



Wearable Physical Activity Monitoring in Patients with Coronary Artery Disease: Feasibility, Validity and Clinical Utility

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Abstract

Background

Patients with symptomatic coronary artery disease (CAD) frequently experience limitations in daily activities and quality of life. While medication is the first line treatment for angina, percutaneous coronary intervention (PCI) also relieves symptoms in obstructive CAD. Treatment success is evaluated through patient reported outcomes, lacking objective assessment methods.

Objective

To explore alternative methods for assessing patient response to coronary revascularisation in stable angina using prolonged physical activity monitoring.

Methods

The Virtu-5 study recruited 37 symptomatic CAD patients, using wrist-worn activity trackers. Patients underwent fractional flow reserve (FFR) guided PCI and were monitored continuously before and after their procedure. Activity data were collected for three months pre-procedure and for three to six months post-procedure. Additionally, questionnaires and six-minute walk tests (6MWT) were conducted at baseline and follow-up.

Results

Twenty-five patients underwent PCI, whilst twelve patients with FFR negative disease continued medical management. Compliance with activity tracker usage was high, and device step counting accuracy was confirmed against manual counting. Patients with FFR positive disease achieved higher daily moderate to vigorous physical activity levels versus patients who were found to have FFR negative disease. The PCI group did not demonstrate an improvement in objective physical activity behaviours between baseline and follow up. Questionnaire responses and 6MWT outcomes were shown to be superior in the FFR positive group. Several variables were found to be significantly correlated with changes in physical activity behaviours, including demographic, wearer compliance and atmospheric factors. Despite low prior experience with activity trackers, user experience was positive.

Conclusion

The findings from this work suggest that prolonged physical activity monitoring with wrist-worn activity trackers is a feasible method of collecting data from patients with CAD. Wearable technology-based monitoring may provide valuable and objective information for clinicians and researchers to assess the impact of CAD and revascularisation in patients with angina.

Declaration

I, the author, declare that the work presented herein is my own work. I contributed to the design of Virtu-5 as well as the writing of the protocols for specific study activities. I undertook the screening of patients for inclusion into the Virtu-5 study, conducting patient interviews and recruitment and follow up in collaboration with my colleague Dr Abdulaziz Al Baraikan. We also performed our study data collection procedures together, including the 6-minute walk test assessments, cardiac magnetic resonance studies, and cardiac catheter laboratory data collection. Dr Abdulaziz Al Baraikan contributed heavily to the process of acquiring ethical approval for Virtu-5 by writing the ethical approval application as well as presenting the study to the Cardiothoracic Directorate Research Committee and the Sheffield NIHR Cardiovascular Patient Panel. The focus of my work within the Virtu-5 study was on collecting and analysing physical activity data using wearable technology and comparing them to clinical metrics, while Dr Abdulaziz al Baraikan focused on processing imaging and pressure data collected during the cardiac catheter laboratory procedures as well as processing the cardiac magnetic resonance images. The cardiac catheter laboratory procedures were carried out by Professor Julian Gunn and Dr Paul Morris.

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Abbreviations

0D	zero dimensional
3D	three dimensional
4D	four dimensional
AC	Active calories
AfD	angina free domain
AHA	American Heart Association
BHF	British Heart Foundation
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCL	cardiac catheter laboratory
CDRE	Cardiothoracic Directorate Research Executive
CMR	cardiac magnetic resonance
CPP	cardiovascular patient panel
CT	computed tomography
ECM	extracellular matrix
EDV	end diastolic volume
EI	England index
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
ESC	European Society of Cardiology
ESV	end systolic volume
FFR	fractional flow reserve
HRA	Health Research Authority
HCRW	Health and Care Research Wales
ICA	invasive coronary angiography
IHD	ischaemic heart disease
KSAU-HS	King Saud bin Abdulaziz University for Health Science
LAD	left anterior descending
LCA	left coronary artery
LCX	left circumflex
LMS	left main stem
LPA	light physical activity
MACE	major adverse cardiac events
MCS	mental component score
MI	myocardial infarction

MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
MVPA	moderate to vigorous physical activity
OM	obtuse marginal (artery)
OMT	optimised medical therapy
PCS	physical component score
PCI	percutaneous coronary intervention
PLD	physical limitation domain
QoLD	quality of life domain
RCA	right coronary artery
SAQ	Seattle Angina Questionnaire
SHC	Sheffield hospital charity
SPECT	single photon emission computed tomography
SV	stroke volume
SVG	saphenous vein graft
SF-12	Short Form-12
SPECT	single photon emission computed tomography
TS	time sedentary
VAS	visual analogue scale
VSMC	vascular smooth muscle cells

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CHAPTER 1

1. Introduction & Background

Coronary artery disease (CAD) describes the pathological narrowing of coronary arteries, vessels which supply oxygenated blood to the myocardium. This process leads to the restriction of blood flow to the myocardium, which is exacerbated during periods of physical exertion where the increased demand for oxygen is unable to be met, resulting in the development of myocardial ischaemia. This stress state can manifest as significant pain or discomfort to the individual, leading to a significant reduction in physical activity, exercise tolerance and quality of life. In this introduction the relevant principles of CAD will be reviewed, including its development, assessment, and current therapies, and how these relate to the use of physical activity as an assessment tool. This will be followed by an overview of physical activity assessments, the methods and tools available, the areas in which they've been applied to medical research and clinical practice, and how it may assist in the management of CAD.

1.1 Coronary artery anatomy

The gross coronary artery vasculature is made up of larger vessels giving off many branches (see figure 1.1). The structure can be divided into the left coronary artery (LCA) and the right coronary artery (RCA), both of which originate from the aortic root. The LCA originates from the left sinus of Valsalva as the Left Main Stem (LMS), which bifurcates into the left anterior descending (LAD) and left circumflex (LCX) arteries, while the RCA originates from the right sinus of Valsalva [1]. These vessels

give rise to branch vessels, namely the diagonal and septal branches from the LAD, the obtuse marginal branches from the LCX, and the marginal branches from the RCA. The presence of a further branch vessel, the posterior descending artery (PDA), is used to describe the dominance of either the left or right coronary artery system, with 70-80% of the general population being right-dominant. There is significant variation in the distribution of branch vessels between individuals, with clinically significant coronary anomalies observed in less than 1% of the general population [2].

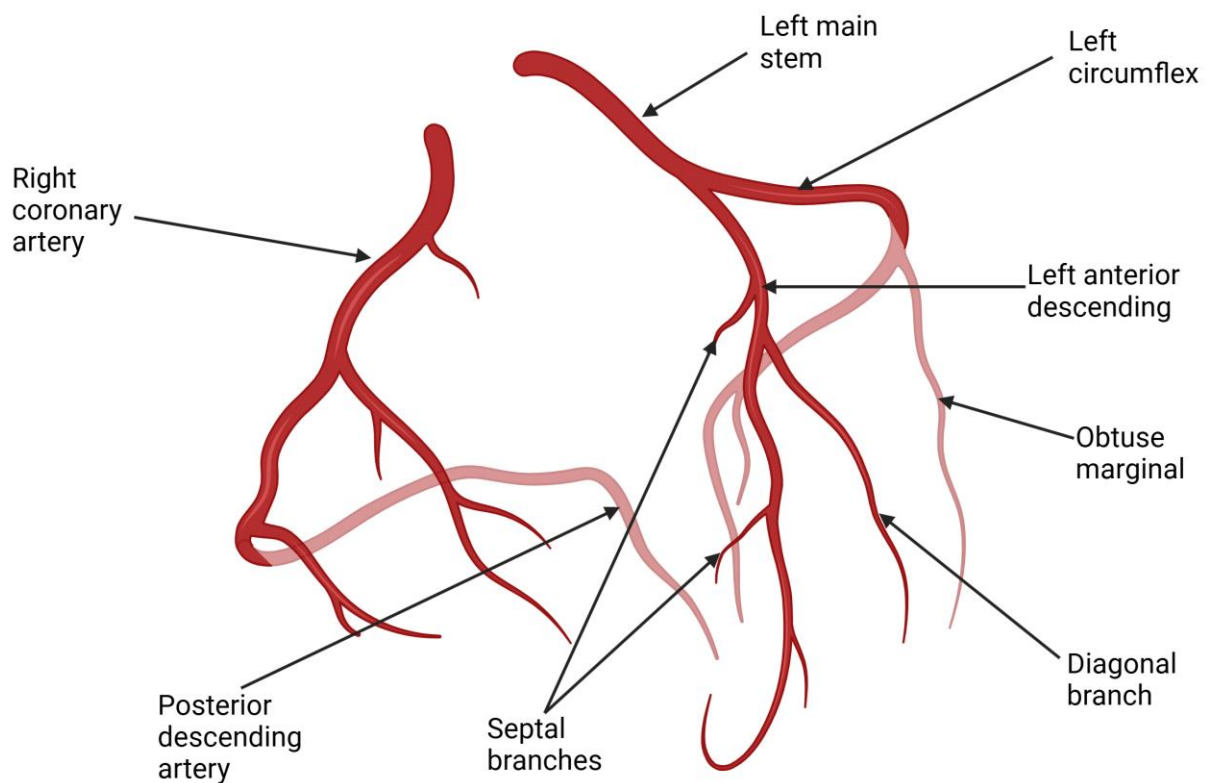


Figure 1.1 Coronary anatomy – right and left coronary artery systems and branches. The right coronary originates from the right coronary sinus, giving off smaller branches and terminating in the posterior descending artery. The left main stem originates from the left coronary sinus and divides into the left anterior descending and left circumflex arteries. The left anterior descending artery gives rise to diagonal and septal branches, while the left circumflex gives rise to obtuse marginal branches. (Generated with Biorender.com)

Similar to all other arteries, the coronary arteries are composed of three microscopic layers known as the *tunica intima*, *tunica media* and the *tunica adventitia* [figure 1.2]. The *tunica intima* is the innermost layer of the arterial wall, a cellular monolayer consisting mostly of squamous endothelial cells which interface directly with circulating blood within the lumen of the vessel and plays a key role in regulating many essential functions, including inflammation, thrombosis, vascular tone, and angiogenesis [3]. The *tunica media* represents the medial section of the arterial wall, which contains vascular smooth muscle cells (VSMCs), extracellular matrix (ECM), and proteoglycans. VSMCs represent the contractile unit of the artery and regulate arterial tone through dilation or constriction [4]. Coronary arteries are noted to have significantly more VSMCs compared to other arteries, indicating their relatively dynamic nature. The outermost layer, the *tunica adventitia*, is composed of connective tissue, fibroblasts and perivascular nerves, acting as an important site of immune surveillance and immune cell migration, as well as having progenitor cell properties which may play a key role in responding to arterial injury [5].

1.2 Pathophysiology

The pathological process which results in the formation of coronary artery narrowing leading to CAD is known as atherosclerosis. Whilst initially considered a lipid storage disorder resulting in excess fats being deposited within the arterial wall, recent decades have made it clear that the formation of atherosclerotic plaque is a complex process involving multiple pathological mechanisms working in concert (See figure 2). The presence of numerous factors such as dyslipidaemia, hypertension, chronic hyperglycaemia, environmental toxins from cigarette smoke and infectious agents

such as bacterial endotoxins stimulate a pathological modulation of arterial endothelial cell surface expression [6]. This process is particularly enhanced within coronary vasculature due to unique circumstances such as disturbed blood flow resulting from vessel tortuosity and predominantly diastolic blood flow. This change in endothelial cell surface expression enhances leukocyte adhesion to the inner vessel wall, which promotes the transmigration of phagocytic monocytes and lymphocytes within the arterial intima [7]. Once present within the arterial wall, monocytes adopt the macrophage phenotype and internalise oxidised low-density lipoproteins (LDL), a harmful cholesterol product which is internally packaged as lipid droplets (LD). Under these pathological circumstances, macrophages are unable to remove the harmful cholesterol effectively and continue to scavenge oxidised LDL, becoming lipid-laden foam cells [8]. The foam cells eventually succumb to the toxicity of the LDs and undergo apoptosis, resulting in the release of harmful LDLs and pro-inflammatory apoptotic products within the arterial wall, further promoting the inflammatory mechanism.

Once the inflammatory medley has taken hold, arterial remodelling begins to change the structure of the vessel wall. Microscopic observations demonstrate the migration and proliferation of smooth muscle cells (SMC) from the tunica media to the intima in response to inflammation [9]. While SMCs have been shown to promote some atheroprotective properties, their proliferation within the arterial intima ultimately contributes to an extensive change in extracellular matrix composition which increases LDL retention and oxidisation, sustains inflammation, and produces calcified deposits within the vessel wall [10-11]. As vessel remodelling continues, the

lesion grows macroscopically to expand the vessel wall, intruding upon the arterial lumen which disturbs the flow of blood, becoming atherosclerotic plaque. The growth of atherosclerotic plaque results in greater restriction of blood flow, eventually leading to the presentation of CAD.

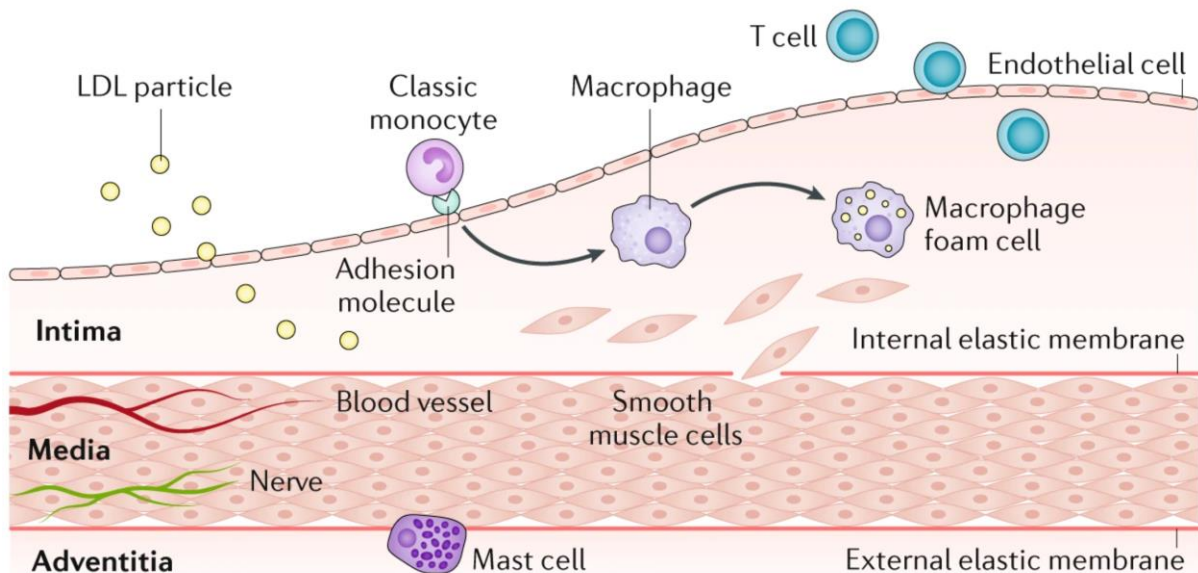


Figure 1.2 The process of atherosclerosis: The normal tri-laminar arterial wall, with the innermost (intima), middle (media) and outermost (adventitia) layers. Atherosclerotic plaque forms within the intima, with low-density lipoproteins (LDL), macrophages and T cells accumulating from the blood stream. Macrophages bind to LDL particles to become foam cells. Smooth muscle cells migrate from the media to intima in response to the accumulating leukocytes. Reproduced with permission from Springer Nature via RightsLink® (License number 5836060270999)

1.3 Epidemiology

CAD represents one of the largest health burdens around the world. Around 68,000 deaths in the UK were recorded as having been caused by CAD each year, with approximately one in seven men and one in 12 women dying from it [12]. Over 200,000 admissions to hospitals in the UK are due to acute presentations of CAD, usually in the form of a myocardial infarction (MI), which is more commonly referred to as a heart attack. Around 1.4 million people alive in the UK are survivors of heart

attacks. Multiple factors contribute to the development of atherosclerosis. Some of the most notable independent risk factors for the development of CAD include increasing age, hypertension, hypercholesterolaemia, diabetes mellitus, tobacco use, obesity, and physical inactivity [13-16]. Genetic factors also play an important and complex role in the development of CAD, commonly with multiple risk-associated alleles resulting in a cumulative effect, as well as rare, high risk, single allele variants [17].

1.4 Symptoms and signs

CAD can present in multiple ways. About 50% of patients who are diagnosed with CAD present with angina, a pattern of chest pain which is characterised most frequently as a crushing or squeezing sensation brought on by physical or emotional stress [18]. Angina can be categorised into different grades of severity based on the level of activity required to provoke symptoms (see table 1.1). However, angina can present atypically with varying descriptions of chest discomfort, which makes ruling out the diagnosis of CAD based on history alone challenging. Some patients present with more non-specific symptoms such as breathlessness, palpitations, and dizzy spells and no chest pain. The presence of CAD is not always evident through any meaningful symptoms and can progress relatively silently, leading to the development of further cardiovascular disorders such as cardiac failure and arrhythmia [18]. In approximately 20% of people diagnosed with CAD, the first clinical manifestation can be cardiac arrest, a cessation of the meaningful pumping activity of the heart, either due to MI or ventricular arrhythmia [19]. Additionally, while symptomatic presentations can vary, the physical examination of a patient with CAD

can be entirely normal as there are no physical examination signs directly caused by CAD. If abnormal examination findings are present, such as hypertension, cardiac murmurs, pedal oedema, or xanthomas, they can be attributed to conditions which are associated with the risk of developing, or as a result of CAD.

Table 1.1 Angina severity grade based on Canadian Cardiovascular Society Angina Classification [20]

Angina severity score	Angina severity description
Grade I	Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina is provoked by strenuous or rapid or prolonged exertion.
Grade II	Slight limitation of ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, cold or wind conditions, or emotional stress can provoke symptoms. Able to walk more than two blocks at level pace and climb more than one flight of stairs at normal pace in normal conditions.
Grade III	Marked limitation of ordinary physical activity. Able to only walk one or two blocks at normal pace and climb one set of stairs at normal pace.
Grade IV	Unable to carry out any physical activity without discomfort; angina may be present at rest.

1.5 Investigations

Once CAD is suspected following an indicative clinical history, the diagnosis and severity can be confirmed through a variety of investigations. The acquisition of an electrocardiogram (ECG) is a valuable component in the initial investigation of a patient with suspected CAD. An abnormal ECG taken at rest displaying changes in Q wave and ST-segment morphology or the presence of left bundle branch block can allude to the presence of CAD by indicating a previous myocardial ischaemic injury [21]. However, ECG changes may not represent conclusive evidence of CAD,

while a normal ECG does not exclude the diagnosis. When combined with clinical history and examination findings, ECG data can be used to stratify patients into risk categories. Further basic investigations of patients with typical angina include blood tests including blood cholesterol levels, renal function, and full blood count to identify risk factors associated with the development of CAD.

1.5.1 Computed tomography coronary angiography

When anginal chest pain is suspected, as defined by the European Society of Cardiology (ESC) and the National Institute for Health and Care Excellence (NICE), patients may be offered computed tomography coronary angiography (CTCA) in the first instance [22-23]. By timing the study sequence of the computed tomography (CT) scanner with an injection of iodine contrast through a peripheral venous cannula, the lumen of the coronary arteries can be visualised as the contrast flows through the coronary vasculature during diastole. With an effective image spatial resolution of as little as 0.3mm, CTCA can identify the presence and extent of atherosclerotic disease [16]. A strength of CTCA is its strong negative predictive value of 99%, which highlights its role as an accessible and powerful tool to rule out occlusive CAD [24]. It is also much easier to set up for individual patients and requires less technical expertise than invasive coronary angiography. Several factors can limit the application of CTCA, such as the presence of coronary calcium which creates image artefacts, reduced image quality of smaller branch vessels or irregular heart rhythms which can make ECG-gated image acquisition difficult. Furthermore, CTCA assessment does not offer objective physiological information, which is essential to identify which coronary artery lesions would benefit from

revascularisation, if any. This would result in the patient requiring further assessment in the cardiac catheter laboratory, incurring further contrast and radiation exposure. Despite these limitations, CTCA can confidently rule out obstructive CAD when used in the correct setting while also gaining important anatomical information which can inform future assessment and therapeutic decisions.

1.5.2 Invasive Coronary Angiography

Invasive coronary angiography (ICA) is an assessment tool that has been utilised by clinicians to diagnose and assess CAD since the mid-20th century [25]. It is a specialist procedure undertaken in a cardiac catheter laboratory (CCL) involving the injection of iodine contrast selectively into the coronary artery ostia via thin tubes inserted percutaneously via the femoral or radial artery. By performing x-ray imaging, the iodine contrast opacifies the lumen of the coronary artery that is engaged with the catheter, producing a 2D image of the coronary vasculature (See figure 1.3). Given its high image resolution and ability to identify disease within smaller branch vessels, ICA is the current gold standard investigation of suspected CAD [25]. ICA has been shown to provide prognostic information for patients with CAD which guides appropriate treatment decisions based on the severity of coronary lumen narrowing [26]. Furthermore, the access and information afforded by coronary angiography allows for the use of advanced coronary investigations, such as fractional flow reserve (FFR), intravascular ultrasound and optical coherence tomography, to better understand nature and severity of the patient's condition. These advanced investigations, as well as the potential for invasive treatment via angioplasty, are possible during the same visit to the CCL, albeit at the cost of

prolonged procedure time. These merits are offset by some limitations, not least of which is the small but important mortality risk associated with coronary angiography, including stroke and myocardial infarction. An elective procedure is regularly reported as having an average mortality risk of 0.1-0.2% [27], while patients suffering acute coronary syndrome can expect an average risk of 1% [28]. Other factors include radiation exposure to both patient and operator, as well as the limitation of a 2D image characterising a 3D pathology which can lead to disease severity underestimation.

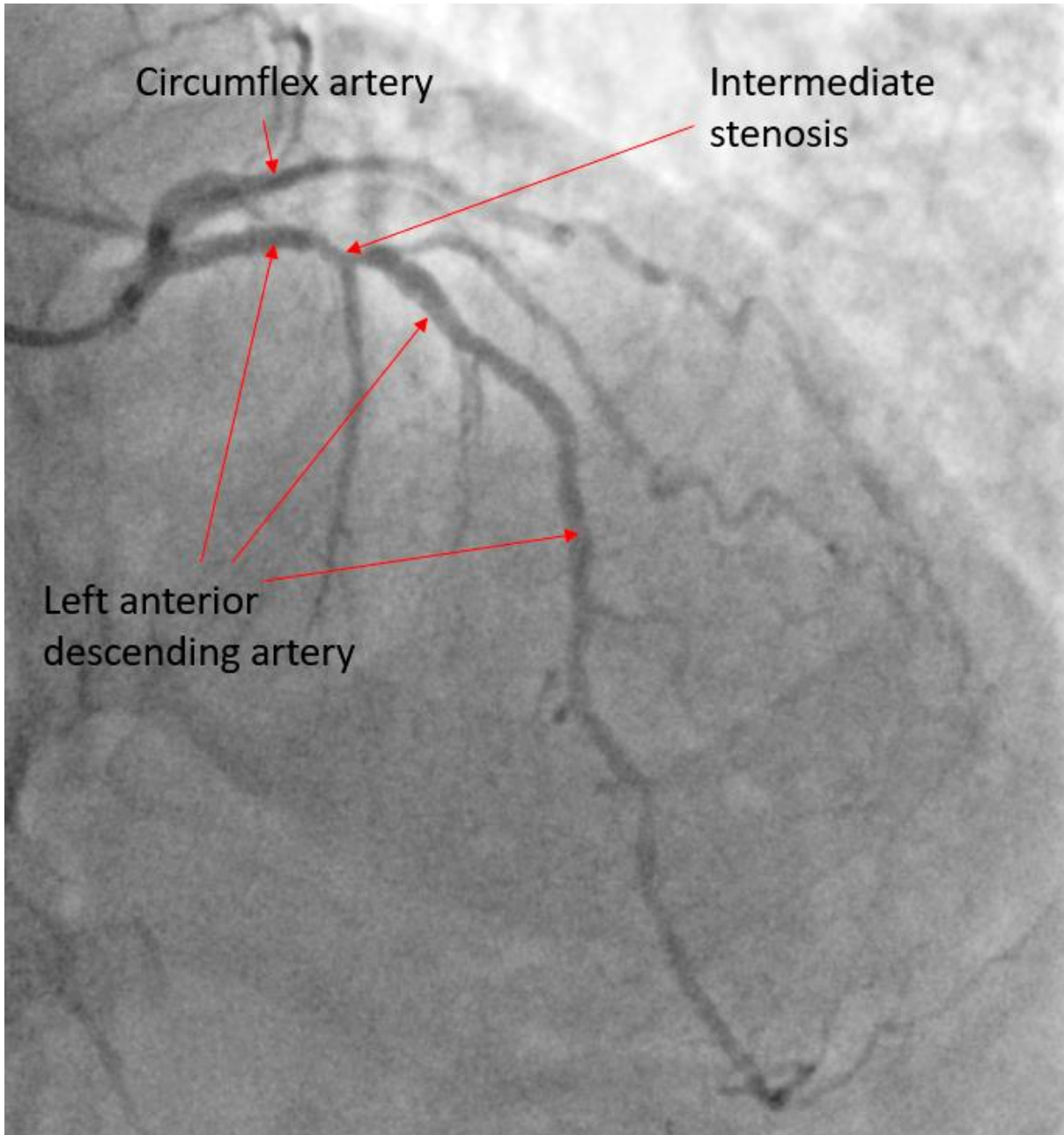


Figure 1.3 Invasive coronary angiogram, demonstrating visually significant vessel stenosis in the proximal left anterior descending artery.

1.5.3 Ischaemia testing

Whilst the visualisation of the coronary lumen provides diagnostic certainty as to the presence or absence of obstructive CAD, it is possible to assess the severity of ischaemia caused by coronary narrowing on the myocardium using techniques which utilise controlled exercise or medication to simulate cardiovascular stress and identify areas prone to ischaemia (See table 1.2). These non-invasive methods can indicate the presence of CAD while providing additional information regarding the severity of disease based on the proportion of the myocardium affected. These assessment tools can also demonstrate the presence of infarcted myocardium as well as provide an objective assessment of global cardiac function which can be valuable when determining an appropriate treatment. Ischaemia assessments can help determine the overall severity of CAD, provide prognostic information, and guide the appropriate offer or withdrawal of invasive therapies in complicated cases.

Table 1.2 *List of clinical non-invasive cardiac ischaemia assessment modalities with comparisons on advantages and disadvantages [29]. SPECT, single photon emission computed tomography; PET, positron emission tomography; MR, magnetic resonance.*

Procedure	Advantages	Limitations
Stress echocardiography	<ul style="list-style-type: none"> - Low cost - No radiation exposure - High diagnostic specificity (80-88%) 	<ul style="list-style-type: none"> - High intra- and interobserver variability. - Poor acoustic windows in some patients reduce image quality.
SPECT/PET imaging	<ul style="list-style-type: none"> - High diagnostic sensitivity (81-97%) - Feasible in cases which would restrict other modalities (renal failure, dyspnoea, etc) 	<ul style="list-style-type: none"> - Low spatial resolution. - Relatively lower specificity. - Radiation burden. - Study protocol can require entire day for rest and stress imaging.
CMR	<ul style="list-style-type: none"> - High spatial and temporal resolution. - No radiation exposure - High quality structural and functional assessments 	<ul style="list-style-type: none"> - Cost intensive - Time intensive - Relatively higher case restriction (kidney failure, implanted devices, claustrophobia)

1.5.3.1 Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI), which can also be called single-photon emission computed tomography (SPECT) or Positron Emission Tomography (PET), is a nuclear imaging technique commonly used in ischaemia stress testing for the evaluation of CAD. During the imaging procedure, patients undergo stress induction, either through exercise or with pharmacological agents to increase the blood flow to the heart. Following the stress induction, a gamma-ray emitting isotope or positron-emitting radionuclides, for SPECT and PET respectively, is intravenously injected into the patient and are taken up within the myocardium in proportion to the blood

flow in different regions of the heart. A gamma camera detects the emitted gamma rays from the tracer, which is then reconstructed into a 3D image of the heart [30]. The images are then processed to quantify the signal strength of the detected radiation in corresponding segments of the myocardium, which can determine the areas of reduced perfusion indicative of CAD.

MPI confers a number of merits and limitations in the evaluation of suspected or known CAD. The diagnostic accuracy for CAD has been proven in multiple studies, with modern techniques achieving an overall sensitivity and specificity of 84% and 69% when compared to invasive coronary angiography [31]. SPECT also offers a quantitative assessment of myocardial perfusion, as well as a functional assessment of the myocardium at rest and under stress. Furthermore, abnormal myocardial perfusion detected by SPECT is associated with an increased risk of adverse events, including myocardial infarction and death, which can help risk stratify patients with CAD and inform treatment decisions [32]. However, one major limitation is the ionizing radiation involved in SPECT imaging, which while relatively low, limits the repeatability of the assessment due to cumulative radiation exposure. Furthermore, SPECT has lower spatial resolution to other imaging modalities such as Cardiac MRI, which may impact the detection of small perfusion defects. Furthermore, various factors can influence image quality, such as respiratory motion and attenuation artefacts, as well as reduced photon penetration through adipose tissue which can result in reduced image quality and diagnostic accuracy in obese patients.

1.5.3.2 Stress Echocardiography

Stress echocardiography is a real-time stress testing modality with some notable advantages over other ischaemia testing techniques. By generating ultrasound waves from piezoelectric crystals within a transducer placed on the skin, it is possible to visualise the various aspects of cardiac structure and function [33]. It offers real-time imaging, providing immediate assessment of myocardial wall motion abnormalities during stress. Stress echocardiography can be performed using various stressors in a similar manner to SPECT, including exercise or pharmacological agents. Depending on the stress technique employed, echocardiography has demonstrated variable sensitivity (78–85%) and specificity (77-91%) for the detection of significant coronary artery stenosis when compared to invasive coronary angiography [34]. Moreover, it has a lower cost than other forms of stress imaging and is more widely available in clinical practice. Nonetheless, stress echocardiography has certain limitations. The image quality is influenced by several factors such as body habitus, acoustic windows, underlying lung disease and chest wall deformities, as well as operator expertise [35]. Suboptimal images can limit the accuracy and reproducibility of results. Additionally, stress echocardiography is limited in its ability to assess myocardial perfusion directly, relying primarily on the evaluation of wall motion abnormalities, which may lead to false-negative or false positive findings.

1.5.3.3 Cardiac Magnetic Resonance Imaging

Stress cardiac MRI is a viable option for ischaemia stress testing in patients with coronary artery disease. Based on the principles of nuclear magnetic resonance,

MRI produces a magnetic field which aligns the spin of hydrogen protons in a patients' body and utilises radiofrequency excitation to cause a controlled shift in the Larmor frequency of the hydrogen protons [36]. The realignment of the hydrogen protons back to their equilibrium state is detected and is spatially encoded to produce a 3D reconstruction of the tissues within the imaged area. The addition of agents which alter the magnetic properties of hydrogen protons, such as gadolinium-based contrast agents, causes an increase in signal intensity of surrounding hydrogen atoms. This can be used to assess the real-time perfusion of blood into the myocardium, as well as the assessment of myocardial soft tissue characterisation.

Stress cardiac magnetic resonance (CMR) offers several merits in the assessment of CAD, most prominently being the excellent spatial and temporal resolution of the images generated. Standard CMR imaging series achieve a temporal resolution of less than 45 milliseconds (ms) between phases, and a spatial resolution 3 x 3 millimetres (mm), which enables accurate visualisation and quantification of cardiac structure and function, wall motion abnormalities and myocardial perfusion defects [37]. As there is no need for ionizing radiation, the procedure is much safer than other comparable methods of myocardial imaging. Furthermore, in addition to assessing myocardial perfusion and wall motion defects, it is possible to assess the tissue characteristics of the left ventricle with gadolinium enhancement, allowing for the quantification of scar tissue and oedema, which can demonstrate other forms of cardiac disease. Despite these advantages there are some limitations to consider with CMR. Firstly, CMR requires specialised equipment and expertise, as well as being much more costly than other conventional myocardial ischaemia tests, which limits its availability in resource-limited settings. A number of patient factors can also

contra-indicate the use of CMR, such as certain implanted devices (pacemakers, defibrillators) or metallic objects within the body, while the presence of non-ferrous metals can cause significant imaging artefacts [38]. Furthermore, motion artefacts can significantly reduce the image quality of CMR, which can be caused by irregular arrhythmias such as atrial fibrillation, or the inability to undertake prolonged breath-hold manoeuvres.

1.6 Clinical management and interventions

The management of patients with CAD is aimed at reducing symptom burden and the occurrence of adverse cardiovascular events. As the presentation of each patient can vary significantly, from asymptomatic incidental findings to severe symptom burden with associated cardiovascular disorders (including heart failure and dysrhythmias), the optimal management for each patient is tailored based on their lifestyle, their disease severity and responsiveness to treatment.

1.6.1 Lifestyle interventions

The foundation of any management strategy for CAD involves modifying a number of contributing factors. Unhealthy lifestyle factors, such as sedentary behaviour, smoking and poor weight control, are fundamentally associated with major risk factors for cardiovascular disease such as hypertension, diabetes and hypercholesterolaemia [39]. Factors such as unhealthy diets, physical inactivity and smoking have been shown to be associated negative vascular remodelling associated with early atherosclerosis which are visible in adolescents [40]. Modification of lifestyle factors alone has been shown to improve outcomes in

patients suffering with coronary artery disease. Consumption of healthy diets such as oily fish, fruits and vegetables, and foods with high fibre have been shown to reduce the risk of adverse cardiovascular outcomes in several prospective trials [41-43]. Tobacco smoking cessation is a cornerstone in all lifestyle modification discussions, with clear trends in worse outcomes with patients who are current smokers versus ex-smokers [44]. Patient education and adherence to significant lifestyle changes remains a key priority of all healthcare services in order to achieve the optimal outcome for each individual.

1.6.1.1 Physical Activity Interventions and Coronary Artery Disease

Physical activity behaviour is a key lifestyle factor in the management of coronary artery disease. Physical activity-based interventions have been shown to attenuate many major cardiovascular risk factors. Prospective studies have shown that exercise-based interventions are able to significantly reduce blood pressure, improve glycaemic control, and support long term weight loss [45-47]. An individual's level of cardiorespiratory fitness alone has been shown to be inversely associated with cardiovascular death and all-cause mortality [48-49]. The effect of physical activity interventions on the development of atherosclerosis has been extensively investigated. Regular physical activity has been shown to stimulate the production of nitric oxide in the endothelial cells of coronary arteries, allowing for improved vasodilatation and oxygen delivery to the myocardium [50]. Increased nitric oxide production from endothelial cells is crucial in the modulation of vascular pathologies through a variety of effects, including reduced inflammation, improved endothelial

regeneration and reduced platelet adhesion [51]. Regular physical activity has also been shown to have a variety of systemic effects which influence coronary artery disease, such as reducing circulating inflammatory markers (C-reactive protein and interleukin-6), promotion of antioxidant enzymes and improving endothelial progenitor cell function [52-54]. Exercise interventions are effectively delivered through cardiac rehabilitation programmes, along with patient education on lifestyle modification. In the United Kingdom, the importance of physical activity as a core target for cardiovascular disease risk factor modification is highlighted in national guidelines [55]. As suggested by the Chief Medical Officer's physical activity guidelines, all adults with risk factors for cardiovascular disease should aim to achieve 150 minutes of moderate physical activity per week (ie brisk walking), or 75 minutes of vigorous activity per week (ie running, or a combination of the two. Additionally, reducing time spent sedentary is a key aspect of this advice, although strict targets are not outlined. Referrals to exercise-based programmes are also advised for patients with a history of cardiovascular disease and a history of physical inactivity or sedentary behaviour [56]. Cardiac rehabilitation programmes are also available to patients with a diagnosis of coronary artery disease suffering with angina, which aims to offer lifestyle modification education to patients as well as individualised physical exercises. Unfortunately, accessing these services remains a significant challenge, despite the evidence for its benefit. The most recent British Heart Foundation (BHF) audit on cardiac rehabilitation highlighted this issue. While the incidence of new cases of angina in the UK is conservatively estimated at 22,600 per annum, only 3,144 patients commenced cardiac rehabilitation in one year according to the most recent BHF audit [57-58].

1.6.2 Medical therapy

The use of medication represents the cornerstone of modern CAD therapy alongside lifestyle and risk factor modification. Medical therapy for CAD can be divided into “event-reducing” and “symptom-control” medication. Lipid-lowering therapies constitute one of the key agents utilised for reducing adverse outcomes in stable angina, with statins most commonly prescribed. Statin use has demonstrated strong benefits in reducing major adverse cardiovascular outcomes through multiple randomised controlled trials of patients with ischaemic heart disease (IHD) [59-61]. Angiotensin-converting enzyme (ACE) inhibitors have also been shown to improve outcomes for patients with CAD and concurrent chronic kidney disease, hypertension, left ventricle systolic dysfunction or diabetes [62].

Antiplatelet agents are also commonly prescribed in a variety of settings of ischaemic heart disease presentations to reduce adverse CVD outcomes, including stable CAD. The use of antiplatelet medication as secondary prevention in patients who have suffered from an acute MI is well described, particularly in those who have undergone percutaneous coronary revascularisation [63]. These strategies generally include aspirin and either Ticagrelor or Prasugrel, with long term monotherapy of one of these agents following the acute event. While aspirin monotherapy is currently recommended in all patients with a diagnosis of stable angina for secondary prevention, more recent studies have questioned its efficacy in lower CVD risk profiles [23]. Three separate randomised controlled trials aimed to assess the benefit of aspirin in reducing the risk of MI in patients with no prior history of CAD with advanced age, moderate risk of CVD and diabetes separately [64-66]. All three trials failed to show a clear benefit of aspirin use in reducing either fatal or non-fatal MI,

while significantly increasing the risk of major bleeding. Observational studies have furthermore failed to demonstrate a benefit in Aspirin use in patients with stable CAD who have not suffered a previous acute ischaemic event [67] [68]. The lacklustre findings in these trials are largely hypothesised to be due to a significant change in the diagnosis and management of CVD risk in the current era as opposed to the early aspirin trials, where smoking cessation, aggressive hypertension management, lifestyle advice and statin prescription were not widely available or advocated, as well as earlier detection of CAD prior to acute ischaemic presentations.

Medications which provide symptom control in angina are available in a variety of forms. Organic nitrate-based agents such as Nitroglycerin, Isosorbide Mononitrate and Nicorandil, have been used to manage angina for over a century, which cause coronary artery dilatation [69-70]. Short acting, sub-lingual nitrates are widely prescribed as first-line therapy for acute symptom control, have a rapid onset of action to provide relief from angina within 1-3 minutes. Longer acting nitrates are indicated to reduce the frequency of angina events when first line agents are ineffective or not tolerated. Beta-blocker and Calcium channel blocker medications are indicated as first line agents for stable angina to reduce the frequency of angina events [71]. Where these medications are insufficient to control symptoms, second line “symptom control” agents include Ranolazine, Ivabradine and longer acting nitrates can be offered [72-74].

1.6.3 Coronary Revascularisation

For patients who do not respond adequately to optimised medical therapy (OMT), more invasive strategies can be offered to treat CAD. One of the accepted approaches is coronary artery bypass grafting (CABG), which involves connecting harvested vein or arterial grafts between a healthy section of the coronary anatomy to a distal portion of the artery beyond the lesion, thereby bypassing the vessel narrowing [75]. CABG is largely employed in cases of extensive CAD which involves multiple major coronary vessels or in cases with left main stem disease [76]. While CABG significantly reduces symptom burden in CAD, the nature of a highly invasive surgical procedure, limited longevity of vein graft patency, and the need for a healthy coronary artery segment distal to the vessel narrowing, restricts the number of cases which are suitable for this procedure.

Percutaneous coronary intervention (PCI) is another revascularisation procedure which can be considered if medical therapy has not sufficiently controlled the symptoms of CAD. PCI involves the inflation of a small balloon within the coronary artery which can open the vessel stenosis, thereby restoring blood flow [77]. The procedure typically involves the placement of a coronary stent to maintain vessel patency and has been shown to improve short- and long-term clinical outcomes [78]. Furthermore, this procedure is performed in the same manner as ICA, requiring the same vascular access at the wrist or hip and can be performed immediately following the acquisition of coronary images. Without the need for major surgery or a general anaesthetic, patients undergoing elective PCI are routinely and safely discharged from hospital on the same day they are admitted. With technological advancements

made through the development of drug eluting stents improving clinical outcomes further, the resulting long term clinical outcomes of PCI are comparable to CABG [79-80]. PCI does involve some risk towards the recipient, including procedural complications such as stroke, myocardial infarction, arrhythmia and acute renal impairment. Additionally, the patient is at risk of coronary restenosis, as well as an increased long term bleeding risk due to the administration of potent antiplatelet therapy necessary to prevent clot formation on modern stent designs. In patients with three-vessel disease, long term outcomes have been shown to be favourable with CABG versus PCI, which is largely driven by increased urgent revascularisation rates in the latter. PCI is widely recommended as the treatment of choice for single vessel CAD, while the decision between stenting and CABG in multivessel disease should be taken in consultation with a specialist heart team [81].

The indications for coronary revascularisation have been shaped by the extensive research available regarding PCI in CAD. In acute presentations such as ST-elevated myocardial infarction (STEMI) and non ST-elevated myocardial infarction (NSTEMI), PCI has shown clear superiority to medication therapy alone in reducing major adverse cardiovascular events and reducing future CAD symptom burden [82-84]. This has led to the universally accepted practice of a routine invasive approach to acute coronary syndrome (ACS), a term which encompasses NSTEMI and STEMI presentations. Additionally, results from the COMPLETE trial demonstrated that treatment of non-culprit disease noted in acute presentations of CAD resulted in superior clinical outcomes in comparison to deferring invasive treatment [85].

Whilst early revascularisation has been widely accepted as the strategy of choice in ACS, presentations of stable CAD have demonstrated different outcomes requiring a considered approach and management remains a controversial topic. A meta-analysis of 28 studies published between 1977 and 2007 demonstrated superior outcomes when revascularisation, either PCI or CABG, was combined with medical therapy to treat CAD versus medication alone [86]. In particular, the MASS II study, which recruited 611 patients with stable CAD, observed a significant improvement in mortality and morbidity by adopting an early revascularisation approach in comparison to medication therapy alone [80]. However, some argued that the approach to medical therapy at the time was lacklustre and that an aggressive medication strategy would be more beneficial. The COURAGE trial demonstrated this by comparing OMT alone versus PCI and OMT as first line strategies for CAD [87]. By focusing on achieving medication therapy targets early and deferring revascularisation, the authors demonstrated similar outcomes in death, MI, stroke and hospitalisation from ACS compared to early PCI (19.5% vs 20.5% respectively with death, MI and stroke collectively, $p=0.62$; 12.3% vs 13.2% with MI, $p=0.33$; 11.8% vs 12.4% with acute hospitalisations, $p=0.56$). However, patients randomised to PCI were more likely to be angina-free, required less nitrate therapy and reported superior improvements in quality of life in comparison to initial OMT. These findings reinforced the practice of PCI deferral in stable CAD in favour of initial OMT, with revascularisation to be considered for symptomatic relief in cases of medication-refractory angina. While these findings have been considered unsurprising to many interventionalists, over one million PCI procedures are undertaken in north America every year [88], with approximately 85% undertaken electively in patients with stable CAD [89]. It is also worth considering the recent ISCHAEMIA trial, the largest

randomised study comparing early revascularisation to OMT alone in stable CAD which recruited over 5,000 patients internationally, of which 35% of the study subjects reported no symptoms within the last month at baseline [90]. With over a third of patients encountered in a large study setting receiving treatment which was not in line international guidance, it is worth reflecting on how this represents routine clinical practice. Additionally, this trial reported that early revascularisation of stable CAD with moderate to severe ischaemia on non-invasive stress testing failed to produce a reduction in major adverse cardiac events compared to OMT alone.

Whilst the practice of offering PCI for medication-refractory angina is reasonably well regarded, the recent ORBITA trial has challenged this approach. The authors hypothesised that the change in symptom burden associated with PCI was in response to the placebo effect of the procedure and not the physiological resolution of CAD [91]. This was due to the absence of any prior trial comparing PCI to OMT conducting any patient or operator blinding, due to the complex nature of coronary revascularisation. Once coronary lesions were identified at the time of ICA, 200 patients were randomised to either receive PCI to visually significant lesions or no revascularisation. The trial involved extensive blinding and masking procedures which hid whether the patient underwent revascularisation or not from both study subjects and recovery staff. At six weeks follow up, the patients remained unaware of which treatment arm they had been randomised to and underwent assessments of symptom severity and exercise tolerance which were compared with recruitment and pre-randomisation stages. At that timepoint, no significant difference was observed between the revascularisation and medication only groups with regards to symptom severity, angina severity grade or exercise tolerance. Several study design limitations have been noted, including small sample size, short follow-up period and

over 30% of study subjects showing non-significant coronary physiology results (Fractional flow reserve >0.8). Whilst the ORBITA trial raised many questions for researchers and clinicians with regards to revascularisation in stable CAD, it demonstrated the feasibility of a novel double-blind placebo-controlled design to PCI research.

1.7 Coronary physiology assessment

Current advancements in the management of CAD have centred on improving patient selection and lesion assessment. This has involved a change in focus from a subjective visual interpretation of 2D images via ICA to physiological assessments of coronary stenoses. In the recent decades this has been shown to be possible using invasive and non-invasive methods.

1.7.1 Fractional Flow Reserve

Fractional flow reserve is an invasive assessment method performed within the CCL which measures the disturbance of blood flow imposed by an atherosclerotic plaque within the coronary artery. Maximum coronary hyperaemia is stimulated using vasodilatory pharmacologic agents which enables optimum blood flow through the coronary arteries. During the period of maximum hyperaemia, a wire which is passed distally through the coronary stenosis that contains a pressure sensor at its tip. Two simultaneous pressure readings are recorded during the assessment: pressure proximal to the stenosis (P_a), and pressure distal to the stenosis (P_d). By considering Poiseuille's Law and fluid dynamics principles, a non-stenotic artery's

blood flow is proportional to the pressure gradient and the fourth power of the vessel's radius [92]. In the presence of a significant stenosis, a reduction in Pd relative to Pa indicates the loss of energy overcoming increased resistance posed by the presence of increased resistance to flow posed by a stenotic lesion. This reduction in flow can therefore be inferred from the ratio of the pressure distal to the stenosis to the pressure proximal to the stenosis (Pd/Pa), which is expressed as a figure between 0 to 1, with 1 representing theoretical normal flow (see Figure 1.4).

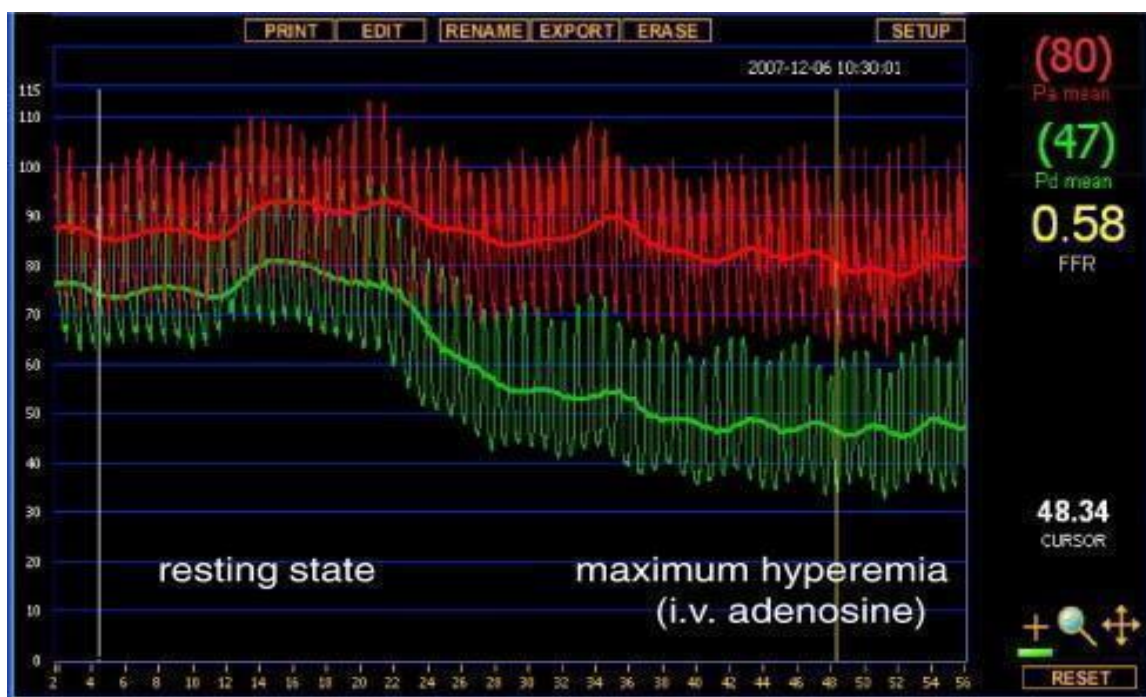


Figure 1.4 Fractional flow reserve assessment, with resting and maximum hyperaemia states demonstrated. Mean proximal (Pa) and distal (Pd) measurements are shown which derives the fractional flow reserve. (Courtesy of Professor Julian Gunn)

The use of FFR in clinical practice within the CCL has become standard practice in recent years. FFR is indicated in cases of CAD where the stenosis is visually assessed as occupying between 50 to 90% of the arterial lumen [93]. PCI confers significant risk to the patient, and the need to justify benefit vs harm is paramount. FFR is used to detect stenoses which cause significant myocardial ischaemia, therefore identifying target lesions which will provide the greatest overall benefit to

the patient. When measuring FFR, a value of 0.8 has been shown to provide a reliable cut-off point between significant and non-significant disease, with stenosis FFR of less than 0.8 strongly indicated for intervention [94-95].

FFR assessments confer several benefits to patients with CAD. It has been demonstrated that PCI which is guided by FFR results in favourable clinical outcomes when compared to visual assessment of ICA alone. The DEFER trial used an FFR value of 0.75 as a cut-off for significant stenosis, with cases of stable CAD with 0.75 or greater randomised to either a reference group to undergo PCI or defer intervention and continue with OMT, while cases of less than 0.75 would proceed to intervention. After a 15 year follow up period, there was no significant difference in the rate of death between the three groups (33% in the $FFR < 0.75$ group, 31.1% in the defer group, 36.1% in the reference group, $p=0.72$ between defer and reference) [96]. Additionally, the rate of myocardial infarction was significantly lower in the deferral group in comparison to the reference group (2.2% vs 10.0% respectively, $p=0.03$). Although the DEFER trial recruited a relatively small cohort, this was the first major study to demonstrate the safety of PCI deferral in stable CAD based on FFR assessment as well as the long-term benefit by reducing adverse myocardial events. The larger FAME trial which followed recruited 1005 patients with CAD to compare FFR-guided PCI against angiography-alone, utilising an FFR value of 0.8 as the cut-off for treatment indication or deferral [97]. At one year, FFR-guided PCI resulted in significantly lower rates of death, nonfatal MI and repeat revascularisation in comparison to visual assessment guided intervention (13.2% vs 18.3% respectively, $p=0.02$). While the FAME trial recruited a combination of patients with acute presentations of CAD as well as stable angina, the subsequent FAME II trial

focused solely on stable CAD. All patients underwent FFR assessment of lesions greater than 50%, with stenosis FFR values of less than 0.8 randomised to PCI or deferral with medical therapy alone, and those with FFR values greater than 0.8 continuing medication therapy alone. The trial recruitment was halted early due to a significant difference in outcomes noted between the patients receiving PCI and the deferral group (4.3% vs 12.7%, $p < 0.001$) [95]. At the five year follow up of FAME II, with the 888 patients randomised to PCI or medical therapy, the composite endpoint of death, MI and urgent revascularisation was significantly lower in the PCI group (13.9% vs 27.0% respectively, $p < 0.001$) [98]. There was no significant difference between the PCI group and the FFR>0.8 registry group that received OMT alone at five years (13.9% vs 15.7% respectively). In addition to clinical benefits, FFR has been shown to be cost effective for the health service, leading to fewer unnecessary urgent admissions with CAD and reducing unnecessary stent implantation, offsetting the initial increase in procedural cost [99]. Overall, these study findings conclude that a coronary stenosis with an FFR value greater than 0.8 is safe treat with OMT alone and avoids the unnecessary risk and potential harm imposed by coronary stent insertion, while lesions with an FFR of less than 0.8 that are treated with PCI result in superior outcomes for patients with CAD.

