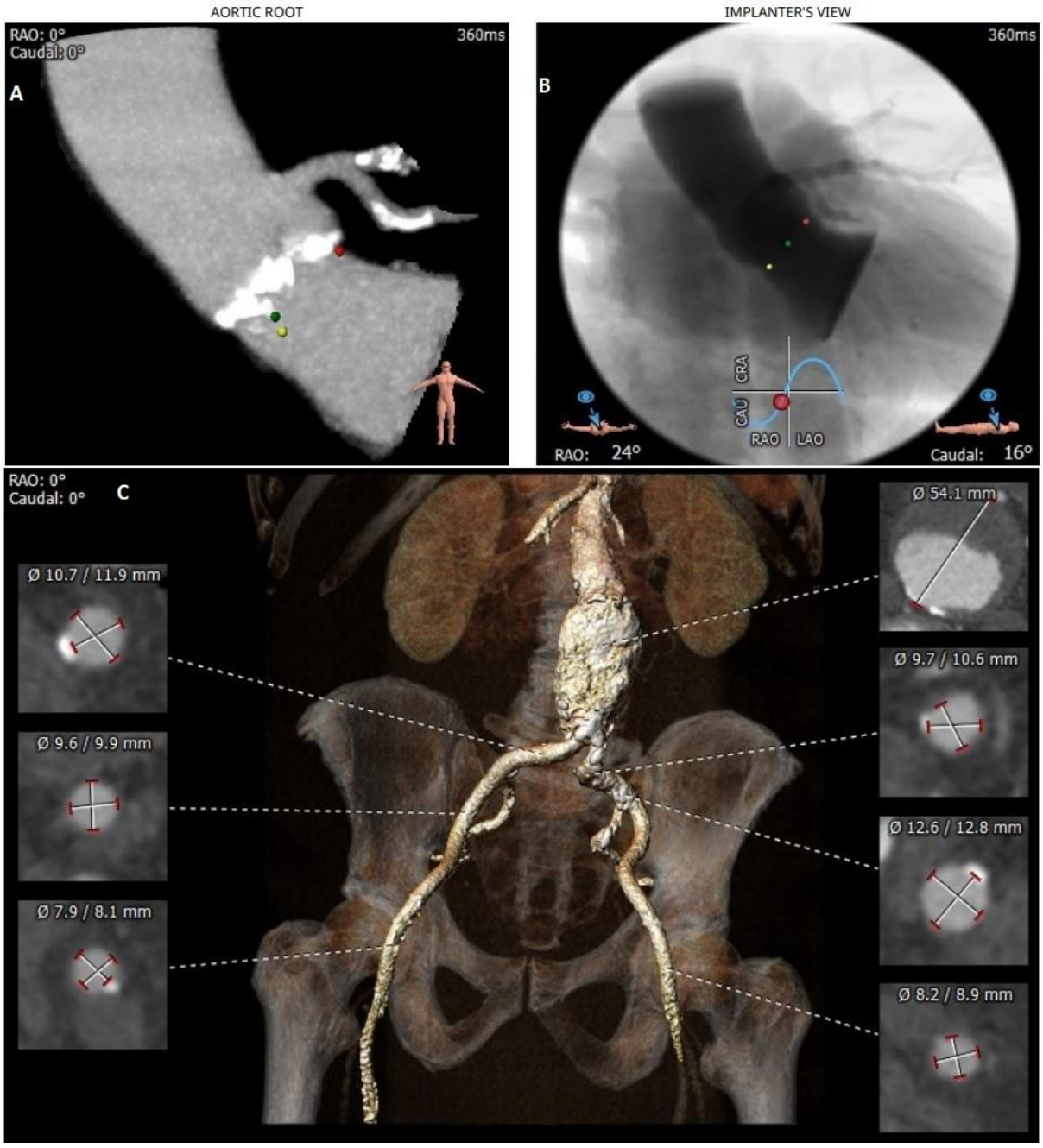


Figure 6. *Example of images from a TAVI-CT scan.*

Images anonymised and obtained with consent from a study patient. Figure 6**A** shows cross sectional CT image of the aortic root and AV annulus with the left coronary ostia arising from it, the white areas represent calcification of the valve and vessel walls. Figure 6**B** demonstrates a CT obtained TAVI-implanter's view of the aortic root and valve. Measurements of the aorta, aortic root and AV annulus are taken from these reconstructions. Figure 6**C** shows a 3D reconstruction of both the right and left femoral and iliac arteries with

cross sectional diameters provided at each level. This image also shows a rather large abdominal aortic aneurysm.

1.3.6.2 Complications of TAVI

TAVI implantation carries a variety of risks, including death. The common complications and risks have been obtained from the NICOR/BCIS National Audit of Interventional Procedures (2021-22) (45). There was a 9.4% rate of PPM insertion as a result of TAVI implantation, with Medtronic branded valves carrying a higher risk than Edwards valves (12.3% vs 8.4%) (45). Paravalvular and transvalvular leak is a complication which can lead to LV failure and the risk of moderate or worse aortic regurgitation was 2.4% (45). The rate of coronary occlusion requiring "bail-out" percutaneous coronary intervention (PCI) is low at 0.38% and there is a 0.94% risk of pericardial tamponade requiring either percutaneous or surgical drainage (45). The rate of vascular complications have been falling over the last 10 years and have fallen to 1.5% from 3.2% in 2013 (45). The overall risk of major bleeding is 1% and life-threatening bleeding is 0.45% (45). The in-hospital CVA risk was 1.87% and this has been gradually falling over the last five years (45). The routine use of cerebral protection devices are not mandated, but 12.9% of cases implemented this technology (45). The BHF-PROTECT study (NCT02895737) is an ongoing UK based randomised control trial which will randomise 7730 patients to cerebral protection device (Sentinel) or standard care and will be largest study of its kind globally when complete (51). In hospital mortality was 1.5% and this has fallen dramatically from 4.8% in 2013 (45).

1.3.6.3 TAVI in high-risk patients

The PARTNER trial (Placement of Aortic Transcatheter Valves) was the first major prospective, randomised, treatment-control, clinical trial to compare TAVI with both medical therapy (where patients were unsuitable for SAVR, 358 subjects randomised) and SAVR (699 subjects randomised) (52, 53). These were parallel arms of the same trial: A and B. Leon et al presented the PARTNER-1B (Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery) data on TAVI versus patients who were unsuitable for SAVR in 2010 (53). At one year, the rate of the composite endpoint of death or rehospitalisation, and all-cause mortality, in patients who received TAVI was 42.5% and 30.7% respectively, compared

with 71.6% and 50.7% in the control arm (P=<0.001) (53). Patients who received TAVI had a significantly increased risk of peri-procedural stroke (5% vs 1.1%, P=0.06) and vascular injury (16.2% vs 1.1%, P=<0.001) (53). Despite this, the data showed a significant difference in the composite endpoints and death in patients who received TAVI over medical therapy alone (53). Smith et al presented PARTNER-1A (Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients) data on TAVI versus SAVR in high-risk patients in 2011 (52). The composite rate of death at one year between the TAVI and SAVR cohort was 24.2% and 26.8% respectively (P=0.44) (52). The rate of major stroke at 30 days (TAVI vs SAVR) was 5.1% vs 2.4% respectively (P=0.07), and the SAVR group had a significantly higher rate of new onset atrial fibrillation (AF) and bleeding (52). PARTNER-1A demonstrated that TAVI and SAVR were associated with similar outcomes at one year in high-risk surgical patients despite a significant difference in peri-procedural complications (52). Five year outcomes for this arm were published in 2015 by Mack et al (54). The five year risk of death in the TAVI vs SAVR group was 67.8% vs 62.4% respectively (P=0.76) (54). However, the development of aortic regurgitation (AR) was significantly higher in the TAVI group (14% vs 1%, p=<0.001), and was associated with a significantly higher risk of death at five years (56.6% with mild AR and 72.4% with more than moderate AR, P=0.003) (54). Similar overall clinical outcomes were demonstrated between the groups over five years. The significantly higher rates of AR in the TAVI cohort and the associated mortality may be due to early generation TAVI implants and growing experience with the technique by operators.

1.3.6.4 TAVI in intermediate-risk patients

The Italian OBSERVANT study (Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment) by Tamburino et al in 2015 was a prospective, observational, multi-centre real world study that propensity-matched 1,300 patients with either TAVI or SAVR and followed them for one year (55). This population of “all comers” was deemed to be of low-intermediate surgical risk. The all-cause mortality at one year for TAVI vs SAVR was shown to be 13.6% vs 13.8% (P=0.936) (55). Five-year data for this cohort was published by Barbanti et al in 2019 (56). The rate of any cause death at five years was significantly higher in the TAVI cohort at 48.3% vs 35.8% in the SAVR cohort (P=0.002) (56). TAVI was also associated with a significantly higher risk of major cardiac and cerebrovascular complications at five years (54% vs 42.5%, p=0.003) (56). Given the observational, “all

comers" nature of the OBSERVANT study, the cohort of patients recruited was likely to have a higher frequency of co-morbidity and unfavourable anatomical features when compared with rigorously controlled randomised trials such as PARTNER (56). Furthermore, OBSERVANT only matched patients who had first-generation TAVI devices, and there was no centralised echocardiography corelab; therefore, given the findings of Mack et al (54), it is not clear whether valvular leak and AR was a major driving factor behind the high mortality demonstrated in this group. This being the case, newer generation TAVI devices may demonstrate better long-term outcomes; the OBSERVANT II study is ongoing.

Multiple randomised trials have validated the safety TAVI against SAVR in intermediate and low risk patients, including in the long-term (57-62). PARTNER-2A (63) and SURTAVI (Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients) (57, 64) were both randomised trials comparing TAVI vs SAVR for intermediate risk patients. PARTNER-2A randomised 2,032 patients, while SURTAVI randomised 1,746. Both trials found TAVI to be non-inferior with respect to major cardiovascular events and death (at two and five years) although, as previously demonstrated, the post-operative risk profiles were significantly different, with SAVR having a greater incidence of bleeding and AF, and TAVI being associated with residual AR and vascular injury (57, 63). The five-year data for PARTNER-2A showed was no statistical difference in the composite endpoint of death from any cause or major stroke between the TAVI and SAVR groups (47.9% vs 43.4%, P=0.21) (62). However, some sub-group analyses were of interest in this cohort. Firstly, the rate of death and disabling stroke was significantly higher in the group of patients who underwent TAVI via trans-apical approach vs SAVR (59.3% vs 48.3%), while the trans-femoral approach was in equipoise with SAVR (62). Secondly, in landmark analyses between two to five years, there was a higher incidence of death and disabling stroke in the TAVI group over the SAVR group (62). Valvular leak, AR and untreated coronary disease are postulated as possible causes (62). Five-year SURTAVI data showed all-cause mortality and stroke for TAVI vs SAVR to be 31.3% vs 30.8% (P=0.85) and years two to five landmark analyses for the same at 21.3 vs 20.7% (P=0.77) (64, 65).

1.3.6.5 TAVI in low-risk patients

PARTNER-3 (61) and EVOLUT-LRT (Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients) (58) are both randomised trials comparing TAVI with SAVR in low risk patients. PARTNER-3 randomised 1,000 patients and the rate of the composite primary end-point of death, rehospitalisation or major stroke was 8.5% in TAVI vs 15.1% in SAVR (P=<0.001) at one year, (61). TAVI was also associated with lower rates of death or stroke at 30 days (0.4% vs 1.1%, P=0.01) (61). The five-year data from PARTNER-3, published in 2023, confirmed long-term non-inferiority between TAVI and SAVR (primary end point reached in 22.8% of TAVI cohort vs 27.2% of SAVR, P=0.07) (66). PARTNER-3, however, excluded patients with significant co-morbidities that would increase their risk of post-operative complications, patients with BAV, and those with no trans-femoral access (61). EVOLUT-LRT randomised 1,468 patients and demonstrated an incidence of the primary endpoints of death or major stroke of 5.3% in the TAVI cohort vs 6.7% in the SAVR cohort at one-year, which achieved a probability of non-inferiority of >0.999 (58). The Nordic Aortic Valve Intervention team (Thyregod et al, NOTION) (59) also noted non-inferiority with respect to major cardiovascular events and death at five-years, albeit with the commonly seen excess risks of AR, vascular complication and pacemaker insertion still present (59).

1.3.7 Antithrombotic therapy

All patients who receive a TAVI should have lifelong single antiplatelet therapy (SAPT) (Class I A recommendation) (14). A DOAC is recommended instead of SAPT if there is an indication for anticoagulation such as AF or pulmonary embolism (14). Longer term dual antiplatelet therapy (DAPT) is only recommended if there is a clear indication for this such as PCI. Current guidance suggests the use of DAPT for three months post-TAVI with lifelong SAPT thereafter in the majority of patients, with earlier de-escalation in those with a higher bleeding risk (14).

A number of studies have investigated antithrombotic therapy following TAVI. The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) trial, published by Rodés-Cabau et al in 2017, randomised 222 patients to either SAPT with Aspirin (80-100mg once a day) or DAPT with Aspirin and Clopidogrel (75mg once a day) following TAVI and followed up at three months (67). Although this was a somewhat small trial which

only published relatively short-term data, it did note that patients receiving SAPT had a tendency towards reduction in MACE events without incurring an increased risk of MI or stroke (67). The composite end point of MACE events and major or life-threatening bleeding occurred in 15.3% of the DAPT group, compared with 7.2% in the SAPT group (p=0.065) (67). There was a statistically significant increase in major or life-threatening bleeding risk in patients receiving DAPT over SAPT (10.8% vs 3.6%; p=0.038) (67). There was no difference in the occurrence of death between the groups at three months (SAPT, 3.6%; DAPT, 6.3%; p=0.37) (67). None of the patients had AF and none were taking a DOAC or VKA. The POPULAR TAVI (Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation) trial by Nijenhuis et al 2020 aimed to tackle this additional question (68). They randomised 313 patients already taking an oral anticoagulant (DOAC or VKA for an appropriate indication) to either receive additional Clopidogrel or not for three months following TAVI (68). The primary outcome of all-cause bleeding was met in 21.6% receiving anticoagulation alone compared with 34.6% of those receiving additional Clopidogrel (RR=0.63; 95% CI=0.43-0.90; p=0.01) (68). The most common cause for bleeding in both groups was from the TAVI access site. The other primary outcome of non-procedure-related bleeding was reported in 21.7% of the anticoagulant only group compared to 34.0% in the group receiving additional Clopidogrel (RR=0.64; 95% CI=0.44-0.92; p=0.02) (68). Analysis of the secondary endpoints of MACE events and cardiovascular death showed non-inferiority between the groups, however the study was not corrected nor powered for these endpoints specifically and therefore no clinical inferences should be drawn (68).

A meta-analysis of three randomised trials comparing SAPT vs DAPT following TAVI was published by Maes et al in 2018 (69). A total of 421 patients were included and there was no difference in the baseline procedural or clinical characteristics. The combined primary end point was death, vascular complications and major bleeding at 30 days (69). The DAPT group demonstrated a higher rate of the combined primary end point compared to the SAPT group (17.6% vs 10.9%; OR=1.73; 95% CI=1.0-2.98; p=0.05) and a higher rate of major or life-threatening bleeding (11.4% vs 5.2%; OR=2.24; 95% CI=1.12-4.46; p=0.022) (69). There was no difference in death or MACE event rates (69). Thus, DAPT was found to proffer patients a

significantly increased risk of major adverse events, primarily driven by bleeding, without providing a reduction in MACE (69).

1.3.8 Durability of TAVI valves

Although the principle aims of the aforementioned TAVI trials focused primarily on short-term safety and efficacy compared to SAVR, increasing attention has turned to long-term valve durability, especially as TAVI expands to younger and lower-risk patients (70). Current data suggest that TAVI valves demonstrate good durability for at least 8-10 years (59, 70). The NOTION trial, which included predominantly low-risk patients, showed no significant difference in valve function between TAVI and SAVR at 8 years (59). Similarly, analysis from the PARTNER 1 and PARTNER 2 trials found low rates of clinically relevant valve dysfunction up to eight years post-TAVI (71). Long-term follow-up beyond a decade is lacking, and newer-generation valves may perform differently than first-generation valves. Ongoing surveillance and future registry data will be essential to fully establish the long-term performance and bioprosthetic durability of TAVI relative to SAVR.

1.4 Coronary anatomy, physiology and pathology

The heart is an organ unique in its ability to provide and regulate its own blood supply. There is a complex interplay between systemic disease, structural diseases of the heart, and disease of the coronary arteries and microvasculature, which can be difficult to treat in isolation.

The coronary circulation can be divided into four categories (see Figure 7) (72):

1. Main epicardial arteries (500µm – 5mm diameter)
2. Pre-arterioles (100- 500µm)
3. Arterioles (10-100µm) – *the microvasculature*
4. Capillaries (5-10µm) – *the microvasculature*

The main epicardial arteries serve predominantly as capacitance vessels and provide little resistance to blood flow in health. These vessels dilate and accumulate elastic energy to aid forward flow of blood to the pre-arterioles and arterioles, which are compressed during systole (73). The intermediate pre-arterioles are responsible for maintaining pressure at the

origin of the microvasculature in response to perfusion pressure changes, and in normal physiological conditions, are important in regulating coronary resistance (73). Finally, the intra-myocardial arterioles and capillaries (<100μm) of the microvasculature are the site of metabolic autoregulation of myocardial blood flow (MBF) via variations in vascular tone, in order to meet myocardial oxygen demand and house the majority of intra-myocardial blood volume (IMBV) (73, 74). The arterioles play a role in maintaining vascular resistance across the myocardial bed as well as containing significant IMBV (74). Figure 7 demonstrates the components of the coronary system with a "microCT" acquired 3D reconstruction and ultra-high-resolution images of a porcine heart, used with permission from Feher et al 2017 (74). It also shows the mean pressure and resistance across these vessels during the cardiac cycle and demonstrates the high IMBV within the microvasculature.

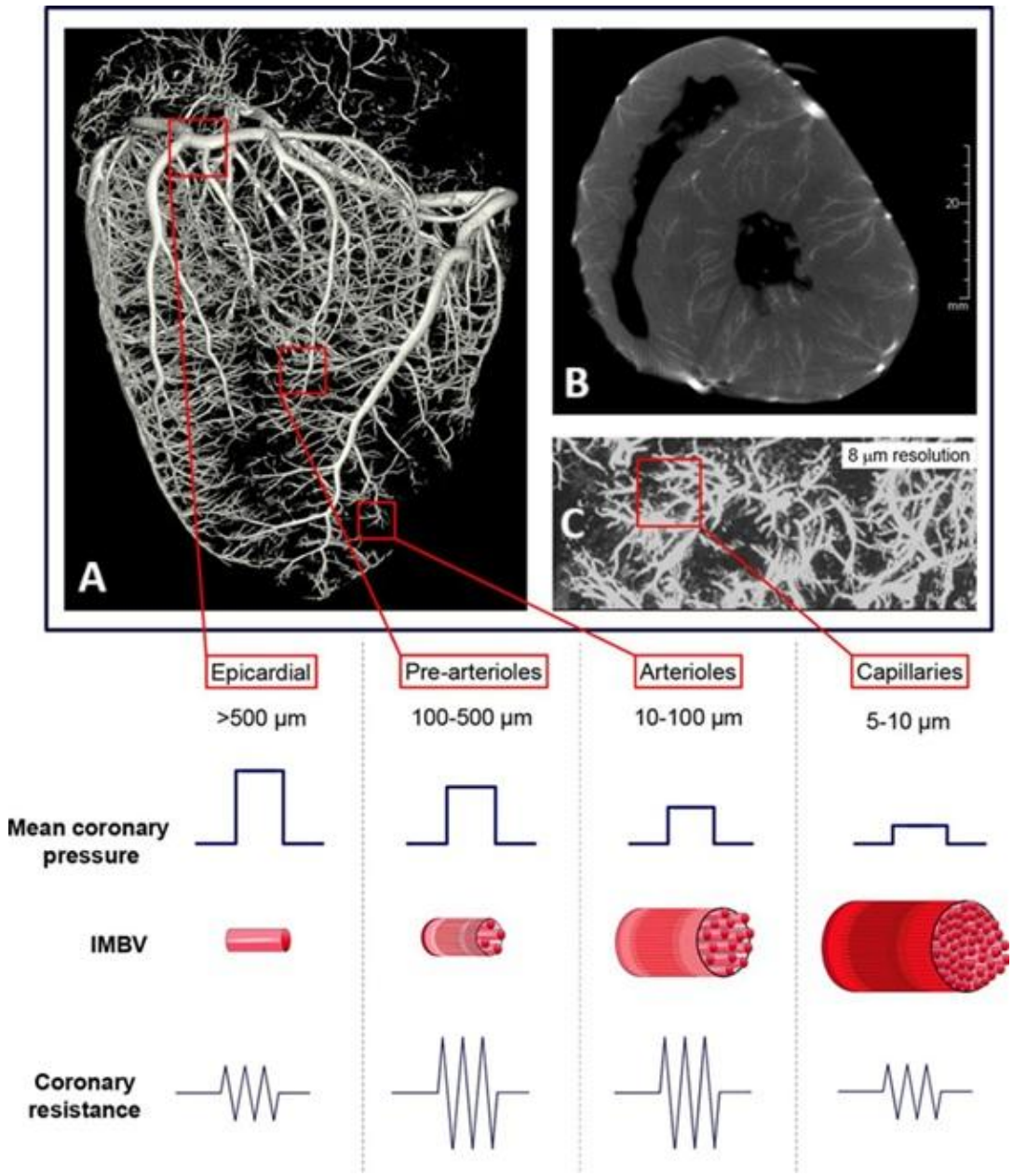


Figure 7. *Components of the coronary tree.*

Components of the coronary tree. 7**A**; a 3D rendering of a porcine heart vasculature using microCT. 7**B**; a short axis/ axial slice of the same heart with maximal intensity projection. 7**C**; ultra-high resolution microCT images of the same heart. The majority of IMBV is contained within the microvasculature, while the most important vessels with respect to resistance are the pre-arterioles and arterioles. Reproduced from Keher et al 2017, with permission from Wolters Kluwer Health Inc (74).

1.4.1 Normal coronary blood flow

Myocardial blood flow is supplied through the main epicardial coronary arteries, which arise from the coronary ostia at the sinuses of Valsalva in the aortic root. These arteries travel over the surface of the heart towards the apex and dispatch thousands of arterioles into the sub-epicardium, which divide transmurally into the sub-endocardium to supply the entire myocardial bed with oxygen (75). Coronary autoregulation is driven by myocardial oxidative metabolism (MVO_2), which allows maintenance of myocardial oxygen supply across a range of perfusion pressures (75). The maintenance of adequate oxygen supply to the myocardium is complex, tightly regulated and governed by a network of neurohormonal, myogenic, metabolic and endothelial processes (76). This is ultimately achieved via modulation of vascular tone and resistance within the sub-endocardial microvasculature (73, 76). However, the myocardial tissue bed is in a constant flux of contraction and relaxation and, as such, the flow through these vessels is affected by the extravascular compression forces generated with each ventricular contraction (75). Therefore, blood flow to the myocardium is reduced in systole as the myocardium contracts, and external compressive forces increase the resistance in the microvasculature. This contraction results in two "decelerating" backward compression waves arising from the myocardium, as documented by Davies et al in 2006 in their landmark paper on wave intensity analysis applied to coronary physiology (77). Relaxation of the ventricle and myocardial tissue bed eases the compressive forces on the microvasculature, reducing resistance and therefore distal pressure, resulting in an "accelerating" backwards decompression wave, thus causing blood to be "sucked" into the microvasculature and coronary bed during diastole (77, 78). Myocardial oxygen supply is almost completely dependent on coronary blood flow and myocardial oxygen extraction is near maximal at resting conditions, thus, an increase in myocardial oxygen demand must be met with an adequate increase in coronary blood flow to avoid a supply-demand mismatch (79). Such a supply-demand mismatch can originate at any level across the coronary-myocardial system and includes coronary atherosclerotic disease, microvascular disease and myocardial disease and presents clinically as ischaemia.

Davies et al implicated six predominant waves in driving coronary blood flow (77, 78). The two most relevant waves which contribute to coronary flow in health are the forward

compression wave in systole (sFCW) and the backward expansion wave in diastole (dBEW) (77). The sFCW is generated by ventricular contraction in systole which propels blood from the aorta into the coronary ostia and arteries. In diastole, myocardial relaxation decompresses the microvasculature resulting in the dominant dBEW, accelerating blood flow into the myocardial bed. The dBEW is the predominant wave and contributor to MBF (77). Thus, coronary blood flow is determined primarily by the varying effects of resistance across the coronary micro-circulation during systole and diastole, and proximal perfusion pressures. This complex series of pressure-flow relationships is termed cardiac-coronary coupling (80), and forms the basis for physiological indices measuring coronary blood flow (81).

1.4.2 Coronary artery disease

Coronary artery disease (CAD) describes disease of the main epicardial coronary arteries, is the second most common cause of death in the UK, and the leading cause of death worldwide (82). Risk factors for CAD include diabetes, hypertension, smoking, genetic predisposition and dyslipidaemia. The pathophysiology of CAD is atherosclerotic and inflammatory. Arterial endothelial injury results in lipoprotein (oxidised/modified-LDL) deposition within the arterial intimal layer, which attracts leucocytes (83). Monocytes from the circulation infiltrate the vessel wall and are transformed into macrophages within the intimal layer which take up lipoproteins and transform into foam cells which in turn replicate and form fatty streaks; the earliest stage of atherosclerotic plaque formation (83). Fatty streaks trigger smooth muscle cells to accumulate; these then proliferate and create a collagen and proteoglycan extracellular matrix which surrounds the fatty streak, generating a fibrous plaque with a soft lipid-rich interior (83). As the fibrous plaque enlarges, it encroaches into the arterial lumen, creating a stenosis within which limits the flow of blood. This may remain asymptomatic for many years, however if the narrowing becomes significant enough to create an oxygen supply and demand mismatch, ischaemia develops. This manifests clinically in a variety of ways, but most notably chest discomfort when myocardial oxygen demand is increased, e.g. with exercise, and is relieved when myocardial oxygen demand is reduced, e.g. with rest. Pain at rest is indicative of severe ischaemia and a coronary system which is unable to supply the myocardium even at rest, and can be the precursor to a myocardial infarction (MI). Coronary artery disease is therefore a spectrum including asymptomatic plaque, stable angina, unstable angina and MI (83). Erosion or sudden rupture of the fibrous cap, even in an asymptomatic

plaque, can trigger a sudden clotting cascade and local platelet activation resulting in an acute intracoronary thrombosis and major MI. CAD affects the perfusion pressure and resistance across the entire coronary vasculature and myocardium, and affects overall myocardial perfusion (84).

1.4.3 Coronary angiography

Invasive coronary angiography (ICA) is the gold standard investigation for epicardial CAD (5). ICA relies on interpretation of X-ray images taken when radiolucent contrast is injected directly into a coronary artery by hand through a specially designed coronary artery catheter which is retrogradely passed through the arterial system from a sheath in a peripheral artery. However, it has several limitations that must be considered when assessing the presence or absence of CAD. Inter-observer variability can make management decisions complex and contentious (85). Poor opacification of the arterial lumen may occur as a result of inadequate contrast injection, inadequate catheter engagement, obesity (due to dissipation of X-rays) and vascular calcification (86). However, the major drawback to ICA in isolation is that it cannot objectively quantify coronary disease or provide physiological data (86, 87). Physiological assessment of coronary disease has proven efficacy, long-term health and economic benefits, and is guideline-based (5). Figure 8 displays typical coronary angiography images of the three major coronary arteries, which are all largely unobstructed with good distal flow.

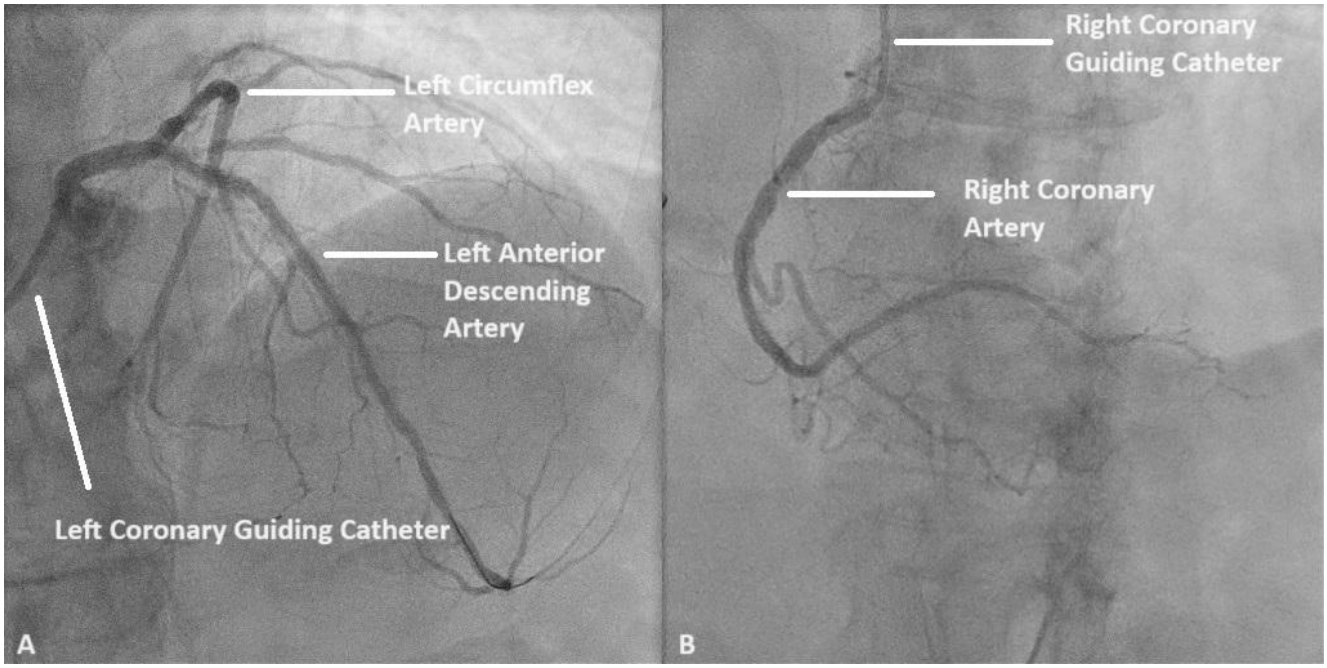


Figure 8. *Coronary Angiogram.*

Coronary angiography images of unobstructed left and right coronary systems. Taken with permission from a study patient. 8**A**; Left coronary. 8**B**; Right coronary artery.

1.4.3.1 Percutaneous coronary intervention

If CAD is identified, determined by a visual appreciation of coronary diameter stenosis or using coronary physiology, treatment can be offered either with medication, PCI or CABG to improve long term prognosis and treat symptoms (5). PCI is a minimally invasive method of restoring coronary blood flow which can be performed relatively quickly in the cardiac catheter laboratory (CCL), without general anaesthetic or a prolonged hospital stay. It can be done as a follow-on procedure to ICA where there is an appropriately equipped CCL and technical expertise, making it an attractive option for the treatment of CAD. It has an ESC Class 1A indication for the treatment of both acute and chronic coronary syndromes and is a guideline driven, gold standard method for the treatment of CAD in various anatomical sub-groups and the evidence base is well established (5). Procedurally, PCI is a percutaneous technique whereby intra-coronary balloons and/or metallic (usually chromium cobalt) stent scaffolds are inflated and deployed over a thin intra-coronary wire which has been passed across a coronary occlusion or stenosis under X-ray guidance. The ESC guidance on myocardial revascularisation recommends the use of drug eluting stents over bare metal stents and

advocates the radial artery route (5). After PCI, patients generally receive 12-months of DAPT, although this is duration may either be extended or reduced based on individual thrombotic and bleeding risk (5). Figure 9 is a schematic diagram demonstrating the technique for single-vessel PCI and Figure 10 shows a PCI procedure (performed by the author of this thesis on a study patient) in a critically stenosed ostial-LAD and the step-wise procedure to deploy a stent from the left main stem into the proximal-LAD and the restoration of blood flow.

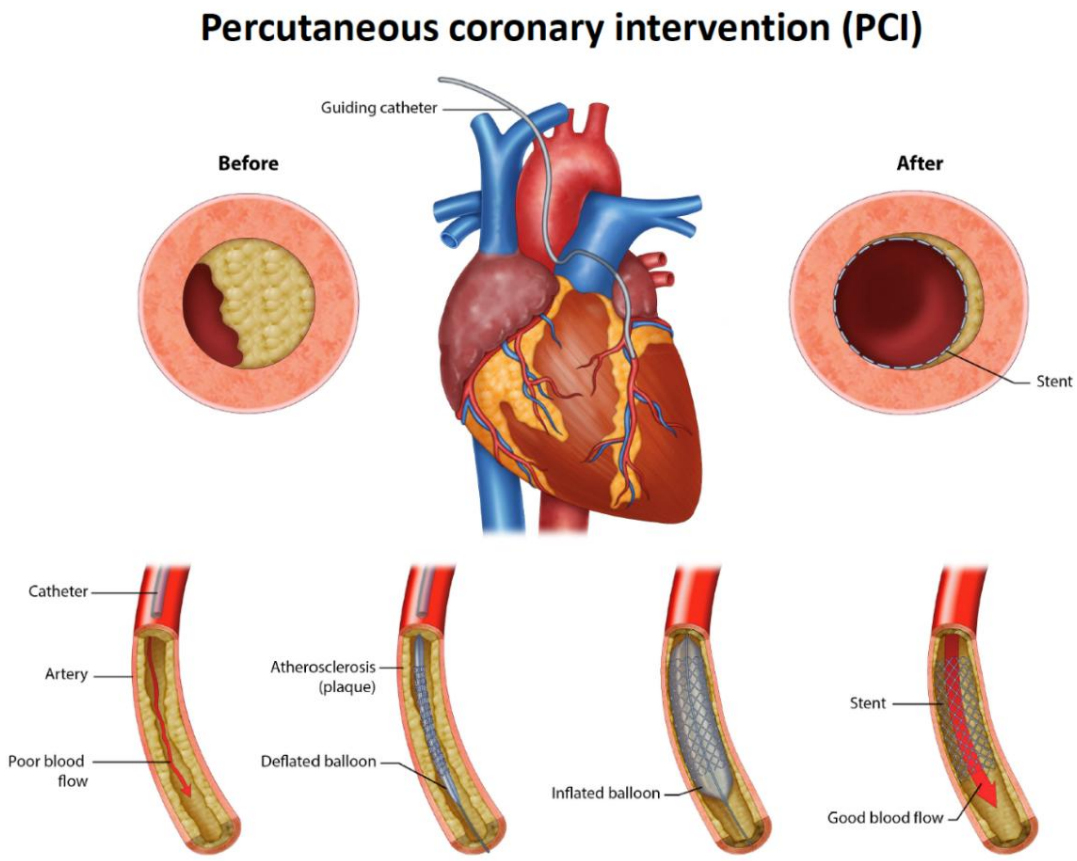


Figure 9. *Schematic diagram of PCI method.*

Image reproduced from the Melbourne Heart Group, Copyright (88).

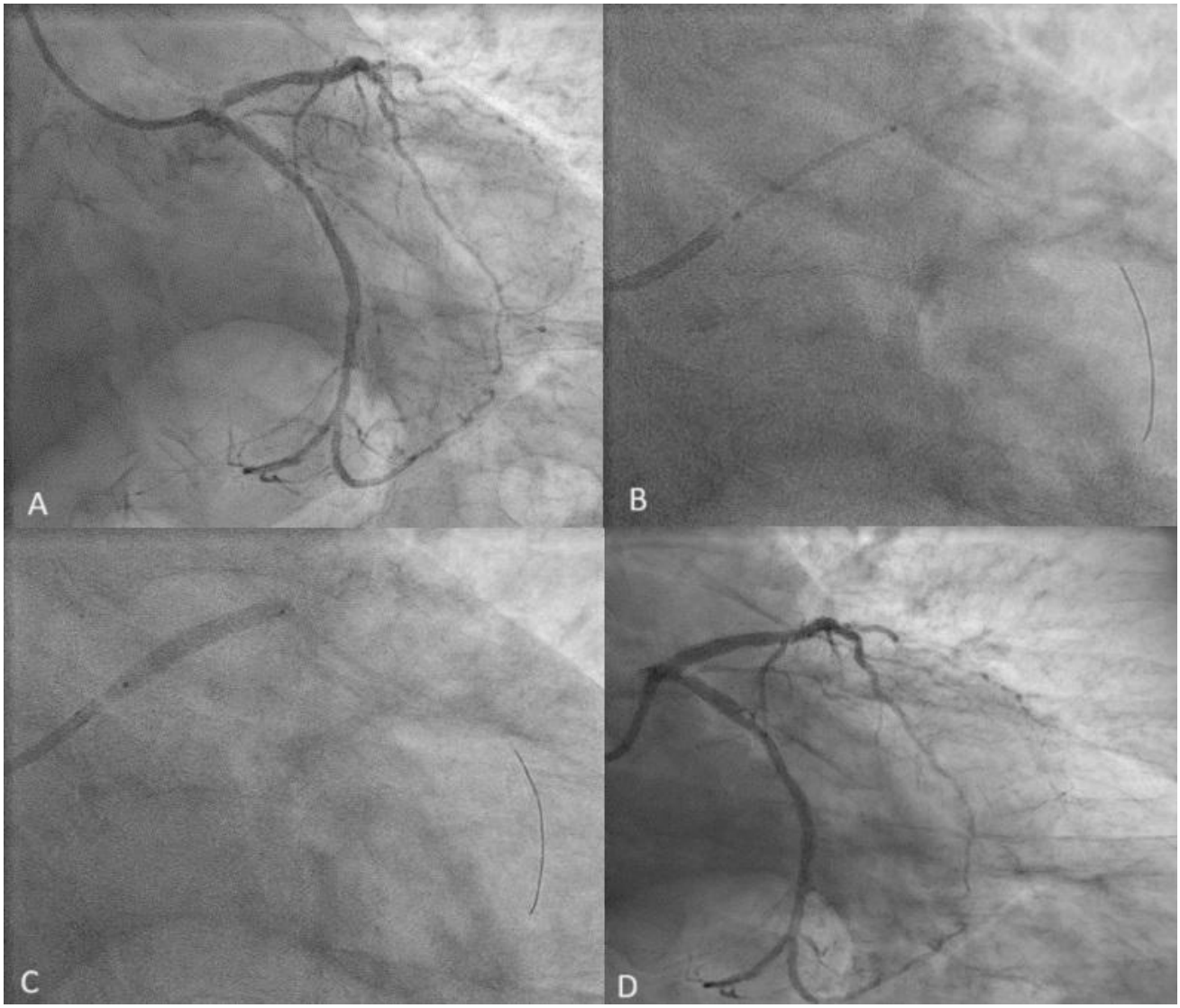


Figure 10. *Angiographic images of PCI procedure.*

PCI of ostial-LAD stenosis with deployment of a stent from the left main stem into the LAD in a study patient, performed by the author, images used with permission. 10**A;** Ostial LAD stenosis demonstrated. 10**B;** Stent sited to correct location. 10**C;** Stent balloon inflated to deploy stent. 10**D;** Deployed stent with clear improvement in lumen size and flow restoration.

1.4.4 Assessment of coronary physiology

Treatment of stable CAD using coronary physiology has been validated with fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR), and is guideline-based (5). In a retrospective study of over 4,000 coronary lesions which underwent quantitative coronary angiography (QCA) and FFR, one third showed discordance between the respective severity

and treatment thresholds, therefore the use of physiological indices in assessment of indeterminate coronary disease is recommended (5, 87, 89).

1.4.4.1 Fractional flow reserve

Fractional flow reserve (FFR) is a pressure-derived index of myocardial blood flow (and ischaemia by proxy), as measured by the maximal flow of blood through a stenosed coronary artery, compared with the theoretical maximal flow of blood in the absence of the stenosis (90). FFR is measured invasively using a pressure sensor-tipped wire placed distally to a coronary stenosis during maximal hyperaemia in order to minimise coronary microvascular resistance. In this state there is an assumed linear relationship between blood flow and physiological coronary perfusion pressures (Figure 12) (90); this is a basic assumption of FFR (84). Vasodilatation is achieved with intra-coronary glyceryl trinitrate (GTN), and hyperaemia is most commonly achieved with intravenous (IV) or intracoronary adenosine infusion (84). FFR is calculated by indexing the mean distal coronary pressure (P_d), measured from the wire tip, to the proximal aortic pressure (P_a), measured from the guide catheter (84, 90). Therefore:

$$FFR = P_d/P_a$$

An optimal FFR, in the absence of any stenosis or flow limitation, is 1.0. A cut-off of ≤0.80 is generally used in clinical practice and guidelines to determine functional significance of a coronary lesion (5, 84). Figure 11 demonstrates an FFR recording being obtained from a study patient using the Coroflow™ system (Coroventis, Uppsala, Sweden).

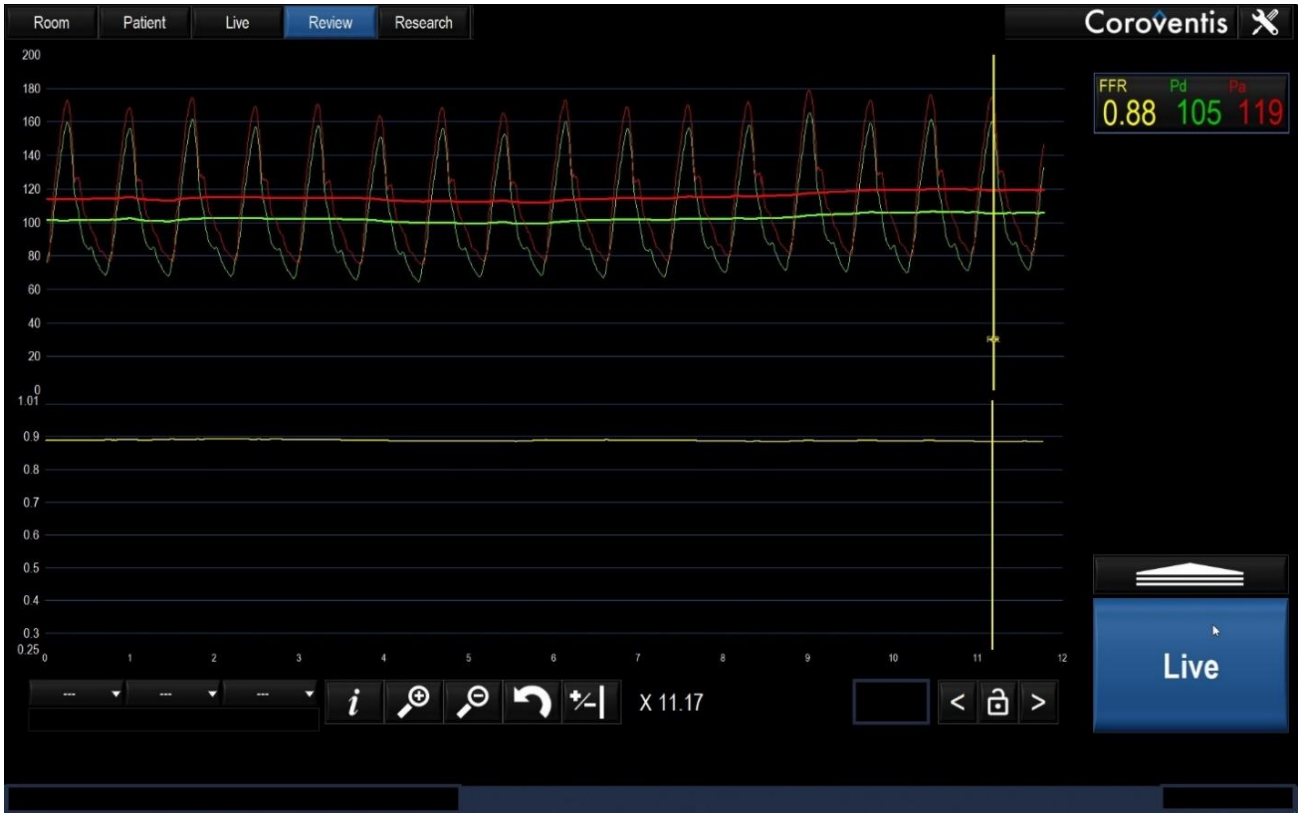


Figure 11. *FFR recording.*

An example of FFR being recorded in a study patient using Coroflow™ (Coroventis™) software. The red pressure trace represents P_a (119mmHg), the green line represents P_d (105mmHg) and the FFR is measured as 0.88.

The experimental basis for FFR was first reported by Pijls et al in 1993 in a landmark paper using a Doppler flow velocity transducer and guidewire in hyperaemic epicardial coronary arteries of five dogs (90). The same group validated this method in 45 human subjects in an observational study comparing the efficacy of FFR with several non-invasive measures of reversible myocardial ischaemia in 1996 (91). The first randomised-control trial to either defer or offer PCI based on FFR was the DEFER trial (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis) by Bech et al in 2001 (92). In 325 patients without documented ischaemia who had single vessel CAD, FFR was measured. If <0.75, PCI was performed (reference group), however if >0.75, patients were randomised to either defer (medical therapy) or perform (PCI) (92). Long-term analyses of this registry were published at five years by Pijls et al (93) and 15 years by Zimmerman et al (4). At 15

years, the rate of death for all three groups was similar (33.0% in defer, 31.1% in perform and 36.1% in the reference group, P=0.79) (4). The rate of MI was significantly lower in the defer group vs the perform group at 2.2% vs 10.0% (P=0.03) respectively (4). Therefore, the authors declared the safety of deferring PCI in functionally non-significant coronary lesions and that PCI may in fact cause a higher rate of MI in this cohort (4). However, these patients received bare metal rather than drug-eluting stents (DES), and newer-generation DES may have reduced this rate in practice (4). The trial was limited in its conclusions in that it did not demonstrate any significant benefit from FFR guidance over standard therapy; rather, it showed the safety of deferral based on FFR, and as all patients with FFR <0.75 were treated, no conclusions can be drawn about this cohort (4). The FAME-1 trial (Fractional Flow Reserve versus Angiography for Multi-Vessel Evaluation) by Tonino et al in 2009 compared FFR guided vs angiography guided PCI in 1,005 patients with multivessel coronary disease (94). A treatment threshold of FFR ≤0.8 was used in patients with at least two coronary stenoses of >50%. Those in the standard treatment arm did not undergo FFR testing (94). This was the first major trial to show favourable outcomes with FFR-guided treatment. There was significant reduction in the combined endpoint of death and major adverse cardiovascular events (MACE) at one year between in the angiography group and FFR group (18.3% vs 13.2%, P=0.02) (94). Subsequent two year and five year analyses by Pijls in 2010 (95) and van Nunen in 2015 (96) respectively confirmed the safety of FFR-guided PCI in multivessel CAD. The reduction in mortality and MI persisted at two years (12.9% vs 8.4%, P=0.02) (95) and at five years there was no significant difference in MACE outcomes (31% vs 28%, P=0.31) (96). The FAME-2 trial by De Bruyne et al in 2012 randomised patients with stable coronary disease and FFR ≤0.80 to either PCI or medical therapy (97). Patients with FFR >0.80 were also followed up. Recruitment was halted prematurely after 888 patients underwent randomisation, due to an early and significant difference between the cohorts with respect to primary endpoint events of death, MACE or urgent revascularisation, 4.3% vs 12.7% respectively (p=0.001) (97). This was primarily driven by urgent revascularisation (1.6% vs 11.1%, P=0.001) (97). The three-year and five-year data confirmed the long-term benefits of revascularising functionally significant (FFR ≤0.80) coronary lesions, and confirmed favourable outcomes in patients in whom PCI was deferred (FFR >0.8) (98, 99). At five years, the rate of the primary endpoints was significantly lower in the PCI group vs medical therapy group (13.9% vs. 27.0%, P=<0.001) (98). However, this difference was once again primarily driven by urgent revascularisation

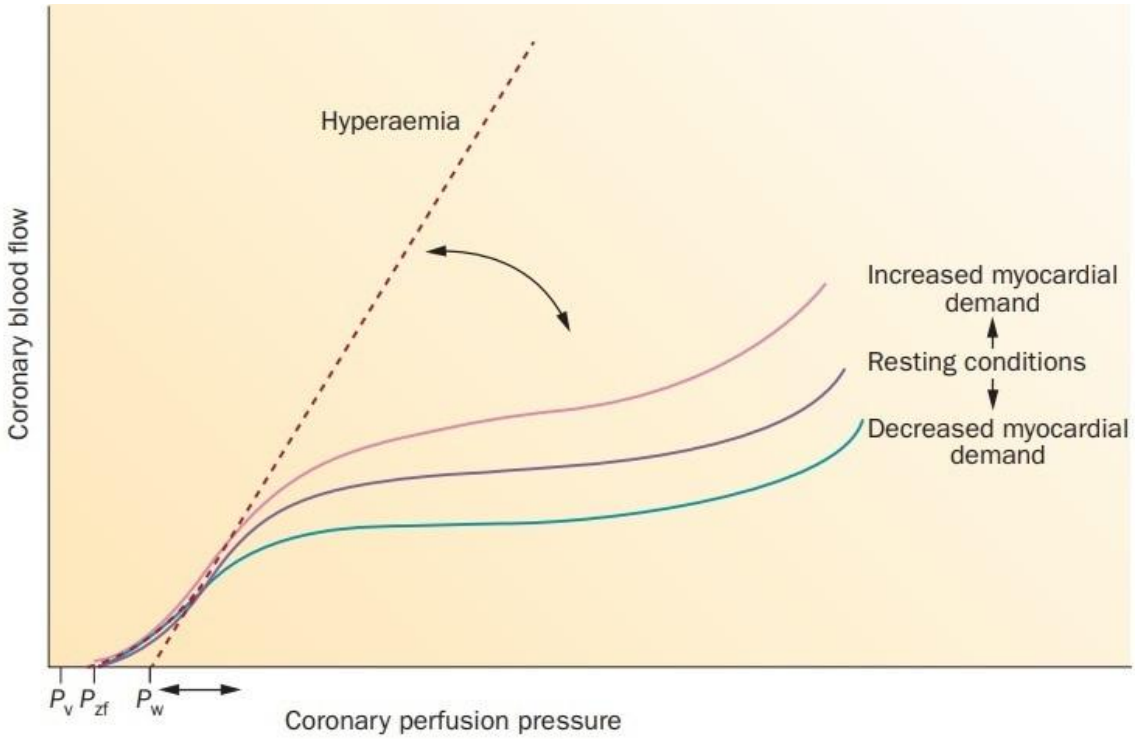
(6.3% vs 21.1%), and the rates of cardiac death or MI were similar at 5.1% vs 5.2% and 8.1% vs 12.0% respectively (98). Therefore, the authors concluded that an FFR-guided revascularisation approach was associated with a lower composite primary endpoint rate at five years compared with medical therapy alone (98).

1.4.4.2 Limitations of FFR

The theoretical basis for FFR assumes some fundamental relationships regarding coronary perfusion pressure (Figure 12), flow, and microvascular resistance which may not necessarily be valid in all patients (100). FFR measures pressure as a surrogate for flow due to the technical challenges associated with invasive flow measurements, and thus assumes a proportional and linear relationship between intracoronary pressure and flow when maximal hyperaemia is achieved and microvascular resistance minimised (100). However, coronary flow and pressure are not linearly related (101). The actual relationship is curvilinear, even at maximal hyperaemia and vasodilation, and there is a "non-zero" pressure intercept, as coronary perfusion falls to zero at a perfusion pressure of 20mHg (Figure 12) (100). This "intercept pressure" is also affected by central venous pressure, collateral coronary flow, and intramyocardial compliance (100). In the original validation models of FFR, venous pressure was subtracted from the Pa and Pd values (91), however in practice this is assumed to be negligible and therefore removed from the final equation (100). Aside from the fundamental misassumption of a linear pressure and flow relationship, the degree of interference of these other individual factors varies from person to person and introduces the potential for error and inaccuracy (100). In order to facilitate a linear pressure and flow relationship, there is also an assumption of pharmacologically achieved minimal microvascular resistance (91). Thus, as FFR estimates the ratio between maximal theoretical blood flow with and without a stenosis, an assumption is made that the microvasculature has the same characteristics in the presence and absence of an epicardial stenosis (100). However, it has been proven that the microvasculature is an important feature of overall myocardial blood flow, and that with reduced distal perfusion pressure, the resistance to flow increases in order to maintain intravascular pressure (and vice versa) (102). Thus, theoretically, restoration of perfusion pressure by PCI of an epicardial vessel should see a fall in the minimal microvascular

resistance back to baseline (100). In a 2005 study by Verhoeff et al, in which simultaneous pressure and flow velocity measurements were made in a reference vessel, and pre- and post-PCI in a target vessel, it was demonstrated that PCI resulted in an immediate fall in the minimal microvascular resistance to *below* that of the healthy reference vessel (103). This finding corroborates the data from the experimental basis of FFR by Pijls et al in 1993, which suggested a progressive overestimation of the coronary blood flow as stenosis severity increased (90). This in turn suggested long-term microvascular remodelling in response to a chronic low perfusion state, but which notably has the potential for recovery (103). The minimal microvascular resistance is therefore variable from one myocardial territory to another in the same individual, let alone between patients. Thus, when considering the above, assuming a constant minimal microvascular resistance fails to consider the adaptive capacity of the microvasculature, and introduces potential error (100).

The measurement of FFR also has a number of technical limitations which should be noted. There is a fundamental requirement for maximal vasodilation and hyperaemia, usually with GTN and adenosine (91). However, these medications can cause hypotension, shortness of breath and chest pain, and minimal microvascular resistance may not be easily achieved at standardised doses which may increase side effects. Furthermore, some caution is advised in using such potent vasodilators in patients with severe aortic stenosis, due to the potential for significant hypotension, as well as the issue of additional cost. Finally, there is potential for pressure drift to occur as a result of a loss of equalisation between the Pd sensor which may give a false positive result.



| The coronary pressure–flow relationship. Coronary blood flow at rest (solid lines) is controlled to match myocardial oxygen demand and to counteract variations in perfusion pressure by parallel changes in microvascular resistance, resulting in an autoregulatory plateau. During coronary vasodilatation, control is exhausted and blood flow depends on perfusion pressure (dotted line). The coronary pressure–flow relationship is concave at low perfusion pressures. The zero-flow intercept on the pressure axis (P_{zf}) slightly exceeds venous pressure (P_v). Straight extrapolation of the hyperaemic pressure-flow relationship results in an incremental–linear relationship that intercepts the pressure axis at the coronary wedge pressure (P_w), which incorporates collateral flow, heart rate, and ventricular wall tension. Small vessel disease or abnormal left ventricular function decreases the slope of the pressure-flow relationship (curved arrow). Elevated left ventricular end-diastolic pressure or left ventricular hypertrophy cause a parallel shift to the right (straight arrow).

Figure 12. *Diagram showing the coronary pressure-flow relationship.*

Adapted from van de Hoef et al 2013 (100) with permission from Springer Nature, Nature Reviews Cardiology, Copyright (2013).

1.4.4.3 Instantaneous wave-free ratio

The instantaneous wave-free ratio (iFR) is a pressure-derived index of coronary flow which does not require pharmacological vasodilation or hyperaemia. It has a Class IA indication in European guidelines for the assessment of intermediate coronary stenoses (5). It measures maximal theoretical coronary flow ratio, similar to FFR, during a phase in the cardiac cycle in

which microvascular resistance is naturally minimised in order to achieve a linear pressure and flow relationship (104). It was developed and presented by Sen et al in the 2012 ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study (104). The ADVISE-II study by Escaned et al supported a combined FFR/iFR approach to intermediate stenoses, and set the iFR cut-off at the currently widely accepted ≤0.89 (105). Several subsequent trials and a meta-analysis have shown non-inferiority with FFR with respect to diagnostic performance (105-110).

1.4.4.4 Quantitative flow ratio

The quantitative flow ratio (QFR) is the most studied and validated angiography-derived index of coronary severity (111). QFR was first validated by Tu et al in 68 patients (77 vessels) undergoing routine ICA and FFR using 3D-QCA, TIMI-3 frame counting and CFD to compute a virtual-FFR (vFFR) value, which was cross referenced with the invasive FFR (112). The model required the induction of hyperaemia (112). They showed good correlation with FFR (r=0.8, p=<0.001) (112). Subsequently, the FAVOR (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis) and FAVOR-II studies removed the use of pharmacological hyperaemia and demonstrated superiority to standard ICA in the assessment of lesion severity and good agreement with FFR. The authors supported the diagnostic capability and feasibility of QFR (113-115).

1.4.4.5 Absolute coronary blood flow

The use of absolute coronary blood flow (aCBF) as an index to guide the treatment of CAD is not guideline based nor widely used in practice. Measuring aCBF accurately (in mL/min) requires the simultaneous measurement of microvascular resistance and its clinical relevance is related directly to the mass of subtended myocardium. Our ability to measure aCBF has evolved over several decades and the developments are described below.

A Doppler-tipped intracoronary guidewire to measure absolute coronary flow and velocity was first validated by Doucette et al in 1992 (116). This was previously the most commonly used method of assessment of coronary blood flow velocity (CBFV) in practice, however its limitations and inaccuracies associated with variations in vessel size, inaccurate calibration, and turbulent flow obstruction of the catheter have diminished its influence (73). The first

trial to employ a Doppler-tipped wire was the DEBATE trial (Doppler Endpoints Balloon Angioplasty Trial Europe) in 1997, which found significant long-term mortality risk associated with a reduced CBFV of <2.1, further illustrating the importance of the microvasculature in long-term outcomes (117).