1.7.2 CT-derived FFR

The earliest clinical implementation of CFD to coronary artery physiology assessment involved the use of CTCA. By analysing static CTCA datafiles and applying CFD modelling based on vessel geometry, myocardial mass and estimated myocardial blood flow at rest and hyperaemia, an estimation of FFR based on the

CT images (FFR_{CT}) can be computed [100]. The addition of computational physiology assessment to CTCA has made significant advances in recent years. A meta-analysis comparing FFR_{CT} to invasive FFR in 1,289 patients totalling 2,191 vessels demonstrated good agreement with a c-statistic of 0.89 [101]. A positive FFR_{CT} result (ie FFR_{CT} <0.8) has recently been demonstrated to provide superior prognostic information than a positive CTCA result (defined as a lesion >50% indicating CCL assessment) [102]. In this study, in which 206 patients underwent both CTCA and FFR_{CT} followed by invasive FFR, it was observed that the frequency of the primary study endpoints (death, MI, unplanned revascularisation) was higher in the FFR_{CT} positive group than the CTCA-positive group after a 4.7 year median follow-up period (73.4% vs 48.7% respectively, p<0.001). Additionally, no cardiac deaths or MI were observed in the negative FFR_{CT} group. The growing literature describing the use of FFR_{CT} has led to its approval by NICE, with a recommendation that it should be considered as an option for patients undergoing CTCA assessment with CAD [103]. It is worth noting that the implementation FFR_{CT} is limited by the same factors that influence CTCA, which ultimately restricts the case selection of appropriate patients significantly. Nonetheless, the development of FFR_{CT} represents the first significant step in integrating computed coronary physiology to clinical practice.

1.7.2 Virtual FFR - VIRTUheart™

The first successful 3D model of coronary artery flow using ICA was developed at the University of Sheffield with the VIRTUheart™ software. The use of ICA provides higher resolution images to generate detailed 3D models which reflects the geometry

of the coronary artery lumen with better definition than CTCA (see figure 1.5). The segmentation stage requires two orthogonal views of the coronary artery segment of interest, with at least 30 degrees between the two views needed. Given the nature of ICA, it is also possible to ascertain the aortic pressures which would reflect the inlet pressures of the coronary segment, a figure which is not directly available for FFR_{CT} and must be estimated. Furthermore, given the availability of ICA across a variety of hospital settings, it is possible that vFFR models could be generated for a much larger number of patients with CAD outside of tertiary centres, therefore addressing the need to improve disease management by accessing physiological assessments more easily.

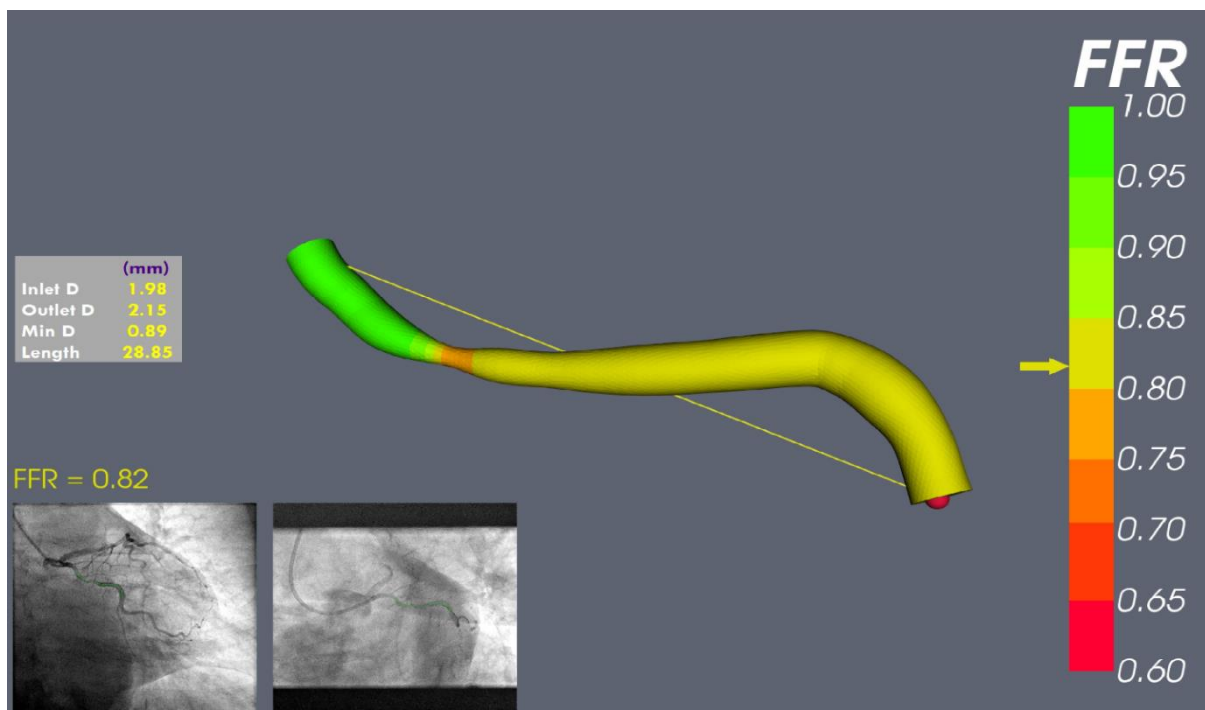


Figure 1.5 Screenshot of VIRTUheart vFFR post-processing result for circumflex coronary stenosis. vFFR result is shown as 0.82, indicating that lesion would not reach the threshold for PCI.

The Virtu-1 study was the first to demonstrate the potential of ICA-derived vFFR by analysing 35 coronary artery segments from 19 patients who underwent ICA for CAD assessment [104]. Using rotational angiography to obtain the views needed for

segmentation, the VirtuHeart software was able to produce vFFR results with an accuracy, sensitivity and specificity of 97%, 86% and 100% respectively in comparison to measured FFR. It was shown that vFFR deviated from the measured FFR reading by ± 0.06 with good correlation ($r=0.86$). The computation time required to generate the model was approximately 24 hours, although this was significantly improved through workflow process optimisations which resulted in computational times of less than 4 minutes [105]. Additional utility has been added to the VIRTUheart tool with the development of outlet boundary condition personalisation. While inlet parameters can be gained directly through measuring aortic pressures, outlet parameters must also be considered in the workflow, which was initially generalised to a population average of coronary microvascular resistance. However, it is known that changes in microvascular resistance can significantly influence FFR results, and that microvascular resistance can vary significantly between individuals [106]. By considering patient parameters which influence microvascular resistance, such as hypertension, diabetes mellitus, serum haematocrit level and cardiac structure, a personalised estimation of microvascular resistance can be tailored to the patient. This in turn provides a personalised CFD model tuned to the patient's characteristics, which can theoretically result in geometrically identical arterial segments resulting in different vFFR results, and therefore treatments, between different patients.

1.8 Assessing physical activity behaviour

The delivery of targeted interventions aimed at improving lifestyle factors associated with cardiovascular risk relies on the identification of these characteristics. Most of

these factors, such as body weight, smoking habit, and diet, are easily identifiable and quantifiable, with reasonably ubiquitous standards applied across adults of all ages and genders. Assessing physical activity behaviour in a free-living population represents a unique challenge in this regard, as the objective assessment of physical activity behaviours is not easily obtained or standardised as there are numerous assessment methods. Such assessments must consider several specific factors, such as the mode, frequency, duration, and intensity of each activity the individual undertakes, as well as the day-to-day variability that can be expected in such activities. This makes identifying individuals who require physical activity interventions accurately difficult, as well as assessing sufficient improvements in these parameters, either because of direct behaviour change or the result of medical intervention.

1.8.1 Criterion methods

Criterion methods allow for the direct measurement of physical activity parameters by measuring the energy expended by various physical activities. The direct measurement of expended energy through physical activity involves quantifying the rate of an individual's metabolism over a period of time. By expending energy for various functions and processes, oxygen is consumed, and heat is generated through metabolism. Metabolic rate describes the rate at which the body consumes energy in order to carry out these processes; the higher the energy demand of the activities, the higher the metabolic rate [107]. Whilst these criterion methods are less commonly used to assess physical activity than either objective or subjective methods due to their individual limitation, it is important to note that these methods

allow for the quantification and comparison between various physical activity states across a variety of populations. This information is extrapolated into less intrusive and complex methods by which physical activity can be quantified in the general population and provide accurate assessments of physical function.

There are several methods to express the energy expended through different activity states that are used in the assessment of physical activity. The total amount of energy expended by an individual over a 24-hour period is termed the total energy expenditure (TEE), which is made up of three key components: resting energy expenditure (REE), thermic effect of food (TEF) and activity energy expenditure (AEE) [108]. REE denotes the energy expended to maintain standard metabolic activities of the internal organs of the body (ie brain, heart, lungs, kidneys, etc), while TEF describes the amount of energy needed to fully digest, transport and absorb food through the gastrointestinal tract. AEE represents the energy expended through physical activities and represents the most variable component of TEE, both interpersonally and intrapersonally. By observing an individual's energy expenditure in various states, with a set period of resting used to calculate the REE and applying the assumption that TEF utilises roughly 10% of an individual's TEE, it is possible to calculate the AEE through the following equation [109]:

$$\text{AEE [kcal]} = \text{TEE [kcal]} \times 0.9 - \text{REE [kcal]}$$

A common method of expressing the intensity of a particular activity is through metabolic equivalent of task (MET) units, where one MET represents the energy expenditure rate during the resting state [110]. MET can be further defined as the

rate of oxygen consumption, where 3.5ml O₂/kg/min is equivalent to one MET. As MET is tied to the consumption of oxygen and therefore metabolic rate, it can also be approximated into the rate of kilocalories (Kcal) consumed through metabolism, where 1 MET = 1 Kcal/kg/h. Exercise values of energy expenditure can therefore be described as in the following example: an activity which consumes 10.5ml O₂/Kg/min (equivalent to 3 METs) is performed over 30 minutes, resulting in 112.5 kcals of energy expenditure.

Direct behavioural observation is one of the earliest methods of quantifying physical activity, which involves the observation of subjects by experts over periods of time, classifying different physical activities behaviours into distinct categories [111]. While this provides contextual information to quantifiable assessments of overall physical activity outcomes, direct behavioural observation is highly time consuming and impractical for long term monitoring in free living environments. Furthermore, subject behaviour is likely to be significantly influenced by constant direct observation, while the categorisation of behaviours may be influenced by the subjectivity of the observer.

Direct calorimetry measures the total amount of heat produced by an individual in a specialised chamber, which represents an accurate measure of the individual's metabolic rate and energy expenditure [112]. Alternatively, indirect calorimetry measures the consumption of oxygen and the release of carbon dioxide, which is closely tied to metabolic rate [113]. Using either technique, by observing a subject over varying physical activity states, such as resting, sitting, standing, running and so on, it is possible to capture a temporal resolution of the changes in energy

expenditure, allowing for the accurate, quantitative assessment of physical activity. However, both have significant limitations: both require specialist equipment that requires careful calibration and can only be used in controlled laboratory environments, limiting the application of either of these methods from being used in a free-living state. Additionally, they are both expensive and time consuming, both for the monitoring of subjects and the analysis of data. However, it is by these methods that common physical activities can be quantified by their estimated effect on the human metabolic rate based on the findings of these techniques.

A further criterion method assessing physical activity behaviour is the use of doubly labelled water (DLW). This method involves the ingestion of water containing stable isotopes of hydrogen (^2H) and oxygen (^{18}O) [114]. Over a period of weeks, the water gradually leaves the body after reaching equilibrium within the various human tissues and cells. The rate of the isotope elimination from the body is modulated by the individual's metabolic rate and physical activity levels. By examining the interval changes in isotope elimination, it is possible to calculate the TEE of the subject in between each sample collection, and when compared to their resting metabolic state, an assessment of the energy spent due to physical activity can be ascertained [115]. DLW allows for the assessment of physical activity behaviours in any environment and does not rely on direct observation or supervision, making it the gold standard assessment of human TEE under free living conditions [116]. However, while it provides a summary of the total energy expended during a certain period, it cannot provide data of the intensity, frequency, nature or length of individual physical activities performed during the monitoring period. Additionally, the analysis of DLW requires specialised laboratory equipment and facilities and is more

complex than either direct or indirect calorimetry, making it technically difficult and costly.

1.8.2 Objective methods

Over recent decades, the development of wearable devices capable of monitoring the health characteristics of an individual has led to new avenues of physical activity measurement. Through advancements in sensor technology miniaturisation, low powered electronics, and wireless technology, devices capable of collecting a variety of data which can be translated into health parameters are now widely available and applied in medical research [117]. The ease in which these technologies can be mass produced has led to them becoming widely available to the general public as “health and fitness devices” and are already acquired by consumers as methods of assessing and monitoring their own health and fitness [118]. In health research, the use of these devices is considered an “objective method” of assessing physical activity, and can provide different metrics of activity behaviour.

1.8.2.1 Heart rate sensors

Heart rate monitoring sensors are commonly found in many commercially available wearable devices. These devices typically utilise an optical sensing method called photoplethysmography (PPG), which consists of a light emitting diode (LED) and a photodetector [119]. The underlying principle of PPG relies on the absorption of light by oxygenated blood, where the LED emits both red and infrared light emitted directly onto the skin. The pulsatile nature of blood flow leads to variations in blood volume in the underlying vessels, which absorbs and reflects light from the LED. The

photodetector senses the changes in reflected light caused by variations in blood volume, which is then processed and used to calculate numerous variables. PPG sensors are used ubiquitously in healthcare settings to monitor heart rate and oxygen saturations, able to detect changes in a patient's condition, alert healthcare professionals to clinical deterioration and monitor response to treatments [120]. Advanced PPG data processing also allows for estimations in blood flow, which aren't currently used routinely in clinical practice but are the subject of ongoing research in applications such as non-invasive blood pressure measurements [121-122]. As such, PPG based sensor technology is a well-recognised and widely used sensor modality and can provide useful information through integration with wearable technology.

The assessment of physical activity behaviour is possible through PPG based wearable heart rate sensors. By estimating age-appropriate heart rate thresholds for light, moderate and vigorous physical activity, one can estimate the time spent undertaking different levels of intensity of exercise an individual is performing while being monitored [123]. This assessment has been shown to correlate well with DLW based energy expenditure assessments and can estimate the total energy consumed through various physical activities in free living environments [124]. Meta-analyses comparing the accuracy of Fitbit (Fitbit Inc., San Francisco, CA) physical activity monitoring devices to criterion methods of energy expenditure found that the wearable devices were prone to underestimate energy expenditure on average [125-126]. Many of the studies also compared the devices' PPG-based heart rate accuracy to ECG monitoring, which found a similar pattern of underestimation. These findings are important but unsurprising given that PPG based heart rate

sensors are known to encounter significant difficulties when estimating heart rate during exercise, primarily through motion artefact [127]. It is worth noting that all devices reviewed in both meta-analyses referenced are discontinued Fitbit products and newer devices have replaced them. This issue highlights a significant challenge of device validation in this field as the development pace of new wearable devices, including new sensor hardware and frequently updating data processing software, outstrips the attempts to validate them.

1.8.2.2 Motion sensors

Motion sensors are devices which have the capability to detect changes in movement, position, or physical alterations in the environment. They are widely used in a variety of settings, including healthcare, robotics, navigation, and security systems, to mention a few. They are commonly used to quantify and track human movements, making them valuable tools in fields such as sports science, rehabilitation, and fitness tracking. A variety of different sensor technologies have been incorporated into tracking human movements, including accelerometers, pedometers, gyroscopes and magnetometers [128]. Inertial measurement units have also been utilised in quantifying human movement, which combine multiple sensor modalities to provide more precise motion tracking.

Accelerometer sensors are the most popular technology used in the field of wearable technology, having undergone widespread adoption into consumer devices such as smartphones, smartwatches, and fitness trackers [129]. The design of modern accelerometers is based on microelectromechanical systems (MEMS) technology, where very small accelerative masses move in response to changes in motion [130].

The displacement of these masses generates electrical signals, which are then processed to determine motion. Tri-axial accelerometers, which are commonly found in many commercial devices, can provide information on the acceleration of the device in three dimensions (namely, X, Y and Z axes) simultaneously [131]. Accelerometers are capable of providing a wide range of functionalities in the assessment of physical activity, including identifying different forms of human movement (ie walking, cycling, swimming, etc), step counting and measuring the distance travelled [132]. Furthermore, wrist-worn accelerometer data has been shown to estimate TEE and AEE with a high level of accuracy in free-living conditions when compared to criterion methods such as doubly-labelled water [133]. Wearable accelerometers can be placed on various parts of the body to collect movement and activity data, such as the wrist, hip, upper arm and ankle, improving their versatility. Furthermore, their low power consumption and small profile make them ideal for unobtrusive, continuous monitoring. It is worth noting that not all forms of physical activity are suited to accelerometer-based monitoring due to the limited context available to the device. Some forms of movement are more difficult to distinguish as they demonstrate similar accelerometer patterns [134]. Furthermore, actions which require isometric contractions, such as weightlifting and yoga, may not be accurately captured by wearable-based accelerometers.

1.8.2.3 Wearable motion sensors in clinical research

Accelerometer-based physical activity monitoring is widely used by researchers in various fields to assess physical activity behaviours and fitness. Physical activity monitoring has led to novel insights in people with respiratory and neurological

conditions, as well as advanced age [135-137]. Various cardiovascular conditions have also been investigated using accelerometers to understand their impact on physical activity behaviour. In heart failure, wearable physical activity monitoring has demonstrated that lower levels of physical activity behaviour are associated with greater morbidity, mortality and hospital admissions [138-139]. In pulmonary hypertension, wearable monitoring demonstrated a lack of improvement in physical activity behaviours following inspiratory muscle training, which correlated with exercise assessments and patient reported outcomes [140]. Furthermore, the use of inhaled nitric oxygen therapy in pulmonary hypertension led to improved wearable-based physical activity parameters in comparison to a control group [141]. The applicability of wearable physical activity monitoring to a variety of patient settings allows for exciting new innovations and understanding into how a variety of pathologies can impact on quality of life and function.

Physical activity monitoring in patients with CAD has similarly been used in clinical research to understand physical activity behaviours of patient populations. It has been shown through wristwatch accelerometry monitoring that many patients who have suffered an ACS event undertake minimal to no amount of cardiovascular exercise, despite it being recommended and encouraged through cardiac rehabilitation [142]. In this small observational study, only 16% of participants achieved the levels of exercise recommended 6 weeks after their index event, whereas 56.5% of patients undertook no level of exercise by this time. In a prospective study of patients with coronary artery disease attending cardiac rehabilitation, improved levels of moderate to vigorous exercise as well as reduced sedentary time were observed, although the proportion of patients meeting

recommended levels of exercise activity remained low at 21% [143]. A study of 139 Finnish patients waiting to undergo CABG surgery wearing triaxial accelerometers showed that physical activity parameters were significantly different to that of healthy aged-matched population samples [144]. In this group, levels of moderate to vigorous physical activity were comparatively lower in the pre-CABG patients, while they undertook longer periods of sedentary behaviour. These results demonstrate that engaging patients in undertaking positive physical activity behaviours known to improve cardiovascular risk factors, which should be achievable for most patients, remains a significant challenge. It is unclear if the levels of physical activity after revascularisation therapy, as measured by accelerometers, is predictive of worse outcomes, and there is ongoing work looking at addressing this question [145].

1.8.2.4 Influential factors in objective physical activity monitoring

When utilising objective physical activity monitoring in clinical research, there are a number of important factors to consider that can influence an individual's physical activity behaviour. Several demographic factors are known to influence physical activity levels such as age, gender, socioeconomic status and ethnicity/cultural background [146-148]. Physiological factors such as body mass index (BMI) and health status, including the number and severity of chronic diseases an individual suffers from, can also influence physical activity behaviour [149]. These factors are commonly taken into account in most forms of clinical research and are not specific to physical activity research.

There are other potential confounding factors that may also need to be considered when monitoring daily physical activity behaviour. These include measurement-related factors, environmental factors, social factors and temporal factors.

Measurement-related factors refer to the use and interpretation of physical activity monitoring devices, which includes device accuracy and raw data interpretation, which can vary between different manufacturers, as well as device wearing compliance, which describes how consistently, frequently and correctly users wear monitoring devices. Environmental factors include weather conditions such as temperature, humidity and precipitation which can vary significantly with changing seasons and can affect outdoor activity [150]. The geographic location (urban versus rural settings) as well as the presence of accessible built environments, such as parks, gyms and infrastructure, can also be considered significant environmental factors [151]. Social factors include cultural norms and attitudes towards physical activity and types of behaviour, as well as support networks such as friends and family. Lastly, the time of day physical activity is recorded, as well as weekday versus weekend physical activity patterns, are termed temporal factors [152].

1.8.3 Subjective methods

The assessment of physical activity behaviour is most commonly performed through subjective methods. These methods include recall interviews, questionnaires or surveys and diaries [153]. Recall interviews are ubiquitously applied in routine clinical assessments of a variety of clinical conditions, particularly cardiovascular disease, during a patient's history taking. Structured questionnaires and surveys are frequently employed during clinical research trials to apply a level of objectivity and

comparability between subjects and to compare outcomes with baseline function, while diaries or logs provide more in-depth active monitoring of a patient's perceived physical activity behaviour. In comparison to the methods discussed earlier, subjective methods of physical activity assessment are far easier to implement, are less expensive, and have the benefit of providing a unique view into the patient's personal experience and views that the other methods are simply incapable of quantifying. However, subjective methods of assessing physical activity are well known to be flawed. Recall interviews rely heavily on a patient's perception of their physical activity behaviour and it can be difficult to obtain accurate information on exact parameters such as exercise intensity, frequency, and duration. Recall interviews have been shown to correlate poorly with objective methods of physical activity to determine minutes spent in MVPA exercise [154]. Questionnaires vary significantly in their design and detail and can rely on arbitrary descriptions or scales which patients can find difficult to gauge. The International Physical Activity Questionnaire (IPAQ), a popular questionnaire method for assessing physical activity, has been shown to correlate poorly with objective methods of physical activity, including in heart failure patients [155-157]. A systematic review of studies comparing a range of subjective methods of physical activity assessment to either criterion or objective methods found that the correlations between the two were generally low to moderate, with significant underestimations and overestimations observed [153]. Ultimately, while being much easier to use in routine clinical practice, the scientific value of subjective methods of physical activity is questionable, and the need for robust, standardised methods to record a variety of physical activity parameters is evident to standardise this key assessment of patient function in clinical practice.

1.9 Summary

Despite many advances in the management of CAD, it remains a leading cause of mortality and morbidity worldwide. Treatments for the symptoms associated with CAD, primarily angina, improve the quality of life of patients, allowing them to undertake the activities of their daily lives free from symptom burden. PCI is one such treatment option, which is regularly utilised in the management of refractory symptoms despite multiple anti-anginal medications, as well as reducing the risk of future adverse cardiovascular events in certain cases. Current international guidelines support this treatment of chronic coronary syndromes, and further efforts are made to select the appropriate patients to enhance treatment benefit through FFR.

The true impact of revascularisation in stable CAD on the day-to-day activities of patients remains uncertain. Current understanding of functional capacity before and after intervention rely largely on recall questionnaires or discrete assessments of exercise capacity in a clinical environment. Such questionnaire assessments aim to understand how much their symptoms impact their lifestyle and activities, while functional exercise assessments simply ask how much exertion an individual can undertake during a single visit. These assessments offer little insight into the relative activity behaviour of a patient, such as the time spent physically active versus sedentary, and how often they undertake physical exercise and how long. These parameters are important to understanding the physical activity behaviours of an individual, and whether they fall into categories of either healthy levels of physical activity and exercise or unhealthy inactivity. Patients identified in the latter category may be offered targeted therapies and support aiming to improve such behaviours

where possible, which is well known to improve the quality of life and outcomes of patients with CAD. As described earlier, patients with CAD are more likely to undertake lower levels of physical activity and display more sedentary behaviour. Whether this is the result of their symptom burden or a contributing factor to their development of CAD will likely vary between individuals. Therefore, an objective, validated assessment of patient physical activity behaviour in their own environment may help identify those with poorer physical activity behaviours, and therefore highlight them as patients who may benefit from targeted physical therapies through cardiac rehabilitation programs.

There are many uncertainties regarding the use of objective physical activity monitoring devices for the assessment of CAD and their response to treatment. It is currently unclear if an individual's objective physical activity behaviour interacts with their revascularisation outcomes. It is not known whether parameters gained from physical activity behaviours such as daily step count, minutes spent in moderate to vigorous physical exercise and daily sedentary time can be used to infer an improvement or a deterioration in a CAD patient's quality of life or symptom burden. Lastly, there is no standardised agreement as to how patients with CAD should be monitored to objectively assess their physical activity behaviour with such devices. While many studies have undertaken monitoring of physical activity behaviours over discrete periods of time before and after certain interventions, this approach falls short of the potential wealth of data that continuous physical activity monitoring through wearable devices can provide. Whether this form of monitoring is feasible and an acceptable approach to patient assessment remains to be seen, as well as whether it provides a better understanding of a patient's physical activity behaviour.

1.10 Hypothesis

Wearable physical activity monitoring can provide an objective assessment of physical activity behaviours for patients suffering with CAD and being treated with PCI.

1.11 Aims

The aims of the current thesis are to answer the following questions:

1. How acceptable and successful is continuous wearable physical activity monitoring in a CAD population?
2. How accurate is the Fitbit Charge 4 wearable device step-counting function?
3. What are the associations between objective physical activity parameters gained from wearable monitoring and traditional assessments in CAD?
4. Does PCI lead to an improvement in objective physical activity parameters, and is this associated with clinical outcomes?
5. Do factors such as demographics, wearer compliance and weather influence objective physical activity behaviour in the CAD population?

CHAPTER 2

2. Methods

This chapter describes the design of the Virtu-5 study, a single centre prospective cohort study undertaken at Sheffield Teaching Hospitals NHS Foundation Trust between August 2020 and October 2022, in which I addressed the hypothesis and aims stated earlier.

2.1 Overview

The Virtu-5 study is a parallel project with two main objectives: first, to collect data for using wearable technology to monitor physical activity in patients suffering from angina, and second, to develop and test a novel computer model for assessing myocardial blood flow. Patients were recruited to the study who were awaiting invasive coronary artery physiology assessment with the view to proceed to PCI for symptoms of angina despite optimal medical therapy as defined by ESC guidelines [22]. To maximise recruitment of suitable patients, those with recent coronary imaging, either ICA or CTCA, which demonstrated at least one coronary artery stenosis between 50-90% stenosis severity were included. As recommended by current clinical guidelines, all patients underwent coronary physiology assessments via FFR for all suitable target vessels, and the decision for proceeding to PCI would be based on the result of these findings. Patients with negative FFR values (i.e. non-significant flow reductions) did not proceed to PCI, but provided a valuable 'control' group, experiencing all the study inputs, albeit without stent deployment. Relevant clinical, imaging, activity monitoring, six-minute walk test, and patient

reported outcome measures were recorded before, during and after their CCL procedure. These data were collected throughout the period of study monitoring, from the point of recruitment prior to their CCL, and up to 6 months after their procedure.

The Virtu-5 study involved many research and clinical team members who played a variety of roles in the project, including clinicians, radiographers, physiologists and non-clinical researchers. Two PhD research students were assigned to the Virtu-5 study, myself and Abdulaziz Al-Baraikan. All aspects of the Virtu-5 study activity were carried out with the involvement of the research students, either by leading, supervising, or observing. All data recorded for the study was done by the research students. The study lead for Virtu-5 was Professor Julian Gunn. Where relevant, all other members of the team who were involved in the Virtu-5 study activities will be acknowledged in the relevant sections.

2.2 Ethics and funding

The study received a favourable opinion from the Health Research Authority (HRA) and the Health and Care Research Wales (HCRW) [IRAS: 272069] (see appendix 2). The Sheffield Teaching Hospital Cardiothoracic Directorate Research Executive (CDRE) and NIHR Cardiovascular Patient Panel (CPP) approved the study protocol. Funding was granted by Sheffield Hospitals Charity (Grant number: 192027), the Engineering and Physical Sciences Research Council (EPSRC) student scholarship, and the King Saud bin Abdulaziz University for Health Science (KSAU-HS) student grant.

2.3 Patient screening and recruitment

Patient screening and recruitment began in August 2020. Potential study participants were identified by two rounds of screening. The first round of screening involved reviewing a pooled waiting list of patients who had been listed for an elective coronary angiogram. This was performed by the research students by accessing the Sheffield Teaching Hospital's electronic waiting list system. All patients identified were considered by reviewing relevant clinical documents available through the hospital's electronic system, including clinic letters and imaging reports. Access to all relevant electronic systems, including a STH computer user login, was given to the research students on the grounds of accessing data for clinical research. All patients were screened with the study's inclusion and exclusion criteria (see section 2.3.1). If the patient met the relevant inclusion criteria and no exclusion criteria was present at this stage, they were discussed with the study lead to confirm their suitability for the study and a study invitation letter and patient information sheet was sent to the patient via the cardiology department secretaries (see appendix 3). If there was any missing information that would not allow for a full review of the inclusion and exclusion criteria at this stage, cases would be reviewed by the study lead and proceed at their discretion.

Once the patient had received the letter and returned the study invitation, a second round of screening was performed. Each patient who responded to the letter who indicated an interest in partaking in the study were contacted by telephone to arrange a meeting with the research students. Prospective study participants were offered a choice between online virtual appointments using a virtual meeting platform (Google Meet or Zoom, depending on their preference), or by meeting face to face.

Face to face meetings were offered either as home visits by the research students, or by organising an appointment at the Hallamshire Hospital University site offices. Family members were welcomed to these meetings at the patient's discretion. All screening criteria were reviewed at the meeting with the patient to confirm all the details were correct and to clarify any missing information that could not be obtained at the first round of screening. At this stage, if all the inclusion criteria were met and no exclusion criteria were present, the patient was offered to enrol within the Virtu-5 study.

2.3.1 Inclusion and exclusion criteria

Inclusion Criteria:

- Able to provide informed consent.
- Diagnosis of angina.
- Referred for coronary artery physiology assessment with the view to proceed to coronary angioplasty.
- Recent coronary imaging, either CTCA or ICA, demonstrating at least one obstructive coronary lesion amenable to physiological assessment and angioplasty.

Exclusion Criteria:

- Age < 18 years.
- Inability or refusal to give formal consent.
- Emergency intervention.
- Previous CABG or recent PCI.
- Any significant valvular heart disease of at least moderate severity.

- A diagnosis of heart failure affecting the left or right ventricle.
- Inability or refusal to complete follow up.
- A diagnosis of active cancer or a terminal illness with a prognosis of less than 1 year.
- Contraindications to MRI such as implanted pacemaker, metallic foreign bodies, implants or severe claustrophobia.
- Contraindications to Gadolinium administration, such as a documented allergic reaction or chronic renal failure (Creatinine > 180 µmol/dL).
- Contraindications to pharmacological stress testing such as asthma or heart block.

2.3.2 Consent

All patients recruited to the Virtu-5 study were required to provide informed, written consent. During the first in-person meeting with each patient, following the second screening process, all patients would have a discussion with the research student about the Virtu-5 study and their involvement. The research student undertaking the consenting process was trained and experienced in obtaining clinical consent, including consent for coronary angiography and PCI. Consent for clinical procedures, including CCL procedures and CMR, were taken separately by the relevant professionals.

Each consent process included a comprehensive discussion with the patient which covered several relevant key topics, which began by discussing the fundamental aspect of their experience of angina. This involved exploring the patient's

understanding of their diagnosis, the nature of the procedure they were waiting for, and their expectations following their procedure. From this, the research students would discuss the research questions and aims of the Virtu-5 study, and the different research activities involved. Once all the relevant information was discussed, the patient was offered an opportunity to ask questions about the study. Once all questions were addressed, the patient was offered the opportunity to enrol within the Virtu-5 study and complete the study consent form in triplicate (see appendix 1). One copy of the consent form was kept alongside the physical research records on site at the University of Sheffield office, another was filled within the patient's own notes, and a third was given to the patient to keep.

2.4 Clinical study protocol

The Virtu-5 study protocol involved the recording of a range of clinical parameters. As the focus of the study was to capture a comprehensive dataset focused on the various aspects of CAD, a variety of relevant parameters were collected, including patient reported outcomes, clinical imaging and coronary physiology assessments, as well as wearable physical activity monitoring. Furthermore, as the emphasis of the study is to observe the changes seen in patients suffering with angina following a PCI, data is collected before, during and after their CCL procedure.

The Virtu-5 study comprised three phases; baseline, recovery, and follow up. An overview of each study phase and what data collection activity occurred at that time is illustrated in figure 2.1.

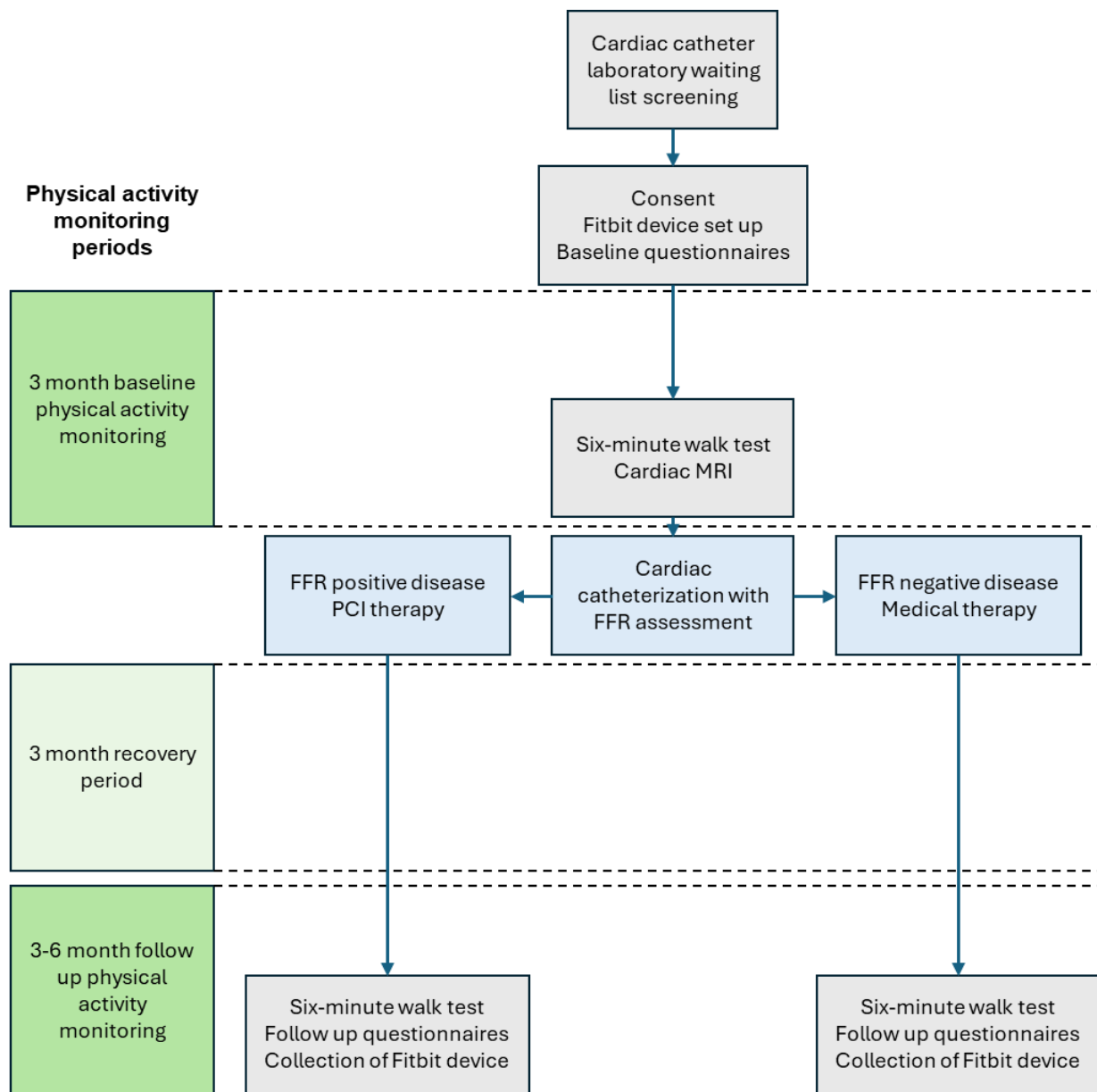


Figure 2.1 Flowchart of overall study protocol for Virtu-5 project with planned physical activity monitoring. FFR = fractional flow reserve.

The baseline (pre-CCL) phase began during the same appointment as the first in-person meeting. The research student administered the study questionnaires to the patient and set up the wearable physical activity monitoring. Once a CCL appointment date was given to the patient, a separate appointment was organised with the research students to undertake further pre-procedure data collection, which involved a 6-minute walk test (6MWT) and a CMR study. This appointment was

carried out at the Northern General Hospital as close to the CCL appointment date as feasible (ideally within 5 days). The baseline phase terminated the day before the patient undergoes their clinically indicated ICA assessment and the collection of all relevant data by the research students. Once the patient was discharged from their elective CCL appointment, they entered the recovery period which lasted for three months. The follow up period activities occurred between 3 months to 6 months after the patient's CCL procedure. If the patient wished to complete their follow up within the study early, they were offered the earliest date that suited them. At their final appointment, either at six months post CCL or earlier at the patient's discretion, the physical activity device was collected and follow up assessments of 6MWT and questionnaires were administered.

2.5 Data management

2.5.1 Imaging data

Two sources of imaging data were collected during the Virtu-5 study, namely diagnostic coronary angiography images and research CMR studies. With regards to coronary angiography images, these were transferred to XNAT, a secure university-managed platform, once all patient demographics were removed and replaced with virtu-5 study numbers. This transfer of data was performed by the research students. The research CMR studies were logged with Virtu-5 study identifiers and were stored directly on a separate secure university-managed repository, Polaris XNAT. Both platforms could only be accessed through university managed internet access, either via university managed devices or Virtual Private Networks.

2.5.2 Non-imaging data

Data collected through activities conducted by the research students was initially recorded on paper documents. This included baseline patient characteristics, 6-minute walk test assessments and ICA procedure details. All paper documents were stored in a secure area once completed, either in the Northern General Hospital or at the University of Sheffield. All paper documents were dated and contained only the patient's study number as the identifier, no other patient identifiable details were recorded.

Non-imaging data were transcribed to relevant electronic spreadsheets to maintain a central repository which was stored on the University affiliated Shared Google drive. Access to the Shared drive was restricted to the research students alone and required two-factor authentication as per the University of Sheffield's "Protecting Personal Data" and "Protecting Research Data" policies.

2.6 Baseline clinical data

2.6.1 Basic demographics

A standard set of demographics associated with physical activity was collected from the patients following their recruitment to the study. The demographics collected included age, weight (kg) and height (cm). Body mass index was calculated for each patient based on these parameters.

2.6.2 Relevant medical history

Patient past medical history was sought during the initial in-person consultation. Each patient was asked whether they had been previously diagnosed with the following conditions: hypertension, hypercholesterolaemia, diabetes, myocardial infarction or cerebrovascular accident/stroke. Clinic letters, which routinely detailed a list of relevant clinical diagnoses, were used to screen for these conditions, which were confirmed with the patient during the recruitment interview. All patients were asked whether they smoked, categorising each patient as either never having smoked, previously smoked but now quit, or continued to smoke.

2.7 Questionnaires

The assessment of the patient's quality of life and symptom burden was undertaken by three separate questionnaires completed by the patient. The details for each questionnaire is included below. Furthermore, an additional questionnaire was given to all study subjects at their final follow up assessment.

2.7.1 EQ-5D-5L

The level 5 EuroQoL version questionnaire, or EQ-5D-5L, is a descriptive system designed to assess an individual's general quality of life. The questionnaire consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (see appendix 5b). Each aspect of the descriptive system has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Additionally, the EQ visual analogue scale (VAS) records the

patient’s self-rated health on a vertical visual analogue scale, with endpoints labelled ‘The best health you can imagine’ for 100, and ‘The worst health you can imagine’ for 0. All aspects of the EQ-5D-5L focused on how the subject views their health status that day.

Two scores were generated from the EQ-5D-5L questionnaire. The first was the EQ VAS, which represented the patient’s view of their overall health and wellbeing. The second was the England Index value, a score which was based on index value sets based on the preferences of the general population of England. The England Index scores indicate differing states of health based on a 20-parameter model, where a score of 0 suggests a state of health equivalent to death, and 1 indicating full health [158]. The possible scores based on the England Index values range from -0.285 (suggesting an overall perceived state “worse than dead”) and 0.950. The set values for each response is shown in table 2.1.

Table 2.1 – EQ-5D-5L England Index value model for domains and responses

	No Problems	Slight	Moderate	Severe	Unable
Mobility	0	0.058	0.076	0.207	0.274
Self care	0	0.050	0.080	0.164	0.203
Usual Care	0	0.050	0.063	0.162	0.184
Pain & discomfort	0	0.063	0.084	0.276	0.335
Anxiety & depression	0	0.078	0.104	0.285	0.289

2.7.2 Short Form 12

The Short Form-12 survey (SF-12) is a widely used self-reported health-related quality of life (HRQOL) instrument which measures the effect of health on an

individual's quality of life (see appendix 5b). The SF-12 questionnaire consists of 12 questions aimed at assessing a distribution of 8 dimensions of health: General health perception, physical health, limited physical role function, physical pain, vitality, mental health, limited emotional role function, social functioning. Each question relates the patient's perception of their health over the last 4 weeks. The latest version of the SF-12 questionnaire (SF-12v2) was utilised for this study.

The scores for each SF-12 survey is calculated automatically by a dedicated software (PRO CoRE 2.0 Smart Measurement®), SF-12v2® Health Survey. For each completed survey, a physical component score (PCS) and a mental component score (MCS) are derived. Values for PCS and MCS range from 0 to 100, with higher values indicating better function in each component. For context, a PCS score of 50 or below is considered to indicate a significant physically limiting condition, while a score of 42 or below on the MCS can indicate clinical depression [159].

2.7.3 Seattle Angina Questionnaire

The third questionnaire completed by each participant, the Seattle Angina Questionnaire (SAQ), aims to assess the disease-specific burden of angina on a patient's quality of life. The self-administered tool includes a 19-item questionnaire with 5-domains: physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception/quality of life (see appendix 5c). Similar to the SF-12, the SAQ utilises a 4-week recall period to answer relevant domains. The UK version of the SAQ was utilised for this study.

The scoring for each domain of the SAQ was performed manually by the research students as per the official Outcomes Instruments LLC scoring instructions. A total of 3 scores were produced for each completed questionnaire: the physical limitation domain, the quality-of-life domain, and the angina frequency domain, each score ranging from 0 to 100. SAQ scores can be categorised into set ranges to give clinical context to each score; for the physical limitation and quality of life domains, a score of 0 to 24 equates to poor health, 25 to 49 as fair, 50 to 74 as good, and 75 to 100 as excellent. For the angina frequency domain, 0 to 30 represents daily angina, 31 to 60 to weekly angina, 61 to 99 as monthly angina, and 100 as no angina [160].

2.7.4 Patient experience of wearable technology

A further questionnaire was offered to all patients during their final follow up assessment. This self-reported questionnaire, designed by the research students, focused on understanding the study subject's overall experience of wearable technology and mobile devices (see appendix 5d). The questionnaire included 7 items which addressed different aspects of wearable and mobile technology use, including their experience prior to their enrolment to the study as well as their experience of using the devices given to them during the study. The questionnaire also asked about their impressions of using such devices again in the future, for either clinical or research purposes. The questionnaire also contained a free text area in which the patient could record any further thoughts, impressions or comments related to the wearable device that they felt was not covered fully by the questionnaire.

2.8 Physical activity monitoring

Following enrolment to the Virtu-5 study, each study subject was given a Fitbit™ Charge 4 fitness tracker wristwatch (Fitbit Inc, California, USA). The purpose of the Charge 4 devices was to collect physical activity data in free living conditions for the duration of the study. The Charge 4 uses Fitbit Operating System and cloud storage to transfer, store and export data. The Charge 4 contains a number of relevant sensors, including a MEMS tri-axial accelerometer and a PPG-based optical heart rate sensor. The reported battery life of a Charge 4 device is quoted at 7-10 days. All devices were purchased by the study funding available through the University of Sheffield's procurement service.

2.8.1 Device initialisation

All devices went through an initialisation process conducted by the research students. Firstly, 2 anonymous accounts were created for each study subject; a personal Fitbit account and a personal Gmail account. Each account activation was cost free but required a number of details regarding the individual creating the account, including a unique username, forename, surname and date of birth. Details provided for the Gmail and Fitbit accounts were not patient specific; all account forenames and surnames were given as "John" and "Smith" respectively. For date of birth, the first of January of the patient's birth year was used for the Fitbit account (for example, a birthday of 17/07/1968 would be submitted as 01/01/1968 to the Fitbit account). This was done to avoid providing any patient-identifiable information while being able to utilise age-specific functions of the Fitbit algorithm of exercise intensity, as discussed later. Usernames for each Fitbit and Gmail account were generated

using the following formula: VH5<Date of recruitment> (for example, a patient recruited on the 3rd of April 2022, the subsequent username would be VH5030422). All accounts are password protected, which were generated randomly using the free Norton™ Password Generator webpage, using 8 characters of varying letters, numbers and symbols. The usernames and passwords for all accounts were retained by the research students and held on the 'Virtu-5 study' shared Google drive. Study subjects were not given the usernames or passwords for these accounts.

Once both accounts were created for each subject, the Charge 4 was paired via wireless Bluetooth connection to an available mobile phone device. This device was either the patient's own personal device, or a blank mobile phone device provided to the patient by the research students which was connected to a local Wi-Fi network. The patient was provided with a blank mobile phone device if they did not own a mobile phone device which was compatible with the current Fitbit application. The blank mobile phone model chosen was a Samsung Galaxy A10, which was acquired through the university's procurement service. Once the Charge 4 was paired with the mobile phone, a standard approach to device settings were set during the initialisation period. This included disabling the GPS function of the device, which aimed to maintain the anonymity of the study subjects using the device. Furthermore, all but one of the Charge 4 device notifications were silenced, such as "Move reminders", a function designed to encourage physical activity during periods of inactivity detected by the device, "Daily goals", which notified users if they had reached a pre-set activity goal, such as walking 10,000 step, and other miscellaneous notifications. These changes were intended to reduce the interaction

of the study subject with the Charge 4 device and to ensure that the physical activity of the individual was representative of their usual behaviour as opposed to the result of encouragement from the device. The only device notification that remained active was the “low battery” notification, which would notify the user of when the Charge 4’s battery had been reduced to 10% on the watch face.

2.8.2 Patient instruction

Patients were instructed in a number of aspects of how to use the Charge 4 device. Patients were instructed to wear the Charge 4 device as often and as long as possible throughout the study. They were also instructed that they could choose to wear the watch at night if it was felt comfortable to do so, but that there was no preference indicated by the research team as to whether the patients wore the device all day or only during the daytime. The patients were instructed to occasionally take short breaks from wearing the watch, such as when bathing or showering, to avoid any issues of skin irritation caused by prolonged wear times. The patients were advised to charge the device once a week, as this would fall well within the device’s battery capacity, however they were welcome to charge their device however they saw fit which suited their wear style (i.e. charge each night if only wearing in daytime, etc). Patients were shown the basic means of maintaining the Charge 4, including connecting the device to its charging cable.

Finally, each patient was shown how to “synchronise” their Charge 4 with their mobile device. This involved accessing the Fitbit mobile phone application, and initialising a manual synchronisation of the device. Synchronisation of the Charge 4

to the mobile device would transfer all device-collected data to the Fitbit cloud storage. While the Charge 4 would normally synchronise automatically without any user input, during preliminary testing by the research students, it was noted that this automated synchronise function would occasionally fail, leading to periods where data was not being recorded and could lead to potential data loss. The Charge 4 has the memory capacity to retain up to 2 weeks of physical activity data at any one time, after which it would start overwriting old data with newer data recorded by the patient. As such, patients were taught how to manually synchronise their Charge 4 device and instructed to do so when setting the device aside to recharge if they felt able to do so.

Patients were informed to use the Charge 4 device as instructed above throughout the study period, from the time of enrolment up to the final follow up session in their post-procedure period. Patients were informed that they could take breaks from wearing the device anytime they wished for as long as they wanted, and were asked to inform the study team if and when they chose to do so and when they resumed wearing the device.

2.8.3 Data monitoring, download and storage

Data collected by each Charge 4 device was regularly monitored by the research students via the Fitbit webpage. By logging into the Fitbit webpage via the study subject's assigned username and password, all data collected by the Charge 4 device could be accessed, reviewed and downloaded remotely. Accounts were routinely reviewed every 2 weeks, with a particular note made of the most recent

device synchronisation date. Using the Fitbit webpage, raw data was regularly downloaded in Microsoft Excel format and subsequently transferred to the 'Virtu-5' shared Google drive.

2.8.4 Troubleshooting

All patients were given contact details for the research students in the event of any issues encountered during the study period. Issues such as physical damage to the Charge 4 would be reviewed by the research students and, if necessary, the damaged device would be replaced by a new Charge 4. Furthermore, device synchronisation was regularly monitored as described above. In the event of a device not synchronising for over two weeks, the patient would be contacted by the research student to ascertain if any issues had been encountered (eg device fault or damage, travel abroad, or a break from wearing the watch). In the event that no device-specific issue had been encountered, the study subject was advised to manually resynchronise their Charge 4 with their mobile device. The account would be re-checked the following day, and if the issue had not been resolved, the study subject would be offered an in-person visit by the research student to attempt to ascertain the issue and resolve it, at their earliest convenience. In the event the issue could not be resolved, a new Charge 4 device was linked to the account and offered to the patient. Furthermore, at each patient visit, the device and application OS was reviewed by the research student to ensure that the most up-to-date software available was installed and, if necessary, update the application or device software.

2.8.5 Physical activity data

For each subject enrolled in the physical activity monitoring aspect of the Virtu-5 study, a number of daily parameters were collected through their wearable device.

These parameters included the following:

- Step count
- Minutes spent sedentary
- Minutes spent lightly active
- Minutes spent fairly active
- Minutes spent very active
- Active calories

All of the above parameters are calculated by a proprietary method via the Fitbit website using accelerometer data, except for “Active calories” which is calculated using continuous heart rate data. Minutes spent fairly active and minutes spent very active data have been shown to be consistent to moderate and vigorous intensity physical activity respectively, therefore the minutes for both of these parameters per day are combined to a single value of minutes spent in moderate to vigorous physical activity (MVPA).

2.8.6 Quality control

In order to determine a valid day of monitoring, a criteria of “valid wear day” is needed. This is to ensure that data captured by the Charge 4 is representative of a patient’s usual physical activity. This generally involves assessing the patient’s use of their device, specifically how long they wore their device for each day, and if

possible, in what context (ie awake vs asleep), and whether this was sufficient to be classed as a “valid wear day”. Therefore, for each patient, a parameter of “wear time” and “awake wear time” was recorded for each day they were monitored by the Charge 4 during the study.

For each day, the number of minutes the patient wore their watch was recorded by the research student. This method involved reviewing the continuous heart rate data available through the Fitbit website for each user. By reviewing the day’s continuous heart rate data, represented by a line graph starting from midnight and finishing the subsequent midnight, heart rate averages collected every five minutes could be viewed across each day. Any gaps in the line graph would indicate a period of at least 10 minutes where heart data had not been collected by the device, which would indicate “non wear time”. The total amount of non-wear time from each separate non-wear episode was calculated for each day, and a subsequent daily wear time was calculated by subtracting the total non-wear time from the total amount of minutes in a day (1440 minutes). Therefore, the following calculation was used:

$$\text{Daily wear time} = 1440 - \text{total non-wear time}$$

2.8.6.1 Valid wear day / valid monitoring week

Currently, there is no universally recognised standard by which a “valid wear day” is defined based on daily wear time. Therefore, as part of the work for this study, a number of “valid wear day” criteria were used to investigate the impact of different cut-off methods. These included the following absolute cut off values for minimum wear time: 1 hour, 4 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours and 23 hours and 24 hours. A range of minimum wear time cut-offs were used to assess the impact of more and less strict criteria for wear time in this cohort. This cut off value would then be applied to both pre and post intervention datasets for each patient. The purpose for using this method would be to control for potential variations in device compliance between the pre- and post-intervention period resulting in different physical activity parameter values. This method was applied to all datasets as a proof of concept, whether the wear time values were normally distributed or not.

Using each of the values outlined for determining the minimum values for “valid wear days”, data for physical activity are then represented using two main methods. The first method is through weekly averages of valid wear days, or valid monitoring weeks. As described in other similar work looking to determine physical activity behaviour, a valid monitoring week will be based on at least four valid days occurring over a 7-day period [161]. Physical activity variables will be averaged over three-month periods of monitoring. The monitoring values will be split into two distinct periods in which physical activity parameters are averaged over the entire period. The two periods are defined as follows: baseline period (data collected between the day before the patient’s CCL appointment date and up to three months before) and

follow up (data collected after 3 months have passed following the CCL procedure). There will be a three-month gap in between the baseline and follow up monitoring periods to allow for recovery from the CCL procedure. A minimum of four valid monitoring weeks will be required to produce the data needed for each averaged monitoring period. Each of the different criteria used to classify minimum wear time criteria for a valid day described earlier will be used to assess the impact of different quality control measures on this method of data analysis.

2.9 6-minute walk test

To validate the use of wearable physical activity monitoring as assessment tools of functional capacity in patients suffering with angina, a standard clinical assessment of physical activity is required. The 6-minute walk test (6MWT) is a widely used assessment tool in clinical and research setting to assess the sub-maximal exercise capacity of individuals with cardiac conditions, including angina. All patients recruited to the Virtu-5 study were consented to undertake a 6-minute walk test assessment prior to their CCL assessment and at their follow up.

2.9.1 Assessment protocol

All 6MWT assessments performed during the Virtu-5 study adhered to the Heart Online: Health Education Assessment Rehabilitation Toolkit – 6MWT instructions sheet [162]. All 6MWT assessments were conducted in the Northern General Hospital. The assessments were conducted in a quiet, obstacle free corridor adjacent to a clinical area on hospital grounds which was accessible only by staff with keycard access. The test was conducted along a straight, flat, 20 metre track. A

6MWT walk test protocol and results recording document, which was adapted from the Heart Online 6MWT toolkit for the purposes of this study, was brought to each assessment to ensure consistency for all assessments (See appendix 4a). All equipment listed on the 6MWT were checked before commencing each assessment. Upon arrival, the patients were instructed to take a seat and rest for 15 minutes. During this initial rest period, all baseline physical assessments were documented, after which the patient was given the formal instructions detailed in the 6MWT protocol sheet. During the formal instruction process, one of the research students would demonstrate one full lap to the patient. Once the 15-minute rest period had elapsed, and if the patient was happy to proceed, the first 6MWT attempt was commenced, with pre-specified instructions given each minute of the test. Following the completion of the first assessment, the documented distance travelled during the assessment was measured and documented as the 6-minute walk distance (6MWD), and the patient was returned to the original seating position prior to the first attempt. The patient was then given 15 minutes of rest while sitting down, during which time repeat observation assessments were performed. After 15 minutes, once the patient was ready, a second attempt to complete the 6MWT assessment was undertaken in the same manner as the first attempt. A second attempt was carried out for all patient visits to avoid learning bias observed in 6MWT assessments. Once the second attempt was completed, and their second 6MWD result recorded, a further set of physical observations were collected and documents, and the patient observed for 15 minutes in the sitting position, after which the appointment ended.

Each assessment was supervised by two research students, with at least 1 student having valid Advanced Life Support (ALS) certification. One student would lead the

assessment as per the 6MWT protocol, the second student would undertake a manual count of steps. This was performed with a manual tally counter which the student used to count during the assessment. The student would ensure that the participant's Fitbit 'walking exercise' function would be activated so that recordings of steps and distance walked could be recorded specifically for each assessment.

Following completion of both 6MWT assessments, the best 6MWD achieved was recorded as the result for that assessment period. Estimations of expected 6MWD results were used to gauge the findings of these assessments in order to personalise the results. These personalised values were calculated from the patients' demographics, which included gender, height, weight and age. For male participants, expected 6MWD and lower limit of normal values were calculated using the following formula:

$$\begin{aligned} \textbf{Expected 6MWD} &= (7.57 \times \text{height in cm}) - (5.02 \times \text{age}) - (1.76 \times \text{weight in Kg}) - 309 \\ \textbf{Lower limit of normal} &= 6MWD - 153 \end{aligned}$$

For female participants, expected 6MWD and lower limit of normal values were calculated using the following formula:

$$\begin{aligned} \textbf{Expected 6MWD} &= (2.11 \times \text{height in cm}) - (2.29 \times \text{weight in kg}) - 5.78 \times \text{age} + 667 \\ \textbf{Lower limit of normal} &= 6MWD - 139 \end{aligned}$$

2.10 Cardiac Magnetic Resonance Imaging

All patients enrolled into the study were invited to undertake a CMR scan as part of the study activity. Baseline pre-CCL CMR studies are arranged before each patient's

appointment. While having been screened for contra-indications to MRI scanning and pharmacological stress with Regadenoson during the screening process, a further safety check for these contra-indications was carried out at their appointment as per local Radiology department safety procedures. All studies were supervised by an ALS certified doctor. During physiological stress, a doctor familiar with administering and monitoring the effects of Regadenoson was present at all times, with regular assessments and documentation of heart rate, blood pressure, pulse oximetry and patient symptoms on the standardised recording sheet (see appendix 4c).

The Virtu-5 CMR protocol for the study patients included the following components, which took roughly 1 hour to complete:

1. Survey
2. Baseline cine imaging for functional imaging
3. Tissue characterisation with native T1-mapping (rest)
4. 4D flow CMR
5. 2D q flow of 2 chamber view (rest)
6. Start pharmacological stress (Regadenoson)
7. First gadolinium contrast injection (half dose)
8. First pass perfusion imaging – short axis 3 slices (Stress)
9. 2D Q-flow imaging of 2 chamber view (stress)
10. 15 minutes to return patient to resting state
11. Late gadolinium enhancement imaging (short axis)
12. Second gadolinium contrast injection (Half dose)
13. First pass perfusion imaging – short axis 3 slices (Rest)

The Virtu-5 CMR protocol involves a variety of standard and research assessments of cardiac structure, function, perfusion and tissue characterisation, including 4-dimensional flow assessment. The focus of the work described herein will focus on the standard datasets available through CMR scanning, and advanced techniques such as 4D flow imaging is reserved for other avenues of work associated with the Virtu-5 project.

Ventricular volumetric assessment and myocardial perfusion quantification was performed by a trained research student using the commercially available software (Qmass 8.0, Medis, Medical Imaging, Leiden, The Netherlands). Any issues or difficulties arising from image quality, acquisition or processing was discussed with the research lead.

2.11 Left heart catheterisation

All patients recruited to the Virtu-5 study underwent an invasive left heart catheterisation procedure as standard care for their CAD, following local protocols for pre-assessment, preparation and procedural consent. Typically, patients would undergo coronary angiography via a right radial artery approach, with the choice of catheters used for imaging to be decided at the discretion of the operator. The standard protocol for invasive coronary angiography included:

- Five to six views of the left coronary artery system, and three views of the right coronary artery system.
- At least two views of each diseased vessel, at least 30° apart.
- Image must be centred before acquiring.
- No panning or magnification.
- Adequate contrast injection.
- At least 4 cardiac cycles acquired per image.
- Good catheter engagement.

Following the acquisition of all coronary angiogram images, an assessment of all vessels was made by the operator. Any epicardial vessels visually assessed by the operator to be amenable to percutaneous revascularisation, such as a vessel diameter greater than 2.5mm with a diameter stenosis between 50% - 90%, was assessed with a coronary pressure wire (PressureWireX™, Abbott, Uppsala, Sweden). The FFR assessment was performed as per a standard clinical protocol, using an adenosine-induced hyperaemia, with pressure measurements proximal and distal to the target stenosis (Pa and Pd) recorded. A dedicated software platform

(Coroflow®, Coroventis, Abbott) was used to measure the Resting Full-Cycle Ratio (RFR) and FFR. Based on the angiographic findings and the measured FFR assessment, a decision to proceed to PCI was made by the operator. PCI was performed according to standard clinical practice with the deployment of drug eluting stents for each appropriate target vessel stenosis. Repeat angiography and FFR assessment of the target vessel following PCI whenever possible. Angiogram images were anonymised and transferred to the University's XNAT image storage database (University of Sheffield).

2.12 Weather data

Weather parameters were kindly provided from the Weston Park Sheffield Museum, which provides local meteorological information to the Met Office, the UK's national meteorological service. The following daily parameters were recorded throughout all monitoring periods for each patient: maximum temperature (°C), hours of sunshine, total solar radiation (W/m²), total precipitation (mm), average relative humidity (%), maximum wind speed (Knots). The following devices were used to record the relevant atmospheric values: Campbell Scientific HC2A-S3 Temp and RH sensor; Campbell-Scientific W200P/CP Wind Vane and A100L Anemometer; Campbell-Scientific CM3 Pyronometer (sunshine hours readings calibrated to be equivalent of Campbell-Stokes sunshine recording device for parity with historic readings); Casella Tipping Bucket rain gauge. The data provided was focused on the geographical area of Sheffield and all patients lived within a 20-mile radius of the city.

2.13 Statistical analyses

All statistical analyses were carried out using IBM SPSS® Statistics software version 29. All statistical analyses performed were undertaken as post hoc analyses. Advice was taken from the University of Sheffield's Maths and Statistics Help department with regards to the development of the generalised linear mixed model, particularly around suitability for analysing this dataset, appropriate model parameters and quality assurance, which was discussed during one-to-one meetings with designated statisticians. Data were reported as means, standard deviations of the means, and percentages unless stated otherwise. Assessments of skew were performed for each relevant parameter to assess the normality of distribution. If any of the parameters contained non-normally distributed data, the analysis was conducted with the appropriate non-parametric method, otherwise if all the data were normally distributed, parametric statistical analyses would be used. Agreement between manual and wearable measures of step count and distance walked during 6MWT assessments was assessed using Pearson's correlation coefficient and Bland-Altman plots to assess the limits of agreement (± 1.96 SD). Pearson's correlation coefficient was used to calculate the linear correlation between wearable parameters of physical activity and clinical assessments. Correlation matrices were used to assess the correlation coefficient in the percentages of change between the variables before and after PCI.

With regards to the weather data analysis, a specific statistical analysis was performed. Due to the multiple observations within each participant and given that the given the longitudinal design of the study, a generalised linear mixed model was used to analyse the association between different meteorological recordings and

each physical activity parameter. We used each physical activity parameter separately as the target model (the dependent variable) for each generalised linear mixed model to analyse their association with maximum temperature, hours of sunshine, total solar radiation, total precipitation, average relative humidity and maximum wind speed (independent variables). The models were further weighted for wear time, age (> 65 years / < 65 years), gender (male / female), BMI (normal / overweight / obese), and treatment group (PCI / medical therapy). Statistical significance from the generalised linear mixed models were calculated using the Satterthwaite method with robust estimation of fixed effects and coefficients.

Chapter 3

3 Results

3.1 Baseline characteristics and follow up

A total of forty patients met the inclusion criteria and were recruited to the Virtu-5 study. One patient was recruited within one week of their planned CCL procedure, and therefore did not have enough time to collect baseline wearable physical activity data. A further two patients did not have access to wi-fi internet connection at home, which made continuous physical activity data transmission impractical. That resulted in a total of 37 patients who undertook wearable physical activity monitoring. Based on coronary physiology assessments (which will be discussed in section 3.3), from the wearable physical activity monitoring group, 25 patients underwent PCI, while 12 continued with medical therapy. The characteristics of these patients are shown in Table 3.1. The average age of the whole cohort was 65 years (± 8), 24% of the recruited participants were female, and the average BMI was 29 (± 4). In regard to relevant past medical history, 70% of the recruited participants had been clinically diagnosed previously with hypertension, 38% with hypercholesterolaemia, 14% with T2DM, and 60% reported a history of cigarette smoking. There was a significant difference noted between the PCI and medical therapy groups, with a greater proportion of the medical therapy group containing women (12% in the PCI group, 50% in the medical therapy group, $p=0.012$) and higher number of patients with diabetes in the medical therapy group (4% in PCI group vs 33% in medical therapy group, $p=0.015$). Otherwise, there was no statistically significant difference between the two treatment groups.

Table 3.1 Patient characteristics of subjects recruited to the wearable technology study of Virtu-5 at baseline. Relevant values are presented as means and standard deviation.

Characteristic	Whole cohort N=37	PCI group N=25	Medical therapy group N=12	P value
Age (years)	65(±8)	67(±8)	63(±8)	0.175
Gender (female)	24%	12%	50%	0.012
Weight (kg)	84(±16)	86(±16)	78(±15)	0.163
Height (m)	170(±8)	172(±9)	167(±6)	0.065
BMI	29(±4)	29(±4)	28(±4)	0.607
Hypertension	70%	68%	75%	0.663
Hypercholesterolaemia	38%	50%	32%	0.291
T2DM	14%	4%	33%	0.015
Current/Ex smoker	60%	56%	67%	0.724

During the study, one patient who underwent PCI developed a separate illness during the follow up period, which was not related to their coronary disease, which required urgent investigations and work up and was offered to leave the study, which they accepted. Another patient's procedure was delayed due to a new finding of anaemia, to which the patient had no specific symptoms but required further investigations and management before undergoing the CCL appointment. The second patient was found to have physiologically negative disease, and thus did not undergo PCI. As a result, these two patients did not complete the minimum 3 months early follow up period, and therefore were not included in the post CCL analysis. Therefore, a total of 35 patients completed the baseline and 3 months early follow up

period. The characteristics of these patients are demonstrated in table 3.2. There was no statistically significant difference between the two treatment groups.

Table 3.2 Averaged patient characteristics of subjects recruited to the wearable technology study of Virtu-5 who completed follow up. Relevant values are presented as means and standard deviation unless otherwise stated.

Characteristic	Whole cohort N=35 Average (SD)	PCI group N=24 Average (SD)	Medical therapy group N=11 Average (SD)	P value
Age (years)	65(±8)	67(±9)	62(±7)	0.164
Gender (female)	23%	13%	45%	0.077
Weight (kg)	85(±15)	87(±15)	81(±12)	0.282
Height (m)	171(±8)	172(±9)	168(±6)	0.137
BMI	29(±4)	29(±4)	29(±4)	0.822
Hypertension	71%	67%	82%	0.447
Hypercholesterolaemia	40%	33%	55%	0.283
T2DM	11%	4%	27%	0.082
Current/Ex smoker	63%	58%	73%	0.478

3.2 Left heart cardiac catheterisation

A total of 37 patients underwent ICA during the study period. Characteristics such as number of diseased vessels and locations of coronary lesions with a stenosis of greater than 50% of the lumen. A summary of the ICA procedure findings is detailed in Table 3.3. The mean number of diseased vessels per patient for the whole cohort was 1.8, with an average of 2.2 and 0.9 diseased vessels per patient for the PCI and medical treatment group respectively. Despite having CTCA imaging suggestive of obstructive coronary disease, along with symptoms of angina, four patients were found to have no significant epicardial coronary disease (i.e. no stenosis greater than 50% luminal diameter). A summary of the angioplasty details for the PCI therapy group is detailed in table 3.4.

Table 3.3 Cardiac catheter lab characteristics of subjects recruited to the wearable technology study of Virtu-5 at baseline. Relevant values are presented as means and standard deviation unless stated otherwise.

Characteristic			
No of diseased vessels (>50% stenosis)	Whole cohort N=37 (%)	PCI N=25 (%)	Medical therapy N=12 (%)
0	4 (11%)	0 (0%)	4 (33%)
1	10 (27%)	5 (20%)	5 (42%)
2	17 (46%)	14 (56%)	3 (25%)
3	4 (11%)	4 (16%)	0 (0%)
4	3 (8%)	3 (12%)	0 (0%)
Total (mean)	65 (1.8)	54 (2.2)	11 (0.9)
Lesion locations			
Left main stem	6 (16%)	6 (24%)	0 (0%)
Left anterior descending	26 (70%)	19 (76%)	7 (58%)
Diagonal	1 (3%)	1 (4%)	0 (0%)
Circumflex artery	12 (32%)	10 (40%)	2 (17%)
Obtuse marginal	1 (3%)	1 (4%)	0 (0%)
Right coronary artery	19 (51%)	17 (68%)	2 (17%)
Posterior descending artery	2 (5%)	2 (8%)	0 (0%)

Table 3.4 Summary of angioplasty characteristics of the PCI therapy group.

Number of vessels treated	
1 vessel	11 (44%)
2 vessels	10 (40%)
3 vessels	3 (12%)
4 vessels	1 (4%)
PCI characteristics	
Left main stem	8 (32%)
Left anterior descending	19 (76%)
Diagonal	1 (4%)
Circumflex artery	4 (16%)
Right coronary artery	10 (40%)
Posterior descending artery	2 (8%)
Total vessels treated (average±SD)	44 (1.8±0.8)
Total stents deployed (average±SD)	58 (2.3±1.1)

3.3 Physical activity data

Throughout the monitoring period of the Virtu 5 study, a total of 10,555 days of physical activity data was collected using the Fitbit monitoring devices. 3979 days of data was collected during the baseline pre-CCL monitoring period, while 6540 days of data was collected for the follow up post-CCL monitoring period, with 36 days of data collected on the same day as their planned procedure. An average of 108 days of data monitoring pre-CCL was captured for each patient, along with an average of 182 days per patient post-CCL. With regards to recorded wear time, the average daily wear time recorded for all study participants was 1174 minutes (19.6 hours). The values for the treatment groups and standard deviations are detailed in table 3.5.

Table 3.5 Total and averaged wearable physical activity monitored days.

Characteristic	Total cohort	PCI	Medical
Total monitoring period			
Total days recorded	10555	7232	3323
Mean days recorded (SD)	285 (± 67)	289 (± 69)	277 (± 64)
Mean daily wear time, minutes (SD)	1174 (± 441)	1191 (± 420)	1136 (± 481)
Pre-CCL monitoring			
Total days recorded	3979	2611	1368
Mean days recorded (SD)	108 (± 57)	104 (± 57)	114 (± 59)
Post-CCL monitoring			
Total days recorded	6540	4636	1944
Mean days recorded (SD)	182 (± 65)	185 (± 62)	176 (± 76)

3.3.1 Wearer compliance

By analysing the data available through the Fitbit dashboard, it was possible to assess the length of time each participant wore their device each day. The Fitbit Charge 4 device recorded data throughout the day for each participant while worn, which allowed for the recording of daily physical activity trends.

3.3.1.1 Case study illustrating total wear time calculation

The total wear time for every day the patient was monitored following their recruitment to the Virtu-5 study was manually calculated by the research students. Figures 3.1-3.3 demonstrates 3 separate 24-hour periods for the same user which illustrates how daily wear time is determined manually for each day.

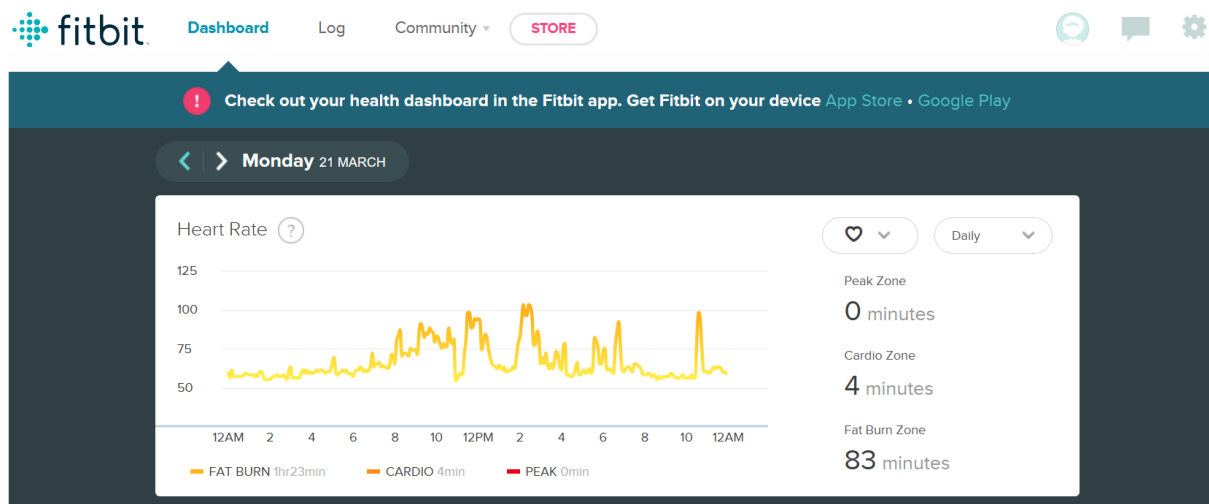


Figure 3.1 Case illustration from a study participant's Fitbit dashboard illustrating a full day's wear time.

By placing the cursor across the graph, the researcher can highlight each 5-minute interval, which details the average heart rate recorded during that interval. As indicated in Figure 3.1, when a continuous line is seen from the beginning of the 24-hour period to the end, this indicates a full day's compliance with the device, which implies that at no point during the day the device was removed for a significant period of time. This day's total wear time is therefore 1440 minutes, the total number of minutes in a day.

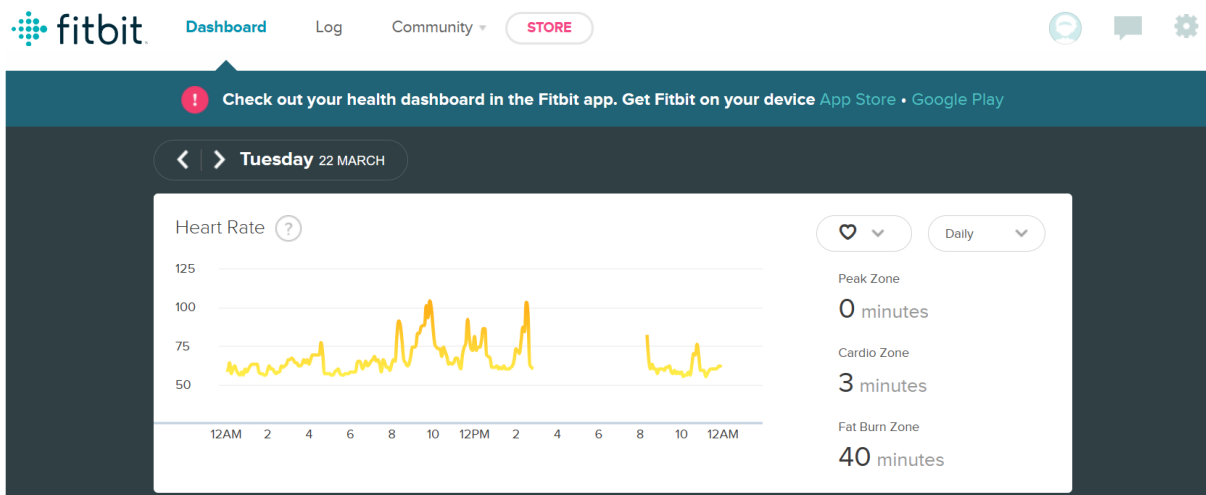


Figure 3.2 Case illustration from a study participant's Fitbit dashboard illustrating a partial wear time during a 24-hour period.

Figure 3.2 illustrates a 24-hour period where there is a period of time where no heart rate data was recorded, indicating a period of time where the device was not worn for a significant period of time. To calculate the wear time for this period, the last 5-minute interval before the gap is recorded, followed by the first interval after the gap. In this case, the former interval is 14:50-14:55, and the latter is 20:20 – 20:25. The gap between these two intervals is calculated as the time difference between 14:55 and 20:20, which is 325 minutes. All gaps noted in each 24-hour period are measured in this manner, with the total number of minutes within each gap added together to represent the amount of time the device was not worn throughout that day. As there are no other gaps in this 24-hour period, the total time the device was not worn for this day was 325 minutes. As a result, the resultant total wear time is calculated as the total time device not worn subtracted from the total number of minutes in a day (1440 minutes). This results in a total wear time for this day as 1115 minutes.

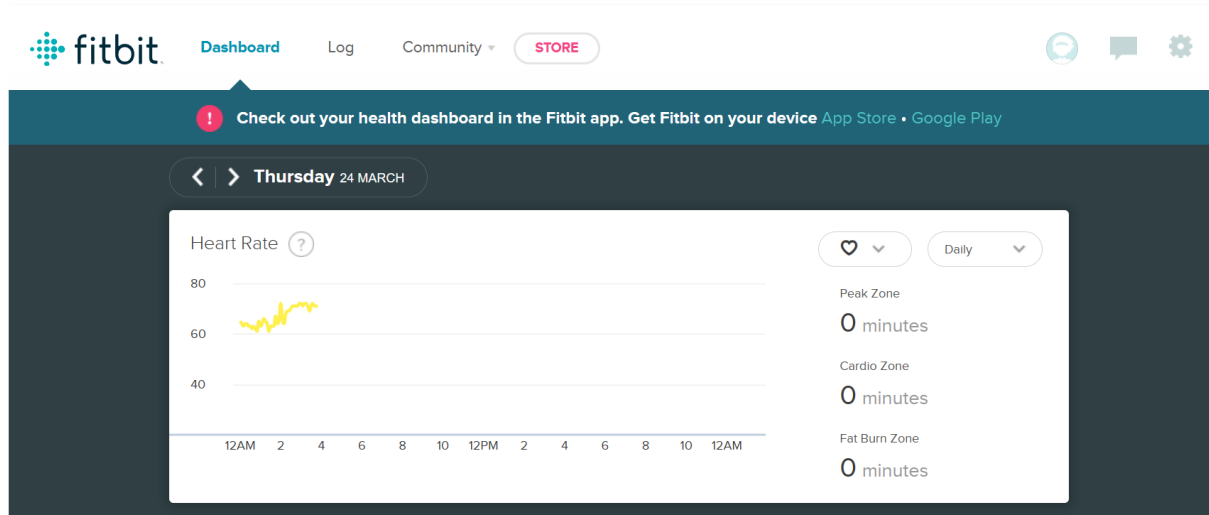


Figure 3.3 Case illustration from a study participant's Fitbit dashboard, illustrating a low wearer compliance with their device during a 24-hour period.

Figure 3.3 illustrates a larger absence of heart rate data where the line does not reach the end of the 24-hour period. This appearance indicates that the device was taken off at an earlier point in the day and was not worn again during that 24-hour period, or that the battery had run out during the 24-hour period. This appearance can in turn appear in reverse, so that there is no heart rate data at the start of the day and begins recording data at any time during the day and continues to the end of the day. This may indicate the watch being taken off the day before and worn again the following day. To calculate the time the device was not worn for this period, the last 5-minute interval period is highlighted, which in this case is 03:50 – 03:55. As there is no other data recorded for the remainder of the day, the gap extends to 00:00. The resulting non-wear time is calculated as the number of minutes between 03:55 and 00:00, which is 1205 minutes. As there are no other wear time gaps recorded, the resulting total wear time for this day is calculated as 235 minutes.

3.3.1.2 Cohort wear time compliance

As mentioned earlier, the determination of sufficient wear time is based on the perceived minimum amount of time needed to record sufficient subject activity which is informative to the patient's behaviour. As there is currently no universal definition for minimum wear time for clinical or research monitoring of physical activity behaviour with wearable devices, a range of minimum wear time thresholds were outlined. This would illustrate the relative compliance of the study participants to each threshold, by demonstrating what proportion of their monitored days met each criterion. Figure 3.4 is a graph of the whole cohort's averaged proportional compliance to each minimum wear time criteria, while figure 3.5 illustrates the spread of data for each valid day threshold. For the value for valid wear day of 600 minutes per day, which was used in the virtu-5 data analysis to identify the "valid wear day" minimum, the per patient valid day average compliance was 88.3%, with a median value of 89.9%.

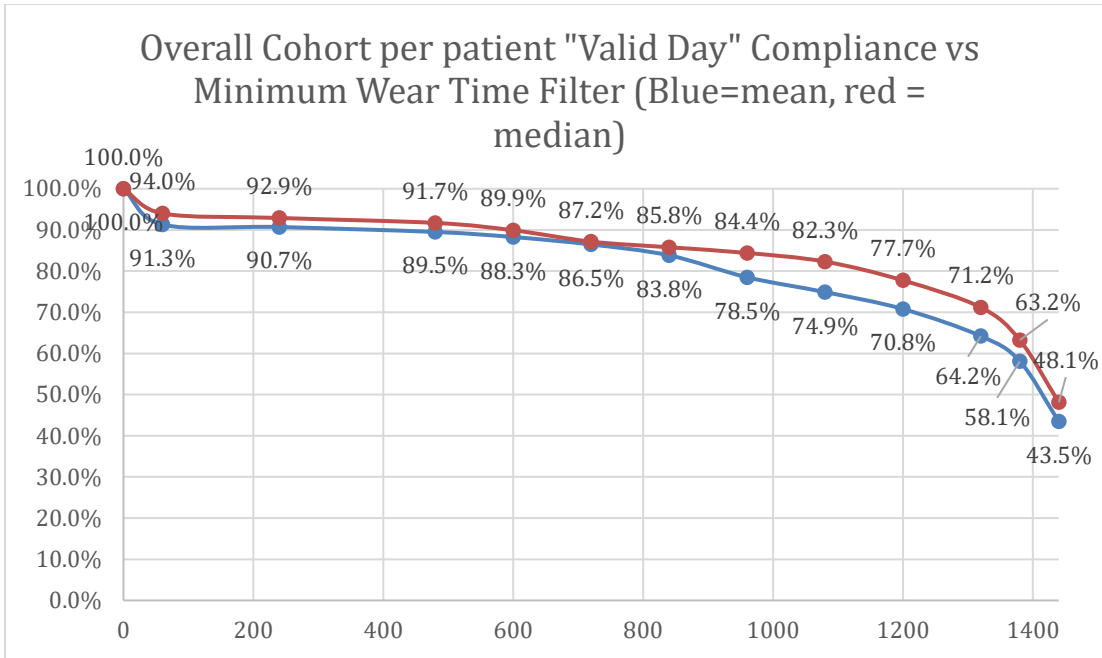


Figure 3.4 – line graph of overall cohort “valid day” compliance versus minimum wear time criteria. Blue points = mean, red = median. Minimum wear time criteria were defined as follows: 0 minutes, 60 minutes, 240 minutes, 480 minutes, 600 minutes, 720 minutes, 840 minutes, 960 minutes, 1080 minutes, 1200 minutes, 1320 minutes, 1410 minutes and 1440 minutes.

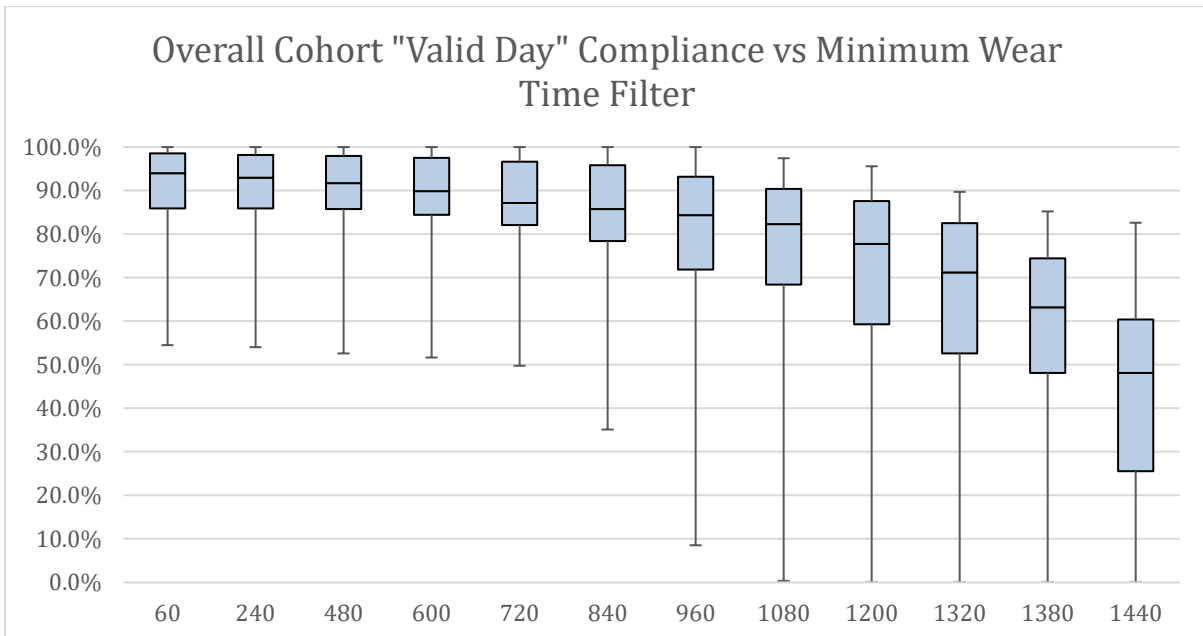


Figure 3.5 – Box and whisker graphs illustrating wear time “valid day” compliance versus minimum wear time criteria. Lower whisker = minimum value, lower box = 25th quartile, middle box = median, upper box = 75th quartile, upper whisker = maximum value.

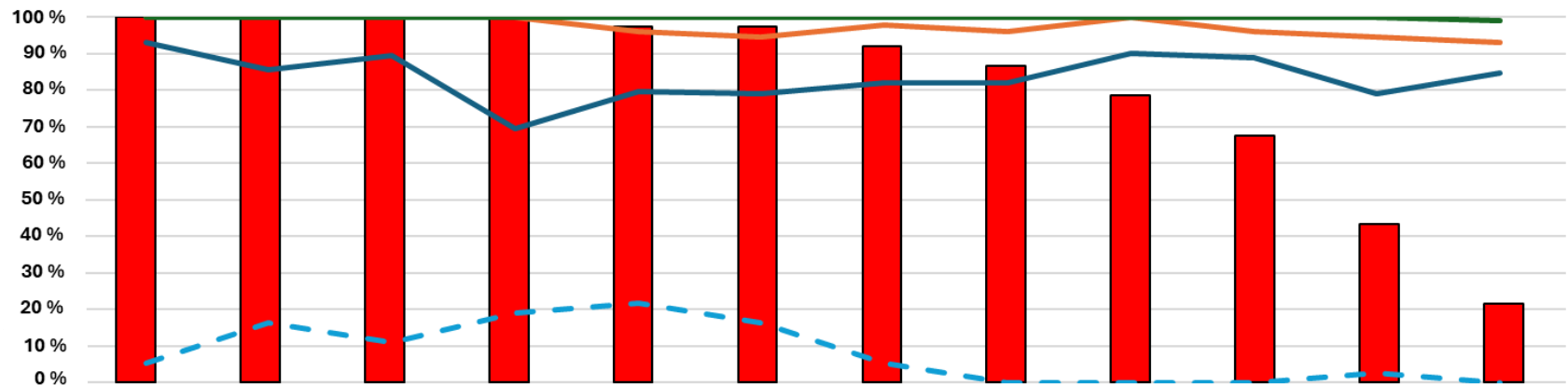
3.3.1.3 Wear time compliance with monitoring duration

To assess the potential impact of “reporting fatigue”, given the extended period of monitoring utilised in this study, the monthly wear time compliance was calculated for each patient. The minimum wear time criteria for this analysis was set to the study’s minimum wear time target of 600 minutes per day. An analysis of the descriptive statistics of each month’s data demonstrated that there was significant negative skew in the compliance results, which necessitated a non-parametric analysis (see table 3.6). The median and upper and lower quartiles for each month are illustrated in figure 3.6, alongside the proportion of monitored cohort participants who had data collected for that duration. Additionally, the percentage of patients who underwent their CCL procedure for each month was also illustrated in this graph, as a potential source of disruption to wearer compliance. The median compliance is maintained at 100% for the first 4 months and is maintained above 90% for the duration of the monitoring period. The highest consecutive occurrence of CCL appointments was during the fourth, fifth and sixth month of monitoring (19%, 22% and 16%, respectively), which did correspond with the lowest 25th percentile values (70%, 80% and 79% respectively). However, overall, compliance with minimum wear time parameters of 10 hours or greater was maintained in most study participants.

Table 3.6 Descriptive statistics of monthly wear time compliance from the time of recruitment.

Months	1	2	3	4	5	6	7	8	9	10	11	12
Mean	94%	90%	90%	83%	85%	84%	87%	91%	92%	90%	90%	91%
Std. Deviation	12	21	23	27	26	25	25	10	13	20	12	10
Skewness	-3.04	-3.09	-3.29	-1.75	-2.28	-2.02	-2.66	-1.50	-1.62	-3.80	-0.86	-1.42
25th quartile	93%	86%	90%	70%	80%	79%	82%	82%	90%	89%	79%	85%
50th quartile	100%	100%	100%	100%	96%	95%	98%	96%	100%	96%	95%	93%
75th quartile	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	99%

Monthly “valid wear day” compliance across monitored cohort



		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
—	Upper Quartile	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	99%
—	Median	100%	100%	100%	100%	96%	95%	98%	96%	100%	96%	95%	93%
—	Lower Quartile	93%	86%	90%	70%	80%	79%	82%	82%	90%	89%	79%	85%
- - -	CCL date	5%	16%	11%	19%	22%	16%	5%	0%	0%	0%	3%	0%
■	Proportion of monitored cohort	100%	100%	100%	100%	97%	97%	92%	86%	78%	68%	43%	22%

Figure 3.6 – illustration of average monthly wear time compliance relative to the duration of monitoring achieved, plotted alongside the proportion of participants from the whole cohort who collected data for each successive month, as well as the proportion of patients who underwent their planned CCL procedure relative to their recruitment date. The solid line graphs indicate the cohort compliance values (dark blue = lower quartile, orange = median, green = upper quartile), the broken light blue line indicates the percentage of patients who underwent their CCL appointment for the respective month, and the red bar chart indicates the percentage of patients who have data collected during that month.

3.3.1.4 Association between “valid day” cut-off values and physical activity parameters

Based upon the predetermined set of “minimum wear time” values required to indicate a valid wear day, association between daily wear time and each physical activity parameter was investigated. The Pearson’s R value with 95% confidence intervals was plotted on a graph corresponding to each minimum wear time cut-off value (See figure 3.7). Moderate to vigorous physical activity demonstrated no significant correlation with any of the minimum wear time values. At 0 minutes minimum wear, daily step count, light physical activity and active calories demonstrated weak correlations with wear time ($R = 0.32$, $R = 0.594$ and $R = 0.453$, respectively). All other minimum wear time values for these parameters did not demonstrate any significant correlation with wear time. Time sedentary demonstrated significant negative correlation with wear time between 0 minutes and 960 minutes which decreased with each successive cut-off, after which all Pearson R values were between -0.2 and 0.2.

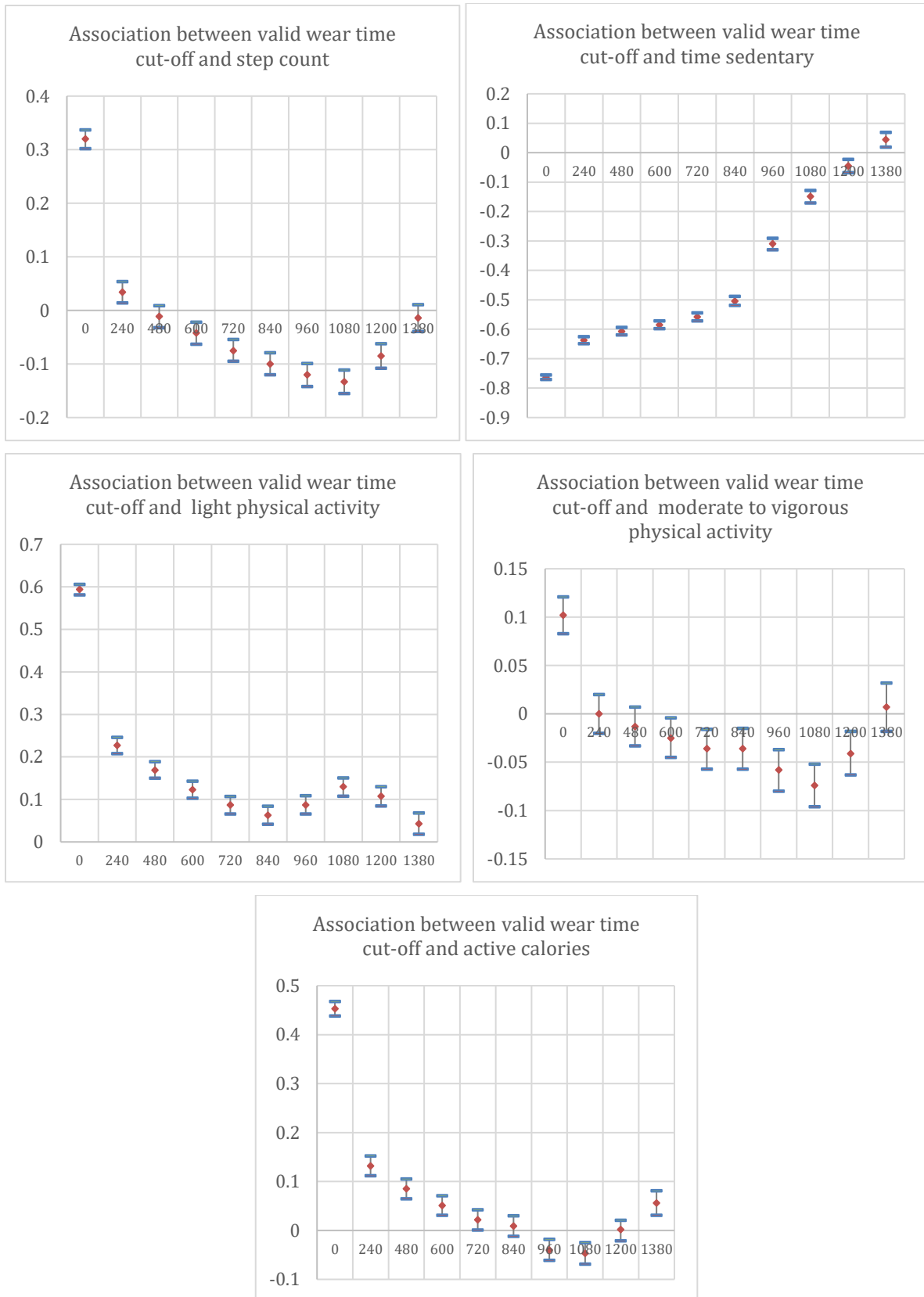


Figure 3.7 Graphs illustrating Pearson's correlation R values with 95% confidence intervals between different definitions of "minimum wear time" values and each wearable physical activity parameter.

3.3.2 Physical activity data outcomes

Data collected from the wearable physical activity monitoring devices were grouped into two categories; baseline (ie pre-CCL) and follow up (post CCL). The pre-CCL period includes up to 3 months of physical activity data collected before each study subject's CCL appointment. The follow up data includes physical activity data collected during the period of physical activity monitoring after 3 months had passed up until their final follow up appointment. The minimum number of days required to produce valid data for any given period was set at 20 days. For each day recorded, the following physical activity parameters were recorded: active calories, minutes of MVPA, step count, light physical activity (LPA), and time sedentary (TS). Additionally, the total number of valid monitoring days for each monitoring period was recorded.

During the pre-CCL period, 35 study subjects collected sufficient physical activity monitoring days to produce averaged values of physical activity parameters. 24 study subjects went on to undergo physiology-guided PCI, while 11 patients were found to have physiologically negative disease and did not receive PCI. 2 study subjects did not have sufficient pre-CCL data to meet the minimum requirement of 20 days of valid wear day data; one was due to device failure from accidents (broken watch strap and broken screen) which necessitated replacement devices, the second was due to an expedited CCL appointment which led to insufficient pre-CCL monitoring to supply valid data. The descriptive analysis demonstrated significant skew in some of the recorded values, therefore the data was analysed and illustrated in a nonparametric approach (see table 3.7). The median value for valid days recorded was 84 days, which was noted to be negatively skewed (-1.18). The

median daily values for the whole cohort active calories were 927.4 Kcal, MVPA was 25.9 minutes, step count was 6614 steps, LPA was 203.5 minutes, and TS 815.2 minutes. There was a statistically significant difference noted for the MVPA and TS values between the PCI and medical therapy group (36.7 vs 15.6, $p=0.033$, and 779.6 vs 728.1, $p=0.047$, respectively). There was otherwise no statistically significant difference between valid days, active calories, step count and LPA between the PCI and medical therapy group (See table 3.8).

Table 3.7 Descriptive statistics for whole cohort baseline physical activity parameters. MVPA = moderate to vigorous physical activity, LPA = light physical activity, TS = time sedentary.

	Mean	Minimum	Maximum	Percentiles			Skewness Statistic
				25 th	50 th	75 th	
Valid Days	71.3	27.0	84.0	54.0	84.0	84.0	-1.18
Active calories	1041.3	299.1	2088.8	764.3	927.4	1245.3	0.69
MVPA	40.2	1.2	144.9	15.6	25.9	64.8	0.12
Steps	7963.0	2791.1	20920.7	4965.2	6614.0	10863.4	1.04
LPA	210.7	128.2	339.7	166.8	203.5	240.5	0.50
TS	777.5	551.8	1175.2	708.3	771.6	815.2	1.04

Table 3.8 Descriptive statistical comparison for baseline physical activity parameters for the PCI and medical treatment groups, MVPA = moderate to vigorous physical activity, LPA = light physical activity, TS = time sedentary.

		Median	Shapiro -Wilk	P value	Mann- Whitney U	Z statistic	P value (2-tailed)
Valid days	PCI	84	0.703	<0.001	125	-0.28	0.78
	Medical	84	0.632	<0.001			
Active calories	PCI	1045.9	0.939	0.157	82	-1.78	0.08
	Medical	871.0	0.886	0.124			
MVPA	PCI	36.7	0.910	0.035	72	-2.13	0.03
	Medical	15.6	0.700	<0.001			
Steps	PCI	8380.0	0.937	0.141	85	-1.67	0.10
	Medical	5226.0	0.757	0.003			
LPA	PCI	206.3	0.965	0.552	129	-0.11	0.93
	Medical	201.3	0.891	0.141			
TS	PCI	779.6	0.903	0.024	76	-1.99	0.05
	Medical	728.1	0.908	0.230			

After completing their follow up, 35 study subjects had sufficient follow up monitoring to produce valid data (24 PCI treatment group, 11 medical therapy group). 2 patients had insufficient data; 1 patient had their follow up terminated early due to a new urgent medical issue becoming apparent following their PCI which was not associated with either their coronary disease or CCL procedure, a second patient did not have any follow-up as their CCL procedure had been postponed which led to their being insufficient time to complete their follow up due to the time constraints of the study.

The median whole cohort valid days achieved was 86 days. The whole cohort median values for active calories was 1052.5, MVPA was 31.3 minutes, step count was 7428.1 steps, LPA was 212.7 minutes, and TS was 749.4 minutes (See table 3.9). MVPA and active calories values between the PCI and medical therapy group was statistically significantly different (41.7 vs 14.5, $p = 0.008$, and 1116.6 vs 939.4, $p=0.023$, respectively). The other physical activity parameters were not significantly different between the two groups (See table 3.10).

Table 3.9 Descriptive statistics for the whole cohort follow up physical activity parameters. MVPA = moderate to vigorous physical activity, LPA = light physical activity, TS = time sedentary.

	Mean	Minimum	Maximum	Percentiles			Skewness statistic
				25 th	50 th	75 th	
Valid Days	94.9	27.0	190.0	72.0	86.0	123.0	0.52
Active calories	1088.6	365.01	2109.2	846.6	1052.5	1317.5	0.54
MVPA	40.4	4.8	162.4	14.5	31.3	53.6	1.74
Steps	7978.2	2569.9	22346.9	4941.8	7428.1	9943.1	1.46
LPA	221.8	112.1	394.9	193.5	212.7	260.5	0.67
TS	772.5	496.6	1170.0	704.2	749.4	831.0	1.02

Table 3.10 Descriptive statistical comparison for follow up physical activity parameters for the PCI and medical treatment groups. MVPA = moderate to vigorous physical activity, LPA = light physical activity.

		Median	Shapiro Wilk	P value	Mann-Whitney U	Z statistic	P value (2-tailed)
Valid days	PCI	94.0	0.964	0.525	114	-0.64	0.52
	Medical	78.0	0.893	0.150			
Active calories	PCI	1116.6	0.975	0.791	68	-2.28	0.02
	Medical	939.4	0.882	0.109			
MVPA	PCI	41.7	0.869	0.005	57	-2.67	<0.01
	Medical	14.5	0.722	<0.001			
Steps	PCI	8184.1	0.898	0.020	87	-1.60	0.11
	Medical	5515.3	0.873	0.085			
LPA	PCI	211.2	0.935	0.125	113	-0.68	0.50
	Medical	219.5	0.965	0.827			
Time sedentary	PCI	774.8	0.906	0.028	96	-1.28	0.20
	Medical	725.6	0.905	0.212			

3.3.2.1 Change in physical activity following CCL assessment

A total of 33 study subjects achieved sufficient pre-CCL and post-CCL monitoring to perform a comparison of physical activity parameters before and after their CCL procedure. As mentioned earlier, two study subjects did not collect sufficient pre-CCL data, and two separate patients did not have post-CCL data to analyse. The descriptive statistics for the paired groups of physical activity data are described in Table 3.11. The data for MVPA, step count and time sedentary were found to be significantly skewed as per the Shapiro Wilk test, as such a non-parametric assessment was performed to compare the pre-CCL and post-CCL data. The Wilcoxon signed rank test demonstrated no significant differences between any of

the pre-CCL physical activity parameters and their respective post-CCL values in either treatment groups (See table 3.12)

Table 3.11 Descriptive statistics for the pre-CCL and post-CCL paired data cohort physical activity parameters. MVPA = moderate to vigorous physical activity, LPA = light physical activity.