Pijls et al were first to use the thermodilution technique to measure FFR and CFR simultaneously in order to differentiate the effects of epicardial and microvascular disease in practice (118). This technique uses a specially designed intra-coronary guiding catheter with a micro-infusion catheter placed more distally and a pressure-temperature sensor-tipped wire placed even further distally into a coronary artery (118-120). Saline is constantly infused through the micro-catheter, and changes in pressure and temperature are detected by the sensor-tipped wire (119). This method can measure simultaneous absolute coronary flow as well as hyperaemic microvascular resistance (HMR) (121).

The novel Rayflow™ (Hexacath, Paris, France) catheter is presently the most commonly used intra-coronary catheter used to measure aCBF using the continuous thermodilution technique and has been validated *in vitro* and in humans (122-124). This is a rapid exchange infusion-tipped catheter which slides over a standard pressure-temperature sensor-tipped wire, continuously infuses intracoronary saline, and uses Coroflow™ (Coroventis, Uppsala, Sweden) software (122). During a 'steady-state' infusion, the temperature of the blood and saline mixture is measured distally by the wire, which is then pulled back into the catheter to measure the infusion temperature of the saline, and make an absolute flow calculation based on these parameters (122, 124). This technique is reportedly a more reproducible method of coronary blood flow, microvascular resistance (MVR) and HMR assessment than bolus thermodilution which is more prone to inter-operator variability (122-124).

Both techniques of thermodilution are invasive, require at least 6Fr guiding catheters and a significant amount of specialist equipment, software and expertise, while reproducibility remains difficult in practice (119). Furthermore, the parameters measured cannot be interpreted without the distribution territory of myocardium being known, nor can values be compared between patients as there is no guideline endorsed normal reference range (119,

122). Fournier et al 2021 aimed to provide reference values for hyperaemic aCBF and resistance in a prospective multi-centre study of 69 patients (177 vessels), of whom 25 were controls and 44 had mild, non-obstructive CAD (125). They used the Rayflow™ catheter continuous thermodilution technique to measure aCBF in mL/min and resistance in Wood units (WU) (125). They measured aCBF in all three coronary arteries in 49 of their patients to determine whole heart hyperaemic coronary flow and used cardiac CT scanning in 40 patients to determine myocardial mass in order to present flow data in mL/min/g in this cohort (125). This study found whole heart hyperaemic aCBF to be 668±185mL/min in healthy controls and 582±138mL/min in the cohort with mild CAD (125). Mean minimal microvascular resistance is reported as approximately 150 WU across the microvasculature (125). Flow in the left anterior descending artery (LAD) was 293±102mL/min in healthy controls versus 228±71mL/min in the mild CAD cohort although a very large range of flows were observed across different vessels and patients (125). When corrected for mass, there was no significant difference between mean aCBF in the major coronary artery myocardial territories (5.9±1.9mL/min/g in LAD, 4.9±1.7mL/min/g in LCx and 5.3±2.1mL/min/g in the RCA) albeit with significant inter-patient variability (125). Ultimately, despite showing that aCBF can be measured relatively quickly and safely in practice, the data obtained is difficult to interpret between patients due to the wide range of flow and resistance values, although intra-patient pre- and post-treatment measurement may be more useful in guiding or assessing the effectiveness of treatment (125). The primary reason postulated for the wide range of values obtained is the relation between flow and myocardial mass, which does hold some reason, as when corrected for mass, the flow across the three major vascular territories is similar (125). Variability in proximal coronary perfusion pressure in hyperaemia across different patients may be another contributing factor (125). No rest data were obtained and we therefore cannot make any assessment of aCBF at rest in these patients.

Aubiniere-Robb et al 2022 presented a retrospective study from The University of Sheffield, in which aCBF was measured using the CFD software virtuQ™ (which also forms the basis of part of this thesis) and compared its relationship with invasively measured FFR in 143 patients with varying degrees of CAD (203 arteries) (126). The absolute values obtained were significantly lower than those reported invasively from normal patients by Fournier et al,

although many patients in this study had CAD (125). Median aCBF across all vessels and patients was 85.2mL/min (IQR 63.5-116.3mL/min) and microvascular resistance was 0.71mmHg.min/mL (IQR 0.52-0.98mmHg.min/mL) (126). When assessed by vessel, the left main stem, LAD and Right Coronary Artery (RCA) had non-significantly higher aCBF (95.6mL/min, 85.6mL/min and 98.8mL/min respectively) than the Left Circumflex (LCx), diagonal or marginal branch arteries (78.1mL/min, 79.9mL/min and 56.7mL/min respectively) (126). As would be expected, FFR positive cases were closely associated with a greater reduction in aCBF and a reduction of >23mL/min was deemed to be significant (126). Overall discordance between FFR and aCBF was low, however it was greatest in the FFR range 0.75-0.8 which is slightly disappointing as this generally regarded as the "grey-zone" for treatment and the data for FFR is described in more detail in section *1.4.4.1*. Ultimately, this study demonstrated good overall concordance between FFR and aCBF reduction (r=0.89, Cohen's Kappa 0.71), however as with previous studies measuring aCBF, the figures obtained demonstrate wide inter-patient variability and again make inter-patient interpretation difficult. The figures obtained are significantly lower than those presented by Fournier et al, and this is likely to be due to the fact that these figures represent coronary outlet flow, rather than inlet flow, and blood is lost to side branches (126). Beyond this, the patients in Fournier et al had either no or minimal CAD, whereas a wide range of epicardial stenoses were present in this study (126). The use of CFD and virtuQ^{TM} for this study will be expanded upon later in this thesis.

1.4.5 Microvascular coronary disease

Abnormalities in the structure and function of the microvasculature affects total MBF, contributes to myocardial ischaemia and is associated with adverse long-term outcomes (73). In some registry data, up to half of patients presenting with symptoms of myocardial ischaemia are found to have no obstructive CAD, but their high rates of MACE suggest MVD (127). At present, no guideline directed treatment recommendations for patients with MVD exist and a number of co-existing factors including obesity, diabetes, heart failure with preserved ejection fraction (HFpEF) and traditional CAD are recognised as risk factors (79).

1.4.5.1 Classification of microvascular coronary disease

Microvascular dysfunction can be broadly divided into four categories. These are; MVD in the absence of CAD, MVD in the presence of other myocardial disease, MVD in the presence of CAD, and iatrogenic MVD (72). Table 1, reproduced from Camici et al 2007, expands on these clinical classifications (72).

Table 1. Clinical Classification of Coronary Microvascular Dysfunction.

Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and coronary flow reserve can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors.
Coronary microvascular dysfunction in the presence of myocardial diseases	This type is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be identified by invasive or noninvasive assessment of coronary flow reserve and may be severe enough to cause myocardial ischemia. It has independent prognostic value. It remains unclear whether medical treatment may reverse some cases. It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular).
Coronary microvascular dysfunction in the presence of obstructive CAD	This type may occur in the context of either stable CAD or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors. It is more difficult to identify than the first two types and may be identified through the use of an integrated approach that takes into account the clinical context with the use of a combination of invasive and noninvasive techniques. There is some early evidence that specific interventions might prevent it or limit the resultant ischemia.
Iatrogenic coronary microvascular dysfunction	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures.

Table 1. *Clinical classification of MVD.*

Reproduced with permission from Camici et al 2007 (72), Copyright Massachusetts Medical Society.

1.4.5.2 Pathophysiology of microvascular coronary disease

The pathogenesis of MVD is initiated and sustained via a number of different mechanisms that may overlap in their influence between the different pathological causes (72). Ultimately, these mechanisms lead to impaired capacity to alter MBF to meet myocardial oxygen demand. Broadly speaking, the pathophysiological mechanisms behind MVD can be categorised into structural, functional and extravascular (72).

Adverse structural remodelling of the microvasculature is characterised by medial and intimal arteriolar thickening, caused by smooth muscle hypertrophy and collagen deposition, which occurs in conditions causing LVH such as hypertension and hypertrophic cardiomyopathy (HCM) (73). Functional mechanisms for MVD are largely a result of endothelial dysfunction and are characterised by reduced capacity for dilatation or increased constriction of the microvasculature (73). Risk factors for endothelial dysfunction-mediated MVD are similar to CAD and include diabetes, smoking, hypertension and dyslipidaemia. These patients may present with typical angina despite normal epicardial vessels on ICA (73). MBF predominates in diastole, it is therefore strongly affected by pathological alterations in intra-ventricular or intra-myocardial pressures that alter this phase of the cardiac cycle (73). Thus, raised intra-myocardial and LV filling pressures create a secondary LVH and impair myocardial blood flow through excessive extravascular compressive force and reduced diastolic relaxation (73). This is therefore not necessarily a pathology of the microvasculature itself *per se*, and may be viewed instead as an acquired abnormality in cardiac-coronary coupling (Figure 14) (80).

1.4.5.3 Assessment of microvascular coronary disease

There are no imaging modalities which allow visualisation of the coronary microvasculature *in vivo* (73). Therefore, microcirculatory function is assessed using a number of invasive and non-invasive techniques (73).

Coronary flow reserve (CFR) is the ratio of hyperaemic to baseline total myocardial blood flow, and can be measured invasively using the thermodilution or Doppler methods (120, 128) and non-invasively using cardiac MRI (CMR) (121, 129) and positron emission tomography (PET) imaging (130, 131). Trans-oesophageal echocardiography has also been compared alongside Doppler wire measurements with some success (132). CFR is most commonly measured invasively using an intra-coronary pressure-temperature sensor-tipped wire with either bolus or continuous saline thermodilution to measure coronary blood flow velocity both at rest and stress (79). Hyperaemia is induced pharmacologically using IV adenosine or acetylcholine. It is an integrated measure of blood flow through the major epicardial vessels and the microvasculature, it provides information about the ability of the vascular bed to respond to

hyperaemia, and is a useful test to assess MVD in normal coronary arteries (120, 128). A CFR of <2.0 is considered abnormal and is associated with increased overall mortality risk (128).

The index of micro-circulatory resistance (IMR) is defined as the minimal resistance during maximal hyperaemic flow and is independent of variations in vascular tone, the epicardial vessels and heart rate (73). It is measured invasively using a pressure-temperature sensor-tipped intra-coronary wire, and is calculated as the mean distal pressure multiplied by the thermodilution-derived mean transit time of a bolus of saline during maximal hyperaemia (133). An IMR of >25 U is the widely accepted cut-off value for pathologically high microvascular resistance (79). High IMR is associated with poor long-term survival outcomes across the spectrum of epicardial coronary disease (79). This has been demonstrated in patients who have had PCI for acute MI (128, 133) and stable CAD (134).

Both the CFR and IMR, when measured invasively, are prone to inter-operator variability and are difficult to interpret at the individual patient level (127). As such, De Bruyne et al 2021 proposed microvascular resistance reserve (MRR) as a novel marker of MVD which is theoretically free of inter-operator variability (when measured using continuous thermodilution) and can be applied more consistently across varying degrees of epicardial coronary flow (127). It is obtained invasively using continuous thermodilution of saline through a dedicated intracoronary catheter to simultaneously measure all relevant physiological indices (127). They have defined the MRR as the true ratio of resting to hyperaemic microvascular resistance, thus raising the obvious comparison with FFR (127). Thus, as with FFR, the MRR measures the microvascular resistance if the epicardial coronary arteries were free of stenotic disease (127). In the presence of an epicardial stenosis, the microvascular resistance will theoretically decrease as a compensatory autoregulation mechanism to maintain myocardial oxygen supply, and thus the measured resistance is artificially low and is directly affected by the presence of up-stream flow reduction (127). The MRR is reportedly unaffected by epicardial coronary disease and can be calculated using a simple formula:

$$MRR = (CFR/FFR) \times (Pa.\ rest / Pa.\ hyperaemia)$$

Thus, using this formula, the MRR can be simply described as the ratio of myocardial resistance at rest and hyperaemia in theoretically unobstructed epicardial coronary vessels and is therefore proposed as the first true specific measure of isolated microvascular disease (127). The authors of the theoretical basis of MRR did not provide optimal reference values and only presented their study based on 30 coronary arteries, and there are clearly limitations including little widespread uptake and experience with continuous thermodilution techniques (127). Beorhout et al presented a comprehensive evaluation of the diagnostic and prognostic performance of MRR in 1481 stable patients with an indication for ICA from the global ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) Registry in the European Heart Journal in 2023 (135). The ILIAS Registry is a retrospective, international registry of coronary physiology and clinical outcome data from over 20 centres (135). They used the formula described above to calculate MRR, however the key difference between this analysis and De Bruyne et al's proposal is the use of the bolus, rather than continuous thermodilution technique to measure resting and hyperaemic transit times. Thus, there is a clear difference in the fundamental methods and the key factor implicated in the inter-operator variability of measuring CFR and IMR invasively remains present here (135). Notwithstanding this, they found a median MRR of 2.97 and demonstrated good correlation between MRR and CFR (135). Furthermore, the difference between CFR and MRR increased with falling FFR values, thus demonstrating the consistency of MRR despite falling proximal perfusion pressures and an abnormal MRR was associated with a significantly higher 5-year MACE rate, especially when the FFR was <0.75 (135). In patients with an FFR of <0.75, MRR outperformed CFR in its association with 5-year MACE and target vessel failure, and this suggests that MRR is a more reliable marker of MVD, especially where there is epicardial coronary disease (135). This study, although retrospective and methodically slightly different to the initial proposal for MRR, has positive conclusions on the potential use of MRR as a novel measure of MVD (135). They suggest an optimal cut-off value of >3.0 as a normal MRR and suggest additional prospective studies are needed to validate the index further (135). All three indices of MVD described above will be measured in this study.

1.5 Coronary artery disease in aortic stenosis

A significant proportion of patients with AS have concomitant CAD (136). The PARTNER-1 trial detected a 74.9% frequency of significant CAD in high risk patients randomised to TAVI, while

the PARTNER-2 trial demonstrated a frequency of 62.5% in their intermediate risk cohort (52, 57). Mack et al demonstrated a coronary disease frequency of 27.7% in the low risk cohort of the PARTNER-3 trial (61), thus demonstrating the wide variability of CAD in AS, but a clear pattern of rising frequency and severity with higher risk groups.

The 2021 ESC/EACTS guidance on the management of valvular heart disease recommends ICA in the majority of patients undergoing any valvular intervention (Class IC) (14). Treatment of concomitant CAD is recommended based purely on severity as per diameter stenosis. The use of FFR and iFR to guide myocardial revascularisation in patients with AS is actively discouraged (5, 14). Coronary artery bypass grafting (CABG) is recommended in patients undergoing SAVR with CAD of >70% (Class IC) (14). However, the guidance for patients undergoing TAVI is less robust, and suggests that treatment should be "considered" where there is >70% "proximal segment" coronary stenosis (Class IIaC) (14). Patients undergoing SAVR with concomitant CABG have an increased risk of peri-operative complications and post-operative mortality compared to those undergoing SAVR alone (137). However, the impact of treating CAD in TAVI patients remains unclear and the guidance on revascularisation is notably in need of greater individualisation and validation (138, 139).

1.5.1 TAVI and CAD in the UK

According to the 2021-22 BCIS and NICOR Audit, 2.9% of patients undergoing TAVI had planned PCI prior to their procedure, and this rate has been gradually falling from 7% in 2014 (45). 11.4% of patients had prior PCI, unrelated to their TAVI procedure (45). The likelihood, from the available literature, is that treatment of co-existing CAD is being deferred or managed medically prior to TAVI, rather than only 2.9% of patients undergoing TAVI having significant CAD.

1.5.2 TAVI and CAD at Sheffield Teaching Hospitals

TAVI was first performed at Sheffield teaching hospitals (STH) in 2017 and 431 procedures were performed in the six years 2017-2022, inclusive. Of these, 47% (n=206) had CAD at ICA, which is defined as >50% in stenosis diameter in a major epicardial vessel. Of this cohort, 15.7% (n=68) had planned PCI prior to TAVI. Only 5.8% (n=12) had FFR measured. All

measured FFRs were >0.80 and PCI was deferred in all cases. The mean SYNTAX score was 3.4 (n=431). In patients with 50-70% diameter stenosis (n=62) in at least one vessel, the mean SYNTAX score was 5.2 and none of these received planned PCI prior to TAVI. In patients with >70% diameter stenosis in at least one vessel (n=88), the mean SYNTAX score was 7.8 and 72% (n=63) went on to have planned PCI prior to TAVI. 56 of 431 patients had a chronically occluded vessel of 100% diameter stenosis, eight of whom had planned PCI prior to TAVI. Of the total cohort, 10.4% (n=45) had prior CABG and 7.4% (n=32) had prior PCI. In 2022, of 93 TAVI procedures at STH, 14 patients (15%) received planned PCI prior to TAVI. These figures demonstrate that although the rate of planned PCI performed prior to TAVI at STH is higher than the 2.9% quoted for the same time period in the latest BCIS/NICOR audit data (45), the number of patients with a previous history of PCI was lower than the national average of 11.4% and ultimately, only a small number of patients receiving TAVI at STH had planned PCI. Of patients attending for TAVI, 19.5% (n=84) were on dual anti-thrombotic therapy (DATT), with either DAPT or SAPT and a DOAC. 80.5% (n=347) were on SAPT or no anti-thrombotic therapy at all. After TAVI, 63.5% (n=274) patients were using DATT. In patients receiving DATT prior to TAVI, 7.1% required a blood transfusion during their admission, compared to 2% in patients not receiving DATT (OR 3.74, 95% CI 1.22-11.42, p=0.021). 17.8% (n=15/84) of patients receiving DATT suffered a vascular complication compared to 6.3% of those on SAPT or no anti-thrombotic therapy (OR 1.54, 95% CI 0.81-2.92, p=0.19). Finally, the CVA rate was similar across the groups, with 7.1% of those on DATT suffering a CVA compared with 7.8% of those on SAPT or no anti-thrombotic therapy (OR 1.04, 95% CI 0.41-2.61, p=0.942).

1.5.3 TAVI and CAD in the literature

A number of early studies demonstrated conflicting results in patients undergoing TAVI who had either previously-treated or untreated CAD (137, 140-142). A meta-analysis of seven similar studies (2,472 subjects) by D'Ascenzo et al demonstrated a prevalence of CAD of 52% and found no statistically significant difference in all-cause mortality between patients with or without CAD (OR=1.0, 95% CI=0.67-1.50) (143). The timing of PCI in TAVI patients is another contentious issue. Kotronias et al performed a meta-analysis of nine studies with 3,858 patients undergoing TAVI with or without PCI and found that patients who had PCI had a higher rate of vascular complications (OR=1.86, 95% CI=1.33-2.60) and all-cause 30-day mortality (OR=1.42, 95% CI=1.08-1.87) (144). There was no significant statistical difference in

cardiovascular death at 30 days (OR=1.03, 95% CI=0.35–2.99) or one-year mortality (OR=1.05, 95% CI=0.71–1.56) (144). A similar meta-analysis by Lateef et al in 2019 looked at 11 cohort studies (5,580 subjects) to determine whether PCI before or during TAVI proffers any additional benefit to TAVI alone (145). The findings were similar to those of Kotronias et al; there was no statistical difference between 30-day (OR=1.30, 95% CI=0.85-1.98) or one-year (OR=1.19, 95% CI=0.92-1.52) all-cause mortality between the groups (145).

A recent large meta-analysis and systematic review of patients undergoing TAVI with significant concomitant CAD by Aarts et al investigated 13 observational studies and one randomised controlled trial (146). “Significant” CAD was defined in some studies as >50% diameter stenosis in a major epicardial vessel and >70% in others, no physiology was used to guide revascularisation. They found no significant difference in short- or long-term clinical outcomes between TAVI patients who did or did not undergo PCI (146). The 30-day all-cause mortality among between isolated TAVI vs TAVI and PCI was 5.9% vs 4.7% (OR: 1.27, 95% CI: 0.91-1.77, P=0.17). The one-year mortality between the groups was 13.6% vs 16.4% (OR: 0.91, 95% CI: 0.64-1.29, P=0.59) (146). Furthermore, patients undergoing isolated TAVI had significantly lower bleeding rates than those who had PCI also (7.5% vs 9.4%, OR:0.66, 95% CI: 0.46-0.94, P=0.022) (146). Ultimately, Aarts et al demonstrated no significant short- or long-term clinical benefit in treating patients with CAD undergoing TAVI with PCI, and in fact demonstrated an increased risk of bleeding in this cohort (146).

The above meta-analyses mimic the findings of studies investigating the same question in patients without AS, i.e. whether PCI in stable CAD without inducible ischaemia can provide survival benefit (147-150). Katritsis et al demonstrated no survival benefit in PCI vs medical management in patients with chronic stable CAD in a meta-analysis of 2005 (147). Similar results were reported in a meta-analysis including 14,877 patients by Bangalore et al in 2020, although PCI was associated with higher rate of freedom from angina (149). The COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) by Boden et al in 2007 and the ISCHEMIA trial (Initial Invasive or Conservative Strategy for Stable Coronary Disease) by Maron et al in 2020 both randomised patients with stable CAD to PCI or medical therapy studies, and again showed a statistically significant improvement in freedom

from angina in the PCI group, but no overall survival benefit or reduction in MACE (148, 150). The ISCHEMIA trial enrolled patients with stable CAD who demonstrated moderate to severe ischaemic burden on non-invasive stress testing, such as stress nuclear imaging, stress echocardiography, or cardiac MRI (150). The landmark ORBITA trial (Percutaneous coronary intervention in stable angina) by Al-Lamee et al randomised and blinded 200 patients with stable CAD to PCI and medical therapy or a "sham" PCI procedure plus optimal medical therapy, and demonstrated no significant difference in exercise time between the groups, thus demonstrating the potential placebo effect of a PCI procedure for angina relief (151).

The ACTIVATION trial (Percutaneous Coronary intervention prior to transcatheter aortic valve implantation) is a randomised, controlled trial comparing angiography guided PCI with medical therapy in patients undergoing TAVI (152). In this trial, 235 patients listed for TAVI with significant coronary artery disease and Canadian Cardiovascular Society (CCS) class ≤2 angina were randomised to either PCI or medical therapy. Similar rates of the composite endpoint of all-cause death and re-hospitalisation at one year were reported, (PCI 41.5% vs medical therapy 44.0%, P=0.067), although the non-inferiority margin was not met and recruitment was discontinued prematurely (152). The secondary endpoints of major CVA and MACE events at 30 days and one year were also similar, but major bleeding events were significantly higher in patients who had PCI (P=0.021), likely to be driven by their need for DAPT (152). As with the observational meta-analyses noted above, no objective markers of ischaemia are measured and "significant" CAD was defined as >70% stenosis in a major epicardial vessel. Importantly, patients with left main stem or ostial CAD were excluded from the ACTIVATION study and represent a vulnerable cohort who may indeed benefit from PCI before TAVI (152). Beyond this, the mean age of patients in the ACTIVATION trial was 84 years and it is not clear whether it is appropriate to apply these findings to the increasingly younger cohort of patients who are being offered treatment with TAVI. It should also be noted that isolated AS is known to cause angina without discernible CAD on ICA (153), therefore attributing angina to visualised CAD alone in the context of AS is intrinsically flawed.

The NOTION-3 (Revascularisation in Patients Undergoing Transcatheter Aortic Valve Implantation) trial randomised 455 patients with severe AS and at least one coronary artery

with an FFR of <0.8 to either full revascularisation (with PCI) followed by TAVI, or TAVI alone (154). Therefore, all patients in this study had functionally significant CAD, as assessed by FFR, and this is the only study of its kind. In patients with >90% coronary stenosis, revascularisation was performed without FFR-guidance if randomised to the treatment arm. At a median 2-years follow-up, the composite end point of all-cause death and MACE events occurred in 26% of patients in the PCI group and 33% in the conservative therapy group (HR 0.71, 95% CI 0.51-0.99, P=0.04) (154). A bleeding event occurred in 28% of the PCI group and 20% in the conservative therapy group (HR 1.51, 95% CI 1.03 – 2.22) (154). This is the first such trial where intra-coronary physiology has been used to confirm lesion significance in patients undergoing TAVI, and the authors recommended the use of FFR-guided PCI this cohort. The FAITAVI (Functional Assessment in TAVI) trial is ongoing and will randomize 320 patients to FFR or angiographically guided revascularisation (ClinicalTrials.gov Identifier: NCT03360591 (155)).

Murray et al have performed a large meta-analysis to further investigate the question of PCI timing in patients undergoing TAVI (156). They highlighted 13 studies, which included 15,412 patients who had an indication for routine PCI. In some patients, PCI was performed pre-TAVI and in others, at the same procedure, and these were compared with patients who had PCI after TAVI. There was no difference in the 30-day mortality, stroke rate or major bleeding risk between patients who had PCI pre-TAVI and those who had PCI done at the same time as their TAVI procedure (OR 0.91, 95% CI [0.67-1.24]) (156). When these patients were compared to those who had PCI post-TAVI, however, there were significant differences. The 30-day mortality among patients who had combined concomitant and pre-TAVI PCI was significantly higher than the post-TAVI cohort (OR 5.70, 95%CI [1.34-24.36]) and the two year mortality was similarly high also (OR 4.40, 95% CI [2.6-7.44]) (156). There were similar stroke and bleeding rates in both groups as both eventually had PCI, whether before or after TAVI.

Tarantini et al presented a clinical consensus statement on the treatment of CAD in patients with severe AS undergoing TAVI from the European Association of Percutaneous Cardiovascular Interventions and ESC working group on Cardiovascular Surgery and

highlighted key areas of uncertainty in this growing cohort (139). The key recommendations from this consensus paper were:

1. Where there is significant CAD (>70% stenosis in a proximal major epicardial artery, and >50% left main stem), PCI should be performed before TAVI, especially in the context of MI or vessels with >90% stenosis (139).

2. An individualised Heart Team approach should be taken for all patients, based on co-morbidities, extent of CAD and presence of ischaemia (139).

3. Where there is CAD, or future PCI is anticipated, a balloon expanded intra-annular TAVI valve is preferable to a supra-annular valve. Where a supra-annular valve is used, care must be taken to achieve optimal commissural alignment to aid future coronary access (139).

The question of revascularisation of CAD in patients undergoing TAVI remains a contentious one. Only the NOTION-3 trial has demonstrated positive outcomes in patients receiving PCI alongside TAVI, and several others, including large meta-analyses noted above have failed to demonstrate any benefit either in the short- or long-term. In fact, there is a consistent finding of significantly increased bleeding demonstrated across multiple studies and meta-analyses. As such, routine PCI in patients undergoing TAVI should not be recommended for all patients and careful, individualised decision making is crucial. A number of patient related factors should be taken into consideration including presence (or absence) of ischaemia/ myocardial infarction, frailty, bleeding risk and renal disease in order to mitigate for peri-procedural complications and mortality risk. In patients with stable but significant CAD, it may be difficult to disentangle symptoms of angina from those caused by severe AS and a strategy of offering TAVI with reassessment of symptoms after this and only performing PCI if symptoms remain, is not unreasonable. TAVI has proven survival and mortality benefit (62) whereas treatment of stable CAD with PCI does not (150) and as such, offering TAVI as the initial treatment seems logical. More randomised trial data are required as the majority of the available data are observational, but in the meantime, a Heart Team approach should be taken and individual patient related factors should be considered for this cohort of patients.

1.5.3.1 Coronary angiography after TAVI

TAVI indications are expanding to include increasingly younger patients with lower risk (44), as such, the number of planned, unplanned or emergency PCI procedures in TAVI recipients are likely to increase in future. ICA and PCI can be challenging following TAVI due to anatomical changes during implantation as well as TAVI model-type and alignment with coronary ostia restricting selective catheter engagement.

Section 1.5.3 touches upon the concept of commissural alignment of TAVI valves in patients with CAD. Commissural alignment refers to the orientation of the TAVI valve's leaflets and commissures (the junctions between leaflets) relative to the native aortic valve and root anatomy. In SAVR, commissural alignment is achieved under direct visual guidance. In TAVI, however, the alignment is determined by the orientation of the delivery system and valve deployment technique. Achieving optimal commissural alignment is particularly important in supra-annular self-expanding valves, as misalignment can lead to obstruction of coronary ostia and impaired coronary access at a later stage(157). Inability to successfully engage coronary arteries during ICA can have very serious deleterious consequences in time-critical situations such as acute MI. Yudi et al 2018 presented an informative review and troubleshooting guide for achieving coronary artery access after TAVI with various valve types and have highlighted a number of anatomical and valve related factors which contribute to difficult coronary engagement (158). A summary of their main findings is reproduced with permission from The Journal of the American College of Cardiology, Elsevier, in Figure 13.

The RE-ACCESS study (Reobtain Coronary Ostial Cannulation Beyond Transcatheter Aortic Valve Stent) aimed to investigate the feasibility of successful coronary engagement following TAVI in a prospective, single centre study of 300 patients (159). They demonstrated that only 23 patients had unsuccessful ICA due to TAVI, however, 22 of these patients had an Evolut R Pro (Medtronic) branded TAVI valve, which is a self-expanding, supra-annular valve implant and extends beyond the coronary ostia (Figure 13) (159). Use of the Evolut R Pro valve, in combination with a high implant location were the key factors associated with inability to achieve coronary access (159). No Sapien (Edwards Lifesciences) valves were associated with

inability to obtain coronary access and engaging the RCA was more commonly challenging than the left coronary system overall (159).

The ALIGN-ACCESS study (TAVR with Commissural Alignment Followed by Coronary Access) prospectively aimed to achieve perfect intra-procedural commissural alignment in patients receiving supra-annular Evolut R Pro and Accurate Neo TAVI valves and compare post-implantation coronary access with each other, and with intra-annular Sapien 3 valves (which cannot be specifically aligned) in 206 patients (160). They found that despite achieving favourable alignment in 86% of Evolut and 88% of Accurate Neo valves, successful coronary access was still significantly higher in intra-annularly deployed Sapien valves (160). Adequate coronary engagement was achieved in 95% of patients who had an Edwards Sapien valve, however this was significantly lower at 71% in patients with a favourably aligned supra-annular valve, and this falls even lower to 46% in patients with a non-aligned supra-annular valve implant (160). Misalignment of a supra-annular valve and sinus of Valsalva height were both significantly associated with failure to achieve coronary access post TAVI (160). Thus, despite pre-emptively aiming to achieve perfect commissural alignment with supra-annular valves, it remained easier to obtain successful coronary access with non-aligned intra-annular Sapien valves, and it was impossible in 54% of those with a non-aligned supra-annular valve (160).

To assess the real-world demand for post-TAVI PCI, Stefanini et al performed a large retrospective, international, multi-centre systematic review of 15,325 patients who had unplanned PCI between 2008 and 2019 (161). They found that only 133 patients (0.9%) required unplanned PCI in this time and the highest incidence is in the first week, with a progressive decline thereafter (161). Within the first two years of TAVI, the commonest need for PCI was MI and beyond two years, chronic coronary disease was the primary indication (161). They found that PCI was successful in 95% of patients who had a self-expanding valve and 100% of balloon-expanded valves (161). The mean age of patients attending for unplanned PCI was 80 years and 70% of them had prior revascularisation with either PCI or CABG (161). 89% had hypertension, 67% had dyslipidemia, 36% had diabetes and 20% had CKD (161). The results of this large study show an overall low re-presentation rate for PCI

post-TAVI and very positive outcomes regarding achieving coronary access. However, the overall number of patients attending for ICA and follow on PCI were very low and predominantly of an elderly and co-morbid population. The results do not consider the number of patients who attended with an indication for ICA/PCI but were managed medically due to their age, comorbidity and frailty, which will be a much less clinically appropriate treatment decision as TAVI is offered to younger patients. Ultimately, the low re-catheterisation rates are likely driven by the fact that patients in this aged and frail cohort who re-presented with angina or MI were not taken back to the CCL due to their high-risk. Beyond this, 70% of those who returned for PCI had prior revascularisation and this suggests a possible cohort where optimisation of CAD may be beneficial pre-TAVI to avoid future re-presentation. The low re-presentation figures should be observed with caution as TAVI is offered to younger and lower risk patients who are more physiologically robust and have a longer life expectancy than the presently studied population.

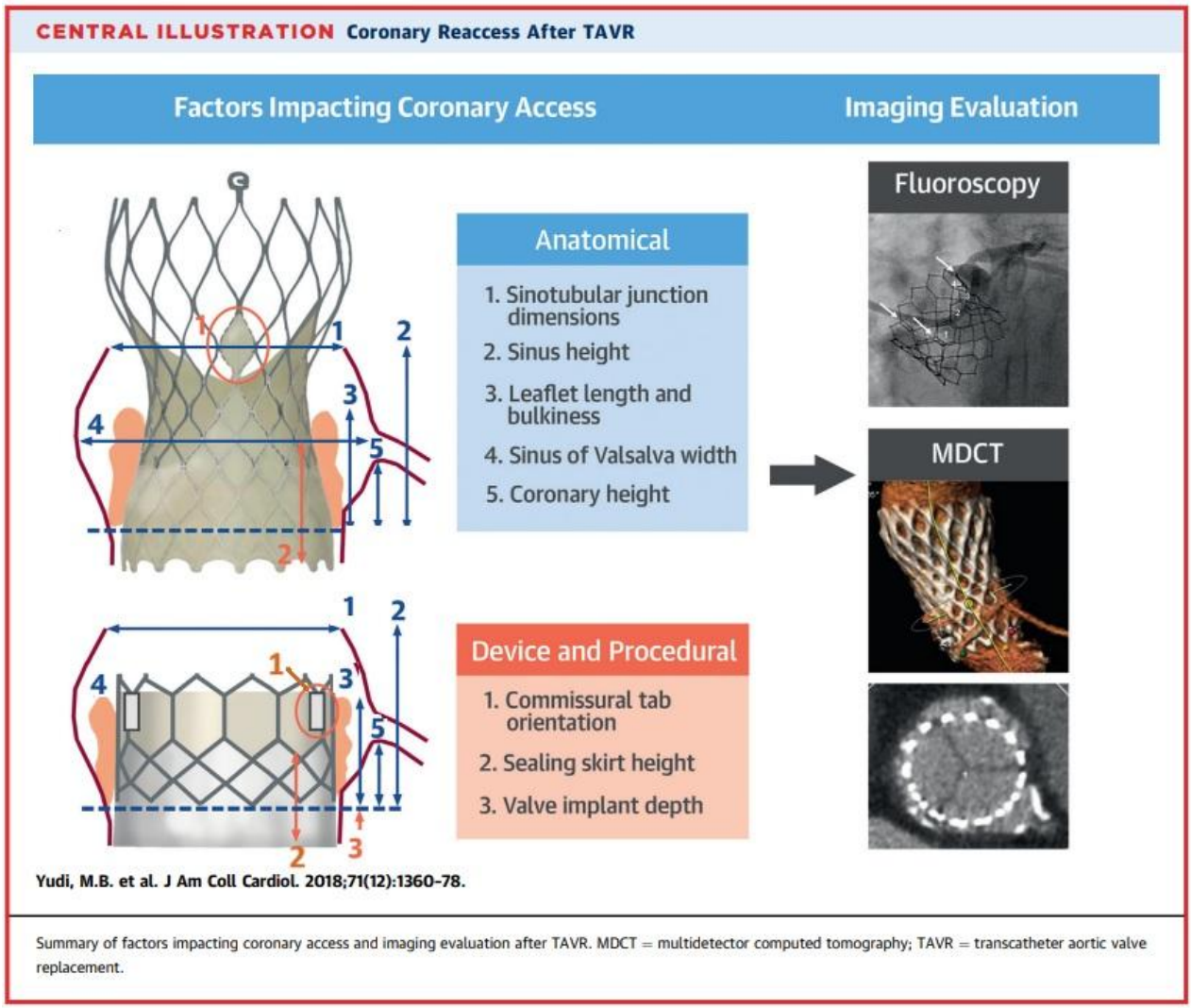


Figure 13. *Factors impacting coronary access after TAVI.*

The top valve is an Evolut R Pro valve and the bottom valve is an Edwards Sapien XT valve. Reproduced from Yudi et al (158), with permission from The Journal of the American College of Cardiology, Elsevier, Copyright 2018.

1.5.4 Aortic stenosis and myocardial blood flow

Aortic stenosis commonly presents with typical anginal symptoms of ischaemia despite no discernible CAD on ICA, and these patients have a higher risk of sudden cardiac death (20). The primary physiological adaptation in patients with severe AS is LVH, in an attempt to reduce LV wall stress and overcome the restricted LV outflow (162). LVH progresses with AS severity in order to counter rising LV filling pressure and afterload, and intra-ventricular and intra-myocardial pressures increase as a result (163). Proximal perfusion pressure also falls as

the stenotic aortic valve orifice becomes incrementally smaller, and less blood drains into the coronary ostia (163). The progressively hypertrophied myocardium demands more oxygen, which in health is augmented by an increase in coronary perfusion pressure and reduction in microvascular resistance in order to allow blood to fill the myocardium (Figure 14) (163). However in AS, this regulatory function is becomes progressively exhausted, and impaired further by increasing systolic filling pressures and time, reduced capillary density, perimyocytic fibrosis and reduced diastolic filling time, all of which impair the physiological vasodilatory capacity of the microvasculature by decoupling the regulatory mechanisms that would normally augment MBF (Figure 14) (163, 164). The ultimate result is vulnerability to ischaemia when oxygen demand rises (164). The haemodynamic conditions of AS and LVH are therefore characterised by high LV pressure, low coronary perfusion pressure and high extravascular compressive forces from myocyte hypertrophy, all of which are detrimental to myocardial perfusion (162). Furthermore, there is a reversal of the normal endocardial: epicardial MBF ratio, which in health is around 1.2:1 (20). This reversal results in sub-endocardial ischaemia and fibrosis. Total resting MBF increases as a physiological response to these conditions in order to match rising myocardial oxygen demands (73). CFR is typically reduced in patients with AS, demonstrating an impaired capacity to further increase MBF in response to hyperaemia, due to exhaustion of the vasodilatory capacity of microvasculature (73, 162). Patients with severe AS adapt their haemodynamic state in order to create a baseline state of hyperaemia and there is a subsequent struggle to respond to further physical or pharmacological stress, due to impairment of the vasodilatory capacity of the myocardial bed, resulting in ischaemia even without CAD and a blunted hyperaemic response to pharmacological stress. In patients who have concomitant CAD, the ischaemic effect of these pathophysiological processes are exacerbated further. Myocardial ischaemia at the end of this pathological cascade underlies the aetiology of sudden cardiac death, heart failure and malignant arrhythmia in patients with severe AS (165). Removal of the mechanical outflow tract obstruction provides an instant relief from the high-pressure state and increases proximal perfusion pressure while reducing intra-ventricular and intra-myocardial pressures (166). This may form the basis for the instant relief of angina post SAVR or TAVI in some, despite LVH regression taking months or years (20, 164).

Schwartzkopff et al described the pathological characteristics of peri-myocytic fibrosis and rarefaction of arterioles in the hypertrophied myocardium of patients with AS (19). Reduced CFR is also noted in patients with other causes of LVH such as hypertension or HCM, however MVD in these patients was found to be primarily driven by structural maladaptations within the intra-mural arterioles, resulting in intimal and medial thickening (section 1.4.5.2), whereas these features were not present in patients with LVH secondary to AS (19), further implicating extravascular forces rather than disease of the arterioles themselves (162). Figure 14, below, demonstrates the aforementioned pathological consequences of AS on myocardial blood flow.

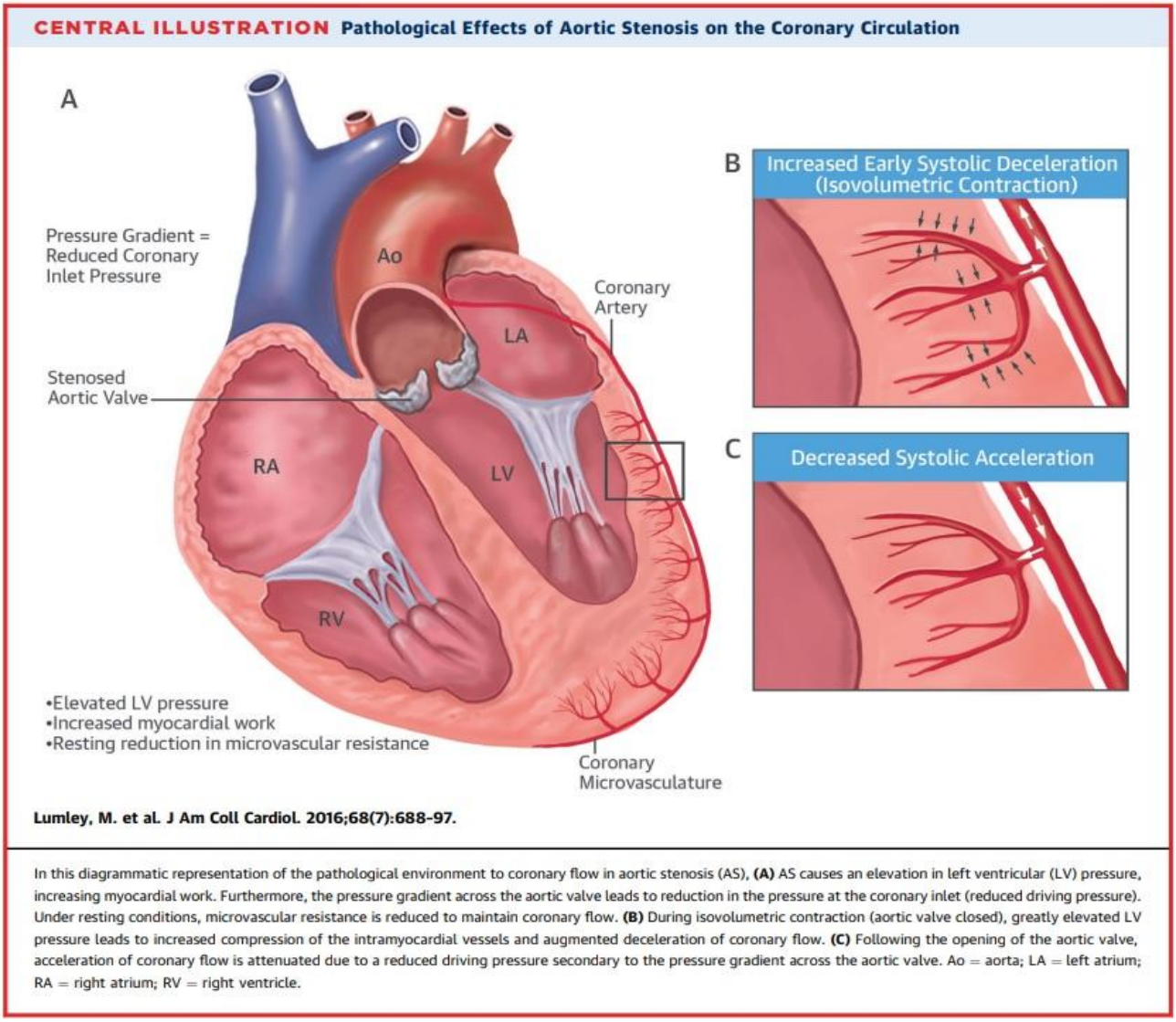


Figure 14. *Pathological effects of AS on coronary circulation.*

Reproduced from Lumley et al 2016 (80), with permission from the Journal of the American College of Cardiology, Elsevier, Copyright 2016.

1.6 Aortic stenosis and coronary physiology

The functional assessment of CAD with FFR has proven survival and economic benefits (99). Other indices such as iFR and QFR show good diagnostic accuracy when compared to the gold standard FFR, but long-term survival and economic data are awaited (108, 114). However, patients with severe AS were excluded from the trials used to validate these indices; as such, it is not known how best to assess functional severity of CAD in patients with severe AS. The ESC/EACTS guidelines on valvular heart disease and revascularisation actively discourage physiological assessment of CAD in this cohort despite recommending FFR- and iFR-guided revascularisation in patients without AS as a Class IA indication (5, 14). This arises from uncertainty about whether patients with severe AS undergoing SAVR or TAVI require revascularisation based on a number of conflicting studies (139, 145). The value of functional assessment of lesion severity is clear, but their appropriateness and interpretation in AS remains unvalidated. The interplay between myocardial blood flow, microvasculature and the complex haemodynamic environment of AS remains somewhat poorly understood and are clearly multi-faceted. This section will highlight the current literature around AS and coronary physiology indices and future directions.

1.6.1 AS and FFR

The fundamental assumptions made during FFR measurement are noted in section *1.4.4.2.* FFR is measured over the entire cardiac cycle and taken during a 'steady-state' of hyperaemia. However, as described in section *1.5.2*, the capacity of the microvasculature to respond to hyperaemia in AS is sub-maximal due to the baseline physiological increase in resting MBF to meet the hostile haemodynamic conditions of AS (166). Theoretically, FFR measured with a blunted hyperaemic response will underestimate the severity of a coronary lesion. Conversely, when AS is treated and hyperaemic flow is able to increase in response to pharmacological stimulation, the FFR measurement across the same lesion should fall (166). Thus, the incapacity to respond to pharmacological hyperaemia suggests that the physiological coronary conditions required to accurately measure FFR cannot reliably be met.;

therefore, FFR measurement has questionable validity when standard cut-off values are used, and may lead to inappropriate deferral of functionally significant lesions (6). To date, only one randomised, controlled trial prospectively recruited and measured FFR to guide revascularisation in patients undergoing TAVI, and the NOTION-3 trial has already been described in section *1.5.3* (154). Before the publication of this trial, a number of retrospective and observational studies aimed to investigate the effect of TAVI on FFR values and these are described below and in table 2.

A study of phasic intra-coronary pressure and waveforms directly before and after TAVI in 11 patients by Davies et al found a significant fall in the sFCW and dBEW waves, with a loss of the relationship between systolic-diastolic filling patterns in untreated AS when myocardial oxygen demand is increased, suggesting a failure to decompress the microcirculation adequately in these conditions (164). After TAVI there was a slight fall in the dBEW at rest with a rise in the sFCW, but a significant rise in the hyperaemic dBEW wave intensity, with an improved relationship to the normal cardiac-coronary coupling during whole cycle analysis (164). They reported an immediate improvement in the hyperaemic coronary physiological reserve by reducing the LV and intra-myocardial pressures and thus "decompressing" the microvasculature (164). This study, however, only included 11 elderly and co-morbid patients, all of whom were mechanically ventilated, and right ventricular (RV) pacing was used as a marker of increased cardiac work rate rather than pharmacological agents. All of these factors make interpretation and reproducibility somewhat questionable and cumbersome in the current state of TAVI, where patients are generally younger, healthier and not ventilated. A similar study by Rolandi et al showed a rise in both resting and hyperaemic dBEW intensity in 15 patients (167). Adenosine was used to induce hyperaemia and the hyperaemic dBEW intensity increased comparably to controls post-TAVI (167). Both studies found an immediate response and suggest that FFR measured immediately post-TAVI may be reliable, as the microcirculation can be recruited once compressive forces have been treated.

A number of studies have assessed FFR pre-and post-TAVI in order to determine the acute and longer-term effects of TAVI, and these are summarised in Table 2. Some conflicting results have been demonstrated, but some notable and valuable data have also been gathered.

Wiegerinck et al demonstrated a significant fall in mean FFR pre- and post-TAVI from a baseline of 0.97 to 0.95 in 27 patients undergoing TAVI without angiographic CAD (21). Similar findings are demonstrated by Ahmad et al who showed a mean drop 0.87 to 0.85 (p=0.008) immediately post-TAVI in 30 patients. In a larger study by Pesarini et al however, 54 patients undergoing TAVI had FFR measurements taken pre- and post-TAVI, and showed no overall difference between values (0.89 to 0.89, P=0.73) (168). Despite this, sub-group analysis of this cohort produced some valuable data: namely that when the FFR value was ≤0.80, there was significant drop in FFR post-TAVI from 0.71 to 0.66 (P=<0.001), and where FFR was >0.80, there was a significant increase in FFR (168). Furthermore, seven patients with pre-TAVI FFR ≤0.80 had a reclassification and down-grading of functional severity after TAVI (168). These findings are supported separately by Scarsini et al (169), Stoller et al (170) and Sabbah et al (171). Scarsini et al 2020 found no overall change in acute or long-term FFR measurements after TAVI, however sub-group analysis of their (albeit small) group of 14 patients, in whom only 3/23 lesions had FFR ≤0.8, showed similarly that sub-normal FFR values tend to fall post-TAVI (169). Sabbah et al 2022 similarly found no significant overall change in FFR values at 6 months post TAVI, however sub-group analysis of lesions with FFR of ≤0.80 demonstrates a clear trend towards a fall at 6 months (171). Stoller et al 2018 also demonstrated a rise in the FFR value, when the value was >0.80, a finding which can be explained by the acute aortic pressure increase following TAVI (170). Conversely, Vendrik et al 2020 found a large and significant decrease in the FFR post-TAVI, both immediately and with a further drop at 6-month follow-up (0.85 to 0.79 immediately, and to 0.71 at 6 months), albeit only in 13 patients (172). This was attributed to the simultaneous increase in hyperaemic whole-cycle coronary flow as measured by FFR-flow which rose significantly from 26.3cm/s to 30.78cm/s immediately post-TAVI and even further to 40.20cm/s (p=<0.001) at 6 months (172). Scarsini et al 2023 measured FFR as a secondary endpoint in a relatively large study of 134 patients and found a significant fall in FFR when measured immediately post- TAVI, although all FFR results were >0.8 and there was no angiographic CAD (173). The conflicting results in these small observational and non-randomised studies confirm the pitfalls of FFR measurement in patients with AS. However, in a single-centre retrospective study of 216 patients who underwent TAVI and PCI, Lunardi et al demonstrated favourable long-term (two year) outcomes in patients in whom FFR guidance was used in the decision to treat CAD, thus at

least demonstrating the safety of treating FFR-positive CAD, albeit with no guidance on deferral (174).

Minten et al have performed a meta-analysis of the use of hyperaemic and non-hyperaemic pressure indices in patients with severe AS undergoing TAVI and found a mean underestimation of FFR by 0.02±0.07 (P=0.0038) pre-TAVI (175). This demonstrates that although there is a slight risk of under-estimation of FFR, for reasons already touched upon, strongly positive or negative results can be relied upon to guide revascularisation.

Authors	**N**	**Index**	**Baseline**	**Immediately Post**	***P*-value**	**Long-term**	***P*-value**	**Conclusion**
Wiegerinck et al 2015 (21)	27	FFR	0.97	0.95	0.042	NA	NA	*Significant reduction acutely.*
Pesarini et al 2016 (168)	54	FFR	0.89	0.89	0.73	NA		*No change acutely in **overall** analysis.*
Sub-analysis of Pesarini et al 2016			**0.92**	**0.93**	**<0.001**	***Significant increase acutely when FFR >0.80.***		
Sub-analysis of Pesarini et al 2016			**0.71**	**0.66**	**<0.001**	***Significant reduction acutely when FFR ≤0.80.***		
Ahmad et al 2018 (166)	30	FFR	0.87	0.85	0.008	NA	NA	*Significant reduction acutely.*
Stoller et al 2018 (170)	40	FFR	0.90	0.93	0.0021	NA	NA	*Significant increase acutely when FFR >0.80.*
Scarsini et al 2020 (169)	14	FFR	0.87	0.88	0.49	0.88 *(mean-14 months)*	0.33	*No overall change acutely or at long term.*
Stundl et al 2020 (176)	12	FFR	0.77	-	-	0.76 *(mean 6-8 weeks)*	0.11	*No change medium term.*
Vendrik et al 2020 (172)	13	FFR	0.85	0.79	<0.001	0.71 *(mean-6 months)*	<0.001	*Significant reduction acutely and long-term.*

Sabbah et al 2022 (171)	40	FFR	0.84	-	-	0.84 *(mean-6 months)*	0.72	*No change long term (6m)*
Scarsini et al 2023 (173)	134	FFR	0.9	0.88	0.014	NA	NA	*Significant reduction acutely.*
Sabbah et al 2023 (177)	34	FFR	0.9	NA	NA	0.91	0.39	*No change long term (6m)*

Table 2. Summary of FFR pre- and post-TAVI in the literature.

1.6.2 AS and iFR

The iFR is a non-hyperaemic index of coronary flow measured during a period of diastole when coronary pressure and flow is theoretically linear (77). During this period, the myocardium is neither actively contracting nor relaxing and the aortic valve is naturally closed (166). Thus, theoretically, if pressure and flow relationships are linear and the aortic valve does not contribute to coronary flow in this period, then iFR may experience less confounding than FFR (166). However, the haemodynamic conditions of AS, as described in section *1.5.2*, suggest that increased MBF due to a high MVO_2 will cause an increase in trans-stenotic flow, and thus an artificially low iFR, thereby potentially overestimating lesion significance (178). In a number of small observational studies, iFR values have consistently been found to remain stable following TAVI, as outlined in Table 3. Scarsini et al 2020 is the only study to investigate long-term changes in iFR following TAVI, with a mean follow-up period of 14 months. Although this study demonstrated no significant short- or long-term change in iFR, there was a re-classification rate of 21.7% in lesion functional severity assessment, compared with only 4.3% in FFR (169). This was driven entirely by functionally significant lesions pre-TAVI being reclassified into the non-significant range post-TAVI (169). However, this finding in itself is not easily interpretable and should be viewed cautiously. The same group, along with several others, has postulated that the haemodynamic conditions of AS result in discordance between FFR and iFR when standard cut-off values are used (179). Scarsini et al 2017 demonstrated a low diagnostic accuracy with respect to FFR when standard thresholds were used, but a significant improvement when the iFR cut off value for significance is reduced to 0.83 (179). Values ranging at the lower end from 0.73 (180, 181) to 0.83 at the upper end

(179, 182) have been postulated in studies aiming to validate the diagnostic accuracy of iFR against FFR in AS. These studies are however intrinsically flawed, as they are all attempting to validate the iFR against FFR, which itself is not validated in AS and has many pitfalls in this context. Furthermore, despite the fact that iFR values do not change post-TAVI, the findings of Scarsini et al do demonstrate that its use may overestimate functional severity when the standard cut-off value of 0.89 is used (169, 179). Table 3 summarises the literature in iFR pre- and post-TAVI.

Authors	**N**	**Index**	**Baseline**	**Immediately Post**	***P*-value**	**Long-term**	***P*-value**	**Conclusion**
Ahmad et al 2018 (166)	30	iFR	0.88	0.88	0.94	NA	NA	*No change.*
Scarsini et al 2018 (183)	66	iFR	0.89	0.89	0.66	NA	NA	*No change.*
Scarsini et al 2020 (169)	14	iFR	0.88	0.90	0.30	0.91 *(mean-14 months)*	0.30	*No change.*
Vendrik et al 2020 (172)	13	iFR	0.82	0.83	0.735	0.83 *(mean-6 months)*	0.735	*No change.*

Table 3. Summary of iFR pre-and post-TAVI in the literature.

1.6.3 AS and CFR

CFR is used as a marker of total coronary hyperaemic capacity (20). CFR is typically reduced in AS due to an existing state of reduced microvascular resistance, in order to up-regulate total MBF at rest (184). Therefore, despite hyperaemia, the capacity of the microvasculature to augment MBF further in stress is exhausted and the CFR is consequently blunted (184). These mechanisms have been described in *1.5.4*. CFR has long known to be reduced in severe AS, with or without CAD, and its long-term effects following SAVR have been studied (185). Nemes et al demonstrated a rise in the CFR from baseline to 12 months post SAVR (1.96 to 2.57), however at three years found a significant reduction back down to a mean of 2.01 in their small cohort of 30 patients, despite regression of LVH (185). The longest-term data in

TAVI patients is by Camuglia et al who followed up eight patients with invasive Doppler wire CFR measurements at 12 months and found a significant improvement to above the normal cut-off limit (186). Vendrik et al followed up 13 patients at six months and found a significant improvement also, albeit not an improvement above the normal cut-off value (172).

There is conflicting evidence concerning whether CFR improves immediately post-TAVI. Wiegerinck et al demonstrated a significant immediate improvement in CFR in the sub-analysis of patients who had no significant (i.e. less than moderate) AR post TAVI, but not in the overall cohort (21). However, over the last several years TAVI protheses and operator experience have improved, partly driven by findings from major trials suggesting that residual AR is associated with worse long-term outcomes. This is reflected in the small study by Vendrik et al, which demonstrates a significant improvement in CFR immediately post-TAVI, again albeit not an improvement above the normal threshold (172). Sabbah et al 2023 also noted a significant improvement when measured six months after treatment with TAVI or SAVR (177). The largest study to measure CFR change acutely post-TAVI, Scarsini et al 2023, used the index as a secondary end point and found no acute change in 134 patients (173). The primary end point in this study is MRR and will be discussed in more detail the appropriate section. Table 4 summarises the available data in this area.

Authors	**N**	**Index**	**Baseline**	**Immediately Post**	***P*-value**	**Long-term**	***P*-value**	**Conclusion**
Camuglia et al 2014 (186)	8	CFR	1.53	1.58	0.41	2.18 *(mean-12 months)*	<0.01	*No change acutely, significant increase long-term.*
Wiegerinck et al 2015 (21)	27	CFR	1.9	2.1	0.113	NA	NA	*No change acutely.*
Sub-analysis of *Wiegerinck* et al 2015			1.9	2.2	0.009	*Significant increase in CFR in patients without AR (moderate or severe) post TAVI*		

Stoller et al 2018 (170)	40	CFR	1.9	2.0	0.72	NA	NA	*No change acutely.*
Vendrik et al 2020(172)	13	CFR	1.28	1.65	<0.001	1.94 *(mean-6 months)*	<0.001	*Significant increase acutely and long-term.*
Scarsini et al 2023 (173)	134	CFR	2.0	2.12	0.805	NA	NA	*No change acutely.*
Sabbah et al 2023 (177)	34	CFR	2.5	NA	NA	3.1 *(mean-6 months)*	<0.001	*Significant increase long-term.*

Table 4. Summary of CFR pre- and post-TAVI in the literature.

1.6.4 AS and absolute coronary blood flow

Invasive assessment of absolute coronary blood flow has only been measured pre- and post-aortic valve replacement for severe AS by one group (177). Sabbah et al 2023 measured hyperaemic aCBF in the LAD using Rayflow™ and continuous thermodilution in 34 patients with no flow limiting CAD pre- and six months post-aortic valve replacement, with either TAVI or SAVR (177). The also measured CFR, IMR and FFR in the LAD at the same time and measured LV parameters with CMR and echocardiography, but did not perform stress perfusion CMR (177). Although the numbers studied are small, and only 17 patients had TAVI, this is the largest study of its type so far. They showed a non-significant numerical increase (230mL/min vs 250mL/min, p=0.26) in hyperaemic aCBF in the LAD pre- and post-treatment with either SAVR or TAVI at six months (177). They did however find a significant improvement in CFR (2.5 vs 3.1, p=0.005) but FFR and IMR remained unchanged (177), these values can be found in the relevant tables. Microvascular resistance, as measured in WU were similar to previously recorded values in healthy controls and did not seem to change significantly after treatment of AS (347 WU vs 287 WU, p=0.20) (177). LV mass, as measured on CMR, reduced significantly (174g vs 137g, p=<0.001) after treatment of AS (177). They concluded that; as hyperaemic aCBF and MVR remained similar pre- and post-treatment, but CFR improved, the improvement could either be explained by a reduction in baseline aCBF (which was not measured) due to reduced myocardial oxygen demand, or an increase in

aCBF/g of myocardium when regression of LVH is considered (177). Ultimately, this was a hypothesis generating study and definitive conclusions cannot be drawn.

Paolisso et al measured absolute coronary blood flow (as well as MRR and CFR), invasively using the continuous thermodilution method with a Rayflow™ catheter in the LAD of 29 control matched patients with severe AS at rest and hyperaemia (187). All patients had an unobstructed LAD (<50% stenosis) and preserved LV function (LVEF >50%), measurements were only taken prior to treatment and no post-TAVI data were obtained (187). They found that absolute resting flow in the LAD was significantly higher in patients with severe AS compared to controls (86mL/min vs 67mL/min), however there was no difference between the groups in hyperaemic flow (200mL/min vs 186mL/min) (187). Hyperaemic myocardial perfusion (in mL/min/g), CFR and MRR were all significantly reduced in the AS cohort (187). This is a very informative and useful study, demonstrating increased baseline coronary flow in AS to meet high myocardial oxygen demand, and the key role this has on impairment of CFR in these patients. However, flow and MRR were only measured pre-TAVI and compared with controls, and no post-treatment data are presented, which is the basis of this thesis.

Ben-Dor et al, performed trans-oesophageal echocardiography (TOE) Doppler-based coronary flow assessment in 90 patients undergoing TAVI by using peak-systolic and diastolic velocity as a surrogate marker of absolute coronary flow (188). They found a significant increase in peak-systolic velocity from 24.2cm/s pre-TAVI to 30.5cm/s post-TAVI (p=<0.001). CMR has also been used following SAVR to confirm an increase in coronary flow following stent-less SAVR bioprosthesis implantation (189). Studies investigating coronary physiology pre-and post-TAVI similarly have measured hyperaemic myocardial perfusion using a number of techniques, including hyperaemic systolic coronary flow velocities (SFV). These unanimously demonstrate a significant increase in the SFV following TAVI. Although the exact mechanisms are unclear, this finding is likely to be a result of the increased proximal perfusion pressure and reduced LV and intra-myocardial pressures. These studies are very small in sample size and SFV was assessed as a secondary measure only; therefore, definitive conclusions cannot be drawn.

Authors	N	Index	Baseline	Immediately Post	*P*-value	Long-term	*P*-value	Conclusion
Wiegerinck et al 2015 (21)	40	SFV (cm/s)	44.5	51.1	0.027	NA	NA	*Significant increase.*
Ahmad et al 2018 (166)	30	SFV (cm/s)	33.44	40.33	0.004	NA	NA	*Significant increase.*
Vendrik et al 2020 (172)	13	SFV (cm/s)	26.36	30.74	<0.001	40.2	NA	*Significant increase acutely and long term.*
Sabbah et al 2023 (177)	34	aCBF (mL/min)	230±106	NA	NA	250±101	0.26	*No change long term (6-months).*

Table 5. Summary of aCBF and SFV pre-and post-TAVI in the literature.

1.6.5 AS and HMR, IMR and MRR

The mechanisms of microvascular disease and resistance have been described earlier in this review. Little data exists on the effects of TAVI on acute or long-term microvascular resistance using HMR or IMR, however, theoretically, a reduction in LVEDP, LV filling pressures, and intra-myocardial pressures should result in an improvement in these indices. Some of the studies which measured FFR and iFR also measured HMR and the results are noted in Table 6. Ahmad et al and Vendrik et al both noted a significant immediate reduction in IMR while Wiegerinck noted a non-significant reduction. This is consistent with the accepted paradigm of high microvascular resistance and hostile haemodynamic conditions of AS with instant relief after treatment. These studies are very small, and HMR was a secondary endpoint in all. Sabbah et al 2023 measured IMR pre- and post-treatment with SAVR or TAVI at six months and found no significant difference, albeit with a baseline low IMR in patients pre-treatment (177).

Scarsini et al 2023 measured microvascular resistance reserve (MRR) in 134 patients pre- and immediately post-TAVI (173). The physiological basis and evidence base of MRR as a novel

marker of microcirculatory resistance. has already been discussed in this thesis. As MRR is a relatively novel measure of MVD, data on this method in AS is scant, but as an expert group, Scarsini et al have presented an elegant multi-centre international study and further divided groups depending on their tertile of MRR measured, AS phenotype and LV function (173). They found that a very low MRR (<2.0) was significantly associated with low-flow AS and LV dysfunction (173). Furthermore, characteristics associated with lower MRR were female sex, AF and CKD (173), which may warrant further scientific exploration . They found that the across the entire cohort, there was a non-significant increase in the MRR, however there was a statistically significant improvement when applied to the patients in the lowest tertile of pre-TAVI MRR and those with significant LV failure (173). Lower MRR confers a higher degree of MVD as the reserve of the microvasculature is impaired, as in CFR, and a result of <3.0 is abnormal (135, 173). They also measured FFR and CFR and those results can be found in the respective tables, but unfortunately, no long-term data are presented and given the long-term haemodynamic changes in severe AS, the long-term effects of TAVI on MVD are probably more important than the short-term effects. Nonetheless, Scarsini et al suggest MRR as a useful marker of disease severity in patients with AS undergoing TAVI (173).

Authors	**N**	**Index**	**Baseline**	**Immediately Post**	***P*-value**	**Long-term**	***P*-value**	**Conclusion**
Wiegerinck et al 2015 (21)	40	HMR	2.10	1.83	0.072	NA	NA	*Non-significant fall in HMR.*
Ahmad et al 2018 (166)	30	HMR	2.42	2.14	0.03	NA	NA	*Significant fall in HMR acutely.*
Vendrik et al 2020 (172)	13	HMR	2.54	2.18	<0.001	1.95	<0.001	*Significant fall in HMR acutely and long-term.*
Sabbah et al 2023 (177)	34	IMR	13	NA	NA	13	1	*No change long term.*
Scarsini et al 2023 (173)	134	MRR	2.40	2.66	0.094	NA	NA	*Non-significant increase in MRR*

Sub-analysis of Scarsini et al 2023 – Lowest MRR Tertile	1.4	1.88	<0.001	NA	NA	*Significant increase in MRR*
Sub-analysis of Scarsini et al 2023 – LV/ cardiac disease	1.8	2.69	0.014	NA	NA	*Significant increase in MRR*

Table 6. Summary of MVD pre-and post-TAVI in the literature.

1.6.6 AS and QFR

A number of studies have sought to validate the accuracy of QFR against FFR in assessing lesion significance in patients with AS (190-192). In a retrospective observational study using the angiographic and physiology data from Ahmad et al (181), Sejr-Hansen et al measured QFR in 28 patients who had undergone ICA and TAVI with immediate pre- and post-TAVI FFR and iFR measurements, and found reasonable diagnostic accuracy with post-TAVI FFR (83%, *p*= 0.008) (191). However, the angiograms were not designed for QFR measurement and the drop-out rate was27%. Furthermore, only pre-TAVI QFR was measured due to the retrospective nature of the analysis, and this was validated against post-TAVI FFR. Similar studies have produced similar results. Kleczynski also found good agreement between QFR and FFR in patients with severe AS, and even better concordance when iFR was used as the reference value (190). These studies all suffer from the same major problem, i.e validation of a novel measure of functional significance against another novel measure is fraught with complexity and potential error. This study will compare vFFR with invasively measured FFR in study patients in order to explore the accuracy and viability of using this method in patients with severe AS. This will be expanded on later in this thesis.

1.6.7 AS and CT-FFR

The most recent and relevant valdiation of CT-based FFR assessment is a study by Michail et al who recruited 42 patients with severe AS to invasive and CT based FFR assessment (193). Due to drop-out from CT interpretation limitations, 39 full sets of data were acquired (60 vessels). Mean invasive FFR was 0.83 and mean CT-FFR was 0.77 (193). There was a 76.7% diagnostic accuracy and the authors declared the safety and feasibility of CT-FFR in this context. This was however, a small single-centre study that excluded patients with ischaemic heart disease heart failure and had a relatively young cohort (mean age - 76 years old). Ageing

affects the quality of CT coronary angiograms due to calcium artefact and it therefore might be difficult to achieve useful data in older patients. Furthermore, the results arise from a single CT-FFR software analysis package; there are several competing systems available, and the results cannot be interpreted outside of the technology used in this particular study.

Michiels et al 2022 measured CT-FFR, LV-mass and total coronary volume pre- and post-TAVI or SAVR in 23 patients (194). Although a statistically significant decrease in LV-mass after was noted treatment of severe AS, total coronary volume and CT-FFR values remained unchanged despite this. They concluded therefore that CT-FFR was not subject to the confounding factors of MVD and LVH as it remained unchanged despite significant regression of LVH (194). However, CT-FFR measured in this small study was not validated against invasive FFR and no patients with a coronary stenosis of >50% were included. Therefore, no patients with haemodynamically significant CAD are included in this study, and as already noted in the studies measuring invasive FFR pre- and post-TAVI, when pre-TAVI FFR is >0.80, it rarely becomes reclassified to become haemodynamically significant post-TAVI. Therefore, the real-world validity of assessing the significance of a coronary stenosis using CT-FFR remains a question to be answered.

1.6.8 Future directions

TAVI has revolutionised the treatment of AS, but the treatment of concomitant CAD is clearly experiencing a “catch-up” period at present. The studies above highlight the complexities and pitfalls associated with coronary physiology in context of severe AS, and demonstrate the need for robust randomised trial data. The evidence of long-term health benefits of physiologically assessed CAD are clear. The evidence of the long-term effects of PCI with or before TAVI based on visual ICA assessment of CAD are much less definitive. Therefore, functional measures of CAD in AS, those which consider the significant influence of the microcirculation as well as the hostile haemodynamic conditions, are needed to translate the positive effects of coronary physiology advances over the last 20 years into patients with AS. Only then can we validate one measure against the next, as presently we do not know which index of coronary severity should be used, which accepted cut-off point is relevant, nor the measures against which to validate. Computational fluid dynamics and advanced imaging

techniques may hold valuable answers to these problems. The next sections will expand on CMR and CFD.

1.7 Cardiac MRI

Cardiac MRI is a non-invasive imaging modality which is able to provide high resolution image quality without using ionising radiation. It can provide a wide array of data, including (but not exclusively) precise quantification of myocardial structure, mass and LV function, tissue characterisation, viability and scar burden, blood flow quantification and a precise evaluation of valve structure, size and function from a single scan (195). The role of CMR has grown dramatically over recent decades and it is a gold standard technique to investigate cardiac function and structure (195). It has a Class I indication for the investigation of various forms of cardiomyopathy in ESC guidance on myocardial disease and heart failure (196) and has a Class II B indication as a non-invasive functional test of ischaemia in patients with suspected or confirmed CAD (5). It is also recommended in EACTS/ESC guidance on valve disease for the assessment and quantification of AS severity where echocardiography has provided inadequate or discrepant data (14).

The use of CMR to assess ischaemia has benefits with respect to both diagnostic yield and long-term outcomes, as well as guiding treatment. Kwong et al presented a retrospective US based study of 2,349 patients who had CMR for the assessment of stable angina symptoms without prior proven angiographic CAD and found that patients with ischaemia on CMR had a four-fold increased risk of MACE events at one year and a ten-fold increased risk of requiring PCI within the study period of five years (197). Furthermore, Nagel et al presented the MR-INFORM trial in 2019, a non-blinded randomised trial of 918 patients who had either FFR or CMR guided revascularisation (198). They demonstrated non-inferiority between CMR vs FFR guided treatment strategies with respect to MACE events at one year and actually showed that number of PCI procedures performed in the CMR cohort was lower without proffering an increased risk of MI (198).

1.7.1 Stress perfusion CMR

Stress perfusion CMR is a non-invasive and validated method of quantifying coronary and myocardial blood flow and has higher diagnostic yield than other non-invasive techniques such as nuclear perfusion imaging or stress echocardiography (199). Stress perfusion CMR can assess coronary blood flow and myocardial viability, and also provides definitive data on LV function, structure and size at the same time, making it an attractive and effective single investigation in patients with heart disease of various aetiology (199). It has shown non-inferiority with FFR in guiding revascularisation in stable CAD and superiority compared to nuclear perfusion imaging (200). Methods of analysing and reporting images obtained from stress perfusion CMR include qualitative, semi-quantitative and quantitative. These methods provide differing data and require varying degrees of expertise (199). Qualitative analysis requires significant experience and expertise in CMR reporting and provides operator defined data on areas of restricted perfusion and tissue viability using late Gadolinium enhancement images (199).

Stress perfusion CMR utilises dynamic contrast enhanced imaging to detect the signal changes which occur when a Gadolinium based contrast agent passes through the cardiac chambers and myocardium (199). T1-sensitive, ECG gated images (slice thickness 8-10mm and temporal resolution 100-125ms) are obtained using during stress and rest (199). Stress is induced with the use of an IV vasodilator stressing agent such as Dipyridamole, Adenosine or Regadenoson (199). Once the stressing agent has been delivered and state of microvascular vasodilation has been achieved, the Gadolinium based contrast agent is injected to a peripheral vein to visualise the passage of blood through the heart (199). In a normal heart, with normal coronary arteries and microvasculature, there is an even distribution of contrast seen passing through the cardiac chambers and myocardium. However, where there is restriction of myocardial perfusion, either due to epicardial CAD, MVD, avascular scar tissue or cardiomyopathy, there is a slower rate of perfusion with reduced T1 signal intensity when compared to normal territories of myocardium (Figure 15) (199). Where there is little or no contrast uptake in a region of myocardium, this represents a significant reduction, or complete absence of, perfusion, as can be appreciated in the infero-lateral LV wall in Figure 15D.

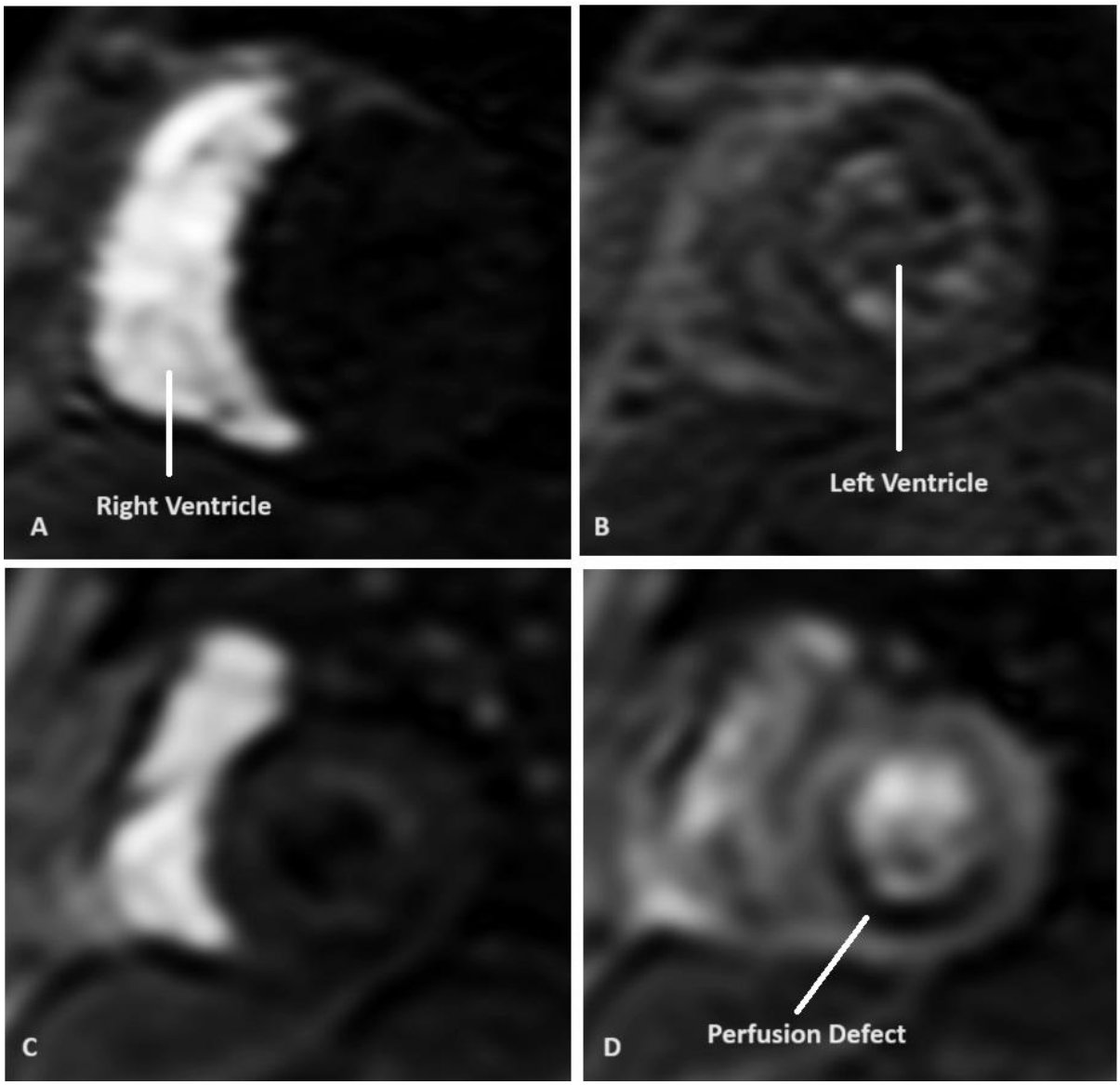


Figure 15. *Contrast enhanced stress perfusion images.*

Figure 15 demonstrates two images from a normally perfused myocardium (A and B) and two images from a study which shows restricted perfusion (C and D). All images are basal ventricular short-axis slices with stress perfusion using Regadenoson and a Gadolinium based contrast agent. All images are obtained from study patients, with permission. 15**A;** The Gadolinium based contrast is seen passing first through the RV. 15**B;** The contrast can now be seen highlighting the LV cavity and LV myocardial walls. There is equal diffusion of contrast within all myocardial territories. 15**C;** Contrast passing through the RV in the second patient. 15**D;** There is diffusion of contrast in the anterior LV wall, however as the label has shown,

there is a significant area of infero-lateral LV wall which has severely restricted T1 signal and no contrast is seen in this territory of myocardium indicating a significant perfusion defect.

Quantitative stress perfusion CMR utilises time-signal intensity curves which are produced using first-pass Gadolinium contrast images (199). The time-signal curve data is generated by the reporting software detecting the T1 signal intensity of images as contrast passes through the cardiac chambers and myocardium over the cardiac cycle (199). The LV contours (epicardial and endocardial borders) and RV insertion point must be entered into the reporting software manually for all three short-axis slices through the LV (basal, mid-chamber and apical) and across 60 images per slice and cardiac cycle (180 images total), during stress and rest. When the regions of interest have been successfully contoured, the reporting software divides the short axis LV images into six segments for all three slices, and this forms the basis of the American Heart Association (AHA) short axis "bullseye" segmentation model which shows MBF in each individual cardiac territory, as can be appreciated in Figure 16B (201). Time-signal intensity curves (Figure 16C) are produced once all phases and 180 images have been contoured and segmented. MBF is produced in mL/min/g for every pixel myocardium within the contoured region of interest, including the blood pool (Figure 16) (199). Segmental MBF is recorded in mL/min/g and total MBF can be calculated by multiplying the mean of these values (Figure 16B) by total LV mass (in g), which is obtained at the same scan (199). The process of reporting using quantitative stress perfusion and the time-signal intensity method is done in both stress and rest phases, and ratio of the total MBF at stress divided by the total MBF at rest has been termed the myocardial perfusion reserve (MPR), when measured using CMR (199). It is essentially akin to CFR measured by CMR.

Figure 16. *Quantitative stress perfusion CMR with time-signal intensity curves.*

Figure 16 demonstrates the quantitative stress perfusion CMR reporting process using MASS reporting software (Version 2023 EXP, Leiden University Medical Centre, Netherlands). 16**A;** Short axis mid-LV chamber contoured first pass image. The green line is the contoured epicardial line, the red line is the endocardial line and the small blue dot is the RV insertion point. The myocardium has been divided into six separate segments and this is done across all 180 images. 16**B;** The AHA 16-segment myocardial segmentation model is produced and MBF is given in each individual territory as well as a mean across all segments. The mean can be multiplied by total LV mass for total MBF. 16**C;** Time-signal intensity curves produced which denote T1 signal intensity in each segment of myocardium (and blood pool – red line) across the cardiac cycle. This data is then used to produce the bullseye model and give MBF in each pixel of myocardium in mL/min/g. The *x* axis denotes time and the *y* axis denotes signal intensity.

A reduction in MBF at stress, either globally or in a specific coronary myocardial territory, is most commonly caused by MVD or epicardial CAD respectively (199). A reduced MPR is associated with MVD as this implies impaired vasodilatory capacity of the microvasculature (199). Although standard CMR has an ESC/EACTS guideline recommendation for the assessment and quantification of severe AS, there is no recommendation for measurement of MBF using stress perfusion CMR in patients with severe AS. Thornton et al measured MBF

in 46 patients with and without severe AS using stress perfusion CMR and re-measured the same parameters after treatment with SAVR (202). The cohorts were divided equally, however the AS cohort had a higher degree and rate of CAD than the control group, although none required coronary revascularisation. AS patients were found to have a lower stress MBF compared to controls (1.63mL/g/min vs 1.96mL/g/min, p=0.009) (202). Stress MBF increased after treatment with SAVR to 1.97mL/g/min, which was similar to controls (p=0.90) (202). MBF at rest was numerically but not statistically higher in the AS cohort (0.88mL/g/min vs 0.76mL/g/min, p=0.4) and did not increase after SAVR (202). MPR was also lower in the AS cohort (1.86mL/g/min vs 2.72mL/g/min, p=0.003) but improved after SAVR (202). The patients examined in the above study differ somewhat from this study as the median age was significantly lower at 71 years and patients underwent SAVR rather than TAVI, which implicitly suggests less co-morbidity and frailty. Beyond this, the degree of CAD between Thornton et al's study and this one is not comparable as patients had varying degrees of revascularised and non-revascularised CAD. Nonetheless, the above study is useful and rare one which demonstrates the changes in MBF which occur in severe AS, and reassuringly, that stress MBF can improve with SAVR (202). The VIRTU-AS will utilise stress perfusion CMR in patients with severe AS having treatment with TAVI, and will explore the effects of MVD and the question of revascularisation. The stress perfusion CMR scanning protocol and reporting techniques used for this study will be described in further detail in the methods section.

1.7.2 Coronary sinus flow in CMR

The coronary sinus (CS) is the major vein of the cardiac venous system and responsible for draining 95% of deoxygenated blood from the myocardium (203). Thus, the CS has been proposed as an accurate surrogate marker of total MBF (204), albeit without the capacity to determine regional perfusion abnormalities, hence its limitation in guiding revascularisation. CS flow was first measured invasively by Ganz et al in 1971 who compared CS flow in patients with angiographically confirmed CAD and healthy volunteers (205). They found a mean CS flow of 122mL/min in healthy controls vs 128mL/min in patients with CAD (205). In modern clinical practice, invasive CS flow is not routinely measured. CS flow, however, can be measured non-invasively using CMR and may have a useful role in providing information in patients with MVD, as well as epicardial CAD (203, 204). Using 2D phase contrast flow CMR imaging, Indorkar et al calculated the ratio CS flow at stress and rest to calculate a surrogate

form of CFR in 507 prospectively recruited patients with varying degrees of CAD in order to investigate long-term cardiovascular outcomes (206). They demonstrated increased risk of MACE events in patients with lower CFR, when measured using CS flow, whether they had epicardial CAD or not (206).

CS flow is calculated at CMR using 2D phase contrast flow images and can measured at stress and rest (203). Typically, the CS lies in the atrioventricular groove and is best seen in the 2-chamber long axis view (Figure 17A). The CS is contoured and the region of contoured CS is corroborated with the phase contrast flow images. The software measures flow across the CS in mL/s across the entire cardiac cycle and produces a time-flow curve. When multiplied by the heart rate taken during image acquisition, a value of CS flow in mL/min can be obtained, which will be used a surrogate marker of total MBF. Figure 17, below, demonstrates a 2-chamber LV long axis view (17A) with the CS clearly seen in the atrioventricular groove and the corroborating area in the phase contrast flow image (17A) and the final time-flow chart which is produced (17C).

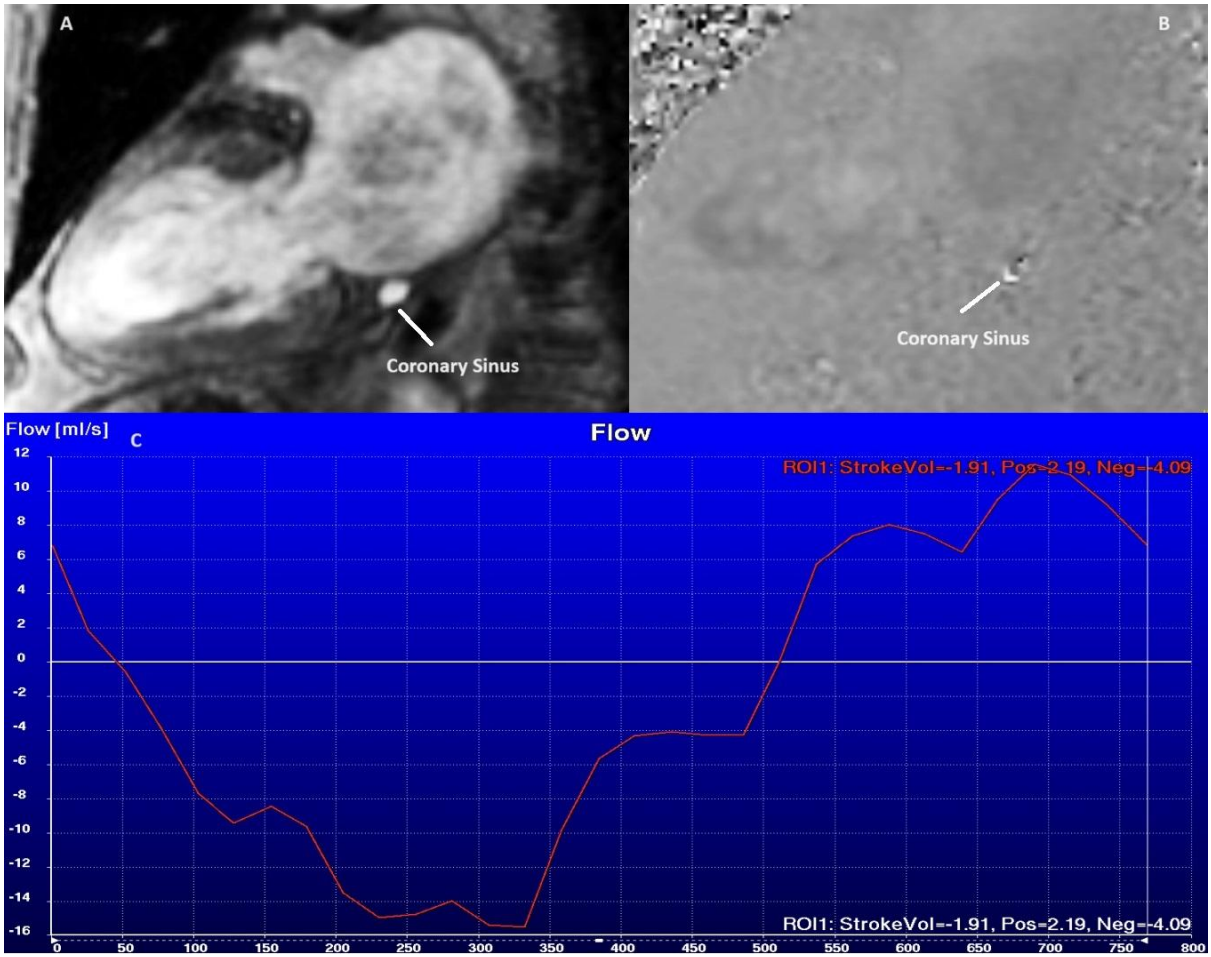


Figure 17. *Coronary sinus imaging at CMR.*

Figure 17 shows coronary sinus imaging of a study patient, used with permission. The CS has not been contoured for visbility. 17**A;** Long axis 2-chamber LV view with CS clearly visible in the atrioventricular groove. 17**B;** Corroborating phase contrast flow image. 17**C;** Time-flow curve produced with CS stroke volume provided in mL/s at 1.91mL/s.

1.7.3 Limitations of CMR

Despite the clear advantages of CMR over various other imaging modalities, several key limitations remain in current practice. Firstly, access to CMR remains largely restricted to larger teaching hospitals in the UK. The MRI scanner can also feel claustrophobic and loud and many patients cannot tolerate lying flat in the scanner for the 30-45 minutes it takes to complete a full scan. This touches upon a further limitation, which is the length of time required to complete a scan being significantly longer than an echocardiogram, for example. Patients undergoing CMR are also asked to hold their breath during certain acquisitions,

during both inspiration and expirations, and many patients with underlying cardiac or pulmonary conditions struggle to achieve adequate breath holds, which can impair image quality. Other factors which can cause movement artefact are arrhythmias and ectopy. CMR is also a relatively costly investigation when compared to other non-invasive investigations and significant time and expertise is required for the reporting of scans. All patients are taken through a careful multi-point MRI safety questionnaire by an experienced radiographer before they are deemed safe to have an MRI.

1.8 Computational fluid dynamics

CFD is a computed method of quantifying the mechanical response of fluids to external forces in order to assess flow velocity and pressure (207). A CFD model makes these calculations by solving the Navier-Stokes and continuity equations, which describe the conservation of energy, mass and momentum, creating a simulation using inputted physiological and anatomical data to reconstruct a physiological 3D arterial model (see Figures 18 and 19) (208). CFD is used commercially in aeronautical travel, vehicle design, medicine and safety technologies. Examples of CFD in measuring coronary pressure and flow include the QFR and CT-FFR indices already touched upon. Methods of coronary physiology assessment using CFD do not usually require invasive pressure wire assessment or pharmacologically induced hyperaemic conditions.

1.8.1 VIRTUheart™

VIRTUheart™ is the first successful angiography-based software tool to measure vFFR, developed at the University of Sheffield by Morris et al 2013 (208). It uses images obtained during ICA to reconstruct a 3D arterial model, and subsequently applies principles of CFD to calculate a vFFR (208) . It has been studied extensively and shown to have efficacy and value in both acute and chronic coronary syndromes (209, 210). To compute vFFR using angiographic images and CFD, physiological and anatomical data (ICA images) are inputted into the model (208). A 3D reconstruction of the artery is then produced using a mesh of around 1 million tetrahedra (208). The next stage is to define the inlet and outlet boundary conditions (i.e. arterial inflow and outflow physiological conditions) (208). A CFD solver software package (ANSYS CFX) is recruited to solve the equations, set the boundary limits and

generate the pressure and flow values (208). The vFFR is measured from the results of these calculations (208). Figure 18, below, shows the final vFFR results screen of an LAD from a study patient. The vFFR is recorded at 0.73, the invasively measured FFR was also 0.73 in this case. Processing ICA images through the VIRTUheart™ software requires a series of steps to be performed by an experienced and trained operator. This series of steps is termed the workflow (208). The steps taken through the workflow have been adapted from Morris et al 2013 (208) and are described below:

1. **Image acquisition**. *Images obtained from ICA are used in VIRTUheart™. The workflow requires two high quality, well opacified orthogonal views of the coronary artery of interest to produce an accurate 3D reconstruction. The images are uploaded to the VIRTUheart™ software in DICOM (digital imaging and communications in medicine) format and the operator chooses two images which have a minimum of 30 degrees between the views in the left-right anterior oblique or cauda-cranial planes.*

2. **Segmentation and reconstruction**. *The operator then outlines the vessel centreline and boundaries for both images using the software. The software uses this segmentation to generate a 3D mesh reconstruction of the portion of artery measured. The segmentation tool used in VIRTUheart™ has been developed using at the University of Sheffield using MATLAB™ software (Mathworks, Massachusetts USA).*

3. **Mesh preparation**. *The 3D mesh is divided into millions of tetrahedral shaped cells to produce a volumetric mesh – this process is termed discretisation. The mathematical equations described are applied to this volumetric mesh later in the process.*

4. **Boundary conditions**. *The vessel inlet, outlet and walls are defined for CFD analysis. Boundary conditions are defined as the physical conditions at the vessel inlet and outlet. The inlet conditions are determined by proximal aortic perfusion pressure and the outlet conditions are determined by the microvascular resistance. A generic value of 8.721e09 Pa/m^3s^{-1} is used for*

VIRTUheart simulations (210). This value represents the general population mean microvascular coronary resistance, as calculated during the initial VIRTUheart™ validation studies by Morris et al (208).

5. **Simulation.** *A CFD solver software package (ANSYS CFX), which is embedded into VIRTUheart™ is recruited to apply the Navier-Stokes and continuity equations to the 3D model to produce a final vFFR value.*

6. **Data collection/ post-processing.** *The operator is able to view the results of the equations and coronary physiological parameters produced (see Figure 18).*

7. **Validation.** *The computed values can be compared to the gold standard method of obtaining these data i.e. invasive pressure wire measurement.*

The segmentation process requires considerable training and experience of interpreting coronary angiograms, notwithstanding the speed of the computation. The steps are expanded upon in the methods section.

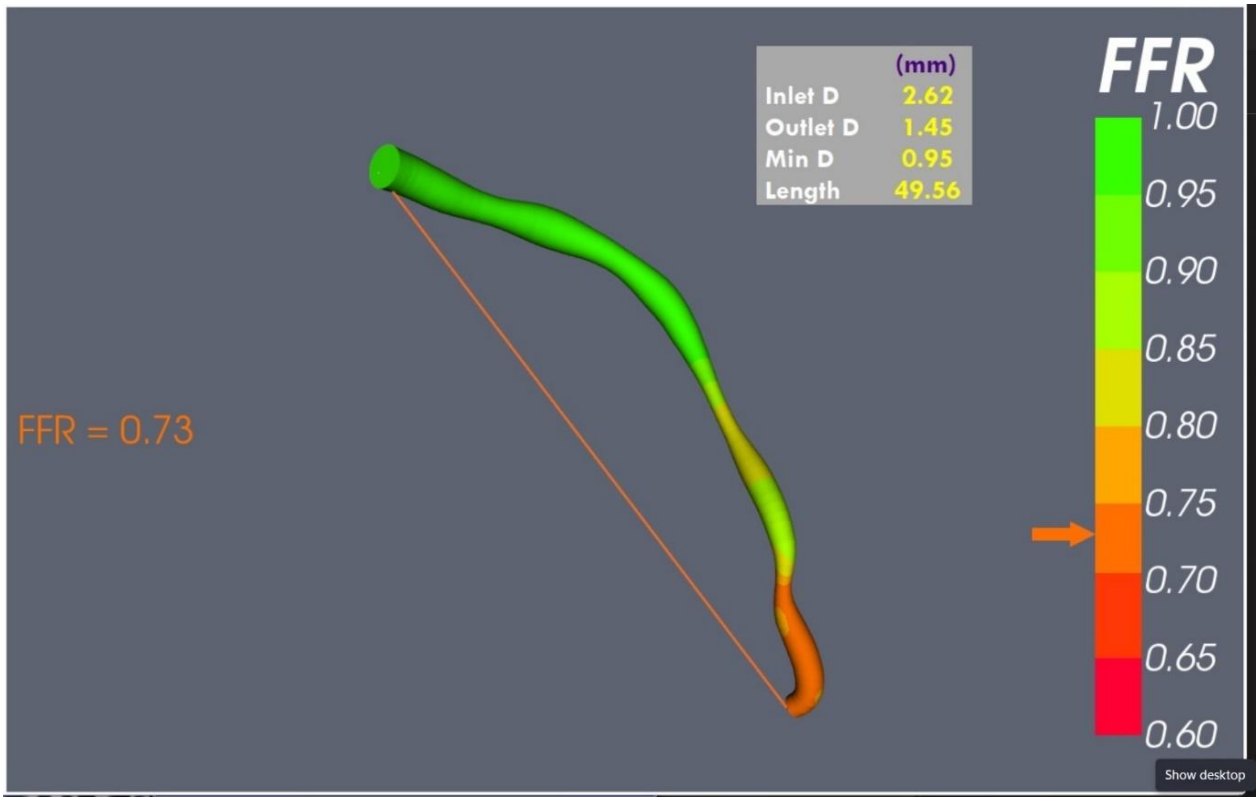


Figure 18. *Example of a VIRTUheart™ interface and results screen.*

An LAD is reconstructed using the workflow and a vFFR of 0.73 is recorded at the distal point. The invasively measured FFR was also 0.73 in this patient.

1.8.2 Limitations of CFD

A discordance between invasive FFR and angiography-derived vFFR measurements affects around 30% of cases (211). The principle cause for this discrepancy is a failure to appreciate fully the complex flow relationships and effects of microvascular resistance upon which conventional FFR is based (211). An assumption of hyperaemia and minimal microvascular resistance is made. This may be valid in the majority of patients, but certainly not all, and is affected by a number of disease processes including, heart failure, hypertension and AS. In order to mitigate for this, personalised boundary conditions and resistance values can be inputted into the latest VIRTUheart™ software in order to improve accuracy. These parameters include patient height, weight, blood pressure, heart rate and two separate coronary artery specific scores: Myocardial Jeopardy Index (MJI) and Duke Jeopardy (DJ) score (210). Using these personalised boundary conditions improves the accuracy of VIRTUheart™ significantly, with a diagnostic accuracy of 90% achievable for stenoses with FFR of ≤0.8 (210). Therefore, patient-level specific models are valuable in CFD modelling (211).

1.8.3 virtuQ™

virtuQ™ is a novel CFD based software model built upon the VIRTUheart™ workflow which measures absolute coronary flow (in mL/min) as well as microvascular resistance (in mmHg.min/mL) and CFR from images obtained at conventional ICA and routine invasive pressure wire-derived physiological indices, and was developed at the University of Sheffield by Morris et al 2021 (Mathematical Modelling in Medicine group) (212). It provides aCBF and MVR data both at rest and in hyperaemia, which is valuable as most invasive methods only measure these in hyperaemic conditions. The workflow is similar to VIRTUheart™ and is described in *1.8.1*, however as opposed to VIRTUheart™ (which does not require any invasive data other than angiographic images), virtuQ™ requires invasive resting and hyperaemic P_d/P_a data to be inputted at the simulation phase in order to obtain accurate results (212). Therefore, for virtuQ™ to be accurate, invasive pressure wire data as well as angiographic imaging need to be obtained at coronary angiography (212). It has been validated in 40

patients against invasive Doppler-wire flow measurements *in vivo* and *in vitro*, and was shown to be more accurate and reproducible than this method (212). Aubiniere-Robb et al aimed to validate virtuQ™ by using aCBF to augment the data obtained from invasively measured FFR and this has been described in section *1.4.4.5* (126).

A comprehensive and unique array of coronary physiological parameters can be obtained using virtuQ™ software, including aCBF, MVR, vFFR, stenosis resistance and CFR at rest and during hyperaemia (Figure 19) (212). The pitfalls of measuring absolute coronary flow and microvascular disease have been described earlier in this thesis. virtuQ™ provides a unique opportunity to measure coronary flow and microvascular resistance in absolute units while circumnavigating the aforementioned problems. As a result, the haemodynamic and physiological consequences of severe AS that invalidate interpretation of conventional measures of coronary physiology do not affect virtuQ™ measurements. Furthermore, with conventional CFD and vFFR measurements, the inflow and outflow boundary conditions are unknown and therefore assumed based on averaged patient populations; however, with virtuQ™, these values are known precisely for all patients (212). Absolute, accurate and like-for-like values can therefore be measured and compared in individuals, and a substantial volume of important physiological data can be accrued. virtuQ™ may well be the ideal measure of coronary physiology in patients with severe AS, as it escapes the common cofounders and problems from which other common tools suffer. Figure 19 demonstrates a reconstructed coronary artery from this study using the virtuQ™ software. The results are clearly visible and simple to extract.

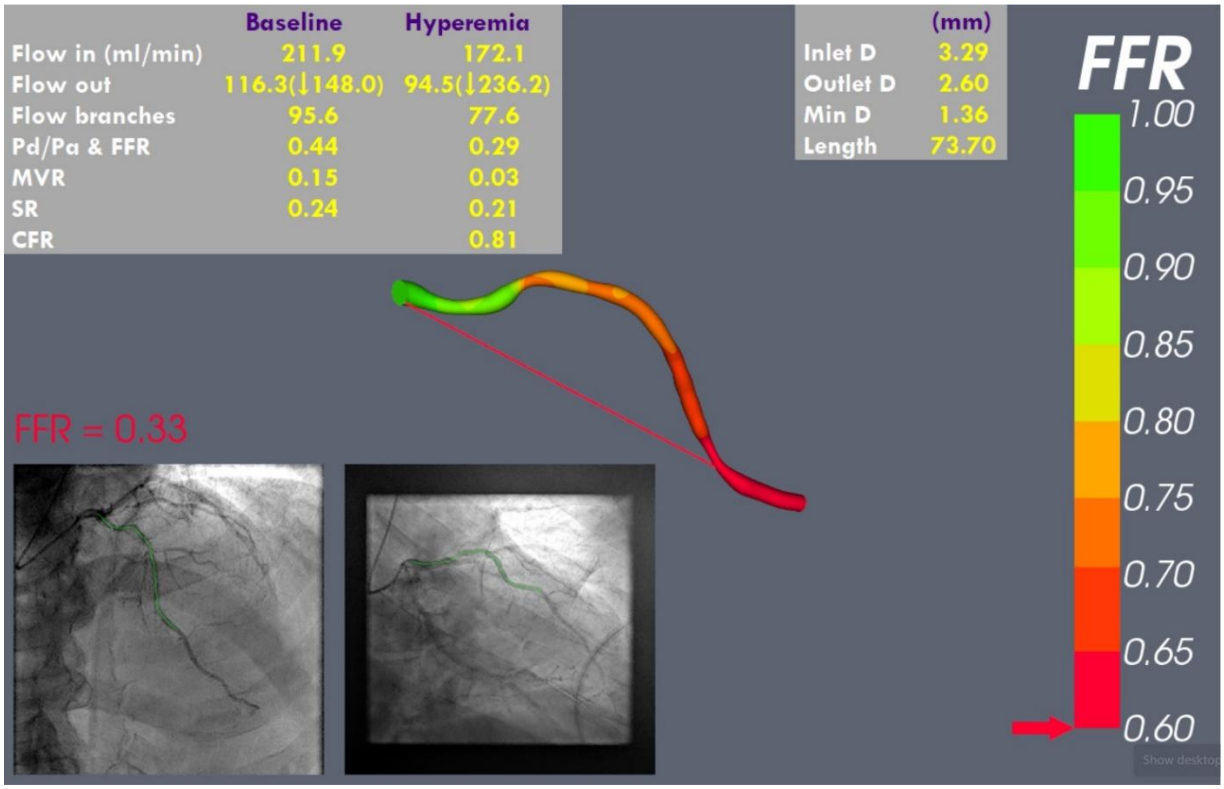


Figure 19. *Example of virtuQ™ interface and results screen.*

These are the results from a study patient with a reconstructed, severely stenosed LAD with a very low FFR. The flow, resistance and CFR values are presented very clearly.

1.8.4 virtuQ™ and VIRTUheart™ in AS

The validity and feasibility of measuring aCBF, MVR and vFFR using virtuQ™ and VIRTUheart™ technology in patients with severe AS is untested and will formed part of the basis of this thesis.

1.9 Hypothesis, aims and outcomes

The principal aim of this study was to assess the haemodynamic effects of treating severe AS at a coronary and microvascular level.

My hypotheses were therefore:

1. Treatment of severe aortic stenosis with TAVI has measurable long-term (3-6-months) haemodynamic benefits with a measurable change absolute coronary blood flow and improvement in parameters of microvascular disease.

2. There are accompanying improvements in symptoms and physical activity levels which align with the reversal of pathological LV remodeling.

1.9.1 Research aims

In patients undergoing TAVI for severe AS, I aimed to:

1. Assess the changes in coronary blood flow and microvascular function pre- and post-TAVI in a selection of patients from Sheffield Teaching Hospitals who had CAD at angiography. These parameters were measured invasively, with CMR and using virtuQ™ CFD technology. They included aCBF, global MBF, CS-flow, CFR, MPR, IMR, MRR, MVR, FFR and RFR. These parameters were measured both pre- and post-PCI (where appropriate) and post-TAVI.

2. Obtain a complementary set of data on changes in LV parameters pre- and post-TAVI from CMR and echocardiography.

3. Compare CMR findings of patients with severe AS with a comparator group of patients without AS who had a similar degree of CAD.

4. Compare measured-FFR (mFFR) with vFFR using VIRTUheart^{TM} in patients with severe AS.

1.9.2 Outcomes

Primary outcomes: The primary endpoints were the long-term (3-6 month) change in absolute coronary blood flow and microvascular disease as assessed invasively, with cardiac MRI and virtuQ™.

Secondary outcomes: The secondary endpoints were changes in all other coronary physiological parameters. I aimed to examine the relationship between these changes and LV performance at CMR and echocardiography, as well as symptom burden and activity level using questionnaires. I also compared CMR findings between patients with and without severe AS to determine the changes in myocardial perfusion and LV performance in AS compared with controls with a similar degree of CAD. Finally, I compared mFFR with vFFR in patients with severe AS.

Chapter 2: Methods

2.1 Study design

This was a single centre, prospective, open label, longitudinal, observational study undertaken at Sheffield Teaching Hospitals NHS Foundation Trust and The University of Sheffield. The STH research reference number is STH21871 and the Integrated Research Application System (IRAS) project ID is 301021. The study was exploratory and hypothesis generating and followed patients through their treatment journey with severe AS and TAVI. Certain activity was purely research driven and informed consent was obtained for participation in the study (see Appendices A, B and C).

2.2 Study population

Elective patients who were listed for a work-up coronary angiogram prior to TAVI for the treatment of severe AS at STH were screened, with a target of 20 patients. These patients had standard indications for TAVI and ICA/PCI in accordance with the ESC/EACTS guidance on valvular heart disease and myocardial revascularisation (5, 14). Diagnosis and quantification of severe AS was made using standard echocardiography and the decision to list for angiography and TAVI was at the discretion of the TAVI Heart Team. Patients had PCI (or not) at the discretion of the TAVI Heart Team and according to conventional guidance (5). Patients came from across the catchment area of the Northern General Hospital, Sheffield (Sheffield, Barnsley, Chesterfield, Rotherham, Doncaster, Worksop and Wakefield) as Sheffield is the tertiary referral centre for PCI and TAVI for the region.

2.3 Recruitment

Patients were recruited from the elective TAVI waiting list at STH. Patients were initially identified at the point of discussion at the TAVI Heart Team meeting or initial clinic appointment with a TAVI operator and a decision to proceed with a work-up ICA or PCI was made at this stage. The TAVI operator then highlighted potentially suitable patients to me by email and patients were approached for the study and had their ongoing investigations arranged. Some patients were identified for ICA without prior knowledge of their coronary anatomy and a decision to proceed to PCI was based on guideline-based criteria (5). However,

as STH is a tertiary referral centre, some patients referred for TAVI from outside the Sheffield area often had a local coronary angiogram. Those with significant CAD requiring PCI prior to TAVI, as agreed by the Heart Team, were also identified. Those not requiring further standard of care ICA or PCI were not approached. A spreadsheet with potential candidates was shared with the TAVI team, STH cardiology secretaries and CCL schedulers to ensure potential recruits to the study had their angiography or PCI with members of the study team. When potential study participants were identified, they were formally approached. A consent form (see appendix A), patient invitation letter (see appendix B) and patient information sheet (see appendix C) were sent to the patient in order to gain fully informed consent. If a patient expressed a willingness to participate in the study, they were contacted by telephone to have their outpatient angiogram and CMR arranged. Formal written consent was taken by me at our first face-to-face meeting, usually at angiography. Patients who are enrolled onto the study were given a unique study number for anonymisation of data at a later stage. All patients undergoing TAVI at STH required a TAVI-CT scan as local protocol. The purpose of this scan has already been described in *1.3.6.1*. Patients with unsuitable anatomy for TAVI were removed from the waiting list and excluded at this stage. Patients were given the contact details of the study team. Patients could leave the study at any point, and continue with their standard care. When patients withdrew, relevant study data could still be used with their consent.

2.4 Inclusion and exclusion criteria

Study inclusion criteria were:

- Diagnosis of severe AS.
- Suitable for elective TAVI at STH.
- Listed for elective ICA/PCI at STH with a >50% coronary diameter stenosis in a major epicardial vessel suitable for pressure wire assessment.
- Informed consent obtained.

Study exclusion criteria were:

- Inability or refusal to give consent.
- Requiring emergency TAVI.
- Unsuitable anatomy for TAVI.
- Unobstructed coronary arteries.
- Diagnosis of a terminal condition.
- Significantly co-morbidity or frailty.

2.5 Research ethics and integrity

This study received a favourable opinion from the research ethics committee (REC) and the NHS health research authority (HRA) on 29/09/2022 (22/NW/0017; see appendix D) and was sponsored by the STH research and development executive committee (STH21871). The study protocol and documentation were registered and approved by IRAS (Project ID: 301021). It was reviewed favourably by the Sheffield national institute for health and care research cardiovascular patient panel on 06/07/2021. A comparator group of CMR patients (patients with CAD but without AS) were taken from the VIRTU-5 study, which was recently undertaken by our research group (STH research number: 20961 and IRAS project ID: 272069). The VIRTU-5 study received a favourable opinion from the REC and NHS HRA on 06/03/2020 (20/NS/0033; see appendix E). All patients had consented to their CMR data to be used in similar projects across our research group.

2.6 Study protocol

The clinical study protocol aimed to measure a broad and comprehensive range of clinical and patient reported data across the duration of the patients' participation. The study captured and utilised data obtained from routine standard of clinical care (SOC) pathways as well as research specific investigations. The study pathway and assessment period can broadly be separated into three phases:

1. Pre-TAVI phase.
2. TAVI Procedure.

3. Post-TAVI phase.

The time differential between the pre-TAVI phase and TAVI procedure varied between patients due to their position on the TAVI waiting list, which was based on individual clinical need and date listed. The post-TAVI phase was a 3-6-month period during which a further research driven ICA and CMR were performed. A summary of the VIRTU-AS study protocol, design and patient journey is illustrated in Figure 20.

2.6.1 Pre-TAVI phase

The pre-TAVI phase of the study included:

1. Consent.
2. Coronary angiogram and pressure wire assessment (SOC).
3. Questionnaires.
4. virtuQ^{TM} processing of angiography derived data.
5. Cardiac MRI.
6. Echocardiogram (SOC).
7. TAVI-CT (SOC) – *patients excluded if unsuitable anatomy.*

The pathway for identifying and approaching patients to consent to the study has been described in section *2.3*. When a patient was identified and listed for ICA/PCI based on TAVI Heart Team agreement, they received an appointment to attend the STH CCL for their ICA based on standard NHS availability and policies. During this procedure, if there was any CAD requiring assessment, a full invasive coronary physiology study was performed, and is described in more detail later in this chapter. The data obtained were used as the pre-TAVI invasive coronary physiology. If patients required PCI based on these results (FFR ≤0.8), they received this at the same procedure (as per ESC guidance (5)) and had the same set of coronary physiology performed on the same vessel after PCI. If their initial physiology results were negative (FFR >0.8), the procedure was complete as PCI was unwarranted. Angiogram images and pressure wire data derived at this stage were systematically recorded for use in the study and processing offline through the virtuQ™ workflow. Patients had their health

questionnaires as part of this visit. A selection of patients also had quantitative stress perfusion CMR pre- and post-TAVI. Due to funding availability, this was limited to 10 patients. Patients who consented for and were deemed suitable for CMR had this arranged after their initial angiogram and PCI procedure. This was performed at STH on the Pulmonary, Lung and Respiratory Imaging Sheffield (POLARIS) University of Sheffield MRI scanner based at the Northern General Hospital, STH, and transportation was provided. The scanning protocol and reporting technique will be described in further detail later in this chapter. All patients had an SOC pre-TAVI echocardiogram and TAVI-CT to make the diagnosis of AS and ensure anatomical suitability and safety.

2.6.2 TAVI procedure

All patients had their TAVI procedure in the standard and clinically indicated way by the STH TAVI team. Choice of valve type and size was made by the TAVI Heart Team based on anatomy and CT-TAVI recommendations. Medtronic Evolut R Pro and Edwards Sapien valves were used at STH during the period spanning this study.

2.6.3 Post-TAVI phase

The post-TAVI phase of the study included:

1. Coronary angiogram and pressure wire assessment.
2. Questionnaires.
3. virtuQ™ analysis.
4. Cardiac MRI.
5. Echocardiogram (SOC).

Following discharge and recovery from the TAVI procedure, patients entered the final phase of the study. A period of at least three months recovery were observed before the follow-up angiogram, questionnaires and CMR were planned. Relevant angiography and pressure wire data were again processed offline through the virtuQ™ workflow. A summary of the VIRTU-AS patient pathway is outlined below in Figure 20.

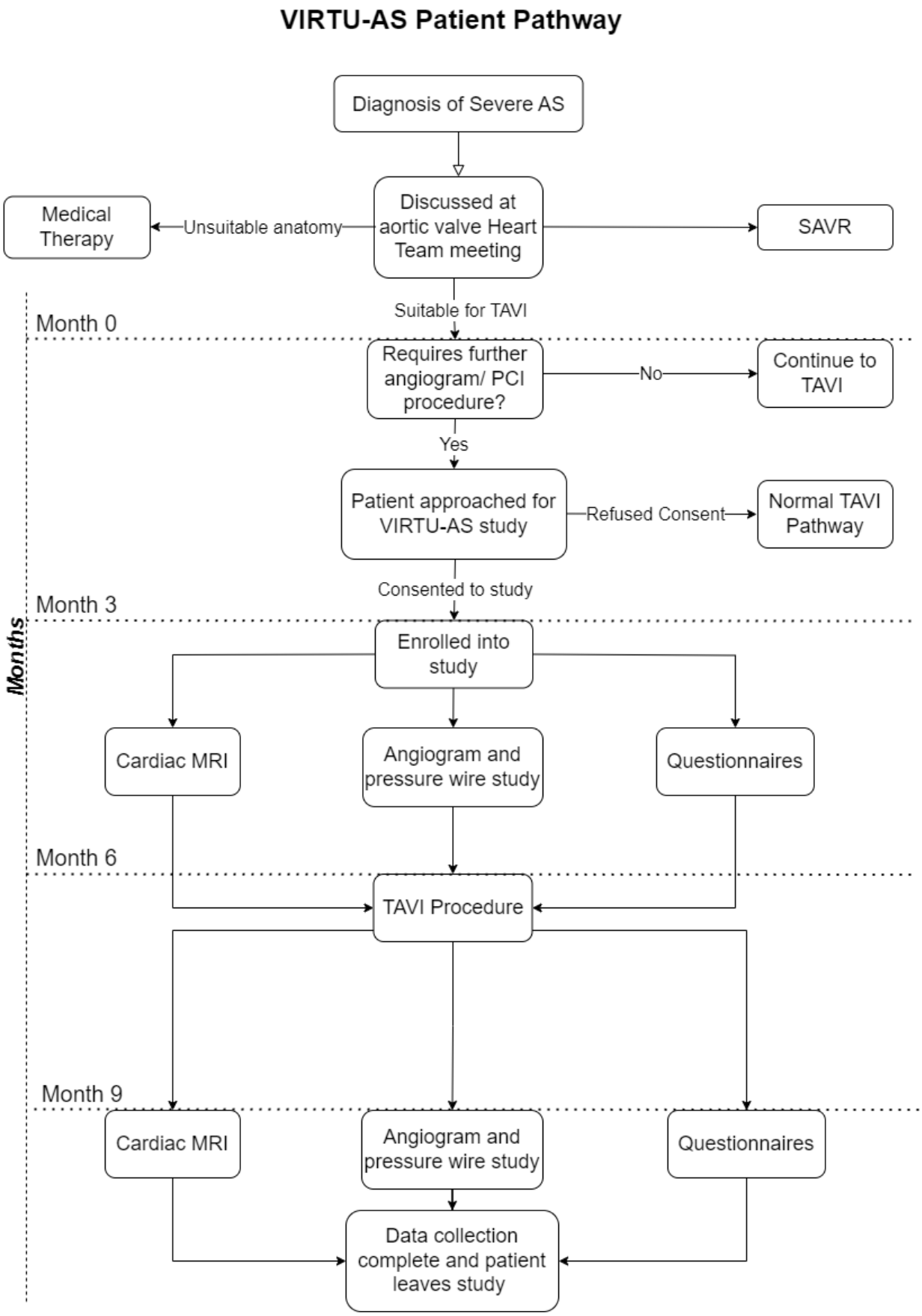


Figure 20. Summary of the VIRTU-AS patient pathway.