		Mean	Percentiles			Shapiro Wilk	
			25 th	50 th	75 th	Statistic	P value
Active calories	Baseline	1065.5	768.1	973.8	1246.3	0.951	0.142
	Follow up	1102.6	866.6	1052.5	1334.4	0.963	0.312
MVPA	Baseline	41.2	15.6	26.3	66.2	0.885	0.002
	Follow up	40.7	13.7	31.1	56.6	0.855	<0.001
Step count	Baseline	8101.3	4779.2	7516.0	11037.2	0.917	0.016
	Follow up	8022.3	4923.4	7428.1	10456.1	0.895	0.004
LPA	Baseline	212.4	168.1	205.3	246.7	0.963	0.308
	Follow up	222.0	196.2	212.7	255.6	0.952	0.149
Time sedentary	Baseline	780.1	717.6	771.6	818.6	0.930	0.035
	Follow up	776.1	706.7	765.2	837.3	0.931	0.037

Table 3.12 Descriptive statistics for the pre-CCL and post-CCL paired data for the PCI and medical therapy groups. MVPA = moderate to vigorous physical activity, LPA = light physical activity.

		Mean	Percentiles		
			25 th	50 th	75 th
PCI Group					
Active calories	Baseline	1142.9	817.0	1088.1	1517.4
	Follow up	1205.8	955.0	1128.6	1481.0
MVPA	Baseline	47.3	22.4	40.7	70.4
	Follow up	48.8	23.9	42.3	64.0
Step count	Baseline	8484.7	5044.6	8849.2	11400.8
	Follow up	8749.8	5147.9	8357.1	11093.1
LPA	Baseline	210.5	169.4	209.1	240.5
	Follow up	220.9	193.5	212.7	250.6
Time sedentary	Baseline	798.7	759.2	779.0	852.2
	Follow up	793.9	709.3	781.4	843.6
Medical therapy group					
Active calories	Baseline	887.6	475.0	882.7	1094.9
	Follow up	865.1	599.0	913	959.3
MVPA	Baseline	27.2	6.1	15.6	34.2
	Follow up	22.0	7.5	13.7	27.9
Step count	Baseline	6529.7	3491.7	5321.1	8856.7
	Follow up	6348.9	4712.6	5366.0	7575.2
LPA	Baseline	216.7	151.3	203.3	277.0
	Follow up	224.6	196.9	215.4	275.9
Time sedentary	Baseline	737.2	681.6	738.9	775.5
	Follow up	735	699.1	726.4	802.1

Table 3.13 Wilcoxon signed ranks test summary for PCI and medical therapy groups comparing pre-CCL and post-CCL results.

			N	Mean rank	Sum of rank	Z statistic	P value (2-tailed)
Active calories	PCI group	Negative ranks	9	9.9	89	-1.49	0.136
		Positive ranks	14	13.4	187		
	Medical therapy group	Negative ranks	5	6.2	31	-0.357	0.721
		Positive ranks	5	4.8	24		
Moderate-vigorous physical activity	PCI group	Negative ranks	11	11.7	129	-0.274	0.784
		Positive ranks	12	12.3	147		
	Medical therapy group	Negative ranks	6	6.5	39	-1.172	0.241
		Positive ranks	4	4.0	16		
Daily steps	PCI group	Negative ranks	11	11.6	127	-0.335	0.738
		Positive ranks	12	12.4	149		
	Medical therapy group	Negative ranks	5	6.4	32	-0.459	0.646
		Positive ranks	5	4.6	23		
Light physical activity	PCI group	Negative ranks	11	9.2	101	-1.125	0.260
		Positive ranks	12	14.6	175		
	Medical therapy group	Negative ranks	4	5.0	20	-0.764	0.445
		Positive ranks	6	5.8	35		
Time sedentary	PCI group	Negative ranks	14	10.9	152	-0.426	0.670
		Positive ranks	9	13.8	124		
	Medical therapy group	Negative ranks	6	1.8	29	-0.153	0.878
		Positive ranks	4	6.5	26		

3.3.3 Demographics and baseline physical activity

All baseline demographic data were assessed for correlations with physical activity parameters. For dichotomous variables, a point-Biserial Correlation assessment was implemented, otherwise a Pearson's correlation assessment was used for continuous variables. A statistically significant positive correlation was noted between daily time spent sedentary and dyslipidaemia ($r = 0.345$). Furthermore, a statistically significant negative correlation was noted between female gender with active calories ($r = -0.540$) and MVPA with age ($r = -0.363$). The remaining physical activity parameters did not demonstrate any statistically significant correlations with the other demographic data (See figure 3.8).

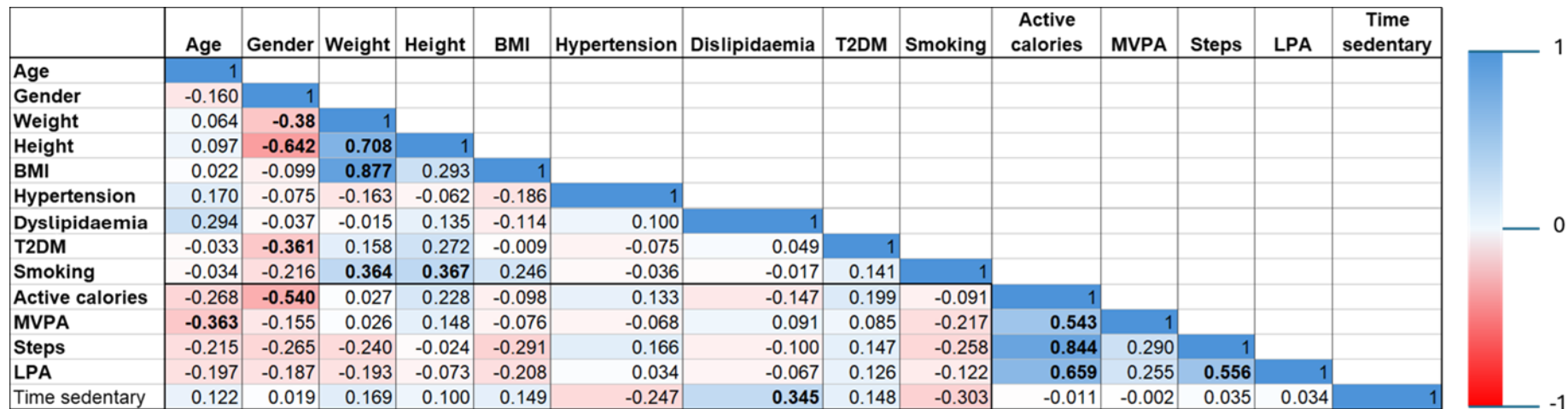


Figure 3.8 Pearson's correlation matrix for baseline physical activity and study subject demographics. Categorical variables tested with point biserial correlation. Figures illustrated in bold have a two-tailed correlation significance below 0.05. T2DM = type 2 diabetes mellitus, MVPA = moderate to vigorous physical activity, LPA = light physical activity.

3.3.4 Summary of physical activity monitoring findings

The main findings of the physical activity monitoring data analysis are summarised in the following points:

- The average length of time the average person wore their Fitbit for the study period was 285 days, with an average daily wear time of 1174 minutes, or 19.6 hours. The length and average wear time did not vary significantly between the PCI treatment group and the medical therapy group.
- When the pre-specified “minimum wear time” criteria of 600 minutes was applied to the cohort, this resulted in a median of 89.9% of monitored days meeting the “valid wear day” criteria. Higher thresholds for valid wear day criteria resulted in lower valid wear day compliance rates, however even the highest thresholds resulted in over half of the monitored days reaching this criterion in the majority of study subjects.
- Compliance with the 600 minutes minimum wear time criteria was most strongly noted within the first 4 months of monitoring for each patient across the cohort, while the median value for each subsequent month of monitoring remained above 90%.
- When daily wear time was compared with each physical activity parameter, it was noted that the value for time spent sedentary tended to have some correlation with wear time, suggesting a correlation between the length of time an individual wore their watch and the time sedentary value. This correlation decreased with stricter minimum wear time criteria and was shown to have no correlation from 1080 minutes.
- With no minimum wear time criteria, there was a modest correlation between wear time and step count, light physical activity and active calories. Once a

minimum wear time criteria was introduced to the analysis, all of these correlations diminished to a non-significant level.

- With regards to the overall baseline physical activity data, the average valid days of data recorded per patient was 71.3 days, with a median of 84 days. The whole cohort average baseline parameters were as follows: daily step count of 7963 steps, minutes of moderate to vigorous physical activity of 40.2 minutes, light physical activity of 210.7 minutes, time sedentary of 777.5 minutes, and active calories 1041.3 kcal. When the parameters of the PCI treatment group versus the medical therapy group were compared, there was a statistically significant difference in the average MVPA values, with greater minutes of MVPA achieved in the PCI group versus the medical therapy group (46.4 minutes vs 26.7 minutes, $p = 0.08$). No other physical activity parameters were found to be significantly different.
- With regards to the overall follow up physical activity data, the average valid wear days of data recorded per patient was 94.9 days, with a median of 86 days. The whole cohort average follow up parameters were as follows: daily step count of 7978.2 steps, minutes of moderate to vigorous physical activity of 40.4 minutes, light physical activity of 221.8 minutes, time sedentary of 772.5 minutes, and active calories 1088.6 kcal. When the parameters of the PCI treatment group versus the medical therapy group were compared, there was a statistically significant difference in the average follow up MVPA and active calories values, with higher minutes of MVPA and active calories achieved in the PCI group versus the medical therapy group (48.4 minutes vs 22.9 minutes, $p < 0.01$, and 1180.3 kcal vs 888.4 kcal, $p = 0.02$, respectively).

No other physical activity parameters were found to be significantly different at follow up.

- When baseline and follow up physical activity parameters were compared to determine if there had been a significant change in any parameter, there was no statistically significant difference between any of the parameters. The analysis for each treatment group's physical activity parameters also demonstrated no significant difference between baseline and follow up values.
- When baseline physical activity parameters were analysed against patient demographics, there was a modest positive correlation between time sedentary and the diagnosis of Hypercholesterolaemia ($r = 0.345$). Additionally, there was a statistically significant negative correlation between female gender and active calories ($r = -0.540$) and MVPA ($r = -0.363$). There was no other significant correlation between the other demographic variables and physical activity parameters.

3.4 6-Minute walk test data

A total of 24 study participants took part in the 6MWT assessment; 119 6MWT assessments were performed, and 21 participants completed both pre- and post-CCL assessments. As per the 6MWT protocol, the best result for each assessment period was recorded for the pre-CCL and post-CCL period. The average baseline 6MWD for the whole cohort was 467.7 m (± 83.8). When the separate treatment groups were analysed, the PCI group average 6MWD was 488.1 m (± 84.1) and the medical therapy group was 416.7 (± 62.7) (See table 3.13). There was no statistically significant difference between the PCI and medical therapy 6MWD

results at baseline ($p = 0.077$) (See table 3.14). The averaged paired cohort follow-up 6MWD result was 500.6 m (± 86.4), with the PCI group achieving 516.9 (± 93.0) and the medical therapy group 459.8 (± 53.6). There was no statistically significant difference between the mean 6MWD results of the PCI and medical therapy groups ($p = 0.178$) The mean whole cohort difference between baseline and follow up was 32.9 m, which a paired T test demonstrated a statistically significant difference between baseline and follow up assessments ($p=0.001$) (See table 3.15). The PCI group demonstrated a mean improvement in 6MWD of 28.8 m at follow up and the medical therapy group demonstrated a 43.2 m improvement, both of which were found to be statistically significant ($p=0.009$ and $p=0.035$, respectively).

Table 3.14 Summary of descriptive statistics of the baseline and follow up 6MWD results for the whole paired cohort data, PCI and medical therapy treatment group.

		Minimum	Maximum	Mean	Std. Deviation	Skewness
Whole cohort (N = 21)	Baseline	332.0	635.0	467.7	83.8	0.260
	Follow up	376.0	660.0	500.6	86.4	0.271
PCI (N = 15)	Baseline	362.0	635.0	488.1	84.1	0.121
	Follow up	376.0	660.0	516.9	93.0	-0.100
Medical (N = 6)	Baseline	332.0	487.0	416.7	62.7	-0.573
	Follow up	400.0	541.0	459.8	53.6	0.622

Table 3.15 Independent sample T test assessment of PCI and Medical therapy group for baseline and follow up 6MWD results

	T-test for Equality of Means						95% Confidence Interval of the Difference	
	t	df	Two-Sided p value	Mean Difference	Std. Error Difference	Lower	Upper	
Baseline	1.871	19	0.077	71.4	38.2	-8.5	151.3	
Follow up	1.398	19	0.178	57.0	40.8	-28.3	142.4	

Table 3.16 Paired T test assessment of pre and post CCL 6MWD assessment.

	Paired Differences					Two-Sided p value
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
				Lower	Upper	
Whole cohort	32.9	36.5	8.0	16.3	49.5	0.001
PCI	28.8	36.8	9.5	8.4	49.2	0.009
Medical	43.2	36.9	15.1	4.5	81.9	0.035

3.4.1 Step count accuracy comparison

During the 6MWT assessments, a total of 121 paired samples of manually counted steps as well as device counted steps using the Fitbit Charge 4 were collected from 34 study subjects. The mean step count collected manually was 664 (SD \pm 76), while the Fitbit values was 667 (\pm 68). The Pearson's r value was 0.855 (95% CI 0.803-0.895, two-tailed $P < 0.001$), with an r^2 value of 0.731. The two-way mixed model intraclass correlation (ICC) value for single measures was 0.849 (95% CI 0.790-0.892, $P < 0.001$). Figure 3.9 illustrates a Bland Altman plot, which demonstrated a 3 steps bias for Fitbit step counting versus manual step counting (SD of 40, 95% limits of agreement -76 to 82). Mean absolute percentage error (MAPE) was calculated at 4.4% (\pm 4.2).

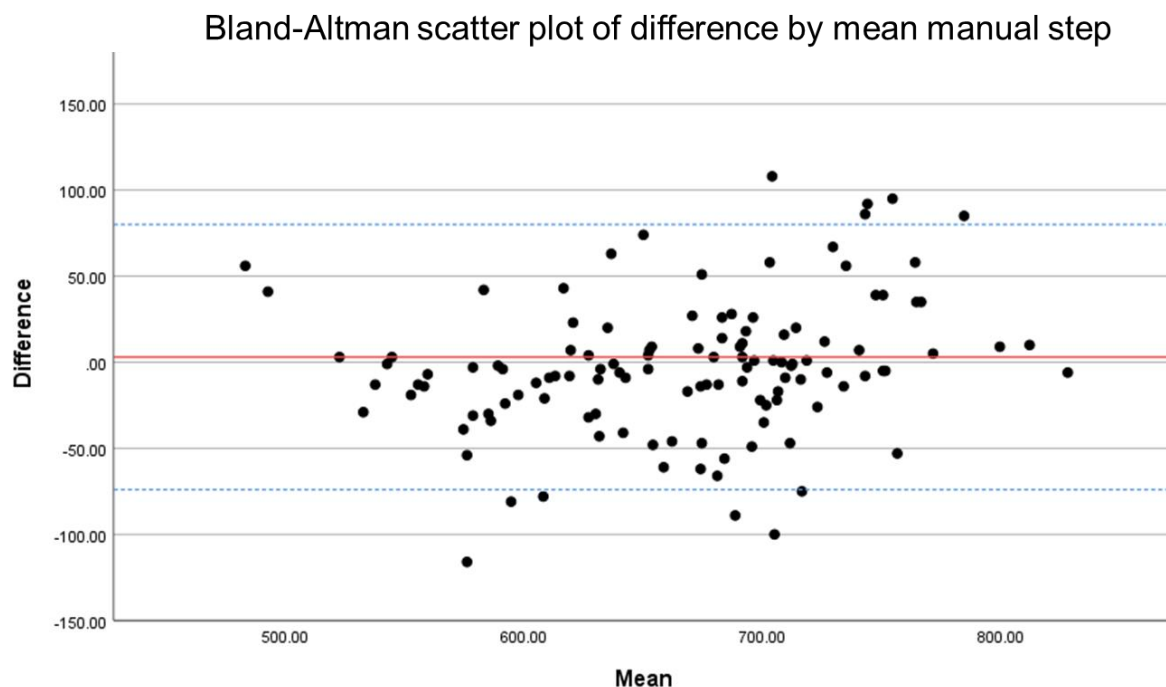


Figure 3.9 Bland Altman plot for the difference between the manual step count values and the Fitbit step count during the 6MWT assessment. Red line = device step count bias value; blue dotted lines = 95% limits of agreement)

3.4.2 6-minute walk test comparison with physical activity

The 6MWD values for each study subject was assessed for correlation with each physical activity parameters. Pre-CCL measures of daily step count, active calories and minutes of light physical activity were positively associated with baseline 6MWD, with R values of 0.614, 0.504 and 0.429 respectively (See table 3.16). When the per subject changes in 6MWD results between baseline and at follow up were compared to subject physical activity parameters, there was no statistically significantly significant association between any of the physical activity parameters and 6MWD result change (See table 3.17)

Table 3.17 Correlation between baseline 6MWD result and PA parameters. MVPA = moderate to vigorous physical activity, AC = active calories, LPA = light physical activity, TS = time sedentary.

	Pearson's R	Confidence interval	2-tailed p value
Steps	0.614	0.279 – 0.815	<0.001
MVPA	0.102	-0.314 – 0.486	0.64
AC	0.504	0.127 – 0.754	0.012
LPA	0.429	0.031 – 0.710	0.036
TS	0.159	-0.261 – 0.528	0.459

Table 3.18 Correlation between changes in 6MWD result and PA parameters between baseline and follow up assessments. MVPA = moderate to vigorous physical activity, AC = active calories, LPA = light physical activity, TS = time sedentary.

	Pearson's R	Confidence interval	2-tailed p value
Steps	0.219	-0.235 – 0.595	0.339
MVPA	0.040	-0.399 – 0.464	0.863
AC	0.200	-0.253 – 0.582	0.384
LPA	0.292	-0.159 – 0.643	0.198
TS	0.179	-0.274 – 0.567	0.438

3.4.3 Summary of 6MWT findings

The main findings of the physical activity monitoring data analysis are summarised in the following points:

- From a total of 24 study subjects who undertook the 6MWT assessment, the average baseline 6MWD achieved was 467.7 (\pm 83.8) metres. There was no significant difference between the PCI treatment and medical therapy groups at baseline (488.1m \pm 84.1 versus 416.7m \pm 62.7, respectively).
- The whole cohort average follow-up 6MWD achieved was 500.6 m (\pm 86.4). There was no statistically significant difference between the follow up 6MWD values for the PCI and medical therapy groups (516.9 m \pm 93.0 and 459.8 m \pm 53.6, respectively).
- Both treatment groups demonstrated a significant improvement in 6MWD at follow-up when compared to their baseline values pre-CCL. The PCI therapy group achieved a 28.8 m improvement (p=0.009) and the medical therapy group achieved 43.2 m (p=0.035).

- Step count accuracy during the 6MWT between the manual counting method and the Fitbit device was found to be in good agreement, with an r^2 value of 0.731 and an ICC value of 0.849. The Bland-Altman analysis demonstrated a 3 steps bias for Fitbit step counting, with 95% limits of agreement between -76 and 82 steps. Lastly, the mean absolute percentage error value was found to be 4.4%.
- Baseline 6MWD values were found to be significantly correlated with step count ($r = 0.614$, $p < 0.001$), active calories ($r = 0.504$, $p = 0.012$) and minutes of light physical activity ($r = 0.429$, $p = 0.036$). There was no significant correlation between baseline physical activity and change in 6MWD values between baseline and follow up measurements.

3.5 Questionnaires

Patient reported outcomes were recorded at the time of recruitment pre procedure and at follow up 6 months post procedure. 34 study participants completed both pre and post CCL questionnaires. One patient did not undergo their CCL procedure prior to the end of the study period, and two patients were not available to complete the follow up questionnaire. This resulted in 23 responses from the PCI group and 11 from the medical therapy group. The data presented is from study subjects with paired baseline and follow up questionnaire responses.

3.5.1 EQ-5D-5L

The EQ-5D-5L questionnaires were completed at the time of recruitment before the subject's cardiac catheter lab procedure and six months after their procedure. Each

questionnaire produces two results: the VAS and the England Index (EI) score (See table 3.18). One study subject from the medical therapy group did not fully complete their follow up questionnaire and was therefore not included in this analysis. The skewness statistic demonstrated that some of the responses were not normally distributed, hence non-parametric descriptives and analyses were performed on this dataset. The median baseline VAS was 75 (IQR 65-82), with the PCI group's median as 70 (65-80) and the medical therapy group as 77.5 (68.25-91.25). The cohort median baseline EI was 0.809 (0.729-0.901), with the PCI and medical group as 0.811 (0.733-0.887) and 0.790 (0.726-1). The follow up median value of VAS at six months was 80 (70-95). The follow up values at 6 months for the PCI and medical therapy group were 85 (75-95) and 77 (47.5 – 95.75), respectively. The follow up mean EI value at six months was 0.892 (0.772-1.0). The follow up values at 6 months for the PCI and medical therapy group were 0.892 (0.795 – 1.0) and 0.855 (0.714-1.0). The detailed results are illustrated in figure 3.10.

A total of 33 pairs of pre- and post-CCL EQ-5D-5L responses were compared for any significant difference. There was no statistically significant difference between the PCI therapy and medical therapy groups for the VAS and EI values at baseline or at follow up. When the paired baseline and follow up scores were analysed for each treatment group, the PCI therapy group demonstrated a significant improvement in VAS scores ($Z = 2.639$, $p=0.008$), which was not seen in the medical therapy group ($Z= 0.949$, $p=0.812$) (See table 3.19). There was also a statistically significant change in EI values following PCI ($Z = 2.695$, $p=0.007$) which was not demonstrated in the medical therapy group ($z = 0.204$, $p = 0.204$).

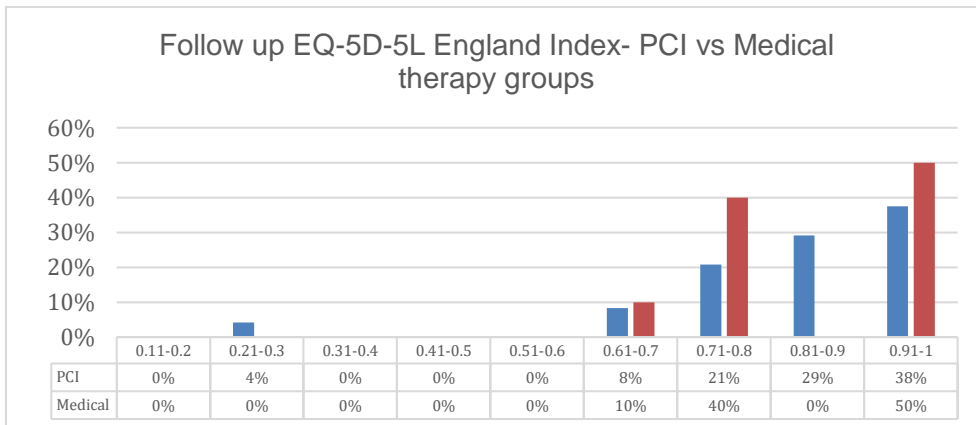
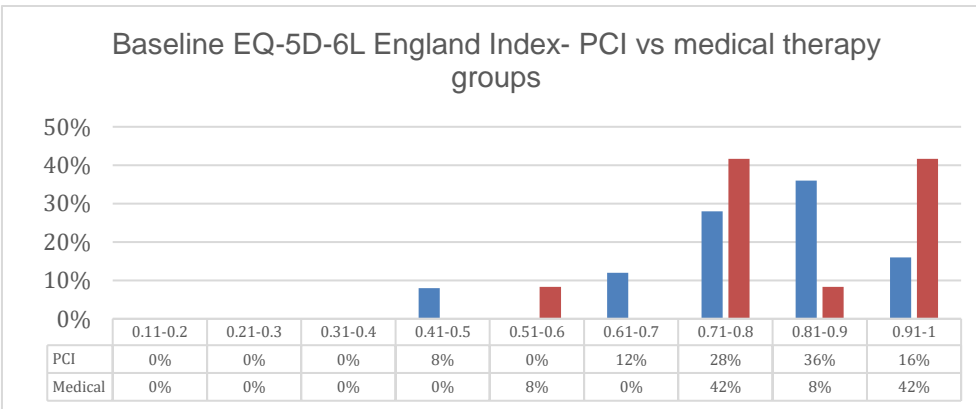
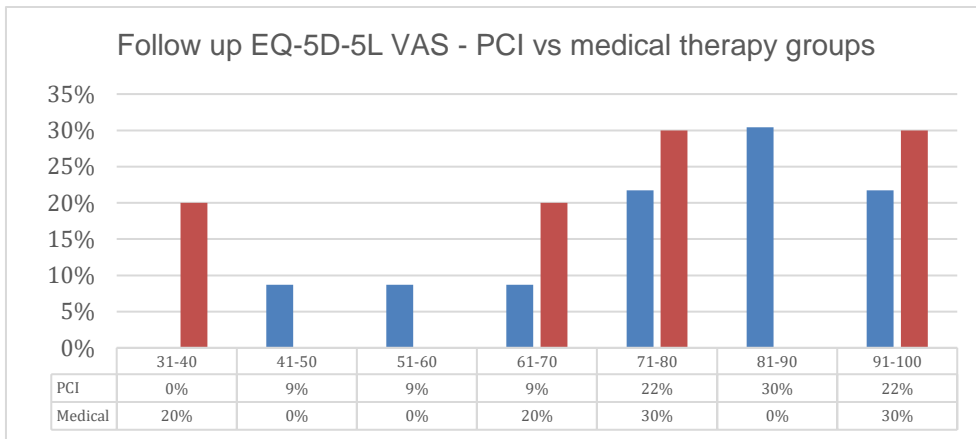
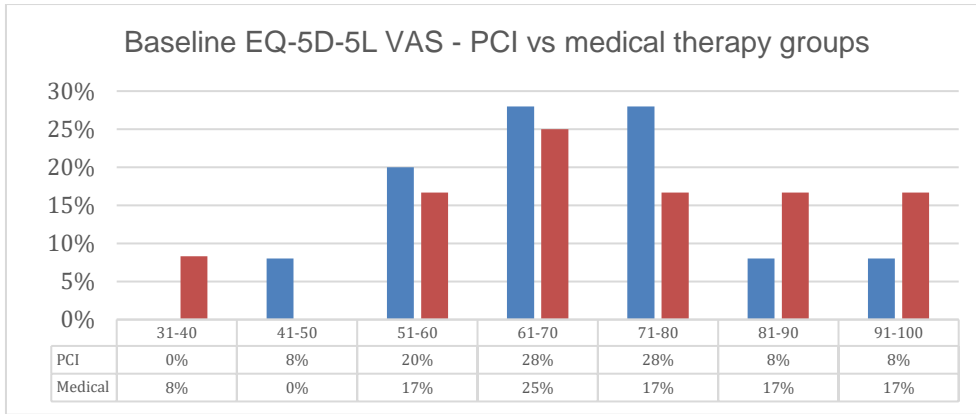


Figure 3.10 Distribution of EQ-5D-5L results at baseline and follow up (Blue = PCI, Red = Medical therapy group)

Table 3.19 Summary of paired baseline and follow up EQ-5D-5L responses across whole cohort and separate PCI and medical therapy groups. VAS = visual analogue scale. EI = England index

		N	Median	IQR	Skewness	Mann-Whitney test (treatment groups)		
						U	Z	P value (2-tailed)
VAS baseline	Whole cohort	33	75	65 – 82.5	-0.180	93.5	0.849	0.406
	PCI	23	70	65 – 80	0.355			
	Medical therapy	10	77.5	68.25 – 91.25	-0.998			
VAS follow up	Whole cohort	33	80	70 – 95	-0.798	89	1.025	0.324
	PCI	23	85	75 – 95	-0.805			
	Medical therapy	10	77.5	75.5 – 95.75	-0.452			
EI baseline	Whole cohort	33	0.809	0.729 – 0.901	-0.785	105.5	0.373	0.714
	PCI	23	0.811	0.733 – 0.887	-1.130			
	Medical therapy	10	0.790	0.726 – 1.0	-0.460			
EI follow up	Whole cohort	33	0.892	0.772 – 1.0	-2.204	99	0.643	0.550
	PCI	23	0.892	0.795 – 1.0	-2.705			
	Medical therapy	10	0.855	0.714 – 1.0	-0.014			

Table 3.20 Wilcoxon signed ranks test comparing baseline to follow up scores for EQ-5D-5L responses. VAS = visual analogue scale. EI = England index.

VAS – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Change in median value	5	15	0
Z value	1.859	2.639	0.949
P value (two-tailed)	0.063	0.008	0.812
EI – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Change in median value	0.083	0.081	0.065
Z value	3.017	2.695	1.270
P value (two-tailed)	0.003	0.007	0.204

3.5.2 SF-12

The SF-12 questionnaires were completed at the time of recruitment before the subject's cardiac catheter lab procedure and 6 months after their procedure. Each questionnaire produces two results: the physical component score PCS and the MCS. The mean baseline PCS was 37 ± 10 , with the PCI group's mean as 36 ± 8 and the medical therapy group as 39 ± 13 . The cohort mean baseline MCS was 46 ± 11 , with the PCI and medical group as 46 ± 11 and 45 ± 10 . The follow up mean values of PCS at 6 months was 43 ± 11 . The follow up values at 6 months for the PCI and medical therapy group were 44 ± 11 and 40 ± 15 , respectively. The follow up mean MCS values at 6 months were 48 ± 10 and 47 ± 12 . The follow up values at 6 months for the PCI and medical therapy group were 0.87 ± 0.12 and 0.87 ± 0.14 . The detailed results are illustrated in figure 3.11.

A total of 33 pairs of pre- and post-CCL SF-12 responses were compared for any significant difference. One study subject from the PCI therapy group did not fully complete their follow up questionnaire and was therefore not included in this analysis. The descriptive statistics for the paired data demonstrated no skewed data, therefore the data was analysed with parametric statistical methods (see table 3.20). There was no statistically significant difference between the PCI therapy and medical therapy groups for the PCS and MCS values at baseline and at follow up. When the baseline and follow up scores were compared for each treatment group, the PCI therapy group demonstrated a significant change in PCS ($p < 0.001$), which was not seen in the medical therapy group ($p = 0.467$) (See table 3.21). There were no statistically significant changes in MCS responses in either the PCI ($p = 0.162$) or medical therapy groups ($p = 0.053$).

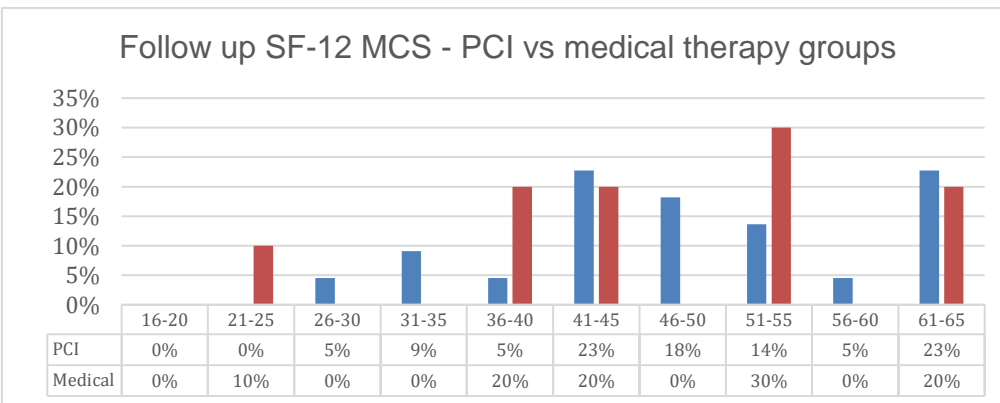
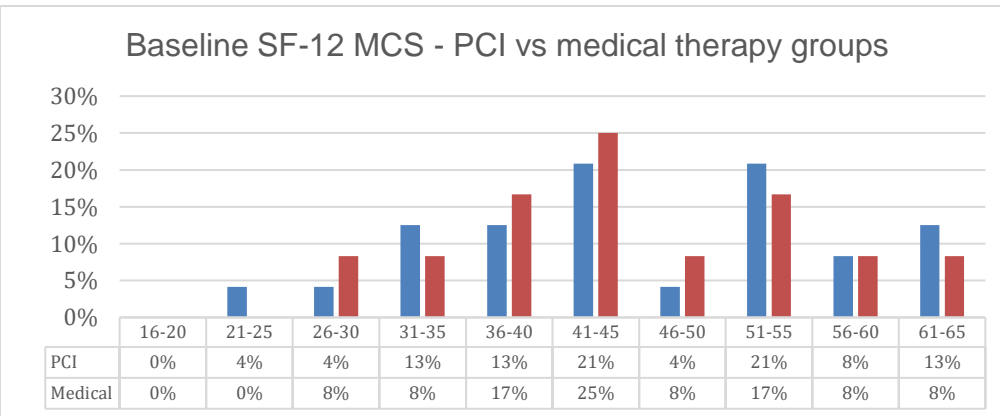
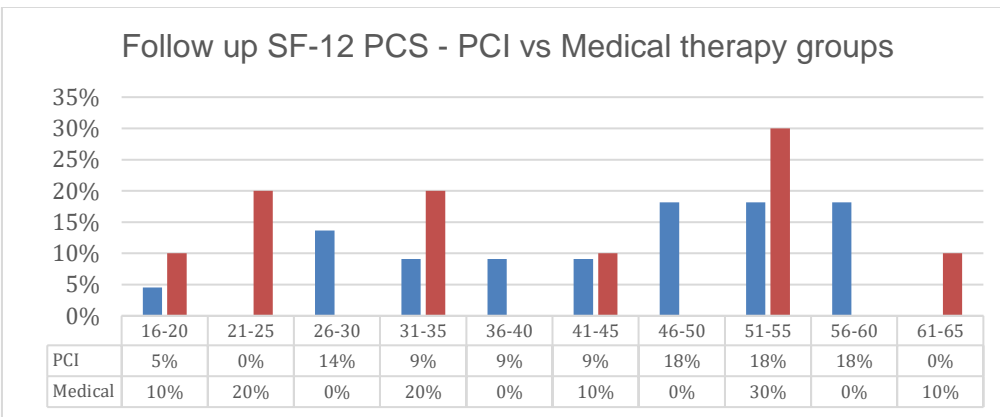
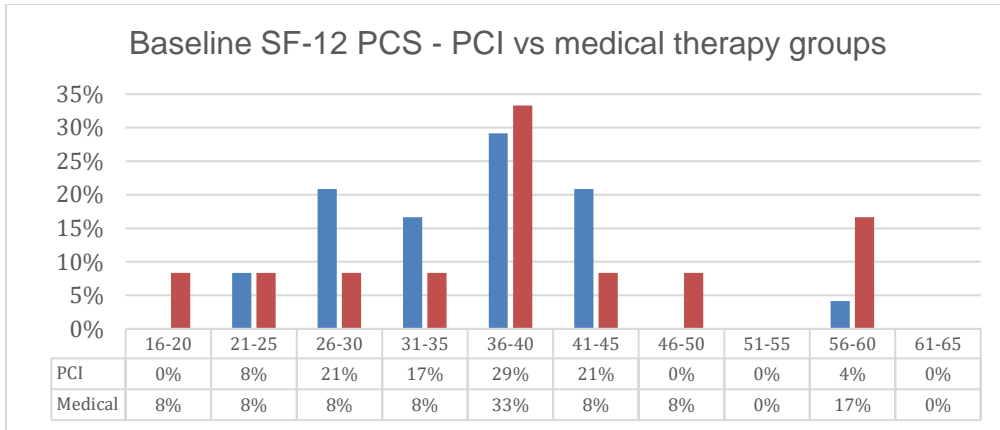


Figure 3.11 Distribution of SF-12 results at baseline and follow up (Blue = PCI, Red = Medical therapy group). PCS = physical component score, MCS = mental component score.

Table 3.21 Summary of paired baseline and follow up SF-12 responses across whole cohort and from PCI and medical therapy groups. The p value was calculated using the independent samples T test, with assumed equal variances. PCS = physical component score, MCS = mental component score.

		N	Mean	Std. Deviation	Skewness	Independent samples T test (Treatment groups)		
						t value	df	P value (2-tailed)
PCS baseline	Whole cohort	33	37.3	9.9	0.520	-0.568	31	0.574
	PCI	22	36.6	7.8	0.802			
	Medical therapy	11	38.7	13.4	0.143			
PCS follow up	Whole cohort	33	44.	11.7	-0.423	1.419	31	0.166
	PCI	22	46.0	9.8	-0.459			
	Medical therapy	11	40.0	14.6	0.071			
MCS baseline	Whole cohort	33	46.0	10.6	0.153	0.595	31	0.556
	PCI	22	46.8	10.9	0.093			
	Medical therapy	11	44.4	10.5	0.278			
MCS follow up	Whole cohort	33	49.0	9.8	-0.291	0.950	31	0.349
	PCI	22	50.2	9.6	-0.431			
	Medical therapy	11	46.7	10.4	-0.021			

Table 3.22 Paired samples T test comparing baseline to follow up scores for EQ-5D-5L responses. PCS = physical component score, MCS = mental component score.

PCS – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Mean change (SD)	6.7 (8.0)	9.4 (9.4)	1.3 (5.6)
t	4.839	5.778	0.755
df	32	21	10
P value (two-tailed)	<0.001	<0.001	0.467
MCS – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Mean change (SD)	3.0 (10.6)	3.4 (10.9)	7.27 (11.0)
t	1.619	1.449	2.193
df	32	21	10
P value (two-tailed)	0.115	0.162	0.053

3.5.3 SAQ

The SAQ questionnaires were completed at the time of recruitment before the subject's cardiac catheter lab procedure and 6 months after their procedure. Each questionnaire produces three results: the physical limitation domain (PLD), the quality-of-life domain (QoLD) and the angina frequency domain (AFD). The mean baseline PLD was 66 ± 21 , with the PCI group's mean as 65 ± 19 and the medical therapy group as 68 ± 26 . The cohort mean value for the baseline QoLD was 39 ± 26 , with the PCI and medical therapy group values as 40 ± 24 and 38 ± 31 . The cohort mean baseline AFD was 64 ± 27 , with the PCI and medical group as 64 ± 32 and 70 ± 13 . The follow up mean values of PLD at 6 months was 77 ± 24 . The follow up values at 6 months for the PCI and medical therapy group were 78 ± 24 and 74 ± 25 , respectively. The follow up mean cohort QoLD value at 6 months were 70 ± 25 . The follow up values for the PCI and medical therapy group were 72 ± 23 and 65 ± 29 respectively. The follow up cohort mean AFD value was 86 ± 19 . The follow up values at 6 months for the PCI and medical therapy group were 89 ± 20 and 80 ± 16 . The detailed results are illustrated in figure 3.12.

A total of 33 pairs of pre- and post-CCL SAQ responses were compared for any significant difference. One study subject from the medical therapy group did not fully complete their follow up questionnaire and was therefore not included in this analysis. The descriptive statistics for the paired data demonstrated some skewed data, therefore the data was analysed with non-parametric statistical methods (see table 3.22). There was a statistically significant difference between the follow up median AFD scores between the PCI and medical therapy group (100 vs 80, $p = 0.013$). Otherwise, there was no statistically significant difference between the PCI

therapy and medical therapy groups for the PLD and QoLD values at baseline or at follow up, and no difference in AFD values at baseline. There was a statistically significant difference between the paired baseline and follow up PLD, QoLD and AFD scores for the whole cohort ($p < 0.001$ for all response domains). When the separate treatment groups were analysed, the PCI treatment group demonstrated an improvement in all three scores ($p < 0.001$ for all response domains). However, the medical therapy group only demonstrated a significant difference in QoLD ($p = 0.008$), with no significant difference in PLD and AFD values (See table 3.23).

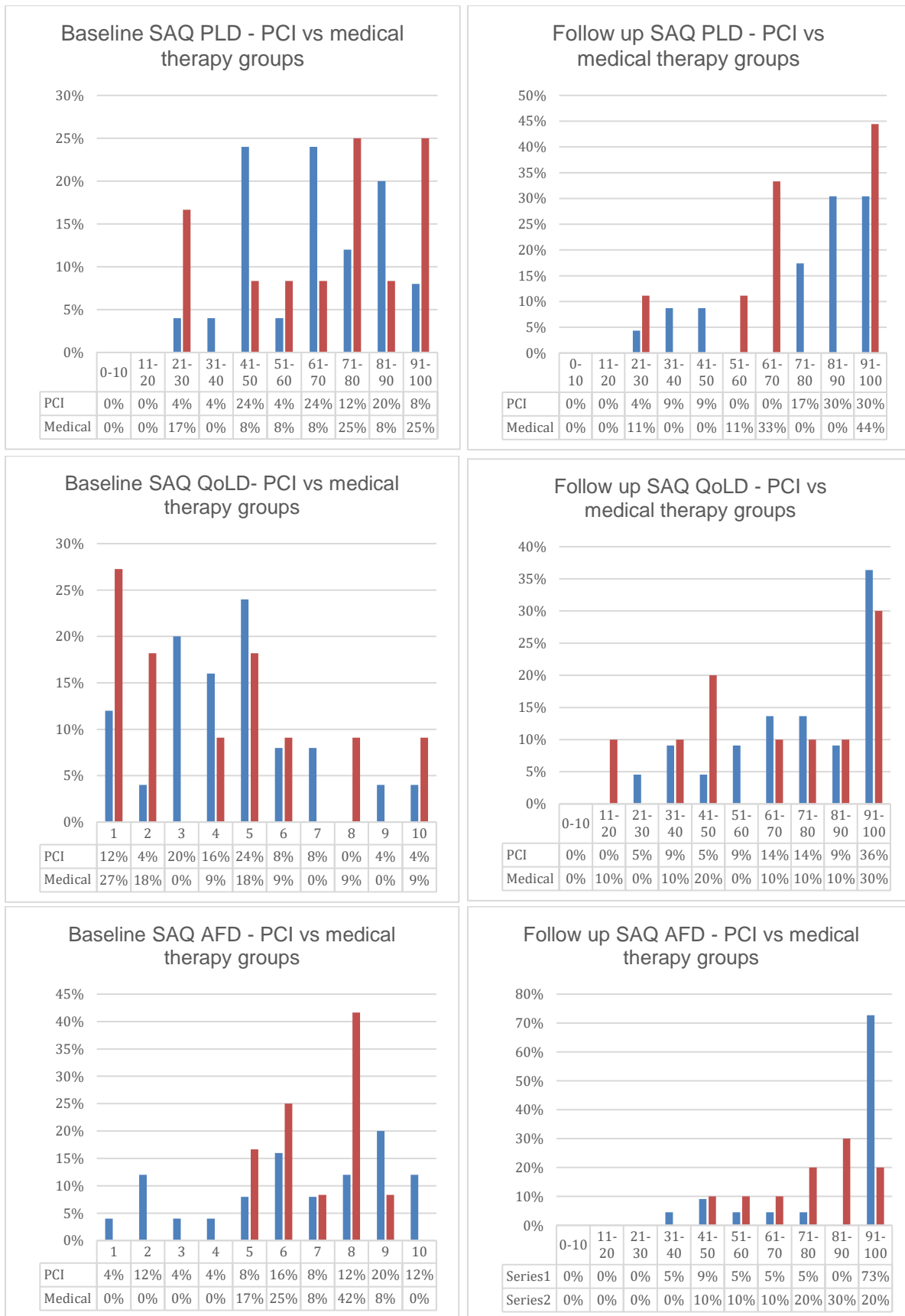


Figure 3.12 Distribution of SAQ results at baseline and follow up (Blue = PCI, Red = Medical therapy group). PLD = physical limitation domain, QoLD = quality of life domain, AFD = angina frequency domain.

Table 3.23 Summary of paired baseline and follow up SAQ responses across whole cohort and from PCI and medical therapy groups. The p value was calculated using the Mann-Whitney-U test. PLD = physical limitation domain, QoLD = quality of life domain, AFD = angina frequency domain.

		N	Median	IQR	Skewness	Mann-Whitney test (treatment group)		
						U	Z	P value (2-tailed)
PLD baseline	Whole cohort	33	75	54 – 84	-0.394	94	0.824	0.428
	PCI	23	67	50 – 82	-0.27			
	Medical therapy	10	75	56 – 94.75	-0.864			
PLD follow up	Whole cohort	33	84	64 – 100	-0.536	91	0.950	0.363
	PCI	23	84	75 – 100	-0.895			
	Medical therapy	10	65.5	60.5 – 97.75	0.137			
QoLD baseline	Whole cohort	33	42	21 – 58	0.519	110	0.194	0.862
	PCI	23	42	25 – 58	0.447			
	Medical therapy	10	37.5	8 – 62.5	0.703			
QoLD follow up	Whole cohort	33	75	58 – 92	-0.847	72	1.707	0.96
	PCI	23	83	67 – 92	-1.127			
	Medical therapy	10	58	39.75 – 85.25	-0.046			
AFD baseline	Whole cohort	33	70	50 – 82	-0.796	119.5	0.260	0.800
	PCI	23	70	40 – 90	-0.597			
	Medical therapy	10	70	60 – 80	-0.086			
AFD follow up	Whole cohort	33	100	80 – 100	-1.093	60.5	2.678	0.013
	PCI	23	100	90 – 100	-1.96			
	Medical therapy	10	80	70 - 90	-0.129			

Table 3.24 Wilcoxon signed ranks test comparing baseline to follow up scores for SAQ responses. PLD = physical limitation domain, QoLD = quality of life domain, AFD = angina frequency domain.

PLD – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Change in median value	9	17	-9.5
Z value	3.677	3.980	0.474
P value (two-tailed)	<0.001	<0.001	0.635
QoLD – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Change in median value	33	41	20.5
Z value	4.645	3.918	2.673
P value (two-tailed)	<0.001	<0.001	0.008
AFD – baseline vs follow up scores			
	Whole cohort	PCI	Medical therapy
Change in median value	30	30	10
Z value	3.914	3.542	1.794
P value (two-tailed)	<0.001	<0.001	0.073

3.5.4 Wearable technology user experience questionnaire

During the final follow up session, patients were asked to complete a user experience questionnaire designed by the research students for the Virtu-5 study (See appendix 5D). Patients were given the option to complete the questionnaires during their follow up appointment or to return their responses via mail to the researchers. A total of 29 study participants completed the user experience questionnaire. 8 subjects did not return their questionnaires to the research team. A summary of the descriptive statistics for the demographic data and physical activity parameter recorded for the cohort that completed the questionnaire are detailed in table 3.24. As demonstrated in the table, a number of parameters were shown to be skewed, therefore non-parametric analyses were conducted to compare questionnaire responses to the recorded parameters.

Table 3.25 Descriptive statistics of demographic and physical activity data of user experience questionnaire responders. BMI = body mass index, LPA = light physical activity, MVPA = moderate to vigorous physical activity, TS = time sedentary.

	Mean	Std. Deviation	Skewness
Age	65.8	8.8	0.107
BMI	28.6	3.9	0.408
Valid days	67.4	23.1	-1.107
Active calories	1063.1	490.5	0.636
Daily steps	7970.0	4441.9	1.150
LPA	215.7	55.8	0.460
MVPA	40.5	36.8	1.267
TS	772.6	120.7	1.173

The questionnaire responses were split into 3 sections of multiple-choice questions – pre-study experience of wearable physical activity monitoring, experience of wearable technology use during study, and future aspects of wearable technology use. A fourth optional section included a space for the participants to include a free text for any additional comments they wished to make regarding their experience with the wearable monitors.

Questions relating to study participant experience with wearable devices and smartphones included two questions. According to the responses to the first question, 65% of the participants had never owned a smartwatch before, with a vast majority having no interest in obtaining one prior to the study (see figure 3.13(a)). Only 14% of responders currently used a smartwatch, with the remaining subjects having previously used a smartwatch. The second question related to the study subjects' use of mobile phones. The responses to this question demonstrated that

93% of the study subjects owned a smartphone, with 48% familiar with using their device for activities such as browsing social media and internet connectivity. 7% of the study participants reported that they owned a phone that was not classified as a smartphone.

The next set of questions included three questions related to the study subject's experience of using the wearable device during their time in the study. With regards to the user's experience of the wearable device's ease of use, 66% of participants indicated that the wearable device was either easy or very easy to use, while 6% of participants indicated that the device was either difficult or very difficult to use (See figure 3.13(b)). With regards to the comfort of wearing the Fitbit device, 72% of responders indicated that the device was either comfortable or very comfortable to wear, while 6% of the responders indicated that the device was either uncomfortable or very uncomfortable to wear. Finally, given the frequent recharging of the device needed for continuous use, a specific question relating to the ease of recharging was included. With regards to the convenience of recharging, 76% of the participants indicated that the device was either convenient or very convenient to recharge, while 10% of the cohort indicated that the recharging procedure for the device was inconvenient.

The final multiple-choice section of the questionnaire asked about the participants' thoughts on future use of the device following their involvement in the Virtu-5 study. Following their involvement in the study, 86% of the responders suggested that they would be interested in using wearable physical activity monitoring devices such as the one in the study for personal use, while 14% indicated that they would not be

interested in using such a device for personal use (See figure 3.13I). When asked if they would be interested in using a wearable device again in the future for medical purposes, all responders indicated that they would be interested in using a device for this reason, with 83% of participants indicating that they would be interested in using a device for a prolonged period of time in a similar way to the study.