2.6.4 Clinical data

Routine patient characteristics data were obtained and reported for all study patients. This included age, weight, body mass index (BMI) and heart rate. Data on past medical history included hypertension, hyperlipidaemia, diabetes, smoking status, COPD, AF, CKD, peripheral vascular disease, MI, previous PCI or CABG, CVA and presence of a PPM.

2.6.5 Clinical scores and questionnaires

This study utilised the extensively validated Short Form 12-point questionnaire (SF-12) to obtain a patient reported measure of health and well-being. The SF-12 questionnaire (see appendix G) is a measure of overall health and mental wellbeing, it is a 12-item questionnaire which produces separate physical and mental wellbeing scores and is validated for use in the general public (213). The SF12 questionnaire produces a numerical result which is compared to the population mean of 50±10 in each domain. The first set of questionnaires were carried out on the day of the pre-TAVI work-up angiogram. The second set of questionnaires were conducted at least three months after recovery from TAVI at the second angiogram visit or CMR. They were in paper format and the completed questionnaires were stored securely in the individual patient research folder held in STH. The SF-12 questionnaire is non-proprietary free to use. The Rockwood clinical frailty scale (see Appendix H) was used to categorise patients' degree of frailty prior to their TAVI procedure and the New York Heart Association (NYHA) scoring system was used to assess symptoms (see Appendix I).

2.7 Data protection

Images obtained from coronary angiography, echocardiography and TAVI-CT were stored in DICOM format on the STH Picture Archiving and Communications System (PACS) as per standard local NHS protocol. Relevant files were subsequently transferred electronically in anonymised format (using the patient specific study identifier) to the Mathematical Modelling in Medicine XNAT (MMMXNAT) database, which is a password protected and secure database created by the Scientific Computing team at The University of Sheffield specifically for clinical research and is located on the secure University of Sheffield server. All patients were given a unique study identifier and images were downloaded from the MMMXNAT database onto an encrypted laptop in anonymised format for offline processing

through the VIRTUheart™ workflow. Coronary physiology data obtained using Coroflow™ (Coroventis) in the CCL were stored locally on the STH clinical server and specific images were transferred to the PACS. These data remained on the secure STH server. The data were extracted in anonymised format using the patient specific identifier. Cardiac MRI images were saved directly onto the secure POLARIS imaging ArQ database which is located securely on The University of Sheffield server. These images were transferred by specialist radiographers in anonymised format to the to MMMXNAT database where they were downloaded onto an encrypted laptop for reporting. All data were used lawfully, subject to the Data Protection Act 2018, and only authorised members of University staff and the research team had access to the secure POLARIS, ArQ and MMMXNAT databases. Only clinical STH staff had access to the STH secure server and PACS and any data stored on this server are held according to STH and NHS policies.

2.8 Coronary angiography and pressure wire assessment

All patients in this study had their ICA and PCI performed at the STH CCL under the care of the research team. All procedures adhered to standard STH clinical protocols and ESC guidance for the investigation and management of CAD (5). Patients were consented separately for each ICA procedure according to standard NHS clinical practice. I personally consented for and performed all pre- and post-TAVI angiogram, pressure wire and PCI procedures.

2.8.1 Coronary angiography

Vascular access was achieved through the radial artery in preference to the femoral artery with a 6Fr peripheral sheath. Images were obtained using 6Fr guiding catheters and an iodine-based contrast solution. As per clinical guidance, patients received 70-100IU/kg of unfractionated Heparin, administered intra-arterially through the guiding catheter to achieve an activated clotting time (ACT) of between 250-350s. The ACT was measured every 30 minutes and patients were given supplemental boluses of intra-arterial unfractionated Heparin if the ACT was <250s. Intra-arterial GTN was generally avoided due to the risk of significant hypotension in patients with severe AS. Image acquisition was performed using our protocol for computational modelling (good opacification, minimal overlap, minimal magnification, minimal panning, and at least three views of the right, and five of the left

coronary artery) to allow accurate reconstruction and modelling in the VIRTUheart™ workflow. Once image acquisition was complete, any visually intermediate coronary stenoses (50-90% luminal stenosis) were subject to physiology assessment according to standard clinical and study protocols. Patients underwent a full invasive pressure wire study with a 0.014" pressure-temperature sensor-tipped Abbott Pressure-Wire™ X (Abbott Vascular, Santa Clara, CA, USA) which was zeroed outside of the body and equalised to central aortic pressure in the aortic root. The wire was advanced carefully beyond the coronary stenosis to a distal point in the coronary artery of interest. Trans-lesional data were transmitted from the transducer near the distal end of the wire to Coroflow™ software (Coroventis, Uppsala, Sweden) wirelessly using Bluetooth™ technology for interpretation and extraction. Trans-lesional pressure and temperature data were obtained at baseline and during hyperaemia. Hyperaemia was induced with an IV Adenosine infusion given at a standard rate of 140ug/kg/min. RFR and resting P_d/P_a were measured at baseline conditions and FFR and hyperaemic P_d/P_a were measured two minutes after commencing IV Adenosine when the operators were happy that a stable state of hyperaemia was achieved. Bolus thermodilution, with 3mL of room temperature 0.9% saline, was performed at baseline and during hyperaemia in order to measure CFR and IMR. If the FFR was recorded at ≤0.8, PCI was deemed necessary and therefore offered according to current ESC guidance on myocardial revascularisation (5). This was performed at the same sitting and within local guidance and protocols. Only newer generation drug-eluting stents or drug-coated balloons were used if PCI was deemed necessary. In any treated vessel, the full range of baseline and hyperaemic coronary physiology was repeated to ensure adequate treatment had been provided and accurate up-to-date data were obtained for comparison later. Once the procedure was completed, all equipment was removed and haemostasis achieved with either a TR Band™ (Terumo) radial compression device or an Angio-Seal™ (Terumo) femoral closure device. Patients were discharged later that day if well and had no post-procedural complications. This protocol was used for both the pre- and post-TAVI angiogram and pressure wire assessments, and the same set of data were obtained each time. Figure 21, below, demonstrates an angiogram image of an LAD with a distally placed pressure-wire measuring the FFR during hyperaemic conditions.

Figure 21. *Angiogram and FFR.*

Angiogram of LAD with distally placed pressure-wire and Coroflow™ (Coroventis) screen of FFR measurement with steady state hyperaemia.

2.8.2 Bolus thermodilution

The bolus thermodilution method for the measurement of CFR and IMR is briefly described in section *1.4.5.3*. The Abbott Pressure-Wire™ X has one pressure sensor and two temperature sensors. The temperature sensors are placed proximally and distally, and the mean transit time (between these two sensors) of a bolus of saline is measured by forcefully injecting 3mL of room temperature 0.9% saline directly into a coronary artery through the guiding catheter. The lower temperature of the saline bolus is detected by the temperature sensors on the wire and the transit time between the two points is used as a surrogate for volumetric blood flow. As such, the transit time of a bolus of saline through a coronary artery is inversely proportional to the volumetric flow rate. Hence, a short mean transit time indicates a high flow rate. The distally placed Pressure Wire™ X (Abbott) temperature sensors record the mean transit time of three boluses of saline at rest and during hyperaemia and sends these to the Coroflow™ (Coroventis) system, which records and calculates the ratio of these to measure CFR. IMR is measured as the mean distal pressure (P_d) multiplied by the thermodilution-derived mean transit time of a bolus of saline during maximal hyperaemia, and is measured using the mean of three hyperaemic transit times. Multiple bolus injections

of saline cannot always be exactly equal with respect to flow rate and volume when done by hand. To mitigate for this, all procedures and injections were performed by the author and where a discrepant value was obtained, the reading was repeated until three similar readings (within 0.2 seconds) were achieved. In cases where the equalisation pressure of the pressure-wire had "drifted" away from the accepted baseline of 1.0-0.99 upon withdrawal to the left main stem, the wire was re-equalised and entire procedure repeated to ensure accuracy.

Figure 22, below, demonstrates a Coroflow™ recording of simultaneously measured CFR, IMR, FFR and resting indices. The thermodilution temperature curves can be appreciated in the lower part of the image. The FFR, RFR, P_d/P_a values, CFR and IMR can all be extracted easily as can be appreciated below. These values were used to calculate the MRR offline, using the equation described in section *1.4.5.3*.

Figure 22. *Full Coroflow™ (Coroventis) study.*

Coroflow™ (Coroventis) screen of study patient with thermodilution derived temperature curves and simultaneous measurement of FFR, resting P_d/P_a, CFR and IMR. 22**A**; The pressure-

wire is equalised to central aortic pressure and passed distally in resting conditions. The resting pressure tracings are recorded, the red trace is P_a and the green trace is P_d. 22**B**; The temperature is zeroed so the pressure-wire accepts the body temperature as zero, as can be appreciated on the y axis. 22**C**; Resting transit times (in seconds) of a 3mL bolus of 0.9% saline. 22**D**; The temperature detected by the distally placed pressure-wire transducer falls to around -2.5-3.0^{o}C below the zero line with a 3mL bolus of saline. The blue temperature curves denote resting conditions and the orange lines denote hyperaemia. The orange lines are clearly seen to dip earlier along the x axis (time), suggesting a shorter transit time (thus greater flow rate), as would be expected in hyperaemic conditions. The temperature lines gradually drift back to the zero level as the saline passes through the myocardium. 22**E**; Hyperaemic transit times of a 3mL bolus of 0.9% saline. 22**F**; Adenosine infusion has been commenced for at least two minutes and hyperaemic P_d/P_a pressure tracings are recorded. Note the separation between P_d/P_a during hyperaemia, compared with resting conditions. 22**G**; The software simultaneously displays final results once resting and hyperaemic parameters have been measured. The FFR is 0.66, the resting P_d/P_a is 0.89, the CFR is 2.0 and the IMR is 16.

2.9 Computational fluid dynamics techniques

The VIRTU-AS study utilised the VIRTUheart^{TM} software package (Mathematical Modelling in Medicine, Division of Clinical Medicine, University of Sheffield, v4.0.0.6) to measure aCBF and MVR (virtuQ^{TM}) and vFFR (VIRTUheart^{TM}). The coronary artery segmentation tool is embedded within the main software package (v4.a.5). The process of using VIRTUheart^{TM} can be broadly divided into three phases; angiogram acquisition (described in *2.7.1*), artery segmentation and reconstruction, and CFD simulation. The detailed VIRTUheart^{TM} workflow is described in section *1.8.1* and is expanded upon below. The segmentation tool requires two angiographic images of the coronary artery of interest, with projections of at least >30^{o} apart and with good lumen opacification, during end-diastole. Coronary angiograms were downloaded in DICOM format, fully anonymised. All segmentations and CFD processing were performed using the approved software only and, on a password, protected and encrypted OMEN^{TM} by Hewlett Packard Laptop (15-dh1xxx, Intel^{R} Core^{TM} i7-10750H CPU 2.60GHz processor, 16GB RAM).

2.9.1 Coronary artery segmentation and reconstruction

The segmentation and reconstruction phase generated the volumetric 3D mesh of the coronary artery of interest using the VIRTUheart^{TM} segmentation tool and the epipolar line transaction technique. It utilised MATLAB^{TM} software (Mathworks, Massachusetts USA) to create the 3D mesh, which is created from millions of tetrahedral shaped cells. The first stage of the segmentation and reconstruction process was to select two angiogram images with good lumen opacification and were at least 30^{o} apart spatially. The next stage was to calibrate the software with the images spatially by measuring and confirming the diameter of the guiding catheter and placing two points in the same place along the artery of interest. The next step was to draw the "centreline" of the artery, which is a line along the central point of the artery and denotes the beginning and end of the 3D reconstruction. Next, the segmentation tool automatically detected the vessel edges and any discrepancy or error could be manually corrected at this stage to ensure the vessel lumen was accurately depicted. The next stage was to perform the same steps on the corresponding angiogram image. Once this was done, the segmentation tool was able to produce an accurate 3D reconstruction and volumetric mesh of the artery. The mathematical equations used by the CFD solver (ANSYS CFX) were applied to this 3D volumetric mesh to process results. The same reconstructed 3D volumetric mesh was used in both VIRTUheart^{TM} and virtuQ^{TM} on the same software package and the process of doing so is outlined below. The step-wise process of creating a 3D arterial reconstruction using the segmentation tool is outlined in Figures 23-35 below.

Figure 23. *Step 1 of segmentation.*

Two angiographic views of the coronary artery were chosen with good opacification and 30^{o} apart. Images were taken in end-diastole when coronary filling is optimal.

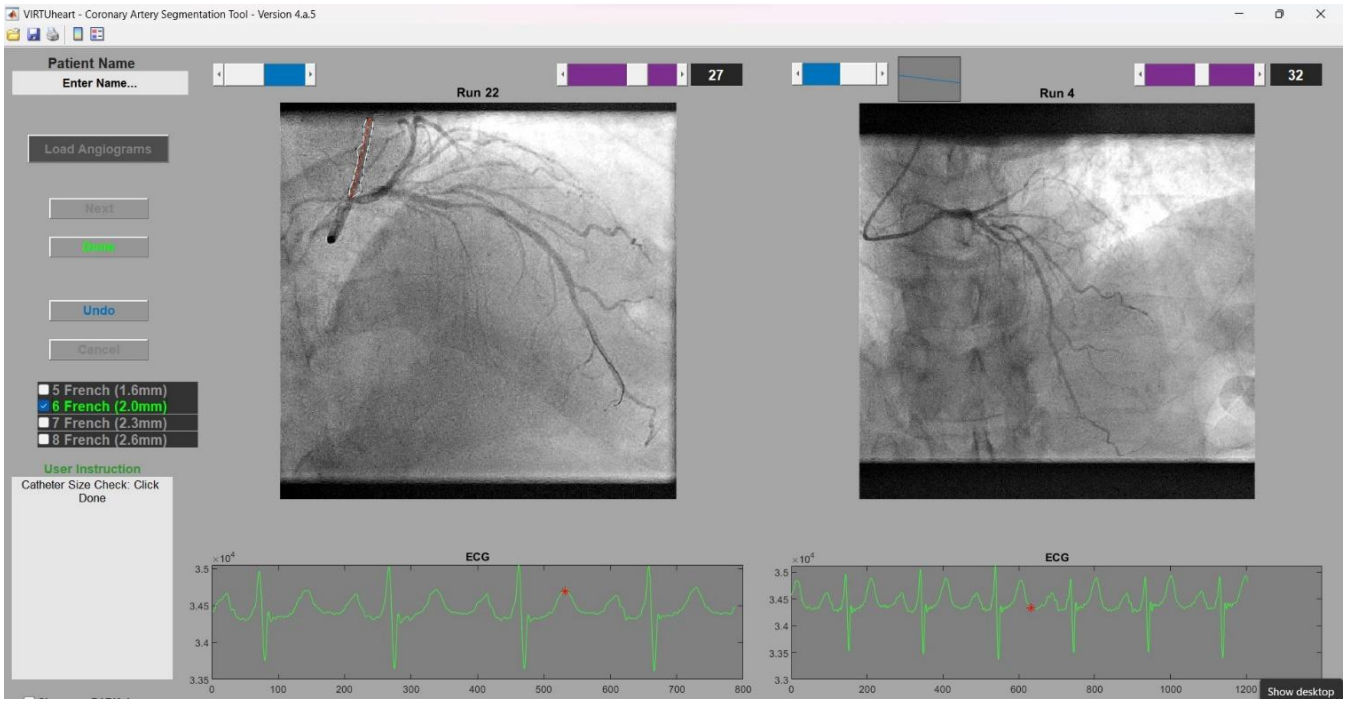


Figure 24. *Step 2 of segmentation.*

The diameter of the guiding catheter was measured and size confirmed in order to calibrate the software spatially.

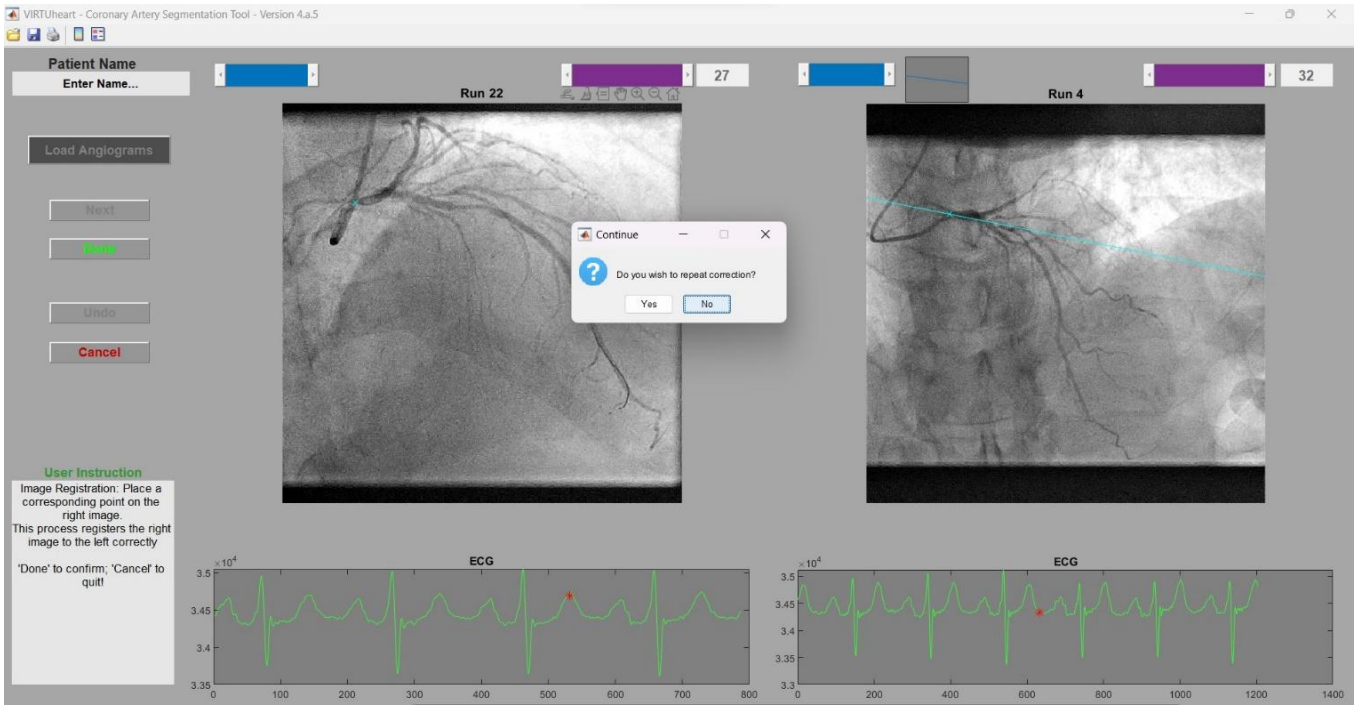


Figure 25. *Step 3 of segmentation.*

To further calibrate the software spatially, two corroborating points were placed in the same location on each image.

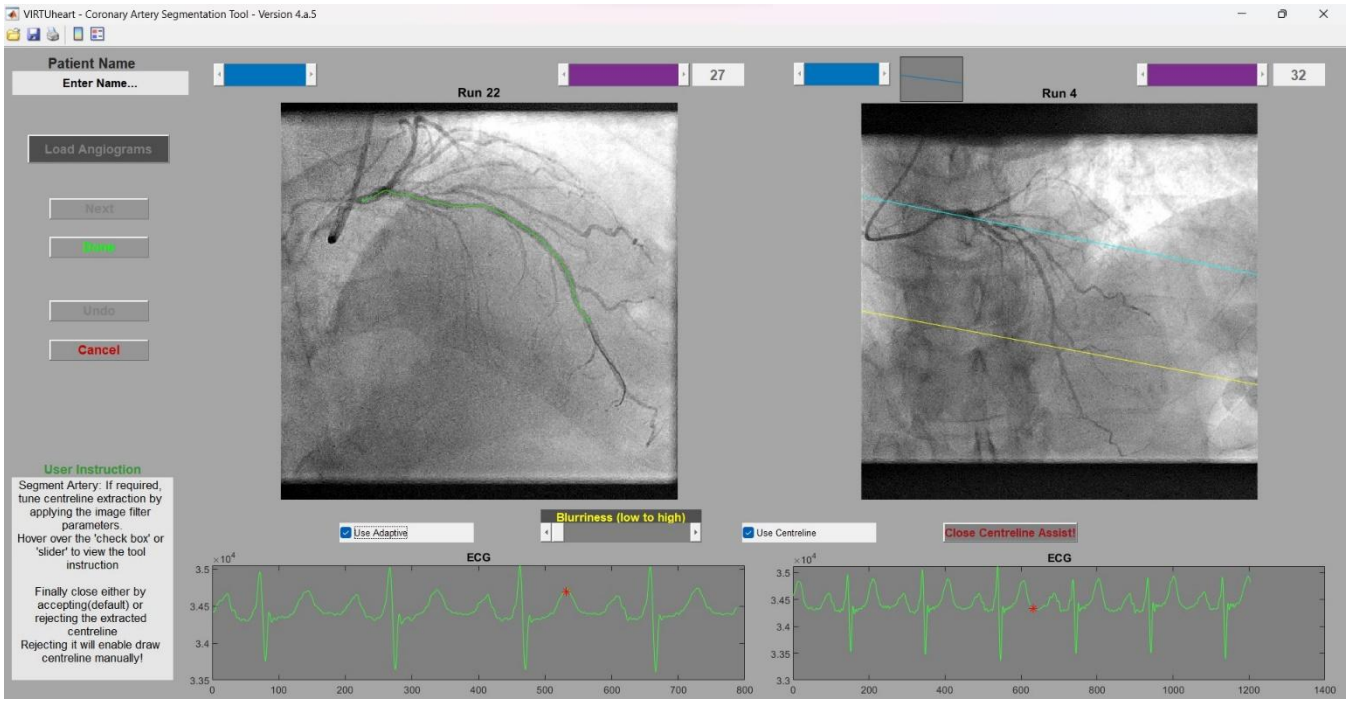


Figure 26. *Step 4 of segmentation.*

The “centreline” of the artery was drawn on the left image and taken down to the pressure-wire transducer for accuracy in virtuQ^{TM}.

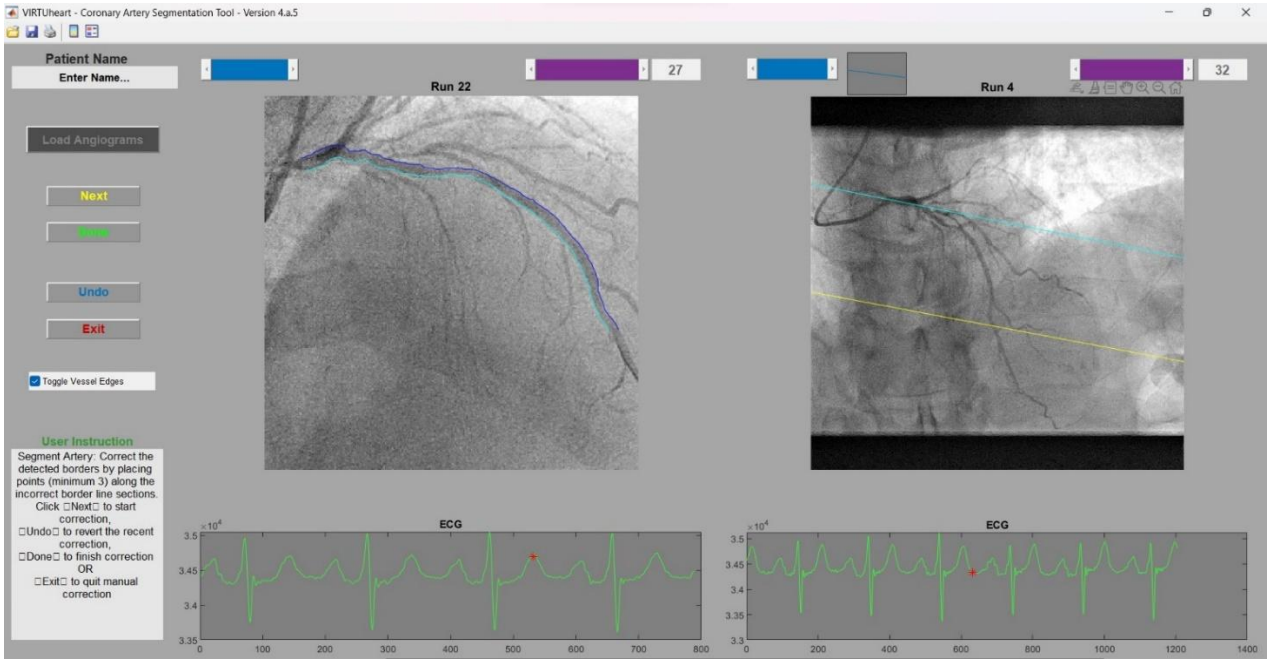


Figure 27. *Step 5 of segmentation.*

The software automatically detected the artery edges. Manual correction would be performed at this stage for errors.

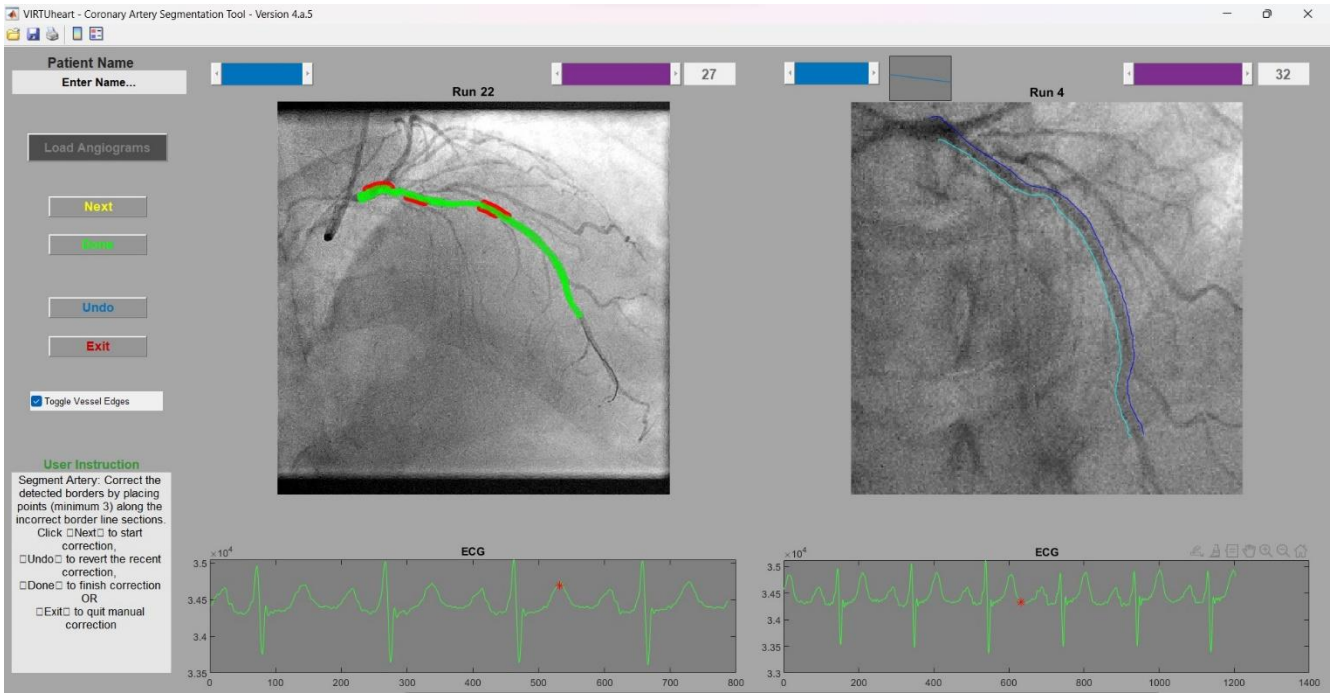


Figure 28. *Step 6 of segmentation.*

The same steps as above were performed on the right image.

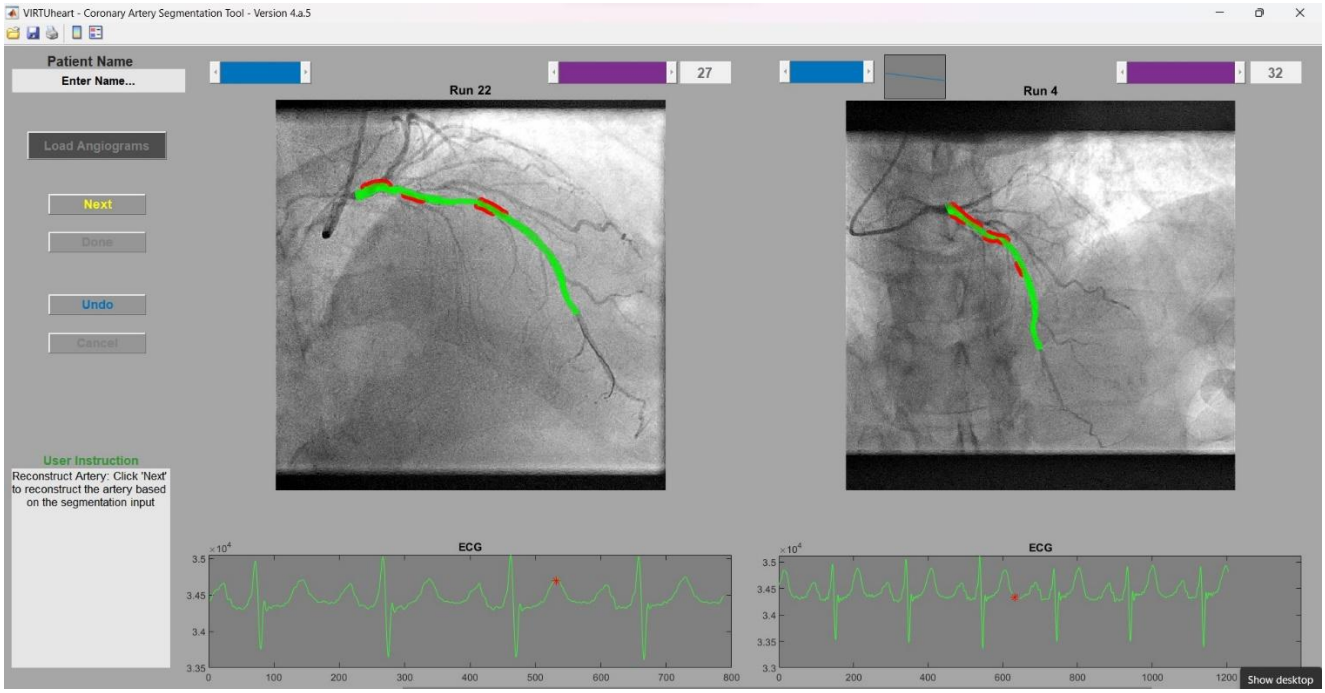


Figure 29. *Step 7 of segmentation.*

Both images were segmented and the 3D reconstruction ready to be produced.

Figure 30. *Step 8 of segmentation.*

The 3D reconstruction of the LAD is ready to be processed on either VIRTUheart™ or virtuQ™ using the CFD solver.

Figure 31. *Step 9 of segmentation.*

The 3D mesh could be processed using Estimated boundary conditions (VIRTUheart™, for vFFR measurement) or with Measured boundary conditions (virtuQ™, for aCBF, MVR and CFR).

Figure 32. *Step 10 of segmentation.*

The virtuQ^{TM} data entry screen. Resting and hyperaemic P_d/P_a values were entered and a standard branch flow exponent of 2.33 was used for CFD analysis.

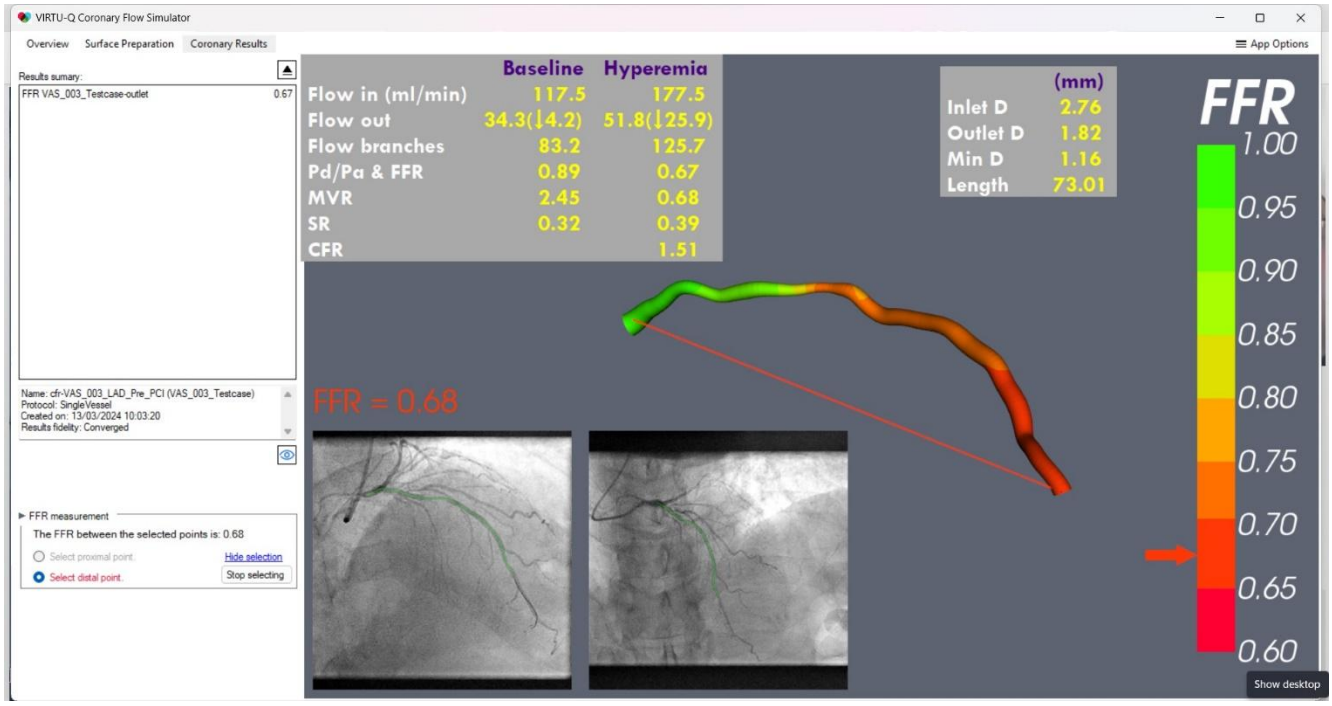


Figure 33. *Step 11 of segmentation.*

virtuQ^{TM} results screen for the above segmentation was produced with easily extracted data for aCBF, MVR, CFR, among other data.

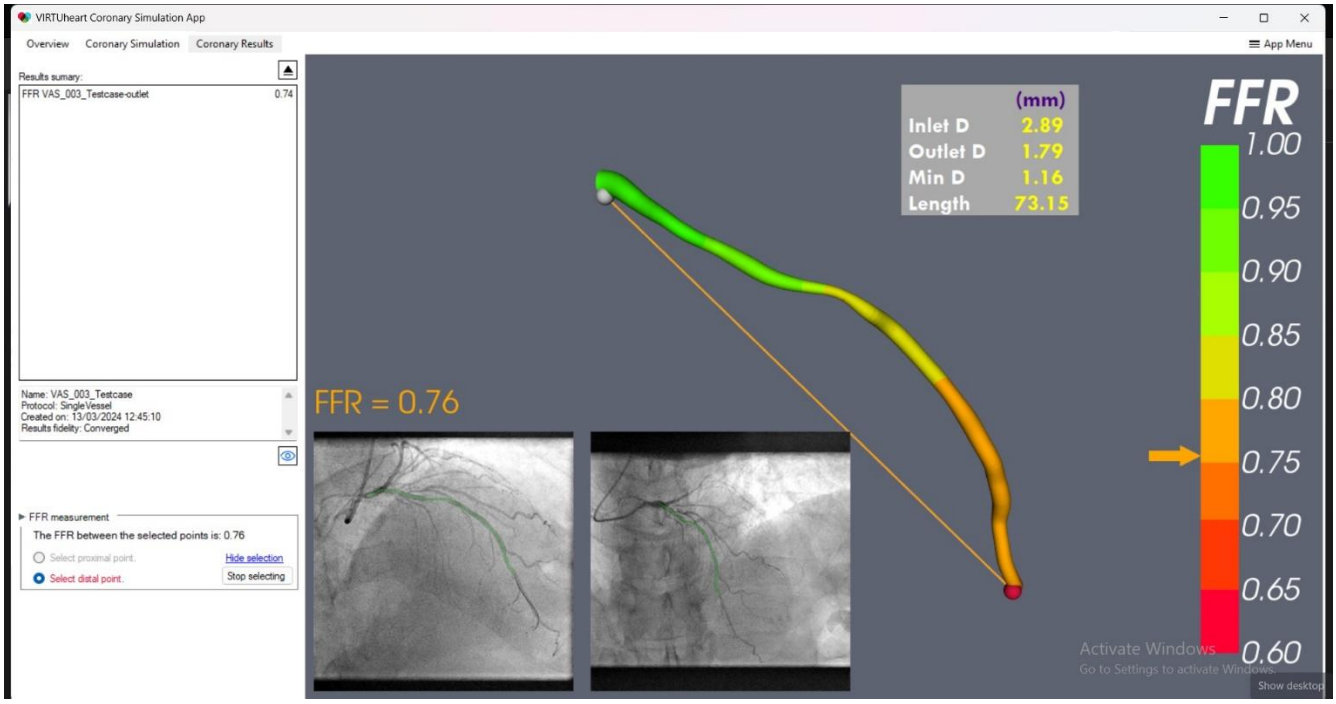


Figure 34. *Step 12 of segmentation.*

VIRTUheart™ results screen for the same reconstruction. A standard resistance value of 8.721e09 was used in this case. The vFFR is measured at 0.76 which is slightly discrepant from the mFFR.

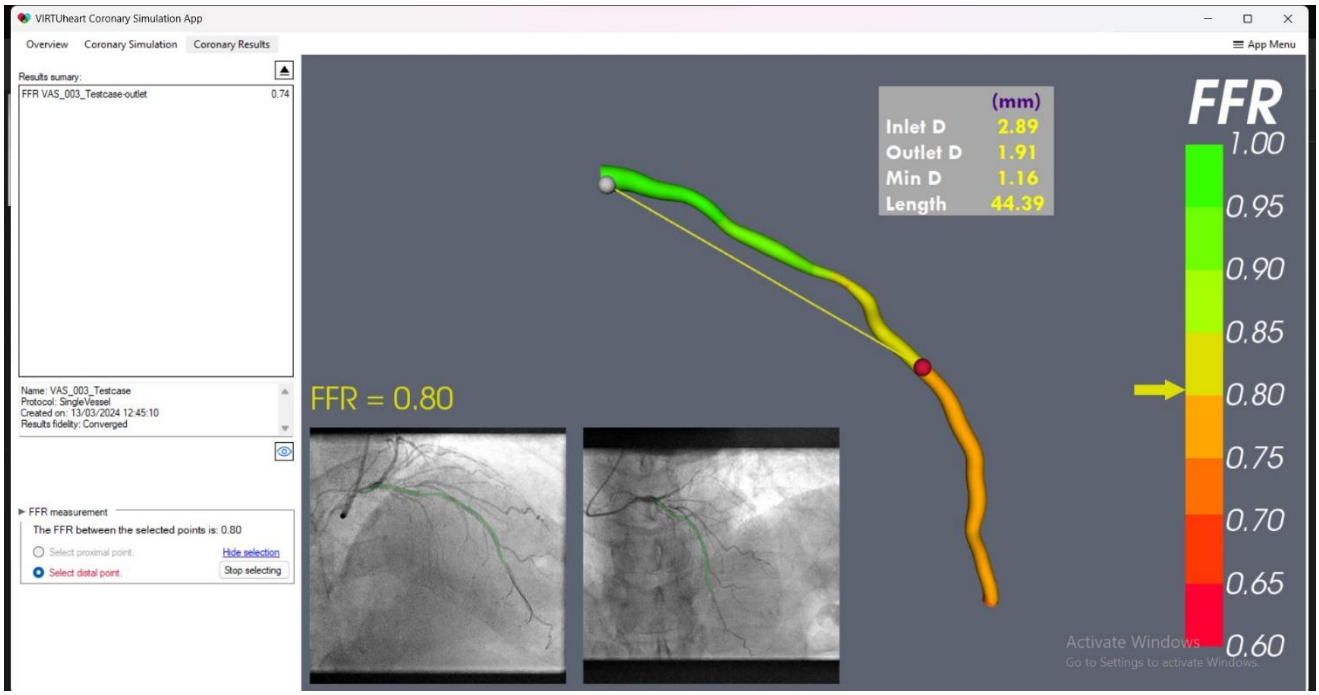


Figure 35. *Step 13 of segmentation.*

VIRTUheart™ results screen demonstrating the ability of the software to perform a virtual "pull-back" and measure the vFFR along any point along the vessel.

2.9.2 virtuQ™ processing

The process of using the VIRTUheart™ workflow has already been described in detail in *1.8.1* and *2.9.1* and Figures 23-35. The volumetric mesh created at the segmentation stage was uploaded onto the virtuQ™ platform and invasively measured resting and hyperaemic pressure values were inputted to provide accurate boundary condition data (see Figure 32). The software package used ANSYS CFX (version 222) CFD solver software to solve the incompressible Navier-stokes and continuity equations on the 3D volumetric mesh and produced primary values of vessel inlet and outlet aCBF (in mL/min) and MVR (in mmHg.min/mL) (see Figure 33). The outlet aCBF value is the blood flow achieved distal to a coronary artery stenosis in both resting and hyperaemic conditions. Therefore, care was taken to produce a segmentation where the distal end of the centreline corresponded to the tip of the pressure-wire transducer used to obtain invasive P_d/P_a data (see Figure 26). The model requires a trans-lesional pressure gradient of at least 4mmHg and an invasively measured FFR of <0.95 in order to be accurate. All simulations used standard blood density (1056kg/m^3) and viscosity (0.0035Pa) with a homogenised (using vessel taper) side branch flow-diameter scaling exponent of 2.33, as recommended by the software developers. Absolute MVR was calculated using the hydraulic equivalent of Ohm's law and is calculated as the P_d divided by aCBF measured distally (P_d/aCBF). The model was also able to calculate the reduction in aCBF caused by the presence of epicardial stenosis and can be seen in the main results page (see Figure 33). Data on artery diameter size and length was provided, as well as CFR. All results were processed on a vessel specific basis and values were provided at rest and during hyperaemia. The primary outcomes measured for this study included both resting and hyperaemic indices of aCBF (in mL/min) and MVR (in mmHg.min/mL) obtained from virtuQ™. Additional values obtained, including CFR, were used as secondary outcomes. Measuring aCBF in patients with severe AS may hold more value than measuring standard indices of coronary physiology, such as FFR, as we can measure absolute changes in flow and it is not unreasonable to consider large reductions (or improvements) of aCBF to hold more prognostic and symptomatic significance, than lesion specific proportional changes.

2.9.3 VIRTUheart™ processing

VIRTUheart™ was utilised to compare vFFR with mFFR. This was a secondary outcome and aimed to compare accuracy of vFFR in patients with severe AS, as the major studies studying the efficacy of vFFR were all in patients with either stable or acute coronary syndromes who are not necessarily subject to the complex haemodynamic conditions which exist in severe AS (209, 210). The workflow and step-wise process of using VIRTUheart™ has been extensively described already in this thesis (sections *1.8.1* and *2.9.1* and Figures 23-35). A standard resistance value of 8.721e09 Pa/m^3s^{-1} was used to calculate the vFFR (208).

2.9.4 VIRTUheart™ training and reproducibility

I received training in how to operate VIRTUheart™ in order to produce accurate coronary artery segmentations from senior, expert members of the MMM group (my thanks to Dr Morris, Dr Haley and Dr Williams). I was able to hone my skills by participating in other studies within our group which utilised VIRTUheart™ and when the team and I were confident that my skill-set was appropriate, I began producing the final segmentations for the VIRTU-AS study. To ensure reproducibility and accuracy, segmentations were reviewed by a second expert user (my thanks to Dr Taylor) who was blinded to invasive physiology results. If there were discrepancies or inaccuracies detected, the segmentation was repeated until it was accurate and both researchers were satisfied that the segmentation accurately reflected the coronary artery in question.

2.10 Cardiac MRI

Stress perfusion CMR was performed in ten patients who had consented and were medically suitable. Once a suitable patient was identified, the POLARIS academic radiology team were informed and an appointment was made. As per the patient information sheet (appendix C), travel expenses were paid for. All pre-TAVI CMR studies were performed after coronary angiography/ pressure wire study and (where appropriate) revascularisation with PCI. Patients had their follow-up CMR 3-months after treatment with TAVI. All scans were performed in a 1.5 Tesla GE 450W whole body MRI scanner (GE Healthcare, Milwaukee, Wisconsin) and imaging was acquired using a 16-channel cardiac coil. The MRI scanner was based at the Northern General Hospital, STH, and run by The University of Sheffield POLARIS

team (led by Professor Jim Wild). All safety procedures outlined in STH MRI protocols and in Kramer et al 2020 (214) were followed carefully and all patients had a pre-scan safety questionnaire to ensure that they were safe to proceed. All scans were performed by superintendent MRI radiographer at The University of Sheffield, Mr. David Capener or senior radiographer, Mr. Jody Bray and I was present for all scans. Patients who had a PPM could not have a CMR in The University of Sheffield MRI scanner, regardless of the MRI compatibility of the device.

2.10.1 CMR image acquisition

Patients who were safe to proceed had a standard stress perfusion CMR protocol as outlined in Kramer et al in the Standardized CMR Protocols 2020 update, published in the Journal of Cardiovascular Magnetic Resonance (214). This included:

1. LV structure and function.
2. RV structure and function.
3. Late Gadolinium Enhancement (LGE).
4. Stress Perfusion.
5. Blood flow quantitation.

The protocol included baseline scout scans, cine images (short-axis, long-axis, 4-chamber, LV volume stacks), 4D flow sequencing, stress and rest first pass perfusion, 2D phase contrast at rest and stress (CS flows) and late gadolinium acquisitions. Cine images were ECG-gated and acquired during breath holds at end-expiration. The full protocol can be appreciated in Appendix F. A Gadolinium based IV contrast agent was used and IV Regadenoson (400ug standard dose) was used as the stressor agent. Adequate stress was deemed to have been achieved when the heart rate increased by >10bpm. Images were anonymised according to unique study number and saved onto the ArQ database where they were securely transferred to the MMMXNAT server for download and offline analysis.

2.10.2 CMR reporting and analysis

CMR reporting in the VIRTU-AS study was supported and supervised by Dr Rebecca Gosling, a clinical research cardiologist specialising in CMR at STH and The University of Sheffield.

Image analysis and reporting was done offline using MASS research reporting software (Version 2023 EXP, courtesy of Professor van der Geest, Leiden University Medical Centre, NL).

Analysis of LV volumes, LV mass (LVM) and LV function were done by manually tracing the epicardial and endocardial borders on the LV short-axis stack cine images in all slices. The MASS software has an artificial intelligence (AI) module which could do this very accurately and quickly. AI was used to initially report the LV parameters and draw the epicardial and endocardial boundaries. These were then checked over carefully to ensure boundary accuracy. Data obtained include LVEF, LV mass, LV chamber volume, and wall thickness.

Quantitative perfusion analysis was done by tracing epicardial and endocardial borders on the stress and rest perfusion image series. First pass perfusion images were used to highlight the endocardium and epicardium and the borders were copied across all image phases. This was done for all three short-axis image slices. Once this was done, the RV insertion point was marked and the software created a 16-segment AHA myocardial segmentation “bullseye” model (201). MBF was given in each 16-segment area and also as a mean across all segments. The mean MBF is given in mL/min/g and was multiplied by the LV mass (obtained in the earlier analysis phase) to provide the global MBF in mL/min for the whole LV. The individual coronary artery territories could be assessed for MBF and a colour coded bullseye schematic was produced. The areas supplied by the LAD are 1,2,7,8,13 and 14, the areas supplied by the LCx are 5,6,11,12 and 16 and the areas supplied by the RCA are 3,4,9,10 and 15 (215). The same process was performed in both the stress and rest phase image series. The MPR was then calculated as the ratio of global MBF at stress to the global MBF at rest. Figure 36, below, shows a stress perfusion image series from a study patient with the AHA 16-segment bullseye myocardial segmentation model.

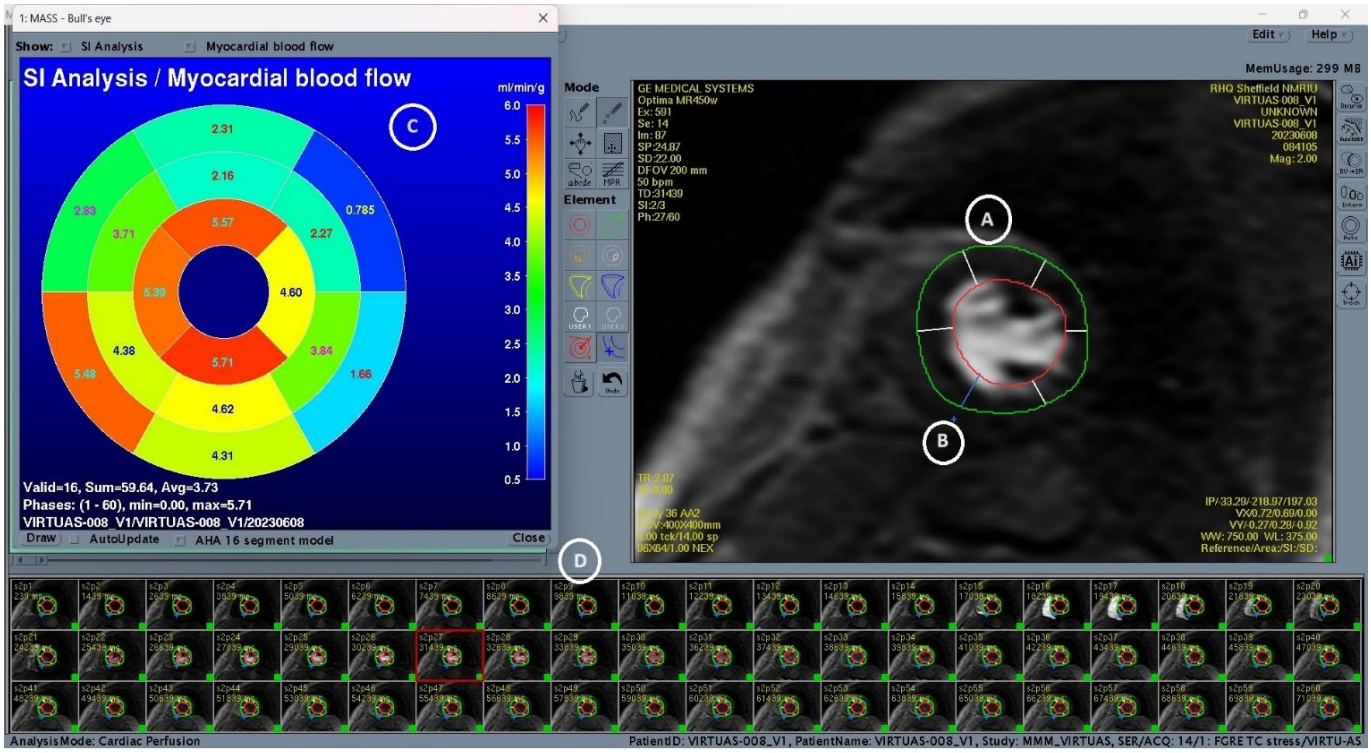


Figure 36. *MASS stress perfusion reporting.*

Example of MASS software reporting technique for stress perfusion imaging. 33**A**; The epicardial (green line) and endocardial (red line) borders were drawn during first pass perfusion imaging. 33**B**; The RV insertion point was marked for the software. 33**C**; A bullseye diagram of MBF in each 16-segment area was created by the software and the MBF in each segment in mL/min/g is given. The average MBF is also shown and is 3.74mL/min/g. This was multiplied by the LV mass (in g) to achieve the global MBF in mL/min. 33**D**; The contours were drawn along all phases and slices to produce the results.

Coronary sinus flow was measured using 2D phase contrast-flow analysis and was used in this study as a surrogate measure of total coronary blood flow. The CS is typically found in the atrioventricular groove (Figure 17 and 37). The contours of the CS were drawn in the long-axis 2-chamber view and a small area of myocardium was contoured to provide background velocity correction (203). The software calculated CS flow in mL/s, which was multiplied by the heart rate to achieve CS flow in mL/min. This analysis was done in both stress and rest phases. Figure 37, below, demonstrates the technique of obtaining CS flow data from long-axis 2-chamber and 2D phase contrast-flow images.

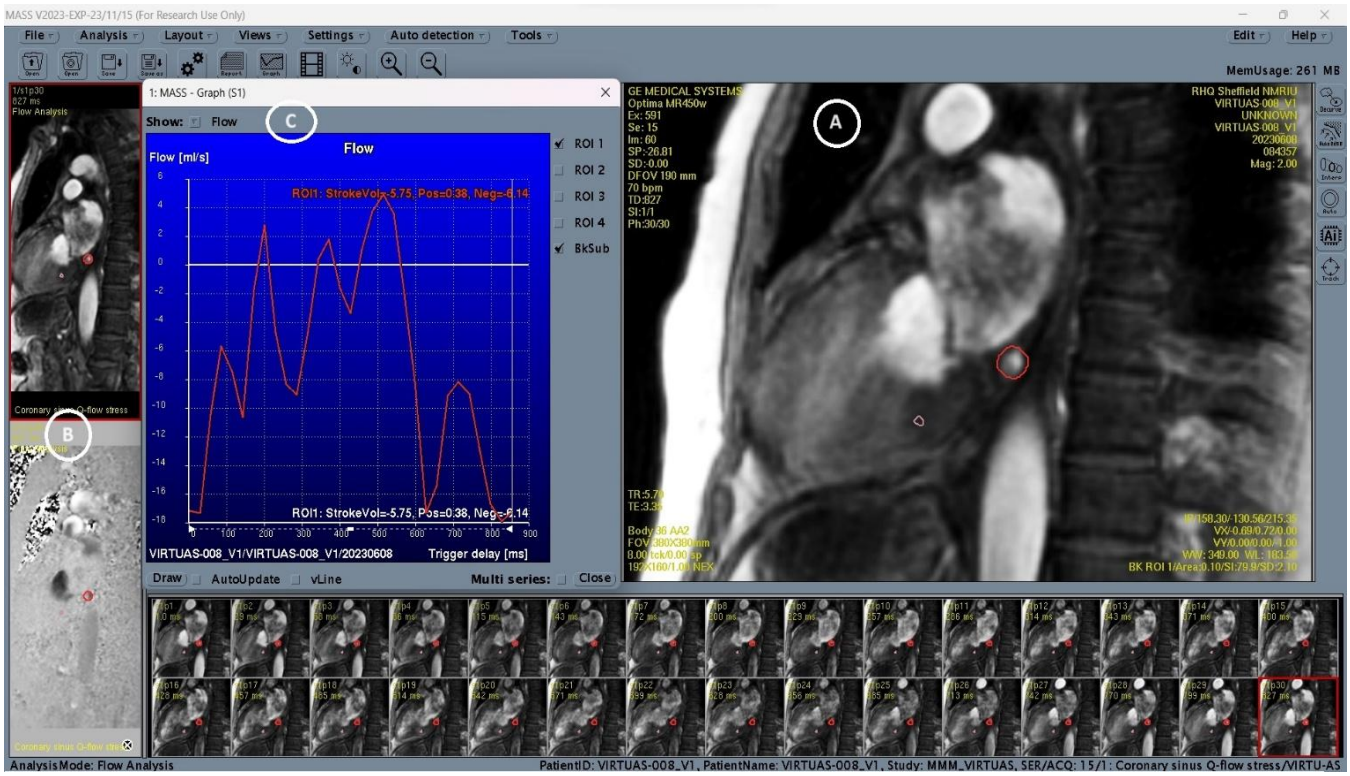


Figure 37. *MASS CS-flow reporting.*

Example of MASS software reporting technique for CS-flow using 2D phase contrast-flow analysis. 34**A**; The CS was contoured (red circle) and a region of adjacent myocardium was contoured for background correction (pink circle). 34**B**; The same regions of interest were marked on the phase contrast-flow image. 34**C**; Results for CS flow are provided across the whole cardiac cycle. The results demonstrate a CS flow of 5.75mL/s. This was multiplied by the heart rate to achieve CS flow in mL/min.

2.10.3 CMR in VIRTU-5 comparator group

Our research group have recently undertaken the VIRTU-5 study, utilising stress perfusion CMR in patients with stable CAD, without valvular heart disease. As in the VIRTU-AS study, patients who had physiologically significant CAD (FFR ≤0.8) received revascularisation with PCI, and those who did not were treated medically. All patients had consented to their CMR data being used across other studies within our research group, and as such, an appropriate selection of ten patients from the VIRTU-5 study were selected as a comparator group.