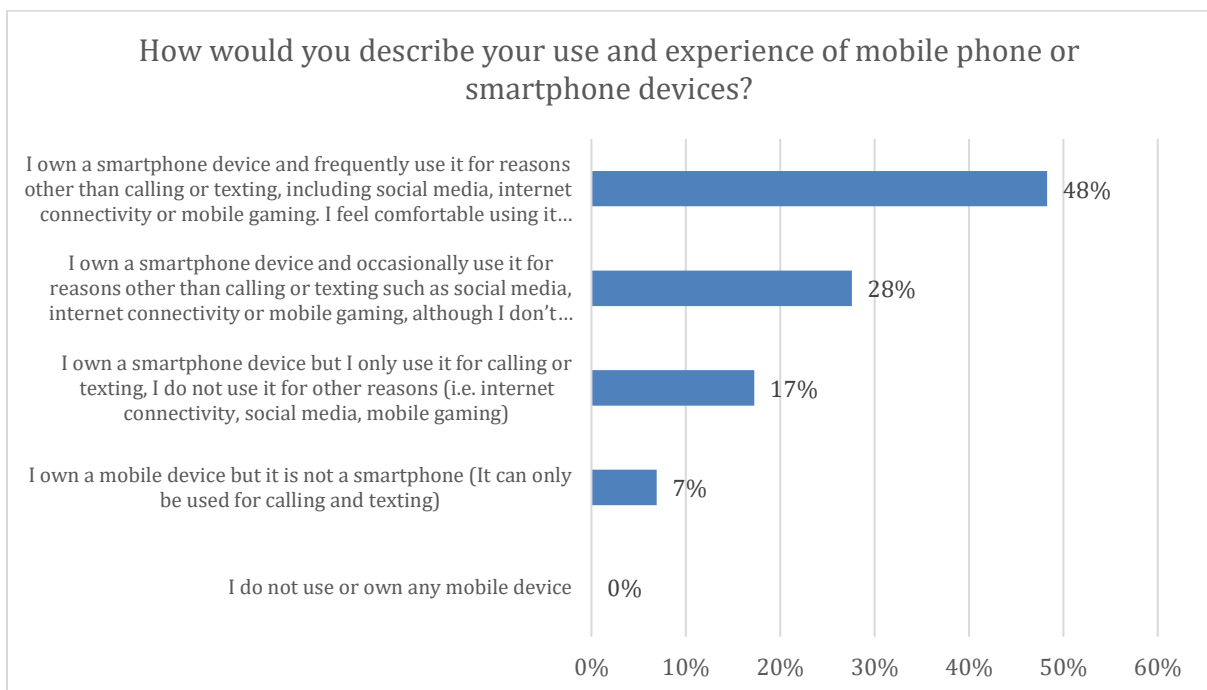
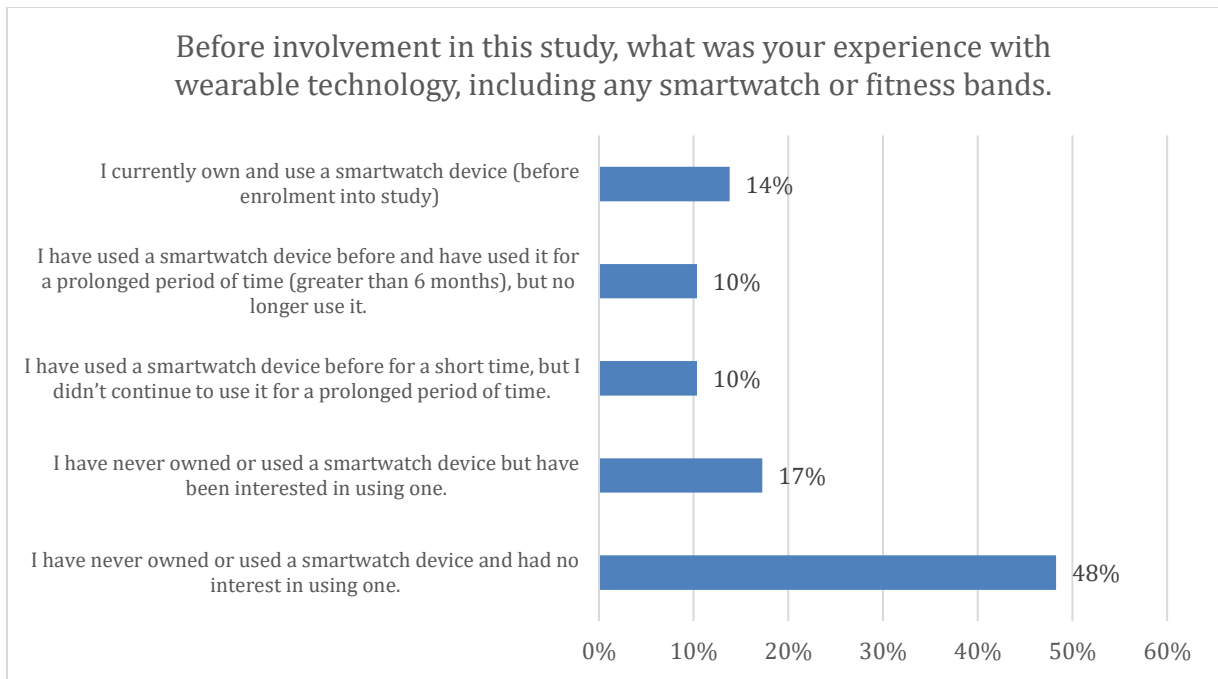


Figure 3.13(a) User experience questionnaire responses relating to use of wearable technology prior to study involvement.

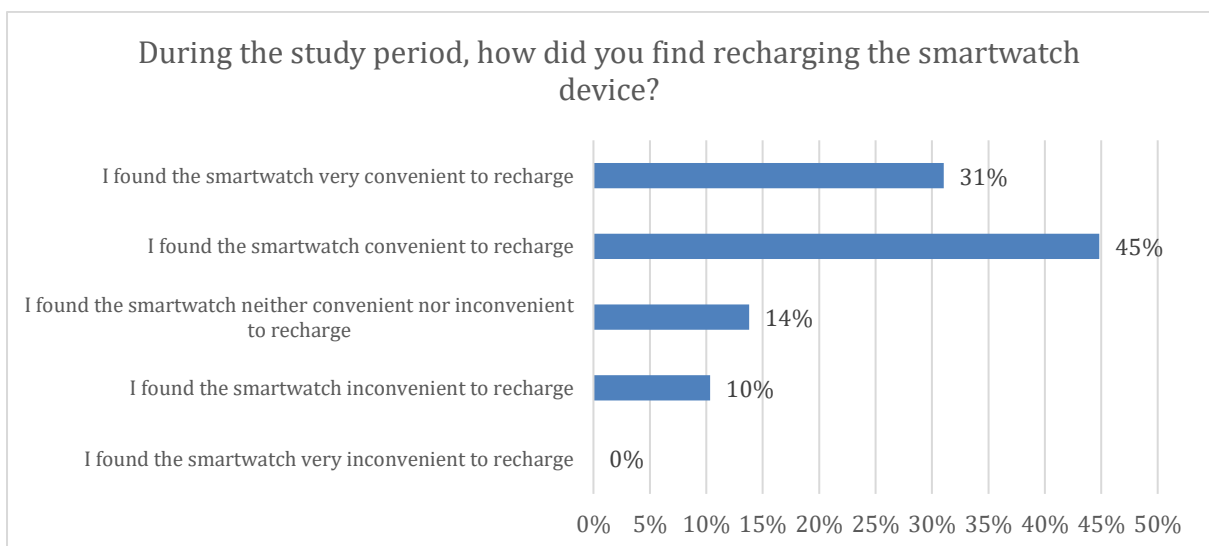
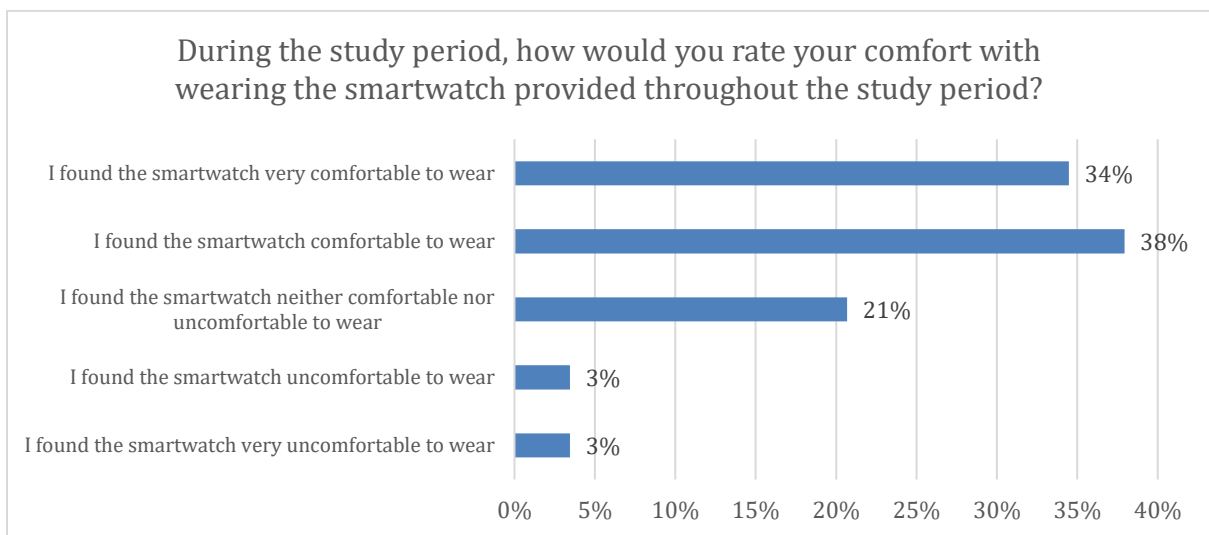
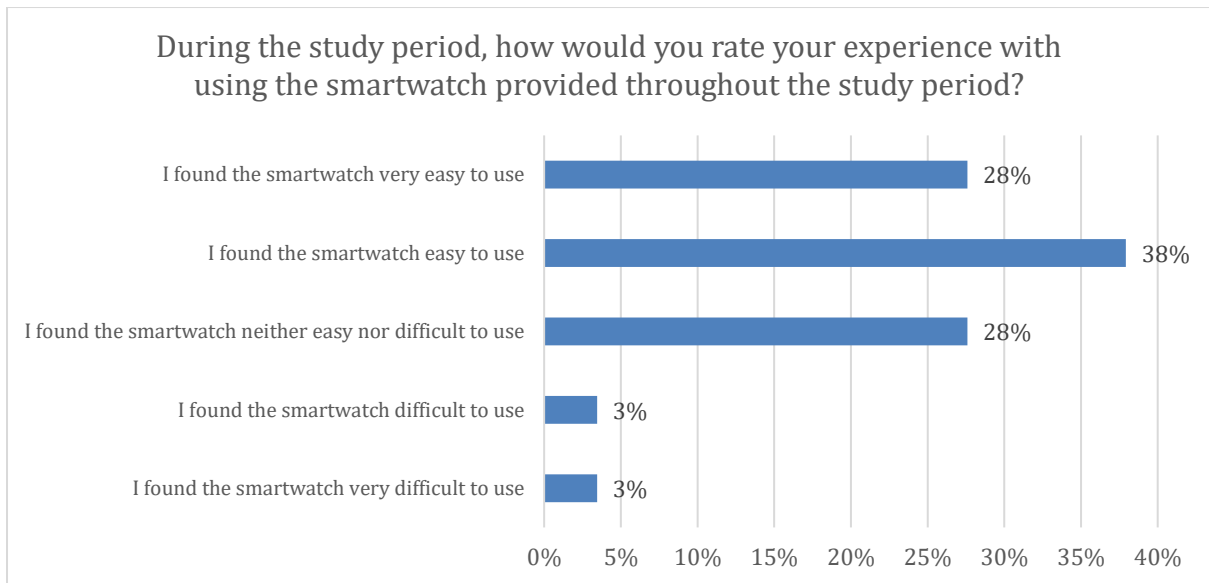


Figure 3.13(b) User experience questionnaire responses relating to use of wearable technology during the Virtu-5 study.

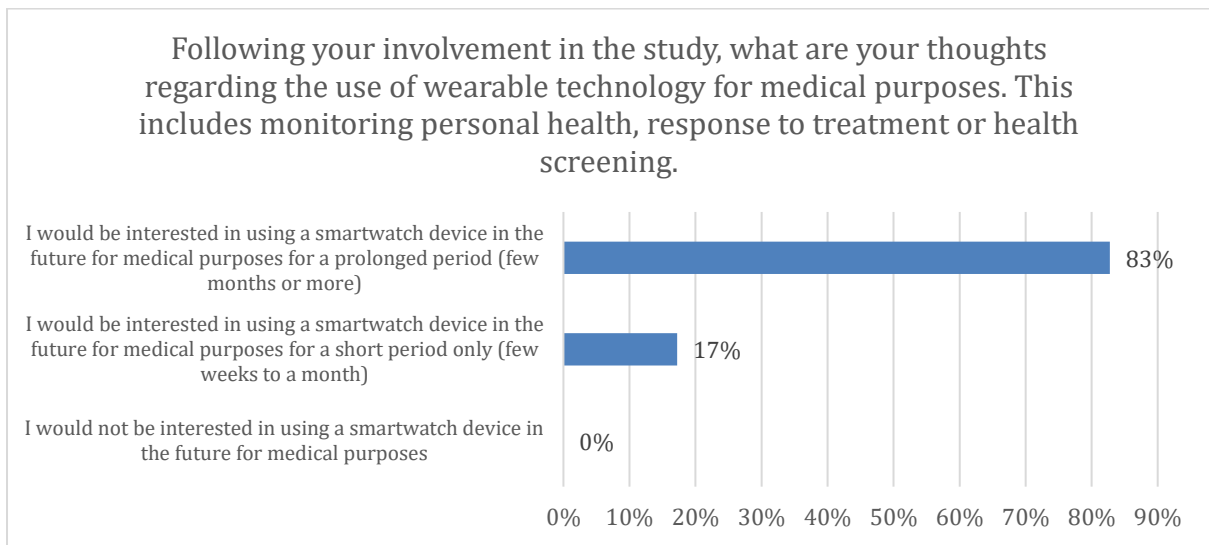
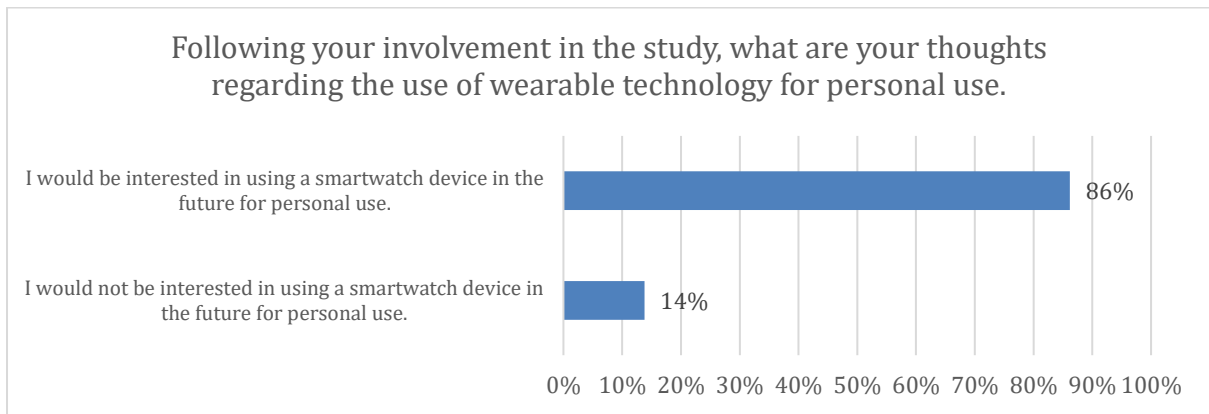


Figure 3.13(c) User experience questionnaire responses relating to potential future use of wearable technology after involvement in Virtu-5 study.

3.5.4.1 User experience additional feedback

Each user experience questionnaire gave respondents the opportunity to provide feedback or additional comments on their experience using the Fitbit device during the study in the form of a free text space at the end of the questionnaire. A total of nine free text responses were completed on the questionnaire, with each response transcribed to table 3.25.

Table 3.26 Free text responses to user experience questionnaire.

Response #	Free text feedback and comments
1	<i>"I would have been more involved in operating the functions of the smartwatch if it was mine (I viewed it as a 'reporting device' for the study). The watch did not function well in bright daylight with a black background."</i>
2	<i>"The fitbit needs to be larger, easier to recharge, a colour screen, a better touch screen."</i>
3	<i>"It would be ideal if it could be used to monitor the health of people with heart conditions."</i>
4	<i>"I will continue to wear a smartwatch. It has been a positive experience and I like monitoring my activity."</i>
5	<i>"Very fiddly to get it to charge fully."</i>
6	<i>"I found the smartwatch easy to use and very motivating."</i>
7	<i>"The issue I had with the smartwatch was I found it inaccurate showing correct pulse while exercising. Eg Fitbit showed a pulse measurement as 131 whereas cardio monitor showed 164. However, sometime sits reassuring when chest pain is experienced to know what my heart rate is like."</i>
8	<i>"The smartwatch could have been easier to recharge in my opinion. The charger and cables took some getting used to, not as easy as phone to recharge."</i>
9	<i>"Provides motivation to do physical activity. I have not worked out the full functionality of the smart watch."</i>

3.5.4.2 Association between user experience and recorded physical activity parameters

Each question response was analysed for association with each physical activity parameter, along with age, BMI and “valid day” records. Responses were grouped into negative responses and positive or neutral responses to estimate the association of negative user experience with physical activity parameters. As the descriptive statistical summary of the data demonstrated skewness with some data, the two response groups were compared using the Mann-Whitney U test. Any universally positive or neutral responses were not analysed in this manner.

All suitable question responses were analysed to compare negative responses to positive or neutral responses (See Table 3.26). Question 7 was not analysed as all responses were universally positive. There was no significant difference in age or BMI between the response groups for all of the questions. With regards to the responder’s experience prior to their enrolment to the Virtu-5 study, whether the patient had previously owned a wearable device or smartphone was not significantly associated with a change in any of the physical activity parameters or change the number of valid days recorded. The patient reported comfort of wearing the device was associated with a significant change in active calories and MVPA, with user discomfort associated with lower values ($P=0.026$ and $p = 0.032$ respectively). Furthermore, ease of use and convenience of recharging the device was not associated with changes in any of the physical activity parameters and number valid days recorded. Lastly, interest in future personal use of wearable devices was not associated with any statistically significant change in valid wear days or any of the physical activity parameters recorded.

Table 3.27 Summary of comparison between negative and positive or neutral responses to demographics and physical activity parameters. BMI = body mass index, LPA = light physical activity, MVPA = moderate to vigorous physical activity, TS = time sedentary.

	Age	BMI	Days	Active Calories	Daily Steps	LPA	MVPA	TS
Question 1								
Mann-Whitney U	75	79	92	57	94	69	96	95
Z	-1.274	-1.104	-0.577	-1.866	-0.161	-1.313	-0.069	-0.115
P value (two-tailed)	0.203	0.270	0.564	0.062	0.872	0.189	0.945	0.908
Question 2								
Mann-Whitney U	84.000	75.500	63.500	74.000	65.000	92.000	57.000	67.000
Z	-0.878	-1.258	-1.947	-1.021	-1.439	-0.186	-1.811	-1.346
P value (two-tailed)	0.380	0.208	0.052	0.307	0.150	0.853	0.070	0.178
Question 3								
Mann-Whitney U	13.000	9.000	11.000	8.000	5.000	1.000	12.000	10.000
Z	-0.120	-0.602	-0.393	-0.681	-1.052	-1.547	-0.186	-0.433
P value (two-tailed)	0.905	0.547	0.694	0.496	0.293	0.122	0.853	0.665
Question 4								
Mann-Whitney U	12.000	15.500	8.000	1.000	5.000	20.000	2.000	13.000
Z	-1.293	-0.997	-1.792	-2.230	-1.873	-0.535	-2.141	-1.160
P value (two-tailed)	0.196	0.319	0.073	0.026	0.061	0.592	0.032	0.246
Question 5								
Mann-Whitney U	37.000	33.500	28.500	20.000	24.000	23.000	14.000	25.000
Z	-0.143	-0.397	-0.824	-0.535	-0.178	-0.268	-1.070	-0.089
P value (two-tailed)	0.886	0.692	0.410	0.592	0.858	0.789	0.284	0.929
Question 6								
Mann-Whitney U	48.500	38.000	24.000	31.000	29.000	29.000	40.000	41.000
Z	-0.095	-0.764	-1.802	-1.116	-1.247	-1.247	-0.525	-0.460
P value (two-tailed)	0.924	0.445	0.072	0.264	0.212	0.212	0.599	0.646

3.5.5 Association of questionnaire responses with physical activity assessment

Questionnaire responses for the EQ-5D-5L, SF-12 and SAQ at baseline were compared with their respective period of physical activity monitoring and baseline 6MWD. A total of 35 study subjects had both physical activity monitoring parameters and questionnaire responses, while 22 patients had paired questionnaire data and 6MWD results. On analysing the baseline EQ-5D-5L results, MVPA had a weak but statistically significant correlation with VAS ($R = 0.363$, $p = 0.032$) and light physical activity had a weak correlation with the England Index score ($R = 0.336$, $p = 0.048$) (See table 3.27). None of the SF-12 responses demonstrated a statistically significant correlation with any of the physical activity parameters. With regards to the SAQ, the physical limitation domain was noted to be correlated with daily step count ($R = 0.428$, $p = 0.010$) and MVPA ($R = 0.378$, $p = 0.025$). The 6MWD values were significantly correlated with MCS ($r = 0.495$, $p = 0.019$) and AfD scores ($r=0.439$ (0.041)).

Table 3.28 Summary of Pearson's correlation analysis between baseline questionnaire responses and physical activity monitoring and 6MWD results. VAS = visual analogue scale, PCS = physical component score, MCS = mental component score, PLD = physical limitation domain, QoLD = quality of life domain, AfD = angina frequency domain, MVPA = moderate to vigorous physical activity, LPA = light physical activity. Figures in bold illustrate statistically significant values.

	Step count (p value)	MVPA (p value)	Active calories (p value)	LPA (p value)	Time sedentary (p value)	6MWD (p value)
VAS	0.285 (0.097)	0.363 (0.032)	0.214 (0.217)	0.000 (1.000)	-0.064 (0.717)	-0.043 (0.849)
England Index	0.325 (0.056)	0.230 (0.185)	0.178 (0.307)	0.336 (0.048)	-0.082 (0.641)	-0.030 (0.896)
PCS	0.288 (0.098)	0.265 (0.130)	0.169 (0.339)	0.140 (0.429)	0.089 (0.617)	-0.141 (0.540)
MCS	0.186 (0.291)	0.045 (0.799)	0.012 (0.946)	0.208 (0.237)	-0.188 (0.286)	0.495 (0.019)
PLD	0.428 (0.010)	0.378 (0.025)	0.292 (0.089)	0.273 (0.113)	0.103 (0.555)	0.185 (0.410)
QoLD	0.317 (0.068)	0.277 (0.113)	0.149 (0.401)	-0.008 (0.964)	0.156 (0.377)	0.238 (0.298)
AfD	0.115 (0.509)	0.197 (0.256)	0.093 (0.597)	-0.154 (0.377)	-0.023 (0.896)	0.439 (0.041)

3.5.6 Summary of questionnaire findings

The main findings of the patient questionnaire data analysis are summarised in the following points:

- With the EQ-5D-5L questionnaire, the PCI group demonstrated a significant improvement in their VAS score ($Z = 2.174$, $p = 0.012$) which was not seen in the medical therapy group ($Z = 0.238$, $p = 0.812$).
- With the SF-12 questionnaire, the PCI group demonstrated a significant improvement in PCS values from baseline to follow up ($p = 0.001$), which was not observed in the medical therapy group ($p = 0.662$).

- With the SAQ questionnaire, the PCI group achieved a significant improvement in all three parameters of physical limitation, quality of life and angina burden ($p = 0.008$, $p < 0.001$, and $p = 0.003$, respectively). The medical therapy group demonstrated an improvement in the quality of life domain only ($p = 0.018$).
- With the patient experience questionnaire, 65% of the participants had never used a smartwatch before. While 93% of participants reported owning a smartphone, only 48% felt comfortable doing activities on their phone beyond texting and calling. 66% of participants found the watch easy to use, and 72% found the smartwatch comfortable to wear, while 76% indicated that the watch was easy to recharge. 6% of the cohort found the watch difficult to use and uncomfortable, while 10% indicated that the device was difficult to recharge. 86% of the participants indicated that they would be interested in using a smartwatch for monitoring their physical activity for personal reasons in the future, and all respondents indicated that they would consider using wearable technology such as this for medical purposes.
- When negative responses in the patient experiences questionnaire were analysed along with baseline demographics and physical activity parameters, it was found that patient discomfort with the watch was associated with lower values of active calories and MVPA ($p = 0.026$ and $p = 0.032$, respectively). Otherwise, negative patient responses to the remaining questions were not associated with significant changes in baseline demographics or physical activity parameters.
- When physical activity parameters were analysed with each questionnaire EQ-5D-5L VAS was shown to have a weak but significant correlation with

MVPA ($r = 0.363$, $p = 0.032$), while LPA demonstrated a statistically significant correlation with EI values ($r = 0.336$, $p = 0.048$). None of the SF-12 values correlated with any of the physical activity parameters. With regards to the SAQ, the PLD was found to correlate with step count ($r = 0.428$, $p = 0.010$) and MVPA ($r = 0.378$, $p = 0.025$).

- 6MWD values were positively correlated with MCS ($r = 0.495$, $p = 0.019$) and AfD scores ($r=0.439$ (0.041)).

3.6 Cardiac Magnetic Resonance Imaging

A total of 26 patients underwent baseline CMR assessment. Eleven study subjects who were recruited for the wearable technology monitoring aspect of the Virtu -5 study did not undergo a baseline CMR study. Three of the study subjects were found to have contra-indications to the CMR study that had not been discovered during patient screening and recruitment; two were due to a history of penetrating metal shard injury to the eye, and a third was due to an MRI contra-indicated breast implant. The remaining eight patients who did not receive a CMR study were unable to attend their given appointment prior to their angiogram. These were due to unexpected issues which included cancellations to CCL procedures due to hospital bed space pressures, changes to COVID rules regarding social isolation policies prior to elective procedures, staff absences due to COVID positive test results leading to a cancellation of their CMR appointment.

All studies were successfully analysed for left ventricle volumes and function. Each value was indexed with body surface area where appropriate. Body surface area was calculated for all patients using height and weight using the Mosteller formula. For each CMR study performed, the following values were calculated: end diastolic volume – indexed (EDVi), end systolic volume – indexed (ESVi), stroke volume – indexed (SVi), mass – indexed, cardiac output – indexed, and ejection fraction (See table 3.28). There was no statistically significant difference between the different treatment groups and any of the CMR derived measurements. Of note, the mean ejection fraction for the whole cohort was 54%, and there was no statistically significant difference between the PCI and medical therapy group (53.5% vs 55.2% respectively, $p=0.46$). The distribution of each category of cardiac function category

assessed via ejection fraction is illustrated in figure 3.13. Around half of the PCI and medical therapy cohorts both had ejection fraction measurements greater than 54%, with around 35% in each group measurements between 50-54%, and the remainder had measurements below 50%. It is worth noting that all patients who were recruited to Virtu-5 were screened for heart failure, and none had a clinical diagnosis of heart failure. The mean whole cohort heart rate was 63 bpm, and a statistically significant difference was noted between the PCI and medical therapy group (60bpm vs 70 bpm respectively, $p=0.01$).

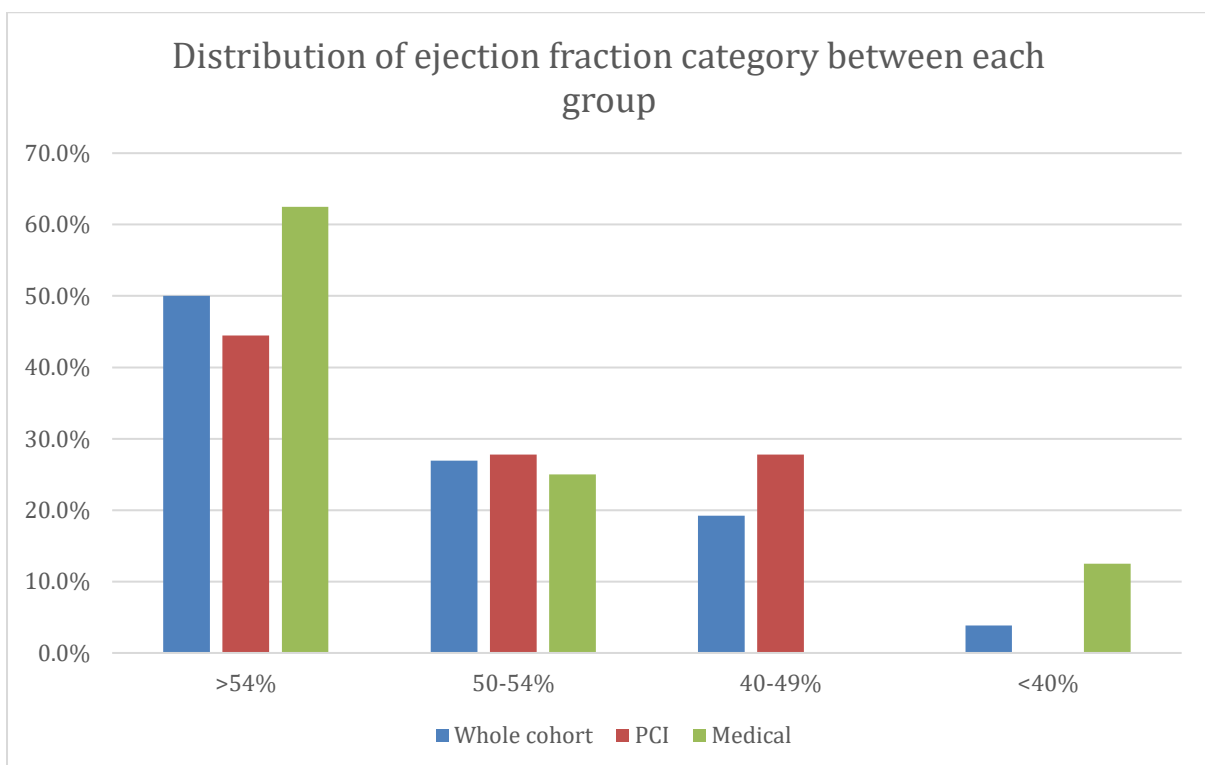


Figure 3.14 Distribution of ejection fraction categories between each treatment group.

Table 3.29 Whole cohort and treatment group summary of CMR derived parameters, including comparison of means between treatment groups.

Whole cohort = 26 PCI group = 18 Medical therapy group = 8		Mean	Median	Std. Deviation	Skewness	Comparison treatment groups		
						Mann-whitney U	Z	P value (2-tailed)
Heart rate (bpm)	Whole cohort	63	62	9.7	1.148	28.50	-2.42	0.01
	PCI	60	60	7.8	1.154			
	Medical	70	67	10.6	1.172			
End diastolic volume (ml)	Whole cohort	156.2	156.3	36.2	0.228	71.00	-0.06	0.98
	PCI	157.6	156.3	39.7	0.223			
	Medical	153.3	155.1	28.6	-0.146			
End systolic volume (ml)	Whole cohort	73.1	71.3	25.1	0.574	63.00	-0.50	0.64
	PCI	74.7	74.6	26.8	0.635			
	Medical	69.6	63.5	22.1	0.074			
Stroke volume (ml)	Whole cohort	83.1	83.7	17.2	-0.016	70.00	-0.11	0.94
	PCI	82.9	83.3	18.2	-0.001			
	Medical	83.4	84.0	15.9	-0.046			
Mass (g)	Whole cohort	103.2	99.2	28.3	1.310	53.00	-1.44	0.31
	PCI	106.8	103.3	32.0	1.122			
	Medical	95.2	90.4	16.6	-0.115			
End diastolic volume (indexed)	Whole cohort	79.2	76.5	16.4	0.965	65.00	-0.39	0.72
	PCI	79.3	74.4	18.4	1.021			
	Medical	78.9	77.6	12.1	0.253			
End systolic volume (indexed)	Whole cohort	37.0	35.1	12.6	1.263	69.00	-0.17	0.89
	PCI	37.5	35.9	13.6	1.388			
	Medical	35.7	33.0	10.8	0.544			
Stroke volume (indexed)	Whole cohort	42.2	42.9	7.4	-0.425	67.00	-0.28	0.81
	PCI	41.8	42.5	7.6	-0.561			
	Medical	43.1	42.9	7.4	-0.055			
Mass (Indexed)	Whole cohort	52.4	49.4	13.5	2.021	66.00	-0.33	0.77
	PCI	53.8	49.8	15.4	1.831			
	Medical	49.2	48.4	7.5	0.015			
Ejection Fraction (%)	Whole cohort	54	55	8.0	-0.301	58.00	-0.78	0.46
	PCI	54	52	7.7	0.086			
	Medical	55	57	9.1	-1.176			

The baseline demographic data were analysed alongside the CMR output to assess for potential confounding factors. Age was found to be negatively correlated with SVi and indexed cardiac output, female gender was negatively correlated with SVi and positively correlated with ejection fraction, dyslipidaemia was correlated with cardiac mass and T2DM was positively correlated with SVi and ejection fraction. All other demographics were not shown to be significantly correlated with the derived CMR values (see Table 3.29). Furthermore, treatment with PCI was not significantly correlated with any of the derived CMR values.

Table 3.30 Summary of Pearson correlation analysis between derived CMR values and study subject demographics. BMI = body mass index, T2DM = type 2 diabetes mellitus.

	EDVi (p value)	ESVi (p value)	SVi (p value)	Mass - Indexed (p value)	Cardiac output – Indexed (p value)	Ejection Fraction (p value)
Age	-0.260 (0.220)	-0.013 (0.952)	-0.560 (0.004)	-0.224 (0.293)	-0.706 (<0.001)	-0.382 (0.065)
Weight	-0.020 (0.925)	-0.039 (0.856)	0.013 (0.951)	-0.035 (0.870)	-0.215 (0.312)	-0.035 (0.873)
Height	0.194 (0.365)	0.204 (0.339)	0.085 (0.692)	0.201 (0.346)	-0.081 (0.708)	-0.263 (0.215)
BMI	-0.139 (0.518)	-0.156 (0.467)	-0.055 (0.799)	-0.184 (0.389)	-0.228 (0.283)	0.086 (0.690)
Gender (Female)	-0.351 (0.093)	-0.464 (0.022)	-0.001 (0.996)	-0.340 (0.104)	0.144 (0.501)	0.576 (0.003)
Hypertension	0.042 (0.846)	0.115 (0.591)	-0.108 (0.614)	0.105 (0.627)	-0.080 (0.709)	-0.173 (0.419)
Dyslipidaemia	0.328 0.118	0.302 0.151	0.233 0.274	0.432 (0.035)	-0.109 (0.612)	-0.220 (0.302)
T2DM	0.234 0.270	-0.058 0.788	0.621 0.001	0.226 0.288	0.312 0.137	0.477 0.019
Smoking	0.083 (0.699)	0.054 (0.802)	0.101 (0.637)	0.300 (0.154)	0.029 (0.894)	0.081 (0.708)
PCI	-0.060 (0.781)	-0.080 (0.709)	-0.007 (0.975)	-0.218 (0.307)	0.363 (0.081)	0.084 (0.697)

3.6.1 Association between MRI and physical activity

All CMR study assessments were analysed for associations with each wearable monitoring parameter. Baseline assessments of daily active calories, moderate to vigorous physical activity and step count was associated with ESVi, SVi and indexed cardiac mass. Light physical activity and time sedentary weren't significantly associated with any of the CMR derived values (See table 3.30).

Table 3.31 Summary of Pearson correlation analysis between derived CMR values and baseline physical activity parameters. AC = active calories, MVPA = moderate to vigorous physical activity, LPA = light physical activity, TS = time sedentary, EDVi = end diastolic volume indexed, ESVi = end systolic volume indexed, SVi = stroke volume indexed. Figures highlighted in bold indicate that statistical significance was reached.

	EDVi (p value)	ESVi (p value)	SVi (p value)	Mass – Indexed (p value)	Cardiac output – Indexed (p value)	Ejection Fraction (p value)
AC	0.586 (0.003)	0.593 (0.002)	0.316 (0.132)	0.664 (<0.001)	0.243 (0.252)	-0.367 (0.077)
MVPA	0.573 (0.003)	0.593 (0.002)	0.287 0.173	0.662 (<0.001)	0.203 0.340	-0.340 (0.104)
Steps	0.551 (0.005)	0.574 (0.003)	0.270 0.202	0.640 (0.001)	0.220 0.301	-0.295 (0.161)
LPA	0.187 (0.383)	0.213 (0.318)	0.061 (0.778)	0.147 0.492	0.243 0.254	-0.120 (0.578)
TS	0.058 (0.789)	-0.017 0.939	0.167 0.436	0.149 0.486	-0.070 0.744	0.122 (0.571)

3.7 Weather data

Atmospheric parameters were successfully collected for the entire monitoring period of the study. A total of 820 days of atmospheric data was recorded between the 1st of September 2020 and 30th of November 2022. The daily value for maximum temperature, total sunshine hours, total radiation, total precipitation and average relative humidity during each monitoring day over the entire monitoring period, as well as average trends, are illustrated in figures 3.15-3.20.

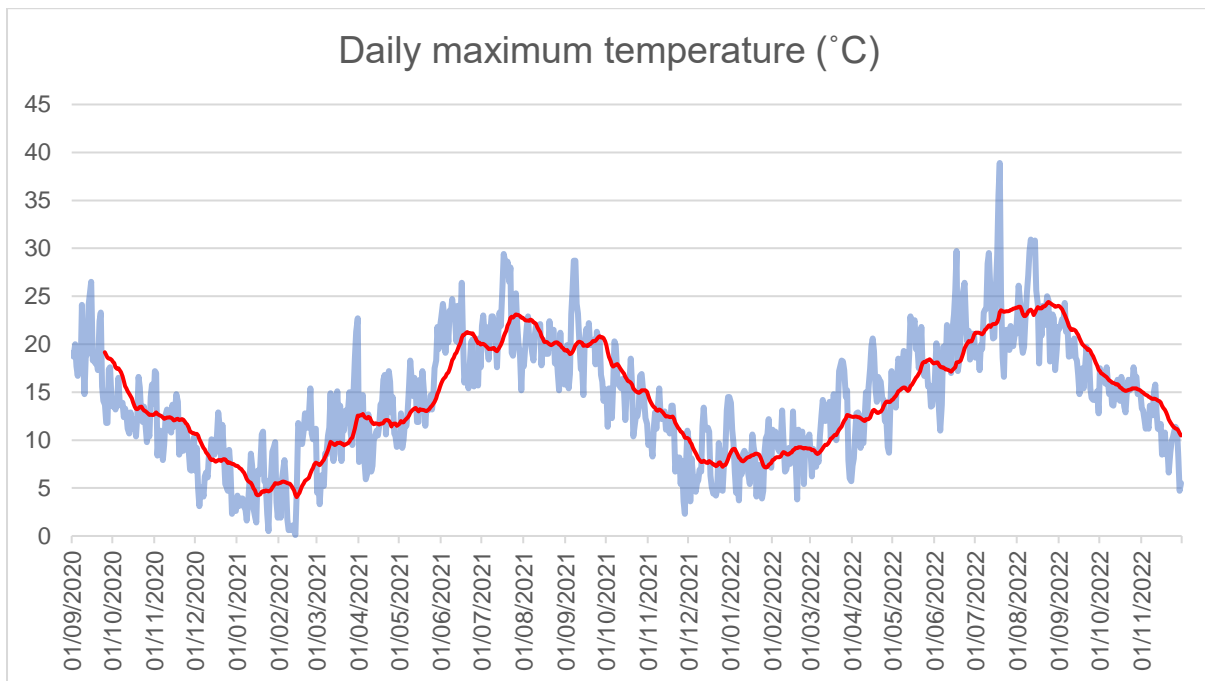


Figure 3.15 Graph of daily maximum temperature values alongside corresponding date. Blue data points signify the daily values; Red line signifies the rolling 30-day average.

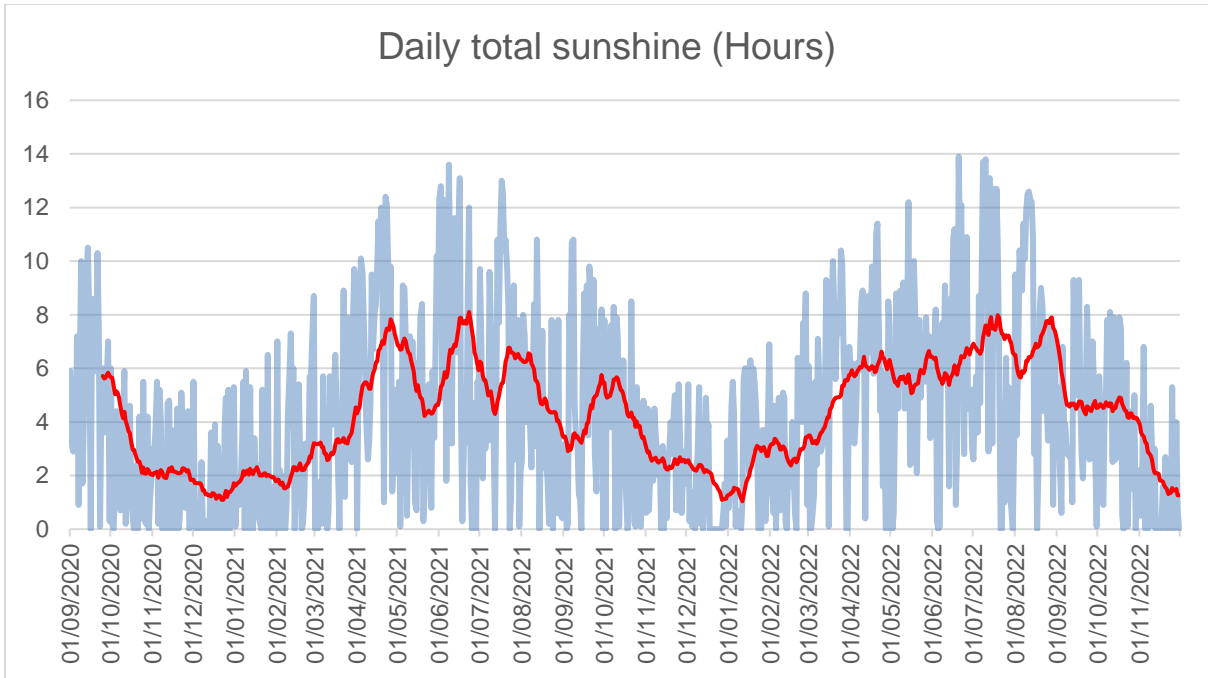


Figure 3.16 Graph of daily total sunshine values alongside corresponding date. Blue data points signify the daily values; Red line signifies the rolling 30-day average.

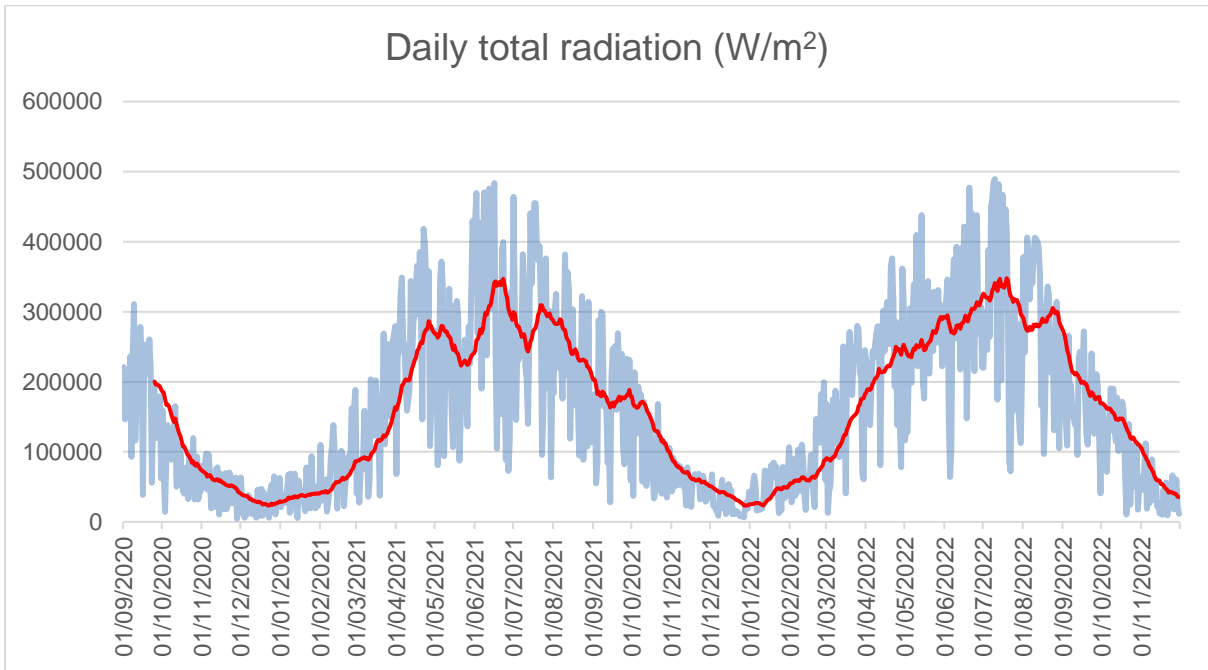


Figure 3.17 Graph of daily total radiation values alongside corresponding date. Blue data points signify the daily values; Red line signifies the rolling 30-day average.

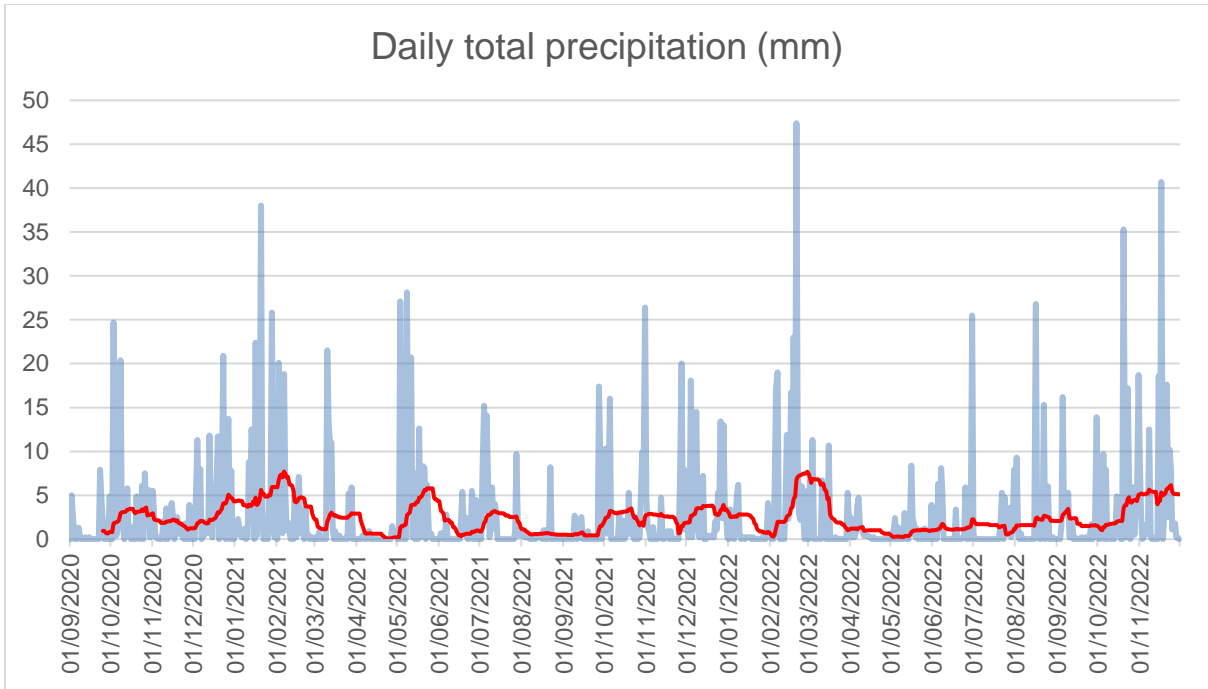


Figure 3.18 Graph of daily total precipitation values alongside corresponding date. Blue data points signify the daily values; Red line signifies the rolling 30-day average.

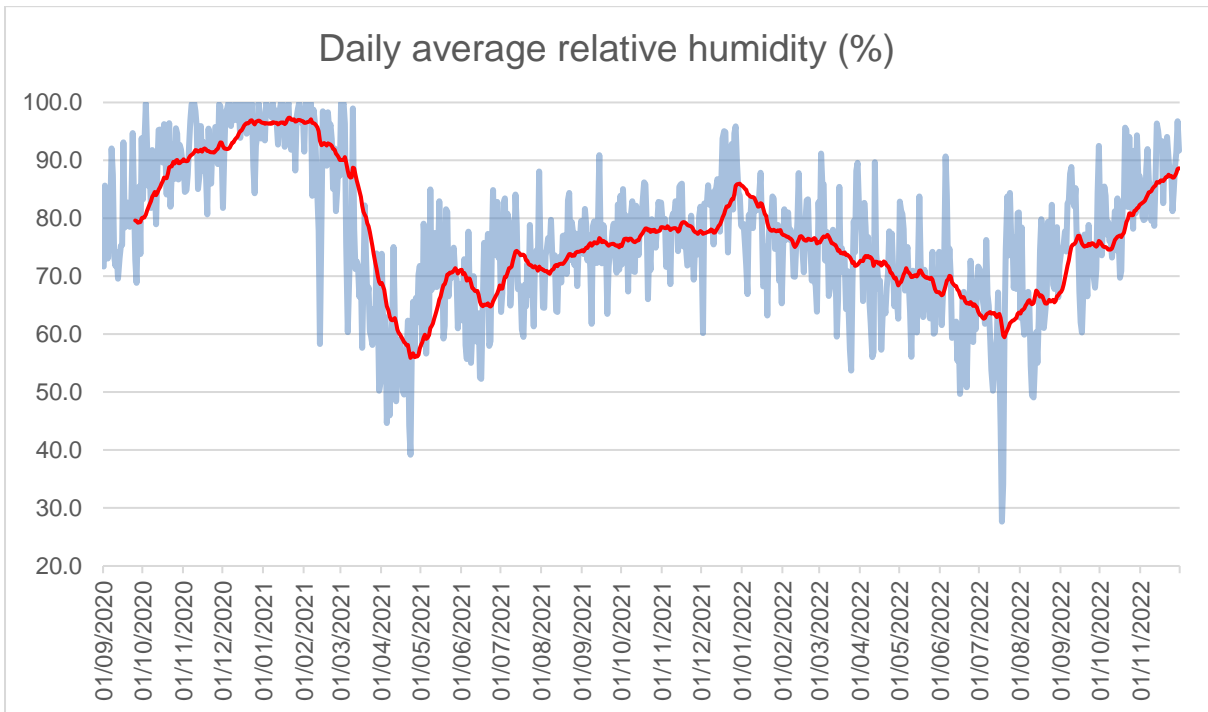


Figure 3.19 Graph of daily average relative humidity values alongside corresponding date. Blue data points signify the daily values; Red line signifies the rolling 30-day average.

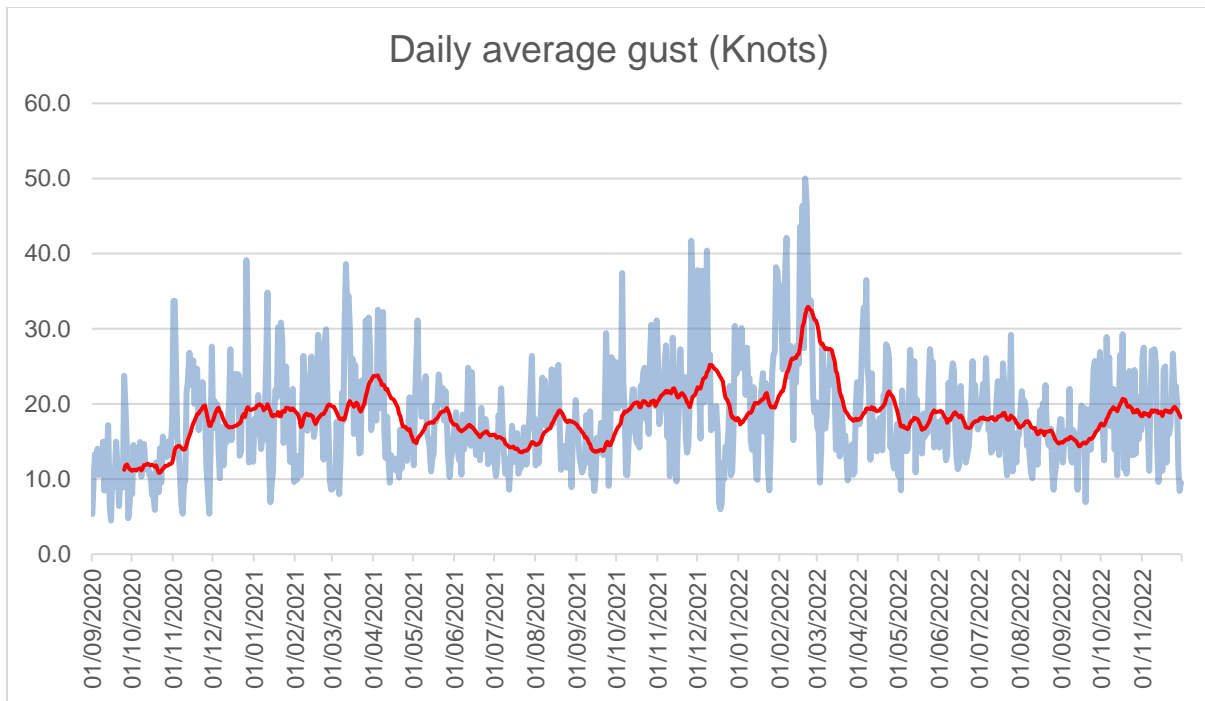


Figure 3.20 Graph of daily average gust values alongside corresponding date. Blue data points signify the daily values; Red line signifies the rolling 30-day average.