Pre-TAVI CMR studies from the VIRTU-AS study were used for this comparison and these were all performed after revascularisation (where appropriate) with PCI, or in patients who did not require coronary revascularisation. As such, ten comparator CMR studies from the VIRTU-5 project were carefully selected from patients who, similarly, had CMR after revascularision with PCI or did not require coronary revascularisation due to physiologically non-significant CAD. I therefore aimed to ensure that both groups had a similar degree of stable CAD (either fully revascularised CAD or physiologically non-significant CAD), the major variable being severe AS, in order to compare the effects of severe AS on MBF and LV parameters. All VIRTU-5 patients had their scans according to the same protocol outlined in this thesis and all scans were done in the same MRI scanner as this study, and were similarly supervised by senior radiography staff from The University of Sheffield and a clinical research fellow. All scans were reported by Dr Rebecca Gosling using MASS reporting software.

2.11 Echocardiography

All patients considered for TAVI had standard two-dimensional (2D) transthoracic echocardiography (TTE) as a SOC investigation. This formed the basis of their referral to the TAVI Heart Team. TTE was performed according to British Society of Echocardiography (BSE) guidance for TTE assessment of AS (216). Grading of AS severity was performed according to the ESC/EACTS guidance for the treatment of valvular heart disease and described earlier in this thesis (14). The TTE was performed and reported by a BSE accredited sonographer. As this is a SOC investigation, the data will remain on the STH PACS.

2.12 Statistics

Continuous data were presented as mean values with standard deviation (SD) or median values with interquartile range (IQR). Categorical data were presented as counts (n) and percentage values. Shapiro-Wilk testing was used to determine normality of data. Continuous paired data points, such as FFR, aCBF, CFR, MBF, CS-flow, LVM and LVEF, were analysed with paired t-test or Wilcoxson's signed rank test as appropriate. Paired categorical variables were analysed with McNemar's test. Correlations were analysed with Spearman's and Pearson's correlations as appropriate. A two-tailed P-value of <0.05 was considered to be significant. Statistical analysis and figures were produced using SPSS (Version 29, IBM, NY, USA).

2.13 Intended benefits of research

As an exploratory study, VIRTU-AS had the potential to produce hypothesis generating results, which in time could benefit a significant and growing cohort of patients. First, if coronary blood flow changed significantly following treatment with TAVI, and MVD regression was the key component of this increase, then it may deem many PCI procedures done prior to TAVI based on visual estimation of angiographic CAD unnecessary. This would avoid unnecessary risk exposure for patients, both procedurally and with respect to additional medication. As already described in section *1.3.7*, patients taking DAPT who receive TAVI have a significantly higher complication rates, primarily driven by excess bleeding. Furthermore, as patients who undergo TAVI tend to be elderly, they often have quite complex and calcific CAD, requiring complex PCI, which is associated with longer procedure times and higher complication rates. Avoidance of unnecessary PCI would also benefit patients with respect to their waiting time to TAVI. Second, observing the changes in aCBF, MVR, MBF and LV function after treatment with TAVI will also allow prediction of relative benefit from TAVI and PCI. If TAVI alone produces the desired changes in these parameters and renders patients free of angina (as angina in AS is commonly due to MVD, as described in section *1.5.4*) then PCI serves only to increase risk and waiting times for this frail cohort of patients. Third, reducing the number of procedures needed before TAVI reduces healthcare costs of excess PCI, hospital stays and medication costs. There are therefore also potential health economic benefits of studying coronary blood flow in AS. Although VIRTU-AS was not powered to detect statistically significant results, it was a useful exploratory study and the hypotheses generated may form the basis for larger future trials to help improve our understanding of coronary disease and blood flow in AS, the benefits of which are clear.

2.14 Outcomes

The primary outcomes of the VIRTU-AS study were the long-term (3-6 month) changes in absolute coronary blood flow and microvascular disease as measured invasively (at ICA), with cardiac MRI and virtuQ™, before and after TAVI. The parameters obtained for primary outcomes were aCBF (at rest and in hyperaemia), total MBF (at rest and in hyperaemia), MPR, IMR and CFR.

Secondary endpoints were changes in other coronary parameters or LV. These were FFR, RFR, resting Pd/Pa, LVEF, LVM, MRR, CS-flow (at rest and in hyperaemia). I measured general physical and psychological wellbeing using the SF-12 questionnaire.

I also compared pre-TAVI stress perfusion CMR data with a comparator group of patients without severe AS and a similar degree of CAD in order to examine the effects of severe AS on MBF and LV parameters.

Finally, as a sub-analysis of this study, I compared invasively measured FFR (mFFR) with vFFR in patients with severe AS.

Chapter 3: Results

3.1 Screening and enrolment

Patients were screened and enrolled into VIRTU-AS from September 2022 to August 2023. During this period, two to three TAVI procedures were being performed at STH per week and the elective waiting time was about 12 months. A total of 47 patients were formally approached for recruitment. A target of 20 patients was set, and although 22 patients attended for a pressure wire study, several were subsequently excluded and the final number who proceeded to TAVI was 12. Pre-TAVI characteristics data were processed for 17 patients. Pre-TAVI coronary physiology indices were processed for 15 patients, as two patients withdrew consent for the study. Three patients had a full set of pre-TAVI data obtained but later self-withdrew or were withdrawn (by the TAVI Heart Team) from the TAVI waiting list but allowed use of their data. Nine patients returned for a post-TAVI angiogram and pressure wire study. Coronary access could not be achieved in two patients. Three patients declined to return for post-TAVI angiogram. Pre-TAVI stress-perfusion CMR data were processed for 10 patients. Post-TAVI CMR data were processed for seven patients. One patient required PPM after TAVI and could not therefore have post-TAVI CMR and a second patient developed endocarditis while on the TAVI waiting list and needed SAVR, and was excluded. A third patient did not attend for post-TAVI CMR as they were removed from the TAVI waiting list. A consort diagram outlining the recruitment process is shown below in Figure 38.

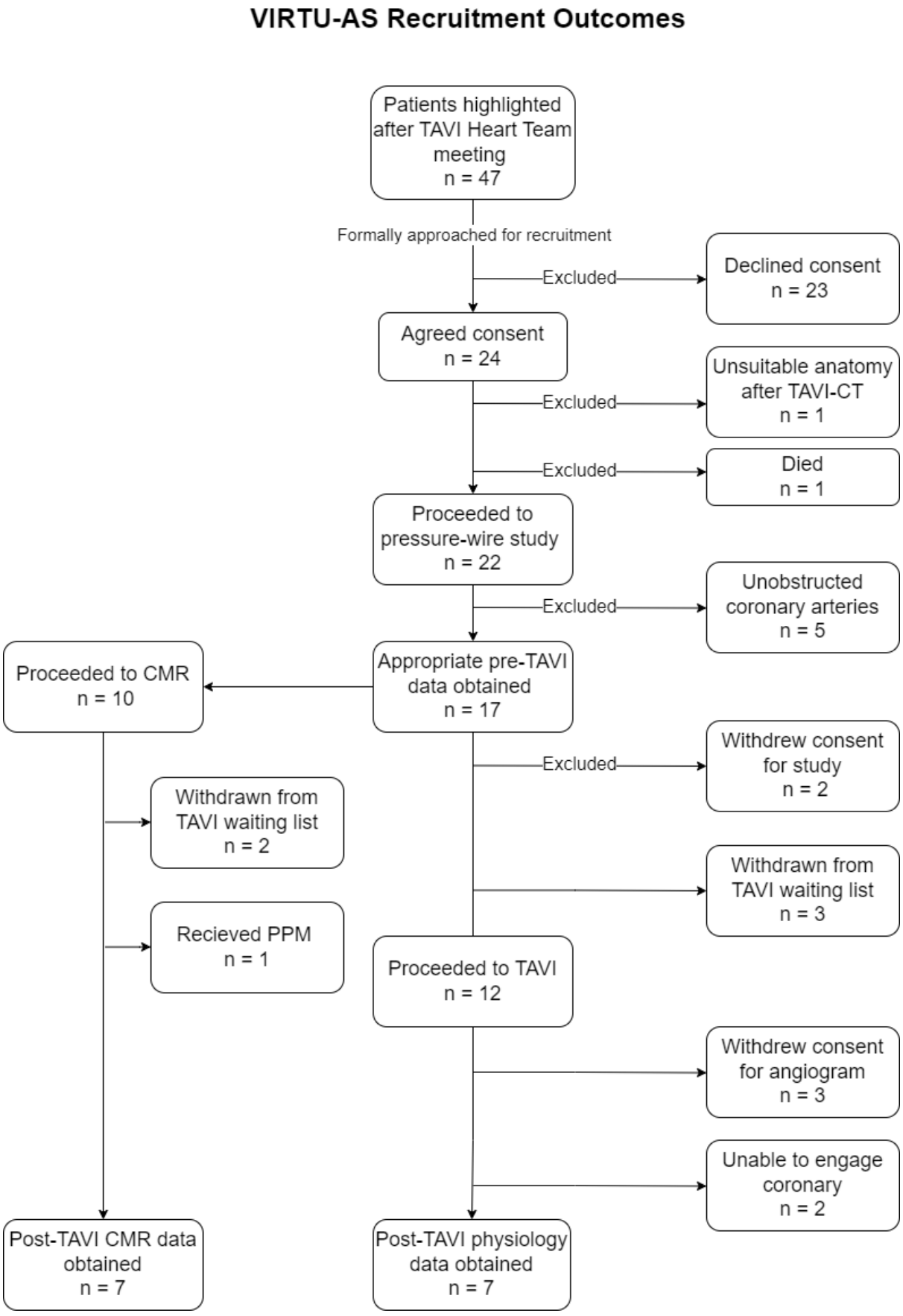


Figure 38. *VIRTU-AS recruitment flowchart.*

3.2 Clinical information

Clinical characteristics were presented for 17 patients who attended for ICA at the STH CCL and had any degree of CAD warranting pressure wire assessment. All figures relate to patient characteristics before treatment with TAVI. Table 7 summarises the baseline clinical characteristics, comorbidities, medications and clinical scores of patients in the VIRTU-AS study.

Baseline Clinical Characteristics	***n*=17**
Age	82±4.7
Male sex *n (%)*	11 (65%)
Female sex *n (%)*	6 (35%)
Weight (kg)	80±15
BMI	29±4.3
Heart Rate (bpm)	68±9
Comorbidities	
Hypertension *n (%)*	10 (59%)
Hyperlipidaemia *n (%)*	13 (76%)
Diabetes *n (%)*	1 (6%)
History of Smoking *n (%)*	6 (35%)
Chronic Obstructive Airways Disease *n (%)*	2 (11%)
Atrial Fibrillation *n (%)*	4 (23%)
Pacemaker *n (%)*	1 (6%)
Chronic Kidney Disease *n (%)*	2 (11%)
Peripheral Vascular Disease *n (%)*	2 (11%)
Previous PCI *n (%)*	12 (70%)
Previous Stroke or TIA *n (%)*	4 (23%)
Medication	

Aspirin *n (%)*	11 (65%)
P2Y12 inhibitor *n (%)*	11 (65%)
DOAC *n (%)*	4 (23%)
Statin *n (%)*	13 (76%)
Beta-blocker *n (%)*	11 (65%)
ACE-inhibitor *n (%)*	3 (17%)
Calcium Channel Blocker *n (%)*	4 (24%)
Loop Diuretic *n (%)*	7 (41%)
Clinical Scores	
Rockwood Frailty Score (see Appendix H)	4 (IQR 4-6)
New York Heart Association Score (NYHA) (see Appendix I)	2.7±0.5

Table 7. Baseline clinical characteristics.

Comorbidities, medications and clinical scores. Figures are given in counts and percentages, mean±SD or median with IQR.

3.3 Echocardiography results

All patients undergoing TAVI had SOC echocardiography and table 8 demonstrates the results obtained from SOC echocardiography pre- and post-TAVI. The primary values of interest were the parameters of AS severity.

	Pre-TAVI ***n*=17**	**Post-TAVI** ***n*=12**	**p-value**
LVEF (%)	53±5	54±6	*0.50*
LV End Diastolic Diameter (LVEDD) (mm)	45±5	44±5	*0.41*
Mean Transvalvular Gradient (mmHg)	47±9	11±5	*<0.05*
Peak Transvalvular Gradient (mmHg)	78±13	21±10	*<0.05*

Peak Transvalvular Flow Velocity (m/s)	4.4±0.3	2.1±0.5	*<0.05*
Aortic Valve Area (cm^2)	0.70±0.15	NA	
LV E/e'	17±5.5	15±6	*0.56*

Table 8. Echocardiography results.

3.4 Questionnaire Results

The SF-12 questionnaire was used before and after TAVI to assess overall physical and psychological wellbeing. Table 9 demonstrates the changes in the pre- and post-TAVI SF-12 scores.

	Baseline ***n*=17**	**Post-TAVI**	**p-value**
SF12 Physical score	35.2±9.3	45.2±11.2	*<0.05*
SF12 Psychological score	52.9±8.5	58.4±4	*0.57*

Table 9. SF12 Questionnaire results.

There was a significant improvement in SF12 physiological component score and no statistical change in the psychological index.

3.5 Invasive coronary physiology results

I aimed to achieve a full series of invasive coronary physiology data at baseline, post-PCI (where appropriate) and post-TAVI. All pre-TAVI procedures were done via the radial artery and performed exactly as described in section *2.8.1*. All patients tolerated IV Adenosine well and there were no significant post-procedural complications. Pre-TAVI coronary physiology data were presented for 15 patients. A total of 22 vessels (13 LAD, 6 RCA and 3 LCx) were interrogated with a full pressure wire study. Eight patients (10 vessels) received PCI and seven patients (12 vessels) did not receive PCI. Where appropriate, the same set of physiology data were repeated post-PCI for comparison with post-TAVI data. Nine patients attended for a

post-TAVI coronary physiology study and we were unable to gain coronary access in two. The reasons for exclusion and attrition are outlined in Figure 38.

3.5.1 Invasive coronary physiology in PCI cohort

Table 10 demonstrates the pre- and post-PCI invasive physiology data for the eight patients who received PCI (10 vessels).

	Baseline ***n*=10**	**Post-PCI** ***n*=10**	**p-value**
P_d rest (mmHg)	67±21	82±16	*<0.05*
P_a rest (mmHg)	89±18	90±15	*0.74*
P_a/ P_d rest (mmHg)	0.81 (0.7-0.86)	0.92 (0.88-0.93)	*<0.05*
RFR	0.68 (0.52-0.75)	0.89 (0.84-0.94)	*<0.05*
P_d hyperaemia (mmHg)	49±19	68±13	*<0.05*
P_a hyperaemia (mmHg)	72±21	79±15	*0.21*
FFR	0.74 (0.66-0.75)	0.87 (0.82-0.89)	*<0.05*
CFR	1.2 (1.1-1.5)	1.35 (1.2-1.6)	*0.61*
IMR (mmHg.sec)	22±14	21±14	*0.72*
MRR	2.3 (1.9-2.7)	1.78 (1.6-2.5)	*0.17*

Table 10. Coronary physiology results pre- and post-PCI.

There was a significant increase in the FFR (and RFR) after treatment with PCI, as can be appreciated in Figure 39 and 40. There was no change in the pre- and post-PCI CFR, IMR or MRR.

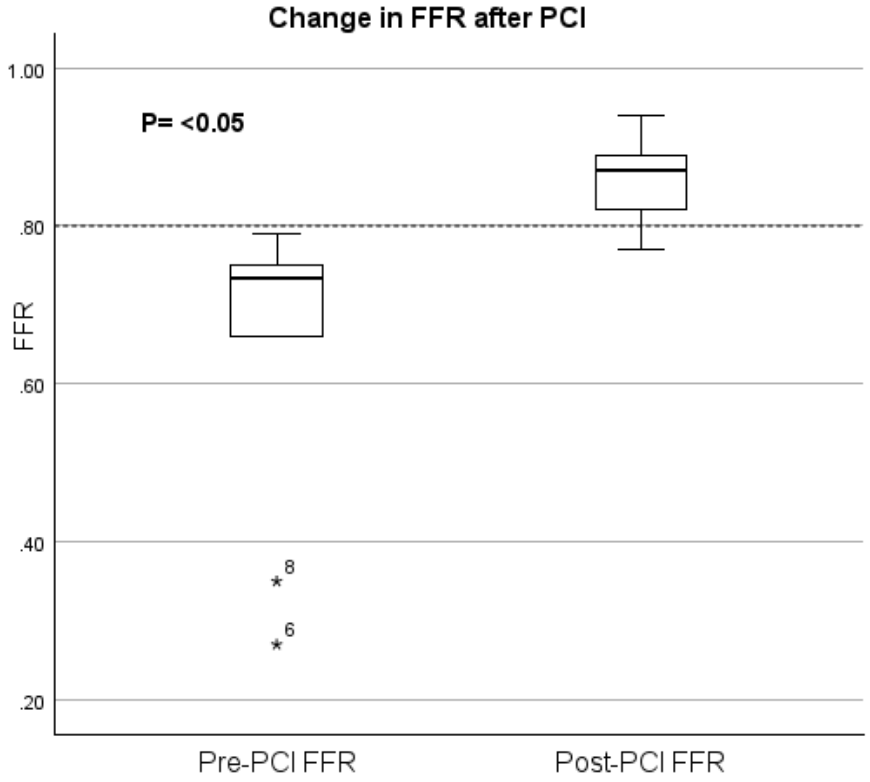


Figure 39. Change in mean FFR after PCI.

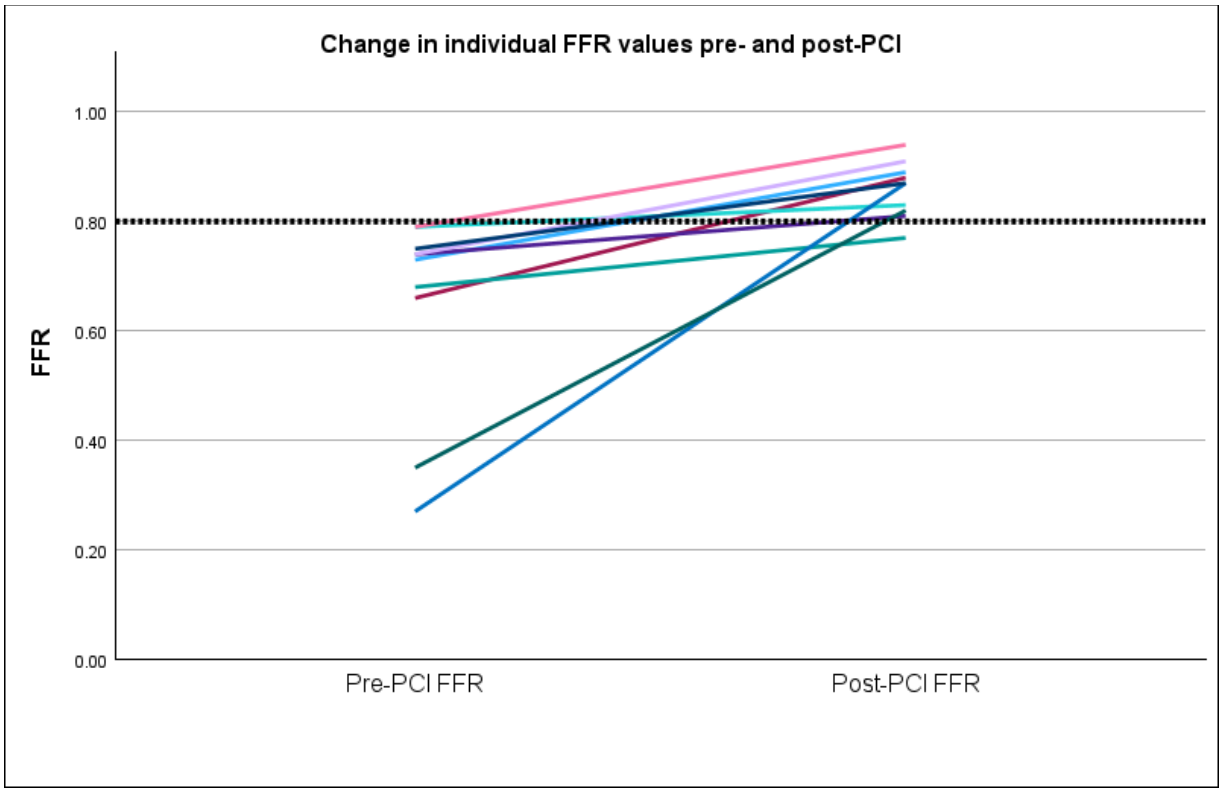


Figure 40. Changes in individual FFR values pre and post-PCI.

Table 11 demonstrates a comparison of the post-PCI physiology data (10 vessels) for the eight patients who required revascularisation with their post-TAVI physiology data (8 vessels) taken 3-6 months after TAVI.

	Post-PCI ***n*=10**	**Post-TAVI** ***n*=8**	**p-value**
P_d rest (mmHg)	82±16	84±17	*0.07*
P_a rest (mmHg)	90±15	90±17	*0.12*
P_a/ P_d rest (mmHg)	0.92 (0.88-0.93)	0.93 (0.91-0.97)	*0.09*
RFR	0.89 (0.84-0.94)	0.90 (0.90-0.93)	*0.17*
P_d hyperaemia (mmHg)	68±13	68±18	*0.51*
P_a hyperaemia (mmHg)	79±15	78±21	*0.81*
FFR	0.87 (0.82-0.89)	0.88 (0.86-0.89)	*0.054*
CFR	1.35 (1.2-1.6)	2.4 (2.1-2.8)	*<0.05*
IMR (mmHg.sec)	21±14	27±15	*0.33*
MRR	1.78 (1.6-2.5)	3.3 (2.7-3.7)	*<0.05*

Table 11. Coronary physiology results post-PCI and post-TAVI.

There was a significant increase in the invasively measured CFR post-TAVI in the PCI cohort (see figures 41 and 42). There was also a significant increase in the MRR (see figures 43 and 44). No other measured parameters reached statistical significance.

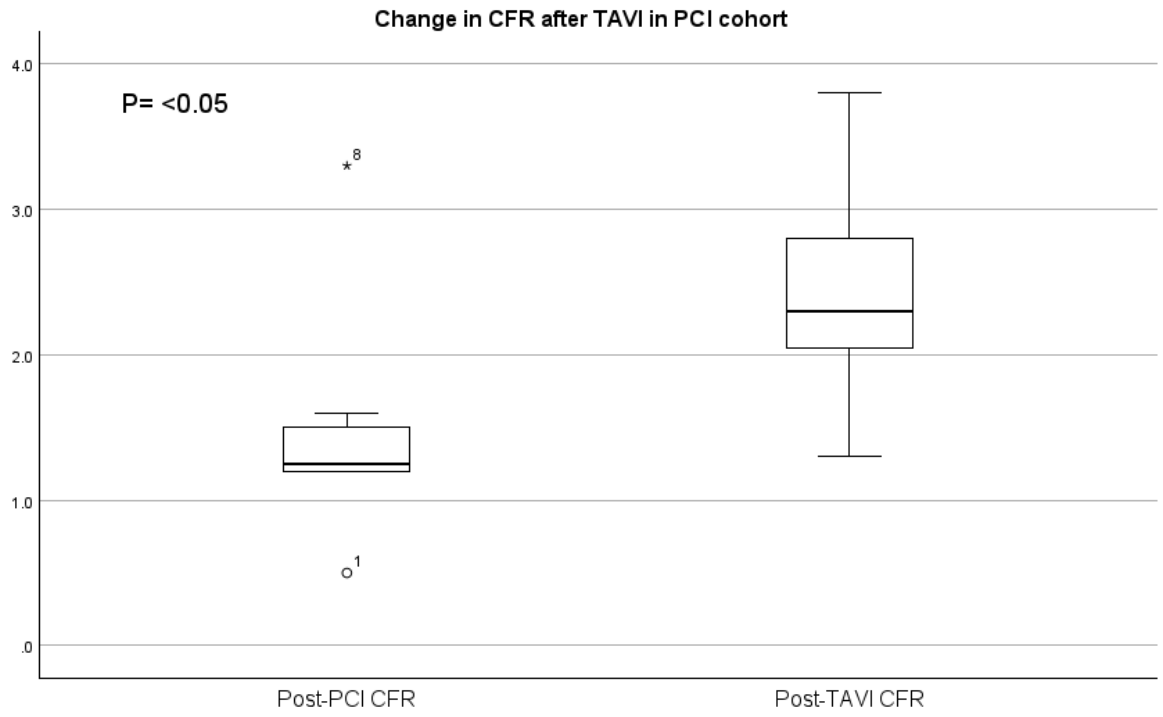


Figure 41. Changes in CFR after TAVI in PCI cohort.

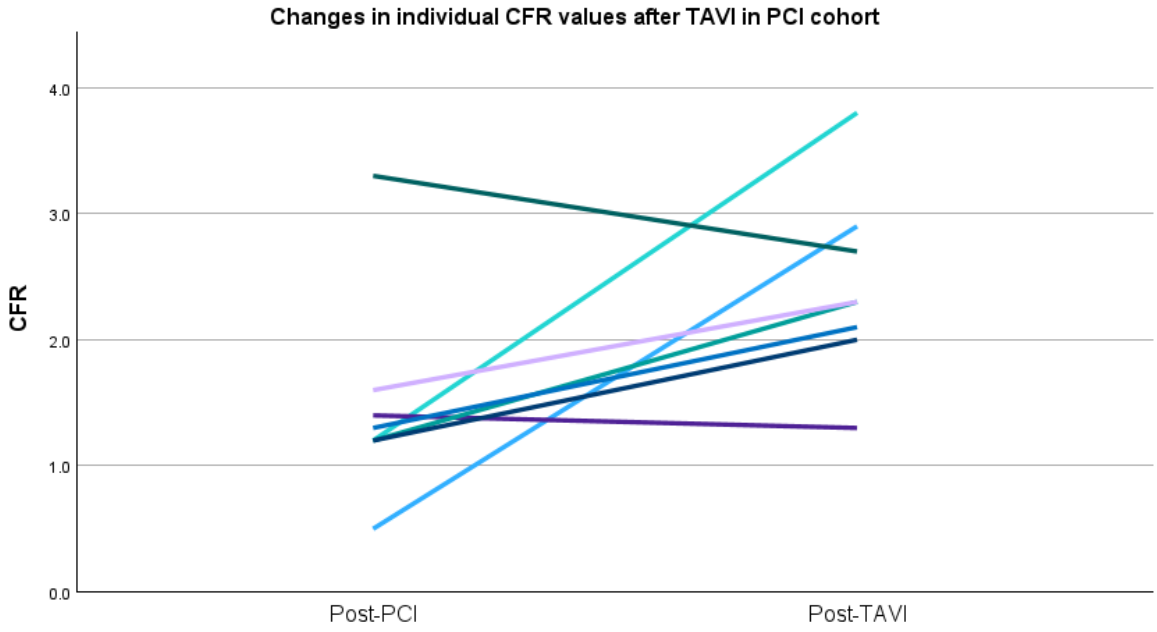


Figure 42. Changes in individual CFR values post-TAVI in PCI cohort.

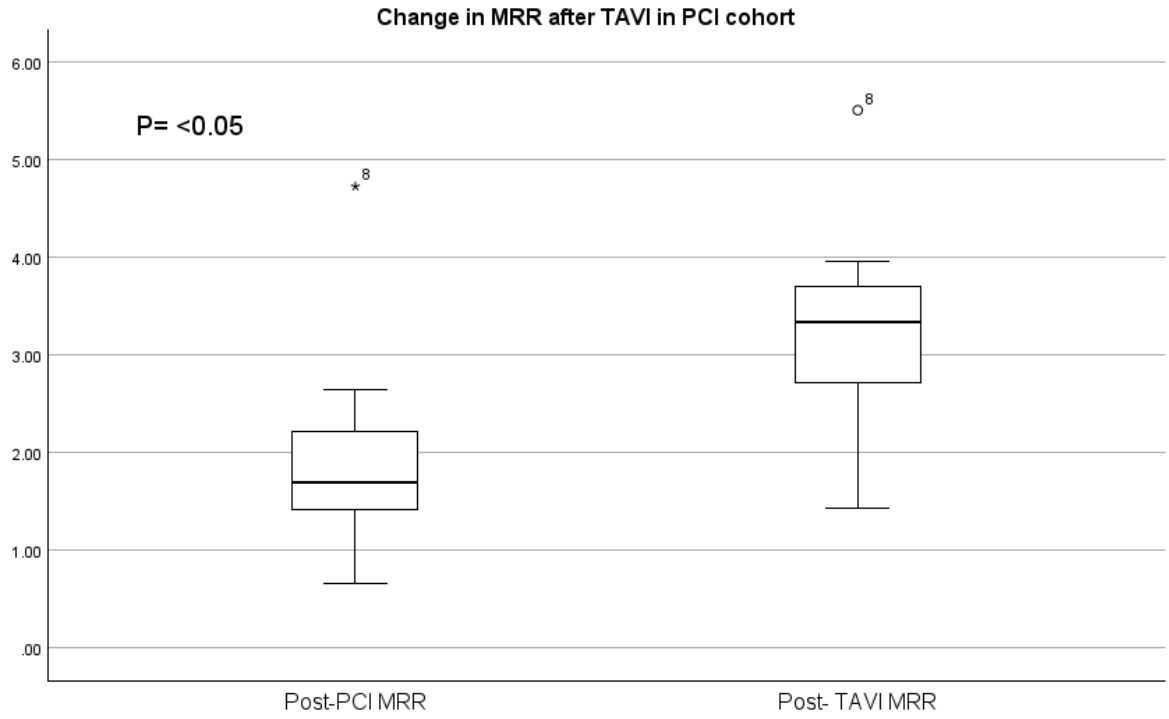


Figure 43. Box plot of changes in MRR post-TAVI in PCI cohort.

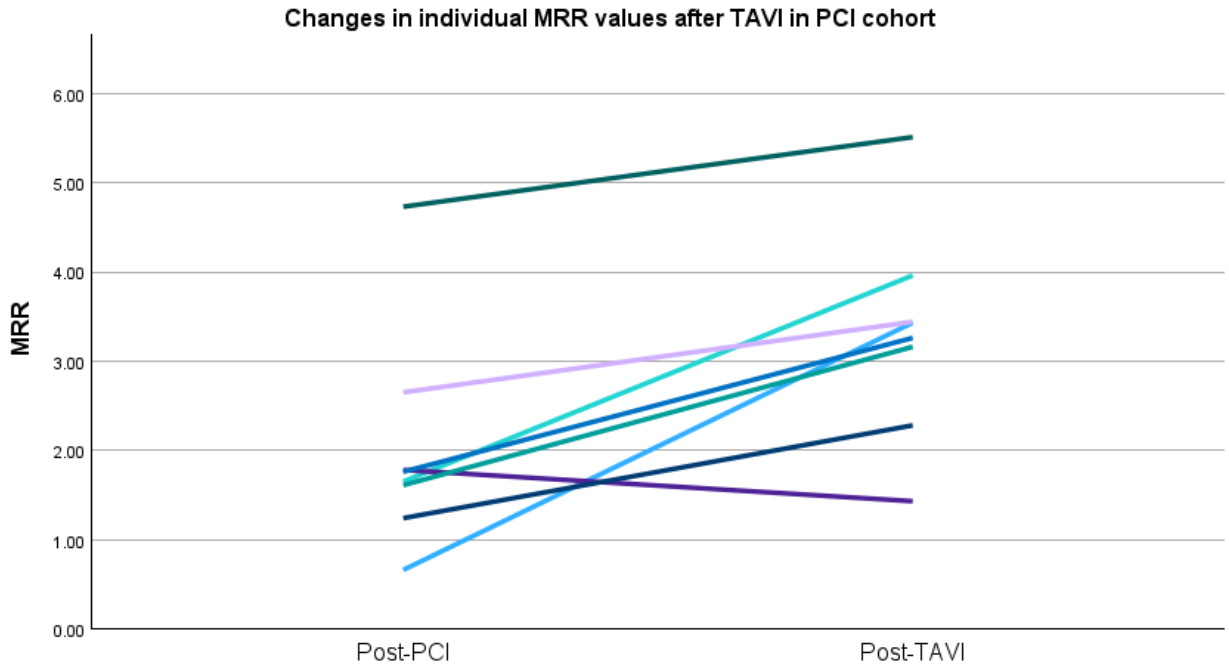


Figure 44. Changes in individual MRR values post-TAVI in PCI cohort.

3.5.2 Invasive coronary physiology in medical therapy cohort

Table 12 demonstrates a comparison of invasive physiology data for the seven patients (12 vessels) who did not receive PCI due to physiologically non-significant CAD with their post-TAVI physiology data. Two patients (two vessels in total) re-attended for post-TAVI angiography and pressure wire study.

	Baseline ***n*=12**	**Post-TAVI** ***n*=2**	**p-value**
P_d rest (mmHg)	85±20	77±13	*0.75*
P_a rest (mmHg)	91±20	78±13	*0.63*
P_a/ P_d rest (mmHg)	0.94 (0.93-0.98)	0.98	*0.50*
RFR	0.91 (0.85-0.94)	0.96	*0.72*
P_d hyperaemia (mmHg)	72±18	68.5±5	*0.43*
P_a hyperaemia (mmHg)	80±16	73.5±4	*0.38*
FFR	0.91 (0.85-0.94)	93.5	*0.18*
CFR	1.6 (1.2-1.9)	2.0	*0.76*
IMR (mmHg.sec)	19±10	21.5±17	*0.66*
MRR	2.0 (1.2-2.8)	2.3	*0.81*

Table 12. Coronary physiology results pre- and post-TAVI for patients who had functionally non-significant CAD.

No parameters reached statistical significance due to the low numbers of patients who re-attended.

3.5.3 Invasive coronary physiology in entire cohort

In order to compare changes in coronary physiology pre- and post-TAVI across the entire cohort, table 13 demonstrates the baseline invasive physiology results of the patients who

did not receive PCI, combined with the post-PCI coronary physiology of the patients who did receive PCI. Thus, combining the baseline data of patients who had physiologically non-significant CAD with the post-PCI data of the patients who required revascularisation, in order to demonstrate accurate and up-to-date pre-TAVI coronary physiology data. All pre-TAVI data presented here, therefore, represent the physiology at the close of each procedure. The post-TAVI physiology data used for statistical analysis were taken from the same vessels as in the pre-TAVI group for direct comparison.

	Pre-TAVI ***n*=22**	**Post-TAVI** ***n*=10**	**p-value**
P_d rest (mmHg)	84±18	83±16	*0.18*
P_a rest (mmHg)	91±18	88±17	*0.39*
P_a/ P_d rest (mmHg)	0.93 (0.89-0.96)	0.95 (0.91-0.98)	*0.052*
RFR	0.91 (0.84-0.94)	0.91 (0.90-0.96)	*0.13*
P_d hyperaemia (mmHg)	70±16	68±16	*0.69*
P_a hyperaemia (mmHg)	80±15	77±18	*0.98*
FFR	0.87 (0.82-0.90)	0.89 (0.86-0.92)	*<0.05*
CFR	1.45 (1.2-1.7)	2.3 (2.0-2.7)	*<0.05*
IMR (mmHg.sec)	20±12	26±15	*0.56*
MRR	1.8 (1.3-2.8)	3.2 (2.3-3.4)	*<0.05*

Table 13. Coronary physiology pre- and post-TAVI in entire cohort.

There was a significant increase in the CFR and MRR across the entire cohort after TAVI (figures 45-48) but no significant change in the IMR pre- and post-TAVI (figures 49 and 50). There was a significant increase in the FFR when measured 3-6 months after TAVI (figures 51 and 52).

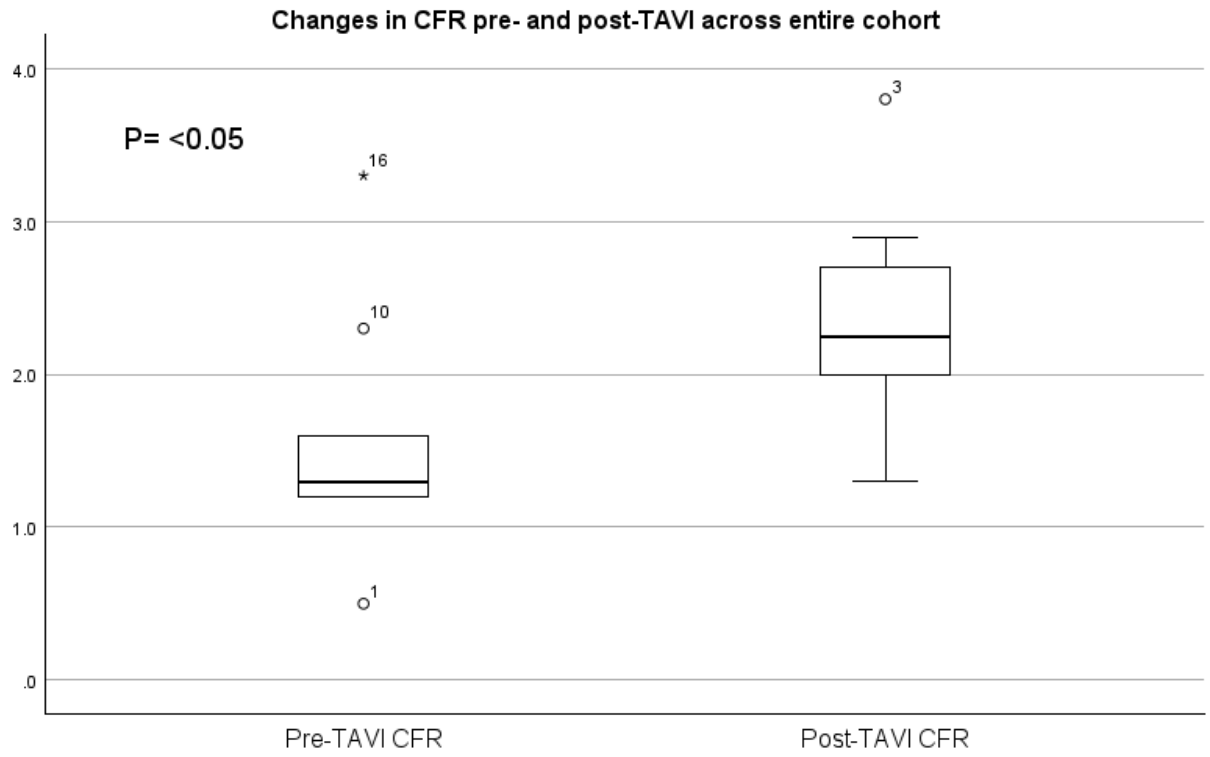


Figure 45. Change in CFR post-TAVI in entire cohort.

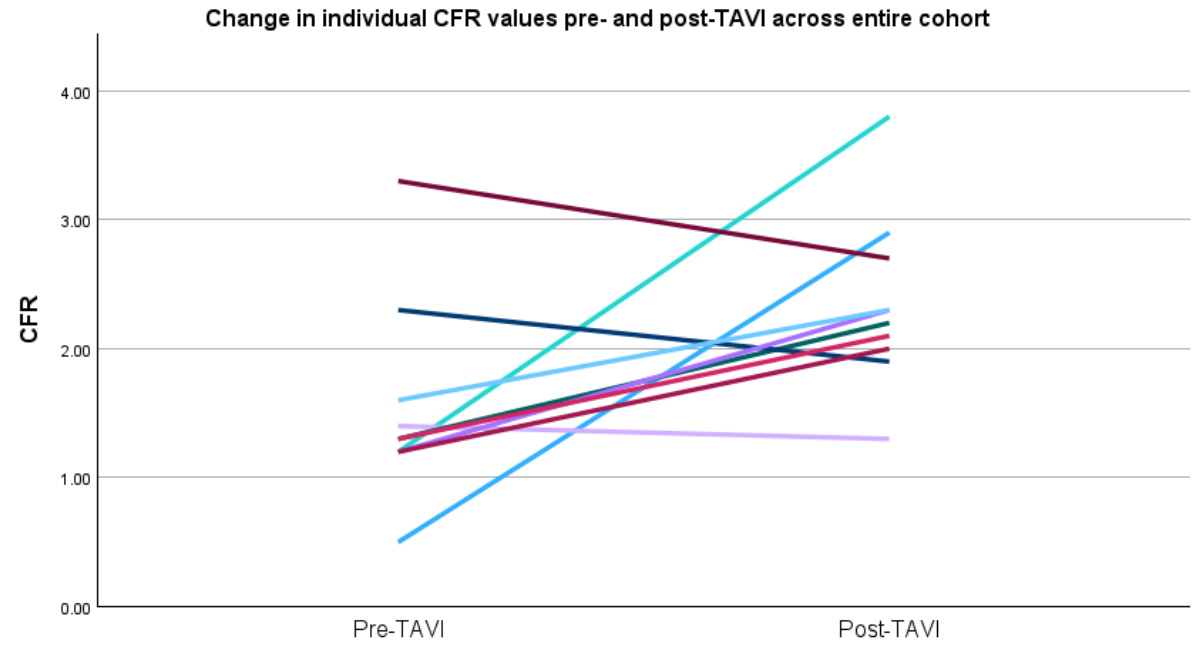


Figure 46. Change in individual CFR values post-TAVI across entire cohort.

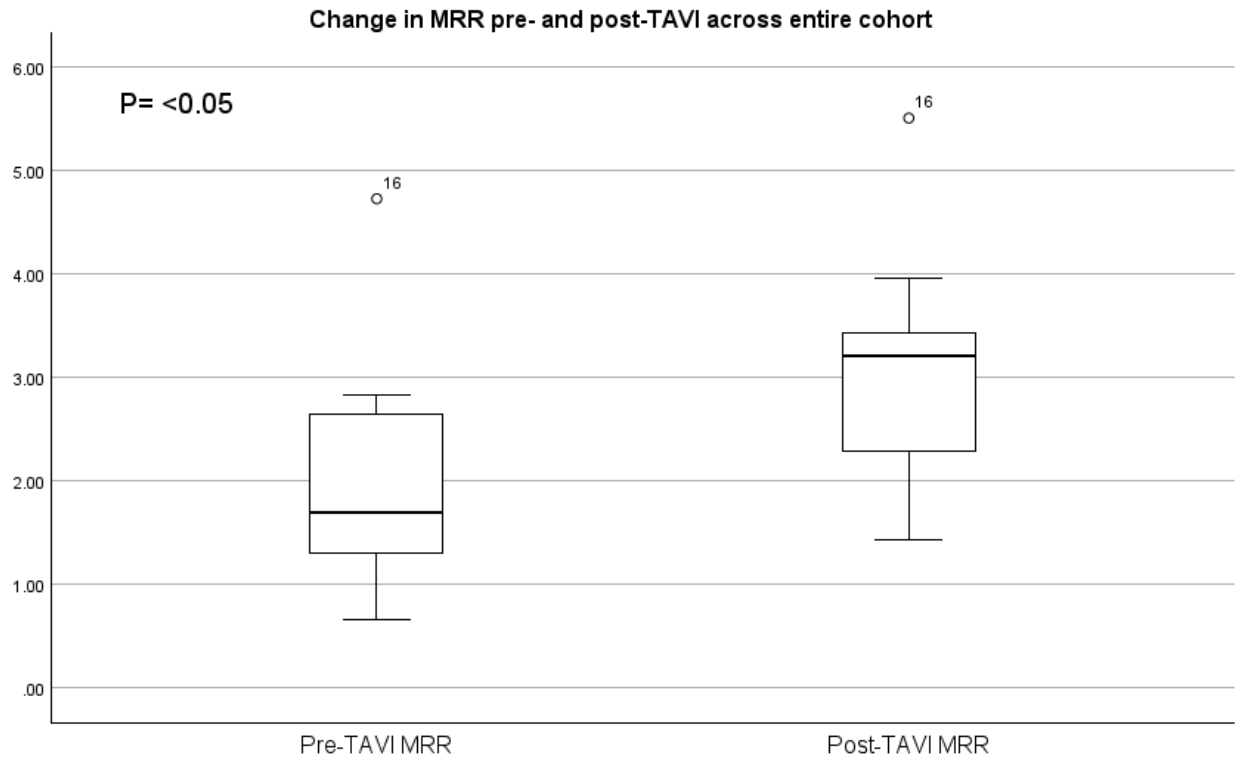


Figure 47. Change in MRR post-TAVI across entire cohort.

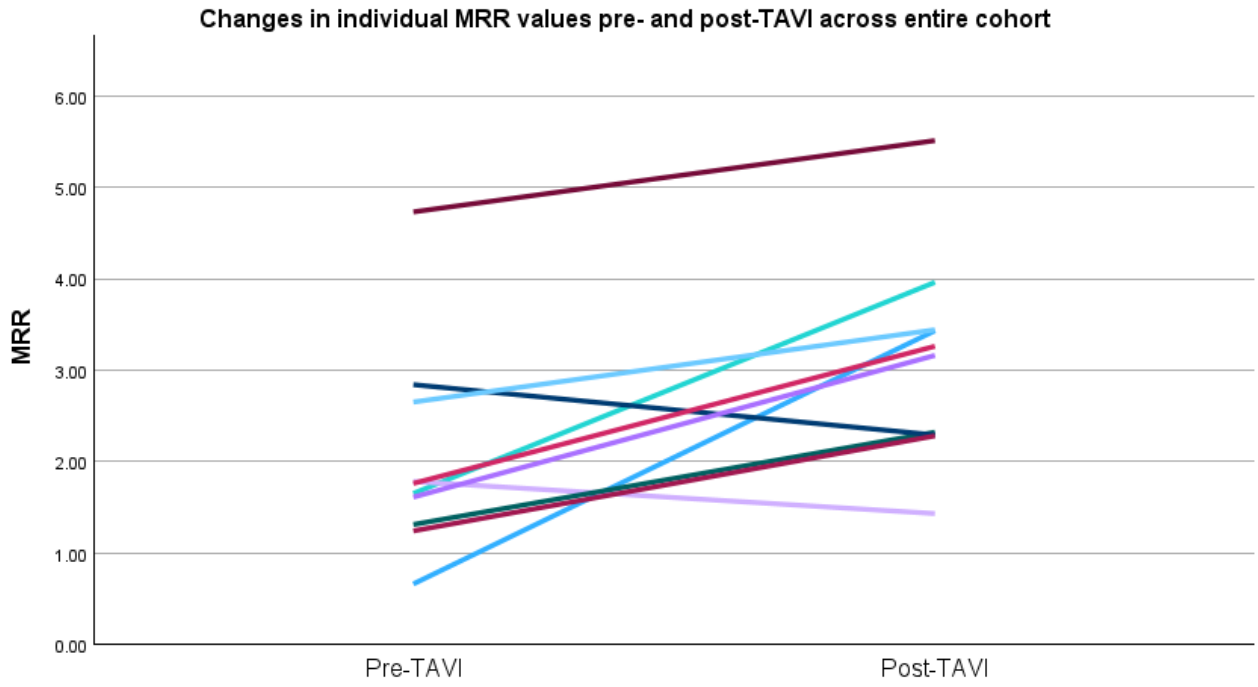


Figure 48. Change in individual MRR values post-TAVI across entire cohort.

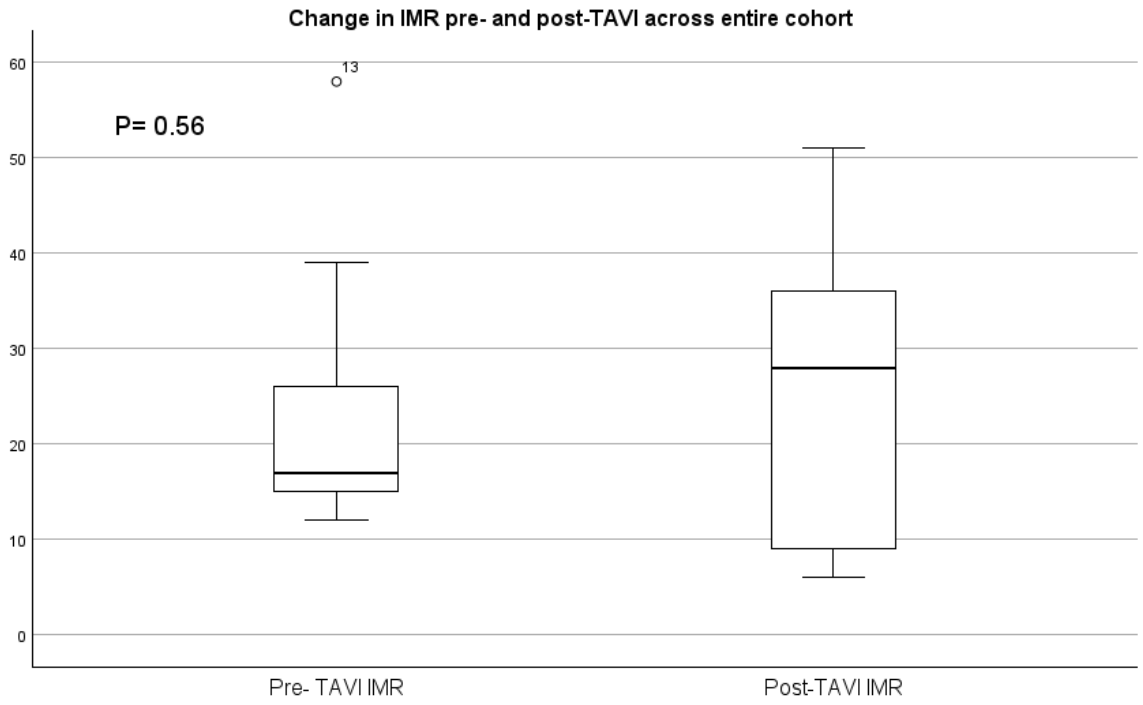


Figure 49. Changes in IMR pre- and post-TAVI across entire cohort.

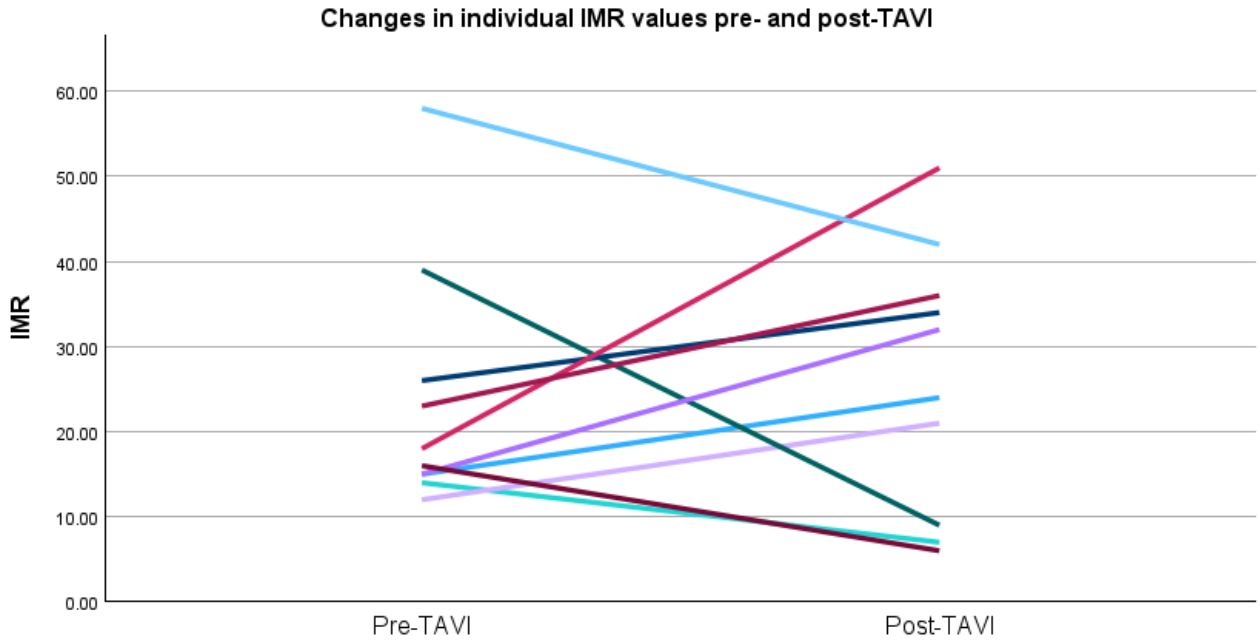


Figure 50. Changes in individual IMR values pre- and post-TAVI across entire cohort.

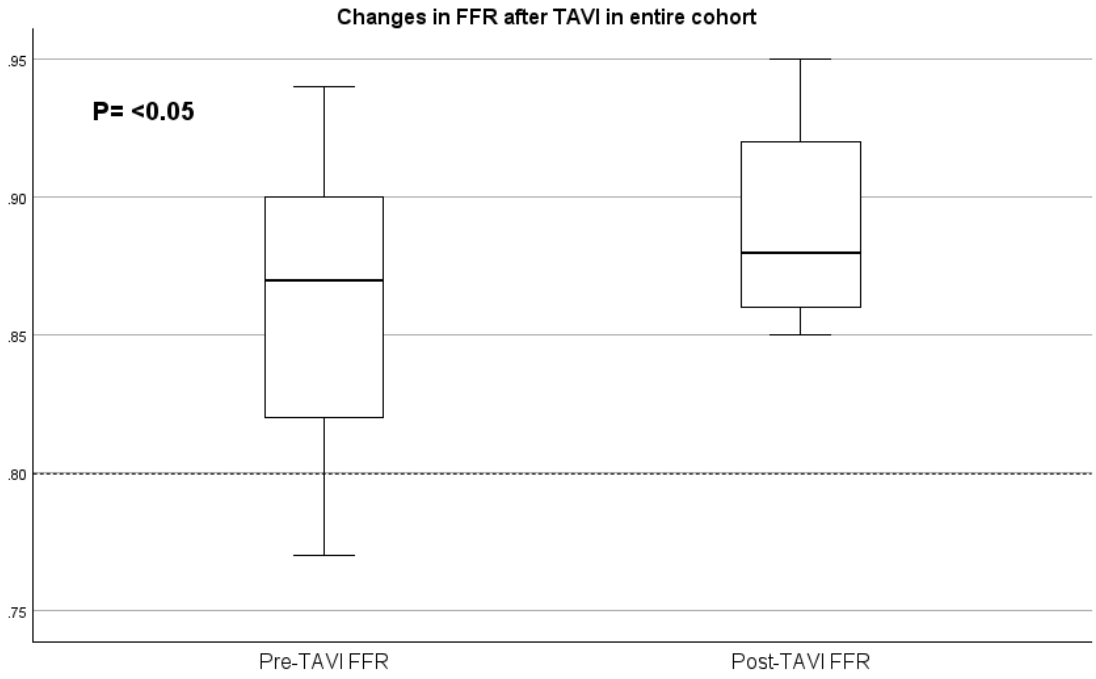


Figure 51. Changes in FFR after TAVI in entire cohort.

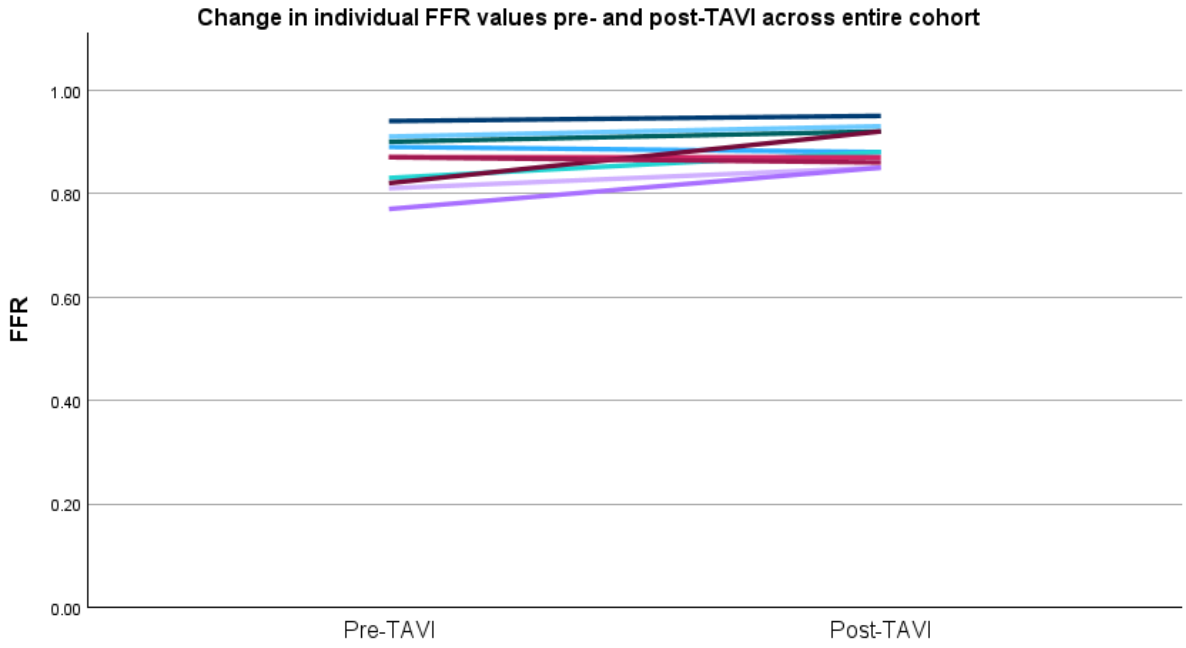


Figure 52. Change in individual FFR values post-TAVI across entire cohort.

3.6 Computational fluid dynamics results

All vessels were segmented and processed through the VIRTUheart™ workflow for analysis through virtuQ™. There were no processing errors and the software successfully modelled segmentations for all vessels. The same vessels were analysed as those which had invasive coronary physiology data measured and the results will be displayed in the same order.

3.6.1 Computational fluid dynamics results in PCI cohort

Table 14 demonstrates the pre- and post-PCI CFD data for the eight patients who received PCI (10 vessels).