To analyse whether atmospheric conditions varied between treatment groups and between monitoring periods (pre-cath versus post-cath), independent samples T tests were used to compare the means of each variable. Table 3.31 and 3.32 detail the comparison of atmospheric parameters between treatment groups and monitoring periods respectively. With regards to treatment groups, only average wind speed was shown to be slightly significantly different between PCI and medical therapy treatment groups (18.7 vs 19.1 knots, $p=0.017$). All other atmospheric parameters were not shown to be significantly different between the two treatment groups. With regards to monitoring periods, it was demonstrated that the follow up monitoring period experienced higher daily maximum temperatures (15°C vs 13°C , $p<0.001$), total sunshine hours (4.5 vs 4.1, $p<0.001$), total radiation (173,388 vs 149,498, $p<0.001$) and wind average wind speed (19.0 vs 18.6, $p = 0.036$) as well as

lower average relative humidity (74% vs 78%) and total precipitation (2.2 vs 2.4 mm, $p = 0.04$) when compared to baseline monitoring period atmospheric data.

Table 3.32 Comparison of average atmospheric parameters between PCI and medical therapy treatment groups.

	Treatment group	Mean (SD)	Mean Difference (SD)	T value	P value (two-sided)
Maximum temperature (°C)	PCI	14.2 (± 6.3)	-0.1 (± 0.1)	-0.834	0.405
	Medical	14.3 (± 6.3)			
Total sunshine hours	PCI	4.3 (± 3.5)	0.1 (± 0.1)	1.279	0.201
	Medical	4.2 (± 3.3)			
Total radiation (W/m ²)	PCI	165206 (± 122436)	2821 (± 2719)	1.038	0.299
	Medical	162386 (± 116215)			
Rain (mm)	PCI	2.3 (± 5.0)	0.0 (± 0.1)	0.281	0.779
	Medical	2.3 (± 5.0)			
Average humidity (%)	PCI	76 (± 12.0)	0.4 (± 0.3)	1.473	0.141
	Medical	75 (± 10.3)			
Average gust (Knots)	PCI	18.7 (± 6.9)	-0.4 (± 0.2)	-2.378	0.017
	Medical	19.1 (± 7.0)			

Table 3.33 Comparison of average atmospheric parameters between pre-CCL and post CCL monitoring periods.

	Monitoring period	Mean (SD)	Mean Difference (SD)	T value	P value (two-sided)
Maximum temperature (°C)	Pre-CCL	13.0 (± 6.1)	-2.0 (± 0.1)	-15.486	<0.001
	Post-CCL	15.0 (± 6.1)			
Total sunshine hours	Pre-CCL	4.1 (± 3.4)	-0.4 (± 0.1)	-5.668	<0.001
	Post-CCL	4.5 (± 3.5)			
Total radiation (W/m ²)	Pre-CCL	149498 (± 117531)	-23890 (± 2566)	-9.309	<0.001
	Post-CCL	173388 (± 121523)			
Rain (mm)	Pre-CCL	2.4 (± 5.1)	0.2 (± 0.1)	2.053	0.04
	Post-CCL	2.2 (± 4.9)			
Average humidity (%)	Pre-CCL	78 (± 12.9)	3.4 (± 0.2)	13.811	<0.001
	Post-CCL	74 (± 10.3)			
Average gust (Knots)	Pre-CCL	18.6 (± 7.0)	-0.3 (± 0.1)	-2.095	0.036
	Post-CCL	19.0 (± 6.8)			

3.8 Multivariable analysis of physical activity data

Multivariable analysis using a generalised linear mixed models approach was performed to assess the degree of association between different influential factors on physical activity parameters. Patient characteristics data which was included in the models, as well as temporal factors such as monitoring period and which day of the week, were allocated to appropriate categories. The categories and distribution of patient and data characteristics are shown in table 3.33. The daily atmospheric parameters collected throughout the study were plotted alongside daily physical activity parameters of patients whose monitoring coincided with the appropriate date.

Table 3.34 Distribution of patient and data characteristics described as categorical variables used in the generalised linear mixed model analyses.

Characteristics	# of patients (%)	# of recorded days (%)
Age		
< 65 years	17 (46%)	4313 (46%)
> 65 years	20 (54%)	5000 (54%)
Gender		
Male	28 (76%)	7033 (76%)
Female	9 (24%)	2280 (24%)
BMI		
Normal (18-24.9)	5 (14%)	1295 (14%)
Overweight (25-29.9)	20 (54%)	4739 (51%)
Obese (>30)	12 (32%)	3279 (35%)
Treatment group		
PCI	25 (68%)	6485 (70%)
Medical therapy	12 (32%)	2828 (30%)
Monitoring period		
Pre-CCL	-	3523 (38%)
Post CCL	-	5790 (62%)
Day of the week		
Weekday		6679 (72%)
Weekend		2634 (28%)

A linear regression analysis was performed between the physical activity parameters and the independent variables (atmospheric parameters) to identify potential

multicollinearity between each value. Table 3.34 illustrates the collinearity statistics which illustrates the tolerance and Variance Inflation Factor values for each atmospheric parameter. Total radiation demonstrated a low tolerance value (0.129) with a variation inflation factor value greater than the critical threshold of 5 (7.724). This indicates that the total radiation variable has a high multicollinearity value which is likely to cause significant instability within the generalised linear mixed models.

Table 3.35 – Collinearity statistics of all atmospheric parameters derived via linear regression analysis. VIF = variance inflation factor.

Independent variable	Tolerance	VIF
Maximum temperature	0.459	2.181
Total sunshine	0.22	4.537
Total radiation	0.129	7.724
Total precipitation	0.767	1.304
Average relative humidity	0.373	2.682
Average gust	0.757	1.322

Due to the findings described above, the linear regression analysis was re-run with the removal of total radiation as an independent variable. Table 3.35 illustrates the collinearity statistics derived from this assessment. The analysis demonstrated more favourable tolerance values in comparison with the previous multicollinearity assessment with total radiation included. All variance inflation factor values were also below the critical threshold of 5, indicating that there was no significant multicollinearity that required further corrective action. As a result of this finding, total radiation was removed from all generalised linear mixed models analysis to optimise model stability and reliability.

Table 3.36 – Collinearity statistics of all atmospheric parameters apart from total radiation derived via linear regression analysis. VIF = variance inflation factor.

Independent variable	Tolerance	VIF
Maximum temperature	0.651	1.535
Total sunshine	0.466	2.146
Total precipitation	0.781	1.28
Average relative humidity	0.447	2.235
Average gust	0.8	1.251

3.8.1 Generalised linear mixed models analysis of physical activity and influential factors

Five separate generalised linear mixed models were conducted with each of the physical activity parameters to assess their association with demographic, temporal, device use and atmospheric variables. The findings of each generalised linear mixed models analysis are detailed for daily step count, MVPA, LPA, TS and AC, including fixed effects and coefficients of associations for each variable analysed (See table 3.36 - 3.40).

Table 3.37 Fixed effects and correlation coefficients of weather variables and covariates with daily step count value calculated from the generalised linear mixed model. BMI = body mass index, CCL = cardiac catheter lab.

	F	Fixed coefficient	Standard Error	95% Confidence Interval		p-value
				Lower	Upper	
Maximum temperature	0.03	-1.75	10.03	-21.40	17.90	0.861
Total sunshine	3.18	37.99	21.31	-3.78	79.76	0.075
Total precipitation	15.08	-44.11	11.36	-66.37	-21.85	<0.001
Average relative humidity	15.74	-25.96	6.54	-38.78	-13.13	<0.001
Average gust	0.13	-2.98	8.29	-19.24	13.28	0.719
Gender (female)	86.80	-1089.65	116.96	-1318.91	-860.39	<0.001
Age (> 65 years)	357.56	-2200.45	116.37	-2428.56	-1972.34	<0.001
BMI (Overweight)	391.59	91.28	139.96	-183.08	365.64	0.514
BMI (Obese)		-2734.71	139.65	-3008.45	-2460.97	<0.001
Treatment group (medical therapy)	513.81	-2875.62	126.86	-3124.30	-2626.95	<0.001
Monitoring period (post CCL)	9.39	-326.67	106.59	-535.60	-117.73	0.002
Day of the week (weekend)	89.02	-1030.35	109.21	-1244.42	816.29	<0.001
Wear time	0.20	-0.12	0.27	-0.64	0.40	0.655

Table 3.38 Fixed effects and correlation coefficients of weather variables and covariates with daily MVPA value calculated from the generalised linear mixed model. BMI = body mass index, CCL = cardiac catheter lab.

	F	Fixed coefficient	Standard Error	95% Confidence Interval		p-value
				Lower	Upper	
Maximum temperature	4.82	0.22	0.10	0.02	0.42	0.028
Total sunshine	0.24	-0.10	0.21	-0.52	0.32	0.627
Total precipitation	9.59	-0.35	0.11	-0.57	-0.13	0.002
Average relative humidity	29.12	-0.35	0.06	-0.48	-0.22	<0.001
Average gust	0.60	0.06	0.08	-0.10	0.22	0.44
Gender (female)	191.77	-15.28	1.10	-17.44	-13.12	<0.001
Age (> 65 years)	383.94	-22.57	1.15	-24.82	-20.31	<0.001
BMI (Overweight)	202.15	5.59	1.30	3.04	8.14	<0.001
BMI (Obese)		-15.53	1.30	-18.07	-12.99	<0.001
Treatment group (medical therapy)	520.13	-27.93	1.22	-30.33	-25.53	<0.001
Monitoring period (post CCL)	6.12	-2.55	1.03	-4.58	-0.53	0.013
Day of the week (weekend)	24.41	-5.46	1.11	-7.63	-3.29	<0.001
Wear time	1.79	<-0.01	<0.01	<-0.01	<0.01	0.181

Table 3.39 Fixed effects and correlation coefficients of weather variables and covariates with daily LPA value calculated from the generalised linear mixed model. BMI = body mass index, CCL = cardiac catheter lab.

	F	Fixed coefficient	Standard Error	95% Confidence Interval		p-value
				Lower	Upper	
Maximum temperature	0.06	0.04	0.16	-0.28	0.36	0.801
Total sunshine	22.52	1.65	0.35	0.97	2.33	<0.001
Total precipitation	0.15	-0.07	0.17	-0.40	0.27	0.701
Average relative humidity	0.00	0.01	0.11	-0.21	0.22	0.947
Average gust	27.35	-0.70	0.13	-0.96	-0.44	<0.001
Gender (female)	98.05	-22.15	2.24	-26.53	-17.76	<0.001
Age (> 65 years)	50.97	-12.94	1.81	-16.49	-9.39	<0.001
BMI (Overweight)	228.87	5.57	2.64	0.40	10.75	0.035
BMI (Obese)		-31.05	2.54	-36.03	-26.06	<0.001
Treatment group (medical therapy)	13.20	8.30	2.29	3.82	12.78	<0.001
Monitoring period (post CCL)	26.66	8.98	1.74	5.57	12.39	<0.001
Day of the week (weekend)	130.72	-20.37	1.78	-23.87	-16.88	<0.001
Wear time	137.45	0.05	<0.01	0.05	0.06	<0.001

Table 3.40 Fixed effects and correlation coefficients of weather variables and covariates with daily TS value calculated from the generalised linear mixed model. BMI = body mass index, CCL = cardiac catheter lab.

	F	Fixed coefficient	Standard Error	95% Confidence Interval		p-value
				Lower	Upper	
Maximum temperature	3.15	-0.63	0.35	-1.31	0.07	0.076
Total sunshine	0.01	-0.06	0.74	-1.51	1.39	0.939
Total precipitation	0.45	0.30	0.45	-0.58	1.18	0.502
Average relative humidity	6.54	0.62	0.24	0.14	1.09	0.011
Average gust	0.15	0.11	0.29	-0.46	0.68	0.7
Gender (female)	52.06	36.76	5.09	26.77	46.74	<0.001
Age (> 65 years)	30.35	21.43	3.89	13.80	29.05	<0.001
BMI (Overweight)	38.01	39.62	6.26	27.35	51.90	<0.001
BMI (Obese)		55.53	6.43	42.93	68.13	<0.001
Treatment group (medical therapy)	163.80	-65.45	5.11	-75.47	-55.42	<0.001
Monitoring period (post CCL)	10.80	12.24	3.73	4.94	19.55	0.001
Day of the week (weekend)	2.65	6.41	3.94	-1.32	14.14	0.104
Wear time	3969.83	-0.60	0.01	-0.62	-0.58	<0.001

Table 3.41 Fixed effects and correlation coefficients of weather variables and covariates with daily AC value calculated from the generalised linear mixed model. BMI = body mass index, CCL = cardiac catheter lab.

	F	Fixed coefficient	Standard Error	95% Confidence Interval		p-value
				Lower	Upper	
Maximum temperature	9.51	3.06	0.99	1.11	5.01	0.002
Total sunshine	2.38	3.23	2.10	-0.88	7.34	0.123
Total precipitation	8.71	-3.29	1.12	-5.48	-1.11	0.003
Average relative humidity	28.71	-3.44	0.64	-4.70	-2.18	<0.001
Average gust	2.38	-1.22	0.79	-2.78	0.33	0.123
Gender (female)	1885.92	-454.23	10.46	-474.74	-433.73	<0.001
Age (> 65 years)	566.97	-264.63	11.11	-286.41	-242.84	<0.001
BMI (Overweight)	262.13	159.43	11.34	137.20	181.65	<0.001
BMI (Obese)		-98.01	11.35	-120.26	-75.77	<0.001
Treatment group (medical therapy)	283.97	-200.31	11.89	-223.61	-177.01	<0.001
Monitoring period (post CCL)	0.08	3.08	10.62	-17.74	23.89	0.772
Day of the week (weekend)	128.96	-122.65	10.80	-143.82	-101.48	<0.001
Wear time	30.47	0.15	0.03	0.10	0.20	<0.001

It was estimated that women in this cohort recorded on average 1090 steps fewer than men ($F = 86.8, p < .001$), participants older than 65 years had 2200 fewer steps than younger participants ($F = 357.56, p < 0.001$), and obese patients achieved 2735 fewer daily steps than patients with a normal BMI ($F = 391.59, p < 0.001$). A number of weather parameters were found to have a significant relationship with daily step count. Total precipitation and average humidity were found to have a significant negative correlation with daily step count with a coefficient of -44.11 ($F = 15.08, p < 0.001$) and -25.96 ($F = 15.74, p < 0.001$) respectively. Maximum temperature, total sunshine and average gust were found to have a non-significant association with daily step count with coefficients of -1.75 ($F = 0.03, p = 0.861$), 37.99 ($F = 3.18, p = 0.075$) and -2.98 ($F = 0.13, p = 0.719$). Furthermore, allocation to the medical therapy group, monitoring during the post CCL period and weekend recordings were also negatively correlated with daily step count. Wear time demonstrated no significant relationship with daily step count.

Demographic characteristics including as female gender, age greater than 65 years old and obese BMI were significant negative predictors of daily MVPA. Women in this cohort recorded on average 15 minutes fewer MVPA than men ($F = 191.77, p < 0.001$), participants older than 65 years had 22 minutes fewer than younger participants ($F = 383.94, p < 0.001$), and obese patients achieved 15 minutes fewer minutes than patients with a normal BMI ($F = 202.15, p < 0.001$). Maximum temperature demonstrated a significant positive correlation with daily MVPA with a coefficient of 0.22 ($F = 4.82, p = 0.028$). Total precipitation and average relative humidity were found to have a significant negative correlation with daily MVPA, with coefficients of -0.35 ($F = 9.59, p = 0.002$) and -0.35 ($F = 29.12, p < 0.001$)

respectively. Total sunshine and average gust were found to have a non-significant association with daily MVPA with coefficients of -0.10 ($F = 0.24$, $p = 0.627$) and -0.06 ($F = 0.60$, $p = 0.44$). Additional variables included in the GLMM were also found to significantly influence daily MVPA values. Furthermore, allocation to the medical therapy group, monitoring during the post CCL period and weekend recordings were also negatively correlated with daily MVPA values. Wear time demonstrated no significant relationship with daily MVPA.

With regards to LPA, it was estimated that women in this cohort recorded 22 minutes fewer of LPA fewer than men ($F = 98.05$, $p < 0.001$), participants older than 65 years had 13 minutes fewer than younger participants ($F = 50.97$, $p < 0.001$), and obese patients achieved 31 fewer minutes than patients with a normal BMI ($F = 228.87$, $p < 0.001$). Total sunshine demonstrated a significant positive correlation with daily LPA with a coefficient of 1.65 ($F = 22.52$, $p < 0.001$). Average gust was found to have a significant negative correlation with daily LPA, with a coefficient of -0.70 ($F = 27.35$, $p < 0.001$) and -0.35 ($F = 29.12$, $p < 0.001$) respectively. Maximum temperature, total precipitation and average relative humidity were found to have non-significant associations with daily LPA with coefficients of 0.04 ($F = 0.06$, $p = 0.801$), -0.07 ($F = 0.15$, $p = 0.701$) and 0.01 ($F = 0.00$, $p = 0.947$) respectively. Furthermore, allocation to the medical therapy group, monitoring during the post CCL period, device wear time and wear time were also positively correlated with daily LPA values, while weekend monitoring demonstrated a significant negative relationship with daily LPA.

Female gender, age greater than 65 years old and obese BMI were also significant predictors of daily TS. It was estimated that women in this cohort recorded 37

minutes more TS than men ($F = 52.06$, $p < 0.001$), participants older than 65 years had 21 more minutes than younger participants ($F = 30.35$, $p < 0.001$), and obese patients achieved 56 more minutes than patients with a normal BMI ($F = 38.01$, $p < 0.001$). Maximum temperature, total sunshine, total precipitation and average gust were found to have non-significant associations with daily TS with coefficients of -0.63 ($F = 3.15$, $p = 0.076$), -0.06 ($F = 0.01$, $p = 0.939$), 0.30 ($F = 0.45$, $p = 0.502$) and 0.11 ($F = 0.15$, $p = 0.700$) respectively. Furthermore, allocation to the medical therapy group and monitoring during the post CCL period were also positively correlated with daily TS values. Wear time was noted to be the most significant predictor of TS amongst the variables observed with a negative correlation coefficient of -0.60 ($F = 3969.83$, $p < 0.001$).

Lastly, a number of variables in the generalised linear mixed models analysis were also found to significantly influence daily AC values. Female gender, age greater than 65 years old and obese BMI were significant positive predictors of daily AC. It was estimated that women in this cohort recorded 454 kcal fewer than men ($F = 1885.92$, $p < 0.001$), participants older than 65 years burned 265 fewer Kcal than younger participants ($F = 566.97$, $p < 0.001$), and obese patients recorded 98 fewer kcal minutes than patients with a normal BMI ($F = 262.13$, $p < 0.001$). Conversely, patients with overweight BMI on average recorded 159 more kcal of AC than patients with normal BMI ($F = 262.13$, $p < 0.001$). Maximum temperature demonstrated a significant positive correlation with daily AC with a coefficient of 3.06 ($F = 9.51$, $p = 0.002$). Total precipitation and average relative humidity were also found to have a significant negative correlation with AC, with correlations of -3.29 ($F = 8.71$, $p = 0.003$) and -3.44 ($F = 28.71$, $p < 0.001$). Total sunshine and average gust were found

to have non-significant associations with daily AC with coefficients of 3.23 ($F = 2.38$, $p = 0.123$) and -1.22 ($F = 2.38$, $p = 0.123$). Allocation to the medical therapy group and weekend monitoring were negatively correlated with daily AC values, with coefficients of -200.31 ($F = 283.97$, $p < 0.001$) and -122.65 ($F = 128.96$, $p < 0.001$). Wear time was noted to be a significantly positive predictor of AC coefficient of 0.15 ($F = 30.47$, $p < 0.001$).

3.8 Summary of multivariable physical activity analysis

The main findings of the physical activity monitoring data analysis are summarised in the following points:

- 820 days of daily weather parameters were recorded which demonstrated varying patterns atmospheric conditions on a weekly and seasonal basis throughout the study period.
- A total of 9313 days of daily weather data were analysed alongside daily physical activity levels using generalised linear mixed models analyses to assess the impact of each atmospheric parameter on separate physical activity parameters with weighting from demographic, temporal and measurement-related factors.
- Total radiation was found to have significantly high multicollinearity with the other atmospheric parameters, which has the potential to confound GLMM computation and results. Its removal from the list of considered atmospheric parameters led to reduced multicollinearity within the remaining atmospheric parameters, which would improve the stability of the GLMM used in this work.
- The analysis confirmed previous findings in this work that gender, age and BMI significantly influenced physical activity parameters. All physical activity

parameters were correlated with these demographics, with all but TS being positively correlated. The fixed effects of the demographics were shown to be consistently more influential than weather variables based on calculated F values.

- The allocation to the medical therapy group versus the PCI group was significantly correlated negatively with daily step count, MVPA, TS and AC, while also positively correlated with LPA. Additionally, the post CCL monitoring period was correlated step count, MVPA, while positively correlated with LPA.
- Each atmospheric parameter was found to be significantly correlated with different physical activity parameters. Maximum temperature was positively correlated with MVPA and AC, total sunshine was positively correlated with LPA, total precipitation was negatively correlated with daily step count, MVPA and AC, average relative humidity was negatively correlated with steps, MVPA and AC and positively correlated with TS, and average gust was negatively correlated with LPA.
- Wear time was shown to be significantly positively correlated with LPA and active calories, while also negatively correlated with TS. Weekend monitoring versus weekday recording was also shown to significantly influence physical activity values. Step count, MVPA LPA and AC were all negatively correlated with weekend monitoring, while TS was positively correlated.

3.9 COVID-19

At the start of 2020, reports of a new respiratory virus, designated SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) had emerged from Wuhan, China and was spreading across the world. On the 11th of March 2020, the World Health Organisation (WHO) declared the novel coronavirus outbreak, COVID-19, as a global pandemic [163]. The rising number of cases seen worldwide, as well as unprecedented reports of health services overrun with critically ill adults of all ages, led to widespread national lockdown measures, and on the 23rd of March the first national lockdown was announced in Britain. The following two years saw the largest disruption to daily life in the UK since the second world war, including two national lockdowns, restrictions on travel within and outside of the country, social distancing, as well as the suspension of all non-essential goods and services. Between the 1st of February 2020 until the 18th of May 2022, over 22 million cases of COVID-19 infections were reported in the UK, leading to over a million reported hospital admissions. Between the 1st of February 2020 until the 10th of October 2023, 232,052 deaths have been reported in the UK that were either directly caused by or associated with COVID-19. Millions of people continue to live with the consequences of the COVID-19 pandemic, either due to personal experience of ill health or chronic symptoms related to the infection, also known as “long COVID”, or the death of friends and family. This section describes the impact that the COVID-19 pandemic inflicted upon the Virtu-5 study, and the adaptations made to continue the work.

3.9.1 Pause in recruitment

The Virtu-5 study received a favourable (with additional conditions) approval letter from the North of Scotland Research and Ethics Committee on Monday the 2nd of March 2020. In line with the national lockdown announcement on the 23rd of March, all University of Sheffield research activities were suspended. At this time, no patients had been screened for the Virtu-5 study. Research activity for the Virtu-5 study did not commence until October 2020, when the study received 'restart approval' by the Clinical Research & Innovation Office (CRIO).

3.9.2 Impact on NHS services and study recruitment

The COVID-19 pandemic brought significant disruption to the NHS. Elective procedures and appointments were significantly delayed or cancelled, including urgent services such as cancer care. Elective day case procedures such as invasive coronary angiography were also impacted by the pandemic, with significant delays between referral time and procedure date. Multiple logistical issues arose around this time, including patient infection with COVID-19, staff shortages and a lack of available hospital beds. Outpatient clinics were severely disrupted, such that patients suffering with angina who were referred to specialist services experienced delays to being assessed by a Cardiologist before being referred for ICA, as well as reduced access to other diagnostic modalities which are routine in the work up of many angina patients.

With regards to the Virtu-5 study, the following issues impacted the study design:

- Long waiting lists for elective ICA procedures resulted in delays in study participants proceeding through the Virtu-5 study protocol.
- Procedure cancellations and rescheduling was common during the COVID-19 pandemic due to patient sickness, staff shortages or bed shortages.
- Social distancing, particularly in the early period of the pandemic, led to strict social distancing rules and limitations of staff numbers to the minimum numbers needed in each given space in the clinical environment. As research students, our presence in clinical spaces during this period was monitored closely by clinical staff and, in several circumstances, contact with study participants was significantly limited.
- The planning of pre-catheter lab assessments (i.e. 6MWT and CMR), which were designed to occur as close to the procedure date as possible, was significantly hampered by last minute changes in procedure dates. This led to a number of pre-procedural appointments being missed as the study participants would occasionally be unable to attend two separate hospital appointments at short notice, as well as organising the minimum staffing level needed to undertake CMR scanning.
- For some time during the pandemic, a period of isolation was mandated for elective day case procedures, including ICA. This led to a significant impact on pre-procedural assessments, as the design of the study was to undertake these assessments within a few days of their catheter lab assessment. Combined with the short notice of several procedure appointments, this made organising pre-procedural assessments additionally challenging.
- The Medical Education Centre for the Northern General Hospital was utilised as a COVID-19 testing hub. An adjacent corridor to the Medical Education

Centre was initially designated as the assessment area for the Virtu-5 6MWT. With the opening of the COVID-19 testing centre, which utilised the adjacent corridor as a queue for patients, 6MWT assessments were suspended for the Virtu-5 study until a suitable alternative corridor was designated. Given that the ICA procedures could not be delayed for study activities, this led to some of the study participants not undertaking the 6MWT assessment.

3.9.3 Patient contact and COVID screening

A significant impact of the COVID pandemic was the restrictions placed upon interpersonal contact. Several guidelines and updates were issued by the university for staff and students who undertook clinical activities during the COVID pandemic, which included regular COVID screening and wearing of Personal Protective Equipment (PPE) during patient contact. All such guidelines were adhered to by the research students throughout the Virtu-5 study. The following actions were followed by the research students during the Virtu-5 study, which were in keeping with university guidelines at the time:

- PPE, including disposable masks, aprons, and gloves, were worn when conducting any form of personal patient contact.
- Students would conduct regular lateral flow tests to screen for COVID, generally once a week. Additionally, students would conduct a lateral flow test the day before any planned patient contact. Patients were also requested to undertake a lateral flow assessment before any study appointments.
- In the event a student experienced symptoms of upper-respiratory tract infection, such as coughing, sore throat or fever, they would undertake a

COVID PCR swab test at one of the local NHS testing centres. If the test was positive, the student would follow current COVID guidelines on strict isolation, generally requiring isolation for 2 weeks. If the test was negative, the student would continue to avoid any patient or university contact until their symptoms resolved.

Chapter 4

4. Discussion

This project was a proof-of-concept study, designed to investigate the feasibility of using wearable physical activity monitoring devices in patients suffering with coronary artery disease and receiving treatment; to collect physical activity data, and determine whether this assessment can provide meaningful information regarding patient assessment. In summary, the physical activity monitoring devices provided a large volume of data which provided a variety of insights into the physical activity behaviours of the participants. There was good adherence to the wearable devices observed across the cohort, which was largely maintained irrespective of the duration of monitoring. Several significant associations were noted between wearable physical activity parameters and recorded participant characteristics and clinical assessments, highlighting the potential relevance of physical activity monitoring to the patient assessment. It is worth noting that, despite the difference between PCI and medical therapy groups regarding the presence of physiologically significant epicardial disease, as well as the extent of coronary disease (mean SYNTAX score of 22 in the PCI group versus 11 for the medical therapy group), there was no statistically significant difference in any of the baseline questionnaire responses, 6MWD scores and CMR characteristics between the two treatment groups. Whilst these findings may be explained by the small sample size represented in this study, it highlights the challenges of determining the severity of coronary disease as well as appropriate treatment based on non-invasive assessment methods alone. Information gained through wearable physical activity

monitoring may provide novel insights that may help clinicians to plan appropriate treatments with patients for their CAD, as well as provide follow up monitoring to objectively assess for improvements in physical activity.

4.1 Study design & patient cohort

The number of patients recruited to the Virtu-5 study was small; a total of 40 patients were recruited to the study, of which 37 were eligible to undergo wearable physical activity monitoring. Studies investigating outcomes associated with the management of stable CAD are familiar with thousands of study participants, such as the ISCHAEMIA trial (5179 patients), the COURAGE trial (2287 patients) and FAME 1 (1005 patients). Furthermore, the follow up period was up to six months in Virtu-5 study, which in comparison to the earlier trials is significantly shorter (3.2 years for ISCHAEMIA, 4.6 years for COURAGE, 5 years for FAME) [164] [87] [97]. However, these larger studies were powered for clinical endpoints such as major adverse cardiovascular events, which include cardiovascular death, myocardial infarction and urgent revascularisation.

Studies which have investigated the treatment of angina, physical activity and quality of life in patients with CAD have included smaller numbers and involved shorter follow up. In one study by Parisi et al, 212 patients with single vessel CAD suffering with angina were randomised to either medical therapy or PCI [165]. At six months follow up, the investigators reported superior angina relief in the PCI treatment arm in comparison to the medical treatment arm (64% angina free versus 46% respectively, $p < 0.01$) as well as greater exercise tolerance (2.1 minutes exercise duration versus 0.5 minutes, $p < 0.0001$). More recently, the ORBITA trial enrolled

230 patients who were commenced on optimal medical therapy for angina and randomised to PCI or placebo with a placebo-controlled double-blinded design, which after 6 weeks of follow up demonstrated no significant improvement in exercise time or anginal frequency [91]. Similarly, the ORBITA II study recruited 301 patients with CAD to investigate the effect of PCI on patients with minimal to no anti-anginal medication in a similar placebo-controlled double-blinded method [166]. At 12 weeks follow up the investigators demonstrated a significant improvement in angina symptom score versus placebo control.

With respect to studies which have utilised wearable technology-based physical activity assessments, there is little in the literature which describes this method being used to assess patients suffering with angina or following treatment with coronary revascularisation. Freene et al compared device-based physical activity monitoring in patients attending cardiac rehabilitation following PCI in Sweden and Australia [167]. With 183 participants enrolled, patients were asked to wear a hip-worn tri-axial accelerometer for seven consecutive days, which demonstrated increased levels of physical activity in the Swedish cohort in comparison to their Australian counterparts, although assessments of angina severity or comparisons of underlying coronary pathology leading to PCI between the two cohorts was not described. A further cross-validation study by Kambic et al enrolled 91 patients with CAD attending cardiac rehabilitation which compared 8 days of hip-based physical activity monitoring with patient-reported physical activity levels [168]. The authors found the agreement was poor between patient-reported physical activity levels and device-based measurements, with a trend to overestimate daily MVPA and underestimate SB. To my knowledge, there has not been any previously described work which

investigates the use of wearable physical activity monitoring before and after any form of treatment for CAD.

With regards to patient demographics, the study participants were largely representative of patients typically seen clinically, as well as in recent literature. The average age of the patient cohort was 65 years, the average BMI was 29, and 23% of the participants were of the female gender. The presence of traditional cardiovascular risk factors in this cohort was also representative of this patient population (hypertension 70%, hypercholesterolaemia 38%, T2DM 14%, current/ex-smoker 60%). A few notable differences were observed between the PCI and medical therapy groups. A higher proportion of females in the medical therapy versus PCI group (50% vs 12%, $p=0.012$), as well as a higher proportion of diabetes in the medical therapy group (4% vs 33%, $p=0.015$). This variation between the two treatment groups may be explained by the increased prevalence of angina with unobstructed epicardial coronary arteries, or microvascular angina, observed in women and in patients with diabetes [169-170].

4.2 Coronary angiography and PCI

The distribution of CAD observed in the study participants was variable. The most common location of significant CAD lesions was the LAD (70%), followed by the RCA (51%) and the LCx (32%). Six of study participants (16%) were noted to have significant LMS disease. A total of 65 vessels were identified as being significant enough to warrant physiological assessment, with an average of 2.2 diseased vessels per patient. 46% of the whole cohort were found to have two vessels with

significant stenoses, while 27% had only one significantly narrow vessel, with 28% of the cohort having three or more significantly narrow vessels. Of note, the remaining four patients (11%) were found to have no obstructive coronary disease with a stenosis greater than 50%, despite CTCA findings of at least one vessel with obstructive disease and typical features of angina. This distribution and extent of coronary disease can be considered typical of the UK population. The proportion of multivessel disease is noted to be higher than that of recent published work, such as that of ORBITA II, which described 80% of its recruited cohort as having single vessel disease, with an average number of diseased vessels per patient of 1.3 [166]. It is worth noting that while the proportion of disease locations in major coronary vessels were higher in this study in comparison to ORBITA II (LAD 55%, RCA 22%, LCx 9%), when the volume of diseased vessels are taken into account, distribution is comparable, with LAD stenoses being most common, followed by RCA and then LCx. stenoses Additionally, there was a significant number of LMS disease included in this cohort, which is typically excluded in other studies involving PCI revascularisation. However, the distribution of CAD described here represents the typical workload of the local interventional cardiology centre working alongside a cardiothoracic surgical department, which has considerable experience in complex multivessel disease and LMS angioplasty.

There was a relatively high proportion of vessels treated in the Virtu-5 PCI cohort in comparison to other studies. The PCI cohort had an average of 1.8 vessels treated per patient, whereas the ORBITA II study reported an average of 1.3 treated vessels per patient [166]. The reduction in average diseased vessels identified angiographically (2.2 vessels) to the average number of treated vessels is explained

by the routine use of FFR assessment to determine physiological severity and guide PCI decisions in this cohort, which is a typical pattern seen in physiological assessments of coronary disease. Additionally, despite the proportionally higher volume and complexity of disease present in this cohort, there were no significant adverse outcomes related to PCI observed in any of the participants during the study. This reflects the workload and expertise of the local cardiac centre to manage this population.

4.3 Wearable technology and physical activity monitoring

4.3.1 Compliance

One of the key research questions investigated in this study was the feasibility of prolonged physical activity monitoring in a representative sample of the CAD patient population. With a total number of 10,555 monitored days of physical activity data recorded, an average of 285 days of monitoring per patient, and an average of 1174 minutes (19.6 hours) of daily wear time recorded, the feasibility and acceptability of this form of patient assessment is self-evident. No patients enrolled requested for the physical activity monitoring to be stopped or temporarily paused. As far as the author is aware, the volume of physical activity monitoring achieved per patient in this study is greater than in any published work in CAD.

Quality assurance of physical activity data monitoring was a further key research objective. Minimum wear time was utilised to ensure that a representative minimum number of hours were recorded each day, with the assumption that study participants were not expected to wear their device all day. All day device wearing,

which is frequently described in other work using wearable physical activity monitoring, was not mandated in this study. There were a few reasons why a patient-directed approach to device wear was chosen. The duration of monitoring in this study was significantly longer than most published work in wearable physical activity, which would have made all day wearing impractical due to the need for frequent recharging which can take hours at a time. A solution may have been to mandate six days of all day wearing, with no more than 30 minutes of non-wear time to wash and bathe each day, and a seventh day where the participants would have been instructed to recharge their device battery to full and the physical activity data from this day would be discounted. This could arguably be preferable to patient-directed wearing as the device would capture the patient's physical activity for the whole 24-hour period, making it potentially more accurate or representative of the participant's activity behaviour. However, this would have limited the translation of the study findings as this would necessitate strict wear patterns which are not consistent with the heterogenous wear patterns observed in this study, which can be considered representative of the variability of device use in the general population. Outside of clinical research, the use of wearable physical activity monitoring is initiated and monitored by patients, and the generalisability of any findings in this area must consider the variable nature of device use between individuals in the general population. The success of such devices lies in their unobtrusive and convenient nature to consumers, which would be significantly diminished if individuals were instructed to wear such devices differently to how they would like to, including overnight. Significant variability in wear time patterns between individuals was noted in this cohort, which improves the generalisability of this study's findings, but

necessitates the requirement for a quality assurance method such as minimum wear time criteria.

There exists an equipoise in the literature with regards to the ideal minimum wear time criteria in wearable physical activity monitoring. Fini *et al* have demonstrated that differences in minimum wear time can result in significant variation in physical activity data [171]. The associations between wear time and each physical activity parameter were assessed with different wear time criteria. My findings demonstrated that the lack of a minimum wear time criteria could lead to potential confounding in daily values of step count, LPA, and active calories. The association between wear time length and each of these parameters became insignificant with a low minimum wear time criteria of 4 hours onwards. Additionally, MVPA was not associated with duration of wear time, even without a minimum wear time criteria. An explanation of the difference between my findings and that of Fini *et al* is that the volume of data we collected per patient was considerably larger (271 days from 69 patients, average of 4 monitored days per participant). This variation illustrates the potential advantages of longer durations of monitoring to acquire larger data samples in reducing the confounding risk of wear time variability versus shorter monitoring durations. As a result of this analysis, I demonstrated that these physical activity parameters were not significantly associated with minimum wear time. This suggests that, for these parameters, strict wear time parameters would not lead to more representative physical activity data, and that higher thresholds would only lead to fewer valid data.

It was noted that sedentary time was significantly associated with wear time duration until stricter minimum wear time criteria (1080 minutes) were applied. The difference

between this parameter and other physical activity data collected is explained by the method in which time sedentary is calculated and how this differs from the other metrics. By using Fitbit devices, time sedentary is derived from accelerometer data. While the device is worn, minutes spent sedentary, lightly physically active, moderately physically active and vigorously physically active are calculated based on the “counts per minute” from the tri-axial accelerometer. However, for any length of time the device is not worn, this is counted as time sedentary. This makes time spent sedentary the only physical activity parameter for which a value is counted when the device is not worn; hence the significant association with daily wear time. This becomes increasingly problematic when taking into account wearing patterns and sleep. The device software is able to register subtle movements of the wearer which are associated with sleep and does not register this as time sedentary, but as time sleeping. This results in a higher value of time sedentary recorded for patients who do not wear their device while sleeping, or frequently recharge their device overnight. As a result of this finding, results associated with time sedentary in this study must be interpreted carefully.

Ten hours was the most common published criterion for minimum wear time, which resulted in 9314 valid monitored days (88.2%). The median proportion of days which met this criteria across the cohort was 89.9% (IQR 84.4 – 97.5%). Compliance with this criteria was shown to be well maintained with each successive month of monitoring up to twelve months. This demonstrates that diminishing wearer compliance due to prolonged monitoring was not observed in this cohort and further supports the feasibility of continuous physical activity monitoring in this population.

4.3.2 Baseline physical activity

Previous work examining objective physical activity monitoring in CAD has primarily focused on patients attending cardiac rehabilitation, which typically occurs after a cardiac event or procedure. To the best of my knowledge, no work has previously been published describing the assessment of patients with stable CAD prior to a major cardiac event or intervention using wearable physical activity monitoring.

Using the minimum wear time criterion of ten hours, an excellent level of valid day monitoring was achieved, with a median of 84 days (IQR 54 – 84) out of a possible 84 days within the three-month pre-CCL period. My findings demonstrated that there is a high degree of variability in physical activity behaviours within the stable CAD patient population. The difference between the lowest and highest quartile ranges for steps (2791 - 4,965 and 10,863 - 20,920), active calories (299 - 764 and 1,245 - 2089) and MVPA (1 - 16 and 65 - 145) highlights the range of behaviours observed in patients suffering with angina. These findings demonstrate that the patients suffering with symptomatic CAD can achieve high levels of physical activity behaviours. Many within this cohort would meet the recommended physical activity behaviours that are intended to lower CVD risk, and thus lifestyle advice is unlikely to improve this aspect of cardiovascular risk further. It is also possible to objectively identify patients whose physical activity behaviours consistently fall well below recommended targets. The identification and prioritisation of such groups of patients with lower physical activity values may be used to direct targeted lifestyle interventions.

A number of insights were also gained when comparing the two treatment groups before they underwent their CCL procedure. All patients recruited to the Virtu-5 study were considered to have CAD amenable to PCI based upon prior coronary imaging and had been treated with at least two anti-anginal therapies before being referred for further assessment. Therefore, other than the number of vessels involved, the distinction between these patient groups could only be made by invasive physiological assessment undertaken during their CCL procedure. However, there were some notable characteristics between the two groups at baseline. Median values for step count and active calories were numerically higher in the participants who subsequently underwent PCI versus the medical therapy group (8380 vs 5226 steps, 1045.9 vs 848.7 Kcal, respectively); however neither of these were shown to be statistically significantly different. Interestingly, time sedentary was also noted to be numerically higher in the PCI therapy group in comparison to the medical therapy group (779.6 vs 728.1 minutes) which was close to reaching statistical significance. However, it is possible that this signal may have been associated with the issues mentioned above with recording the TS parameter and patient wear characteristics, and thus this observation does carry some uncertainty. Time spent in MVPA was however noted to be significantly higher in the PCI therapy cohort versus the medical therapy group (36.7 vs 15.6 minutes, $p = 0.03$).

This was the first study to demonstrate an objective physical activity behaviour (specify) which was associated with the presence of physiologically significant CAD in patients suffering with angina, which differs from that of clinical stress tests such as treadmill testing and exercise stress imaging. The low patient numbers may have contributed to some of these results not meeting statistical significance. It is not clear

whether the physical activity behaviour is because of the differing phenotypes of CAD, or whether sedentary behaviour is more likely to lead to microvascular dysfunction. However, when taken as a whole, these findings suggest that there are potentially meaningful differences in the physical activity characteristics of patients who suffer with angina but with different CAD phenotypes (ie obstructive versus non-obstructive / microvascular disease).

4.3.3 Change following CCL procedures

Several studies have described the objective physical activity behaviours of patients with CAD after revascularisation, which have included daily step count monitoring. Bränström and colleagues used pedometers to measure physical activity in patients six months after suffering a MI, aged ≤ 65 years [172]. Following seven days of monitoring, mean daily step count in 89 participants was 6719, with the following lower and upper quartile ranges of 913 – 3408 to 8957 – 19980. The authors did not describe whether patients attended cardiac rehabilitation following their MI admission or what the association revascularisation strategy had with outcomes (76% of participants underwent PCI, 9% had CABG and 15% were managed medically). Houle *et al* also described the seven-day monitoring of post ACS patients with pedometer step counting [173]. At six and 12 months following their ACS event, patients were dichotomised into either active or inactive group based upon whether they achieved an average of 7,500 steps of greater. Twenty-five participants met the criteria for high activity, with a mean daily step count of 11,320 at six months; and 16 patients were classified as less active, with an average daily step count of 5,503.

Patients in the active group were noted to have lower triglycerides, lower waist circumference and higher high-density lipoprotein cholesterol.

Other work has also evaluated the role of time spent undertaking various levels of physical activity alongside step count. Freene *et al* describe the use of hip-worn accelerometers to measure activity levels in 67 patients with CAD following a cardiac rehabilitation programme [174]. Data were collected over seven days at baseline, six weeks, six months and 12 months follow up. Most participants (79%) attended cardiac rehabilitation following a PCI procedure for stable CAD, and the mean baseline MVPA was 32.7 minutes/day and time sedentary was 723 minutes/day. There was a positive correlation between MVPA and HDL, and higher levels of TS were negatively associated with 6MWD results. At six months follow up, only 60% provided sufficient data for analysis, while at 12 months this dropped to 49%. Lastly, Kambic *et al* described the physical activity characteristics of patients who were referred for cardiac rehabilitation following an ACS event [175]. Ninety-one patients were monitored with a tri-axial accelerometer for eight days prior to cardiac rehabilitation, with daily measures of physical activity levels, including sedentary time, was counted. The authors reported a mean daily MVPA of 63 minutes / day and 248 minutes / day of LPA, with daily sedentary times averaging 484 minutes / day and an average daily step count of 6422. The presence or burden of angina in this cohort was not reported by the authors.

To my knowledge, mine is the first work that describes the objective assessment of physical activity parameters before and after coronary revascularisation for stable CAD. Furthermore, as demonstrated earlier, previous work has recruited from patient

cohorts who have suffered ACS events and have undergone revascularisation for this indication. This cohort underwent CCL assessment due to the presence of ongoing anginal symptoms in stable CAD, despite the use of medication to ameliorate their angina burden. This work therefore is also the first to analyse the monitoring of patients' physical activity before and after treatment aimed at reducing the angina burden. During the follow up period, the average value for daily step count was 7978, MVPA 40 minutes / day, LPA 222 minutes / day and TS 773 minutes / day. These features are generally in keeping with the earlier work describing physical activity behaviours following coronary revascularisation. These results reinforce my earlier findings with baseline physical activity that patients with stable CAD are able to achieve high levels of physical activity behaviours. As in the baseline results, the variation observed among the cohort was also substantial.

When the two treatment groups of PCI and medical therapy were compared, a number of differences were also observed. As in the baseline results, the average MVPA in the PCI group was significantly higher than in the medical therapy group (48.4 minutes versus 22.8 minutes, $p < 0.01$). Additionally, the active calories value was significantly higher in the PCI group (1180.3 kcal vs 888.4 kcal, $p = 0.02$). Step count averages were numerically higher in the PCI group versus medical therapy, although this was not statistically significant (8,184 versus 5,515, $p = 0.11$). However, when paired baseline and follow up datasets were compared for any interval change, no significant changes were observed in any of the physical activity parameters. This was further confirmed when the PCI and medical therapy paired datasets were compared separately. This finding suggests that coronary revascularisation with PCI for stable angina does not result in a significant change in physical activity. This

highlights the concept that revascularisation is not a lifestyle intervention which leads individuals to become more or less active than they were previously. Lifestyle interventions, such as involvement in cardiac rehabilitation, aims to improve the participant's awareness of healthy physical activity which aims to improve cardiovascular risk both directly by improving exercise behaviours and reducing sedentary time as well as through secondary effects such as improved rates of weight loss and better blood pressure control as a consequence of physical exercise.

4.4 6MWT

The 6MWT assessment is frequently utilised in patients suffering with CVD, but its use in CAD is less well described. 6MWD has been shown to correlate well with self-reported exercise tolerance in CAD patients as well as maximal oxygen consumption [176-177]. 6MWT assessments have largely been utilised in the cardiac rehabilitation setting, occurring generally after an ACS presentation or revascularisation procedure. A shorter 6MWD after an ACS presentation has been shown to correlate with a higher risk of MACE [178-179]. Data pertaining to the effect of coronary revascularisation in stable CAD on 6MWD is limited. The assessment of 6MWD in patients undergoing CABG both pre- and post-operatively has not been directly described. Rossello et al described the use of the 6MWT before and after CTO PCI, which demonstrated a significant improvement in 6MWD with successful recanalisation of CTO disease [180]. It is arguable that the 6MWT is a safe and useful assessment of exercise tolerance in patients with CAD, although our understanding of its relationship with symptomatic CAD (angina) and its alleviation, either with revascularisation or medication, are not well described.

The present work describing the use of the 6MWT before and after PCI does provide some interesting insights. First, there was no statistically significant difference between the PCI and medical therapy groups at baseline, although the PCI group was numerically superior. This lack of a statistical significance may have resulted from the low number of paired data collected in this study, but it seems paradoxical that patients with more disease exercised to at least an equivalent level as those who had less. Second, both the PCI and medical therapy groups demonstrated a significant improvement in 6MWD following their CCL procedure. While this may be unsurprising in the PCI group, it is noteworthy in the medical therapy group, given that they had no change in their medication, and underwent no cardiac rehabilitation between the two assessments. One explanation is that patients who are found to have physiologically negative disease during their procedure received a different form of therapy during this clinical encounter. Following their procedure, each patient was informed of the nature of the assessment performed by a knowledgeable and experienced doctor and reassured that their CAD is not significant enough to warrant an invasive procedure. By being informed that their “heart condition” may not have been as severe as previously thought, the encounter may have a psychological component which helps to modify the patient’s perception of their condition and thus their perception of their overall health and wellbeing. While the patient has clear evidence of CAD requiring medical therapy, this inadvertent form of counselling may have a beneficial placebo effect. This may explain how the medical therapy group achieved an average improvement of 43.2 m in 6MWD following their CCL procedure, while the PCI group achieved an average improvement of 28.8 m.

Lastly, comparisons were drawn between the baseline 6MWT assessment and wearable physical activity monitoring data. Baseline 6MWD was found to be positively correlated with daily step count, LPA and active calories. It is interesting that 6MWD did not correlate significantly with MVPA values, which would intuitively indicate the level of regular physical exercise an individual undertakes. However, this finding highlights one of the areas of poor understanding with 6MWT and physical activity behaviour. It is not well understood how a healthy individual would achieve a greater 6MWD result over the average cohort value without exercise training. Whether higher levels of habitual “light” physical activity are correlated with superior results to higher moderate to vigorous exercise training is not well described. Additionally, the parameters of daily step count, LPA and AC are intrinsically linked to the most common forms of physical activity, namely walking, while MVPA is associated with other forms of physical activity, such as running, swimming and cycling. It may simply be that patients with greater 6MWD but low MVPA values exercise primarily by walking, while other individuals with lower 6MWD values with relatively high MVPA values may indicate that they exercise through different forms of physical activity other than walking. This theory is supported by the findings of the questionnaire data, which the full results will be discussed in greater detail later in this chapter. With regards to the correlation between questionnaire responses and 6MWT results, it was noted that the 6MWD values only correlated with SF-12 MCS scores and SAQ AfD scores. None of the questionnaire physical activity assessments, including the EQ-5D-5L EI value, the SF-12 PCS score or the SAQ PLD score, were significantly correlated with 6MWD. Of note, the PLD score comprises of questions which enquires into more vigorous forms of exercise such as running, jogging, swimming, and tennis. Further speculation on this theory is limited

within this study as patients were not directly asked to list all forms of physical exercises they partook in. However, these findings highlight that 6MWT results are partially informative of an individual's physical activity behaviours.

Lastly, it is worth noting that 6MWD improved in both PCI and medical therapy groups, despite no significant change in objective physical activity values gained from the Fitbit device. This finding highlights the potential discrepancy encountered between an individual's exercise tolerance and habitual physical activity / exercise behaviour. It does seem paradoxical that none of the physical activity behaviours significantly improved despite the clear overall improvement in exercise tolerance. However, the receipt of PCI or the re-assurance of a "non-significant" CAD is likely have a significant impact on an individual's perception of what physical activity they are prepared to undertake. This would therefore have a potential influence on the results of a 6MWT while having little impact on daily activities with which they have grown accustomed to.

4.4.1 Step count accuracy

Measurement accuracy is of paramount importance to ensure any device's reliability as a clinical assessment tool. Step counting accuracy assessments in wearable devices are well described in the literature given the vast options available for consumer-based physical activity monitoring. Germini et al described the state of step counting accuracy in the literature of modern wearable devices published between 2013 and 2018, with a total of 31 studies investigating 72 different devices from 29 different brands, highlighting the variety of devices and manufacturers

available [181]. While reporting step counting accuracy in wearable technology has gained popularity, a variety of reference step counting methods are reported, leading to significant variations observed in the literature. The different reference methods include manual step counting, automated step counting through video analysis, or using a reference step counting device. Expert consensus suggests that video recorded free-living step counting with 2 observers should be the gold standard of measuring device accuracy [182]. While this method provides a rigorous assessment of a patient's usual activity in their own environment rather than a clinical space or with restricted types of walking, its main drawback is its laborious nature. Assessing 45 participant recordings during a 10-14 waking hours period would require 450-630 hours of video recording to be analysed. Additionally, this method fails to capture outdoor activity which can introduce several influential factors in step counting, as well as being far more intrusive than other methods of physical activity monitoring. In free living conditions, only 9% of studies used this reference method to assess device step counting accuracy. Thus, the expert consensus has called for a feasible alternative gold standard criterion measure of free-living step counting in order to provide an accessible, standardised method to quantify device accuracy.