	Pre-PCI ***n*=10**	**Post-PCI** ***n*=10**	**p-value**
Baseline flow in (mL/min)	149±35	245±81	*<0.05*
Baseline flow out (mL/min)	58±29	73±38	*0.337*
Baseline MVR (mmHg.min/mL)	1.2 (0.5-1.5)	1.2 (0.8-1.6)	*0.855*
Hyperaemic flow in (mL/min)	170±28	286±102	*<0.05*
Hyperaemic flow out (mL/min)	66±30	91±58	*0.224*
Hyperaemic MVR (mmHg.min/mL)	0.56 (0.4-1.3)	0.82 (0.5-1.3)	*0.438*
CFR	1.2 (0.93-1.5)	1.1 (1.0-1.4)	*0.828*

Table 14. CFD results at baseline and post-PCI in the PCI cohort.

There was a significant increase in baseline and hyperaemic coronary inlet flow after PCI. There was no significant change in coronary outlet flow, however this figure fails to completely account for side branch flow and vessel leakage. There was no difference in MVR or CFR after PCI. Table 15 demonstrates a comparison of the post-PCI CFD data for the eight patients (10 vessels) who required revascularisation with their post TAVI CFD data.

	Post-PCI ***n*=10**	**Post-TAVI** ***n*=8**	**p-value**
Baseline flow in (mL/min)	245±81	170±81	*<0.05*
Baseline flow out (mL/min)	73±38	55±33	*0.16*
Baseline MVR (mmHg.min/mL)	1.2 (0.8-1.6)	1.3 (1.2-2.7)	*0.21*
Hyperaemic flow in (mL/min)	286±102	229±61	*0.15*
Hyperaemic flow out (mL/min)	91±58	85±39	*0.94*
Hyperaemic MVR (mmHg.min/mL)	0.82 (0.5-1.3)	0.85 (0.8-1.0)	*0.77*
CFR	1.1 (1.0-1.4)	1.3 (1.1-2.2)	*0.25*

Table 15. CFD results post-PCI and post-TAVI in the PCI cohort.

Among the PCI cohort, following treatment with TAVI, there was a significant reduction in the baseline coronary inlet flow (figures 53 and 54). There was no change in hyperaemic flow and no other parameters reached statistical significance.

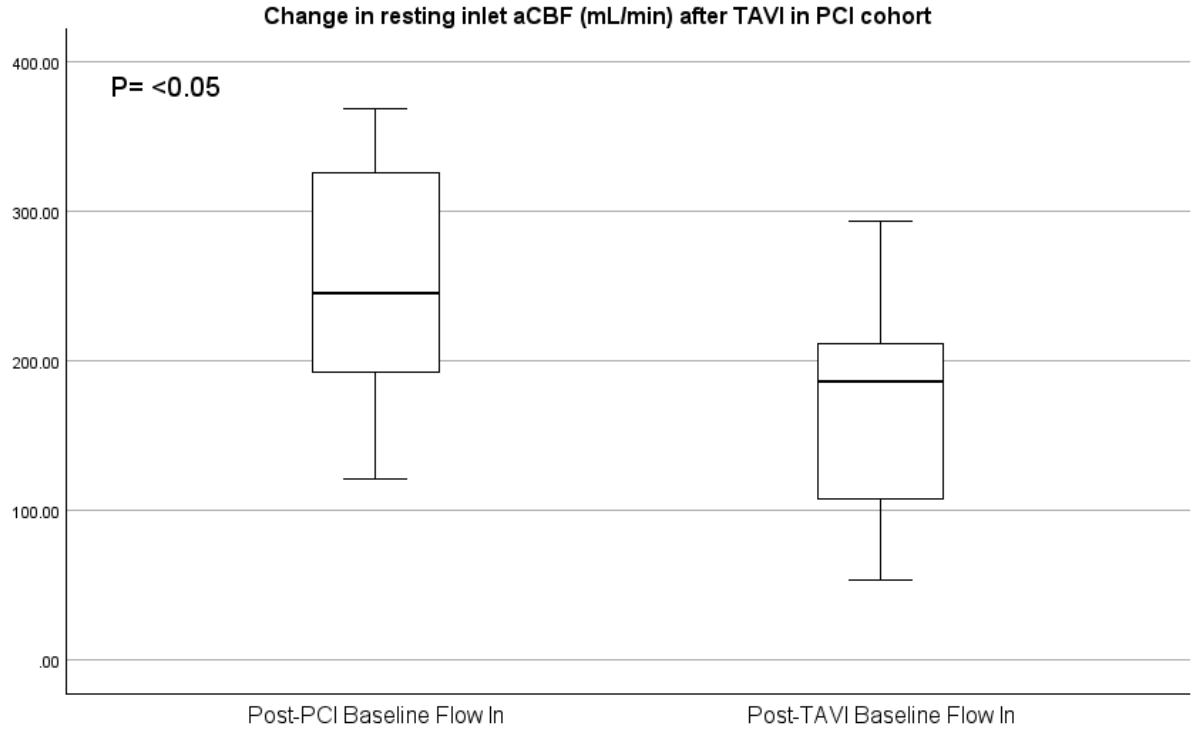


Figure 53. Changes in baseline aCBF (mL/min) post-TAVI in PCI cohort.

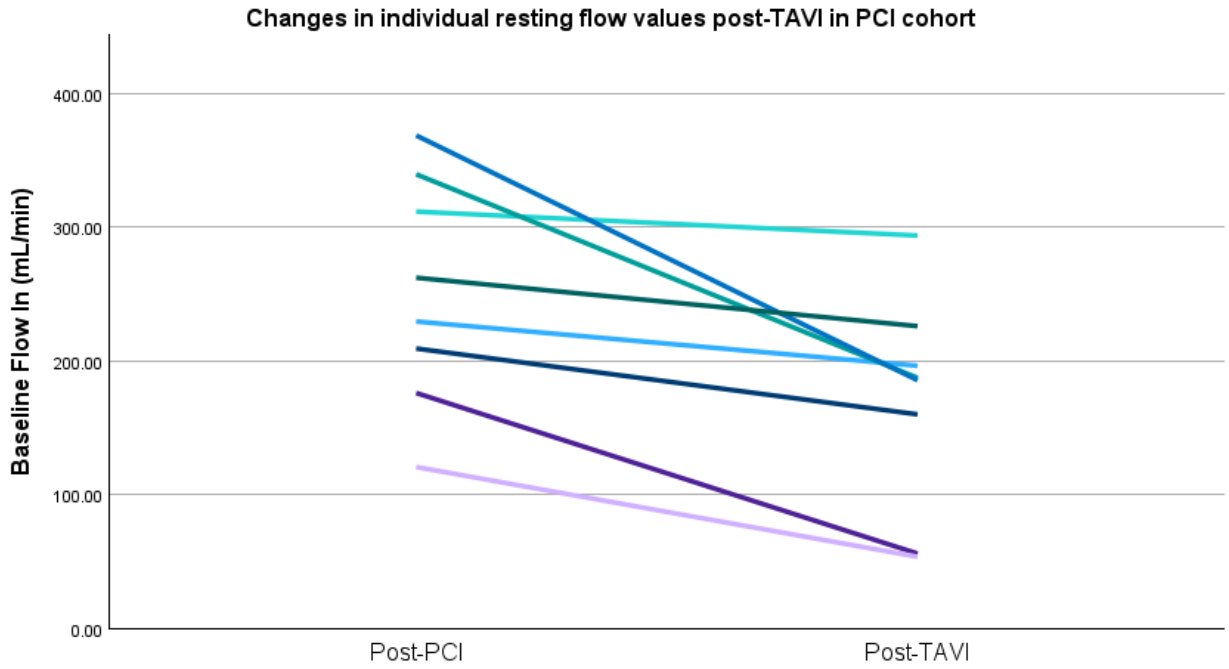


Figure 54. Changes in individual resting inlet flow values in mL/min post-TAVI in PCI cohort.

3.6.2 Computational fluid dynamics results in medical therapy cohort

Table 16 demonstrates a comparison of CFD data for the seven patients (12 vessels) who had physiologically non-significant CAD with their post-TAVI CFD data (two vessels).

	Baseline ***n*=12**	**Post-TAVI** ***n*=2**	**p-value**
Baseline flow in (mL/min)	123±53	49±31	*0.18*
Baseline flow out (mL/min)	54±46	31±28	*0.18*
Baseline MVR (mmHg.min/mL)	2.1 (1.1-2.7)	3.7	*0.45*
Hyperaemic flow in (mL/min)	188±84	160±67	*0.07*
Hyperaemic flow out (mL/min)	80±60	97±72	*0.18*

Hyperaemic MVR (mmHg.min/mL)	1.2 (0.5-1.5)	0.88	*0.20*
CFR	1.4 (1.1-1.7)	3.6	*0.18*

Table 16. CFD results at baseline and post-TAVI in the medical therapy cohort.

No measures reached statistical significance in the medical therapy cohort due to the low re-presentation rate.

3.6.3 Computational fluid dynamics results in entire cohort

Table 17 demonstrates the baseline CFD results of the patients who did not receive PCI, merged with the post-PCI CFD data of the patients who received PCI to form the pre-TAVI data (22 vessels). The post-TAVI data was formed of all patients who returned for a follow up angiogram (10 vessels) in order to perform a direct comparison between the groups.

	Pre-TAVI ***n*=22**	**Post-TAVI** ***n*=10**	**p-value**
Baseline flow in (mL/min)	178±90	146±89	*<0.05*
Baseline flow out (mL/min)	63±42	50±32	*0.07*
Baseline MVR (mmHg.min/mL)	1.5 (0.9-2.2)	2.3 (1.2-3.6)	*0.092*
Hyperaemic flow in (mL/min)	232±104	215±66	*0.13*
Hyperaemic flow out (mL/min)	85±58	87±42	*0.95*
Hyperaemic MVR (mmHg.min/mL)	1.1 (0.5-1.3)	0.9 (0.8-1.0)	*0.51*
CFR	1.2 (1.1-1.5)	1.4 (1.2-3.0)	*0.08*

Table 17. CFD data pre- and post-TAVI for the entire cohort.

There was a significant reduction in the baseline aCBF (mL/min) following TAVI (figures 55 and 56) but no significant change in hyperaemic aCBF (figures 57 and 58). The MVR (mmHg.min/mL) did not change either at baseline or during hyperaemia post-TAVI.

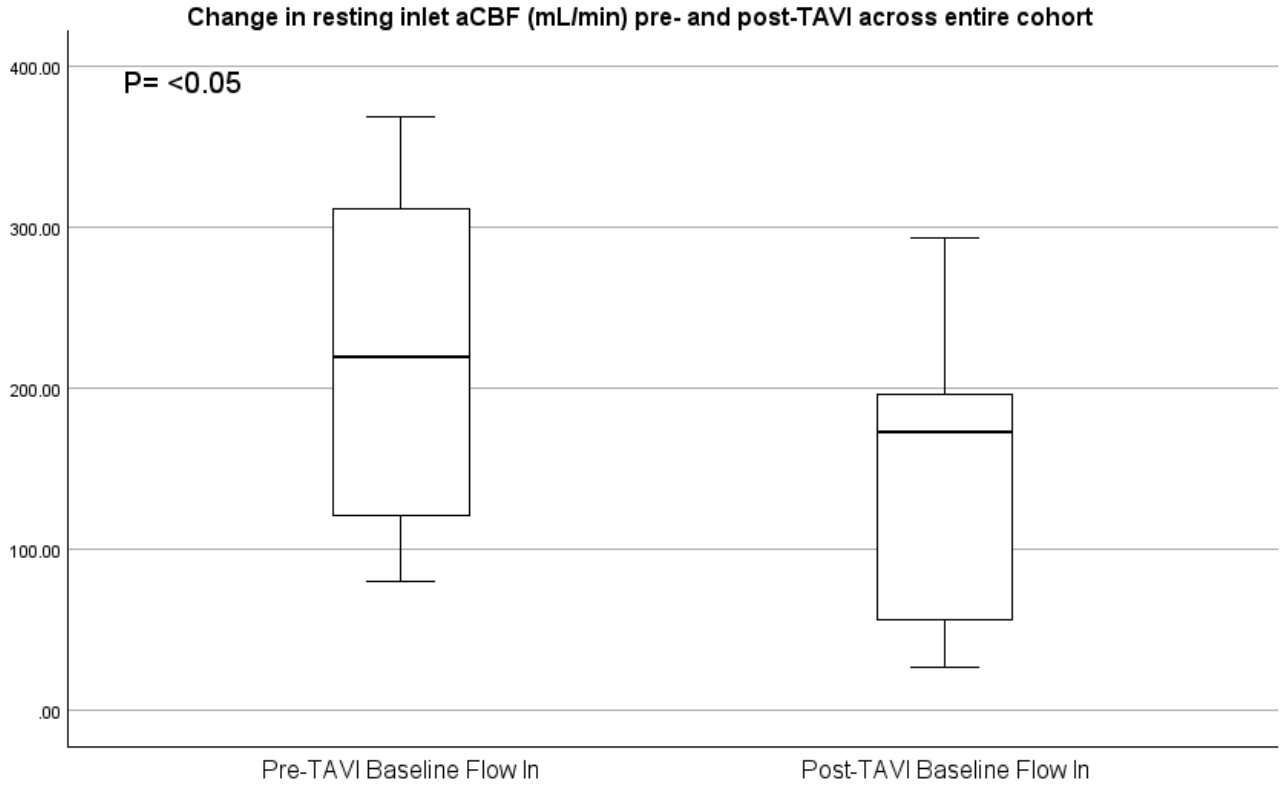


Figure 55. Changes in resting aCBF (mL/min) post-TAVI in entire cohort.

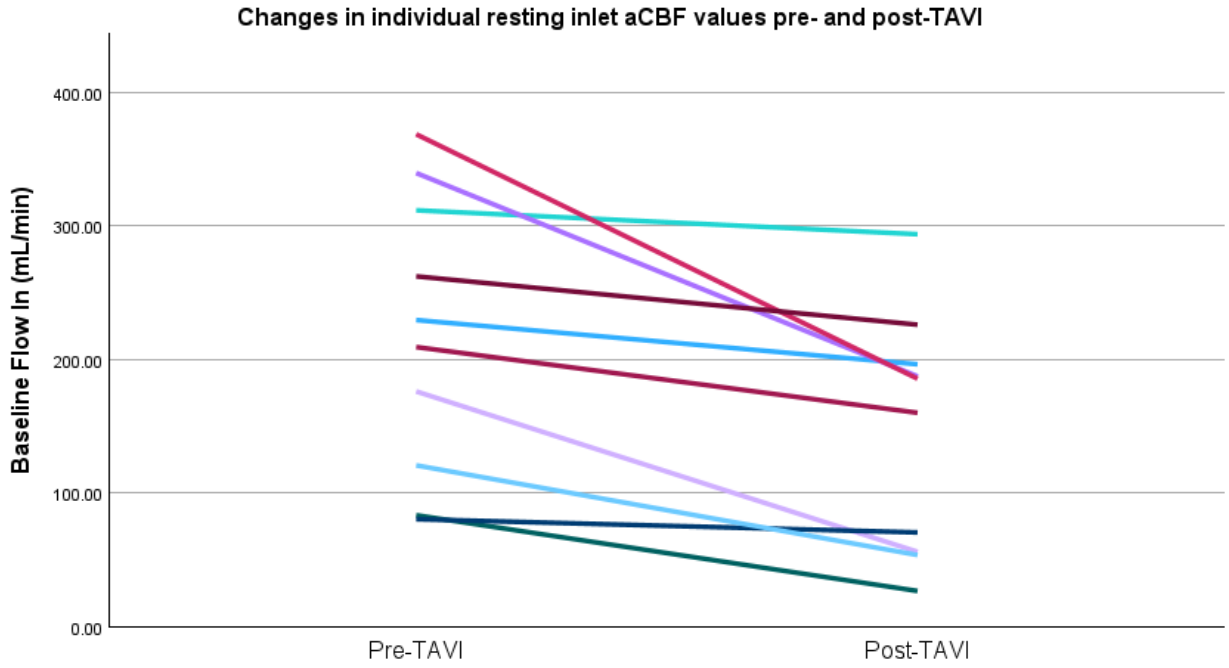


Figure 56. Changes in individual resting aCBF values pre- and post-TAVI across entire cohort.

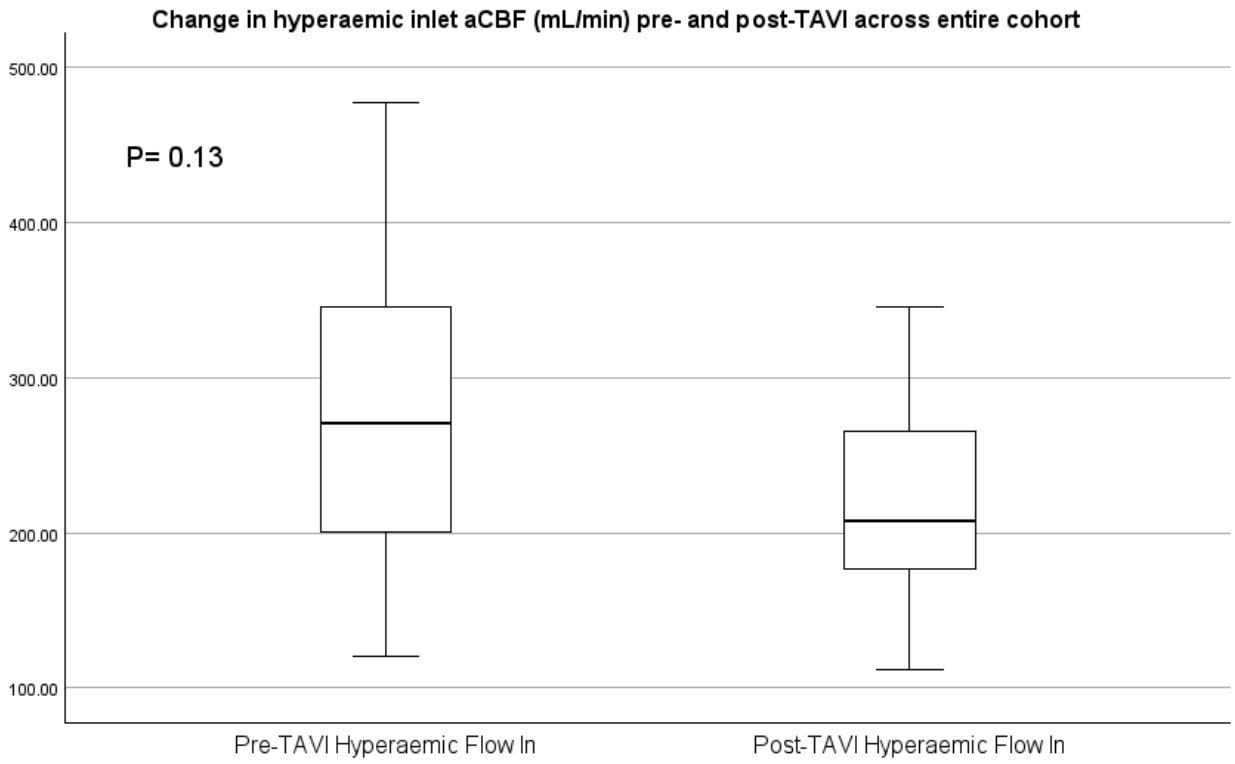


Figure 57. Changes in hyperaemic aCBF (mL/min) post-TAVI across entire cohort.

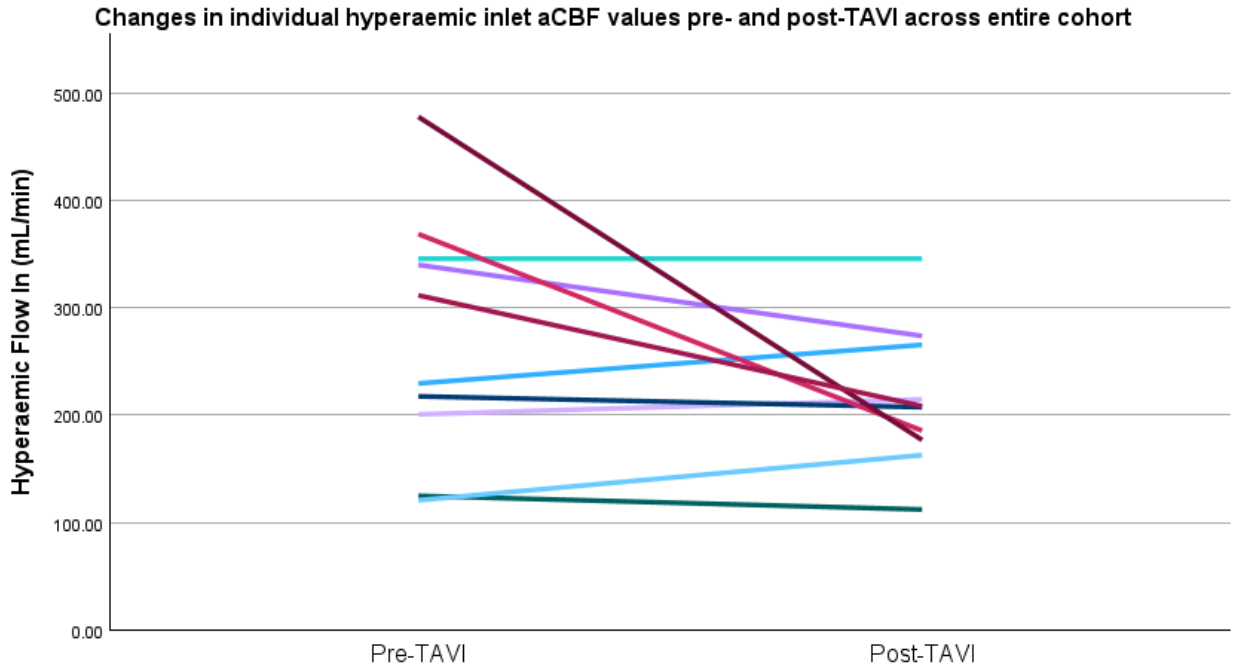


Figure 58. Changes in individual hyperaemic aCBF values pre- and post-TAVI.

3.6.4 VIRTUheart™ vs invasive FFR Results

In all 22 vessels, the vFFR was measured using VIRTUheart™. This was compared with the invasive mFFR to assess for correlation. In all cases used for this sub-analysis, the vFFR was taken from the pre-PCI angiogram (mFFR ≤0.80) or the baseline angiogram (mFFR >0.80) and like for like values were compared. The mean mFFR was 0.78 (±0.2) and the mean vFFR was 0.83 (±0.1). The accuracy, sensitivity, specificity, positive predictive value and negative predictive value were 82%, 64%, 100%, 100% and 73% respectively. The ROC-curve AUC was 96% (95% CI: 0.82-1.03) (figure 59). There was good correlation between mFFR and vFFR (R= 0.76, P= <0.001) (see figure 60). Bland Altman analysis demonstrated a mean difference of -0.051 (see figure 61).

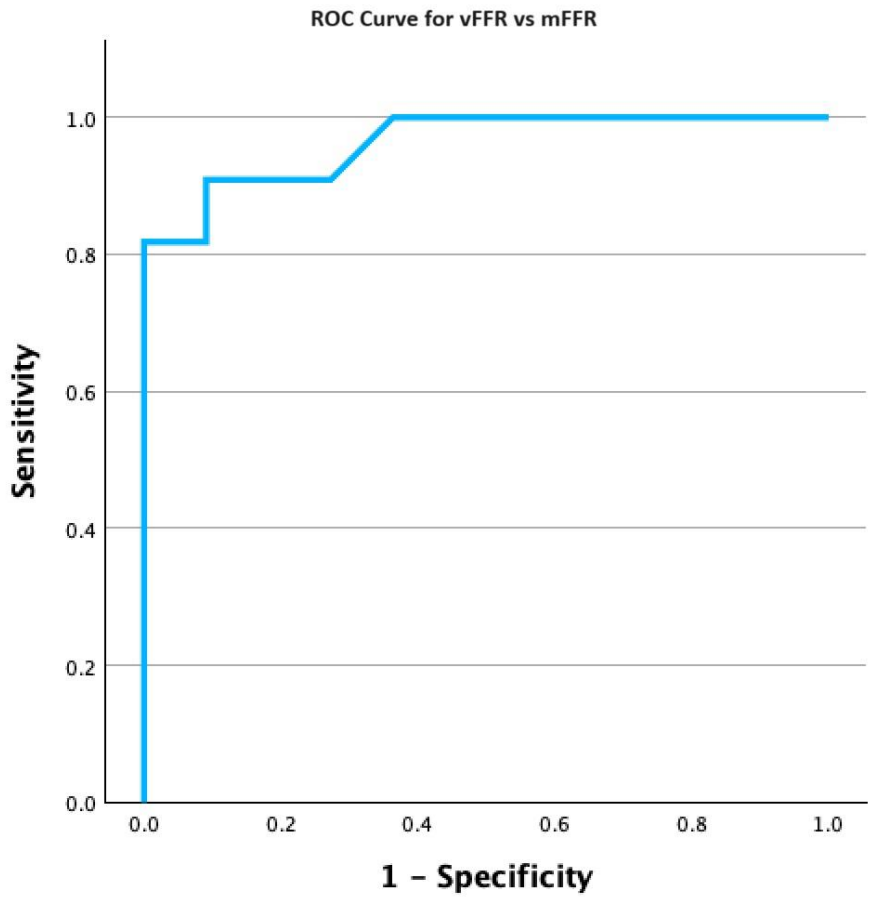


Figure 59. ROC curve for mFFR vs vFFR. AUC 0.96.

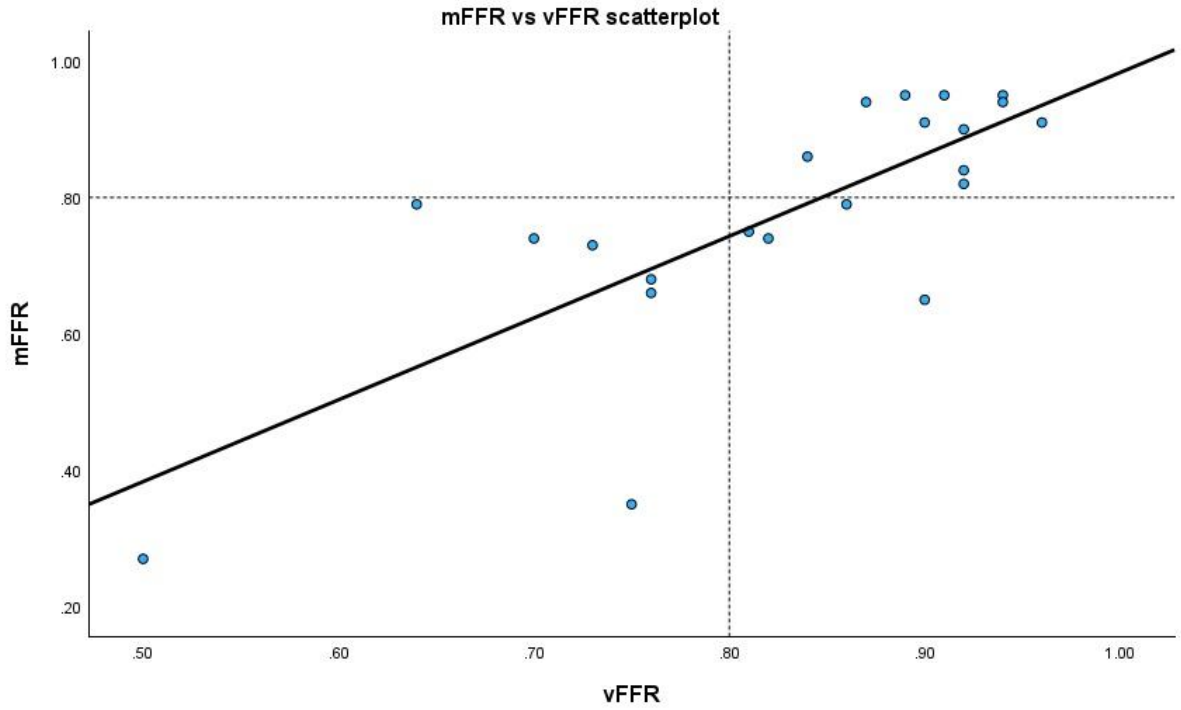


Figure 60. Scatterplot showing correlation between vFFR and mFFR. R= 0.76, P= <0.001.

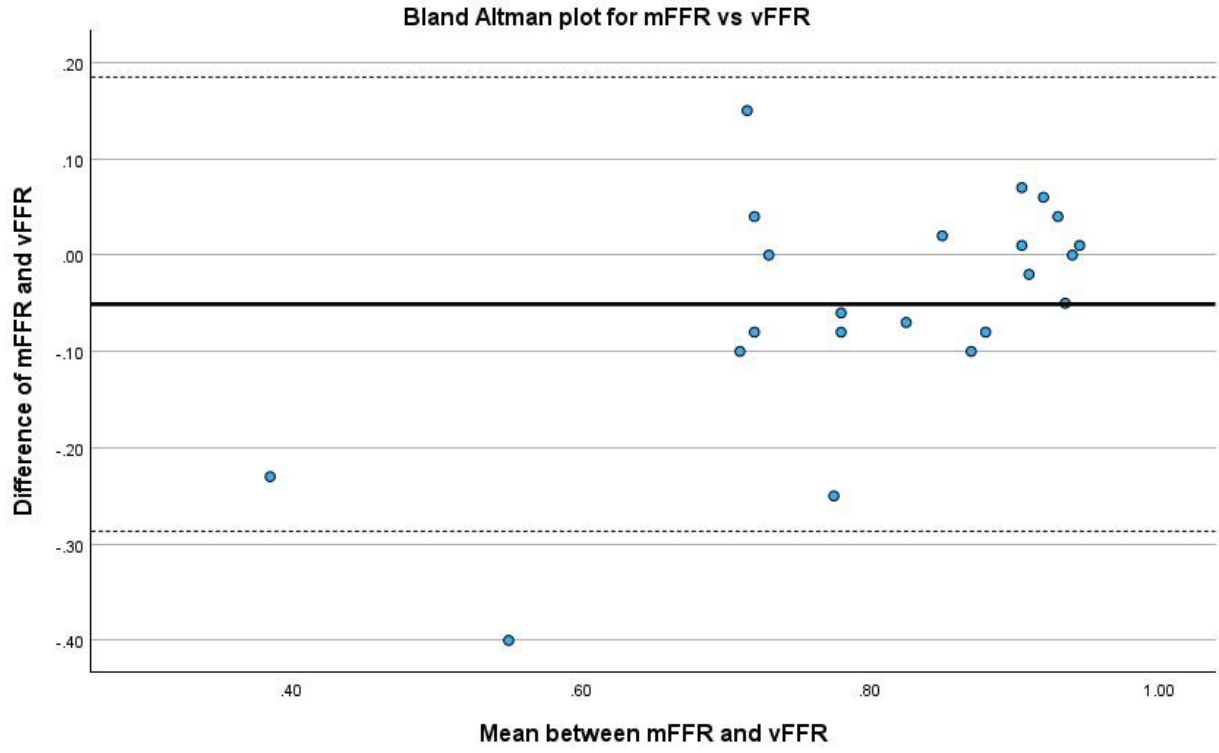


Figure 61. Bland Altman plot showing difference between mFFR and vFFR.

Mean difference: -0.051, limits of agreement: -0.29 – 0.18 (1.96 SD represented by dotted lines).

3.7 Cardiac MRI results

Ten patients were investigated with stress perfusion CMR pre-TAVI. There were no complications and all patients tolerated the scanning protocol and Regadenoson stressing agent. There were no contrast reactions. All pre-TAVI CMR studies were done after angiography and coronary physiology assessment, therefore all patients had either revascularised CAD or physiologically non-significant CAD at the time of the first CMR. Seven of the ten patients who attended for CMR had PCI to at least one vessel and the other three had physiologically non-significant CAD which did not require revascularisation.

In the comparator arm, ten patients with appropriate data sets were taken from the VIRTU-5 study. The method and rationale for their selection has been described in the methods chapter. This cohort did not have CS-flow measured. Furthermore, two patients from this group had inadequate image quality for assessment of quantitative stress perfusion. The comparator patients all had CMR after treatment with PCI (i.e. after revascularisation), or did not receive PCI (due to negative physiology) and these studies are compared with the pre-TAVI CMR data. Thus, both groups had revascularised CAD or physiologically non-significant CAD. Where relevant, some values were indexed to body surface area (BSA) for more accurate like for like comparison between patients.

3.7.1 Cardiac MRI results pre- and post-TAVI

Ten patients attended for stress perfusion CMR pre-TAVI. In all pre-TAVI studies, patients attended for CMR after their coronary angiogram and physiology assessment and therefore all patients had either revascularised CAD (seven patients) or functionally non-significant CAD (three patients). Seven patients attended for CMR post-TAVI. One patient could not attend due to implantation of PPM post-TAVI and two did not proceed to TAVI due to being withdrawn from the waiting list by the TAVI heart team (see Figure 38). Table 18 demonstrates the full results for the CMR cohort pre- and post-TAVI.

	Pre-TAVI ***n*=10**	**Post-TAVI** ***n*=7**	**p-value**
LVEF (%)	58±12	57±10	*0.98*
LV EDV (mL)	181±27	165±30	*0.19*
LV EDVi (mL/m^2)	91±14	83±14	*0.17*
LV ESV (mL)	78±29	72±26	*0.21*
LV ESVi (mL/m^2)	38±13	36±13	*0.18*
SV (mL)	103±25	93±16	*0.33*
SVi (mL/m^2)	52±13	47±6	*0.32*
CO (L/min)	6.7±1.1	6.0±1.4	*0.22*
CI (L/min/m^2)	3.4±0.6	3.0±0.5	*0.23*
LVM ED (g)	156±26	142±31	*<0.05*
LVMi (g/m^2)	79±14	71±16	*<0.05*
MBF at rest/g (mL/min/g)	3.1±0.98	1.9±0.7	*<0.05*
Total MBF at rest (mL/min)	478±141	265±95	*<0.05*
MBF at stress/g (mL/min/g)	3.6±0.57	2.7±0.7	*<0.05*
Total MBF at stress (mL/min)	554±119	378±120	*<0.05*
MPR	1.1 (1.0-1.3)	1.5 (1.2-1.7)	*0.18*
CS flow at rest (mL/min)	92±11	125±36	*0.054*
CS flow at stress (mL/min)	257±74	339±66	*0.19*

Table 18. Stress perfusion CMR results pre- and post-TAVI.

Data are presented as mean±SD or median and IQR. LVEF: LV ejection fraction; LV EDVi: LV end diastolic volume indexed to BSA; LV ESVi: LV end systolic volume indexed to BSA; SV: stroke volume; SVi: stroke volume indexed to BSA; CO: cardiac output; CI: cardiac index (CO indexed

to BSA); LVM ED: LV mass in end diastole; LVMi: LV mass indexed to BSA. P-values are obtained with paired two-tailed t-test.

There was a significant reduction in the LV mass and LV mass when indexed to BSA after TAVI (P= <0.05) (see figures 62 and 63). There was also a significant reduction in hyperaemic and resting MBF both in mL/min/g and globally in absolute terms after TAVI (P= <0.05) (see figures 64 to 71). None of the other parameters measured on CMR changed significantly after TAVI and CS-flows increased numerically without reaching statistical significance.

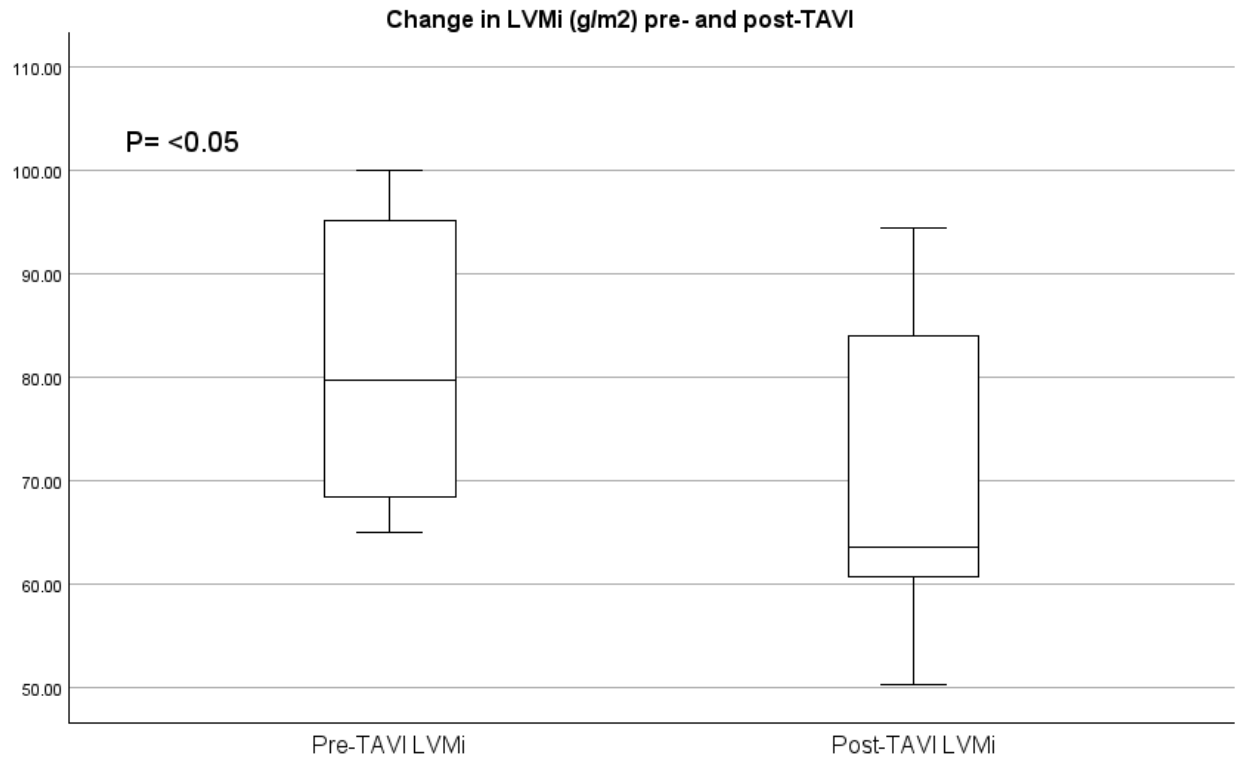


Figure 62. Changes in mean indexed LV mass (LVMi, g/m^2) pre- and post-TAVI.

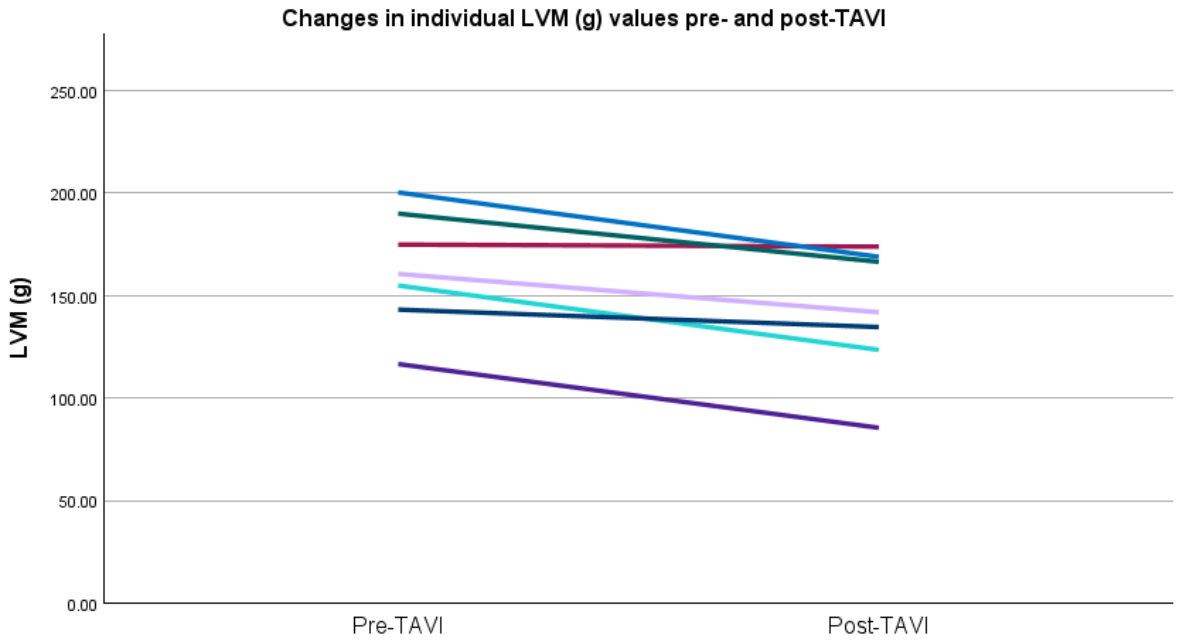


Figure 63. Changes in individual absolute LV mass (g) values pre- and post-TAVI.

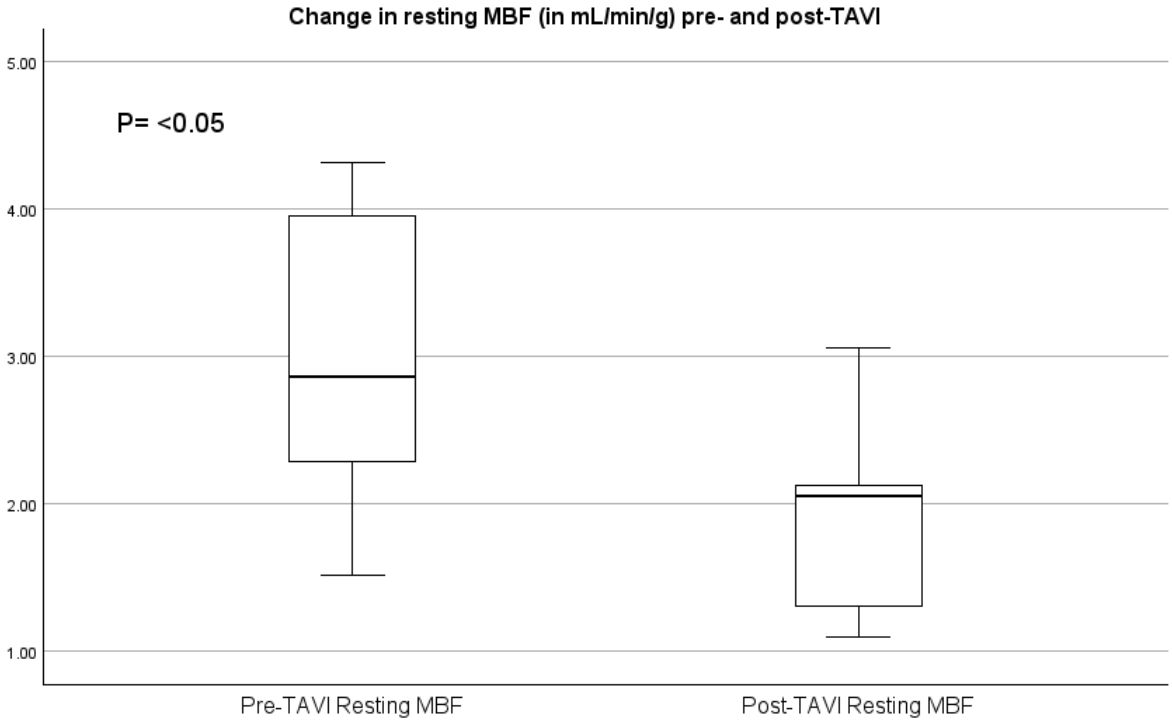


Figure 64. Changes in resting MBF (mL/min/g) pre- and post-TAVI.

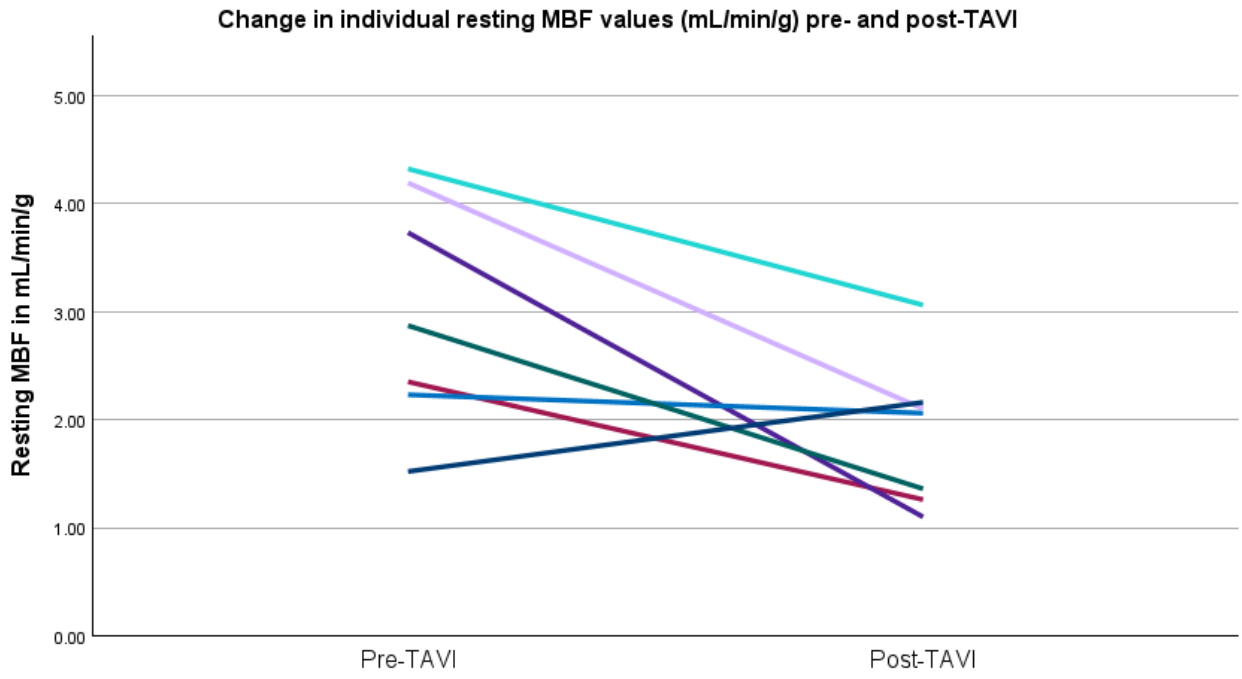


Figure 65. Changes in individual resting MBF values (mL/min/g) pre- and post-TAVI.

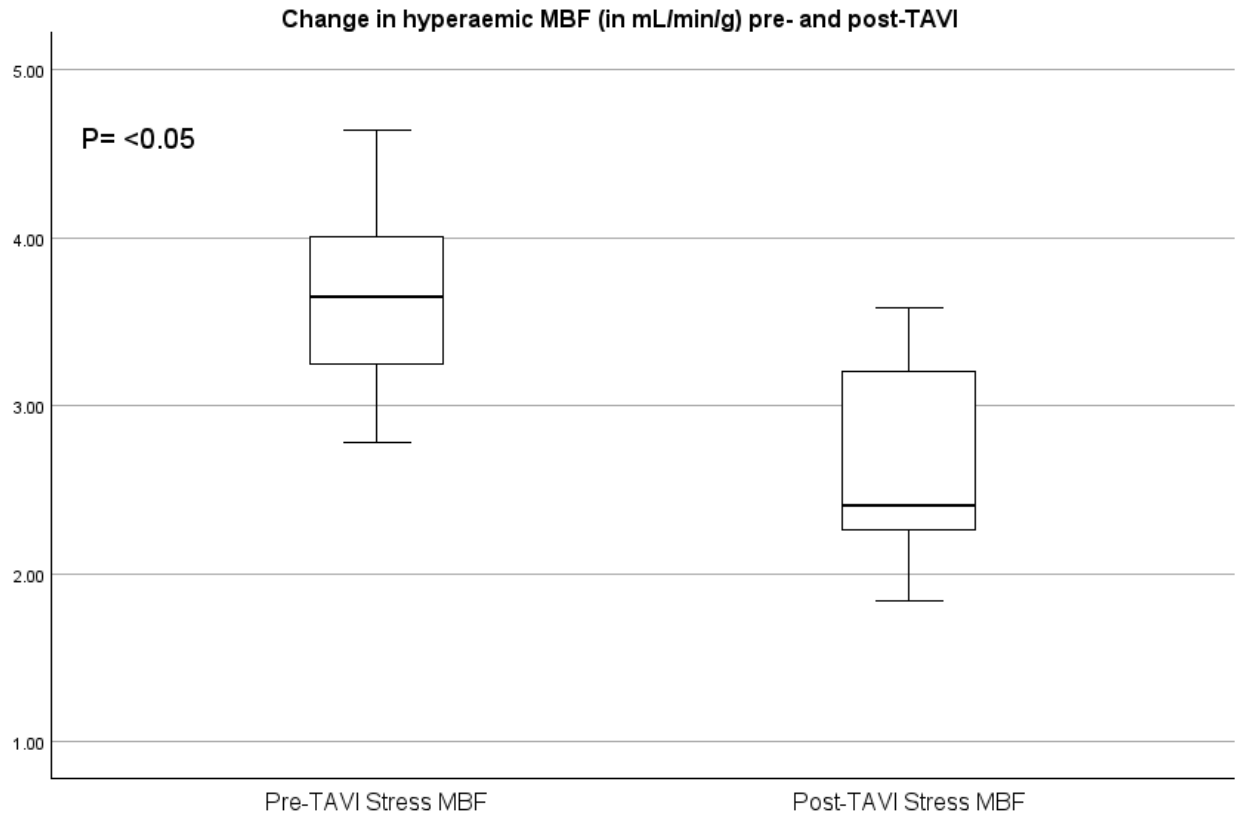


Figure 66. Changes in hyperaemic MBF (mL/min/g) pre- and post-TAVI.

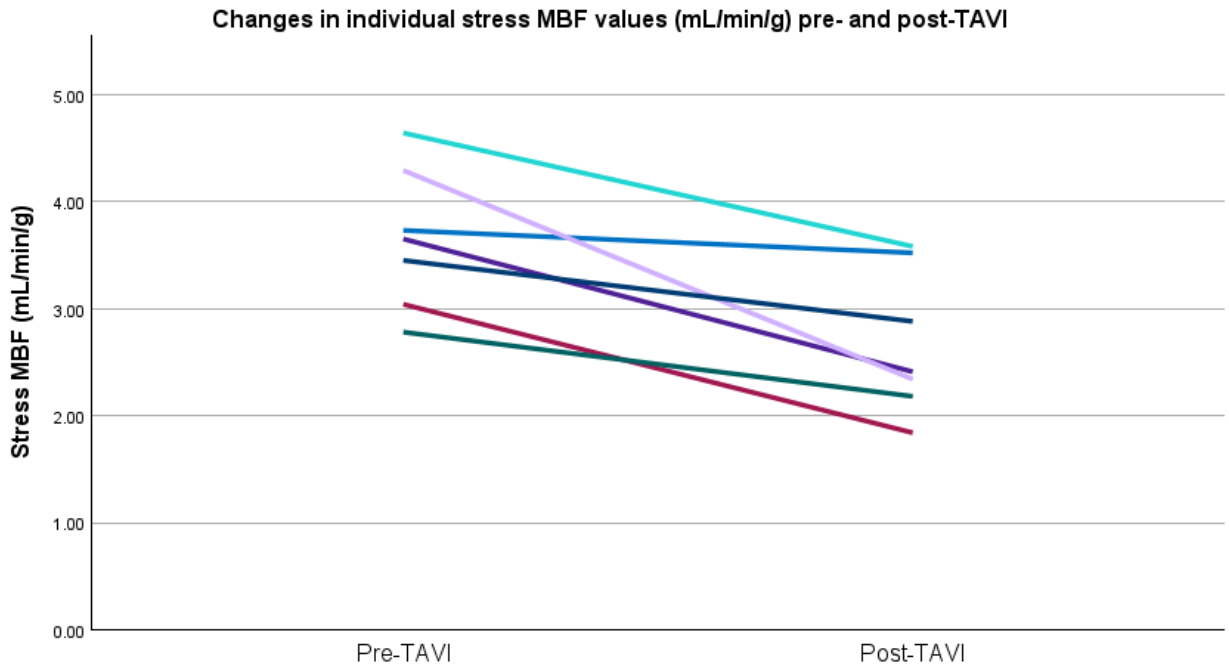


Figure 67. Change in individual stress MBF values (mL/min/g) pre- and post-TAVI.

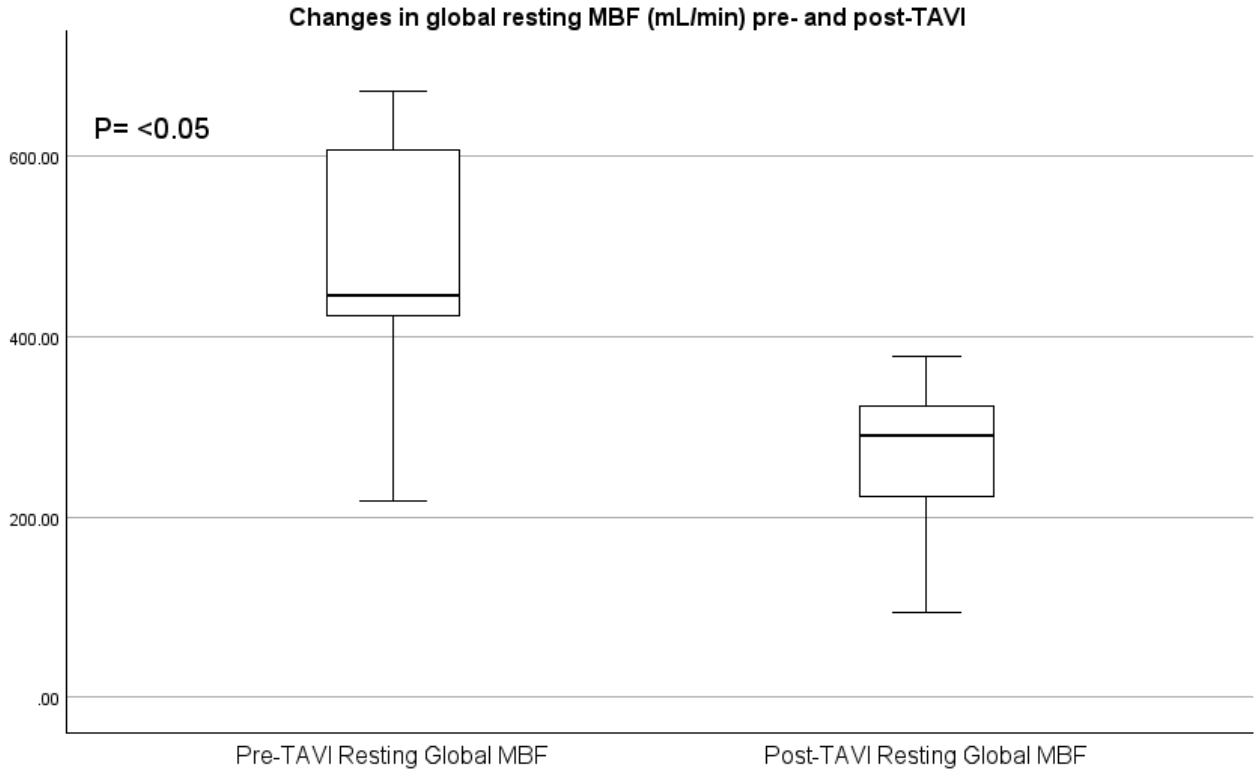


Figure 68. Changes in global resting MBF (mL/min) pre- and post-TAVI.

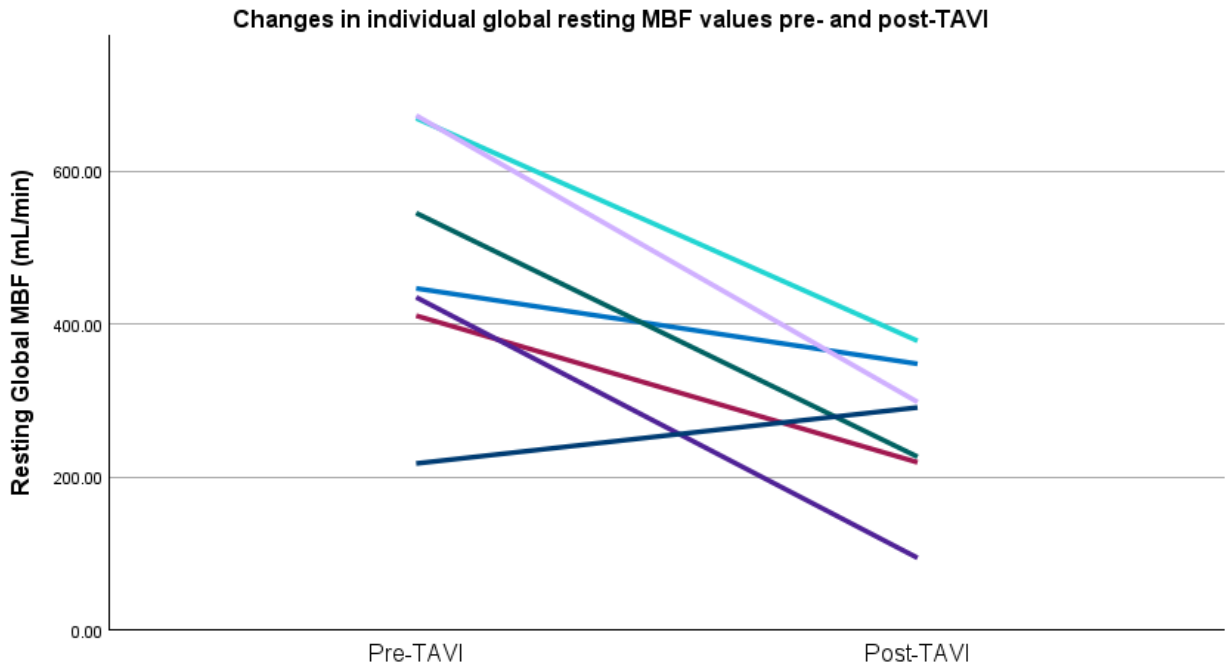


Figure 69. Changes in individual global resting MBF values (mL/min) pre- and post-TAVI.