Visual observation step counting is a popular reference method for assessing device accuracy, accounting for 24% of reported studies [182]. This work is primarily conducted under laboratory conditions, utilising different forms of ambulation such as treadmill or track / overground walking. While visual observation step counting has notable limitations in comparison to free living step counting methods, it represents an important first step in the validation of wearable devices as accurate physical activity monitors.

The Virtu-5 study investigated the step count accuracy of the Fitbit Charge 4 device in patients suffering with CAD. As outlined by expert consensus guidelines, I have reported the recommended statistical analyses, namely of Bland-Altman limits of agreement analysis, ICC, and mean absolute percentage error, as well as Pearson's R and R² values. Using directly observed step counting as a reference during 6MWT assessments, these findings suggest that the Charge 4 device achieved good accuracy overall in all relevant tests. This includes achieving a mean absolute percentage error of 4.4% which is within the desirable criteria of accuracy for wearable devices to suggest an extremely low level of measurement error (<5%). It is worth noting that, as part of the 6MWT instruction, this assessment was conducted during brisk walking conditions which can reduce the accuracy of step counting devices.

To my knowledge, very little has been described concerning a comparison of the Fitbit Charge 4 device with direct observation step counting in a laboratory environment with all recommended statistical analyses in a typical gait population. Waddell and colleagues reported on the assessment of step counting accuracy of the Fitbit Charge 4 device in 30 healthy adults with two one-minute bouts of treadmill walking [183]. The authors reported an ICC of 0.75 which was statistically significant ($p < 0.001$) but failed to provide a mean absolute percentage error value or Bland-Altman analysis for their findings in this environment. They also reported a 'free living' assessment with a "research-grade" step count monitor as the reference method, which resulted in a poor mean absolute percentage error value of 26%. Unfortunately, this work failed to report their laboratory-based assessments with all

the recommended analyses, and the reference measurements for their free-living assessment was not considered a “gold-standard” method. As such, this work represents the first robust laboratory-based assessment of the Fitbit Charge 4 device’s step count accuracy.

4.5 Questionnaires

Beyond clinical endpoints such as mortality and MACE, patient reported outcomes are relied upon to provide a comprehensive understanding of the impact of medical interventions on patients’ quality of life and symptom burden. The importance of incorporating these outcomes into clinical research and practice is underscored by their ability to capture the patient’s perspective on health status, functionality, and well-being, which may not be fully reflected by clinical measures alone. Recent work utilising patient reported outcome measures have provided novel insights into CAD. The application of the questionnaires used in my work has previously been well described in CAD populations. A systematic review and meta-analysis demonstrated an inverse relationship between baseline values or changes in health-related quality of life (HRQOL) and MACE in patients with CAD, which included assessments with EQ-5D-5L, SF-12 and SAQ [184]. Both EQ-5D-5L and SF-12 demonstrated that patients with typical angina suffer worse overall health-related quality of life when compared to patients with atypical angina and non-anginal discomfort [185]. Interestingly, the presence of obstructive versus non-obstructive CAD in this work was not shown to be associated with HRQOL. The revascularisation of patients with stable CAD, either with PCI or CABG, has been shown to improve long term general, and disease-specific, HRQOL [186]. The ORBITA II study also provided evidence of

the benefits of PCI in a blinded randomised study design of PCI versus control in patients with anginal symptoms [166]. AFD, PLD and QOLD were shown to be higher in the PCI arm of the treatment group versus control, as well as better EQ-5D-5L VAS scores. However, HRQOL assessments were not performed pre-PCI and therefore it was not possible to demonstrate whether there was an improvement following PCI.

This work highlighted a number of important findings with regards to symptomatic CAD and HRQOL. At baseline, no significant difference was found in any of the questionnaire values between the PCI or medical therapy groups. This suggests a similar level of symptom burden and general health status between the two groups, despite having different phenotypes of coronary disease (i.e. 'obstructive vs non-obstructive', as assessed by FFR). Statistically significant improvements were noted in EQ-5D-5L VAS and EI scores and SAQ PCS domains, suggesting an overall improvement in general health-related QoL in the PCI group, but not the medical therapy group. Improvements in SAQ MCS scores were numerically, but non-significantly, higher in the medical therapy group as compared with the PCI group (mean change of 7.27 vs 3.4 respectively, $p = 0.054$). With regards to CAD-specific health burden, both PCI and medical therapy groups reported a significant improvement in their quality of life, whilst only the PCI therapy group demonstrated an improvement in physical limitation and angina frequency. Patients did not have access to their baseline questionnaire responses, and so they would not be biased by previous answers. These findings suggest a clear trend in the improvement of HRQOL of patients with obstructive CAD who underwent PCI, whilst the patients who did not have obstructive disease did not experience a significant change in all

but one domain. These findings are consistent with earlier work which suggests that patients who undergo PCI for stable CAD experience an improvement in HRQOL [184]. In agreement with other work, whilst symptoms of angina improved, most patients continued to experience some angina despite PCI [166]. Overall, the findings suggest that PCI therapy successfully achieves the intended improvement of symptom burden and QoL in stable angina.

I also compared the baseline questionnaire responses to baseline physical activity data to determine whether a relationship existed between objective physical activity assessments and patient perception of health in CAD. My findings demonstrated a number of correlations between the two sets of data. First, MVPA was significantly correlated with general health EQ-5D-5L: VAS ($r = 0.363$) and angina-related physical activity limitation scores ($r = 0.378$). Second, daily step count was also found to be significantly correlated with SAQ PLD values ($r = 0.428$), while LPA was noted to be correlated the EQ-5D-5L EI values ($r = 0.336$). None of these correlations were above 0.5, which suggested a weak but statistically significant correlation. It is expected that patient reported perceptions of physical activity and disability would have some relationship with objective measures of physical activity.

Lastly, given that the objective physical activity parameters did not change significantly after PCI despite the improvements in questionnaire responses, these findings suggest that objective measures of physical activity measures are not synonymous on the individual's perception of their health. These findings therefore provide a novel perspective on a patient's activity behaviour which may differ from the patient's own perception of their activity level. Considering that previous works

have relied largely upon patient recall through questionnaires to describe their physical activity after treatment for CAD, this highlights that this method may not accurately represent an objective change in their physical activity behaviour. Similarly to the 6MWT results, the perception of their condition may have been significantly altered following their PCI procedure leading to a more positive outlook on their health, however this has not been translated into a meaningful change in their habitual physical activity behaviour.

4.5.1 Questionnaires exploring device user experience

I produced a user experience questionnaire for several reasons. First, I aimed to assess the experience of the study participants with smartwatches and smartphones. A potential limitation of the study was the possibility of recruiting participants who were already familiar with these devices, which would hinder the generalisability of my findings to an older population less acquainted with wearable technology. However, my results showed that the majority of patients (65%) had never owned a smartwatch before, suggesting that my findings are applicable to populations not familiar with such devices. In contrast, smartphone ownership was significantly higher in this cohort, with 76% of respondents using them for activities beyond texting and calling, suggesting a reasonable degree of technology literacy. Identifying comfort and wearability issues during the study helps us uncover potential barriers to consistent use. As previously described, I observed a high level of compliance throughout the study period. This aligns with the user experience findings, which indicate that the majority of study participants did not have a negative experience with their device, despite using it for an extended period. Overall, the

responses received through the user experience questionnaire indicated that most study participants had a positive experience with the physical activity monitoring device, even though they had not owned such a device in the past.

Additionally, I sought to determine whether negative experiences with wearable technology, either prior or during the study, influenced the data collected. Regarding negative responses prior to study involvement, which related to either not having used either a wearable device or smartphone use, none of the physical activity parameters showed a significant association with these factors. With regards to negative experiences during the study, the vast majority of patients (94%) did not experience discomfort with their device. Discomfort reported in the user questionnaire was found to have a negative correlation with MVPA and active calories. While this may suggest a relationship between user comfort and observed physical activity behaviour, the small number of participants who reported discomfort is likely insufficient to draw any meaningful conclusions.

4.6 Cardiac magnetic resonance imaging

The CMR component of the Virtu-5 study was intended to provide a detailed assessment of cardiac morphology and function and how this can be linked to physical activity monitoring. CMR imaging allows for the comprehensive assessment of cardiac structure and function, as well as quantifiable assessments of myocardial blood flow relevant to CAD. Due to the technical issues encountered with the CMR, which could not be resolved despite applications specialist input and attempts at post-processing optimisation, myocardial perfusion imaging and tissue

characterisation was not possible due to poor image quality. This limited the opportunity to gain deeper insights into potential differences between patients with obstructive and non-obstructive CAD, such as the presence and extent of scar burden as well as myocardial perfusion characteristics.

Despite this regrettable outcome, analysis of left ventricle structure and function was performed with each CMR study. Cardiac function estimated by ejection fraction (EF) did not significantly vary between the PCI or medical therapy groups. No patients enrolled in the study were previously diagnosed with heart failure, and none had significant symptoms related to heart failure such as breathlessness, pedal oedema, orthopnoea. Despite this, 19% of scanned study participants patients were found to have a left ventricle systolic function which would be classified within the range of heart failure with preserved ejection fraction (HFpEF), and one participant was found to have an ejection fraction of 40% which is equivalent to heart failure with reduced ejection fraction (HFrEF). Without any symptoms of fluid overload or breathlessness, these findings alone would not result in clinical diagnosis of heart failure in these individuals as per current guidelines [187]. Despite the range of systolic cardiac function observed in this cohort, there was no significant correlation between EF value and any physical activity parameters. This finding is notable considering the historical association between significant physical limitation and reduced cardiac function. However, the relationship between symptoms and imaging severity, as in many cardiac conditions including CAD, is not a perfect linear relationship, hence the need for relevant symptoms to make a formal diagnosis of any heart failure.

Whilst changes in left ventricular function were not found to correlate significantly with physical activity behaviours, a number of structural features revealed some interesting findings. Left ventricle cavity size, both in systole and diastole, as well as cardiac mass, were noted to be significantly correlated with daily step count, MVPA and AC. Aerobic exercise has been known to induce positive cardiac remodelling characteristics, such as increased left and right ventricle chamber dimensions as well as wall thickness [188]. Meyer et al demonstrated that individuals with normal ejection fraction who underwent stress echocardiography and exhibited poor exercise capacity had smaller left ventricular chamber sizes compared to those with normal exercise capacity, although cardiac mass was also noted to be higher in this group [189]. The patients being assessed were noted to have a variety of indications for stress echocardiography, with only 12% of patients having CAD. Given that the left ventricle dimensions in this cohort were either normal or within mildly elevated parameters, these findings may represent positive remodelling features associated with regular exercise and activity in keeping with their observed physical activity behaviour. Previous studies describing the association between exercise or physical activity and left ventricle dimensions are very limited. A cross-sectional study of healthy Hispanic/Latino men and women in north America demonstrated an inverse relationship between wearable technology-monitored MVPA and left ventricle mass measured by echocardiography [190]. The comparability between these findings and my own are difficult given a number of key differences, such as a healthy population and a short monitor period of 3-6 days for physical activity behaviour. Additionally, the average MVPA for this population with a mean age of 56 was 21 minutes per day versus our median value of 40 minutes per day from a cohort of patients with mean age of 65 suffering with symptomatic angina. My findings highlight that more

comprehensive work is needed to understand the relationship between physical activity behaviours and left ventricle structure and cardiac remodelling.

4.7 Multivariable analysis and physical activity

During this work, I analysed the influence of various atmospheric conditions on daily physical activity behaviours recorded with wearable technology in this cohort of patients suffering with CAD. By utilising the generalised linear mixed model approach, I was able to analyse a large, complex set of data with multiple parameters. This approach was favoured over other methods, such as generalised linear model as it allowed us to incorporate fixed and random effects which allowed us to model clustered data, such as repeated measurements on the same subjects. Linear mixed models are limited by the assumption of normality from the response variable, which was not the case in this physical activity dataset. Furthermore, generalised linear mixed models do not require an assumption of independence between each fixed and random effect, making it more suitable for real-world data.

Firstly, it allowed us to confirm my earlier findings that factors such as age, gender and BMI are highly influential when objectively measuring physical activity behaviour. Furthermore, with the minimum wear time criteria of 600 minutes applied, wear time was not independently associated with daily step count or MVPA, although it was strongly correlated with TS. My analysis did demonstrate that AC and LPA was also significantly associated with wear time, which was not demonstrated in my earlier findings. For each minute of wear time recorded, this translated to a 3 second increase in LPA and a 36 second reduction in TS. Between a maximum and

minimum value of 600 to 1440 minutes, this would indicate a possible variation of up to 42 minutes of LPA and 504 minutes of TS. The finding of such a small but statistically significant variation is likely due to the high volume of data used in the model. This further highlights the need to monitor and quantify device compliance for each study participant involved in physical activity research and ensure that device compliance is not significantly different between observed cohorts.

My analysis demonstrated several significant associations between weather parameters and daily physical activity behaviours. Average relative humidity was most frequently and often most strongly negatively correlated with changes in physical activity parameters, including daily step count, MVPA, and AC, and was positively associated with TS. Total precipitation was also found to be negatively associated with daily step count, MVPA and AC, while average gust was negatively correlated with LPA. Maximum temperature was positively correlated with daily step count and AC, while total sunshine was positively correlated with LPA. Using GLMM analysis, these correlations and associations are evaluated independently of each parameter, implying that the observed associations are intensified when they occur simultaneously. Due to the significant multicollinearity observed with total radiation in my initial analysis of the weather parameters, it is likely that the parameter is highly influenced by other parameters observed, and its independent value could therefore not be demonstrated. My results demonstrate that during favourable weather conditions such as good sunlight and warm temperature physical activity behaviour is significantly higher, while unfavourable conditions such as humidity, rain and wind speed is associated with lower physical activity patterns.

It is interesting to note the scale of the estimated impact of varying weather conditions on physical activity and how it compares with other influential factors. For example, total average humidity was noted to be most strongly associated above other weather parameters. Assuming a linear correlation, each percentage increase in average relative humidity was estimated to result in a decrease of 26 steps, half a minute of MVPA and 3.4 Kcal of AC, with an increase in TS of over half a minute. Considering the lowest rolling average value of relative humidity and highest during the study period as 57% and 97% respectively, this would indicate a potential variation in physical parameters of 1040 steps, 20 minutes MVPA and TS and 136 kcal between these two values. Daily variations in average relative humidity were noted to be even wider, from 28% to 100%, which could theoretically lead to a daily variation of up to 1872 steps, 36 minutes of MVPA and TS and 244 Kcal. With regards to total precipitation, each increase in recorded mm of precipitation was associated with a decrease in daily step count of 44 steps, half a minute of MVPA and 3.3 Kcal of AC. While rolling average values did not vary greatly (0 mm to 7 mm), daily values were noted to vary on a larger scale, with up to 47 mm of rain recorded on one occasion. This may indicate a variation of physical activity of up to 2068 steps, 23.5 minutes of MVPA and 155 Kcal of AC due to total precipitation values. In comparison, female gender was associated with an average of 1089 fewer daily steps, 15 minutes fewer of MVPA and 22 minutes of LPA with an increase in 37 minutes of TS and 454 Kcal fewer active calories. Age greater than 65 years old was correlated with an average daily reduction of 2200 steps, 23 minutes of MVPA, 13 minutes of LPA and 264 kcal, with an increase of 21 minutes in TS. In comparison to participants with a normal BMI, obesity was associated with a daily reduced average of 2735 steps, 15 minutes of MVPA and 31 minutes of LPA and 98 Kcal of AC, with

an increase of 55 minutes of TS. Therefore, the impact of variations in individual weather parameters on physical activity is comparable to that of other significant factors, such as age, gender, and BMI. This becomes even more significant when considering that these parameters can coincide, further amplifying this potential variation.

My weather records demonstrated a significant variation in atmospheric conditions throughout the study period. Seasonal variations were observed in total sunshine, total radiation and average relative humidity. Given the variation observed, it was considered reasonable to investigate the influence these conditions may have on physical activity behaviours. When the treatment groups were compared, there was a slightly lower wind speed noted in the PCI group, which while statistically significant, would likely have a very small impact on overall physical activity. Based on the generalised linear mixed models analysis, this small difference in averaged atmospheric conditions may account for less than a minute's variation in light physical activity between the two groups. However, atmospheric conditions were noted to be consistently different between pre-CCL and post-CCL monitoring periods. Overall, the differences observed would suggest that the post-CCL monitoring period experienced more favourable weather conditions, which may have significantly influenced any changes noted between baseline and follow up findings. When the findings of the generalised linear mixed model are extrapolated, the differences observed in the atmospheric parameters would account for an increase of 97 daily step count total, 1.7 minutes of MVPA, 0.45 minutes of LPA and an increase in active calories of 19 kcal, with a decrease in time sedentary of 2.1 minutes during the overall follow up period in comparison to the medical therapy

group. These differences are reassuringly relatively small and likely to have little impact on the overall significant differences in physical activity monitoring outcomes observed earlier.

As an independent factor, including when controlled for baseline versus follow up monitoring period, the presence of non-obstructive coronary disease, and thus allocation to the medical therapy group, was significantly associated with a decrease in daily step count, MVPA, LPA and AC, as well as an increase in TS. The scale of step count and MVPA variation between treatment groups was noted to be larger than any other independent factor investigated in these models with an estimated daily reduction of 2876 steps and 28 minutes of MVPA. This observation further supports the finding that the presence of non-obstructive coronary disease in our cohort of patients with IHD is more likely to have unfavourable physical activity behaviours in comparison to patients with obstructive coronary disease. The monitoring period of pre- versus post-CCL procedure was also noted to be a significant factor with regards to physical activity behaviours, independent of treatment group. Weekend versus weekday monitoring was also found to be a significant factor in influencing all physical activity parameters, with a reduction in daily step count of 1030 steps, five minutes of MVPA 20 minutes of LPA 123 Kcal of active calories. Overall, our findings suggest that each of these individual parameters contribute significantly to variations in physical activity behaviour and should be taken into consideration when designing trials and analysing data utilising objective physical activity monitoring.

4.8 Key limitations

The main limitation of this study was the small sample size. The original design of the Virtu-5 study focused on the development of a novel coronary modelling system and thus was powered to demonstrate feasibility. One of the main objectives of this work was to assess the feasibility and acceptability of prolonged wearable device physical activity monitoring, which our work was able to demonstrate the successfully. However, several analyses in our work focused on the comparison between patients with non-obstructive and obstructive CAD, a comparison which was not specifically powered for demonstrating a statistical significance between the two disease subtypes. This led to small cohort numbers that were not controlled for differences in demographics which I demonstrated had a significant impact on physical activity behaviour. Additionally, smaller cohort numbers may have led to exaggerated findings due to a small number of outliers that a larger cohort may have controlled for. In all relevant analyses, the data was assessed for normality of distribution and either parametric or non-parametric methods were applied based on these assessments, which would help to reduce the effect of outlier values.

A further limitation was the lack of blinding to the procedure characteristics during the CCL visit. All patients underwent diagnostic coronary angiography during the study with pressure wire assessment of relevant coronary arteries. It may have been theoretically possible to blind the patients as to whether they had undergone PCI or not, as described in the ORBITA trials. However, the study was planned before the first ORBITA study was published, and introduction of patient blinding during their procedure would have raised technical and ethical challenges that would have increased the complexity of our work, which would have been exacerbated

substantially during the COVID pandemic for many reasons. As such, patients were fully aware of whether or not they underwent PCI for their CAD and would therefore been exposed to a potential placebo bias. Additionally, the disease phenotype between the PCI and medical therapy was not the same, as the former had evidence of obstructive CAD and the latter was non-obstructive. In this work, I have refrained from referring to the medical therapy cohort a “control group”, as this would have suggested that an appropriate treatment was withheld for an equivalent disease as the PCI cohort. Rather, the medical therapy and PCI groups represented distinct phenotypes of CAD that were both managed appropriately. Interpretations as to the benefit of PCI versus no PCI in obstructive CAD, as made in the ORBITA trials, are not possible in this study design.

My assessment of step count accuracy provided some valuable insight into the reliability of the Fitbit Charge 4, which can be extrapolated to normal gait populations. However, our assessment was performed in a single form of walking and did not include normal or slower walking behaviours. The assessments were also performed in a controlled laboratory setting, which is not sufficient to prove adequate accuracy in free-living conditions, as mentioned before. Furthermore, while there was a focus on assessing step count accuracy, no attempt was made to assess the accuracy of the other physical activity parameters observed. Such assessments would have required additional assessment tools, such as exercise treadmills and heart rate monitors for levels of physical activity (ie LPA, MVPA), while assessments of active calories would have also required specialist caloric expenditure assessment methods. Given that these activity parameters were discussed at length for their value in this work, it would be reasonable to validate

their accuracy with relevant reference means. Lastly, our findings on device accuracy are only relevant to this specific model of physical activity tracker. Newer models of the Fitbit Charge product range have been released since the start of our work, and our findings cannot be translated to any other device manufacturer. This issue is a well-recognised limitation of assessing the accuracy of commercial devices when the market and technology develop faster than the validation can keep pace with.

Not all patients were able to complete every aspect of the Virtu-5 study design due to multiple issues encountered during the COVID pandemic. A significant frequency of staff, student and participant illness related to COVID, as well as the impact of social distancing rules, resulted in significant organisational challenges throughout the study. Out of the 37 patients recruited to our study, eight participants could not attend a CMR session directly to staffing reasons or social restrictions prior to their CCL appointment. Additionally, only 24 of the study participants successfully underwent pre- and post-CCL 6MWT assessments, requiring at least two separate hospital visits for each assessment. During the UK's management of the COVID pandemic, periods of social isolation were advised prior to elective hospital admission, which included attendances to other hospital appointments. Due to the changing rules surrounding social isolation around this time, apprehension by staff and students, as well as patients, that appointments would be inadvertently cancelled due to the pre-CCL appointments meant that every effort was aimed at avoiding clashes with advised social isolation rules. This issue was compounded with the fact that patients were usually only given 4-6 weeks' notice of their procedure date, which left us very little time to organise our CMR and 6MWT

appointments. The lack of a dedicated research space to conduct the 6MWT was also a significant factor, as we conducted our assessments in controlled hospital settings. To ensure that our assessments did not impede any nearby clinical activities, as well as inform staff of activities nearby their workplaces, the research students routinely informed relevant senior nursing staff in the relevant clinical areas of our assessment activities. Our assessments were unfortunately cancelled on a number of occasions due to an outbreak of COVID in the nearby unit, resulting in an infection control lockdown of the surrounding area which included our assessment area. These issues reduced the number of participants from our already small patient group in these analyses even further. Regarding both the CMR and 6MWT analyses, only the physical activity data of participants who completed these assessments were analysed for associations with these measures.

A further point of limitation includes the design of the Virtu-5 study. The data for the post-PCI period described occurred following a 3 month “cooling off” period, the intention for which would allow the study PCI group to recover from their procedure and acclimate to a potential new level of physical activity behaviour with their angina burden reduced theoretically reduced. However, there may have been valuable insights gained from presenting data during this cooling off period, including the recovery from the procedure, as well as short term improvements in physical activity that may have been short lived and returned to their baseline activity. These findings could illustrate the need, or not, for a cooling off period at all, including the appropriate length of time, which may inform future works in this area. Additionally, following their cath lab procedures, there was no specific protocol regarding the specific management of patients within the medical therapy group. Patients were

managed on a case-by-case basis as to how their medication was either optimised, reduced or maintained, depending on the clinician's assessment of their symptoms. It was not recorded whether the operator's clinical assessment of the study subject's presenting symptoms was indeed angina, which in the presence of non-obstructive coronary artery disease would suggest an alternative pathology such as microvascular angina or coronary spasm, or whether in the light of their diagnostic procedure a non-cardiac cause was suspected, such as gastroesophageal reflux disease or musculoskeletal pain. The distinction between these two diagnostic categories would have led to significantly different management strategies, one of which would have been the reconciliation of anti-anginal medication in patients who angina was not thought to be the cause. The reduction of anti-anginal medication such as beta-blockers, which have well documented side effects such as lethargy, dizziness and sleep disturbance, all of which may have a significant effect on daily physical activity behaviour.

Lastly, I was unable to control for the effect of the COVID pandemic on free-living physical activity behaviour. While one method considered was to map the national lockdown dates across the study period, the rules of lockdown were not always clear and public advice changed frequently throughout the pandemic, as well as the initiation of local tiered lockdown rules. Furthermore, it was not possible to estimate the psychological impact of a frightening global pandemic on the everyday lives of the UK population which would have likely had a significant impact on whether individuals felt comfortable outside of their homes or in public spaces.

CHAPTER 5

5. Conclusion and further work

5.1 Key findings

Whilst there have been considerable advances in diagnostic tools for cardiovascular disease, assessing CAD symptom burden remains essential for defining disease severity and evaluating treatment response. There are several limitations to the current approach to CAD assessment which make it challenging to quantify the benefit of coronary revascularisation in stable angina. My work demonstrates that it is feasible to monitor patients suffering with coronary disease over prolonged periods of time with the intention of recording baseline and follow up physical activity behaviours. Study participants achieved high levels of device compliance throughout the study period which did not diminish over time. It was found that the use of minimum wear time cut-off to screen wearable physical activity data resulted in reduced bias in most physical activity parameters, although TS remained significantly correlated with wear time until much stricter cut-offs were used. The popular minimum wear time cut-off value 600 minutes was considered an appropriate standard for our work as reasonably stricter values did not improve data quality, while much higher cut-off values and near all-day device wearing were found to greatly reduced the available data with little benefit to most of the key physical activity parameters.

This work provided objective data on the impact of PCI on physical activity behaviours in patients suffering with symptomatic CAD. Wearable physical activity

monitoring provided a range of physical activity parameters which provided novel insights into a range of physical activity behaviours relevant to cardiovascular disease. This cohort of patients demonstrated a wide variety of physical activity behaviours and trends. Patients found to have physiologically significant CAD were associated with higher levels of healthy physical activity, particularly moderate to vigorous physical activity and active calories. However, PCI therapy did not significantly change physical activity behaviours from baseline to follow up at three to six months. This indicates that physical activity behaviour may be helpful to risk stratify patients before undergoing assessment for PCI, but does not necessarily indicate treatment response.

Comparisons between clinical assessments of CAD and objective physical activity monitoring revealed a number of novel insights. Patient reported outcomes indicated that participants who received PCI experienced a significant positive change to their general and disease-specific health related quality of life. This was despite the fact that their physical activity behaviour did not change, indicating a disparity between patient-perceived physical activity and objective measures. Furthermore, CMR assessment indicated a possible correlation between favourable physical activity behaviours and features consistent with positive remodelling of the left ventricle structure. Our findings strengthen the link between objective physical activity behaviour and health related quality of life, which further supports the potential use of objective physical activity monitoring as meaningful clinical end points for future research studies which aim to investigate the treatment of symptomatic CAD.

Our 6MWT analysis demonstrated a significant improvement in the exercise tolerance of patients who underwent either PCI or continued medical therapy. These 6MWD values were also found to be correlated with physical activity behaviours collected at baseline. Given that there were no changes in physical activity behaviour parameters between baseline and follow up assessment, this again highlights the difference in assessing exercise capacity and exercise / activity behaviour. Our step count accuracy work during the 6MWT assessments also demonstrated the good reliability with step count measurement using the Fitbit Charge 4 device in a laboratory setting. As this is the first work that has reported the recommended analysis of accuracy in a lab-based setting for this device, setting the stage for further validation in a free-living environment.

Lastly, I demonstrated the impact of several influential factors on physical activity behaviour, including demographic, temporal, and atmospheric factors. Demographic features such as gender, age and BMI were all significantly and independently correlated with physical activity behaviours, highlighting the need to ensure that any work that measures objective physical activity controls for these characteristics when comparing treatment groups. Weather characteristics were also significantly correlated with different physical activity behaviours, with favourable weather conditions associated with positive physical activity behaviours, and unfavourable atmospheric conditions associated with poorer activity. These findings are relevant when considering the impact of treatment between baseline and follow up measures, highlighting that seasonal variations in weather could significantly influence physical activity characteristics leading which may confound such work. Lastly, physical activity was shown to vary significantly depending on what day of the week was

being monitored. These results highlight that studies which utilise physical activity data collected over shorter monitoring periods must consider the impact of when their data was collected.

5.2 Further work

Given that the Virtu-5 study was designed to assess the feasibility of wearable technology in a small group of patient with CAD, a larger cohort study is warranted to confirm the findings in this thesis. If my findings are replicated in a larger population of CAD, this would support the use of objective physical activity monitoring as a tool for risk stratifying patient before CCL procedures in both clinical and research settings, as well as monitoring physical activity behaviour before and after revascularisation. Furthermore, several research opportunities and questions have arisen from the work carried out.

5.2.1 Step count accuracy in free-living environment

There remains an interest in providing researchers and the general public with robust assessments of wearable device accuracy in assessing physical activity. With the evidence provided in this work illustrating the step count accuracy of the Fitbit Charge 4 in a laboratory-based environment, the next logical step is to assess its accuracy in free-living conditions. According to current expert consensus described earlier, this would require video monitoring of study participants in their own dwelling for over a 24-hour period. While time-intensive, this method would allow for a robust assessment of step count accuracy in real-world settings. However, given the

development of newer models of the Fitbit wearable devices, including the Fitbit Charge 5 and Charge 6, as well as the discontinuation of the Charge 4 model, the value of assessing the accuracy of an outdated device is likely to be limited. The need to produce timely assessments of device accuracy in free living environments in the current climate of commercial technology development is therefore sorely needed in order to consider such devices as reliable clinical assessment tools.

5.2.2 Physical activity and non-invasive therapy for angina relief

My work focused on the use of coronary revascularisation as a treatment for angina refractory to the standard medical therapy approach to CAD. While my findings suggest that PCI is associated with an improvement in angina burden and exercise tolerance, it remains unclear whether relief of angina burden leads to significant changes in objective physical activity behaviours.

Anti-anginal medications are the first line of treatment for patients suffering with angina. Given that access to anti-anginal medication is more readily available than PCI, many patients suffering with angina are already on at least one such medication before they are seen by a cardiology specialist. The impact of anti-anginal medication on physical activity behaviours in symptomatic CAD is an unknown entity. The ORBITA study demonstrated that PCI did not significantly improve exercise capacity in patients who were already prescribed optimised medical therapy for angina relief. Characterising the physical activity behaviours of patients before and after commencing anti-anginal therapy in a step-wise fashion may reveal further insights into the relief of angina and its association with physical activity behaviours.

This could help patients and clinicians understand the impact of anti-anginal medication on their overall health and wellbeing. By analysing the responses to anti-anginal therapy through physical activity monitoring, it may also provide insights into characteristic patterns which might provide predictive information on whether PCI therapy would be effective in controlling their symptoms (i.e. patients who do not respond significantly to initial anti-anginal therapy despite reaching target doses may be less likely to have benefit to PCI).

5.2.3 Microvascular angina

This work demonstrated that patients with symptomatic angina with non-obstructive coronary artery disease had poorer physical activity behaviours in comparison to patients with obstructive coronary disease. While one theory posited for this was that a significant proportion of these patients may have been suffering from microvascular angina, we were not able to confirm this with invasive testing. Given the disparity in physical activity traits between obstructive and non-obstructive coronary artery disease observed in our cohort, it would be worth exploring this subgroup of CAD patients further in a larger cohort. Investigating whether the presence of microvascular dysfunction based on invasive physiological testing is correlated with poor physical activity levels may help to identify these patients at an earlier stage. Given the diagnostic challenges associated with microvascular CAD, identifying important risk factors which help clinicians identify high-risk groups for microvascular dysfunction may help to improve patient selection for targeted therapies in future research. Additionally, whether these patients respond to anti-anginal therapies in the same way obstructive CAD patients do in terms of physical

activity may also be of interest to clinicians to help distinguish the two phenotypes of IHD.

5.3 Final conclusion

Understanding the value of wearable physical activity monitoring in symptomatic CAD may provide clear benefits for patients and clinicians. The Virtu-5 study has shown that prolonged wearable activity monitoring is feasible in the CAD population and can offer meaningful, objective insights into physical activity behaviours along the patient treatment journey. The Fitbit Charge 4 device demonstrated good step count accuracy in laboratory testing and was deemed acceptable by the recruited cohort. My findings revealed that obstructive, FFR positive CAD was associated with higher levels of positive physical activity in comparison to patients suffering with angina but had FFR negative disease. Furthermore, treating angina with PCI in stable CAD did not result in significant changes in objective physical activity behaviours. This is despite clear improvements in questionnaire responses and 6MWT results following PCI. Additionally, several demographic, temporal, device-related, and weather factors significantly influence recorded physical activity parameters, which need to be considered and controlled for in research studies using these patient assessment methods. Further efforts to understand the connections between physical activity and angina relief, as well as symptomatic non-obstructive CAD, are warranted. In summary, objective physical activity monitoring with wearable device technology appears to be a promising tool for assessing physical activity of patients with symptomatic CAD and can provide novel insights into physical activity behaviour and health status.

References

1. Loukas M, Sharma A, Blaak C, Sorenson E, Mian A. The clinical anatomy of the coronary arteries. *J Cardiovasc Transl Res*. 2013 Apr;6(2):197-207. doi: 10.1007/s12265-013-9452-5.
2. Angelini P. Normal and anomalous coronary arteries: definitions and classification. *Am Heart J*. 1989;117:418–34. doi: 10.1016/0002-8703(89)90789-8.
3. Krüger-Genge A, Blocki A, Franke RP, Jung F. Vascular Endothelial Cell Biology: An Update. *Int J Mol Sci*. 2019 Sep 7;20(18):4411. doi: 10.3390/ijms20184411. PMID: 31500313; PMCID: PMC6769656.
4. Metz RP, Patterson JL, Wilson E. Vascular smooth muscle cells: isolation, culture, and characterization. *Methods Mol Biol*. 2012;843:169-76. doi: 10.1007/978-1-61779-523-7_16
5. Majesky MW, Dong XR, Høglund V, Mahoney WM Jr, Daum G. The adventitia: a dynamic interface containing resident progenitor cells. *Arterioscler Thromb Vasc Biol*. 2011 Jul;31(7):1530-9. doi: 10.1161/ATVBAHA.110.221549.
6. Gimbrone MA, García-Cardena G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res*. 2016 Feb 19;118(4):620–36. doi: 10.1161/CIRCRESAHA.115.306301
7. Libby P. Inflammation in atherosclerosis. *Nature*. 2002 Dec 19;420(6917):868–74. doi: 10.1038/nature01323
8. Kruth HS. The fate of lipoprotein cholesterol entering the arterial wall. *Curr Opin Lipidol*. 1997 Oct;8(5):246–52. doi: 10.1097/00041433-199710000-00002

9. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res*. 2016 Feb 19;118(4):692–702. doi: 10.1161/CIRCRESAHA.115.306361
10. Berliner JA, Subbanagounder G, Leitinger N, Watson AD, Vora D. Evidence for a Role of Phospholipid Oxidation Products in Atherogenesis. *Trends Cardiovasc Med*. 2001 Apr 1;11(3):142–7. doi: 10.1016/s1050-1738(01)00098-6
11. Demer LL. Vascular calcification and osteoporosis: inflammatory responses to oxidized lipids. *Int J Epidemiol*. 2002 Aug;31(4):737–41. doi: 10.1093/ije/31.4.737
12. British Heart Foundation: UK Factsheet January 2020 [Internet]. [cited 2024 Jul 20]. Available from: <https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf>
13. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008 Feb 12;117(6):743-53. doi: 10.1161/CIRCULATIONAHA.107.699579.
14. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014 Jun 24;129(25 Suppl 2):S49-73. doi: 10.1161/01.cir.0000437741.48606.98.
15. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021 Feb 23;143(8):e254-e743. doi: 10.1161/CIR.0000000000000950.

16. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation*. 2006 Jan 31;113(4):499-506. doi: 10.1161/CIRCULATIONAHA.105.574087
17. McPherson R, Tybjaerg-Hansen A. Genetics of Coronary Artery Disease. *Circ Res*. 2016 Feb 19;118(4):564-78. doi: 10.1161/CIRCRESAHA.115.306566.
18. Davies SW. Clinical presentation and diagnosis of coronary artery disease: stable angina. *Br Med Bull*. 2001 Oct 1;59(1):17–27. doi: 10.1093/bmb/59.1.17
19. Corrado D, Thiene G, Pennelli N. Sudden death as the first manifestation of coronary artery disease in young people (≤ 35 years). *Eur Heart J*. 1988 Dec 2;9(suppl N):139–44. doi: 10.1093/eurheartj/9.suppl_n.139
20. Campeau L. Letter: Grading of angina pectoris. *Circulation*. 1976 Sep;54(3):522–3.
21. National Institute for Health and Care Excellence. Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis [Internet]. [London]: NICE; 2016 [Updated November 2016, cited 2020 July 1] (Clinical guideline [CG95]). Available from: nice.org.uk/guidance/cg95
22. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020 Jan 14;41(3):407–77
23. National Institute for Health and Care Excellence. *Stable angina: management* [Internet]. [London]: NICE; 2010 [Updated August 2016, cited 2020 July 1]

(Clinical guideline [CG95]). Available from: nice.org.uk/guidance/cg126 [UPDATE THIS]

24. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008 Nov 18;52(21):1724–32. doi: 10.1016/j.jacc.2008.07.031
25. Kočka V. The coronary angiography – An old-timer in great shape. *Cor Vasa*. 2015 Dec 1;57(6):e419–24.
26. Mark DB, Nelson CL, Califf RM, Harrell FE, Lee KL, Jones RH, et al. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. *Circulation*. 1994 May 1;89(5):2015–25. doi: 10.1161/01.cir.89.5.2015
27. Noto TJ, Johnson LW, Krone R, Weaver WF, Clark DA, Kramer JR, et al. Cardiac catheterization 1990: A report of the registry of the society for cardiac angiography and interventions (SCA&I). *Cathet Cardiovasc Diagn*. 1991;24(2):75–83. doi: 10.1002/ccd.1810240202.
28. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *The Lancet*. 2011 Apr 23;377(9775):1409–20. doi: 10.1016/S0140-6736(11)60404-2.

29. Yilmaz A, Sechtem U. Ischaemia testing in patients with stable angina: which test for whom? *Heart*. 2014 Dec 1;100(23):1886–96. doi: 10.1136/heartjnl-2013-304255.
30. Agostini D, Marie PY, Ben-Haim S, Rouzet F, Songy B, Giordano A, et al. Performance of cardiac cadmium-zinc-telluride gamma camera imaging in coronary artery disease: a review from the cardiovascular committee of the European Association of Nuclear Medicine (EANM). *Eur J Nucl Med Mol Imaging*. 2016 Dec;43(13):2423-2432. doi: 10.1007/s00259-016-3467-5
31. Nudi F, Iskandrian AE, Schillaci O, Peruzzi M, Frati G, Biondi-Zoccai G. Diagnostic accuracy of myocardial perfusion imaging with CZT technology: systemic review and meta-analysis of comparison with invasive coronary angiography. *JACC Cardiovasc. Imaging*. 2017;10:787–794.
32. Otaki Y, Betancur J, Sharir T, Hu LH, Gransar H, Liang JX, et al. 5-Year Prognostic Value of Quantitative Versus Visual MPI in Subtle Perfusion Defects: Results From REFINE SPECT. *JACC Cardiovasc Imaging*. 2020 Mar;13(3):774-785. doi: 10.1016/j.jcmg.2019.02.028
33. AIUM Curriculum for Fundamentals of Ultrasound Physics and Instrumentation. *J Ultrasound Med*. 2019 Aug;38(8):1933-1935. doi: 10.1002/jum.15088.
34. Senior R, Monaghan M, Becher H, Mayet J, Nihoyannopoulos P; British Society of Echocardiography. Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the British Society of Echocardiography. *Heart*. 2005 Apr;91(4):427-36. doi: 10.1136/hrt.2004.044396
35. Steeds RP, Wheeler R, Bhattacharyya S, Reiken J, Nihoyannopoulos P, Senior R, et al. Stress echocardiography in coronary artery disease: a practical guideline

- from the British Society of Echocardiography. *Echo Res Pract.* 2019 Jun 1;6(2):G17-G33. doi: 10.1530/ERP-18-0068
36. Ridgway JP. Cardiovascular magnetic resonance physics for clinicians: part I. *J Cardiovasc Magn Reson.* 2010 Nov 30;12(1):71. doi: 10.1186/1532-429X-12-71
37. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson.* 2020 Feb 24;22(1):17. doi: 10.1186/s12968-020-00607-1
38. Klinke V, Muzzarelli S, Lauriers N, Locca D, Vincenti G, Monney P, et al. Quality assessment of cardiovascular magnetic resonance in the setting of the European CMR registry: description and validation of standardized criteria. *J Cardiovasc Magn Reson.* 2013 Jun 20;15(1):55. doi: 10.1186/1532-429X-15-55
39. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol.* 2019 May;26(8):824-835. doi: 10.1177/2047487318825350
40. Staudt A, Stock K, Gande N, Bernar B, Hochmayr C, Pechlaner R, et al. Impact of lifestyle and cardiovascular risk factors on early atherosclerosis in a large cohort of healthy adolescents: The Early Vascular Ageing (EVA)-Tyrol Study. *Atherosclerosis.* 2020 Jul;305:26-33. doi: 10.1016/j.atherosclerosis.2020.05.011
41. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA.* 2006; 296: 1885–1899. doi: 10.1001/jama.296.15.1885

42. Jacobs DR Jr, Gallaher DD. Whole grain intake and cardiovascular disease: a review. *Curr Atheroscler Rep.* 2004; 6: 415–423. doi: 10.1007/s11883-004-0081-y.
43. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr.* 2006; 136: 2588–2593
44. Bouabdallaoui N, Messas N, Greenlaw N, Ferrari R, Ford I, Fox KM, et al. Impact of smoking on cardiovascular outcomes in patients with stable coronary artery disease. *Eur J Prev Cardiol.* 2021 Oct 25;28(13):1460-1466. doi: 10.1177/2047487320918728
45. Herrod PJJ, Lund JN, Phillips BE. Time-efficient physical activity interventions to reduce blood pressure in older adults: a randomised controlled trial. *Age Ageing.* 2021 May 5;50(3):980-984. doi: 10.1093/ageing/afaa211.
46. Zhu X, Zhao L, Chen J, Lin C, Lv F, Hu S, et al. The Effect of Physical Activity on Glycemic Variability in Patients With Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne).* 2021 Nov 17;12:767152. doi: 10.3389/fendo.2021.767152.
47. Jakicic JM, Rogers RJ, Collins AM, Jackson R. Strategies for Physical Activity Interventions in the Treatment of Obesity. *Endocrinol Metab Clin North Am.* 2020 Jun;49(2):289-301. doi: 10.1016/j.ecl.2020.02.004.
48. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002;346:793–801. doi: 10.1056/NEJMoa011858.
49. Lee DC, Sui X, Ortega FB, Kim YS, Church TS, Winett RA, et al. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-

- cause mortality in men and women. *Br J Sports Med.* 2011;45:504–510. doi: 10.1136/bjsm.2009.066209.
50. Di Francescomarino S, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. *Sports Med.* 2009;39(10):797-812. doi: 10.2165/11317750-000000000-00000
51. Napoli C, de Nigris F, Williams-Ignarro S, Pignalosa O, Sica V, Ignarro LJ. Nitric oxide and atherosclerosis: an update. *Nitric Oxide.* 2006 Dec;15(4):265-79. doi: 10.1016/j.niox.2006.03.011
52. Gonzalo-Encabo P, Maldonado G, Valadés D, Ferragut C, Pérez-López A. The Role of Exercise Training on Low-Grade Systemic Inflammation in Adults with Overweight and Obesity: A Systematic Review. *Int J Environ Res Public Health.* 2021 Dec 16;18(24):13258. doi: 10.3390/ijerph182413258
53. Berzosa C, Cebrián I, Fuentes-Broto L, Gómez-Trullén E, Piedrafita E, Martínez-Ballarín E, et al. Acute exercise increases plasma total antioxidant status and antioxidant enzyme activities in untrained men. *J Biomed Biotechnol.* 2011;2011:540458. doi: 10.1155/2011/540458
54. Ribeiro F, Ribeiro IP, Alves AJ, do Céu Monteiro M, Oliveira NL, Oliveira J, et al. Effects of exercise training on endothelial progenitor cells in cardiovascular disease: a systematic review. *Am J Phys Med Rehabil.* 2013 Nov;92(11):1020-30. doi: 10.1097/PHM.0b013e31829b4c4f.
55. National Institute for Health and Care Excellence. *Cardiovascular disease: risk assessment, reduction, including lipid modification.* [Internet]. [London]: NICE; 2014 [Updated May 2023, cited 2023 June 21] (Clinical guideline [CG181]). Available from: nice.org.uk/guidance/cg181

56. National Institute for Health and Care Excellence. *Physical activity: exercise referral schemes*. [Internet]. [London]: NICE; 2014 [Published September 2014, cited 2023 June 21] (Clinical guideline [PH54]). Available from: <https://www.nice.org.uk/guidance/ph54/>
57. Gandhi MM, Lampe FC, Wood DA. Incidence, clinical characteristics, and short-term prognosis of angina pectoris. *Heart*. 1995;73:193-198. doi: 10.1136/hrt.73.2.193.
58. The British Heart Foundation. *The National Audit of Cardiac Rehabilitation: Quality and Outcomes Report 2019*. [Internet]. London. The British Heart Foundation; 2019 [cited 2023 June 26]. Available from <https://www.bhf.org.uk/-/media/files/information-and-support/publications/hcps/nacr-quality-and-outcomes-report-2019.pdf?rev=8199a23df720465fb928be44cde83258>
59. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001 Apr 4;285(13):1711-8. doi: 10.1001/jama.285.13.1711
60. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994 Nov 19;344(8934):1383-9
61. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998 Nov 5;339(19):1349-57. doi: 10.1056/NEJM199811053391902.

62. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004 Nov 11;351(20):2058-68. doi: 10.1056/NEJMoa042739
63. Fanaroff AC, Hasselblad V, Roe MT, Bhatt DL, James SK, Steg PG, et al. Antithrombotic agents for secondary prevention after acute coronary syndromes: A systematic review and network meta-analysis. *Int J Cardiol*. 2017 Aug 15;241:87-96. doi: 10.1016/j.ijcard.2017.03.046
64. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med*. 2018 Oct 18;379(16):1519-1528. doi: 10.1056/NEJMoa1803955
65. Gaziano JM, Brotans C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018 Sep 22;392(10152):1036-1046. doi: 10.1016/S0140-6736(18)31924-X
66. ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med*. 2018 Oct 18;379(16):1529-1539. doi: 10.1056/NEJMoa1804988
67. Bavry AA, Gong Y, Handberg EM, Cooper-DeHoff RM, Pepine CJ. Impact of aspirin according to type of stable coronary artery disease: insights from a large international cohort. *Am J Med*. 2015 Feb;128(2):137-43. doi: 10.1016/j.amjmed.2014.09.028
68. Bavry AA, Elgendy IY, Elbez Y, Mahmoud AN, Sorbets E, Steg PG, et al. Aspirin and the risk of cardiovascular events in atherosclerosis patients with and without

- prior ischemic events. *Clin Cardiol.* 2017 Sep;40(9):732-739. doi: 10.1002/clc.22724.
69. Murrell W. Nitro-glycerine as a remedy for angina pectoris. *Lancet.* 1879;113:80–81. doi: 10.1016/S0140-6736(02)46032-1
70. Feldman RL, Pepine CJ, Conti CR. Magnitude of Dilatation of Large and Small Coronary Arteries of Nitroglycerin. *Circulation.* 1981;64:324–333. doi: 10.1161/01.CIR.64.2.324
71. Pascual I, Moris C, Avanzas P. Beta-Blockers and Calcium Channel Blockers: First Line Agents. *Cardiovasc Drugs Ther.* 2016;30:357–365. doi: 10.1007/s10557-016-6682-1
72. Banon D, Filion KB, Budlovsky T, Franck C, Eisenberg MJ. The Usefulness of Ranolazine for the Treatment of Refractory Chronic Stable Angina Pectoris as Determined from a Systematic Review of Randomized Controlled Trials. *Am J Cardiol.* 2014;113:1075–1082. doi: 10.1016/j.amjcard.2013.11.070
73. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of Ivabradine, a New Selective If Inhibitor, Compared with Atenolol in Patients with Chronic Stable Angina. *Eur Heart J.* 2005;26:2529–2536. doi: 10.1093/eurheartj/ehi586
74. Divakaran S., Loscalzo J. The Role of Nitroglycerin and Other Nitrogen Oxides in Cardiovascular Therapeutics. *J Am Coll Cardiol.* 2017;70:2393–2410. doi: 10.1016/j.jacc.2017.09.1064
75. Rahimtoola SH. Coronary bypass surgery for chronic angina--1981. A perspective. *Circulation.* 1982 Feb;65(2):225–41. doi: 10.1161/01.cir.65.2.225
76. Ramadan R, Boden WE., Kinlay S. Management of Left Main Coronary Artery Disease. *J Am Heart Assoc.* 7(7):e008151 doi: 10.1161/JAHA.117.008151.

77. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979 Jul 12;301(2):61–8. doi: 10.1056/NEJM197907123010201
78. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994 Aug 25;331(8):496–501 doi: 10.1056/NEJM199408253310802
79. BARI Investigators. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol*. 2007 Apr 17;49(15):1600–6. doi: 10.1016/j.jacc.2006.11.048.
80. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation*. 2010 Sep 7;122(10):949–57. doi: 10.1161/CIRCULATIONAHA.109.911669.
81. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes; The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020 Jan 14;41(3):407–77. doi: 10.1093/eurheartj/ehz825.
82. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol*. 2006 Oct 3;48(7):1319–25. doi: 10.1016/j.jacc.2006.06.050.