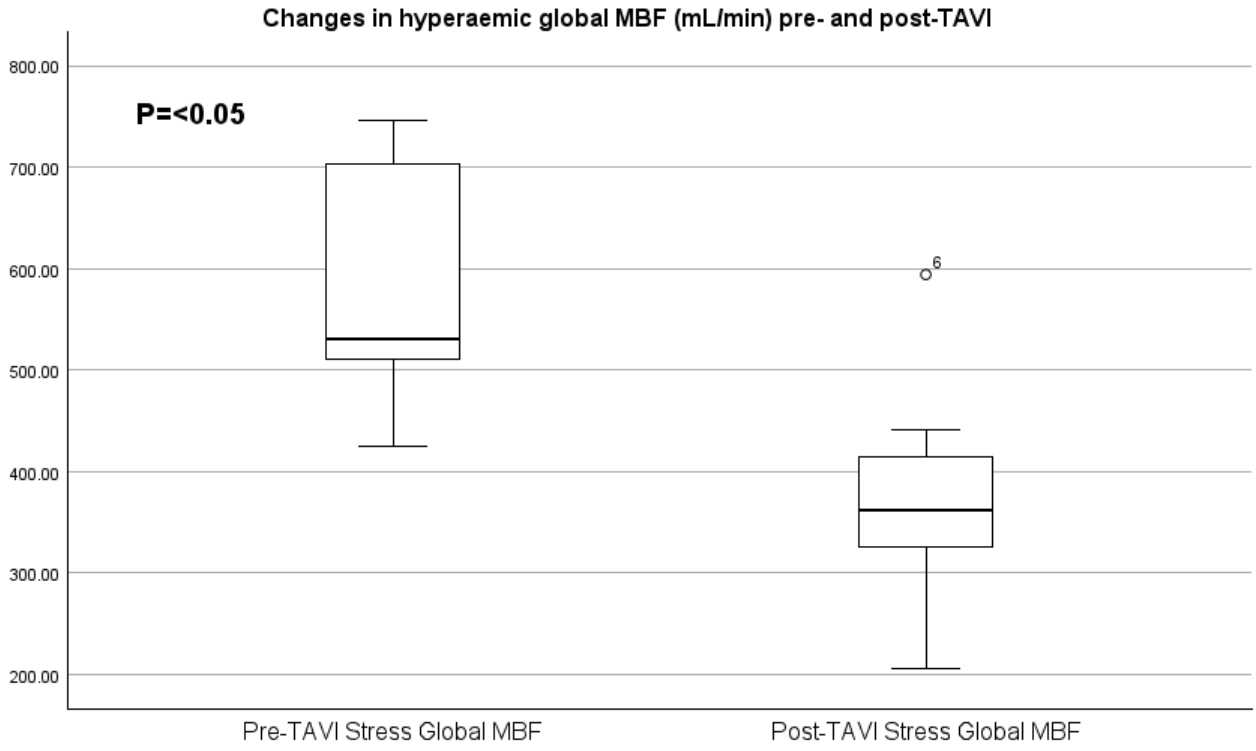


Figure 70. Changes in global hyperaemic MBF pre- and post-TAVI.

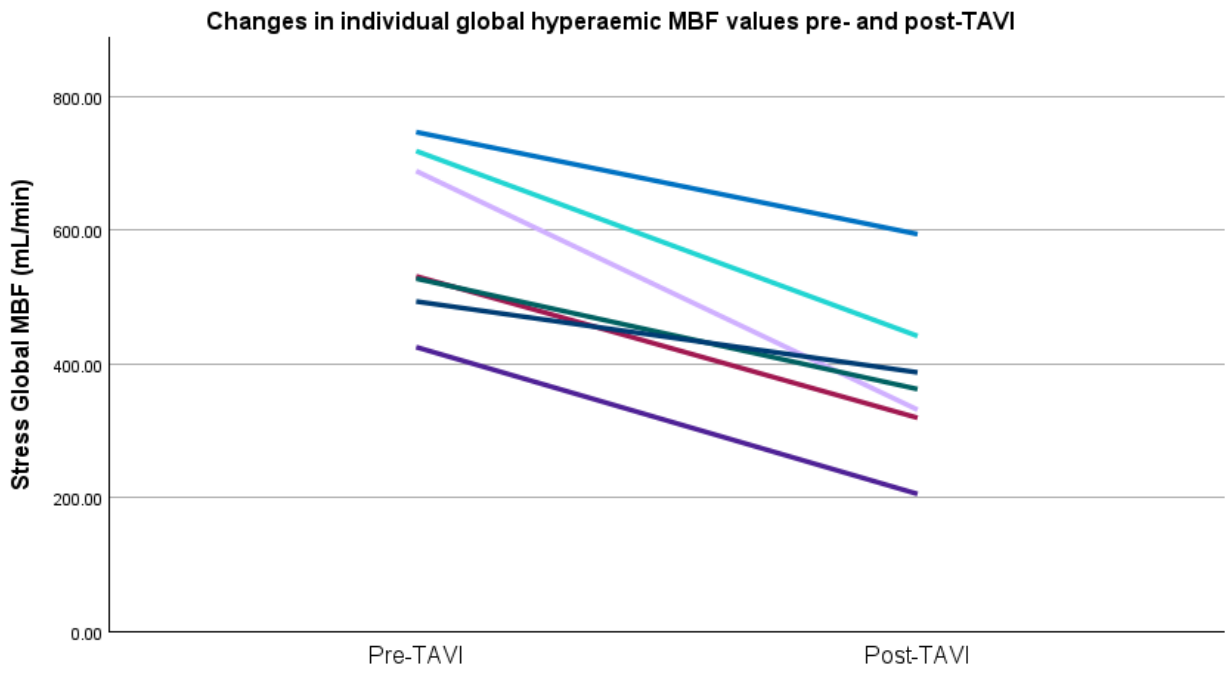


Figure 71. Changes in individual global hyperaemic MBF values pre- and post-TAVI.

3.7.2 Cardiac MRI results in AS vs comparator group

The pre-TAVI CMR dataset was used to compare the effects of untreated, severe AS on LV parameters and MBF at rest and stress in patients with similar degrees of stable CAD. In both arms of this comparison, the CMR study was performed after PCI, where appropriate, or in patients with physiologically non-significant CAD. No patients had symptoms of unstable CAD and none of the comparator group had valvular heart disease. In both groups, seven of ten patients had received PCI prior to CMR. The other three patients in each group had haemodynamically non-significant CAD and did not receive PCI at any point. All scans were performed according to exactly the same protocols, as outlined in the methods chapter. Table 19 demonstrates the results of this comparison.

	Severe AS ***n*=10**	**Comparator group** ***n*=10**	**p-value**
Age	82±4	62±9	*<0.05*

PCI (*n*)	7	7	
LVEF (%)	58±12	57±6	*0.78*
LV EDVi (mL/m^2)	91±14	86±19	*0.56*
LV ESVi (mL/m^2)	38±13	38±14	*0.96*
SV (mL)	103±25	93±13	*0.25*
SVi (mL/m^2)	52±13	48±6	*0.39*
LVM ED (g)	156±26	104±34	*<0.05*
LVMi (g/m^2)	79±14	55±18	*<0.05*
MBF at rest/g (mL/min/g)	3.1±0.98	3.2±0.60	*0.83*
Total MBF at rest (mL/min)	478±141	328±65	*<0.05*
MBF at stress/g (mL/min/g)	3.6±0.57	3.9±0.75	*0.31*
Total MBF at stress (mL/min)	554±119	409±109	*<0.05*
MPR	1.1 (1.0-1.3)	1.4 (1.2-1.5)	*0.52*

Table 19. Stress perfusion CMR results pre-TAVI vs comparator group.

Data are presented as mean±SD or median and IQR. LVEF: LV ejection fraction; LV EDVi: LV end diastolic volume indexed to BSA; LV ESVi: LV end systolic volume indexed to BSA; SV: stroke volume; SVi: stroke volume indexed to BSA; CO: cardiac output; CI: cardiac index (CO indexed to BSA); LVM ED: LV mass in end diastole; LVMi: LV mass indexed to BSA. P-values are obtained with independent-samples two-tailed t-test.

There was a significant age difference between the groups (P= <0.001) and as case numbers were low and the study was underpowered for outcomes, age adjustment was not possible. There was no difference in LVEF (figure 72) or SVi. Patients with severe AS had significantly higher LVM and LVMi compared to the comparator group (figure 73).

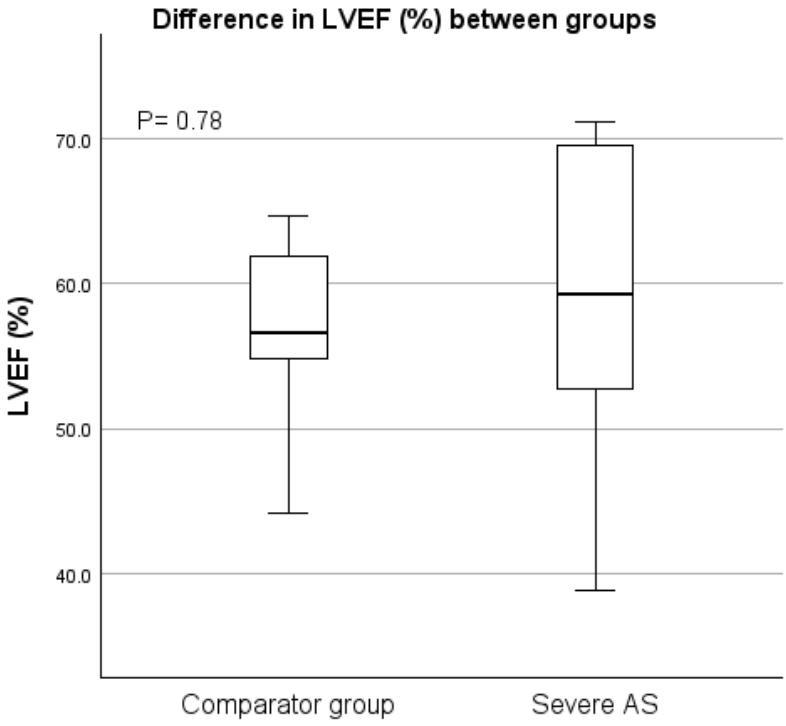


Figure 72. Difference in LVEF % between severe AS and comparator group.

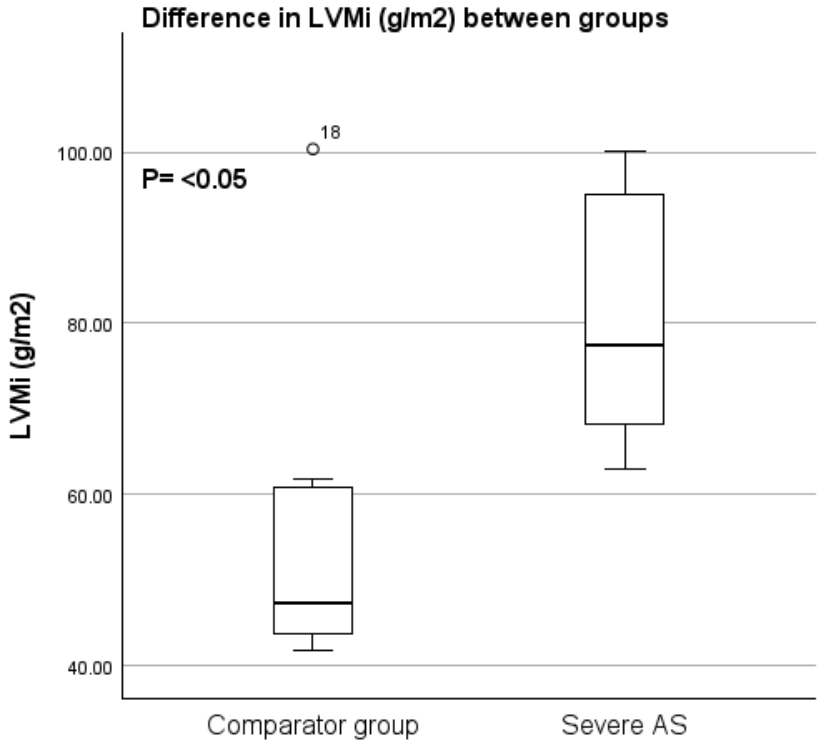


Figure 73. Box plot of LVMi in severe AS vs comparator group.

Patients with severe AS had significantly higher resting and stress total MBF; however, there was no difference when indexed to LVM (figure 74).

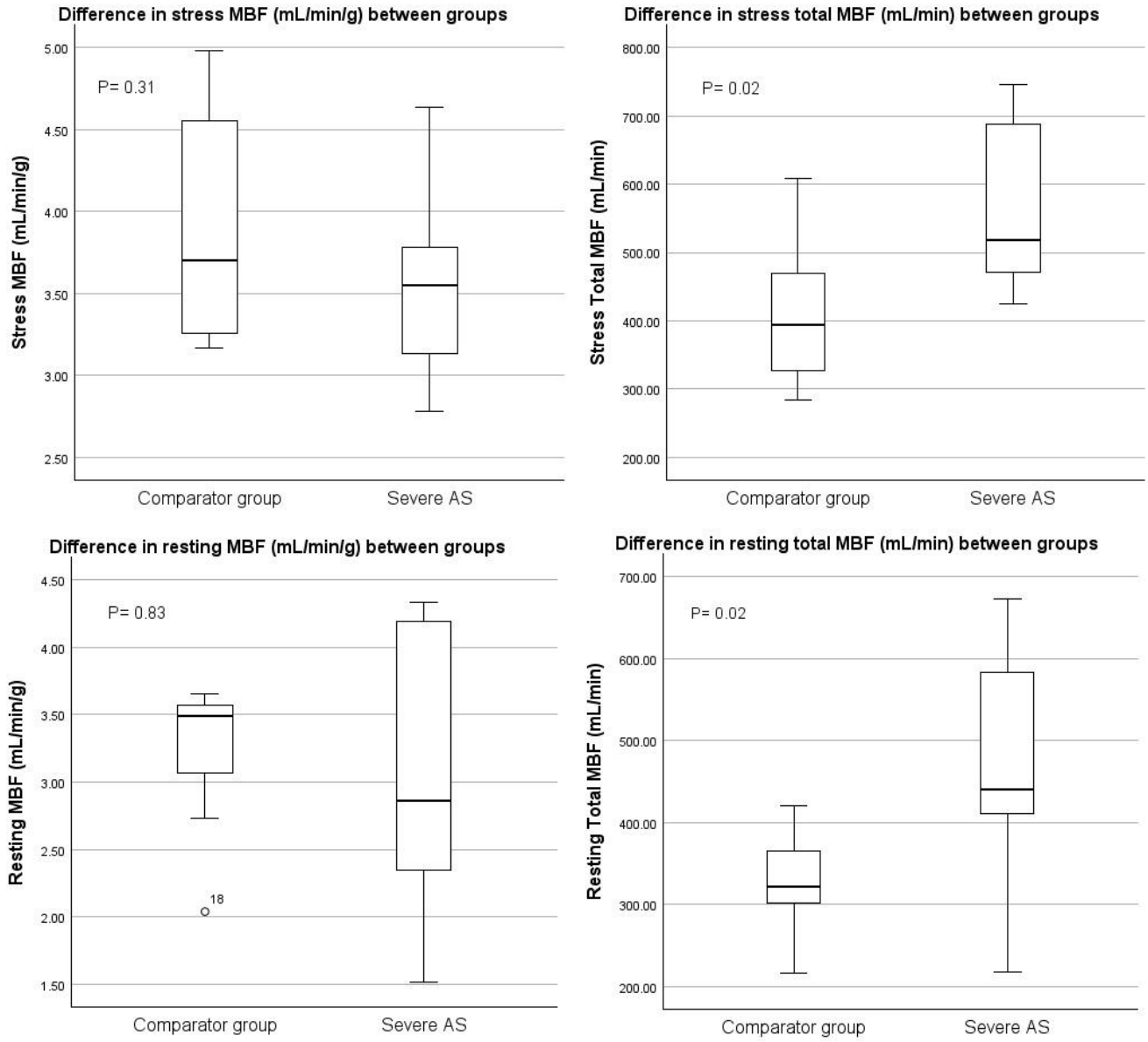


Figure 74. Box plots demonstrating differences in stress and resting MBF between severe AS and comparator group.

Chapter 4: Discussion

The VIRTU-AS study was designed as an exploratory pilot study to investigate the effects of TAVI (for the treatment of severe AS) on coronary and myocardial blood flow using state-of-the art invasive, computational and imaging techniques to capture a large number of data points for each individual patient. There was also an investigation of conventional measures of ischaemia (FFR and RFR) to determine whether any long-term changes occur in these parameters following TAVI at 3-6 months follow-up. This study found that it was technically feasible and safe to obtain a large amount of data for each individual patient. There was a significant improvement in the invasively measured parameters of microvascular capacity and function with improvements in CFR and MRR post-TAVI, although with no change in IMR or MVR, suggesting that resistance was not the predominant reason for this. Resting aCBF (on a vessel specific basis) reduced significantly after TAVI, as did global MBF (at rest and stress) when measured using CMR, suggesting that a reduction in resting flow was the primary reason for improvement in CFR. The clinical value of this data remains to be determined. It was possible to successfully and safely measure aCBF, FFR, total MBF, CS flow and a number of indices of MVD in patients with severe AS. The use of CMR proved particularly enlightening; providing a global and regional measure of MBF as well as CS flow and parameters of LV performance. As CMR is now also able to measure AS severity and guide timing of treatment (217), it may in future provide a one-stop, gold standard, non-invasive multi-modality investigation which can provide a large volume of useful data on valve disease severity, coronary blood flow (and myocardial perfusion) as well as microvascular function. The following chapter will evaluate the successes and difficulties of the VIRTU-AS study and systematically analyse the results produced.

4.1 Study design, patient population and recruitment

This was a prospectively recruited study of an elderly cohort of patients which took place over the course of 2022 until the middle of 2023. The follow-up investigations were performed during the second half of 2023 and through 2024. During this period, two to four TAVI procedures were being performed at STH per week. In 2022, 93 TAVI procedures were performed at STH; however, this under-served the local population, and in 2023 the service

was expanded to 169 procedures per year. The average waiting time from referral to TAVI was about 18 months. The recruitment target was 20 patients, which was in keeping with multiple similar studies (166, 169, 177). A relatively large number of patients were approached and many attended for initial investigations, however, as shown in figure 38, there was a high exclusion and dropout rate due to a multitude of patient related, technical and logistical reasons. This resulted in many cases of missing post-TAVI data. Pre-TAVI data were obtained relatively easily in comparison. These issues are expanded on later in this chapter. Despite these challenges, several measures did reach statistical significance, however the small numbers studied do not allow firm conclusions to be drawn and higher-powered studies with greater patient numbers are required to further elucidate the questions posed by this study.

The mean age of the cohort studied was 81±4.7 years and 65% were male. Hypertension (59%), hyperlipidaemia (76%) and existing coronary disease with previous PCI (70%) were prevalent among the cohort, demonstrating their significantly comorbid background. At STH, TAVI is generally offered to patients who are elderly, frail and unsuitable for SAVR or general anaesthetic. In all likelihood, the majority of these patients would have been denied definitive treatment for their valve disease before the advent of TAVI. These factors are important in explaining the reasons behind the high amount of missing post-TAVI data. Twenty-two patients were taken to the CCL for SOC pre-TAVI angiography and five were excluded due to having non-significant CAD. Of the remaining 17 patients, five did not proceed further, two of whom withdrew consent for further study investigations, citing personal and logistical reasons. The other three were removed from the TAVI waiting list by the Heart Team; one asked to be removed, one was deemed too frail (and subsequently diagnosed with Alzheimer's dementia) and one developed infective endocarditis of the aortic valve and required emergency SAVR. The remaining 12 patients proceeded to TAVI. Of these, nine attended the CCL for post-TAVI ICA and pressure wire assessment. I was unable to gain coronary access in two of these patients due to anatomical and technical difficulty (expanded upon later in this chapter). Three patients declined post-TAVI angiography. One had suffered a post-TAVI CVA and another a splenic infarct, and both did not wish to have any further procedures as a result. Finally, one patient suffered femoral vascular complication following

TAVI and did not wish to return. All patients in whom pre-TAVI data were collected agreed to allow their data to be used in the study despite dropping out at a later stage. Ten patients attended for pre-TAVI CMR. Of these, seven returned for post-TAVI CMR. The patients who developed infective endocarditis and decided against TAVI were in this cohort and therefore did not return. The final exclusion was due to a post-TAVI PPM implantation. All patients tolerated IV Adenosine, Gadolinium and contrast and there were no procedural complications or allergic reactions reported. No patients had alterations of their vasoactive cardiac medications post-operatively. The above narrative and figure 38 demonstrate the difficulties of recruiting frail and co-morbid patients from a single, low volume TAVI centre. Many of the similar studies in this field recruited from multiple sites and across a longer time period, as well as additionally recruiting patients who underwent SAVR (171, 173, 218).

4.2 Echocardiography

There was, unsurprisingly, a significant reduction in the mean and peak gradient across the AV following TAVI. There was also a significant reduction in the peak flow velocity across the AV (4.4±0.3m/s vs 2.1±0.5m/s, $P<0.05$). There was no difference in LVEF, however the baseline LVEF was largely preserved (53±5%) and further improvement above a reasonably good baseline was unlikely. The LV E/e' was also measured for comparison. LV E/e' is a marker of LV diastolic dysfunction and is often abnormal in patients with severe AS (22). The pathophysiology of this is due to LV hypertrophy (due to increased afterload, in turn due to an obstructed outflow tract) in AS resulting in reduced myocardial compliance and subsequently impaired LV relaxation and diastolic dysfunction (22). The normal reference range for LV E/e' is reported as 6.3±3.7 (219). The patients in this study had a significant degree of diastolic dysfunction, and there was no change in LV E/e' when measured 3-6 months post-TAVI (17±5 vs 15±6, $P=0.56$), which corresponds with Gjertsson et al, demonstrating similar findings following SAVR (220). Notably, hypertension is also an important cause of diastolic dysfunction, and 59% of the patients in this study were receiving treatment for this. Patients' blood pressure was not specifically targeted post-TAVI and overall treatment regimens did not change post operatively. As such, it is possible that the LV E/e' could show improvement with targeted, aggressive anti-hypertensive therapy alongside TAVI.

4.3 Questionnaires

The SF-12 questionnaire is well validated measure of patient reported general physical and psychological wellbeing and scored against the national population mean score of 50 in each field, with a reported standard deviation of 10 (213). The SF-12 (appendix G) was performed before, and 3-6 months following TAVI, and comprises physical and psychological components. There was a significant improvement in patient reported physical score from 35.2±9.3 pre-TAVI to 45.2±11.2 post-TAVI, P=<0.05. The pre-TAVI-reported physical score was significantly reduced compared to the national population mean of 50±10 and therefore an improvement following TAVI to a figure closer to the population average was a reassuring and positive finding, demonstrating good patient reported improvements in activity levels post-TAVI. The psychological component score was already within the normal range of the national population mean and increased numerically post-TAVI, but did not reach statistical significance (52.9±8.5 vs 58.4±4 P=0.57). Significant improvement in the psychological quotient above this already relatively normal baseline was not expected. The relatively normal baseline psychological score, even before treatment, despite suffering significant physical limitations and living with a life limiting condition can be viewed from one perspective as a testament to the stoicism of the generation of patients studied in the VIRTU-AS study. Alternatively, it may be viewed as an effect of the *expectation* of stoicism which may have historically been placed on this generation of patients and a general lack of willingness to present or complain of psychological or mental illness. To detect this is not the within the remit of the VIRTU-AS study, but to consider these factors may provide some potential explanation for the results.

4.4 Coronary angiography and pressure wire assessment

This was a real-world study which utilised SOC as well as research driven angiography and intra-coronary physiology to extract a large volume of data for each patient. In the CCL, patients had a mixed range of CAD, and those with no vessel with >50% diameter stenosis were excluded. In the remaining patients, I measured a full range of physiology and if FFR was ≤0.80, PCI was performed according to ESC guidance (5). Eight patients received PCI and seven did not. As a result, the cohort of patients studied had a wide variability in their degree of treated or untreated CAD. For this reason, results were presented separately between the

group who received PCI and those who did not (sections 3.5.1 and 3.5.2). Unfortunately, only two patients who did not receive PCI had post-TAVI angiography and physiology and no meaningful data analysis could be performed in this small group. In patients who did receive PCI, their post revascularisation physiology was repeated and amalgamated with the baseline data of patients who had FFR >0.80 in order to provide a total pre-TAVI data-set (section 3.5.3). Pre-TAVI physiology data were presented for 15 patients and post-TAVI data were presented for seven patients but only like for like results were analysed using paired t-test sampling. Results were presented on a vessel specific basis and discussed as a whole data set. The same protocol, as outlined in section *2.8* was followed for all patients.

The earlier part of this thesis has already outlined the potential pitfalls with using FFR (as well as RFR and iFR) as the basis for revascularisation in patients with severe AS. However, FFR remains the best validated and most utilised measure of coronary physiology globally (221) and data exists to suggest that strongly positive (or negative) results can be used to guide revascularisation decisions (175, 222). The use of resting indices such as iFR and RFR to guide revascularisation are validated but as a full, invasive study was performed as part of the study protocol, a decision was made to use the "gold standard" measure, which in this case was FFR. Furthermore, at STH, we have routine access to FFR and it forms our most utilised invasive measure of coronary physiology. As I measured FFR in all patients pre-TAVI, a pre-emptive decision was made that positive FFR values were to be treated with PCI, according to ESC guidance (5) and negative FFR values were to be deferred. In one case, a positive FFR was not treated with PCI as this was in a diffusely diseased distal LAD. FFR was therefore chosen to guide revascularisation in this study as the best validated and guideline directed measure of coronary physiology.

4.4.1 Invasive coronary physiology pre- and post-PCI

As expected, in patients who received PCI, the invasively measured resting P_d/P_a, RFR and FFR all improved after PCI. In this cohort of eight patients (10 vessels), the baseline FFR was 0.74 (0.66-0.75) and improved to 0.87 (0.82-0.89) post-PCI (P=<0.05). The purpose of FFR guided PCI is to achieve a normal FFR post-PCI and all but one PCI procedures were successful in achieving a post-PCI FFR value of >0.8. There was no change in the IMR or CFR when measured

immediately post-PCI which, in this cohort, is not unexpected due to the haemodynamic conditions of severe AS still being present.

4.4.2 Invasive coronary physiology pre- and post-TAVI

Seven patients had a full range of coronary physiology measured in the CCL at 3-6 months post-TAVI. In all but one case, the pre-TAVI FFR was >0.8 as patients had either non-significant CAD or PCI to treat CAD by the time of TAVI. There was a significant increase in the mean FFR from 0.87 (0.82-0.90) to 0.89 (0.86-0.92) post-TAVI (P=<0.05) (see figure 51). In the single case where the pre-TAVI FFR was 0.77, this improved to 0.85 post-TAVI (see figure 52). This individual result is rather at odds with the studies described in table 2, however this was a single result and significant value cannot be place on this. The general findings with respect to FFR after TAVI were in line with data from Pesarini et al (168) and Stoller et al (170) who demonstrated that FFR values of >0.8 tend to increase immediately post-TAVI (table 2). The same study from Pesarini et al, as well as Vendrik et al (172) demonstrated an acute fall in FFR immediately post-TAVI, and in the case of Vendrik et al, long-term post-TAVI, in FFR values of ≤0.8. As can be appreciated in table 2, multiple studies have demonstrated conflicting results when FFR is measured immediately and long-term post-TAVI. Minten et al have produced a systematic review and meta-analysis of several of these studies (169, 170, 172, 176, 177, 183) and demonstrated a small but significant fall in FFR by a mean difference of 0.02±0.07 (P=<0.05) when measured long-term post-TAVI (175). The same findings were observed when FFR values were in the intermediate zone of 0.7-0.9 were analysed separately (175). Ultimately, the findings by Minten et al suggest that although a significant change in the FFR was observed across multiple studies, the change was nonetheless small and the studies analysed had widely varied sample sizes (13–97 vessels), varying degrees of CAD and in some cases overlapping patient populations (175). These informative results from Minten et al do provide reassurance that across the most relevant data sets on this subject, strongly positive or negative FFR values can be relied upon to guide revascularisation decisions. Care must be taken when borderline values are encountered and previously negative FFR values may gain functional significance when measured after TAVI due to regression of the haemodynamic conditions which contribute to the underestimation of FFR in patients with severe AS. The recently published NOTION-3 trial has confirmed the suitability, and preferability for FFR-guided revascularisation in patients with severe AS undergoing TAVI,

demonstrating improved outcomes with respect to all-cause mortality and MACE events at two years compared to conservative management (154).

The resting index of coronary physiology measured in this study was RFR and this showed no change pre- and post-TAVI (0.91 (0.84-0.94) vs 0.91 (0.90-0.96), P=0.13). This was in keeping with the meta-analysis by Minten et al who demonstrated no significant change in RFR or iFR long-term after TAVI. With this in mind, the use of resting indices to guide revascularisation in patients with severe AS seems flawed as these patients are intrinsically in a state of stress and hyperaemia. As such, even in patients with unobstructed coronary arteries, iFR values tended to be positive (≤0.89) and did not change post-TAVI (table 3) and using resting indices is not recommended as they likely overestimate lesion significance.

There was a significant improvement in the CFR from 1.45 (1.2-1.7) to 2.3 (2.0-2.7) after TAVI (P=<0.05) (see figures 45 and 46). This was in keeping with multiple similar studies outlined in table 4 which showed significant improvements in all studies which measured CFR long term following SAVR or TAVI. The MRR also increased significantly from 1.8 (1.3-2.8) to 3.2 (2.3-3.4) post-TAVI (P=<0.05) (see figures 47 and 48), but the IMR remained similar, albeit with a numerical increase (20±12 vs 26±15, P=0.56) (see figures 49 and 50). The improvement in CFR and MRR confirms the role of TAVI in facilitating the regression of baseline hyperaemic conditions which characterise AS and the improvement in myocardial capacity to respond to stress. The explanation for improved CFR cannot be confirmed using invasive the parameters measured in this study but the computational and CMR results provided data to evidence that falling resting flow following TAVI provides the mechanism. The fact that IMR remained similar pre- and post-TAVI is somewhat surprising, as it would be expected to fall. Pre-TAVI MVR is widely expected to be high due to extravascular compressive forces acting on the microcirculation in severe AS. However, these results were in line with Sabbah et al who also noted IMR to remain unchanged long-term after TAVI (177). Furthermore, Lumley at al (80) and Nishi et al (223) both found patients with severe AS to have similar minimal microvascular resistance and IMR to healthy controls. The reason for this may be due to the inability of the microvasculature to adequately proliferate in line with increasing LV mass associated with severe AS (224). As such, there is rarefaction of the capillary bed in comparison with LV mass

and this may make the LV more efficient at extracting oxygen from the microcirculation, ameliorating the need for capillary proliferation and higher MVR in order to extract more oxygen (177). Therefore, minimal microvascular resistance remains similar and does not change. Instead, increased myocardial oxygen demand is provided by a reduction in the CFR (by recruiting more of the capillary bed at rest) rather than resistance playing a significant role. Conversely, baseline MVR and IMR would be expected to be low rather than high in this context. The relatively normal IMR measured here and other studies suggest that a minimal level of resistance is reached in severe AS which does not fall further, but still allows almost maximal recruitment of the capillary bed. Nonetheless, the unchanged IMR in this study, alongside other similar studies, suggests that changes in myocardial blood flow after treatment of severe AS are not necessarily driven by changes in minimal microcirculatory resistance or IMR but through increased coronary and microvascular blood flow and impaired pathophysiological mechanisms of cardiac-coronary coupling (80). The MRR was measured using values obtained with bolus thermodilution rather than continuous thermodilution, and is designed as marker of microvascular function which should remain comparable across a wide range of CAD. Its role and method have been described in section *1.4.5.3*. Scarsini et al measured MRR pre- and post-TAVI using continuous thermodilution and found very low MRR to be predominantly associated with significant extra-valvular LV damage and low-flow AS phenotype (173). None of the patients in this study had low-flow AS nor significant LV failure. The MRR increased significantly in this study and suggests that with reverse LV remodeling and state of high-flow stress, the theoretical resting to hyperaemic MVR can improve following TAVI. The ability of the microvasculature to increase resistance in response to increased demand, was able to return to normal. The low MRR pre-TAVI adds to the vulnerability to ischaemia which is also contributed to by the low CFR. As with CFR, the improvement suggests a reversal of this vulnerability and a greater capacity to increase myocardial blood flow in response to stress conditions through increasing MVR when it is required.

Bolus thermodilution derived IMR and CFR have been shown to suffer from inter-operator and inter-patient variability (123). In this study, all cases were performed by the author in an attempt to mitigate for this, and all procedures were done strictly according to the protocols

already outlined. Nonetheless, results may have been affected by the well-established limitations of bolus thermodilution. During the period of this study, continuous thermodilution, which is reported to be a more accurate method of obtaining invasive aCBF, IMR and CFR was not available at STH (122, 123). FFR and RFR values were obtained using the same pressure-wire (Abbott Pressure-wire X) and standard weight based IV Adenosine infusion (see section *2.8*) and hyperaemic values were taken when a period of stable hyperaemia was deemed to have been achieved, at least 120 seconds into commencement of the infusion. There were no safety concerns with the use of IV Adenosine and no contrast allergies or procedural complications occurred.

4.4.1 Coronary access post-TAVI

As described in section *1.5.3.1*, coronary access following TAVI can be challenging due to changes in aortic root geometry and anatomy. In this study, there were two cases during which I was unable to gain coronary access for angiography or pressure wire assessment, due to technical difficulties. Both of these cases were associated with self-expanding supra-annular valves. The figures below demonstrate the angiographic images of two failed cases, one difficult case requiring a guide catheter extension and a relatively straightforward case with an intra-annular valve implant.

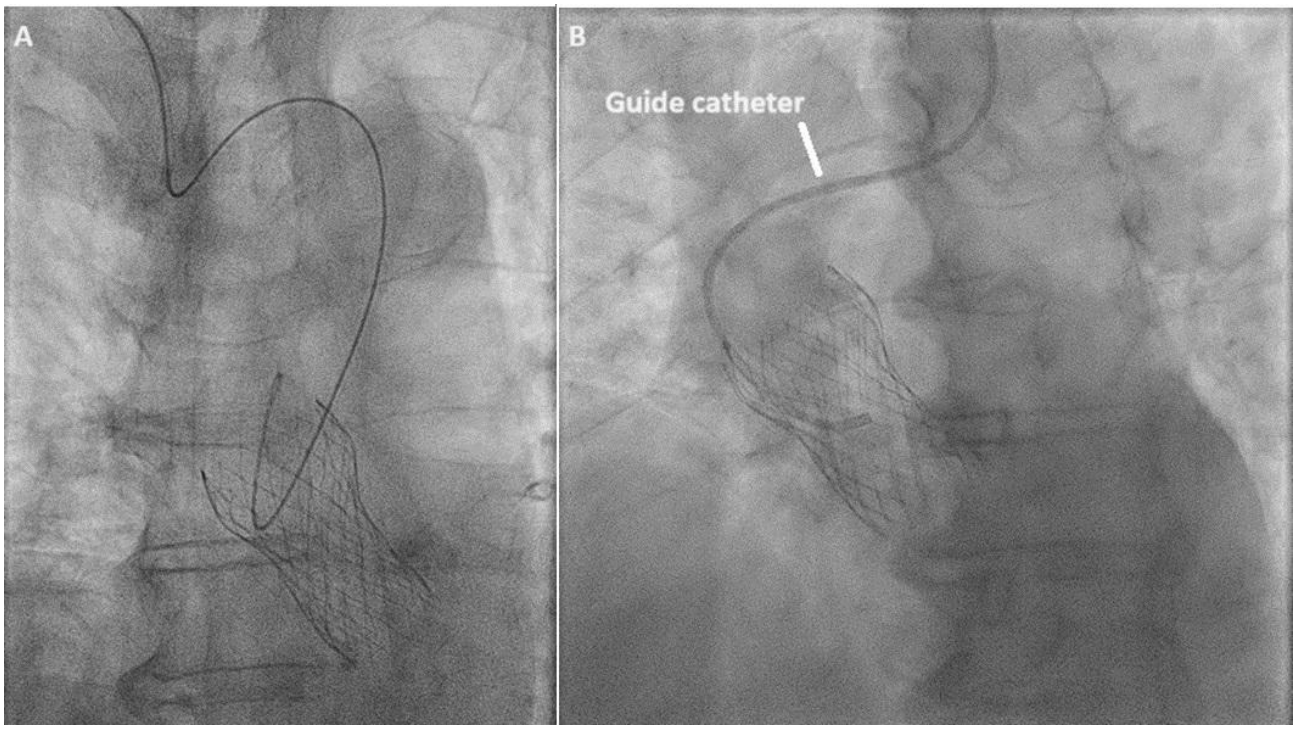


Figure 75. Failed case 1.

Figure 75 shows the first post-TAVI failed angiogram. There was a supra-annular valve in-situ. As can be appreciated in figure 75**A**, the guide-wire took a very tortuous route through the right radial artery and into the subclavian artery and aortic root. There was significant "S" bend on the wire in the aortic arch which significantly impaired my ability to control the wire and pass equipment across it. I nonetheless passed a guiding catheter along the wire into the aortic route and figure 75**B** shows the tip of the guiding catheter within the valve. Unfortunately, due to the severe "S" bend at the aortic arch, I was unable to gain any meaningful control of the distal catheter tip and, despite multiple catheter changes. I was ultimately unable to gain coronary access and abandoned the procedure.

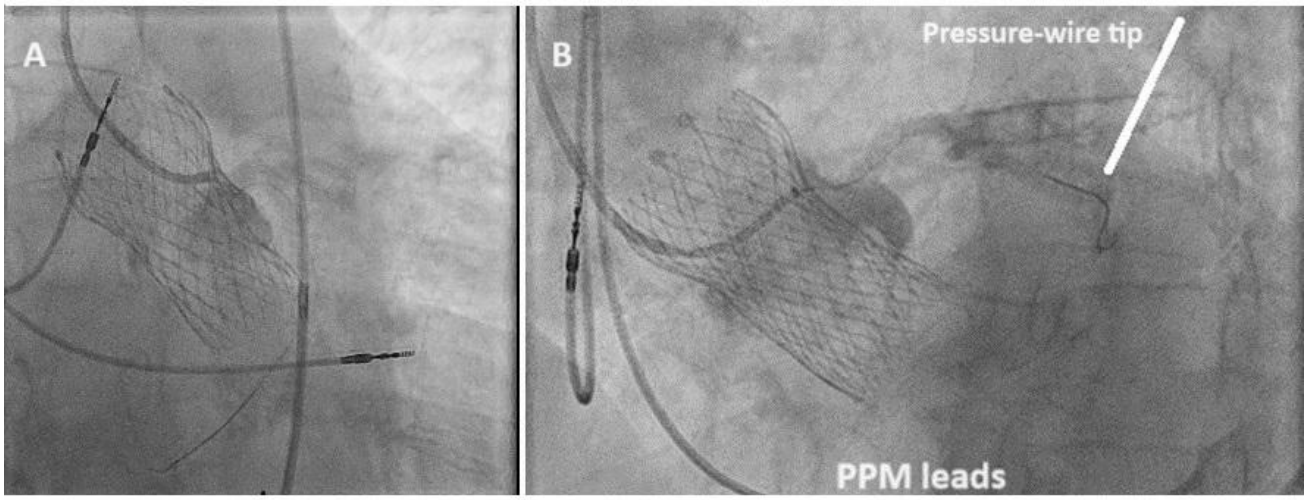


Figure 76. Failed case 2.

The second failed case is shown in figure 76. As with the first failed case, there was a supra-annular valve in-situ. In this case, I was able to get somewhat closer to achieving coronary access than in the first failed case and, as can be seen on figure 76**A**, there is faint opacification of the left main stem, however the catheter position was very unstable and would not engage the ostium. Figure 76**B** shows the use of a guide wire, which I successfully passed into the left coronary system by "floating" it across the valve apparatus into the coronary ostium, in order to provide some support and stability. Unfortunately, despite this, the position remained unstable and I was ultimately unable to gain any meaningful data.

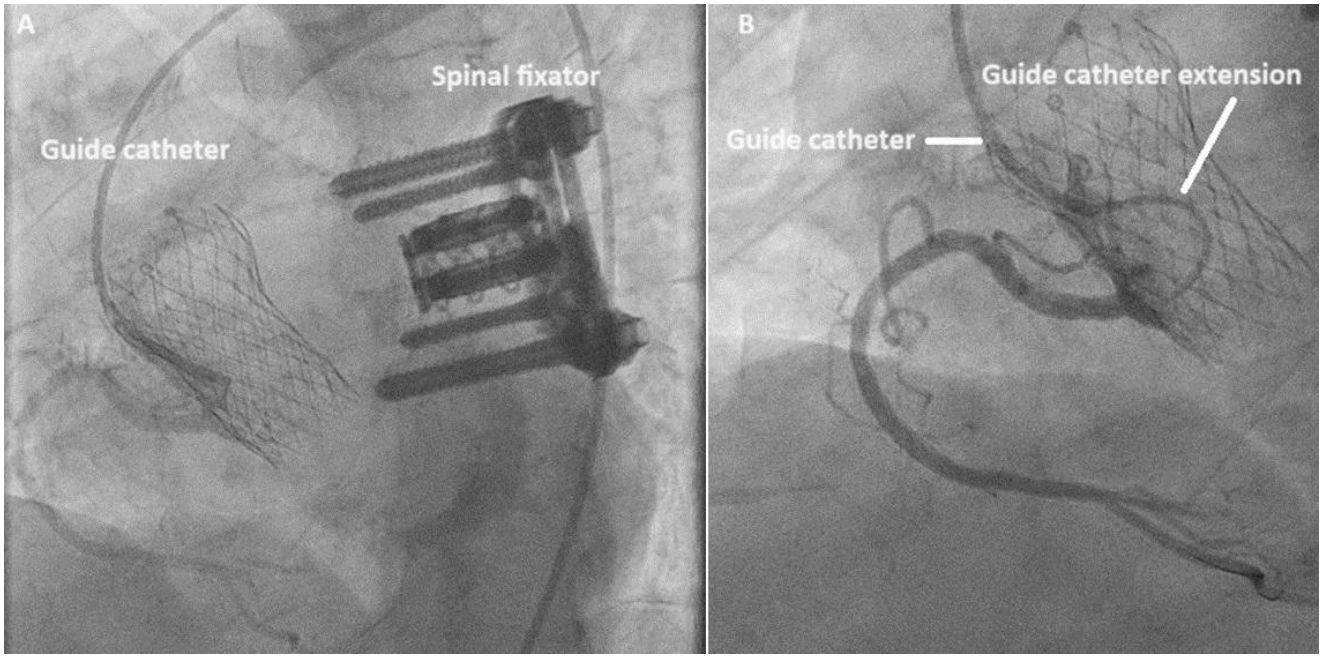


Figure 77. Difficult case.

Figure 77 demonstrates another supra-annular valve case which I eventually managed to access using a guide extension catheter. As can be seen in figure 77**A**, the guide catheter was passed to the aortic root from the femoral artery but, due to the difficult anatomy, I was unable to rotate the Judkin's right coronary guide catheter into the right coronary ostium. However, as in figure 76, above, I was able to "float" an intra-coronary guide wire into the RCA and pass a guide catheter extension over the wire in order to gain access. Through the guide extension, I was able to pass a pressure wire and take images of the vessel. As can be appreciated in figure 77**B,** the actual guide catheter is pointing away from and lies some way above the RCA ostium. Instead, the guide catheter extension has formed a rather large "U" bend and lies well within the RCA for image acquisition and pressure wire passage.

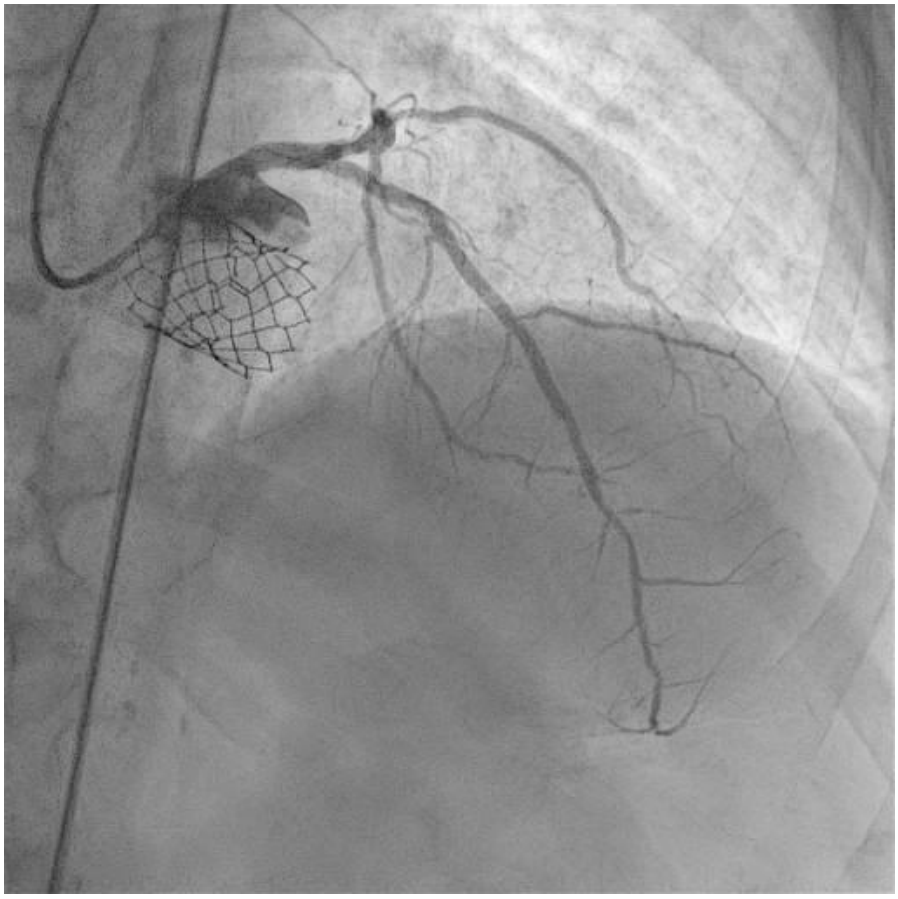


Figure 78. Straightforward case.

Figure 78 demonstrates an intra-annular valve and an angiogram of the LAD. The route of access was via the femoral artery. This procedure was relatively uncomplicated, and as can be appreciated, the guide catheter tip passed into the left main stem ostium above the level of the valve prosthesis, rather than through it, as in the difficult cases above.

My findings with respect to gaining coronary access following TAVI fall in line with the data suggesting that coronary access may be impaired in cases of supra-annular valves which do not have adequate commissural alignment (160). When retrospectively discussed and investigated, it was revealed that no specific measures were taken to ensure commissural alignment in the failed cases above. This may have affected my ability to gain coronary access in the second case, where I was close to achieving access. However, the first failed case was due to the very difficult geometry of the aortic arch, and even with perfect commissural alignment, obtaining adequate coronary access would have been near impossible from the

radial route. In this specific case, a femoral route of access may have mitigated for the severe "S" bend at the aortic arch and allowed for better guide catheter control, however given the research nature of the procedure, and risk of complications (Heparin had already been administered), I did not switch to femoral access. It is worth noting that in this failed case (figure 75), the pre-TAVI angiogram was performed via the right radial artery route and the post-TAVI difficulty using the same route revealed a much-changed aortic root geometry, caused by the new TAVI valve.

Ultimately, I have demonstrated that gaining coronary access following TAVI was possible in the majority of cases taken to the CCL, albeit with some difficult cases requiring patience, care and expertise. Careful pre-procedural planning and review of past angiograms and the TAVI procedure were vital in determining the best and safest vascular access route and equipment. It is relevant to note that the failed angiogram cases were among the first of the post-TAVI cases, and with greater experience, I was able to more successfully and quickly gain coronary access in the latter cases. In all cases, careful pre-procedural planning was key to success. Furthermore, my findings support suggestions that where future coronary access is anticipated, such as in younger patients or those with existing coronary disease, intra-annular valves may provide a more appropriate choice of valve by the TAVI heart team (139, 158) as coronary access was always quickly achieved in these cases.

4.5 Computational fluid dynamics

CFD analysis with virtuQ^{TM} was performed in all vessels which had invasive coronary physiology. There were no modelling or processing failures and the same vessels were analysed pre- and post-TAVI as in the invasive coronary physiology cohort in order to measure vessel specific aCBF.

4.5.1 Computational fluid dynamics pre- and post-PCI

virtuQ^{TM} analysis was performed in all patients who received PCI, before and after PCI, in order to obtain up-to-date pre-TAVI data. As expected, the baseline and hyperaemic inlet aCBF increased significantly after treatment with PCI (see figures 53 and 54). There was no change in the pre- and post-PCI vessel specific MVR or CFR. The purpose of PCI is to increase

coronary blood flow, and therefore the increased flows, both at rest and stress, are not unexpected and demonstrate that restoration of blood flow was achieved in these patients. However, without validated targets or measures of absolute flow improvement following PCI (such as in FFR where a clear treatment cut off of ≤0.8 and target of 1.0 exist), I cannot qualify the degree of flow improvement in relative terms. This aspect of the study was neither a primary nor secondary outcome and post-PCI CFD data were obtained for comparison with post-TAVI data.

4.5.2 Computational fluid dynamics pre- and post-TAVI

The resting inlet aCBF across all vessels fell by almost 20% from 178±90mL/min to 146±89mL/min (P=<0.05) (see figures 55 and 56). Hyperaemic inflow remained similar at 232±104mL/min pre-TAVI vs 215±66mL/min post-TAVI (P=0.13) (see figures 57 and 58). These values were similar to figures presented by Sabah et al, who measured hyperaemic aCBF using continuous thermodilution in 34 patients pre- and post-TAVI or SAVR and also found no significant change (177). In their study, CFR increased significantly post-TAVI and reduced resting aCBF was deduced to be the cause for this, however it was not actually measured and mean transit time of saline at rest was used as a surrogate marker for this (177). I have resolved this question by proving that vessel specific resting aCBF did indeed fall significantly when measured using CFD technology. The only other group to measure aCBF in patients with severe AS are Paolisso et al who invasively measured resting and hyperaemic flow in the non-diseased LAD of 32 patients and compared with a control group using the intracoronary continuous thermodilution method (187). They noted a significantly higher resting aCBF in patients with severe AS (86mL/min (65-107) vs 67mL/min (52-75), P=0.009). Hyperaemic flow was not statistically different between the groups (200mL/min (144-225) vs 186mL/min (13-226), P=0.787). This once again confirms the mechanism for reduced CFR in patients with severe AS, and the AS cohort had significantly lower CFR in this study also. This study also measured LVM using cardiac-CT and indexed resting and hyperaemic LAD flow to LVM to determine perfusion in the LAD territory in mL/min/g. They demonstrated that resting LAD territory perfusion was similar between the groups (0.78mL/min/g (0.66-1.10) vs 0.78mL/min/g (1.71-1.10), P=0.611) but that hyperaemic perfusion was significantly lower in the severe AS arm (1.87mL/min/g (1.4-2.5) vs 2.3mL/min/g (1.9-3.2), P=0.035). The absolute and indexed LV mass was significantly higher in the AS arm (121±25.7g/m^2 vs 98.8±16g/m^2,

P=<0.001). With these findings, Paolisso et al have confirmed the significant vulnerability to ischaemia during hyperaemia suffered by patients with AS is likely to be driven by capillary rarefaction within the myocardium and associated impairment of vasodilatory capacity and subsequent inability to adequately perfuse a hypertrophied myocardium during periods of stress (187). Paolisso et al have demonstrated findings similar to the VIRTU-AS study, albeit with a different study design and methods. Namely that resting vessel specific aCBF is high in patients with severe AS but that hyperaemic flow remained relatively similar, resulting in a reduction in the myocardial reserve capacity (and vulnerability to ischaemia). They did not measure aCBF post-TAVI or SAVR to corroborate the findings of the VIRTU-AS study, but I have shown that when measured on a vessel specific basis (with the significant caveat that I have used computational technology rather than invasive thermodilution), treatment with TAVI does indeed result in a fall in resting aCBF, as seen in controls, without a significant fall in hyperaemic flow. The significant fall in resting aCBF was an interesting and valuable result, and also corroborated the hypothesis of Sabbah et al (177). Treatment with TAVI offered instant relief of the LV outflow tract and 3-6 months later, when aCBF was measured, the haemodynamic demands of the myocardium had reduced to the extent that the resting flow required to maintain adequate oxygen supply was significantly lower (20%) than in severe AS. The hyperaemic flow, when measured here on a lesion specific basis, did not change significantly, which provided the mechanism for the increase in CFR. The CFD derived CFR was measured on a lesion specific basis in virtuQ^{TM}, and did not change significantly but is unlikely to be accurate as a global measure of CFR due to the very low figures produced and discrepancy with the invasively measured CFR which demonstrated global improvement. Similarly, neither resting nor hyperaemic MVR changed when measured using virtuQ^{TM}. IMR did not change significantly, but this is a hyperaemic measure and it was surprising to see no significant change in resting MVR when measured using virtuQ^{TM}. Mean baseline MVR increased numerically from 1.5mmHg.min/mL (0.9-2.2) pre-TAVI to 2.3mmHg.min/mL (1.2-3.6) post-TAVI, but not significantly (P=0.092). This further suggests that MVR, whether at rest or stress, was not the primary driver behind ischaemia and lack of physiological reserve seen in severe AS; rather, an impairment of vasodilatory capacity (due to exhaustion of the normal physiological adaptations to increased oxygen demand), coupled with capillary rarefaction, LVH and impairment of cardiac coronary coupling were the leading causes.

The aCBF values were somewhat higher than those presented by Aubiniere-Robb et al who measured aCBF using virtuQ^{TM} to elucidate its relationship and concordance with mFFR (126). The reason for this is that Aubiniere-Robb et al presented outlet flow (i.e. distal to a coronary stenosis) whereas I presented coronary inlet flow (126). When resting outlet flow was analysed, it fell numerically from 63±42mL/min to 50±32mL/min post-TAVI but the P-value was non-significant at P=0.07. Hyperaemic outlet flow remained similar at 85±58mL/min vs 87±42mL/min (P=0.95) and was very similar to the findings of Aubiniere-Robb et al (126).

The CFD technology, virtuQ^{TM}, was designed to quantify aCBF across coronary lesions, and requires a trans-lesional pressure gradient of at least 4mmHg and an FFR of <0.95 to process segmentations. Its accuracy falls with rising FFR and in cases of <40% coronary artery diameter stenosis (212). Accuracy is highest with FFR values of ≤0.8 and CAD of >40% stenosis. Although all cases processed for this study fulfilled the basic pressure gradient and FFR criteria for processing, segmentations were performed on many revascularised vessels, and a lack of significant coronary stenoses in patients who had PCI may have affected the accuracy of results (212). A mix of coronary vessels were segmented for this study and it has been shown that flow in the LAD is higher than in the LCx or RCA, however due to the low numbers, vessel specific analysis would not have been of scientific benefit (126). Furthermore, a homogenous side branch flow method was used for the purposes of this analysis and this has shown good agreement with a regionalised side branch flow method using virtuQ^{TM} (225). The homogenous side branch flow method relies on vessel taper and this is variable between individuals, as well as across the range of coronary vessels (225). As such, side branch flow can significantly differ between the LAD and RCA, and using the homogenous side branch method may not be suitable for general use across all coronaries (225). Finally, the clinical value of aCBF is yet to be validated and normal reference values to guide treatment do not exist, and further research and development is required (126). A difference of 65mL/min in hyperaemic flow was reported by Fournier et al when comparing patients with normal coronaries and mild CAD, in their paper aiming to provide normal reference values for LAD flow (125). I noted a significant increase in inlet flow from 170±28mL/min to 286±102mL/min (P=<0.05) and a numerical but not significant increase from 66±30mL/min to 91±58mL/min

(P=0.22) in outlet flow pre- and post-PCI in my patient cohort (mixed vessels). The patients in the VIRTU-AS cohort had more significant CAD than in Fournier's study ("mild" CAD vs FFR ≤0.8) and our larger difference (116mL/min) can be explained by the improvement in flow restoration from significant to non-significant CAD. Mean hyperaemic flow in the LAD was reported as 293±102mL/min by Fournier et al, which is relatively consistent with my virtuQ™ findings (125). The values obtained from virtuQ™ represent vessel specific aCBF and not global MBF. In patients with AS, impairment of MBF and the inability to respond to stress is a global failure of the myocardium rather than purely coronary. Although these CFD results have provided interesting and valuable data, they cannot represent the full picture of haemodynamic change post-TAVI. Accurately measuring vessel specific aCBF can be done invasively and virtually, using CFD technology but its clinical utility is yet to be fully realised and further validation is required before these technologies inform clinical decisions and guidelines.

4.5.3 vFFR vs mFFR in severe aortic stenosis

Although this study was neither designed nor powered to validate the use of vFFR using VIRTUheart™ in patients with severe AS, an analysis of all vessels was made nonetheless, because all patients had mFFR as part of the study protocol. The accuracy was good at 82% and the specificity and positive predictive value were both 100%, suggesting that positive results in patients with AS (vFFR ≤0.8) can be relied on using VIRTUHeart™. There was a good correlation between the mFFR and vFFR (R= 0.76, P=<0.001) (figure 60). The ROC-curve AUC was 96% (95% CI: 0.82-1.03) (see figure 59). The good correlation between mFFR and vFFR (figure 61) corroborated the findings by Morris et al and Gosling et al quoting 90% diagnostic accuracy of VIRTUheart™ (208, 226).

4.6 Cardiac MRI

Quantitative stress perfusion CMR was performed in 10 patients pre-TAVI and seven patients post-TAVI. The causes for attrition have been outlined in figure 38. There we no abandoned cases or claustrophobia and the MRI scanner had no cases of malfunction. All pre-TAVI scans were done after revascularisation, where appropriate. All patients tolerated IV Regadenoson.

4.6.1 Cardiac MRI pre- and post-TAVI

Several parameters measured at CMR reached statistical significance despite the relatively low number of patients who attended. There was a significant reduction in the absolute LV mass from 156±26g to 142±31g (9% reduction) and LVMi from 79±14g/m^2 to 71±16g/m^2 (10% reduction) following treatment with TAVI (P=<0.05) (see figures 62 and 63). This demonstrated that maladaptive LVH of severe AS regressed with relief of the LV outflow tract obstruction and corroborated findings from similar studies demonstrating reverse myocardial remodeling in patients who had SAVR (177, 227, 228). VIRTU-AS CMR scans were done only 3-6 months following TAVI and it is possible that LVH and fibrosis may regress even further with more time. The mean LVEF was already relatively normal and did not change with TAVI. Treibel et al measured a number of CMR derived LV parameters in 116 patients with severe AS undergoing SAVR and re-measured at 1-year. They found that LVMi reduced from 88±26g/m^2 to 71±19g/m^2 at 1-year post-SAVR (P=<0.05) (227). Their patient cohort were significantly younger at 70±10 years but their post-SAVR LVMi was almost exactly the same as my result and corroborates my findings of relatively early reverse remodeling. 24% of their patients had concomitant CABG with SAVR and the majority of valves were bioprosthetic; none of the cohort had TAVI. They determined that focal myocardial fibrosis (regional ischaemia, in most cases) did not regress post-SAVR, however, diffuse myocardial fibrosis and cellular hypertrophy regressed significantly. This was associated with an improvement in LVEF (71±16% to 74±12%, P=<0.05) and functional status (227). Sabbah et al also noted a fall in the LVMi from 86±21g/m^2 to 68±15g/m^2 at 6-months in their cohort of 34 patients who had an equal mix of TAVI and SAVR, demonstrating consistent reverse remodeling across a number of studies (177).

The changes in MBF were the most pertinent primary outcomes of the CMR arm of this study. The resting MBF indexed to myocardial mass fell by 39% following TAVI from 3.1±0.98mL/min/g to 1.9±0.7mL/min/g (P=<0.05) (see figures 64 and 65). Stress MBF indexed to myocardial mass also fell significantly from 3.6±0.57mL/min/g to 2.7±0.7mL/min/g (P=<0.05), representing a 25% reduction (see figures 66 and 67). Global resting flow fell from 478±141mL/min to 265±95mL/min (P=<0.05), a 44.5% reduction (figures 68 and 69). Global hyperaemic flow also fell from 554±119mL/min to 378±120mL/min (P=<0.05), representing a

32% reduction (figures 70 and 71). Therefore, myocardial blood flow significantly fell after TAVI, both in absolute terms and when indexed to total myocardial mass. The proportion of reduction was greater in indexed resting flow (39%) compared to indexed hyperaemic flow (25%) and adds to the evidence for improved CFR. These results demonstrate that myocardial blood flow fell post-TAVI, not only in global terms, due to reverse myocardial remodeling and LVH/LVM regression, but also because the stressed and hostile haemodynamic conditions of severe AS seemed to also regress and the myocardium was less demanding of oxygen. As a result, less of the capillary bed was recruited and "resting" conditions did not mandate such high volumes of coronary blood flow, allowing a relaxation of the high demand environment, as evidenced by the fall in indexed MBF. Rajappan et al also found a 21% reduction in resting MBF following treatment with SAVR in 22 patients with severe AS when measured using PET (229). They reported a reduction from 1.33±0.31mL/min/g to 1.05±0.33 mL/min/g following SAVR, which were both significantly lower than the values reported in the VIRTU-AS study. Aside from the obvious technical difference in MBF quantification (PET vs CMR), the cohort studied had an age of 65.5±9.7 years and did not have CAD, and this may explain the lower overall figures. Subsequent studies have shown either an increase or no difference in resting MBF following SAVR (202, 228, 230). Rajappan et al found no change in hyperaemic MBF. Hyperaemic MBF fell in the VIRTU-AS study, however the capacity of myocardium and capillary bed to respond to physiological or pharmacological stress was nonetheless improved (as evidenced by improved CFR) despite the fall in absolute hyperaemic flow. These findings are at odds with similar studies who have shown that hyperaemic MBF actually increased following treatment of AS (230). Jex et al measured MBF using stress perfusion CMR in patients with severe AS undergoing SAVR without CAD at angiography as a sub-analysis of their study measuring myocardial energetics in patients with type 2 diabetes, with and without severe AS (230). A total of 95 patients were analysed pre-SAVR and 65 post-SAVR and the mean age was 70 (67-74) years. They found that resting MBF fell from 0.71mL/min/g (0.67-0.75) to 0.65mL/min/g (0.60-0.69) at 6-months following SAVR. Stress MBF conversely increased from 1.54mL/min/g (1.41-1.66) to 1.74mL/min/g (1.59-1.88) at 6-months following TAVI. The mean LVMi pre-SAVR was 80g/m^2 (72-89) and fell to 67g/m^2 (59-74) post-SAVR (230). Unfortunately, P-values were not presented for these values as the primary outcome of this study was to compare a wide range of indices of myocardial blood flow, energetics and function between patients with and without severe AS and with and without type 2 diabetes,

so direct pre- and post-SAVR statistical analyses were not presented. Nonetheless, a trend can be appreciated suggesting an increase in hyperaemic MBF following SAVR, albeit in a very different cohort of patients to the VIRTU-AS study. Importantly, the age profile was significantly younger, these patients had SAVR (which inherently implies lower risk than patients undergoing TAVI) and patients with >50% CAD or history of revascularisation were excluded (230). Despite the increase, the post-SAVR hyperaemic MBF was nonetheless significantly lower at 1.74mL/min/g (1.59-1.88) than the 2.7±0.7mL/min/g measured in the VIRTU-AS study, so although hyperaemic MBF increased, the indexed resting and hyperaemic values were significantly higher in the VIRTU-AS cohort. These values were indexed to LVM and absolute LVM values were similar between the groups and does not explain the differences. The MASTER (Mechanisms of Excess Risk in Aortic Stenosis) study enrolled 23 patients with severe AS (and 23 controls) to have stress perfusion CMR pre- and 8-weeks post-SAVR (202). No patients had revascularisation or CAD of >70% and the median age was 71 years. They demonstrated an increase in stress MBF from 1.63mL/g/min to 1.97mL/g/min with no significant change in resting MBF (202). Again, despite demonstrating an increase in stress MBF, the 8-week post-SAVR MBF was still nonetheless lower than the 3-6-month post-TAVI value demonstrated in the VIRTU-AS study. Despite the differing absolute MBF values, the consistent finding between mine and other studies remains that hyperaemic *capacity* improved following treatment of severe AS. The reasons for MBF discrepancies are unclear but may be explained by the difference between the age and risk profile differences between these studies and the VIRTU-AS cohort. My patients were significantly older (mean age 82±4.7), more co-morbid and had more significant CAD. As such, their myocardium has had to adapt to the conditions of progressive AS for over ten years longer than the patients in these studies. Therefore, the degree of maladaptive LV remodeling, and subsequent demands on their myocardium were likely to be much higher and may take longer than 3-6-months to regress (if it does at all) to the levels seen in these younger patients who were suitable for SAVR and had non-obstructive CAD. This may be the explanation for the higher resting and hyperaemic flows seen in the VIRTU-AS cohort, despite falling significantly post-TAVI. It may also be explained by the stressor agent used in my study compared with these studies. A standard 400ug dose of Regadenoson was used for all patients whereas these studies used a weight based IV Adenosine infusion. Regadenoson has been shown to be safe and more

effective at achieving tachycardia and hyperaemia than Adenosine without degradation of its effects at different patient weights (231, 232).

Ultimately, I have demonstrated that the vulnerability to ischaemia in patients with severe AS was less related to the absolute volume of coronary blood flow than to the relative capacity to increase coronary blood flow in response to stress, despite a significant reduction in absolute terms (see figure 79).

The MPR improved numerically, albeit not significantly (1.1 (1.0-1.3) vs 1.5 (1.2-1.7), P= 0.18), which was somewhat surprising given the reduction in resting MBF. This was due to the concurrent fall in hyperaemic MBF. Jex et al and Thorntol et al both demonstrated an improvement in the MPR following SAVR, albeit in their relatively younger and lower risk patient cohort who did not have significant CAD (202, 230). Seemingly, in the patients in this study, the hyperaemic capacity of the myocardium reached a new (lower) ceiling following TAVI and did not reach previously seen pathologically high figures. There was still a greater difference between the resting: hyperaemic MBF ratio, but the fall in hyperaemic flow resulted in a persistently impaired MPR. As a surrogate marker for CFR, there was a mild improvement in MPR and this may improve further with time. Studies which demonstrated an improvement re-scanned patient at 6-12 months post-SAVR so delaying the CMR scans for the VIRTU-AS cohort may well have produced different results (228, 230).

Coronary sinus flow did not significantly change after TAVI, although both hyperaemic and resting CS flows numerically increased. The mean hyperaemic post-TAVI CS-flow was remarkably similar to the global MBF, although the resting CS-flow values were significantly lower than the resting global MBF. Mean CS-flow at rest increased from 92±11mL/min to 125±36mL/min but did not quite reach statistical significance (P= 0.054). CS-flow at stress also increased from 257±74mL/min pre-TAVI to 339±66mL/min post-TAVI (P=0.19). This was somewhat at odds with the stress perfusion results suggesting reduced myocardial blood flow across the board, given that the CS is the major vein draining the myocardium. This numerical increase may be explained by the low CFR and high resting flow, mediated by vasodilatory

myocardial bed recruitment and blood pooling for longer within the myocardium to maximise oxygen extraction. This physiological mechanism to maximise myocardial oxygen extraction may be aided by the pathologically impaired ventricle failing to adequately "process" blood through the myocardial bed and into the draining venous system, resulting in low CS-flow. With treatment of the diseased valve, LVM regresses, resting flows fall, impaired vasodilatory capacity reverses and CFR improves; as such, the myocardium is less demanding of oxygenated blood and less blood is pooled within the myocardial bed. Alongside this, the LV is no longer working against a stenosed orifice and its performance is improved, and more blood is pulled through the myocardial bed (in the same processes described in section *1.4.1*) and this may provide a hypothesis for the increased (although not statistically significant) CS-flows. The slightly discrepant CS-flow results were in line with some similar results currently being processed by our group which noted some discrepancy between stress perfusion MBF and CS-flow figures. Ultimately, there was no statistical significance between the pre- and post-TAVI CS-flows and this represents an interesting area for further research and development (203).

I have demonstrated that, after just 3-6-months, there was significant reverse myocardial remodeling, which was in in line with multiple similar studies. My findings regarding global and regional MBF differed slightly from previously published data; there are several possible explanations for this. Firstly, my cohort of patients were significantly older and more comorbid than those in similar studies. My patients also had significant CAD, albeit treated by the time of TAVI. Their more aged, ischaemic and pathologically demanding myocardium may have produced significantly higher MBF values than younger patients, especially those who have not lived with decades of LVH and CAD, among other comorbidities. In line with this point, the studies mentioned earlier all utilised SAVR and not TAVI, which inherently implies a less comorbid and lower risk patient cohort, and as such, direct comparison may not be entirely appropriate. Secondly, all studies used different methodologies and techniques for measuring MBF using CMR. It is widely accepted that there are potential inter-vendor differences between different MRI scanners and these differences are widened by inter-software and inter-hardware differences in scanning and reporting techniques between studies (233, 234). Furthermore, there are potential differences in results produced due to

inter-field differences between MRI scanners (235). Mahmod et al and Jex et al both used 3.0 Tesla MRI scanners, whereas Thornton et al and my study used a 1.5 Tesla scanner, for example (202, 228, 230). All three of those studies induced hyperaemia with a weight based IV Adenosine infusion, whereas I used a standard IV Regadenoson dose for all patients (as is standard of care for stress perfusion CMR in STH), and reported differences in resting/stress MBF may be explained by these significantly differing stressor methods. Finally, my study numbers were much smaller than these similar studies and with greater numbers of patients, different results may have been produced.

4.6.2 Cardiac MRI VIRTU-AS vs VIRTU-5 group

All 10 pre-TAVI CMR cases were compared with cases from the VIRTU-5 study in order to compare MBF and LVMi with patients who had a similar degree of CAD with no valve disease. The VIRTU-AS group were significantly older than the VIRTU-5 patients (82±4 years vs 62±9 years, P=<0.05) and both groups had a similar degree of CAD (seven patients in each group had revascularisation with PCI and three had physiologically non-significant CAD). All patients in this analysis were scanned using the same protocol and on the same MRI scanner. LVEF was similar between the groups 58±12% in VIRTU-AS vs 57±6% in VIRTU-5 (P=0.78) (see figure 72). Patients with severe AS had significant LVH and had much greater LV mass. LVM ED was 156±26g in VIRTU-AS and 104±34g in VIRTU-5 (P=<0.05). LVMi was 79±14g/m^2 vs 55±18g/m^2 (P=<0.05) (see figure 73). This was not an unexpected finding, and was primarily driven by the haemodynamic conditions of AS, but may have also be driven by age and other comorbidities such as CAD or chronic hypertension. These findings corroborated similar findings by Mahmod et al who noted LVMi of 95±30g/m^2 in patients with severe AS compared to 56±13g/m^2 in a sub-set of controls who also did not have CAD (228). Jex et al showed an LVMi of 78g/m^2 (74-82) in patients with severe AS, compared to 53g/m^2 (49-58) in a subset of controls (P=<0.001) (230). The results generated by the VIRTU-AS study are largely in line with these similar studies.

When stress global perfusion results were analysed, MBF was statistically different between the groups, but only in absolute global terms (mL/min). When indexed to LV mass (mL/min/g), there was similar resting and hyperaemic MBF. Patients with severe AS had a significantly

higher global MBF at both stress (554±119mL/min vs 409 ±109mL/min, P=<0.05) and rest (478±141mL/min vs 328±65mL/min, P=<0.05) (see figure 74). The difference in global MBF can be explained by the significant difference in LVM and LVMi between the groups. Global MBF at stress was 26% higher in the VIRTU-AS cohort and resting global MBF was 31% higher. The MPR was non-significantly higher in the VIRTU-5 cohort than the VIRTU-AS cohort (1.4 (1.2-1.5) vs 1.1 (1.0-1.3), P=0.52). Regardless of adaptive LVH in AS, the coronary arteries and microvasculature do not proliferate concurrently to supply the subtended myocardium with oxygenated blood and the VIRTU-AS cohort had a significantly more demanding myocardium, reduced capacity to respond to hyperaemia and were subsequently more vulnerable to ischaemia. These findings corroborated the pre- and post-TAVI CMR results, indicating that patients with severe AS were running at hyperaemic like conditions during rest, mandating significantly higher volumes of global blood flow in order to maintain adequate oxygen supply to the stressed myocardium. This occurred regardless of CAD, but the effects would be expected to be exacerbated in its presence. The numbers of patients compared in this sub-study were small and they were not age-matched. They were scanned using the same protocols, however stress response to Regadenoson may not have been equal between patients and slight differences in reporting techniques may have affected result accuracy nonetheless.

4.9 Key limitations

The VIRTU-AS study had a number of limitations. This section will provide summary of the key limitations of this study, reasons, mitigating steps and future suggestions.

First, the sample size of this study was small. The target of 20 patients was reasonable and in line with a number of other similar studies researched prior to writing the protocol. Unfortunately, as described in the results section and figure 38, the overall number of patients who attended for investigations dropped significantly at various stages for a number of reasons; and, ultimately, statistical comparisons were only performed on seven patients who re-attended for angiography and CMR. The attrition and exclusion rate were high due to various patient related and logistical reasons. The study was therefore underpowered to detect any significant differences despite reaching statistical significance in a number of

parameters. Due to the small number of patients who attended for post-TAVI investigations, no multivariate regression analysis could be performed and I was therefore unable to relate changes in MBF or aCBF to changes in LV parameters or each other. The only statistical analysis used for these measures was paired or unpaired t-testing. The results were purely hypothesis generating and cannot guide treatments.

Second, all patients who participated in the study had preserved LV function. Patients with LV failure were not excluded from the study but due to low study numbers, none had significant dysfunction and therefore no patients had low-flow AS or significant LV failure. As such, these results cannot be broadly applied across the entire AS population and a larger, separate sub-study of these patients would be required to investigate the questions posed by this thesis in this cohort of patients.

Third, the follow-up period of 3-6 months was also relatively short, and ideally patients would have been followed up at 12 months to allow a longer myocardial "healing" and remodeling period. I cannot exclude the possibility of different results with a longer follow-up period. Due to time constraints caused by logistical problems in the early stages, a follow-up period of 3-6 months was deemed appropriate. Nevertheless, similar studies with larger numbers of patients were also hypothesis-generating, and the VIRTU-AS study aimed to add to the knowledge base in this area. Furthermore, a follow-up period of 3-6 months was in line with numerous similar studies, and did nonetheless demonstrate significant changes in various parameters. Larger studies of this kind were multi-centre studies with much longer recruitment and follow-up periods (see tables 2 and 3). To further clarify the hypotheses posed by this study, a larger multi-centre study with several years of recruitment and follow-up would provide more meaningful data which would be powered for regression analyses and long-term survival and MACE outcomes.

Fourth, the vast majority of patients who returned for a follow-up angiography were in the PCI cohort and therefore the results could not be interpreted separately between patients with treated or untreated CAD, as was the original plan. This was a problem caused by the

low overall recruitment numbers and compounded by the issues relating to re-attendance for follow-up angiography. Extending the study for a longer period and across multiple sites would help to clarify differences between these groups. Furthermore, all patients in this study were Caucasian and the majority were male. As such, results may not be generalisable across the general population. Larger and more targeted recruitment would aim to mitigate for this in future.

Fifth, the use of CFD technology, primarily virtuQ^{TM}, in this study was enlightening, but the technology is not yet approved for clinical use, and cannot be used to guide treatment. Some of the key limitations of CFD were described in section *4.5.2*. There are no widely accepted normal reference values available and the clinical interpretation of aCBF in any coronary artery is only possible when described alongside the mass of subtended myocardium, which was not possible in this study (212). The benefits of measuring aCBF, whether invasively or virtually, have yet to be proven and the use of CFD in this study was for purely scientific research and hypothesis generating purposes. Unfortunately, during the time spanned by this study, I could not measure aCBF invasively in the CCL. Measuring aCBF invasively would have proven even more enlightening without adding a further invasive procedure. Results would have been compared with CFD derived values for validation. In future, measuring aCBF in the CCL invasively alongside virtuQ^{TM} would be a worthwhile addition to the study protocol and would not significantly increase procedural risk. Cost would be a factor as only the Rayflow^{TM} catheter is currently licensed to obtain invasive flow data and this is not standard stock in STH. The use of Rayflow^{TM} catheter would have also negated the need for bolus thermodilution, which is known to demonstrate significant data variability, as it is able to measure IMR and CFR using continuous thermodilution, which is likely to be more accurate (122). Furthermore, patients were not selected or screened according to their TAVI valve prosthesis type and I was unable to achieve coronary access in two patients with supra-annular valves, which degraded my already small data set further. A detailed explanation of these cases was outlined in section *4.4.1*. In a larger and multi-centre study, patients with intra-annular valve types may be recruited in preference to supra-annular valves. In those who receive supra-annular valves, care should be taken to achieve coronary ostial alignment by the TAVI operator, which was not necessarily the case here.

Sixth, patients were recruited from not only STH, but from hospitals across the region, and as such, pre- and post-TAVI echocardiogram standard reporting data varied between trusts. The majority of patients (although prognostically useful) did not have consistent reporting of right heart parameters such pulmonary artery systolic or right atrial pressures. These parameters contribute to CFR, CS flow and overall myocardial blood flow and are liable to change after TAVI, which may have affected the results of this study. Right heart pressures can be measured invasively in the cardiac catheter suite at the same time as angiography, however this would have added a further invasive procedure (which also carries intrinsic risk), and did not form part of the protocol of this study.

Finally, a standard 400ug dose of Regadenoson was used as the stressor agent in all patients who attended for CMR. There may be some benefit with using weight-based stressor agents due to significant weight differences. Regadenoson is nonetheless well evidenced as a stressor agent for stress perfusion CMR (236).

4.10 Conclusions

The VIRTU-AS study has demonstrated that it is safe and possible to collect an array of data in patients with severe AS who have CAD and were undergoing TAVI. This was the first study to perform these investigations in a real-world population of elderly and comorbid patients. The mean age of the participants of this study was at least 10 years older than those in similar studies (who did not have TAVI and did not have significant CAD). As such, this was among the first studies to investigate CMR derived MBF, CS-flow and MPR in patients with CAD undergoing TAVI and the first study of its kind measuring CFD derived aCBF pre- and post-TAVI. I have demonstrated that patients with severe AS were living in a state of constant hyperaemia, with a hypertrophied and stressed myocardium, demanding high volumes of blood. Myocardial ischaemia is ultimately a question of oxygen supply: demand. Patients with severe AS and CAD had a high demand (progressive LVH, high LVEDP, and need to maximally recruit the capillary bed) and low supply (progressively falling proximal perfusion pressure and coronary stenosis). Despite being in a state of near maximal hyperaemia, they were critically vulnerable to ischaemia (even without significant CAD), as demonstrated by the extremely low CFR and MPR. Microvascular disease, per se, did not seem to be the primary

issue, and IMR and MVR remained relatively normal and did not change with TAVI (also demonstrated by numerous other studies). Instead, in order to meet the high oxygen demands of a hypertrophied myocardium, the capillary bed must dilate and be recruited in greater and greater proportions as LVH increases. With respect to MVR, there seemed to be a minimum microvascular resistance that was reached which did not fall further. Progressive recruitment of the capillary bed in response to stress was impaired and CFR was reduced. This process was demonstrably reversed after TAVI, despite the high age, frailty and presence of CAD in this cohort. LVMi fell significantly after only 3-6 months, and the myocardial oxygen demands of the heart fell significantly, which was most pronounced at rest. Vessel specific resting aCBF fell (significantly) by 20% following TAVI (measured using CFD), and hyperaemic aCBF fell (non-significantly) by 7%. Global MBF at rest fell by 44.5% and MBF at stress fell by 32% when measured with stress perfusion CMR. Three key factors; namely, significant LVMi reduction, aCBF reduction (rest > stress) and global MBF reduction (rest > stress) provided the mechanism for improvement in CFR. Figure 79 represents a schematic diagram demonstrating, very simply, the changes which I have demonstrated in MBF following treatment with TAVI.

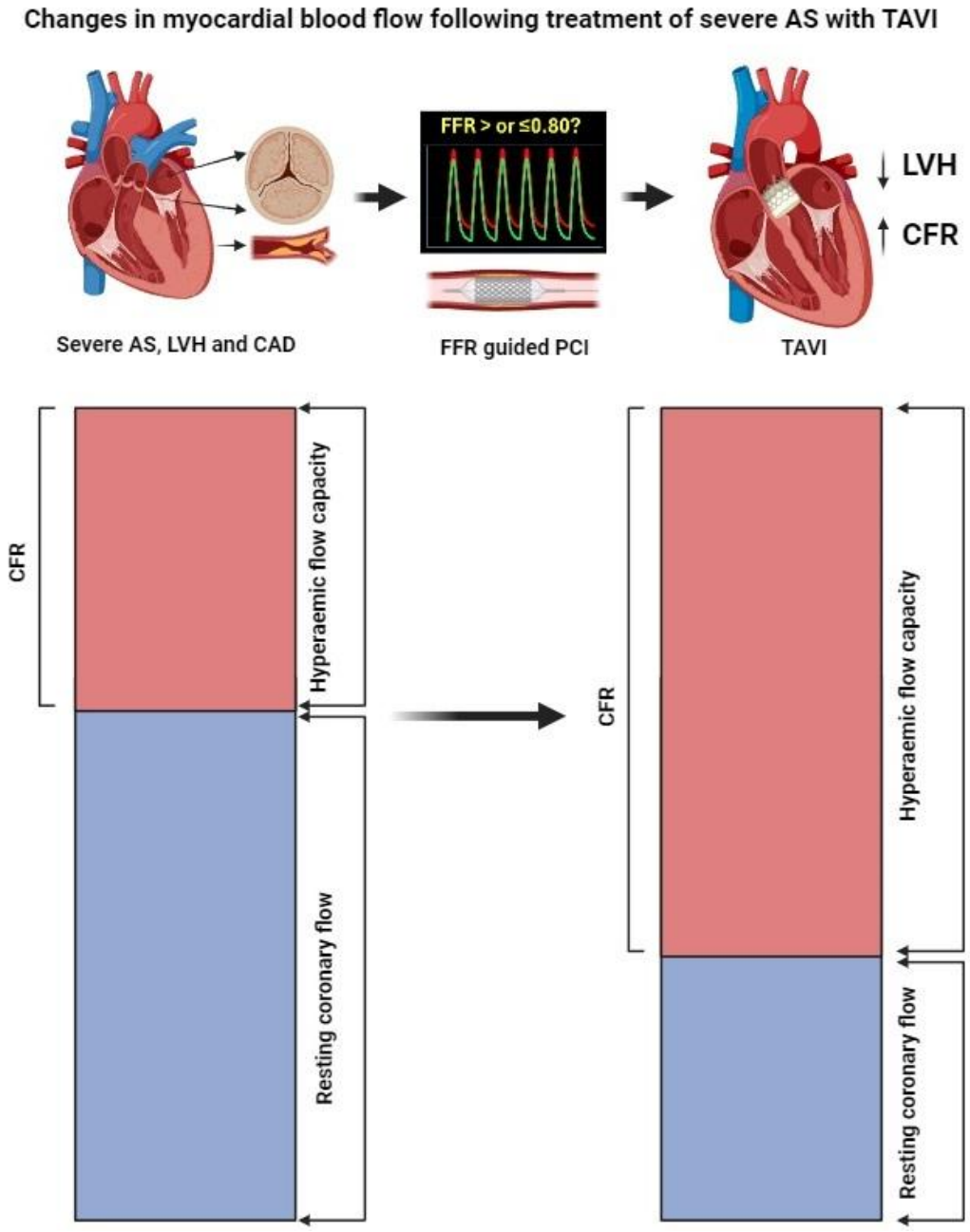


Figure 79. Schematic diagram showing the changes in MBF which occur following TAVI.

FFR increased post-TAVI, albeit in patients without severe coronary disease, who predominantly had pre-TAVI FFR values of >0.8. Due to this fact, and low numbers studied, no definitive conclusions could be drawn on this. However, together with the aCBF and MBF findings using virtuQ^{TM} and CMR respectively, I could provide some enlightenment on the most appropriate index of coronary physiology to use in patients with severe AS. Resting coronary flow, both regionally and globally, fell significantly following TAVI. This was due to

the fact that patients with severe AS have very high resting coronary flow for reasons already described. Patients with severe AS were therefore already hyperaemic, so non-hyperaemic indices of coronary physiology such as RFR and iFR are probably inappropriate for use (as evidenced by table 3, demonstrating ischaemic iFR values of ≤0.89 for patients with no CAD) and are most likely to change as a result of falling resting flow, which occured following TAVI. FFR, conversely, relies upon hyperaemic blood flow. The relatively stable hyperaemic aCBF following TAVI suggests that FFR might be a more reliable marker of coronary ischaemia in patients with AS. This hypothesis has been corroborated clinically by the recently published NOTION-3 trial (154). I have therefore shown that the physiological changes which occur following TAVI support the use of FFR, rather than non-hyperaemic indices, and the standard threshold of ≤0.8, may be preferable in guiding revascularisation for patients with severe AS. Figure, 80, below, represents a treatment algorithm for patients with severe AS and concomitant CAD. I have developed this pathway based on my experiences gained during the VIRTU-AS study, as well as through corroboration through the findings of the NOTION-3 study and expert consensus from Tarantini et al and the EAPCI and ESC working group on cardiovascular surgery (139, 154).

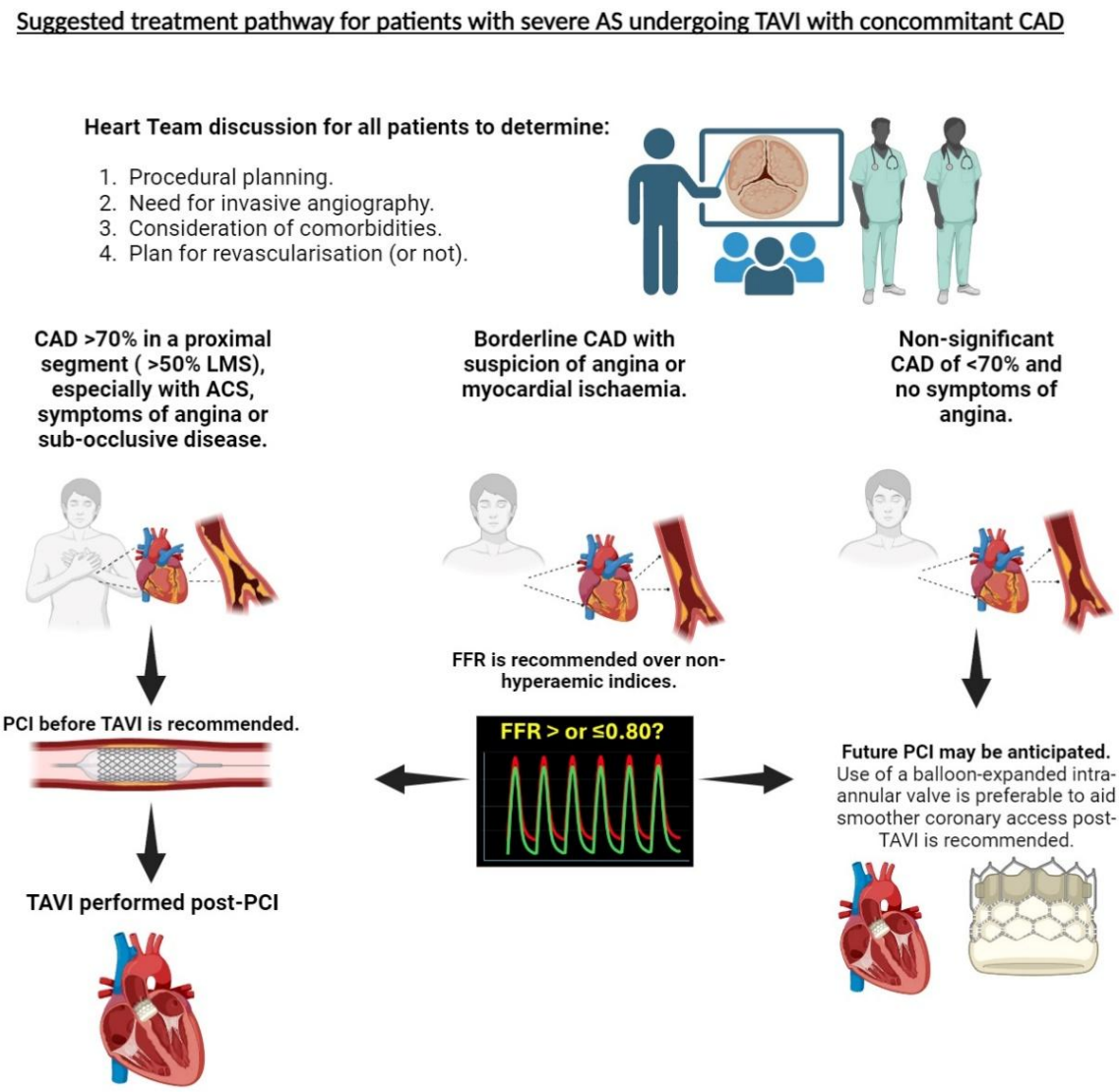


Figure 80. Suggested treatment pathway for patients with severe AS and CAD (222).

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Appendix

Appendix A – VIRTU-AS patient consent form

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Patient Identification Number for this trial: ☐

CONSENT FORM
The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis (VIRTU-AS).
Professor Julian Gunn

*Please **initial** boxes*

1. I confirm that I have read and understand the information sheet Version 2.0 dated 08/02/2022 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust or University where it is relevant to me taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to have the pressure sensor measurements at the time of my valve implantation. ☐
5. I agree to answer the questionnaires. ☐
6. I agree to have the activity monitoring. ☐
7. I agree to perform the 6 minute walk tests. ☐
8. I agree to have a cardiac MRI scan before and after my procedure. ☐
9. I agree to return for the second angiogram and pressure measurements 3-6 months later. ☐

Name of Patient	Date	Signature
Name & Job Title of Person Taking Consent	Date	Signature

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

VIRTU-AS. Consent Form. Version 1.0 20/12/2021. IRAS: 301021 STH21871

Appendix B – VIRTU-AS patient invitation letter

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

ACADEMIC TEAM
Professor J Gunn
Professor of Interventional Cardiology
Dept Cardiology
Northern General Hospital
Herries Road
Sheffield
S5 7AU

Secretaries:
Mrs Tracy Ellender and Mr Neil Shaw: 0114 271 4953

Date:

Dear

The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis (VIRTU-AS).

(Building a computer model of the changes to the blood supply of the heart after treatment of a narrowed aortic valve).

We are working on this project, and you might be interested in taking part.

In this research we are using our skills, and those of our collaborators in the University of Sheffield, to construct a computer model of blood supply to the muscle of the heart before and after the treatment of aortic valve narrowing with a valve implantation procedure. This will enable us to plan treatments more effectively in the future. We have identified you as being suitable to help us with this research.

It will involve our research team going through some questionnaires with you, doing a short walking test, and monitoring your activity at home. You may also be asked to have a MRI scan of the heart. We would like to do these things with you before and after your valve implantation. At the time of your valve implantation procedure, we will make some measurements of the blood flow within the arteries which supply the heart, using the tube that will be already in your circulation.

Some patients will be invited back to hospital to have those measurements repeated with another cardiac catheter procedure. As with the first part of the study, you are free to opt in or out.

I enclose the 'Patient Information Sheet' which contains more details. Please take time to read the sheet and discuss it with your family or friends. If you agree, please complete the enclosed slip and post it in the stamped addressed envelope. One of our research team will then contact you to explain the research in more detail, and answer your questions. If you would prefer not to take part in this research, you do not have to, and that will not affect your treatment.

Thank you for reading this and considering taking part in our research.

Yours sincerely

Professor Julian Gunn MA MD MRCP

Appendix C – VIRTU-AS patient information sheet

Participant Information Sheet

The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis (VIRTU-AS).

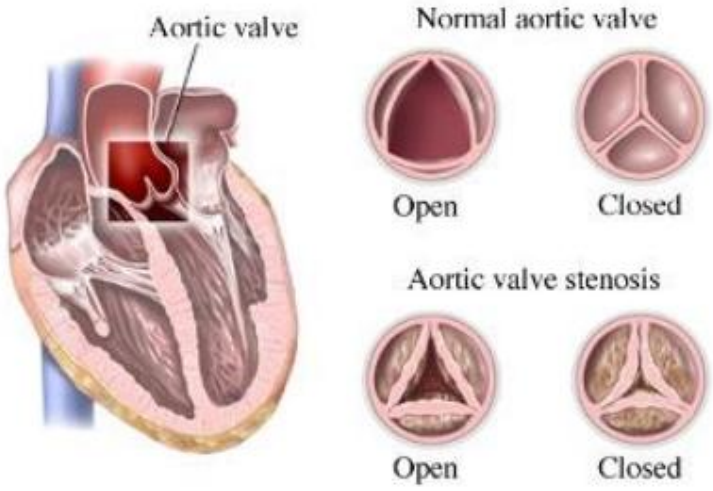
Principal Investigators: Professor Julian Gunn, Dr Ever Grech, Dr Alex Rothman, Consultant Cardiologists, Sheffield Teaching Hospitals NHS Foundation Trust and the University of Sheffield

An invitation to take part in medical research

We invite you to take part in this research study. Before you decide, we would like to explain why the research is being done and what it would involve for you. This information sheet will help you in making the decision. Please take your time to read the following information and, if you wish, discuss it with friends, relatives or your doctor. If anything is not clear, or if you would like more information, one of our team will contact you shortly. If you prefer, please contact Professor Gunn via his secretary on 0114 2714953.

What is the purpose of the study?

Aortic stenosis is a condition in which the opening valve of the large blood vessel which carries blood from the heart to the rest of the body becomes narrowed and restricted.



TAVI (transcutaneous aortic valve implantation) is a minimally invasive method to restore good blood flow through the aortic valve by implanting a new valve, inside your own. This is the treatment that you are *probably* going to have. ['Probably', because the final decision is made by you, with the help of the specialist team taking care of you]. Sometimes, with a narrowed aortic valve, you may also have narrowing affecting the coronary arteries - the arteries which supply the heart with blood. This is determined by having a test called an angiogram (pictures of your arteries), which is normally done before you have any major heart procedure. But it's not always obvious from the pictures how much a particular narrowing restricts blood flow, and how much blood is actually flowing into your arteries and heart. To help find out, we can pass a flexible sensor down to artery to measure pressure gradients. This is standard; but when you have aortic stenosis, the measurements are difficult to interpret. Here in Sheffield, we have developed a computer model of blood flow that can tell the specialist what the blood flow and pressure gradient is. In this project, we will use that model to help us know whether or not arterial narrowings in patients with aortic stenosis need treatment. This is an educational study in conjunction with the University of Sheffield and will form part of a postgraduate degree (PhD or MD) award for the research doctor conducting the project.

Why have I been invited?
You are being invited to participate in this study because you have aortic stenosis.

What do I have to do?
If you take part, there will be five additional procedures:

1) You will be asked some questions about your health with questionnaires. These can be conducted by one of our research fellows visiting you at home, and will take about 20 minutes.
2) When you attend the hospital for your routine pre-assessment appointment, we will ask you to do a walking test that lasts 6 minutes. This will take a total of 30 minutes or so.
3) We will record your activity level (heart rate, steps taken, distance moved etc) at home. This is easily done with a 'smart watch' and a mobile phone. We can supply and fit these for you. Setting up the equipment will take less than an hour in your home. You won't be asked to do anything complicated. All you have to do is lead your normal life. This will be done for a period of 4-6 weeks before your procedure and again for 4-6 weeks a few months after your procedure. Afterwards, we will collect all monitoring equipment back from you either at a routine follow-up hospital visit or from your home.
4) You may be offered an MRI (magnetic) scan of your heart. This involves a visit to hospital, and takes about an hour in a scanner. No X-rays are involved. We will provide a taxi for you to get there and home again.

We will then give you your treatment in hospital, the valve procedure itself being done entirely as normal, using the latest techniques. Immediately before and after placing your new valve, we will pass a pressure sensor into your coronary arteries. We will collect a lot of useful data at

this point of the procedure (such as clinical details, pictures of your arteries and pressures in the vessels). This is for research purposes only and will not affect your treatment.

Afterwards, a few weeks later, when everything has settled down for you, we will repeat the additional procedures listed above. All the measurements and data that we collect will help us construct our model of how blood flow improves, how the heart improves and how you improve with the treatment that you receive.

5) We will ask you if you would also be willing to have further angiogram and pressure sensor assessment of your coronary arteries 3-6 months after the procedure. This will help us understand the long term changes in your arteries after having a new aortic valve implanted.

Do I have to take part?
No you don't. Your participation in this trial is voluntary. It is up to you to decide whether or not to take part. Your decision will not affect the standard of care you receive. If you do decide to take part, you will be asked to sign a consent form. You can also take part in some or all of the study. It's up to you.

What will happen to me if I take part?
The study won't affect your treatment at all. You will receive normal care. This is because this study is designed to ask the 'hypothetical 'questions 'Can we build a computer model of myocardial blood flow before and after treatment of aortic stenosis? 'and 'Will this enable us to predict the treatment that would best suit you?'.

Can I withdraw?
Yes, at any time. That will not affect your treatment either.

What are the possible benefits of taking part?
There won't be any direct benefit to you but, if this project works well, we will be in a better position in the future to 'tailor 'treatments for patients to match their requirements.

What will happen to my clinical information?
We will need to use information from you and from your medical records for this research project. This information will include:

- Name
- Address
- Date of birth
- Contact details
- NHS number
- Sex
- Ethnic origin
- Relevant data about your medical condition

We will use this information to do the research and others to check that the research is being done properly. People who do not need to know will not be able to see your name or contact details. Your data will have a study code instead. Your data will be held safely and securely on a computer kept at the University of Sheffield. No-one other than the study team will have access to it. If for any reason you lose mental capacity during the study, we will retain your data securely and fully anonymised, but will not ask you to participate in any further activities in the study.

Once we have finished the study, we will keep some of the data so we can check the results. Your rights to access, change or move this information are limited, because we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we already obtained, but this should not affect you because your identity will have been removed from the data. We will write our reports in a way that no-one can work out that you took part in the study.

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- https://www.sheffieldclinicalresearch.org/for-patients-public/how-is-your-information-handled-in-research/
- by asking one of the research team
- by sending an email to the Data Protection Office at: sth.InfoGov@nhs.net

Who has reviewed this study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by scientists and doctors appointed by the University, the Sheffield Hospital Trust, the Sheffield Hospitals Charity and the Research Ethics Committee.

Expenses and Incentives?
We will not be offering you a financial incentive to participate. But we do hope that you gain some satisfaction from taking part in an exciting new study, and the possibility that the research will help future patients. We will provide transportation by taxi to the hospital and home again for all additional appointments you attend as part of the study.

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

Are there any possible disadvantages or risks from taking part?
The walking test will be done at your own speed. The activity monitoring will require wearing a smart watch and allowing a Research Fellow into your home to set up the equipment. We may ask a few patients to come back a few months later for a further angiogram and pressure study of the coronary arteries. This is generally a safe procedure. The MRI scans will involve two extra

visits to hospital. Some patients find lying still in the scanner a bit difficult and it is a noisy environment but headphones will be provided. If you are claustrophobic or have any metallic objects in your body (such as surgical clips or a pacemaker), these will be discussed with you by the research team and you may not be suitable to come for an MRI scan. On the day of your MRI scan, a radiographer will go through a separate safety questionnaire with you - there is a small chance you may not be suitable to have an MRI scan if there are any other safety concerns at this stage. The 'contrast' agent used can affect kidney function in a very small minority of patients (but it is used in routine NHS practice). There is a 0.1% risk of being allergic to the contrast.

If you take part in all of the study you will have three "extra" coronary angiograms and pressure measurements taken (two on the day of your procedure, and one later on at 3-6 months). You will have already had a coronary angiogram as a routine part of your pre-procedure investigations. We will also aim to place a hair-thin "pressure wire" inside your arteries to measure the pressure inside them for our study. The total risk of the coronary angiogram with pressure assessment is around 0.1% for any serious complication such as heart attack, need for an emergency stenting procedure or surgery, stroke, damage to your blood vessels and very rarely death. Your procedure will be performed by a skilled and experienced doctor and all steps to minimise these risks will of course be taken. You will be monitored for several hours afterwards to ensure you remain well after the procedure.

Radiation

If you take part in this study you will have several imaging procedures including a TAVI procedure and angiograms. Some of the exposure will be extra to that you would have if you did not take part. This is to allow safe placement of pressure monitoring wires in the heart arteries and a second angiogram procedure. These procedures use ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you from 50% to 50.4%

The MRI scan uses a magnetic field, not ionising radiation, so there is no additional risk from this imaging procedure.

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

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

What will happen if I don't carry on with the study?

Your participation is entirely voluntary. If you change your mind, you are free to stop your participation without giving any reason, and this will not affect the routine clinical care you will receive. If you withdraw from the study, unless you state otherwise, any clinical data which have been collected whilst you have been in the study will be used for research as detailed in this participant information sheet.

Who is organising and funding the study?
Professor Gunn and Dr Grech organised the study. Funding of the TAVI is by the NHS. The 'sponsor 'of the study (the organisation which takes responsibility for it) is the Sheffield Teaching Hospitals NHS Foundation Trust. A Research Fellowship from the Heart Trust Charity will fund the Research Fellow. The Sheffield Hospitals Charity fund the MRI scans.

What happens when the research study stops?
Your treatment and follow-up will continue as before. We hope to publish the results in a scientific journal which will allow specialists all over the world to understand how to treat their patients more effectively. The data that is obtained as part of this study may be used in future projects to assist with the further development in this area. If you would like a copy of the research report, please contact Professor Gunn (details below) and we can send this to you. We will use the information gained in this study to help design a big trial of the technology with more patients. If that is positive, then we will roll out the technology throughout the NHS to help benefit patients like you.

What if there is a problem?
If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, please contact
Professor Julian Gunn, Secretary: +44 114 271 4953, or email julian.gunn1@nhs.net

If you remain unhappy and wish to make a formal complaint about any aspect of the study, or how you have been treated during the study, you can do this through the NHS Complaints Procedure. Details can be obtained from your Study Doctor's hospital or GP practice.

For independent advice or in the case of complaints, please contact:
Name: Patient Services Team
Phone no: 0114 271 2400
Email: sth.pals@nhs.net

Indemnity and Compensation.
In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Sheffield Teaching Hospitals NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

If I have any later questions, whom do I contact?
Professor Julian Gunn, whose contact details are shown above. He is based at the University of Sheffield and also at the Department of Cardiology, Northern General Hospital, Sheffield, S5 7AU.

What do I do now?
If this study is of interest to you, and the researcher is with you, please ask any questions that occur to you. [If you have been sent this by post, please sign and return the 'PhoneSlip 'in the

pre-paid envelope. We will then contact you by phone and arrange to visit you]. Finally, we will ask you to sign the consent form for the study.

Thank you very much for reading this.

Professor Julian Gunn

Appendix D – VIRTU-AS HRA and REC approval letters

NHS
Health Research Authority

North West - Preston Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0207 104 8019

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

28 September 2022

Dr Eron Yones
2 Slinn Street
Sheffield
S10 1NX

Dear Dr Yones

Study title:	**The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis.**
REC reference:	**22/NW/0017**
Amendment number:	**Substantial Amendment 01**
Amendment date:	**07 September 2022**
IRAS project ID:	**301021**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [VIRTU-AS SA01 Tool]	SA01	07 September 2022

Letter from sponsor [Sponsor Review Email SA01]	1	07 September 2022
Letters of invitation to participant [VIRTU-AS Patient Invite Letter V2_CLEAN]	2.0	09 August 2022
Letters of invitation to participant [VIRTU-AS Patient Invite Letter V2_TC]	2.0	09 August 2022
Other [Research Exposure Form]	3.0	09 August 2022
Participant consent form [VIRTU-AS Consent Form V2_CLEAN]	2.0	09 August 2022
Participant consent form [VIRTU-AS Consent Form V2_TC]	2.0	09 August 2022
Participant information sheet (PIS) [VIRTU-AS PIS V3_CLEAN]	3.0	09 August 2022
Participant information sheet (PIS) [VIRTU-AS PIS V3_TC]	3.0	09 August 2022
Research protocol or project proposal [VIRTU-AS_Protocol_Clean]	3.0	09 August 2022
Research protocol or project proposal [VIRTU-AS_Protocol_TC]	3.0	09 August 2022
Summary, synopsis or diagram (flowchart) of protocol in non technical language [VIRTU-AS Lay Summary V2 CLEAN]	2.0	09 August 2022
Summary, synopsis or diagram (flowchart) of protocol in non technical language [VIRTU-AS Lay Summary V2_TC]	2.0	09 August 2022

Membership of the Committee

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

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

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.

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/

IRAS Project ID - 301021:	**Please quote this number on all correspondence**

Yours sincerely

Professor Karen Wright
Chair

E-mail: preston.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Eron Yones*

North West - Preston Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 26 September 2022

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Karen Rouse	Deputy Head of School of Dentistry	Yes	
Professor Karen Wright	Professor of Nursing	Yes	

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Julian Gunn
Dept Cardiology
Northern General Hospital
Sheffield
S5 7AUN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

02 March 2022

Dear Professor Gunn

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis.**
IRAS project ID:	**301021**
REC reference:	**22/NW/0017**
Sponsor	**Sheffield Teaching Hospitals NHS Foundation Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **301021**. Please quote this on all correspondence.

Yours sincerely,
Natasha Bridgeman

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Mrs Samantha Walmsley, Sheffield Teaching Hospitals NHS Foundation Trust*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_23122021]		23 December 2021
IRAS Application Form XML file [IRAS_Form_23122021]		23 December 2021
Letters of invitation to participant [Invite]	1.0	20 December 2021
Letters of invitation to participant [Reply slip]	1.0	20 December 2021
Other [Protocol (tracked changes)]	2.0	08 February 2022
Other [Protocol (clean)]	2.0	08 February 2022
Other [Response to REC requests]	1.0	08 February 2022
Participant consent form [ICF]	1.0	20 December 2021
Participant information sheet (PIS) [PIS]	2.0	08 February 2022
Participant information sheet (PIS) [PIS]	2.0	08 February 2022
Referee's report or other scientific critique report [ISR Pass]		
Referee's report or other scientific critique report [R1 Comments]		
Referee's report or other scientific critique report [R2 Comments]		
Summary CV for Chief Investigator (CI) [CI CV]		01 July 2020
Summary CV for student [Student CV]		21 December 2021
Summary CV for supervisor (student research) [Supervisor CV]		01 July 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Lay Summary]	1.0	20 December 2021
Validated questionnaire [EQ5D]		
Validated questionnaire [SAQ]		
Validated questionnaire [SF12]		

IRAS project ID	301021

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
This is a single site study sponsored by the participating NHS organization therefore there is only one site type.	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This is a single site study sponsored by the participating NHS organization therefore no agreements are expected.	External funding has been secured for this project.	A Principal Investigator should be appointed at study sites.	The sponsor has stated that local staff in participating organisations in England who have a contractual relationship with the organisation will undertake the expected activities. Therefore no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix E – VIRTU-5 REC approval letter

North of Scotland Research Ethics Committee (1)
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

NHS Grampian

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

06 March 2020

Professor Julian Gunn
Professor of Interventional Cardiology
University of Sheffield
Western Bank
SHEFFIELD
S10 2TN

Dear Professor Gunn

Study title:	**VIRTU-5: towards a complete model of myocardial ischaemia**
REC reference:	**20/NS/0033**
IRAS project ID:	**272069**

Thank you for your e-submission on 05 March 2010. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 02 March 2020.

Documents received

The documents received were as follows:

Document	Version	Date
IRAS Checklist XML [Checklist 05/03/2020]		05 March 2020
Letters of invitation to participant	1.3	05 March 2020
Participant information sheet (PIS)	3	05 March 2020

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
Covering letter on headed paper		21 January 2020
IRAS Application Form	272069/1413118/37/927	21 January 2020
IRAS Checklist XML [Checklist 05/03/2020]		05 March 2020
Letter from funder [Sheffield Hospital Charity (SHC) Grant Acceptance Form]		07 November 2019
Letters of invitation to participant	1.3	05 March 2020
Other [EQ-5D licence (registration)]		11 September 2019
Other [Seattle licence (Outcomes Instruments LLC)]		11 September 2019
Other [SF12 licence (Optum)]		25 October 2019
Other [Phone Slip]	1.0	15 February 2020
Other [Appendix 1 - Guidance Doc for Undertaking a Local Risk Assessment for Lone Working]	2	03 March 2020*
Other [Appendix 3 - Lone Worker Off Site Checklist]		03 March 2020*
Other [Lone Worker Policy]	2.1	13 January 2012
Other [Appendix 2 - Lone Working in Building Checklist]		03 March 2020*
Participant consent form [Consent Form]	2	18 February 2020
Participant information sheet (PIS)	3	05 March 2020
Research protocol or project proposal	1.0	08 December 2019
Summary CV for Chief Investigator (CI) [Prof Julian Gunn]		08 August 2019
Summary CV for student [Gareth Wiliams]		16 February 2020
Summary CV for student [Abdulaziz Al-Baraikan]		24 September 2019
Summary CV for supervisor (student research) [Prof Julian Gunn]		08 August 2019
Summary CV for supervisor (student research) [Dr David Hose]		18 February 2020
Summary CV for supervisor (student research) [Dr Paul Morris]		10 February 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language	1.1	14 December 2019
Validated questionnaire [EQ-5D-5L Health Questionnaire © 2009]	1.2	
Validated questionnaire [SF-12 Health Survey © 1994, 2002]	2	
Validated questionnaire [Seattle Angina Questionnaire © 1992-2004]	SAQ-UK	

*date received

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

20/NS/0033	Please quote this number on all correspondence

Yours sincerely

Ms Sarah Lorick
Assistant Ethics Co-ordinator

Copy to: Mr Abdulaziz Al-Baraikan
Mrs Samantha Walmsley, Sheffield Teaching Hospitals NHS Foundation Trust
Lead Nation - England: approvals@hra.nhs.uk

Appendix F – Cardiac MRI protocol

The (virtual) assessment of coronary blood flow before and after treatment of severe aortic stenosis (VIRTU-AS).

Cardiac MRI Protocol

Principal Investigators: Professor Julian Gunn, Dr Paul Morris, Dr Ever Grech, Consultant Cardiologists, Sheffield Teaching Hospitals NHS Foundation Trust and the University of Sheffield.

Simple Protocol for CMR:

1. Localisers
2. LVLA
3. SA cine
4. 4Ch cine
5. SA cine stack
6. 4D flow sequencing
7. FGRE perfusion (stress)
8. 2D phase contrast (of coronary sinus) (stress)
9. FGRE perfusion (rest)
10. 2D phase contrast (of coronary sinus) (rest)
11. T1 scout
12. Late gad acquisitions

Appendix G – SF-12 questionnaire

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
○	○	○	○	○

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b. Climbing several flights of stairs	○	○	○

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	○	○	○	○	○
b. Were limited in the kind of work or other activities	○	○	○	○	○

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	○	○	○	○	○
b. Did work or other activities less carefully than usual	○	○	○	○	○

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	○	○	○	○	○
b. Did you have a lot of energy?	○	○	○	○	○
c. Have you felt downhearted and depressed?	○	○	○	○	○

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the	Most of the	Some of the	A little of the	None of the

time	time	time	time	time
○	○	○	○	○

Appendix H – Rockwood frailty scale

Rockwood Frailty Scale

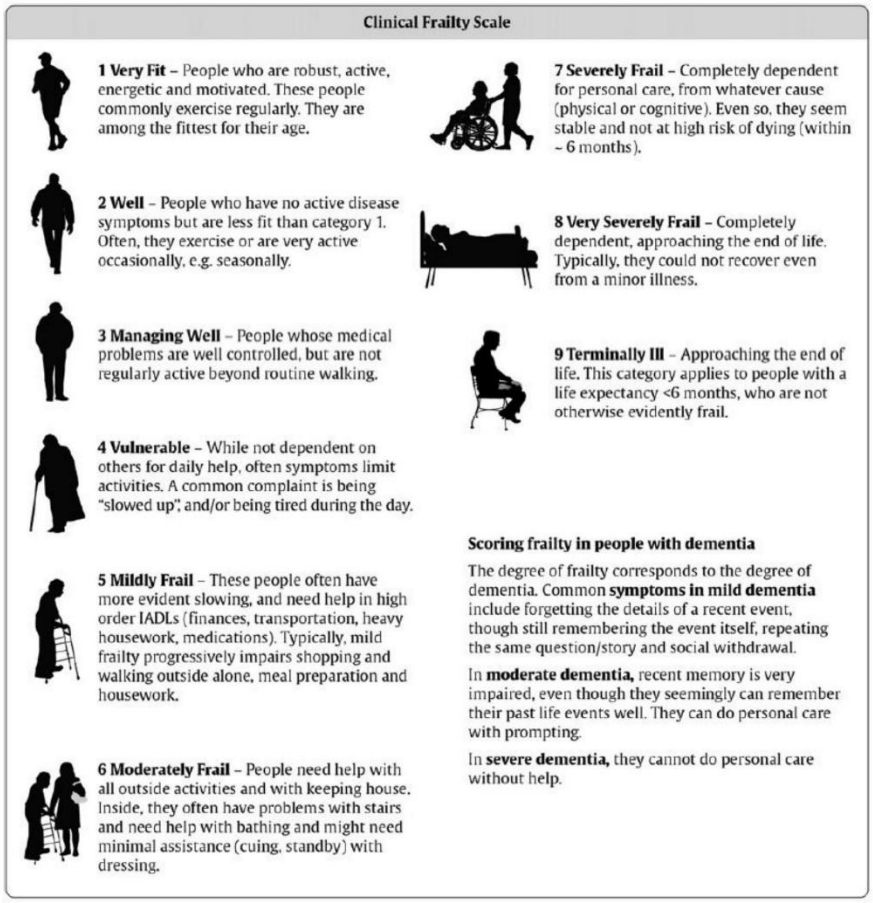


Figure 1.Clinical frailty scale. Adapted with permission from Moorhouse P, Rockwood K. Frailty and its quantitative clinical evaluation R Coll Physicians Edinb. 2012;42:333-340.

Appendix I – New York heart association scoring system

Table 1. New York Heart Association classification of HF

Class	Description
I	Patient with cardiac disease, but no limitation on ordinary physical activity
II	Comfortable at rest, ordinary activity results in symptoms (slight limitation)
III	Comfortable at rest, less than ordinary activity results in symptoms (marked limitation)
IV	Symptomatic at rest, increased discomfort with any physical activity