83. Wallentin L, Lindhagen L, Årnström E, Husted S, Janzon M, Johnsen SP, et al. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. *Lancet Lond Engl*. 2016 Oct 15;388(10054):1903–11. doi: 10.1016/S0140-6736(16)31276-4.
84. Fox KAA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JGP, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol*. 2010 Jun 1;55(22):2435–45. doi: 10.1016/j.jacc.2010.03.007.
85. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019 Oct 10;381(15):1411–21. doi: 10.1056/NEJMoa1907775.
86. Jeremias A, Kaul S, Rosengart TK, Gruberg L, Brown DL. The Impact of Revascularization on Mortality in Patients with Nonacute Coronary Artery Disease. *Am J Med*. 2009 Feb 1;122(2):152–61. doi: 10.1016/j.amjmed.2008.07.027.
87. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007 Apr 12;356(15):1503–16. doi: 10.1056/NEJMoa070829.
88. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. Heart Disease and Stroke Statistics—2007 Update. *Circulation*. 2007 Feb 6;115(5):e69–171. doi: 10.1161/CIRCULATIONAHA.106.179918.
89. Feldman DN, Gade CL, Slotwiner AJ, Parikh M, Bergman G, Wong SC, et al. Comparison of outcomes of percutaneous coronary interventions in patients of

- three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). *Am J Cardiol*. 2006 Nov 15;98(10):1334–9. doi: 10.1016/j.amjcard.2006.06.026.
90. Cole JA, Smith SM, Hart N, Cupples ME. Systematic review of the effect of diet and exercise lifestyle interventions in the secondary prevention of coronary heart disease. *Cardiol Res Pract*. 2010 Dec 19;2011:232351. doi: 10.4061/2011/232351.
91. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *The Lancet*. 2018 Jan 6;391(10115):31–40. doi: 10.1016/S0140-6736(17)32714-9.
92. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VII. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. *J Am Coll Cardiol*. 1986 Jan;7(1):103–13. doi: 10.1016/s0735-1097(86)80266-2.
93. Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization; The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014 Oct 1;35(37):2541–619. doi: 10.1093/eurheartj/ehu278.
94. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, et al. Measurement of fractional flow reserve to assess the functional

- severity of coronary-artery stenoses. *N Engl J Med*. 1996 Jun 27;334(26):1703–8. doi: 10.1056/NEJM199606273342604.
95. De Bruyne B, Fearon WF, Pijls NHJ, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014 Sep 25;371(13):1208–17. doi: 10.1056/NEJMoa1408758.
96. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015 Dec 1;36(45):3182–8. doi: 10.1093/eurheartj/ehv452.
97. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van't Veer M, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *N Engl J Med*. 2009 Jan 15;360(3):213–24. doi: 10.1056/NEJMoa0807611.
98. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med*. 2018 Jul 19;379(3):250-259. doi: 10.1056/NEJMoa1803538.
99. Nam J, Briggs A, Layland J, Oldroyd KG, Curzen N, Sood A, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. *Cost Eff Resour Alloc*. 2015 Nov 14;13:19. doi: 10.1186/s12962-015-0045-9.
100. Villines TC. Can CT-derived FFR better inform clinical decision-making and improve outcomes in stable ischaemic heart disease? *Eur Heart J*. 2018 Nov 1;39(41):3712–4. doi: 10.1093/eurheartj/ehy559.

101. Agasthi P, Kanmanthareddy A, Khalil C, Egbuche O, Yarlagadda V, Sachdeva R, et al. Comparison of Computed Tomography derived Fractional Flow Reserve to invasive Fractional Flow Reserve in Diagnosis of Functional Coronary Stenosis: A Meta-Analysis. *Sci Rep*. 2018 Aug 1;8(1):11535. doi: 10.1038/s41598-018-29910-9.
102. Ihdayhid AR, Norgaard BL, Gaur S, Leipsic J, Nerlekar N, Osawa K, et al. Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography. *Radiology*. 2019 Jun 11;292(2):343–51. doi: 10.1148/radiol.2019182264.
103. National Institute of Health and Care Excellence : HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography [Internet] [London]: NICE; 2017 [Published February 2017, cited 2023 July 14] (Medical technologies guidance [MTG32]) [Internet]. Available from: <https://www.nice.org.uk/guidance/mtg32>
104. Morris PD, Ryan D, Morton AC, Lycett R, Lawford PV, Hose DR, et al. Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary lesions: results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. *JACC Cardiovasc Interv*. 2013 Feb;6(2):149–57. doi: 10.1016/j.jcin.2012.08.024.
105. Morris PD, Silva Soto DA, Feher JFA, Rafiroiu D, Lungu A, Varma S, et al. Fast Virtual Fractional Flow Reserve Based Upon Steady-State Computational Fluid Dynamics Analysis: Results From the VIRTU-Fast Study. *JACC Basic Transl Sci*. 2017 Aug 1;2(4):434–46. doi: 10.1016/j.jacbts.2017.04.003.
106. Garcia D, Harbaoui B, van de Hoef TP, Meuwissen M, Nijjer SS, Echavarria-Pinto M, et al. Relationship between FFR, CFR and coronary microvascular

- resistance – Practical implications for FFR-guided percutaneous coronary intervention. *PLoS One*. 2019 Jan 7;14(1):e0208612. doi: 10.1371/journal.pone.0208612.
107. Pinheiro Volp AC, Esteves de Oliveira FC, Duarte Moreira Alves R, Esteves EA, Bressan J. Energy expenditure: components and evaluation methods. *Nutr Hosp*. 2011;26:430–440. doi: 10.1590/S0212-16112011000300002.
108. Nelms M, Sucher KP, Lacey K, Roth SL. *Nutrition therapy and pathophysiology*. 2nd ed. Belmont (CA): Wadsworth, Cengage Learning; 2011
109. Ndahimana D, Kim EK. Measurement Methods for Physical Activity and Energy Expenditure: a Review. *Clin Nutr Res*. 2017 Apr;6(2):68-80. doi: 10.7762/cnr.2017.6.2.68.
110. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990 Aug;13(8):555-65. doi: 10.1002/clc.4960130809.
111. McKenzie TL. Use of direct observation to assess physical activity. In: Welk GJ (editor): *Physical activity assessments for health-related research*, Champaign, IL: Human Kinetics Publisher, Inc.; 2002, pp. 179–195.
112. Kaiyala KJ, Ramsay DS. Direct animal calorimetry, the underused gold standard for quantifying the fire of life. *Comp Biochem Physiol A Mol Integr Physiol*. 2011;158:252–264. doi: 10.1016/j.cbpa.2010.04.013.
113. Leonard WR. Laboratory and field methods for measuring human energy expenditure. *Am J Hum Biol*. 2012;24:372–384. doi: 10.1002/ajhb.22260.
114. Park J, Kazuko IT, Kim E, Kim J, Yoon J. Estimating free-living human energy expenditure: practical aspects of the doubly labeled water method and its applications. *Nutr Res Pract*. 2014;8:241–248. doi: 10.4162/nrp.2014.8.3.241.

115. Ndahimana D, Lee SH, Kim YJ, Son HR, Ishikawa-Takata K, Park J, et al. Accuracy of dietary reference intake predictive equation for estimated energy requirements in female tennis athletes and non-athlete college students: comparison with the doubly labeled water method. *Nutr Res Pract*. 2017;11(1):51–56. doi: 10.4162/nrp.2017.11.1.51.
116. Colbert LH, Matthews CE, Havighurst TC, Kim K, Schoeller DA. Comparative validity of physical activity measures in older adults. *Med Sci Sports Exerc*. 2011;43:867–876. doi: 10.1249/MSS.0b013e3181fc7162.
117. Khan Y, Ostfeld AE, Lochner CM, Pierre A, Arias AC. Monitoring of Vital Signs with Flexible and Wearable Medical Devices. *Adv Mater*. 2016 Jun;28(22):4373-95. doi: 10.1002/adma.201504366
118. Park Y, Lee S, Park J. Recent progress in wireless sensors for wearable electronics. *Sensors (Basel)*. 2019 Oct 09;19(20) doi: 10.3390/s19204353
119. Tamura T, Maeda Y, Sekine M, Yoshida M. Wearable photoplethysmographic sensors—past and present. *Electronics*. 2014;3:282–302. doi: 10.3390/electronics3020282
120. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas*. 2007 Mar;28(3):R1-39. doi: 10.1088/0967-3334/28/3/R01
121. Elgendi M. On the analysis of fingertip photoplethysmogram signals. *Curr Cardiol Rev*. 2012 Feb;8(1):14-25. doi: 10.2174/157340312801215782
122. Elgendi M, Fletcher R, Liang Y, Howard N, Lovell NH, Abbott D, et al. The use of photoplethysmography for assessing hypertension. *NPJ Digit Med*. 2019 Jun 26;2:60. doi: 10.1038/s41746-019-0136-7

123. Karvonen J, Vuorimaa T. Heart rate and exercise intensity during sports activities. Practical application. *Sports Med.* 1988 May;5(5):303-11. doi: 10.2165/00007256-198805050-00002
124. Brage S, Westgate K, Franks PW, Stegle O, Wright A, Ekelund U, et al. Estimation of Free-Living Energy Expenditure by Heart Rate and Movement Sensing: A Doubly-Labelled Water Study. *PLoS One.* 2015 Sep 8;10(9):e0137206. doi: 10.1371/journal.pone.0137206
125. Chevance G, Golaszewski NM, Tipton E, Hekler EB, Buman M, Welk GJ, et al. Accuracy and Precision of Energy Expenditure, Heart Rate, and Steps Measured by Combined-Sensing Fitbits Against Reference Measures: Systematic Review and Meta-analysis. *JMIR Mhealth Uhealth.* 2022 Apr 13;10(4):e35626. doi: 10.2196/35626
126. Feehan LM, Geldman J, Sayre EC, Park C, Ezzat AM, Yoo JY, et al. Accuracy of Fitbit Devices: Systematic Review and Narrative Syntheses of Quantitative Data. *JMIR Mhealth Uhealth.* 2018 Aug 9;6(8):e10527. doi: 10.2196/10527
127. Lu G, Yang F, Taylor JA, Stein JF. A comparison of photoplethysmography and ECG recording to analyse heart rate variability in healthy subjects. *J Med Eng Technol.* 2009;33(8):634-41. doi: 10.3109/03091900903150998
128. Homayounfar SZ, Andrew TL. Wearable Sensors for Monitoring Human Motion: A Review on Mechanisms, Materials, and Challenges. *SLAS Technol.* 2020 Feb;25(1):9-24. doi: 10.1177/2472630319891128.
129. Arvidsson D, Fridolfsson J, Börjesson M. Measurement of physical activity in clinical practice using accelerometers. *J Intern Med.* 2019 Aug;286(2):137-153. doi: 10.1111/joim.12908

130. Godfrey A, Conway R, Meagher D, O'Laighin G. Direct measurement of human movement by accelerometry. *Med Eng Phys*. 2008 Dec;30(10):1364-86. doi: 10.1016/j.medengphy.2008.09.005
131. Chen KY, Bassett DR. The Technology of Accelerometry-Based Activity Monitors: Current and Future. *Med Sci Sports Exerc*. 2005;37:S490–S500. doi: 10.1249/01.mss.0000185571.49104.82
132. Yeoh WS, Pek I, Yong YH, Chen X, Waluyo AB. Ambulatory monitoring of human posture and walking speed using wearable accelerometer sensors. *Annu Int Conf IEEE Eng Med Biol Soc*. 2008;2008:5184-7. doi: 10.1109/IEMBS.2008.4650382
133. White T, Westgate K, Hollidge S, Venables M, Olivier P, Wareham N, et al. Estimating energy expenditure from wrist and thigh accelerometry in free-living adults: a doubly labelled water study. *Int J Obes (Lond)*. 2019 Nov;43(11):2333-2342. doi: 10.1038/s41366-019-0352-x
134. Lee IM, Shiroma EJ. Using accelerometers to measure physical activity in large-scale epidemiological studies: issues and challenges. *Br J Sports Med*. 2014 Feb;48(3):197-201. doi: 10.1136/bjsports-2013-093154
135. Luzak A, Karrasch S, Thorand B, Nowak D, Holle R, Peters A, et al. Association of physical activity with lung function in lung-healthy German adults: results from the KORA FF4 study. *BMC Pulm Med*. 2017 Dec 28;17(1):215. doi: 10.1186/s12890-017-0562-8
136. Macdonald E, Buchan D, Cerexhe L, Renfrew L, Sculthorpe N. Accelerometer measured physical activity and sedentary time in individuals with multiple sclerosis versus age matched controls: A systematic review and meta-analysis. *Mult Scler Relat Disord*. 2023 Jan;69:104462. doi: 10.1016/j.msard.2022.104462

137. LaMonte MJ, Buchner DM, Rillamas-Sun E, Di C, Evenson KR, Bellettiere J, et al. Accelerometer-Measured Physical Activity and Mortality in Women Aged 63 to 99. *J Am Geriatr Soc*. 2018 May;66(5):886-894. doi: 10.1111/jgs.15201
138. Waring T, Gross K, Soucier R, ZuWallack R. Measured Physical Activity and 30-Day Rehospitalization in Heart Failure Patients. *J Cardiopulm Rehabil Prev*. 2017 Mar;37(2):124-129. doi: 10.1097/HCR.0000000000000204
139. Tan MKH, Wong JKL, Bakrania K, Abdullahi Y, Harling L, Casula R, et al. Can activity monitors predict outcomes in patients with heart failure? A systematic review. *Eur Heart J Qual Care Clin Outcomes*. 2019 Jan 1;5(1):11-21. doi: 10.1093/ehjqcco/qcy038
140. Aslan GK, Akıncı B, Yeldan I, Okumus G. A randomized controlled trial on inspiratory muscle training in pulmonary hypertension: Effects on respiratory functions, functional exercise capacity, physical activity, and quality of life. *Heart Lung*. 2020 Jul-Aug;49(4):381-387. doi: 10.1016/j.hrtlng.2020.01.014
141. Nathan SD, Flaherty KR, Glassberg MK, Raghu G, Swigris J, Alvarez R, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis. *Chest*. 2020 Aug;158(2):637-645. doi: 10.1016/j.chest.2020.02.016
142. Kronish IM, Diaz KM, Goldsmith J, Moise N, Schwartz JE. Objectively Measured Adherence to Physical Activity Guidelines After Acute Coronary Syndrome. *J Am Coll Cardiol*. 2017 Mar 7;69(9):1205-1207. doi: 10.1016/j.jacc.2016.10.087
143. Freene N, McManus M, Mair T, Tan R, Davey R. High sedentary behaviour and low physical activity levels at 12 months after cardiac rehabilitation: A

- prospective cohort study. *Ann Phys Rehabil Med*. 2020 Jan;63(1):53-58. doi: 10.1016/j.rehab.2019.07.008
144. Vasankari S, Hartikainen J, Vasankari V, Anttila V, Tokola K, Vähä-Ypyä H, et al. Objectively measured preoperative physical activity and sedentary behaviour among Finnish patients scheduled for elective cardiac procedures: baseline results from randomized controlled trial. *BMC Sports Sci Med Rehabil*. 2022 Jul 16;14(1):130. doi: 10.1186/s13102-022-00522-1
145. Gonzalez-Jaramillo N, Eser P, Casanova F, Bano A, Franco OH, Windecker S, et al. Prognostic impact of physical activity patterns after percutaneous coronary intervention. Protocol for a prospective longitudinal cohort. The PIPAP study. *Front Cardiovasc Med*. 2022 Sep 30;9:976539. doi: 10.3389/fcvm.2022.976539
146. Ferrero-Hernández P, Farías-Valenzuela C, Jofré-Saldía E, Marques A, Kovalskys I, Gómez G, et al. Physical activity and daily steps cut offs points for overweight/obesity prevention among eight Latin American countries. *Sci Rep*. 2022 Nov 5;12(1):18827. doi: 10.1038/s41598-022-23586-y.
147. Matsudo VK, Ferrari GL, Araújo TL, Oliveira LC, Mire E, Barreira TV, et al. Indicadores de nível socioeconômico, atividade física e sobrepeso/obesidade em crianças brasileiras [Socioeconomic status indicators, physical activity, and overweight/obesity in Brazilian children]. *Rev Paul Pediatr*. 2016 Jun;34(2):162-70. doi: 10.1016/j.rpped.2015.04.003.
148. Eyre EL, Duncan MJ. The impact of ethnicity on objectively measured physical activity in children. *ISRN Obes*. 2013 Jan 22;2013:757431. doi: 10.1155/2013/757431

149. Bassett DR Jr, Toth LP, LaMunion SR, Crouter SE. Step Counting: A Review of Measurement Considerations and Health-Related Applications. *Sports Med.* 2017 Jul;47(7):1303-1315. doi: 10.1007/s40279-016-0663-1
150. Turrisi TB, Bittel KM, West AB, Hojjatinia S, Hojjatinia S, Mama SK, et al. Seasons, weather, and device-measured movement behaviors: a scoping review from 2006 to 2020. *Int J Behav Nutr Phys Act.* 2021 Feb 4;18(1):24. doi: 10.1186/s12966-021-01091-1
151. Kidokoro T, Tian X, Fuku N, Waiganjo LB, Rintaugu EG, Kigaru MD, et al. Segmented physical activity and sedentary behavior patterns among children in Maasai village and Nairobi city. *Am J Hum Biol.* 2022 Mar;34(3):e23649. doi: 10.1002/ajhb.23649
152. To QG, Stanton R, Schoeppe S, Doering T, Vandelanotte C. Differences in physical activity between weekdays and weekend days among U.S. children and adults: Cross-sectional analysis of NHANES 2011-2014 data. *Prev Med Rep.* 2022 Jul 5;28:101892. doi: 10.1016/j.pmedr.2022.101892
153. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act.* 2008 Nov 6;5:56. doi: 10.1186/1479-5868-5-56
154. Welk GJ, Kim Y, Stanfill B, Osthus DA, Calabro MA, Nusser SM, Carriquiry A. Validity of 24-h physical activity recall: physical activity measurement survey. *Med Sci Sports Exerc.* 2014 Oct;46(10):2014-24. doi: 10.1249/MSS.0000000000000314

155. Hagstromer M, Ainsworth BE, Oja P, Sjostrom M. Comparison of a subjective and an objective measure of physical activity in a population sample. *J Phys Act Health*. 2010 Jul;7(4):541-50. doi: 10.1123/jpah.7.4.541.
156. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. *Int J Behav Nutr Phys Act*. 2011;8:115. doi: 10.1186/1479-5868-8-115
157. Ogonowska-Slodownik A, Morgulec-Adamowicz N, Geigle PR, Kalbarczyk M, Kosmol A. Objective and Self-reported Assessment of Physical Activity of Women over 60 Years Old. *Ageing Int*.47:307–320 (2022). doi: 10.1007/s12126-021-09423-z
158. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ*. 2018 Jan;27(1):7-22. doi: 10.1002/hec.3564. Epub 2017 Aug 22
159. Soh SE, Morello R, Ayton D, Ahern S, Scarborough R, Zammit C, *et al*. Measurement properties of the 12-item Short Form Health Survey version 2 in Australians with lung cancer: a Rasch analysis. *Health Qual Life Outcomes* 19, 157 (2021). doi: 10.1186/s12955-021-01794-w
160. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle Angina Questionnaire as an Outcome Measure in Clinical Trials and Clinical Care: A Review. *JAMA Cardiol*. 2021 May 1;6(5):593-599. doi: 10.1001/jamacardio.2020.7478
161. Orstad SL, Gerchow L, Patel NR, Reddy M, Henrandez C, Wilson DK, *et al*. Defining valid activity monitor day: A multimethod analysis of weight-loss intervention participants' barriers to wear and first 100 days of physical activity. *Informatics (MDPI)*. 2021 Jun;8(2):39. doi: 10.3390/informatics8020039.

162. Heart Online. Six Minute Walk Test (6MWT) instructions. 2014 Nov [cited 2024 June 7]. Heart Education Assessment Rehabilitation Toolkit [Internet]. Available from:
https://www.heartonline.org.au/media/DRL/6MWT_standardised_instructions.pdf
163. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. *Biomed J*. 2020 Aug;43(4):328-333. doi: 10.1016/j.bj.2020.04.007
164. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med*. 2020 Apr 9;382(15):1395-1407. doi: 10.1056/NEJMoa1915922
165. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Engl J Med*. 1992 Jan 2;326(1):10-6. doi: 10.1056/NEJM199201023260102
166. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, Nowbar AN, Simader FA, Davies JR, et al. A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina. *N Engl J Med*. 2023 Dec 21;389(25):2319-2330. doi: 10.1056/NEJMoa2310610
167. Freene N, Borg S, McManus M, Mair T, Tan R, Davey R, et al. Comparison of device-based physical activity and sedentary behaviour following percutaneous coronary intervention in a cohort from Sweden and Australia: a harmonised, exploratory study. *BMC Sports Sci Med Rehabil*. 2020 May 9;12:17. doi: 10.1186/s13102-020-00164-1

168. Kambic T, Šarabon N, Hadžić V, Lainscak M. Objectively Measured Physical Activity in Patients with Coronary Artery Disease: A Cross-Validation Study. *Biosensors (Basel)*. 2021 Sep 6;11(9):318. doi: 10.3390/bios11090318
169. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation*. 2014 Jun 17;129(24):2518-27. doi: 10.1161/CIRCULATIONAHA.113.008507
170. Salvatore T, Galiero R, Caturano A, Vetrano E, Loffredo G, Rinaldi L, et al. Coronary Microvascular Dysfunction in Diabetes Mellitus: Pathogenetic Mechanisms and Potential Therapeutic Options. *Biomedicines*. 2022 Sep 14;10(9):2274. doi: 10.3390/biomedicines10092274
171. Fini NA, Holland AE, Bernhardt J, Burge AT. How Many Hours of Device Wear Time Are Required to Accurately Measure Physical Activity Post Stroke? *Int J Environ Res Public Health*. 2022 Jan 21;19(3):1191. doi: 10.3390/ijerph19031191
172. Brändström Y, Brink E, Grankvist G, Alsén P, Herlitz J, Karlson BW. Physical activity six months after a myocardial infarction. *Int J Nurs Pract*. 2009 Jun;15(3):191-7. doi: 10.1111/j.1440-172X.2009.01744.x
173. Houle J, Valera B, Gaudet-Savard T, Auclair A, Poirier P. Daily steps threshold to improve cardiovascular disease risk factors during the year after an acute coronary syndrome. *J Cardiopulm Rehabil Prev*. 2013 Nov-Dec;33(6):406-10. doi: 10.1097/HCR.000000000000021
174. Freene N, McManus M, Mair T, Tan R, Davey R. Association of device-measured physical activity and sedentary behaviour with cardiovascular risk factors, health-related quality-of-life and exercise capacity over 12-months in

- cardiac rehabilitation attendees with coronary heart disease. *BMC Sports Sci Med Rehabil.* 2022 Sep 7;14(1):169. doi: 10.1186/s13102-022-00562-7
175. Kambic T, Šarabon N, Hadžić V, Lainscak M. Objectively Measured Physical Activity in Patients with Coronary Artery Disease: A Cross-Validation Study. *Biosensors (Basel).* 2021 Sep 6;11(9):318. doi: 10.3390/bios11090318
176. Hamilton DM, Haennel RG. Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. *J Cardiopulm Rehabil.* 2000 May-Jun;20(3):156-64. doi: 10.1097/00008483-200005000-00003
177. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest.* 2001 Jan;119(1):256-70. doi: 10.1378/chest.119.1.256
178. Compostella L, Lorenzi S, Russo N, Setzu T, Compostella C, Vettore E, et al. Depressive symptoms, functional measures and long-term outcomes of high-risk ST-elevated myocardial infarction patients treated by primary angioplasty. *Intern Emerg Med.* 2017 Feb;12(1):31-43. doi: 10.1007/s11739-016-1504-9
179. Hassan AK, Dimitry SR, Agban GW. Can exercise capacity assessed by the 6 minute walk test predict the development of major adverse cardiac events in patients with STEMI after fibrinolysis? *PLoS One.* 2014 Jun 6;9(6):e99035. doi: 10.1371/journal.pone.0099035.
180. Rossello X, Pujadas S, Serra A, Bajo E, Carreras F, Barros A, et al. Assessment of Inducible Myocardial Ischemia, Quality of Life, and Functional Status After Successful Percutaneous Revascularization in Patients With Chronic

- Total Coronary Occlusion. *Am J Cardiol.* 2016 Mar 1;117(5):720-6. doi: 10.1016/j.amjcard.2015.12.001.
181. Germini F, Noronha N, Debuno VB, Philip BA, Pete D, Navarro T, et al. Accuracy and Acceptability of Wrist-Wearable Activity-Tracking Devices: Systematic Review of the Literature. *J Med Internet Res.* 2022 Jan 21;24(1):e30791. doi: 10.2196/30791
182. Johnston W, Judice PB, García PM, Mühlen JM, Skovgaard EL, Stang J, et al. Recommendations for determining the validity of consumer wearable and smartphone step count: expert statement and checklist of the INTERLIVE network. *Br J Sports Med.* 2021 Jul;55(14):780-793. doi: 10.1136/bjsports-2020-103147
183. Waddell A, Birkett S, Broom D, McGregor G, Harwood AE. Validating the Fitbit Charge 4© wearable activity monitor for use in physical activity interventions. *J Sci Med Sport.* 2024 May;27(5):314-318. doi: 10.1016/j.jsams.2024.01.007
184. Soloveva A, Gale CP, Han NT, Hurdus B, Aktaa S, Palin V, et al. Associations of health-related quality of life with major adverse cardiovascular and cerebrovascular events for individuals with ischaemic heart disease: systematic review, meta-analysis and evidence mapping. *Open Heart.* 2023 Oct;10(2):e002452. doi: 10.1136/openhrt-2023-002452.
185. Rieckmann N, Neumann K, Feger S, Ibes P, Napp A, Preuß D, et al. Health-related quality of life, angina type and coronary artery disease in patients with stable chest pain. *Health Qual Life Outcomes.* 2020 May 14;18(1):140. doi: 10.1186/s12955-020-01312-4.

186. Abdallah MS, Wang K, Magnuson EA, Spertus JA, Farkouh ME, Fuster V, et al. Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA*. 2013 Oct 16;310(15):1581-90. doi: 10.1001/jama.2013.279208
187. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368
188. Bletsas E, Oikonomou E, Dimitriadis K, Stampouloglou PK, Fragoulis C, Lontou SP, et al. Exercise Effects on Left Ventricular Remodeling in Patients with Cardiometabolic Risk Factors. *Life (Basel)*. 2023 Aug 14;13(8):1742. doi: 10.3390/life13081742
189. Meyer M, McEntee RK, Nyotowidjojo I, Chu G, LeWinter MM. Relationship of exercise capacity and left ventricular dimensions in patients with a normal ejection fraction. An exploratory study. *PLoS One*. 2015 Mar 10;10(3):e0119432. doi: 10.1371/journal.pone.0119432
190. Berdy AE, Upadhyaya B, Ponce S, Swett K, Stacey RB, Kaplan R, et al. Associations between physical activity, sedentary behaviour and left ventricular structure and function from the Echocardiographic Study of Latinos (ECHO-SOL). *Open Heart*. 2021 Jul;8(2):e001647. doi: 10.1136/openhrt-2021-001647.

Appendices

1. Patient consent form



Patient Identification Number for this trial:

CONSENT FORM
Towards a complete virtual (computed) model of myocardial ischaemia (VIRTU 5)
Professor Julian Gunn

Please initial boxes

I confirm that I have read and understand the information sheet Version 2 dated for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

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.

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.

I agree to answer the questionnaires (1).

I agree to have the MRI scan[s] (2).

I agree to have the activity monitoring (3).

I agree to perform the 6 minute walk test[s] (4)

I agree to take in the whole of the above study

Name of Patient

Date

Signature

Name & Job Title of Person
Taking Consent

Date

Signature

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

2. Ethical approval



Professor Julian Gunn
Professor of Interventional Cardiology
University of Sheffield
The University of Sheffield
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Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

23 March 2020

Dear Professor Gunn

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

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

List of Documents

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

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper		21 January 2020
IRAS Application Form	272069/1413 118/37/927	21 January 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 [Seattle licence (Outcomes Instruments LLC)]		11 September 2019
Other [SF12 licence (Optum)]		25 October 2019
Other [EQ-5D licence (registration)]		11 September 2019
Other [Phone Slip]	1.0	15 February 2020
Other [Appendix 1 - Guidance Doc for Undertaking a Local Risk Assessment for Lone Working]	2 *date received	03 March 2020
Other [Appendix 3 - Lone Worker Off Site Checklist]	*date received	03 March 2020
Other [Lone Worker Policy]	2.1	13 January 2012
Other [Appendix 2 - Lone Working in Building Checklist]	*date received	03 March 2020
Other [Response to assessment queries (email)]		10 March 2020
Participant consent form [Consent Form]	2	18 February 2020
Participant information sheet (PIS)	4	08 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 Williams]		16 February 2020
Summary CV for student [Abdulaziz Al-Baraikhan]		24 September 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	

IRAS project ID	272069
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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 organisation 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 organisation therefore no agreements are expected.	External study funding has been secured.	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

<i>This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.</i>
The applicant has indicated they intend to apply for inclusion on the NIHR CRN Portfolio.

3. Patient study invitation & information sheet

Sheffield Teaching Hospitals 
NHS Foundation Trust

ACADEMIC TEAM

Professor J Gunn
Professor of Interventional
Northern General Hospital,
Herries Road
Sheffield,
S5 7AU

Date:

Secretary:
Mrs Tracy Ellender: 0114 271 4953

Dear

Towards a complete virtual (computed) model of myocardial ischaemia (VIRTU-5)
(Building a computer model of blood supply to the heart)

We in Sheffield are working on an exciting research 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. 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 some scans of your heart, doing a short walking test, and monitoring your activity at home. We would like to do these things with you before and after your angioplasty. The changes that we see will help us build the model. The research will not affect your treatment, but it may benefit patients in the future.

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. One of our research team will contact you shortly 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. We look forward to seeing you.

Yours sincerely

Professor Julian Gunn MA MD MRCP
Professor of Interventional Cardiology

Participant Information Sheet

Towards a complete virtual (computed) model of myocardial ischaemia (VIRTU-5)

Principal Investigator: Professor Julian Gunn, Consultant Cardiologist
Northern General Hospital, 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?

Coronary artery disease is a condition in which blood vessels in the heart become furred up. Percutaneous coronary intervention (PCI; 'angioplasty' or 'stenting') is a minimally invasive method to restore good blood flow by widening (stenting) these arteries. This is the treatment that you are *probably* going to have. ['Probably', because the final decision is made on the basis of pictures taken when you attend for the procedure]. But it's not always obvious from the pictures how much a particular narrowing restricts blood flow, and whether it needs a stent. To help decide, the pressure gradient across the narrowing can be measured, but this is tricky, and is not often done. So we have developed a computer model of blood flow that can tell the specialist what the pressure gradient is. So far, we have managed this with one artery. In this project, we are extending the model to the whole heart, which contains many arteries, and making it relevant for the patient's requirements. This will ensure that doctors make the right decisions for their patients, and don't under-treat or over-treat them.

Why have I been invited?

You are being invited to participate in this study because you have one or more narrowings in your arteries, just like the patients in the future that we might be able to help.

What do I have to do?

If you take part, there will be four 'extras'.

- 1) You will be asked some questions about your health with some questionnaires. These can be conducted by one of our research fellows visiting you at home, and will take about 20 minutes.
- 2) You will 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.

3) When you attend the hospital we will ask you to do a walking test that lasts 6 minutes.

4) We will record your activity level (heart rate, steps taken, distance moved etc) at home. This is easily done with a 'smart watch', a mobile phone and some tiny monitors. 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 a normal life.

We will then give you your treatment in hospital, entirely as normal, using the latest techniques. We will collect a lot of useful data at the time of your procedure (such as clinical details, pictures of your arteries and pressures in the vessels).

Afterwards, a few weeks later, when everything has settled down for you, we will repeat the 'extras' listed above. (If you did not need a stent, you won't need another MRI scan or another walking test). 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.

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 your normal care. This is because this study is designed to ask the 'hypothetical' questions 'Can we build a complete assessment of myocardial blood flow for our patients?' 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
- Personal data on your physical or mental health or 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 who you are 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 anonymized, 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 Peter Wilson 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 North of Scotland Research Ethics Committee.

Expenses and Incentives?

We will pay for your taxi to attend for the heart scan, but 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.

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 MRI scans will involve an extra visit to hospital (two if you have a stent). Some patients find lying still in the scanner a bit difficult. The 'contrast' agent used can affect kidney function in a very small minority of patients (but it is used in routine NHS practice). 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.

Radiation

You will not receive any more X-rays than anyone else having an angiogram or angioplasty. The MRI scan uses a magnetic field, not radiation, and is perfectly safe.

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

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

What 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 organised the study. Funding of the PCI is by the NHS. The 'sponsor' of the study (the organization which takes responsibility for it) is the Sheffield Teaching Hospitals NHS Foundation Trust. Research Fellowships (The Engineering and Physical Sciences Research Council, and the Saudi Cultural Bureau) fund the Research Fellows. 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 Advice and Liaison Service

Phone no: 0114 271 2400

Email: sth.pals@nhs.net

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

4. Data collection sheets

A - 6MWT checklist and data collection sheet



Department of Infection,
Immunity and cardiovascular
Disease

6-Minute Walk Test Checklist and Recording Sheet Virtu-5 Study

Equipment Checklist: <ul style="list-style-type: none"> ❖ 6MWT checklist and recording sheet <input type="checkbox"/> ❖ Borg scale sheet <input type="checkbox"/> ❖ Stop watch or timer <input type="checkbox"/> ❖ 2 chairs <input type="checkbox"/> ❖ Automated BP machine and pulse oximeter <input type="checkbox"/> ❖ Trundle wheel for measuring 6MWD <input type="checkbox"/> ❖ Clipboard <input type="checkbox"/> ❖ Portable oxygen and suitable facemask <input type="checkbox"/> ❖ Rescue nitrate therapy <input type="checkbox"/> ❖ 2 small cones <input type="checkbox"/> ❖ SOP document <input type="checkbox"/> 	Test operator: <hr/> Test Date: <hr/> Subject study number: <hr/>
--	---

Clinical Parameters prior to test start:

Heart Rate	bpm	Blood Pressure	mmHg
Worsening chest pain in the last month?	Yes / No	Resting SpO2	% on air
Medications taken this morning and dose			

Stop the test in the event of any of the following:

- ❖ Chest pain suspicious of angina
- ❖ Evolving light-headedness
- ❖ Intolerable dyspnoea
- ❖ Excessive sweating
- ❖ Pale or ashen appearance that occurs during rest
- ❖ Any clinical concern regarding subject safety

Subject Instruction:

The objective of this test is to walk as far as possible for 6 minutes. You will walk back and forth along this course (demonstrate one lap) for 6 minutes. You will walk around the cones (indicate towards cones) clockwise so that the cones are always to your right. I will now show you how to do this (perform one lap of circuit).

You may slow down if necessary. If you stop, I want you to continue to walk again as soon as you feel able to. You will be informed of the time and encouraged each minute.

Please do not talk during the test unless you have a problem or I ask you a question. You must let me know if you have any chest pain or dizziness. Remember, the objective is to walk as far as possible, not as fast, don't jog or run.

When 6 minutes is over I will ask you to stop where you are. I will bring a chair over to you so that you can sit.

The test will be performed twice, after the first 6 minutes there will be a 15 minute break, after which we will start the second test exactly like the first.

Do you have any questions?

Once subject is ready and has no further questions:

When you are ready, please start walking.

At minute one: *You are doing well. You have five minutes to go.*

At minute two: *Keep up the good work. You have four minutes to go.*

At minute three: *You are doing well. You are halfway done.*

At minute four: *Keep up the good work. You only have two minutes left*

At minute five: *You are doing well. You have only one minute to go.*

At six minutes: *Stop, please stay where you are.*

Test results

	1st Attempt		2nd Attempt	
	Before test	After test	Before test	After test
Heart Rate	bpm	bpm	bpm	bpm
Blood Pressure	mmHg	mmHg	mmHg	mmHg
SpO2	%	%	%	%
Borg Scale				
Laps completed				
Distance Walked	m	m	m	m
Reason test terminated + time walked				

B – Catheter laboratory data recording sheet



Department of Infection,
Immunity and cardiovascular
Disease

**Catheter laboratory data recording sheet
Virtu-5 study**

Patient study ID: _____

Operator: _____

Initial HR:		Initial BP:	
Access site:			
Disease location:	1	2	3
Visual severity :	%	%	%
FFR result : Rest/hypaemia			
PCI? :	Yes [] No []	Yes [] No []	Yes [] No []
Post-PCI angiogram?	[]	[]	[]
60 second ventricular pressure snapshot acquired []	Data anonymized and uploaded to G drive []		
Ventriculogram acquired []	Invasive coronary pressure uploaded to G drive []		

Notes:

LV:

AO:

FRF:	LAD	LCx	RCA	Other:
Pre-PCI				
Post-PCI				

Completed by: _____

Date: _____

C – CMR & Regadenoson stress test Safety checklist & data collection sheet

**MRI
REGADENOSON MYOCARDIAL PERFUSION STUDY
WORKSHEET**

PATIENT DETAILS					
Name:			Hospital No:		
Address:			Consultant:		
			OPD / Ward:		
DOB:			Weight:		
CANNULATION RECORD					
Inserted By:			Gauge:		
Removed By:					
PRE – TEST CHECKS					
	Y/N	Comments		Y/N	Comments
Details Checked			Any Blackouts?		? Sick sinus if yes
Diagnosed with epilepsy?		<i>N.B. If yes the pt will need to be stressed with Dobutamine.</i>	Any chest pain or GTN within last 24 hrs?		
Asthma / COPD					
Dipyridamole or Xanthines			ECG Today?		
Viagra			ECG Checked by Clinical Physiologist?		
Pacemaker/ICD					
Pre-Test Instructions			Heart Rate and BP Checked?		
Meds/Symptoms Changed?			Consented?		
Known Allergies?			Any other info?		
DRUG ADMINISTRATION					
Regadenoson		NaCl		Other Drugs (if required)	
Batch No:		Batch No:		Drug:	
Conc: µg/ml		Conc:		Batch No:	
Exp:		Exp:		Conc:	
Dose Given: µg		Dose Given:		Exp:	
Admin By:		Admin By:		Admin By	
Checked By:		Checked By:		Checked By	
OBSERVATIONS					
Time	BP	H.R	Comments		
Rest					

Continue Observations on Reverse if Require

Time	BP	H.R	Comments

5. Questionnaires and licences

A. EuroQuality of life – 5 Dimensions (License)

Dear Mr. Abdulaziz Albarakani,

Thank you for your registration. The study / project titled "Towards a complete virtual (computed) model of myocardial ischaemia (VIRTUS)" you registered fulfils the conditions for you to use the requested version(s) free of charge.

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If you have any questions please contact us by sending an email to userinformation@euroqol.org.

Thank you in advance.

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Agree

Best regards,

Bernhard Slaap
Executive Director
EuroQol Research Foundation



T +31 88 4400196 | E slaap@euroqol.org | www.euroqol.org | Marten Meesweg 107 | 3066 AV Rotterdam The Netherlands

EuroQuality of Life – 5 Dimensions (Questionnaire)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

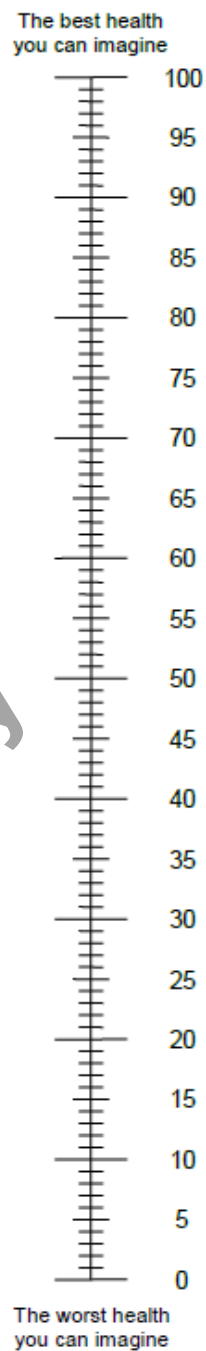
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

For thesis use only

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

YOUR HEALTH TODAY =

For thesis use only



B. Short Form-12 (Licence)



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License Number: QM051067

Licensee Name: University of Sheffield

Licensee Address: Firth Court, Western Bank, , Sheffield S10 2TN UK

Approved Purpose: Towards a complete virtual (computed) model of myocardial ischemia VIRTU 5

Study Type: Non-commercial academic research and/or thesis: Grant Funded

Therapeutic Area: Heart and Circulation

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OptumInsight Life Sciences, Inc.

University of Sheffield

Signature: _____
Name: Martina Bayliss
Title: VP Patient Insights and Principal Consultant
Date: 10/25/2019

Signature: _____
Name: Abdulaziz Albaraikan
Title: Ph.D student
Date: 17/10/2019

Short Form-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. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Climbing <u>several</u> flights of stairs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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. <u>Accomplished less</u> than you would like	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Were limited in the <u>kind</u> of work or other activities	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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. <u>Accomplished less</u> than you would like	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Did work or other activities <u>less carefully than usual</u>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Did you have a lot of energy?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Have you felt downhearted and depressed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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

C. Seattle Angina Questionnaire (Licence)

OUTCOMES **Instruments, LLC**

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10. Indemnification of Licensor. Licensee hereby agrees to hold Licensor harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensor may incur or be obligated to pay, or for which it may become liable or be compelled to pay in any action, claim or proceeding for or by reason of any acts, whether of omission or commission, that may be claimed to be or are actually committed or suffered by Licensee arising out of Licensee's use of the Licensed Properties. The provisions of this paragraph and Licensee's obligations hereunder shall survive the expiration or termination of this Agreement.
11. Indemnification of Licensee. Subject to Section 9 hereof, Licensor hereby agrees to hold Licensee harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensee may incur or be obligated to pay, or for which it may become liable or compelled to pay in

any action, claim or proceeding for or by reason of any breach of any representation, warranty or agreement on the part of Licensor under this Agreement.

12. Nondisclosure. During the term of this Agreement, the parties may have access to trade secrets, proprietary information, or other sensitive materials belonging to the other which are not generally known to the public ("Confidential Information"). During the term of this Agreement and for a period of five (5) years after termination or expiration hereof, the receiving party ("Recipient") agrees to maintain in trust and confidence all Confidential Information of the other party (the "Disclosing Party"). The Recipient agrees to safeguard the Confidential Information using the same standard of care it uses to protect its own Confidential Information. The Recipient will not disclose any Confidential Information to any third party, or make any use thereof other than as expressly permitted hereby, without the prior written consent of the Disclosing Party. As used herein, Confidential Information does not include any information which the Recipient can demonstrate (i) was known to the Recipient or to the general public at the time of disclosure; (ii) was independently developed by the Recipient without the use of any of the Confidential Information; or (iii) was disclosed by a third party without violating any restriction or duty to the Disclosing Party.
13. Publications. Notwithstanding the general restrictions set forth in Section 12 above, the parties agree that publication of the results of research activities serves their mutual interests in improving the quality of health care. Accordingly, Licensee shall be free to publish the results of its research and development activities carried out with respect to the Licensed Properties and the Subject Study. Licensee agrees to refer to Licensor and the Licensed Properties in the bibliography section of the publication.
14. Term. Subject to the provisions of Section 15 hereof, this Agreement shall remain in effect from 01/01/2020 to 01/01/2023. Subsequent renewal of this Agreement shall be optionally available through application through the web site.
15. Licensor's Right to Terminate. Licensor shall have the right to immediately terminate this Agreement by giving written notice to Licensee in the event Licensee: (i) fails to perform any of its duties and obligations set forth herein, and the continuation thereof for thirty (30) days after notice; (ii) files a petition in bankruptcy or is adjudicated a bankrupt or insolvent, or makes an assignment for the benefit of creditors; (iii) makes any use of the Licensed Properties not otherwise expressly permitted herein or (iv) the Subject Study is cancelled, abandoned, withdrawn or suspended. In such event, Licensee shall immediately cease and terminate its use of any of the rights granted hereby and shall, upon the request of Licensor, return to Licensor all records, copies, documents, media and files making use of the Licensed Properties, or furnish evidence, satisfactory to Licensor, of the destruction thereof.
16. Equitable Remedies. The parties further acknowledge that the breach, whether threatened or actual, of any of the terms hereof by Licensee shall result in immediate, irreparable injury to Licensor and its goodwill and that accordingly, Licensor shall be entitled to apply for a preliminary and/or permanent injunction to restrain the threatened or actual violation of the terms hereof by the Licensee or to compel specific performance of the terms and conditions of this License Agreement. Nothing set forth herein shall be construed as prohibiting the Licensor from pursuing any other remedies available for such breach or threatened breach, including the recovery of damages and costs incurred, together with attorneys' fees.
17. Miscellaneous.
 - a. This Agreement together with the exhibits hereto constitutes the entire understanding between the parties with respect to this Agreement. No change or modification of any of the provisions of this Agreement shall be effective unless memorialized by an instrument in writing signed by the parties hereto. All notices required or permitted to be given hereunder shall be given in writing, to the parties at their addresses set forth herein, or to such other address with respect to which notice has been given in accordance herewith. Whenever possible, each

provision of this License Agreement shall be interpreted in such a manner as to be effective and valid under applicable law. If any covenant or other provision of this Agreement, or portion thereof, under circumstances not now contemplated by the parties, is invalid, illegal or incapable of being enforced, by reason of any rule of law, administrative order, judicial decision or public policy, all other conditions and provisions of this Agreement shall, nevertheless, remain in full force and effect, and no covenant or provision shall be deemed dependent upon any other covenant or provision unless so expressed herein. The parties desire and consent that the court or other body making such determination shall, to the extent necessary to avoid any unenforceability, so reform such covenant, term, condition or other provision or portion of this Agreement to the minimum extent necessary so as to render the same enforceable in accordance with the intent herein expressed.

b. This Agreement shall inure to the benefit of Licensor, its successors and assigns. Licensee shall not have the right to assign this Agreement, or delegate its duties, by operation of law or otherwise, without first obtaining the written consent of Licensor.

c. This Agreement shall be governed by and construed in accordance with the laws of the State of Missouri.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed as of the day and year first above mentioned.

Outcomes Instruments, LLC

The University of Sheffield

By: John Spertus

Title: President

"Licensor"

By: Abdulaziz Albaraikan

Title: Ph.D student

"Licensee"

SCHEDULE A: LICENSED PROPERTIES

SAQ – English (UK)

This version of the SAQ has been designed for English-speaking patients in the UK.

This zip file includes two PDF files: the SAQ itself and scoring instructions.

SCHEDULE B: DESCRIPTION OF STUDY

Project Name

Towards a complete virtual (computed) model of myocardial ischaemia VIRTU 5

Project ID

7627

Project Type

Other

Project Dates

Start: 01/01/2020

End: 01/01/2023

Duration: 1096 days

Enrollment

Sites: 1

Seattle Angina Questionnaire (Questionnaire)

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during a normal week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had due to chest pain, chest tightness, or anginal attacks over the past 4 weeks:

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not Limited at all	Limited for other reasons or did not do the activity
Dressing yourself	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking indoors on level ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Showering or bathing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climbing a hill or a flight of stairs without stopping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gardening, vacuuming, or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking more than a hundred yards at a brisk pace	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Running or jogging	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lifting or moving heavy objects such as furniture, or lifting children	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Participating in strenuous sports (e.g. swimming, tennis)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, or **anginal attacks** when doing your **most strenuous activities**?

I have **chest pain**, **chest tightness**, or **anginal attacks**...

- | | | | | | |
|--------------------------|----------------------------|--------------------------|----------------------------|--------------------------|---|
| Much more often | Slightly more often | About the same | Slightly less often | Much less often | I have had no chest pain over the last 4 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

3. Over the past 4 weeks, on average, how many times have you had **chest pain**, **chest tightness**, or **anginal attacks**?

I have had **chest pain**, **chest tightness**, or **anginal attacks**...

- | | | | | | |
|--------------------------------|--------------------------|---|---------------------------|------------------------------|-----------------------------------|
| 4 or more times per day | 1-3 times per day | 2 or more times per week but not every day | 1-2 times per week | Less than once a week | None over the past 4 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

4. Over the past 4 weeks, on average, how many times have you had to take GTN (nitroglycerin tablets or spray) for your **chest pain**, **chest tightness**, or **anginal attacks**?

I have taken GTN...

- | | | | | | |
|--------------------------------|--------------------------|---|---------------------------|------------------------------|-----------------------------------|
| 4 or more times per day | 1-3 times per day | 3 or more times per week but not every day | 1-2 times per week | Less than once a week | None over the past 4 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness** or **anginal attacks** as prescribed?

- | | | | | | |
|-----------------------------|-------------------------------|------------------------------|----------------------------|------------------------------|---|
| Extremely bothersome | Quite a bit bothersome | Moderately bothersome | Slightly bothersome | Not bothersome at all | My doctor has not prescribed pills |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, or **anginal attacks**?

- | | | | | |
|-----------------------------|----------------------------|---------------------------|--------------------------|-----------------------------|
| Not satisfied at all | Mostly dissatisfied | Somewhat satisfied | Mostly satisfied | Completely satisfied |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

7. How satisfied are you with the explanations your doctor has given you about your chest pain, chest tightness, or anginal attacks?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. Overall, how satisfied are you with the current treatment of your chest pain, chest tightness, or anginal attacks?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9. Over the past 4 weeks, how much has your chest pain, chest tightness, or anginal attacks limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. If you had to spend the rest of your life with your chest pain, chest tightness, or anginal attacks the way it is at the moment, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. How often do you think or worry that you may have a heart attack or die suddenly?

I think or worry about it all the time	I often think or worry about it	I occasionally think or worry about it	I rarely think or worry about it	I never think or worry about it
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

D. User experience questionnaire

Study # _____

Virtu-5 wearable technology patient experience questionnaire

For each question, please indicate which answer you agree with most.

1. Before involvement in this study, what was your experience with wearable technology, including any smartwatch or fitness bands.

- a. I have never owned or used a smartwatch device and had no interest in using one.
- b. I have never owned or used a smartwatch device but have been interested in using one.
- c. I have used a smartwatch device before for a short time, but I didn't continue to use it for a prolonged period of time.
- d. I have used a smartwatch device before and have used it for a prolonged period of time (greater than 6 months), but no longer use it.
- e. I currently own and use a smartwatch device (before enrolment into study)

2. How would you describe your use and experience of mobile phone or smartphone devices?

- a. I do not use or own any mobile device
- b. I own a mobile device but it is not a smartphone (It can only be used for calling and texting)
- c. I own a smartphone device but I only use it for calling or texting, I do not use it for other reasons (i.e. internet connectivity, social media, mobile gaming)
- d. I own a smartphone device and occasionally use it for reasons other than calling or texting such as social media, internet connectivity or mobile gaming, although I don't feel fluent in its use.
- e. I own a smartphone device and frequently use it for reasons other than calling or texting, including social media, internet connectivity or mobile gaming. I feel comfortable using it for these purposes.

3. During the study period, how would you rate your experience with using the smartwatch provided throughout the study period?

- a. I found the smartwatch very difficult to use
- b. I found the smartwatch difficult to use
- c. I found the smartwatch neither easy nor difficult to use
- d. I found the smartwatch easy to use
- e. I found the smartwatch very easy to use

4. During the study period, how would you rate your comfort with wearing the smartwatch provided throughout the study period?

- a. I found the smartwatch very uncomfortable to wear
- b. I found the smartwatch uncomfortable to wear
- c. I found the smartwatch neither comfortable nor uncomfortable to wear
- d. I found the smartwatch comfortable to wear
- e. I found the smartwatch very comfortable to wear

5. During the study period, how did you find recharging the smartwatch device?

- a. I found the smartwatch very inconvenient to recharge
- b. I found the smartwatch inconvenient to recharge
- c. I found the smartwatch neither convenient nor inconvenient to recharge
- d. I found the smartwatch convenient to recharge
- e. I found the smartwatch very convenient to recharge

6. Following your involvement in the study, what are your thoughts regarding the use of wearable technology for personal use.

- a. I would not be interested in using a smartwatch device in the future for personal use.
- b. I would be interested in using a smartwatch device in the future for personal use.

7. Following your involvement in the study, what are your thoughts regarding the use of wearable technology for medical purposes. This includes monitoring personal health, response to treatment or health screening.

- a. I would not be interested in using a smartwatch device in the future for medical purposes
- b. I would be interested in using a smartwatch device in the future for medical purposes for a short period only (few weeks to a month)
- c. I would be interested in using a smartwatch device in the future for medical purposes for a prolonged period (few months or more)

Please write any comments you would like to include regarding your experience with the smartwatch device provided. You can use this space to either elaborate on any of the questions raised earlier in the questionnaire, or to comment on any areas you feel have not been raised regarding the use of these devices: