An Exploration of the Role of Exercise in the Secondary Prevention of Coronary Artery Disease

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Abstract

Background: Exercise may reduce inflammation in coronary artery disease (CAD) patients. However, the molecular mechanisms that orchestrate this cardioprotective effect are yet to be elucidated. Moreover, CAD patient participation rates in cardiac rehabilitation (CR) and long-term exercise are poor. Thus, this thesis aimed to further scientific understanding of the role of exercise in the secondary prevention of CAD by investigating these areas. In addition, the factors that influence CAD patient participation in CR and long-term exercise training were qualitatively explored.

Methods: The evidence generated by randomised studies that investigated the effect of exercise on inflammatory biomarkers in CAD patients was examined by a systematic review and meta-analysis (Study 1). A pilot prospective cohort study (Study 2) was performed in post-acute myocardial infarction (AMI) patients who had been invited to a phase-III CR programme. Finally, Study 3 comprised semi-structured interviews with post-AMI patients and their significant others.

Results: Study 1 demonstrated an anti-inflammatory effect of exercise in CAD patients, as indicated by a reduction in C-reactive protein, fibrinogen, and von Willebrand factor post-intervention. The outcome of Study 2 resulted in a future prospective cohort study being deemed feasible with minor amendment (recruitment strategy). Moreover, preliminary evidence for a beneficial effect of exercise on sirtuin-1 in post-AMI patients was generated. Regarding Study 3, post-AMI patients and their significant others reported that health benefits were the primary motive for participating in CR and long-term exercise, with aspects related to motivation, extrinsic influences, and CR experience underpinning the decision.

Conclusion: The results of Study 1 and Study 2 further scientific understanding of the role of exercise in the secondary prevention of CAD, and offer future directions to stimulate progress in this area. Finally, the novel qualitative findings of Study 3 may inform future strategies to promote patient participation in CR and long-term exercise.

Key words: exercise, cardiac rehabilitation, inflammation, molecular mechanisms, coronary artery disease, secondary prevention, enrollment, adherence

Abbreviations

Abbreviation	Definition
°C	Degrees Celsius
μL	Microlitres
μM·L^{-1}	Micromoles per litre
3DEFRs	Three-day estimated food records
A$^{\bullet-}$	Ascorbyl free radical
ACS	Acute coronary syndrome
AIE	Aerobic interval exercise
AMI	Acute myocardial infarction
AUC	Area-under-the-curve
BACPR	British Association for Cardiovascular Prevention and Rehabilitation
BHSCT	Belfast Health and Social Care Trust
BMI	Body mass index
BPM	Beats per minute
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAE	Continuous aerobic exercise
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcome Study
CCL19	Chemokine (C-C motif) ligand 19
CCL21	Chemokine (C-C motif) ligand 21
CD40L	CD40 ligand
CI	Confidence interval
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CR	Cardiac rehabilitation
CRP	C-reactive protein
CV	Coefficient of variation
CVD	Cardiovascular disease
CXCL16	Chemokine (C-X-C motif) ligand 16
DBP	Diastolic blood pressure
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
DVP	Digital volume pulse
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial nitric oxide synthase
EPR	Electron paramagnetic resonance
ESM	Electronic supplementary material
ESR	Erythrocyte sedimentation rate
Fe^{2+}	Ferrous ions
Fe^{3+}	Ferric ions
FMD	Flow-mediated dilatation
FOX	Ferrous oxidation in xylenol orange
g	Gram
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
H_2O_2	Hydrogen peroxide
HDL-C	High-density lipoprotein cholesterol
HPLC	High-performance liquid chromatography
HR	Heart rate
HRP	Avidin-horseradish peroxidase
HS	High-sensitivity
ICAM-1	Intercellular adhesion molecule-1
IL-1	Interleukin-1
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-33	Interleukin-33
IL-35	Interleukin-35
IP-10	Interferon gamma-induced protein 10
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile range
ISWT	Incremental Shuttle Walk Test
K_2EDTA	Dipotassium ethylene-diamine-tetra-acetic acid
kg	Kilogram
kg/m^2	Kilograms per metre squared

LDL-C	Low-density lipoprotein cholesterol
LOOH	Lipid hydroperoxides
LVEF	Left ventricular ejection fraction
m	Metre
m/s	Metres per second
MCP-1	Monocyte chemoattractant protein-1
MeSH	Medical Subject Headings
MET	Metabolic equivalent
MET-minutes/ week	Metabolic equivalent minutes per week
mg/L	Milligrams per litre
Mig	Monokine induced by gamma interferon
mL	Millilitres
$mL \cdot min^{-1}$	Millilitres per minute
mm	Millimetres
mm/ h	Millimetres per hour
$mM \cdot L^{-1}$	Millimoles per litre
mmHg	Millimetres of mercury
mRNA	Messenger ribonucleic acid
n	Number
NACR	National Audit for Cardiac Rehabilitation
NAD(P)H	Nicotinamide adenine dinucleotide phosphate
NAD^+	Nicotinamide adenine dinucleotide
NF-κβ	Nuclear factor-kappa beta
ng/mL	Nanograms per millilitre
NI	Northern Ireland
nm	Nanometres
NO	Nitric oxide
NSTEMI	Non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
O_2^-	Superoxide anion
OD	Optical density
OH•	Hydroxyl radical
$ONOO^-$	Peroxynitrite
ORECNI	Office for Research Ethics Committees Northern Ireland
PBS	Phosphate buffered saline

PCI	Percutaneous coronary intervention
pg/mL	Picograms per millilitre
PIS	Participant information sheets
PP	Polypropylene
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PTX-3	Pentraxin 3
RANTES	Regulated on activation, normal T-cell expressed and secreted
RHR	Resting heart rate
RI	Reflective index
ROB	Risk of bias
ROS	Reactive oxygen species
RPE	Rate of perceived exertion
RPM	Rotations per minute
RPMI	Roswell Park Memorial Institute
RT	Resistance training
s	Seconds
SBP	Systolic blood pressure
SCM	Standard clinical measurement
SD	Standard deviation
SEHSCT	South Eastern Health and Social Care Trust
SEM	Standard error of the mean
SI	Stiffness index
SIRT	Sirtuin
SIRT-1	Sirtuin-1
SMD	Standardised mean difference
SOD	Superoxide dismutase
SPSS	Statistical Product and Service Solutions
SSTs	Serum separating tubes
STEMI	ST-segment elevation myocardial infarction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TC	Total cholesterol
TDF	Theoretical Domains Framework
TG	Triglycerides
TNF-α	Tumour necrosis factor-alpha
TNF-α SR1	Soluble tumour necrosis factor-alpha receptor 1

TP	Time point
UK	United Kingdom
UU	Ulster University
$\dot{V}O_{2peak}$	Peak oxygen uptake
VCAM-1	Vascular cell adhesion molecule-1
vWF	von Willebrand factor
WC	Waist circumference
μm	Micrometre

List of Publications/ Scientific Communications and Statement of the PhD Student's Contributions

Paper 1 (Published)

Thompson, G., Davison, G.W., Crawford, J. and Hughes, C.M. (2020) Exercise and inflammation in coronary artery disease: a systematic review and meta-analysis of randomised trials. *Journal of Sports Sciences*, 38 (7), 814-826.

PhD Student's contribution: First author, drafted and compiled the manuscript, developed search strategy, performed literature search, analysed selected studies, revised manuscript in accordance with co-authors' comments, submitted manuscript to journal, revised manuscript for re-submission to journal, managed the review process.

Paper 2 (submitted for publication)

Thompson, G., Davison, G.W., Crawford, J. and Hughes, C.M. (2020) Exercise and cardioprotection in coronary artery disease: a pilot prospective cohort study. *Journal of Sports Sciences.*

PhD Student's contribution: First author, drafted and compiled the manuscript, co-developed the study alongside the research team, developed methodology, compiled ethics documents and managed the applications process, recruited participants to the study, performed data collection and biochemical analysis, completed data analysis, revised manuscript based on co-authors' comments, submitted manuscript to journal.

Paper 3 (submitted for publication)

Thompson, G., Wilson, I.M., Davison, G.W., Crawford, J. and Hughes, C.M. (2020) "Why would you not listen? It is like being given the winning lottery numbers and deciding not to take them": semi-structured interviews with post-acute myocardial infarction patients and their significant others exploring factors that influence participation in cardiac rehabilitation and long-term exercise training. *Disability and Rehabilitation*.

PhD Student's contribution

First author, drafted and compiled the manuscript, co-developed the study alongside the research team, developed methodology, compiled ethics documents and managed the applications process, recruited participants to the study and conducted interviews, performed data analysis and interpretation of findings, revised manuscript based on co-authors' comments, submitted manuscript to journal.

Dissemination (conference presentations)

1. **Thompson, G.,** Davison, G.W., Crawford, J. and Hughes, C.M. Exercise and inflammation in coronary artery disease: a systematic review and meta-analysis of randomised trials. Inaugural Doctoral Collaborative Conference, Queen's University Belfast, Belfast, Northern Ireland, 2019.

PhD Student's contribution: First author, drafted and compiled the application, created and delivered the presentation.

2. **Thompson, G.,** Wilson, I.M., Davison, G.W., Crawford, J. and Hughes, C.M. "Why would you not listen? It is like being given the winning lottery numbers and deciding not to take them": semi-structured interviews with post-acute myocardial infarction patients and their significant others exploring factors that influence participation in cardiac rehabilitation and long-term exercise training. British Association for Cardiovascular Prevention and Rehabilitation Annual Conference, Online, 2020.

PhD Student's contribution: First author, drafted and compiled the application, created and delivered the presentation.

Planned dissemination

The PhD Student intends to locally disseminate the findings of the research project by attempting to arrange presentations for cardiac rehabilitation teams, Active Belfast, and the Public Health Agency.

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Declaration

I confirm that the content of this thesis is my own work and it has not been submitted, in part or whole, to any other university of institution.

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Chapter 1

Introduction

1.0 Introduction

1.1 Coronary Artery Disease

Cardiovascular disease (CVD) is an umbrella term that encompasses conditions that affect the heart, blood vessels, or circulatory system (Mendis et al., 2011). In particular, coronary artery disease (CAD) is a form of CVD that is characterised by an accumulation of fibrous atherosclerotic plaque (asymmetric focal thickenings of the intimal layer of an artery) in the coronary arteries (Hansson, 2005). This vascular perturbation may result in myocardial cells being deprived of oxygen and nutrients (myocardial ischaemia) as a consequence of progressive narrowing and/or complete occlusion of the coronary arteries that perfuse the myocardium (Libby & Theroux, 2005). Whilst it is common for healthcare professionals to utilise the phrases CAD, coronary heart disease, and acute coronary syndrome (ACS) interchangeably (Sanchis-Gomar et al., 2016), the term CAD will be used throughout this thesis to denote atherosclerotic development in the coronary arteries.

Testament to the seminal evidence generated by the Framingham Heart Study (Kannel et al., 1961; Kannel, 1967; Kannel et al., 1976; Gordon & Kannel, 1976; Schildkraut et al., 1989; Lloyd-Jones et al., 1999), the following conditions are recognised as CVD risk factors that promote CAD development: age (> 65 years old are at a greater risk), male gender, family history, diabetes mellitus, hypertension, dyslipidaemia, obesity, physical inactivity, and smoking.

1.2 Pathophysiology of Coronary Artery Disease

Atherosclerosis is classified as the deposition of cholesterol in large and medium-sized arteries (Savoji et al., 2019). Importantly, it is now believed that chronic low-grade systemic inflammation, which is characterised by modest (2-4 fold) elevations in pro-inflammatory cytokines (*i.e.* interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α)) and acute-phase reactants (*i.e.* C-reactive protein (CRP) and fibrinogen) (Ridker et al., 2000), constitutes a primary pathophysiological mechanism for atherosclerotic development and clinical sequalae (Ambrose & Bhullar, 2019; Bäck et al., 2019). In particular, atherosclerotic development is a gradual process that initiates decades prior to

the consequential cardiovascular complications, with the rate of progression during the subclinical (asymptomatic) phase being accelerated by the presence of CVD risk factors (Berenson et al., 1998). As such, persistent intimal thickening of the developing atherosclerotic plaque may encroach the vessel lumen, which would induce myocardial ischaemia secondary to partial or complete occlusion of a coronary artery (Santos-Gallego et al., 2014). The clinical manifestations of which are characterised by ACS (Ambrose & Singh, 2015):

- Unstable angina pectoris – typically a consequence of partial coronary artery occlusion, with no evidence of myocardial necrosis (damaged myocardial cells); characterised by a sudden deterioration in symptoms (chest pain/ discomfort) of stable angina pectoris, recurring or persistent angina at rest, or new onset of severe angina (National Institute for Health and Care Excellence, 2019). Patients with unstable angina pectoris are at an increased risk of CAD progression to an acute myocardial infarction (AMI) or sudden cardiac death (SCD) (National Institute for Health and Care Excellence, 2019).

- Non-ST-segment elevation myocardial infarction (NSTEMI) – a form of AMI that is often the consequence of partial coronary artery occlusion; characterised by the presentation of symptoms of unstable angina pectoris, evidence of myocardial necrosis (*i.e.* elevated cardiac troponin levels) due to an imbalance in the ratio of myocardial blood supply to myocardial oxygen demand, and detection of transient ST elevation, ST depression, or new T wave inversions on an electrocardiogram (ECG) (Basit et al., 2019). Patients who have suffered an NSTEMI are at an increased risk of CAD progression to ST-segment elevation myocardial infarction (STEMI) or SCD (National Institute for Health and Care Excellence, 2019).

- STEMI – a form of AMI that is typically secondary to complete coronary artery occlusion; characterised by symptoms of unstable angina pectoris, evidence of myocardial necrosis (more significant than NSTEMI), and detection of new ST-segment T wave changes or new left bundle branch block on an ECG (Zipes et al., 2018). Patients who have suffered an STEMI typically sustain irreversible

myocardial necrosis, which increases the possibility of future cardiovascular complications (National Institute for Health and Care Excellence, 2019).

- SCD – defined as an unexpected cardiac-related death within a transient time period (generally < 1 hour from presentation of symptoms) (Zipes & Wellens, 1998), and is typically a consequence of a fatal arrythmia (*i.e.* ventricular fibrillation) secondary to myocardial ischaemia (Ambrose & Singh, 2015).

1.3 Epidemiology of Coronary Artery Disease

CAD is a leading cause of mortality and morbidity globally, with this cardiovascular perturbation being responsible for 9.48 million deaths worldwide in 2016 (Naghavi et al., 2017). Despite improvements in CVD science and medical care over the past few decades, CAD remains a substantial international public health epidemic. The increased survival rate following AMI has resulted in a residual population of CAD patients at risk of suffering recurrent cardiovascular events (*i.e.* ACS or cardiac death) (Smolina et al., 2012; Koch et al., 2015). Studies have shown that approximately 50% of post-AMI patients may suffer a recurrent event or require subsequent revascularisation in the year after the initial cardiovascular complication (Bischoff et al., 2006; Tuppin et al., 2009; Andrés et al., 2012), and up to 75% may experience a recurrent event within 3 years (Andrés et al., 2012). Collectively, healthcare systems worldwide are facing a substantial prevalence of CAD, which emphasises the current importance of effective secondary prevention to improve long-term prognosis of this disease.

1.4 Cardioprotective Effect of Exercise

Recent results from large, prospective cohort studies indicate that higher levels of physical activity are associated with lower cardiovascular mortality rates in CAD patients (Stewart et al., 2017; Lahtinen et al., 2018; Biscaglia et al., 2019). As such, exercise fulfils a pivotal role in the secondary prevention of CAD (Knuuti et al., 2019). In particular, exercise has been referred to as a "polypill" due to the plethora of consequential cardioprotective physiological adaptations (Fiuza-Luces et al., 2013). Firstly, there is evidence that 5-6 hours of moderate-intensity aerobic exercise per week (expending

> 2200 kilocalories per week in leisure-time physical activity) incites regression of coronary atherosclerotic plaque in CAD patients (Hambrecht et al., 1993). This exercise-induced attenuation of CAD progression may be attributed to an improvement in coronary endothelial function (Hambrecht et al., 2000), amelioration of CVD risk factors (*i.e.* dyslipidaemia, hypertension, and obesity) (Taylor et al., 2006; Marzolini et al., 2012), reduced inflammation (Swardfager et al., 2012), diminished oxidative stress (Edwards et al., 2004), and decreased arterial stiffness (Zhang et al., 2018). In addition, exercise may alleviate the symptoms of angina pectoris by improving myocardial perfusion due to enhanced coronary blood flow secondary to improved coronary vasodilation (Hambrecht et al., 2003; Bruning & Sturek, 2015). Moreover, an increased exercise capacity may elicit protection against recurrent cardiovascular complications, with evidence to suggest that every 1 millilitre (mL) of oxygen per kilogram (kg) of body weight per minute increase in peak oxygen uptake ($\dot{V}O_{2peak}$) confers a 14 – 17% reduction in risk for cardiovascular and all-cause death in CAD patients (Keteyian et al., 2008). Collectively, exercise constitutes a secondary prevention intervention that not only improves quality of life for CAD patients by mitigating angina pectoris symptoms and improving exercise capacity, but also bears the potential to directly diminish the progressive course of coronary atherogenisis.

In order to counter CAD development and progression, exercise should be performed at an intensity (*i.e.* > 40% of $\dot{V}O_{2peak}$), frequency ($\geq$ 2 sessions per week), and duration ($\geq$ 20 minutes) that contribute to an improvement in cardiorespiratory fitness (Fletcher et al., 2001; Myers et al., 2002). As such, the European Society for Cardiology recommend for CAD patients to participate in 30-60 minutes of moderate-intensity aerobic exercise (*i.e.* 50-75% of maximum heart rate (HR_{max})) on $\geq$ 5 days per week (Knuuti et al., 2019). Indeed, this exercise modality has been shown to reduce all-cause mortality in CAD patients by approximately 26% (Jolliffe et al., 2002). Whilst studies in this area have primarily focussed on the effects of moderate-intensity aerobic exercise on the health of CAD patients (Bruning & Sturek, 2015), other exercise modalities (*i.e.* high-intensity aerobic exercise, interval training, and resistance training (RT)) have been gaining attention, with evidence to suggest that moderate to high-intensity aerobic exercise positively affects systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and $\dot{V}O_{2peak}$ (Chen

et al., 2017); high-intensity interval training improves $\dot{V}O_{2peak}$ and SBP to a greater extent than moderate-intensity aerobic exercise (Chen & Tang, 2020); and a combination of aerobic exercise and RT is more effective than aerobic exercise alone in augmenting $\dot{V}O_{2peak}$, muscle strength, and muscle hypertrophy (Marzolini et al., 2012). Therefore, the exercise modality and intensity that incites the greatest health benefits in CAD patients is not currently clear, with the response to exercise training potentially depending on the level of cardiorespiratory fitness and disease progression that an individual possesses (Bruning & Sturek, 2015). Nonetheless, the importance of CAD patient adherence to long-term exercise is well recognised, with evidence to suggest that participation in long-term ($\geq$ 1 year) aerobic exercise (60-85% of HR_{max}) results in improved myocardial perfusion (Linxue et al., 1999). Moreover, without sustained adherence, exercise-induced cardioprotective physiological adaptations may be lost (Vona et al., 2009; Theodorou et al., 2016). Indeed, the literature indicates that CAD patients who remain or become physically inactive possess a greater risk for cardiac death than those who remain at least irregularly active (Lahtinen et al., 2018). As such, CAD patients should aim to incorporate exercise into their daily routine (Bruning & Sturek, 2015).

There is evidence to suggest that reductions in inflammatory factors (CRP, fibrinogen, and intercellular adhesion molecule-1 (ICAM-1)) substantially contribute to the inverse association between physical activity and CAD risk (Mora et al., 2007). In particular, a meta-analysis of 23 studies performed by Swardfager et al. (2012) sought to delineate the impact of exercise on inflammation in CAD patients. The results of which suggested that exercise may reduce inflammatory activity, as indicated by lower post-intervention values of CRP, fibrinogen, IL-6, and vascular cell adhesion molecule-1 (VCAM-1). These findings emphasise the salient role of exercise in the secondary prevention of CAD by supporting an anti-inflammatory effect. However, the evidence produced by Swardfager et al. (2012) was generated by pooling randomised and non-randomised studies; the latter study design potentially decreases the validity of the results due to selection bias (Reeves et al., 2008). Therefore, there is a requirement to update the evidence base by synthesising a rigorous evaluation of the capability of exercise to serve as an anti-inflammatory strategy in CAD patients by solely analysing randomised trials. Utilising this approach will mitigate the possibility of overstating the impact of exercise and facilitate a valid examination of intervention effect (Reeves et al., 2008).

Whilst the anti-inflammatory effect of exercise may represent a primary mechanism through which the secondary prevention of CAD is conferred, the molecular transducers that mediate this cardioprotection are yet to be fully elucidated (Sallam & Laher, 2016). Thus, assessing the feasibility of performing a study in this area is warranted. The results of which may guide the hypotheses and study designs of future fully powered investigations that seek to identify the molecular interactions that underlie the physiological adaptations induced by exercise in CAD patients. This future knowledge bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets).

1.5 Cardiac Rehabilitation

The cornerstone of secondary prevention strategies is cardiac rehabilitation (CR), which is a programme for delivering evidence-based management to alleviate the physiological and psychological ramifications of CVD, reduce the risk of recurrent cardiovascular complications, and control cardiac symptoms (Dalal et al., 2015). Lifestyle factors are powerful determinants of CVD risk factors (Piepoli et al., 2016), with evidence to suggest that adopting healthy lifestyle behaviours (*i.e.* smoking cessation, complying with physical activity recommendations, a healthy diet, and maintaining a healthy body weight) decreases the risk of recurrent cardiovascular events and death in CAD patients (Giannuzzi et al., 2008; Chow et al., 2010; Booth et al., 2014). Thus, CR aims to empower patients with the knowledge required to optimise cardiovascular risk reduction by implementing healthy lifestyle adjustments (see Table 1.1 for a summary) (Dalal et al., 2015). The patient populations presented in Table 1.2 are eligible for referral to a CR programme. Whilst exercise is a primary component of CR, current guidelines recommend the implementation of "comprehensive" CR programmes, which typically consist of a synergistic combination of supervised exercise training, optimal pharmacological therapy, psychological support (*i.e.* stress management), and lifestyle advice (*i.e.* cardiovascular risk reduction, physical activity, dietary intake, smoking cessation, weight management, and adherence to prescribed medication) (National Institute For Health and Care Excellence, 2013; Piepoli et al., 2014; British Association

for Cardiovascular Prevention and Rehabilitation, 2017). However, the structure of CR programmes differs across the globe (Supervia et al., 2019), and may be influenced by national guidelines, standards, legislation, and payment factors (Bjarnason-Wehrens et al., 2010). In the United Kingdom (UK), the standard structure of CR comprises four phases:

- Phase-I – prescription of secondary prevention medication and provision of information pertaining to the appropriate management of the patient's cardiovascular condition at a pre-discharge consultation with clinical staff (preferably a member of the CR team). In addition, the patient is invited to participate in phase-III CR (discussed below) (Bethell et al., 2009).

- Phase-II – period of convalescence at home prior to the initiation of phase-III CR; education regarding healthy living and encouragement to increase physical activity levels are provided by telephone or a home visit from a member of the CR or primary care team (Bethell et al., 2009).

- Phase-III – a comprehensive CR programme delivered by a multidisciplinary team (*i.e.* cardiologists, specialist nurses, physiotherapists, exercise therapists, dieticians, and psychologists) to supervised groups in outpatient hospital clinics or community centres (Dalal et al., 2015), which typically begins 2-4 weeks after myocardial revascularisation or AMI, and usually 4-6 weeks after cardiac surgery (Bethell et al., 2009). Prior to the initiation of a phase-III CR programme, an individualised patient care plan is developed following a clinical assessment of medical history, evaluation of the results generated by routine investigations (*i.e.* ECG, echocardiogram, blood lipid panel, and fasting blood glucose), physical examination (*i.e.* body weight, waist circumference (WC), body mass index (BMI), resting heart rate (RHR), and blood pressure), and assessment of exercise capacity (*i.e.* incremental shuttle walk test (ISWT)) (Bethell et al., 2009). A course of supervised exercise training is the centrepiece of a phase-III CR programme, which often comprises 20-60 minutes of moderate-intensity circuit training.

Patients would typically alternate between aerobic exercise and RT interspersed with periods of active recovery (Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2015). Current UK guidelines recommend that patients should be prescribed an exercise intensity between 40-70% of heart rate reserve (HRR) and/or a rating of perceived exertion (RPE) between 11-14 on the Borg scale. Moreover, exercise HR and RPE levels should drop below the prescribed exercise intensity during periods of active recovery to provide patients with temporary respite (Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2015). The supervised exercise component is also supplemented by optimal pharmacological therapy, psychological support, and lifestyle advice (Bethell et al., 2009). Most phase-III CR programmes involve weekly attendance at group sessions for approximately 8-weeks (Dalal et al., 2015). Prior to being discharged from the programme, patients undergo a final clinical assessment to evaluate CVD risk factor levels and to ensure that appropriate secondary prevention medication has been prescribed. Furthermore, strategies for long-term compliance with exercise and healthy lifestyle adjustments would be discussed, and patients would be offered an opportunity to enter a phase-IV CR programme (Bethell et al., 2009).

- Phase-IV – constitutes the lifelong maintenance of positive lifestyle habits (Bethell et al., 2009). Following the clinically supervised phase-III CR programme, patients should be empowered with the knowledge required to independently participate in long-term exercise training to manage their health (*i.e.* an understanding of the appropriate frequency, intensity, duration, and type of exercise) (Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2015). To assist with this long-term adherence, the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) have established a scheme with fitness centres and gyms in the private sector that involves qualified exercise instructors facilitating a phase-IV CR programme for patients who have graduated from phase-III CR. This programme is typically 12-weeks in duration and serves as a continuation of supervised exercise training for patients in a community setting. Patients usually attend one supervised group-based exercise session per week, with the form of exercise corresponding with phase-III CR.

Upon completion of the phase-IV CR programme, patients are informed of appropriate exercise-maintenance schemes that are available within their local communities (Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2015). Medical follow-up is managed by primary care providers via annual assessments of symptoms, secondary prevention medication, body weight, blood pressure, blood lipid panels, and lifestyle factors (*i.e.* exercise habit, smoking status, and dietary intake) (Bethell et al., 2009).

The literature supports the ability of a CR programme to reduce mortality and morbidity in CAD patients (Anderson et al., 2016; Rauch et al., 2016; Abell et al., 2017; Anderson et al., 2017; Kabboul et al., 2018), with evidence to suggest an 8% reduction in cardiovascular mortality (Anderson et al., 2016), 10% reduction in all-cause mortality (Abell et al., 2017), and 26% reduction in hospital admission (Anderson et al., 2016). Moreover, the results of a recent network meta-analysis performed by Kabboul et al. (2018) emphasised the centrality of exercise training as the key component of CR by identifying beneficial effects on the risk of all-cause mortality, risk of total-AMI, and risk of fatal-AMI. Collectively, considerable evidence supports the ability of a CR programme to improve prognosis and quality of life for CAD patients. As such, CR is a Class 1 level A recommendation in clinical guidelines for this patient population (Piepoli et al., 2016; Knuuti et al., 2019).

Table 1.1 Recommended lifestyle adjustments for CAD patients (Knuuti et al., 2019)

Lifestyle factor	Description
Smoking cessation	Utilise pharmacological therapy and behavioural strategies to assist with smoking cessation.
Healthy diet (*i.e.* Mediterranean-style dietary pattern)	High intake of vegetables, fruit, whole grains, legumes, nuts (in moderation), fish, and limited quantities of refined carbohydrates, red meat, low and non-fat dairy products, and liquid vegetable oils. Restrict saturated fats to < 10% of total energy intake, and limit alcohol to < 100 g per week or 15 g per day.
Healthy weight	Obtain and maintain a BMI of < 25 kg/m² through recommended energy intake and increased physical activity.
Physical activity	Participate in 30 – 60 minutes of moderate-intensity aerobic activity on ≥ 5 days per week.
Pharmacological therapy	Adhere to prescribed secondary prevention medication.

%, percent; g, grams; BMI, body mass index; and kg/m², kilograms per metres squared.

Table 1.2 Patient populations who are eligible for referral to a CR programme
(BACPR, 2017)

Priority patient groups	Other patient groups known to benefit
ACS	Stable angina pectoris
Coronary revascularisation (*i.e.* CABG or PCI)	Peripheral arterial disease
Heart failure	Post-cerebrovascular event
	Post-implantation of cardiac defibrillators and resynchronisation devices
	Post-heart valve repair/replacement
	Post-heart transplantation and ventricular assist devices
	Adult congenital heart disease

ACS, acute coronary syndromes; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.

1.6 Participation in Cardiac Rehabilitation and Long-Term Exercise

Despite the clinical benefits, CR programmes are underutilised by patients worldwide (Kotseva et al., 2013; Turk-Adawi & Grace, 2015; Beatty et al., 2018). Locally, the most recent National Audit of CR (NACR) report of data collected between 2017 and 2018 stated that participation in CR programmes across the UK remained suboptimal; overall uptake was 50% (68,074 of 135,861 eligible patients enrolled), with uptake in Northern Ireland (NI) reaching 49% (2,645 of 5,357 eligible patients enrolled) (British Heart Foundation, 2019b). In addition, the literature indicates that adherence to long-term

exercise in CAD patients is poor (Sweet et al., 2011; Blanchard et al., 2014; Kotseva et al., 2019). Thus, identifying methods of promoting patient participation in CR and long-term exercise may result in a reduced burden of CAD by improving CVD risk profiles, with concomitant societal and economic benefits through lower rates of premature mortality, fewer hospital readmissions, and improved quality of life (De Gruyter et al., 2016). To assist with the development of these strategies, more work is needed to identify and understand the factors that influence participation in CR and adherence to long-term exercise training in CAD patients.

1.7 Aims and Objectives of the Thesis

This thesis aims to further scientific understanding of the role of exercise in the secondary prevention of CAD by rigorously evaluating the capability of exercise to serve as an anti-inflammatory strategy in this patient population, and by assessing the feasibility of investigating the molecular mechanisms that may mediate this cardioprotective physiological adaptation. This novel scientific evidence may inform the hypotheses and study designs of future fully powered studies that attempt to identify the molecular transducers that underlie the secondary prevention induced by exercise. Moreover, a better understanding of the factors that influence CR participation and long-term exercise training will be sought by exploring the experiences and perspectives of CAD patients and their significant others. This qualitative knowledge may guide the development of interventions that encourage patient participation in CR and adherence to long-term exercise training.

Objectives:

1) To examine the capability of exercise to serve as an anti-inflammatory strategy in CAD patients by performing a systematic review and meta-analysis of randomised trials (Study 1).

2) To perform a pilot prospective cohort study that assesses the feasibility of investigating the effect of exercise (delivered as a CR programme) on molecular mechanisms that may mediate anti-inflammatory physiological adaptation in CAD patients (Study 2).

3) To conduct semi-structured interviews with patients and their significant others to explore the factors that influence CR participation and long-term exercise adherence (Study 3).

The beforementioned aims and objectives have informed the chapters within this thesis. Specific aims of each study that was performed are presented within the respective chapters.

Chapter 2

Literature Review

2.0 Literature Review

2.1 Background Literature Related to Inflammation and Coronary Artery Disease

The prevailing viewpoint four decades ago attributed atherosclerotic development to a bland proliferative process involving an accumulation of cholesterol and smooth muscle cells in the arterial wall (Ross & Glomset, 1976). However, subsequent investigations into the cell biology of atherosclerosis have supplanted this simplistic concept by identifying the involvement of immune cells and inflammatory mediators in each stage of atherogenesis (Jonasson et al., 1986; Libby, 1991; Kovanen et al., 1995; Hansson & Libby, 2006). As such, the pivotal role that chronic low-grade inflammation fulfils in atherosclerotic development is now well recognised (Ambrose & Bhullar 2019). Inflammation represents a complex cascade of biochemical events that serve as a biological attempt to eradicate noxious stimuli (e.g. pathogens, damaged cells, or irritants) and initiate tissue repair. However, in the case of atherosclerosis, this defence mechanism may become impaired due to an imbalance between pro-resolving and pro-inflammatory mediators, which potentially elicits a state of non-resolving inflammation that drives the development of atherosclerotic lesions (Tabas, 2010). The primary mediators of the inflammatory response during atherogenesis are as follows:

- Pro-inflammatory cytokines (*i.e.* interleukin-1 (IL-1), IL-6, and TNF-α) – a class of high molecular weight polypeptides that facilitate cell-signalling in relation to inflammatory reactions, immunological responses, and basic biological functions (*i.e.* haematopoiesis) (Soeki & Sata 2016). Pro-inflammatory cytokines are generated by and influence the majority of cells implicated in the pathogenesis of atherosclerosis (*i.e.* vascular smooth muscle cells, endothelial cells, macrophages, and monocytes), and orchestrate the inflammatory vascular environment in each stage of atherosclerotic development, from initial endothelial dysfunction to consequential plaque formation and rupture (Tedgui & Mallat, 2006). Indeed, there is evidence to suggest a log-linear relationship between levels of IL-6 and TNF-α and the risk of CAD in initially healthy people (Kaptoge et al., 2013), and IL-6 concentration has been associated with adverse cardiovascular outcomes in CAD patients following ACS (Fanola et al., 2017).

- Anti-inflammatory cytokines (*i.e.* interleukin-10 (IL-10), interleukin-33 (IL-33), and interleukin-35 (IL-35)) – a series of immunoregulatory molecules that mitigate inflammation by modulating the pro-inflammatory cytokine response (Opal & DePalo, 2000). Anti-inflammatory cytokines may elicit protection against atherosclerotic development by tempering various cellular processes that promote atherogenesis, such as: immune cell responses (Miller, 2011), activation of the pro-inflammatory transcription factor nuclear factor-kappa beta (NF-κβ) (Wang et al., 1995), metalloproteinase production (Lacraz et al., 1995), TNF-α synthesis (Rajasingh et al., 2006), and the expression of ICAM-1 on endothelial cells (Lisinski & Furie, 2002). Importantly, low IL-10 levels have been associated with death and non-fatal AMI in CAD patients after ACS (Heeschen et al., 2003; Oemrawsingh et al., 2011).

- Chemokines (*i.e.* interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and fractalkine) – a group of cytokines that are produced in large amounts at inflammatory regions to form a chemotactic gradient that attracts leukocytes to the sites of inflammation or injury (Soeki & Sata, 2016). Chemokines fulfil a pivotal role throughout atherogenesis by promoting inflammation due to the activation and recruitment of various immune cells to sites of vascular injury and atherosclerotic lesions (Zernecke et al., 2008). In particular, elevated concentrations of IL-8 and MCP-1 have been associated with an increased risk of CAD development in apparently healthy individuals (Boekholdt et al., 2004; Hoogeveen et al., 2005), and recurrent cardiovascular complications in CAD patients (de Lemos et al., 2003; Inoue et al., 2008).

- Acute-phase reactants (*i.e.* CRP and fibrinogen) – a class of proteins that increase in concentration during the acute-phase of inflammation, which is characterised by a > 25% change in circulating levels of acute-phase reactants (Armstrong et al., 2006). This reaction is proportionate to the magnitude of the inflammatory stimulus, and is primarily mediated by the production of acute-phase reactants by hepatocytes,

adipocytes, macrophages, and endothelial cells in response to a rise in IL-6 and TNF-α (Gabay & Kushner, 1999). Importantly, the levels of acute-phase reactants may remain persistently elevated in the presence of continuing inflammatory stimuli, which would contribute to a state of chronic low-grade systemic inflammation (Armstrong et al., 2006). Beyond serving as a biomarker of systemic inflammation, acute-phase reactants may possess a direct pathophysiological role in the development and progression of atherosclerosis by promoting endothelial dysfunction (Pasceri et al., 2000), foam cell formation (Zwaka et al., 2001), pro-inflammatory cytokine production (Ballou & Lozanski, 1992), and thrombus formation (Reinhart, 2003). Specifically, CRP is a principal inflammatory biomarker for predicting the risk of CAD development (levels > 3 micrograms per millilitre (μg/mL) confer greater risk) (Madjid et al., 2007; van Holten et al., 2013), and recurrent cardiovascular complications (van Holten et al., 2013). Moreover, there is evidence to suggest that fibrinogen concentration is also associated with incident CAD and adverse future outcomes (Coppola et al., 2005; van Holten et al., 2013).

- Adhesion molecules (*i.e.* VCAM-1, ICAM-1, E-selectin, and P-selectin) – a group of cell-surface proteins that mediate the migration of leukocytes from the bloodstream towards inflammatory foci (González-Amaro et al., 1998). An early phase of atherosclerotic development involves the recruitment and transendothelial migration of inflammatory cells (Nakashima et al., 1998). This process is primarily facilitated by adhesion molecules, which are expressed on endothelial cells in response to inflammatory stimuli (Blankenberg et al., 2003). Additionally, soluble forms of adhesion molecules are released from the surface of endothelial cells upon activation (Blankenberg et al., 2003), which may serve as circulatory biomarkers of endothelial dysfunction (Constans & Conri, 2006). Moreover, soluble ICAM-1 levels may correlate with the magnitude of atherosclerotic plaque burden (Gross et al., 2012), and soluble concentrations of VCAM-1, ICAM-1, and E-selectin have been associated with future death from cardiovascular causes in CAD patients (Blankenberg et al., 2001).

2.1.1 Endothelial Dysfunction

Atherosclerotic development is believed to be triggered by focal endothelial cell dysfunction (Jensen & Mehta, 2016). Importantly, there is evidence to suggest that impaired endothelial function precedes angiographic detection of coronary atherosclerosis in humans (Zeiher et al., 1991; Bugiardini et al., 2004), with the incidence of endothelial dysfunction predicting future CAD development (Schächinger et al., 2000; Yeboah, 2004; Yoboah et al., 2009; Maruhashi et al., 2013). In an unperturbed state, the endothelial cells of the endothelium (interface between the blood stream and vessel wall) maintain vascular health by serving as a semi-permeable barrier that regulates the exchange of macromolecules, nutrients, solutes, hormones, and leukocytes between the blood and tissue; modulates platelet function, inflammatory responses, vascular smooth muscle cell growth and migration; and controls vascular tone by releasing vasodilatory (*i.e.* nitric oxide (NO), prostacyclin, and endothelial-derived hyperpolarising factor) and vasoconstrictive substances (*i.e.* endothelin-1 (ET-1) and angiotensin-II) (Cahill & Redmond, 2016). Importantly, in addition to a vasodilatory effect, NO is primarily responsible for mediating anti-inflammatory and anti-atherogenic (*i.e.* suppression of oxidative stress and smooth muscle cell proliferation) protection of the endothelium (Tousoulis et al., 2012). NO is synthesised from L-arginine by three isoforms of NO synthase (NOS) (neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) (Bruckdorfer, 2005), with eNOS constituting the primary source of NO production under normal physiological conditions in the cardiovascular system and endothelial cells (Dudzinski & Michel, 2007). However, in a dysfunctional state, the endothelium undergoes a maladaptive change in endothelial cell gene expression, eliciting a pro-atherogenic inflammatory phenotype (Gimbrone Jr & García-Cardeña, 2016). This is characterised by impaired endothelial vasodilation due to diminished production and/ or bioavailability of NO; the expression of cellular adhesion molecules including: VCAM-1, ICAM-1, E-selectin, and P-selectin; along with the production of chemokine agents, such as: MCP-1, fractalkine, and IL-8 (Gimbrone Jr & García-Cardeña, 2016). Saliently, an inverse correlation between endothelial function and principal CVD risk factors (*i.e.* diabetes mellitus, dyslipidaemia, hypertension, obesity, physical inactivity, and smoking) has been observed (Celermajer et al., 1994; Benjamin et al., 2004; Maruhashi et al., 2013; Campbell et al., 2019). This data generates a

mechanistic link between traditional CVD risk factors and the initiation of CAD development (Libby, 2012; Park & Park, 2015).

Mechanistically, CVD risk factors (*i.e.* physical inactivity, diabetes mellitus, and obesity) may incite endothelial dysfunction by promoting inflammation and reactive oxygen species (ROS) production (Vita, Keaney Jr al., 2004; Fischer et al., 2007; Bandeira et al., 2012; Maruhashi et al., 2013; Weiner et al., 2014; Smitka & Maresova, 2015). To elaborate, ROS (e.g. superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH•)) are derived from the partial reduction of oxygen during metabolic and enzymatic reactions (Ray et al., 2012). Several endogenous mechanisms may serve as a source of ROS generation, such as: mitochondrial oxidative phosphorylation, xanthine oxidase, cyclooxygenases, peroxidases, uncoupled eNOS, nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidases, and inflammatory cell activation (Bhattacharya, 2015). Despite being highly reactive due to the presence of unpaired electrons, ROS fulfil a pivotal role in mediating cell signalling and regulation, such as: growth factor signalling, hypoxic signal transduction, autophagy, and immune responses (Holmström & Finkel, 2014). An antioxidant is characterised by the ability to delay, prevent, or remove oxidative damage to a target molecule (Halliwell & Gutteridge, 2015). The biological network of antioxidants (see Figure 2.1 for an overview) maintains ROS at an appropriate physiological threshold for mediating essential cellular processes and circumventing a toxic effect (Barbieri & Sestili, 2012). However, a state of oxidative stress would occur if the concentration of ROS overwhelms antioxidant defences, which may result in damage to macromolecules (lipids, proteins, and nucleic acids) (Sies et al., 2017). In particular, elevated levels of O_2^- may directly induce endothelial dysfunction by scavenging NO (Pryor & Squadrito, 1995). In addition, peroxynitrite ($ONOO^-$) is formed as a consequence of this reaction, which would also contribute to impaired endothelial function by stimulating the production of ROS instead of NO by eNOS (eNOS uncoupling) (Kuzkaya et al., 2003). In terms of inflammation, pro-inflammatory mediators (e.g. IL-1, IL-6, and TNF-α) may induce endothelial dysfunction by activating NF-κβ, which would result in the transcription of pro-inflammatory genes (e.g. VCAM-1, ICAM-1, and E-selectin) in endothelial cells (Collins et al., 1995). Importantly, oxidative stress and inflammation share common, overlapping signalling pathways; ROS may promote inflammation by stimulating NF-κβ (Canty Jr et al., 1999), whilst immune

cells may generate ROS as by-products during inflammatory processes (Forman & Torres, 2002).

The presence of endothelial dysfunction initiates a cascade of complex, multi-factorial events that lead to the formation of atherosclerotic lesions. Firstly, endothelial permeability increases, which facilitates the entry of circulating LDL-C into the tunica intima (Tabas et al., 2007). The pro-inflammatory vascular environment is a source of ROS production, which oxidises the accumulated LDL-C, exerting further disruption to endothelial function. Additionally, the inflammatory response is sustained by circulating monocytes and T-lymphocytes selectively attaching to cellular adhesion molecules (*i.e.* ICAM-1, VCAM-1, E-selectin, and P-selectin) expressed by the dysfunctional endothelium. Subsequently, chemoattractant stimuli (*i.e.* MCP-1) incite the migration of monocytes and T-lymphocytes into the tunica intima, where monocytes differentiate into macrophages and engulf oxidised LDL-C (ox-LDL), which contributes to the development of foam cells (Libby et al., 2011). Moreover, the gathering macrophages and T-lymphocytes amplify vascular inflammation by producing MCP-1 and pro-inflammatory cytokines, such as: IL-1, IL-6, interferon-gamma (IFN-γ), and TNF-α. This magnified inflammatory state stimulates the migration of vascular smooth muscle cells from the tunica media into the tunica intima, which would elicit the development of a fibrous cap that encapsulates a lipid-laden, necrotic core (Tabas et al., 2015).

The integrated action of dysfunctional endothelial cells, vascular smooth muscle cells, monocytes, macrophages, and T-lymphocytes during atherogenisis establishes an intricate paracrine milieu of inflammatory mediators and ROS within the vessel wall (Gimbrone & Garcia-Cardena, 2016). Importantly, an augmented vascular production of IL-6 and TNF-α may extend the inflammatory response beyond the initial focal area of endothelial dysfunction by stimulating hepatic synthesis of acute-phase reactants (*i.e.* CRP and fibrinogen) (Hansson, 2005). This induces a state of chronic low-grade systemic inflammation, which perpetuates endothelial dysfunction and the development of atherosclerotic plaque by diminishing NO bioavailability; augmenting the production of ET-1 and inflammatory cytokines; and stimulating an increased endothelial cell expression of vascular cell adhesion molecules (Gimbrone & Garcia-Cardena, 2016). Also, a coagulative vascular environment is provoked through increased synthesis of pro-thrombotic mediators, such as: von Willebrand factor (vWF), plasminogen activator

inhibitor-1, and tissue factor (Libby, 2012). The chronic pro-inflammatory vascular state may culminate in the proteolytic degradation of the extracellular matrix components of the fibrous cap via macrophage production of matrix metalloproteinases, rendering the atherosclerotic plaque structurally unstable (Libby et al., 2002). As a result, atherosclerotic plaque rupture may occur, which would incite luminal release of the highly thrombogenic contents of the necrotic core. Subsequently, an intraluminal thrombus may be formed due to the stimulation of the coagulation cascade. This pathological state may induce ACS (clinical manifestation previously discussed) secondary to partial or complete occlusion of a coronary artery (Santos-Gallego et al., 2014).

Antioxidant network

Endogenous

Exogenous (primarily supplied by dietary intake)

Enzymatic

Non-enzymatic

- Superoxide dismutase

- Catalase

- Glutathione peroxidase

- Glutathione

- Thioredoxin

- Ubiquinone

- Uric acid

- Alpha-lipoic acid

- Vitamins (C & E)

- Beta-carotene

- Trace elements (zinc & selenium)

- Polyphenols (phenolic acids & flavonoids)
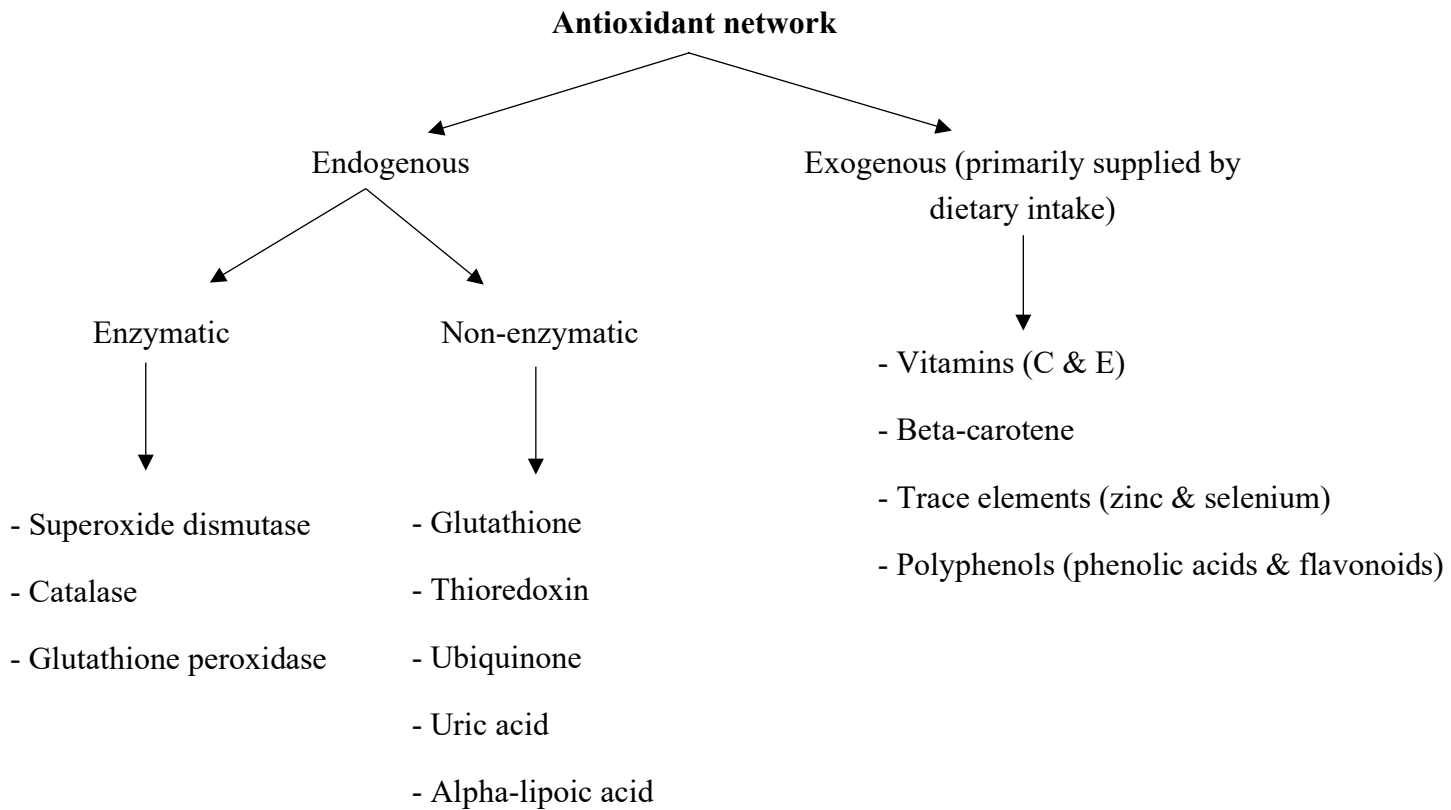
Figure 2.1 Overview of human antioxidant defence system (Bouayed & Bohn, 2010)

2.1.1.1 Measurement of Endothelial Function

The pathological role that endothelial dysfunction assumes in CVD development and sequalae has led to an increasing interest in measuring endothelial function to inform patient risk classification, guide clinical management, monitor responses to interventions (*i.e.* lifestyle changes or pharmacological compounds), and establish if augmenting endothelial function diminishes CVD progression (Alexander et al., 2020). Invasive and non-invasive methods of assessing endothelial function exist, each of which possesses inherent strengths and limitations (Alexander et al., 2020). Across these methods, the fundamental principle involves healthy arteries dilating in response to reactive hyperaemia-induced shear stress (flow-mediated dilatation (FMD)) or in response to endothelial-stimulating pharmacological substances (*i.e.* acetylcholine (ACh)), whilst the

presence of endothelial dysfunction results in a reduced or absent vasodilatory response (Flammer & Lüscher, 2010). Coronary epicardial function is the gold standard technique for measuring coronary endothelial function, which involves the utilisation of quantitative coronary angiography or intra-vascular ultrasound to assess changes in the vessel diameters of epicardial coronary arteries in response to endothelium-dependent pharmacological interventions (*i.e.* ACh). Whilst this method possesses the key advantage of measuring endothelial function in the clinically relevant vascular bed, it is invasive, expensive, time intensive, limited to those undergoing coronary angiography, and impractical for serial measurements (Alexander et al., 2020). These limitations have contributed to the development of non-invasive, inexpensive techniques for evaluating endothelial function in the peripheral vasculature. Across these non-invasive approaches, brachial FMD is the most widely utilised method of evaluating peripheral macrovascular endothelial function (Alexander et al., 2020). This ultrasound-based assessment involves quantifying the endothelium-dependent vasodilatory response of larger conduit arteries to reactive hyperaemia following a transient period of suprasystolic occlusion of the brachial artery. The consequential reactive hyperaemia stimulates the local release of NO by endothelial cells due to an increase in shear stress (tangential force applied by laminar blood flow across the endothelium) (Rodriguez-Miguelez et al., 2016). Importantly, the literature suggests that brachial FMD represents a surrogate measure of coronary artery endothelial function (Takase et al., 1998; Broxterman et al., 2019), is influenced by CVD risk factors (Maruhashi et al., 2013), and may serve as a predictor of recurrent cardiovascular complications in CAD patients (Inaba et al., 2010; Maruhashi et al., 2018). Additionally, shear stress and baseline brachial artery diameter (parameters of the brachial FMD assessment) *per se* have demonstrated correlations with CVD risk factors and cardiovascular outcomes (Huang et al., 2007; Philpott et al., 2009; Yoboah et al., 2009). Nonetheless, brachial FMD constitutes a challenging procedure that warrants extensive operator training and familiarisation. Moreover, the lack of consensus on a standardised protocol for brachial FMD (i.e. variations in cuff placement or duration and magnitude of cuff occlusion) has rendered comparisons between studies difficult. Indeed, a recent position paper published by the European Society for Cardiology recommended for a consensus brachial FMD methodology to be universally adopted to limit technical variation between studies, and for reference FMD values to be determined in different populations (healthy individuals and patient groups) (Alexander et al., 2020). The establishment of uniformity in brachial FMD methodology may increase comparability

between studies, enable the development of reference values, and allow brachial FMD to serve as a marker of atherosclerosis that supplements clinical symptoms and enhances diagnosis and prediction of CVD outcomes (Thijssen et al., 2019). Importantly, progress in this area is being made through the recent publication of expert consensus guidelines for the brachial FMD procedure (Thijssen et al., 2019), along with the determination of reference values for a Japanese population (Tomiyama et al., 2015) and age- and sex-specific reference intervals for brachial FMD in healthy individuals (Holder et al., 2020). Collectively, brachial FMD is a useful tool for investigating the pathophysiology of CVD and examining the acute or long-term effect of physiological and pharmacological interventions on endothelial function in humans (Thijssen et al., 2019).

2.1.2 Arterial Stiffness

The inflammatory state and oxidative milieu induced by endothelial dysfunction may promote pathogenic arterial remodelling that leads to an increase in large artery stiffness, with consequential reductions in arterial compliance and elasticity (Wang & Fitch, 2004). Indeed, endothelial dysfunction and chronic low-grade inflammation have been associated with greater arterial stiffness (van Bussel et al., 2011). Arterial stiffness reflects the rigidity of the arterial wall, and is influenced by the structural (*i.e.* quantity and quality of elastin fibres and collagen) and functional (*i.e.* release of vasodilatory substances (*i.e.* NO) by the endothelium) properties of arteries (Wilkinson et al., 2002; Laurent et al., 2005). The presence of arterial stiffness attenuates the capacity of arteries to accommodate the blood ejected by the left ventricle, which may contribute to substantial pulsatile afterload (Jain et al., 2014). The adverse haemodynamic consequences of which may include increased SBP and pulse pressures (Franklin et al., 1997); myocardial ischaemia secondary to cardiac overload and diminished coronary perfusion (Kingwell, 2002); and peripheral organ damage (*i.e.* brain or kidney) due to the transfer of pulsatile energy (O'Rourke & Safar, 2005). In particular, inflammation may promote arterial stiffening via structural and functional mechanisms. Structurally, the compliance of the arterial wall is contingent on the balance of collagen and elastin fibres (Zieman et al., 2005). However, vascular inflammation and oxidative stress may result in dysregulation of this balance, leading to the overproduction of collagen, repressed quantities of normal

elastin fibres, and proliferation of smooth muscle cells (Jain et al., 2014). Beyond structural changes, arterial stiffness is influenced by vascular smooth muscle cell tone, which is modulated by vasodilatory agents (*i.e.* NO) synthesised by endothelial cells (Zieman et al., 2005). Inflammation and endothelial dysfunction may reduce NO bioavailability and increase the activity of vasoconstrictive substances (*i.e.* ET-1), which would promote arterial stiffening due to an increase in vascular smooth muscle cell tone (Stehouwer et al., 2008). Importantly, the cellular changes related to arterial stiffness may predispose the vasculature to atherosclerotic insult (Wang & Fitch, 2004). Indeed, there is evidence to suggest that arterial stiffness is associated with recurrent cardiovascular complications in CAD patients (Maruhashi et al., 2018). Collectively, arterial stiffness represents the structural and mechanical properties of large arteries. As such, the measurement of arterial stiffness may compliment brachial FMD by capturing the structural and functional health of the arterial wall (Green et al., 2017).

2.1.3 Anti-Inflammatory Treatment for the Secondary Prevention of Coronary Artery Disease

The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) recently tested the inflammatory hypothesis of atherosclerosis by investigating the effect of canakinumab (a monoclonal antibody that targets the interleukin-1 beta (IL-1β) innate immunity pathway, consequently reducing IL-6 and downstream CRP (Ridker, 2016)) on vascular events and mortality in post-AMI CAD patients with residual inflammatory risk (high sensitivity (hs)-CRP values $\geq$ 2 milligrams per litre (mg/L)) (Ridker et al., 2017). The results of this investigation demonstrated that a 150 mg dose of canakinumab every 3 months led to a significant reduction in hs-CRP and the rate of recurrent cardiovascular events compared to placebo (Ridker et al., 2017; Ridker et al., 2018), with decreases in IL-6 also being strongly associated with the relative benefit of treatment (Ridker et al., 2018). Thus, CANTOS generated proof-of-principle evidence for the clinical benefits of anti-inflammatory treatment in post-AMI CAD patients with residual inflammation, and highlighted the potential importance of targeting components of the IL-1β/ IL-6 signalling pathway for the secondary prevention of CAD.

The optimisation of lifestyle factors (≥ 1.5 hours per week of physical activity, healthy diet (Mediterranean diet score > 12 points), and smoking cessation) may eliminate residual inflammatory burden in CAD patients (reductions in hs-CRP value to < 2 mg/L) (Blaum et al., 2019). Thus, the implementation of positive lifestyle changes in CAD patients may constitute a safe and cost-effective form of anti-inflammatory therapy. In particular, a meta-analysis of 23 studies performed by Swardfager et al. (2012) demonstrated that exercise reduces inflammatory activity in CAD patients, as indicated by lower post-intervention values of CRP, fibrinogen, IL-6, and VCAM-1. However, the methodological limitations of this review reduced the validity of the evidence for this effect. Thus, the published systematic review and meta-analysis in section 4.0 provides a robust examination of the influence of exercise on inflammation in CAD patients.

2.2 Summary of Published Systematic Review and Meta-Analysis (Paper 1)

The published systematic review and meta-analysis (**Paper 1**) is presented in section 4.0: *"Exercise and inflammation in coronary artery disease: a systematic review and meta-analysis of randomised trials"*. The Electronic Supplementary Material (ESM) for **Paper 1** is presented in Appendix A. Literature published until August 2019 was included in this review. As such, the search strategy was repeated in November 2020 to ascertain if relevant studies had been published since August 2019. The same inclusion and exclusion criteria were utilised to determine if studies were suitable for inclusion. No new studies were identified. Therefore, the results of the systematic review and meta-analysis (**Paper 1**) are representative of the current literature.

This systematic review and meta-analysis examined the capability of exercise to serve as an anti-inflammatory strategy in CAD by analysing the results of randomised trials that investigated the effect of exercise on inflammation in CAD patients. A systematic literature search of electronic databases and grey literature sources resulted in the identification of twenty-five studies that were suitable for inclusion in the review. Outcomes were pooled in a random-effects inverse variance model to calculate standardised mean differences (SMDs) with 95% confidence intervals (CIs). Descriptive analyses were performed for studies and outcomes that were unsuitable for inclusion in meta-analyses. The results demonstrated an anti-inflammatory effect of exercise in CAD

patients, as indicated by quantitative and qualitative evidence that supports a beneficial effect of exercise on acute-phase reactants (CRP, fibrinogen, and vWF). However, the impact of exercise on proximal mediators of inflammation and anti-inflammatory cytokines is equivocal, which may be attributed to a paucity of research. Altogether, the findings of this review suggest that exercise induces an anti-inflammatory effect in CAD patients. Although, the quality of evidence for this area needs to be improved by further randomised studies with high methodological qualities and large sample sizes. Progress in this area may result in exercise being utilised as a substitute for or an adjunct to anti-inflammatory pharmacological treatment in future clinical practice related to the secondary prevention of CAD.

2.3 Literature Surrounding Cardioprotective Molecular Mechanisms

Through a complex interplay, systemic inflammation mediates numerous pathophysiological pathways that may contribute to CAD development and clinical sequalae, such as: oxidative stress (Kotur-Stevuljevic et al., 2007), endothelial dysfunction (Weiner et al., 2014), and arterial stiffness (van Bussel et al., 2011). Therefore, the anti-inflammatory effect of exercise, as demonstrated in section 4.0, may represent a primary mechanism through which the secondary prevention of CAD is conferred. The beneficial impact of exercise on inflammation in CAD patients may be attributed to indirect and direct anti-inflammatory effects. Traditional CVD risk factors (*i.e.* dyslipidaemia, obesity, and physical inactivity) are principal pathogenic drivers of systemic inflammation (Munkhaugen et al., 2018; Blaum et al., 2019). Thus, exercise may indirectly reduce inflammation by ameliorating CVD risk factors; Swardfager et al. (2012) reported that greater reductions in CRP values following exercise were associated with greater decreases in total cholesterol (TC) concentrations, and Fedewa et al. (2017) observed greater exercise-induced reductions in CRP when accompanied by a decrease in BMI or relative adiposity. Beyond an attenuation of CVD risk factors, exercise may also alleviate inflammation through direct mechanisms (Fiuza-Luces et al., 2018). Firstly, skeletal muscle is an endocrine organ with the capacity to synthesise and release myokines (a cytokine or signalling protein produced by skeletal muscle) (Febbraio & Pedersen, 2005). During exercise, muscle contractions stimulate the release of IL-6 from skeletal muscle cells into systemic circulation, which promotes an anti-inflammatory

milieu by suppressing the generation of pro-inflammatory mediators (*i.e.* IL-1 and TNF-α) and triggering the production of anti-inflammatory cytokines (*i.e.* IL-10) (Steensberg et al., 2003; Starkie et al., 2003). Exercise may also diminish inflammation by modulating the immune system via multiple mechanisms, such as: reducing the quantity of circulating pro-inflammatory monocytes (Timmerman et al., 2008), switching macrophages to a less inflammatory phenotype (M2) (Yakeu et al., 2010; Ranjbar et al., 2019), increasing the concentration of anti-inflammatory regulatory T-cells (Wang et al., 2012), and attenuating the expression of Toll-like receptors on monocytes (Flynn & McFarlin, 2006). As discussed earlier, endothelial dysfunction serves as a vascular source of inflammatory mediator production, which may perpetuate a state of chronic low-grade inflammation by stimulating hepatic synthesis of acute-phase reactants (*i.e.* CRP) (Gimbrone & Garcia-Cardena, 2016). However, repetitive exposure of the endothelium to a shear stress stimulus during exercise may restore endothelial function and diminish inflammatory activity by enhancing NO bioavailability through increased expression of eNOS and by mitigating the transcription of pro-inflammatory genes (*i.e.*VCAM-1, ICAM-1, IL-6, and TNF-α) in endothelial cells through NF-κβ suppression (Hambrecht et al., 2000; Hambrecht et al., 2003; Lesniewski et al., 2011).

Given that inflammation and oxidative stress share interconnected signalling pathways (Canty Jr et al., 1999; Forman & Torres, 2002), an exercise-induced amelioration of oxidative stress may also constitute a mechanism through which inflammation is alleviated and vice versa. The elevated metabolic demands during exercise incite increased oxygen uptake and blood flow to skeletal muscles and other organs. Consequently, ROS generation is increased in several endogenous mechanisms, such as: mitochondrial oxidative phosphorylation, xanthine oxidase, and NAD(P)H oxidase (Ji, 1999). This transient exercise-induced increase in ROS stimulates redox-sensitive transcription factors, such as: peroxisome proliferator-activated receptor-gamma coactivator-1 alpha and activator protein-1, which may result in an adaptive antioxidant response through an increased expression of antioxidant enzymes (*i.e.* superoxide dismutase (SOD), glutathione peroxidase, and catalase) (Vasilaki et al., 2006; St-Pierre et al., 2006). In addition, exercise may alleviate systemic oxidative stress through the reduction of ROS production secondary to NAD(P)H oxidase downregulation (Adams et al., 2005). Indeed, clinical studies have documented decreases in systemic

oxidative stress as indicated by reductions in markers of lipid peroxidation (8-isoprostane-F2α and thiobarbituric acid reactive substances), enhanced antioxidant defence (increased plasma SOD activity), and augmented NO production (increased plasma nitrite and nitrate levels) in CAD patients following an exercise programme (Edwards et al., 2004; Taty et al., 2018). Altogether, the physiological adaptations induced by exercise confer direct and indirect protection against inflammation. These effects may represent a primary mechanism through which exercise induces secondary prevention of CAD. However, the molecular transducers that mediate the anti-inflammatory adaptations of exercise are yet to be fully elucidated (Sallam & Laher, 2016).

The sirtuin (SIRT) network of nicotinamide adenine dinucleotide (NAD^+) dependent enzymes may represent a molecular mechanism that underlies the cardioprotective effect of exercise (Suwa & Sakuma, 2013). Across the 7 SIRT isoforms, sirtuin-1 (SIRT-1) is the most widely studied (Winnik et al., 2015). In particular, SIRT-1 is located in the nucleus and cytoplasm, with a primary function of catalysing deacetylation of histone lysine residues (Winnik et al., 2015). The removal of an acetyl group (deacetylation) from a lysine increases the positive charge of the lysine residues, which enhances the affinity of histone-deoxyribonucleic acid (DNA) interactions. Consequently, gene transcription is decreased as the access of transcription factors to the DNA template is reduced (Eberharter & Becker, 2002). In addition to histones, SIRT-1 may also modulate the function of non-histone proteins via deacetylation, such as: transcription factors, enzymes, cofactors, and structural proteins (Michan & Sinclair, 2007). Deacetylation of these proteins may result in activation or inactivation of the factor (Pillarisetti, 2008). As such, SIRT-1 plays a pivotal role in the regulation of gene expression through chromatin silencing and transcriptional repression, and mediates the activity of a multitude of protein targets (Haigis & Sinclair, 2010). These biological functions place SIRT-1 at the centre of a variety of critical cellular processes, such as: the maintenance of metabolic homeostasis, reduction of cellular damage, and modulation of inflammatory activity (Winnik et al., 2015).

Initial research identified an association between the SIRT family and longevity in lower organisms (Kaeberlein et al., 1999). Since then, efforts have been made to elucidate the mechanisms through which SIRT-1 may improve health (Winnik et al., 2015). Consequently, evidence that supports a beneficial effect of SIRT-1 on various pathogenic states that are implicated in CAD has emerged. To elaborate, experimental *in vitro* and animal studies have shown that SIRT-1 may improve endothelial function by activating eNOS in endothelial cells (Mattagajasingh et al., 2007); reduce inflammation by inhibiting NF-κβ activation (Yeung et al., 2004); and attenuate oxidative stress by mitigating NAD(P)H oxidase activation and inducing the expression of antioxidant enzymes (SOD and catalase) (Ferrara et al., 2008; Rahman et al., 2009; Zarzuelo et al., 2013; Conti et al., 2015). In terms of clinical research, various human studies have observed a decreased gene expression of SIRT-1 in peripheral blood monocytes and peripheral blood mononuclear cells of ACS and stable CAD patients compared to healthy controls (Breitenstein et al., 2013; Hu et al., 2015; Li et al., 2016; Chan et al., 2017). Importantly, Chan et al. (2017) documented that the peripheral blood monocytes of stable CAD patients possessed elevated levels of oxidative stress (increased lectin-like ox-LDL receptor-1 expression, elevated ROS production, and repressed antioxidant enzyme (SOD and catalase) activity) and inflammation (upregulated NF-κβ activity) in comparison to healthy controls. Further, the peripheral blood monocytes of stable CAD patients induced endothelial dysfunction when exposed to human umbilical vein endothelial cells in an *in vitro* experiment. Interestingly, the beforementioned aberrations were reversed by SIRT-1 overexpression and activation. In addition, Li et al. (2016) recorded an inverse correlation between SIRT-1 gene expression in peripheral blood monocytes and plasma levels of inflammatory mediators (IL-6, TNF-α, MCP-1, and hs-CRP) in stable CAD patients with type 2 diabetes mellitus. Moreover, low serum levels of SIRT-1 have been associated with high-risk coronary plaques in asymptomatic CAD patients (He et al., 2019). Collectively, clinical studies have documented repressed levels of SIRT-1 in CAD patients, with concomitant up-regulation of inflammatory activity and oxidative stress. However, experimental research indicates that this protein may confer protection against the pathogenic conditions that are implicated in atherogenesis (*i.e.* inflammation, oxidative stress, and endothelial dysfunction).

The requirement of NAD^+ (cofactor) for fuelling enzymatic reactions links SIRT-1 activity to cellular energy status, with activity and expression increasing during periods of low energy availability, such as: during exercise or caloric restriction (Winnik et al., 2015). The cellular mechanisms that orchestrate an exercise-induced increase in SIRT-1 concentration and activity may involve the stimulation of adenosine monophosphate-activated protein kinase through an elevated adenosine monophosphate/ adenosine triphosphate ratio (Guerra et al., 2010), an increased NAD^+/ NAD^+ dehydrogenase ratio secondary to upregulated expression of nicotinamide phosphoribosyltransferase (Costford et al., 2010), synthesis of the early response element factor-1 due to skeletal muscle contraction (Pardo et al., 2011), increased NO production by virtue of augmented NO synthase expression (Nisolio et al., 2005), and augmented shear stress due to increased blood flow (Chen et al., 2010).

The effect of exercise on SIRT-1 has been primarily investigated in animal models, with evidence to support a beneficial effect on SIRT-1 expression and/ or activity and concomitant alleviations of oxidative stress (enhanced antioxidant enzyme (SOD and catalase) expression and activity, reduced ROS production, decreased protein oxidation, and mitigated lipid peroxidation) and inflammation (NF-κβ inhibition) (Ferrara et al., 2008; Koltai et al., 2010; Chan et al., 2018; Donniacuo et al., 2019; Jia et al., 2019). Various investigations in apparently healthy humans have documented an increase in SIRT-1 expression and/ or activity following a high-intensity interval training programme (Gurd et al., 2010; Little et al., 2010; Gurd et al., 2011). Studies in clinical populations (patients with low-back pain and heart failure patients) have observed an increase in SIRT-1 expression or activity following exercise, which was associated with reductions in inflammation and/ or oxidative stress (Cheng et al., 2015; Russomanno et al., 2017; Corbi et al., 2019). However, only one trial that examined the effect of exercise on SIRT-1 in a CAD patient population has been located. To elaborate, Alavizadeh et al. (2018) documented an increase in serum concentrations of SIRT-1 in post-coronary artery bypass graft (CABG), male CAD patients following an 8-week exercise programme comprising 3 sessions per week of either moderate-intensity aerobic exercise or combined training (moderate-intensity aerobic exercise and RT) in comparison to control, with no statistically significant difference between the two exercise groups. Whilst these results may support the ability of exercise to increase SIRT-1 levels in male CAD patients,

Alavizadeh et al. (2018) failed to investigate the subsequent influence on pathogenic states that are implicated in atherogenesis, such as: inflammation, oxidative stress, endothelial dysfunction, and arterial stiffness. Moreover, this study was not fully powered to detect statistically significant changes in SIRT-1 concentration (Alavizadeh et al., 2018), which limits data reliability (Faber & Fonseca, 2014).

Altogether, SIRT-1 may represent a mechanism that orchestrates the cardioprotective effects of exercise in CAD patients (see Figure 2.2 for a mechanistic overview of SIRT-1 molecular pathway). However, clinical evidence regarding this assertion is scarce. Thus, assessing the feasibility of performing a study in this area is warranted. The results of which may guide the hypotheses and study designs of future fully powered investigations that seek to identify the molecular interactions that underlie the physiological adaptations induced by exercise in CAD patients. This future knowledge bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets).
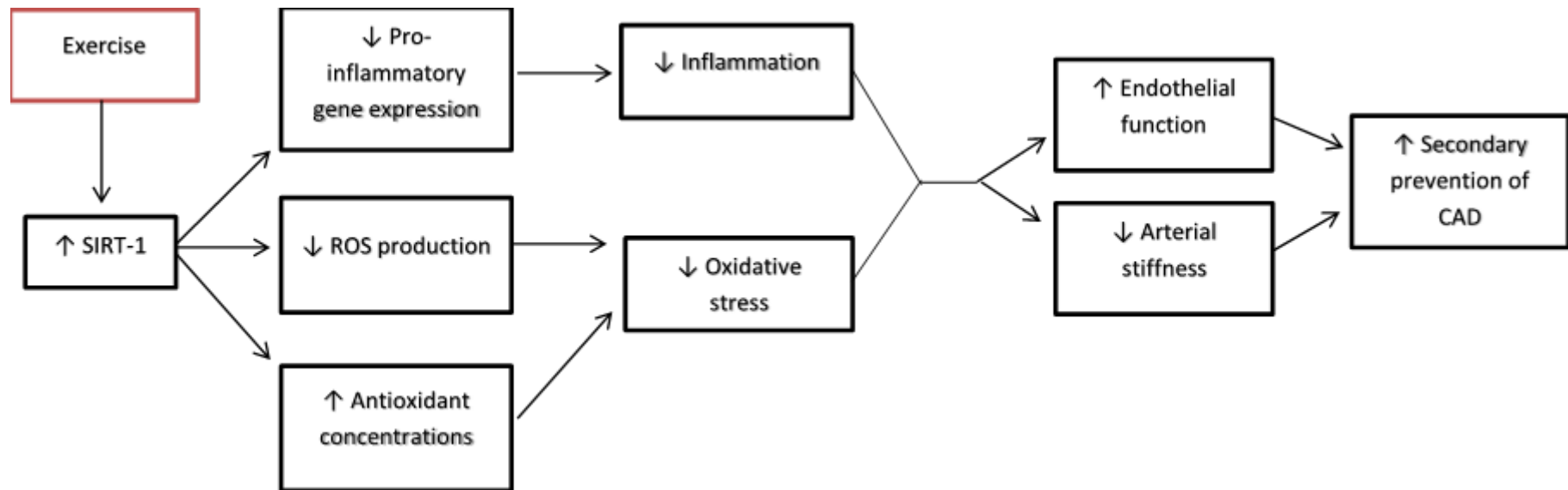
Figure 2.2 Mechanistic overview of SIRT-1 molecular pathway.

SIRT-1, sirtuin-1; ROS, reactive oxygen species; CAD, coronary artery disease

2.4 Literature Surrounding the Factors that influence Coronary Artery Disease Patient Participation in Cardiac Rehabilitation and Long-Term Exercise

The poor participation in CR across the globe is reason for concern as many eligible patients are failing to avail of optimal secondary prevention strategies, and receive the guidance required to implement positive lifestyle adjustments (Kotseva et al., 2013; Turk-Adawi & Grace, 2015; Beatty et al., 2018). Not surprisingly, there is evidence to suggest that a large majority of CAD patients across Europe lead an unhealthy lifestyle (smoking, not adhering to dietary guidelines, and sedentary behaviour) (Kotseva et al., 2019). In addition, patients who participate in CR may experience difficulties with long-term maintenance of exercise training following programme completion (Sweet et al., 2011; Blanchard et al., 2014). Importantly, without sustained adherence to exercise, the cardioprotective physiological adaptations induced by CR may be lost (Vona et al., 2009; Theodorou et al., 2016). Participation in CR is affected by a variety of intrinsic and extrinsic factors; a recent systematic review of quantitative studies performed by Resurrección et al. (2019) illuminated the complexity of this decision by identifying sixty-three factors associated with barriers to participation in CR, which were divided into the following five categories: intrapersonal factors (*i.e.* older age, female gender, low socioeconomic status, comorbidities, depressive symptoms, low-self efficacy for managing disease, and poor perceived benefit of CR), interpersonal factors (*i.e.* unmarried, unemployed or retired, and low social and practical support), clinical factors (*i.e.* smoker, higher BMI, poor functional capacity, uncontrolled cholesterol levels, diabetes mellitus, previous history of CVD, and disease severity), logistical factors (*i.e.* longer travel times, being a non-driver, lack of transport, and living in a rural or geographically inaccessible area), and healthcare system factors (*i.e.* lack of referral to CR and low strength of endorsement from physicians). These results are consistent with previous reviews in this area (Ruano-Ravina et al., 2016; Supervía et al., 2017).

Qualitative research methods possess the potential to generate an understanding of complex phenomena by enabling key knowledge holders to share their personal experiences and perceptions (Hennink et al., 2020). A systematic review of qualitative studies performed by Clark et al. (2012) found that personal factors (knowledge of services, patient identity, perceptions of CAD, financial constraints, and occupational

constraints) and contextual factors (family, and less frequently, health professionals) consistently influenced patients' decisions to enroll in CR. Moreover, Clark et al. (2012) concluded that participation in CR is primarily determined by social aspects, and suggested that future interventions to enhance enrollment in CR programmes should engage both patients and their significant others, such as: a family member, spouse, or close friend to harness social mechanisms (*i.e.* discussing the purpose and benefits of CR with the dyad, promoting the view of patients and significant others being partners in rehabilitation, and encouraging the significant other to support patient attendance by providing transport to centres, accompanying the patient to the programme, providing advice and information, communicating with healthcare professionals, or supporting the normalisation of exercise). These findings were echoed in a recent systematic review and meta-synthesis of qualitative studies that investigated the perspectives of CAD patients on exercise training and factors related to continued participation; internal factors (fear, motivation, and mood) and external factors (safety, accessibility, and social support networks) influenced exercise initiation and sustained participation (Campkin et al., 2017). Importantly, engagement and social support from significant others (*i.e.* offering advice and exercising with the patient) were reported as an integral factor for promoting adherence to long-term exercise in CAD patients (Campkin et al., 2017). Qualitative investigations that were published following the completion of the beforementioned systematic reviews also emphasise the importance of social support from significant others for encouraging patient participation in CR, positive lifestyle changes (*i.e.* smoking cessation, improved dietary intake, and increased physical activity levels), and long-term maintenance of exercise training (Rouleau et al., 2018; Sweet et al., 2019; Hanna et al., 2020).

The capacity of a patient's significant other to serve as a potential source of social support during the rehabilitation process has received increasing attention (Nissen et al., 2018; Resurrección et al., 2019). Significant others are inherently positioned to be affected by the patients' disease (*i.e.* emotional distress) (Son et al., 2013). Moreover, the literature suggests that CAD patients and their spouses often share similar dietary intakes, physical activity levels, and CVD risk factors (Macken et al., 2000; Yates et al., 2015). Social support comprises structural and functional elements (Uchino et al., 1996). In particular, the structural element of social support refers to the size, type, density, and

frequency of contact with the social network surrounding an individual (*i.e.* marital status, living arrangements, and frequency of interactions), whereas the functional element is characterised by the specific social requirements that can provide a person with a social network, and is divided into the following categories: practical (*i.e.* assistance with completing tangible tasks), financial (*i.e.* material aid and gifts), informational (*i.e.* guidance, advice, and counselling), and emotional (*i.e.* development of sympathetic relationships that allow confiding and intimacy) (Lett et al., 2005; Rozanski et al., 2005). As such, social support generates relationships that enable individuals to influence the behaviour of each other through daily interactions and feedback mechanisms, and creates a social network through which individuals can provide emotional support, informative advice, and practical assistance. Importantly, low levels of social support have been associated with elevated levels of emotional stress (Liu et al., 2017), accelerated CAD progression (Wang et al., 2006), and adverse cardiovascular outcomes (Pushkarev et al., 2019). Conversely, the provision of social support from a significant other has been shown to improve the prognosis of CAD patients (Schultz et al., 2017; Pushkarev et al., 2019), which may be attributed to an amelioration of stress via a buffering effect (Wiesmaierova et al., 2019), and promotion of positive lifestyle changes (*i.e.* increased physical activity levels and healthy dietary behaviour) (Aliabad et al., 2014; Nissen et al., 2018; Teleki et al., 2019); CAD patients have also reported that the quality of their recovery was directly contingent on the level of social support received from family and friends (Pryor et al., 2014); and frequent contact with friends and relatives (combination of structural and functional social support) has been associated with greater medication adherence (Mondesir et al., 2018). Thus, the dyad may influence each other when coping with CAD. Altogether, enrollment in CR and participation in long-term exercise training are complex choices for patients, with significant others potentially impacting the decisions (Clark et al., 2012; Campkin et al., 2017). However, qualitative literature in this area has primarily focused on the perspective of the patient (Rouleau et al., 2018; Sweet et al., 2019; Hanna et al., 2020); there is a scarcity of research concerning the experiences and perceptions of the significant other.

2.5 Outline of the Gaps in the Literature

This chapter demonstrated a beneficial effect of exercise on inflammation in CAD patients. However, to generate a comprehensive understanding of the anti-inflammatory effect of exercise in CAD patients, future research should explore the underlying molecular mechanisms that may be responsible for orchestrating this cardioprotective effect. Saliently, SIRT-1 may represent a molecular transducer that mediates exercise-induced cardioprotective physiological adaptation in CAD patients. However, there is a scarcity of clinical evidence regarding this assertion. Progress in this area may result in exercise being utilised as a substitute for or an adjunct to anti-inflammatory pharmacological treatment in future clinical practice related to the secondary prevention of CAD, and bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets). Moreover, a paucity of research regarding the factors that influence participation in CR and long-term exercise from the perspectives of both CAD patients and their significant others was identified. As such, generating qualitative knowledge in this area may promote a deeper understanding of barriers and facilitators to CR enrollment and long-term exercise training, which may inform the development of interventions to promote CAD patient participation. The beforementioned gaps in the literature informed the specific aims and objectives of the studies presented in this thesis.

Chapter 3

General Methodology

3.0 General Methodology

3.1 Study Design

Study 1 was designed as a systematic review and meta-analysis of randomised trials that investigated the effect of exercise on inflammation in CAD patients. This study design was chosen as the explicit, systematic methods facilitated a rigorous evaluation of the research question (Green et al., 2011). Moreover, the exclusion of non-randomised studies permitted a valid examination of intervention effect by decreasing the likelihood of potential biases (*i.e.* selection bias) (Reeves et al., 2008).

Study 2 was a pilot prospective cohort study that recruited a sample of post-AMI patients who had been invited to a phase-III CR programme at the Belfast Health and Social Care Trust (BHSCT) or South Eastern Health and Social Care Trust (SEHSCT), with study measurements being obtained at three Time Points (TPs) over the course of phase-III and phase-IV CR (22 weeks). TP-1 (week-1) and TP-2 (week-8) occurred on the first and final day of the phase-III CR programme, respectively. At TP-2, the participants who completed a phase-III CR programme were offered the opportunity to enter a phase-IV CR programme that was held at gyms or fitness centres in the private sector by the CR nurses as per routine procedure. The participants who agreed to participate in a phase-IV CR programme entered this programme around 2 weeks after the termination of a phase-III CR programme, and completed an additional 12 weeks of supervised exercise training at their routinely allocated site. TP-3 (week-22) occurred at the end of a phase-IV CR programme. The participants who completed phase-III CR supplied the study measurements before the exercise sessions at the corresponding hospital sites at TP-1 and TP-2, and at a time and location that was convenient for them at TP-3, such as: a BHSCT site or Ulster Hospital. Participants who did not take part in phase-III CR provided the study measurements at each TP at a time and location that was convenient for them, such as: a BHSCT site or Ulster Hospital.

Post-AMI patients were recruited as they represent the largest CAD patient group at CR programmes across the UK (British Heart Foundation, 2019b), which served as an

attempt to improve the generalisability of the results. The pilot component of the study design was selected to assess the feasibility of investigating the novel research objectives, with the aim of generating evidence that informs the study designs and hypotheses of future fully powered studies (Lancaster & Thabane, 2019). In addition, the prospective cohort element of the study design was implemented as it prevented disruption to the structure of the CR programmes, which allowed the results to potentially represent the effect of the routinely delivered programmes. This study design also enabled the participants to autonomously decide if they were willing to participate in CR, which prevented interference with the quality of routine care and services received. Finally, the prospective cohort study design did not involve any active attempts to prevent participant withdrawal, which allowed the generation of representative data.

Study 3 possessed a qualitative design that incorporated semi-structured interviews with patients and their significant others to investigate factors that influence CR attendance and long-term exercise adherence. A qualitative design was chosen as this research method facilitates the exploration of complex, subjective processes, such as: the decision to participate in CR or exercise (Silverman, 2016). Semi-structured interviews were selected over other methods of qualitative data collection (*i.e.* focus groups) in order to accommodate an in-depth exploration of an individual's personal perspective, attitude, and feelings towards the phenomena being investigated (Taylor et al., 2015). Additionally, the flexible nature of semi-structured interviews allowed questions that were open-ended and focused to be asked, which encouraged respondents to freely elaborate and emphasise the aspects of their experience that they felt were most important, whilst allowing the researcher to guide the process of the interview (Rubin & Rubin, 2011). Whilst there are advantages and disadvantages to interviewing members of a dyad separately or together, this study sought to prioritise the personal perceptions and perspectives of each individual by interviewing the patients and their significant others separately. This prevented the data that was captured from being influenced by the presence of the other participant, and provided a private space to discuss potentially sensitive topics (Taylor & De Vocht, 2011).

The specific design of each study is discussed in greater detail within the respective chapters.

3.2 Ethical Approval

Study 2 and Study 3 were submitted as a single application for ethical approval. Permission for the research proposal to be submitted for external review was received from the Filter Committee at Ulster University (UU) on the 24th October 2018 (see Appendix B (i)). Subsequently, a provisional opinion was given by the Office for Research Ethics Committees Northern Ireland (ORECNI) on the 5th December 2018 (see Appendix B (ii)), which requested the following amendments:

- The addition of a paragraph to the participant information sheets (PIS) to explain how limits of disclosure would be dealt with and reported (related to poor practice / criminal activity).

- To update the wording regarding the status of ethical approval in the PIS.

- To replace the reference to the Data Protection (1998) legislation with the 'General Data Protection Regulation' in the PIS.

Following the submission of the requested amendments to the ORECNI, a favourable ethical opinion was received on the 13th December 2018, Research Ethics Committee reference number: 18/NI/0213 (see Appendix B (iii)). Research Governance permission for the research project to commence at the BHSCT was issued on 22nd of February 2019, BHSCT reference number: 18123CH-AS (see Appendix B (iv)). Moreover, Research Governance permission for the research project to commence at the SEHSCT was provided on 16th May 2019, SEHSCT reference number: SET.18.35 (see Appendix B (v)). The commencement of recruitment at the BHSCT and SEHSCT was delayed until July 1st 2019 due to the processing of minor amendments (addition of data capture forms, registration of additional members of the research team at the BHSCT, anonymisation of

screening questionnaires, and revised location for the provision of study measurements at the final TP). As such, a request to postpone the termination of the research project from 2nd December 2019 until 1st July 2020, and for the recruitment period to be extended until 31st January 2020 was submitted to the BHSCT and SEHSCT Research Governance Divisions. Approval was received from the BHSCT on 23rd October 2019 (see Appendix B (vi)). The SEHSCT rejected the request for an extended recruitment period due to contractual obligations to another research project. However, approval for performing research activity with recruited participants until 1st July 2020 was issued (see Appendix B (vii)). The research project was performed in accordance with the Declaration of Helsinki (2002). All sample collection, storage, and analysis of human tissue complied with the Human Tissue Act (2004).

3.3 Participant Recruitment

Post-AMI patients who had been invited to participate in phase-III CR were recruited to Study 2 from the BHSCT (Belfast City Hospital, Royal Victoria Hospital, and Mater Hospital) and the SEHSCT (Ulster Hospital). These recruitment sites were chosen as each facilitates a phase-III CR programme that has received official certification from the BACPR/ NACR for satisfying national CR delivery standards (British Heart Foundation, 2019a). Patients who had either agreed or disagreed to participate in a phase-III CR programme were invited to participate in Study 2 to allow a comparison of the study measurements between a group of patients who received an exercise programme and a group of patients who did not. The specific inclusion / exclusion criteria and participant characteristics are presented in chapter 5. In general, post-AMI patients were eligible for recruitment if they were free from cardiovascular contraindications to safe exercise participation (*i.e.* uncontrolled hypertension, unstable angina, or uncontrolled cardiac arrhythmia), and were not consuming supplements that posed as potential confounding variables (*i.e.* vitamins, herbal supplements, exogenous hormones (*i.e.* testosterone or estrogen / progesterone), or antioxidants). The CR nurses across the collaborating sites identified potential participants by reviewing clinical records with a screening questionnaire related to medical conditions (see Appendix C). Subsequently, the CR nurses provided potential participants who agreed to take part in phase-III CR with the PIS (see Appendix D (i)) at their pre-assessment, and posted the PIS to potential

participants who refused phase-III CR (see Appendix D (ii)). To facilitate an organised approach to recruitment, the CR nurses maintained a record of all potential participants who had received PIS (see Appendix E).

The PIS detailed the purpose and protocol of Study 2 and Study 3, and supplied the contact information for the research team. Moreover, the PIS explained that interested patients were required to contact the PhD researcher (Mr Gareth Thompson (GT)). Upon receiving contact, the PhD researcher (GT) provided a verbal explanation of the research project, answered any questions or queries, and invited the interested patient to a meeting for recruitment on the first day of the phase-III CR programme at the corresponding hospital site. If the interested patient had refused phase-III CR, the meeting for recruitment was arranged for a time and location that was suitable for him/ her, such as: a hospital site at the BHSCT or SEHSCT. A 1-week "cooling-off" period occurred between initial patient contact and the meeting for recruitment. During the meetings for recruitment, the PhD researcher (GT) provided a thorough explanation of the research project and answered any questions or queries with an honest and transparent response. Patients who were willing to participate completed a final screening questionnaire (see Appendix F) related to inclusion / exclusion criteria that were not covered during the initial screen performed by the CR nurses. Eligible patients then provided written informed consent (see Appendix G), which confirmed that they were willing to participate in the research project, and provided permission for the following:

- For the research team to access their medical notes to extract information regarding clinical characteristics (see Appendix H (i)).

- For the research team to receive the results of standard clinical measurements (SCMs) routinely obtained by the CR nurses (See Appendix H (ii)).

- To be invited to participate in Study 3 during Study 2.

- For the collection and storage of blood samples.

The patient participants of Study 3 were recruited from the pool of participants in Study 2. In addition, the patients were requested to invite a significant other who had been primarily involved throughout the period of their cardiovascular complication and recovery to participate in this study. Whilst this convenience sampling method may result in diminished generalisability of the results due to limited variation of participant characteristics, it was selected due to the time constraints imposed by the PhD research project, and in consideration of the possibility of generating rich qualitative data by virtue of the level of familiarity between the PhD researcher (GT) and the sample population (Koerber & McMichael, 2008). The specific inclusion / exclusion criteria and participant characteristics are presented in chapter 6. Generally, individuals were eligible for recruitment if they possessed sufficient English language skills to understand and participate in an interview discussion, were over 18 years of age, and if both members of the dyad agreed to take part. The participants of Study 2 who provided informed consent for invitation to Study 3 were approached by the PhD researcher (GT) during the provision of study measurements. Subsequently, the PhD researcher (GT) provided a verbal explanation of the purpose and protocol of Study 3, and supplied the patients with their PIS (see Appendix I (i)) and PIS to provide their chosen significant other with (see Appendix I (ii)). The PIS informed the individuals to consider their willingness to participate during a "cooling-off" period of at least 1-week before contacting the PhD researcher (GT). Upon contact, the PhD researcher (GT) provided a verbal explanation of the study, answered any questions or queries, and arranged a suitable time and venue for the interview to take place, such as: the participant's home, a BHSCT site, or Ulster Hospital. Informed consent was received from the individuals before the interviews were performed (see Appendix J (i) and Appendix J (ii)). During data collection, the Coronavirus Disease 2019 (COVID-19) pandemic rendered face-to-face interviews unsuitable. As such, a number of interviews were performed via telephone calls. Verbal consent was obtained from the participants who were required to complete telephone interviews.

3.4 Data Collection

3.4.1 Study Measurements for Study 2

The study measurements were obtained in quiet, temperature controlled (22 degrees Celsius (°C) - 24 ºC) rooms at the collaborating sites. All study measurements were collected from patients before participation in the exercise sessions to avoid the confounding influence of acute haemodynamic and biochemical responses to exercise. Prior to study measurement acquisition, the participants were required to rest in a seated position for approximately 20 minutes to achieve a haemodynamic steady state. SCMs (ISWT and anthropometric measurements) were routinely collected by the CR nurses from participants at TP-1 and TP-2. The PhD researcher (GT) recorded these measurements at TP-3 in accordance with the methods described in the following sections.

3.4.1.1 Incremental Shuttle Walk Test

Exercise capacity represents the maximum amount of physical exertion that can be sustained, and reflects the ability of an individual to perform activities of daily living that warrant sustained aerobic metabolism (Goldstein, 1990). The integrated response and health of the cardiorespiratory and skeletal muscle systems determine exercise capacity (Arena et al., 2007). Therefore, this assessment provides important prognostic information, with evidence to suggest that exercise capacity is an independent predictor of all-cause and cardiovascular-specific mortality in CAD patients (Keteyian et al., 2008). The gold standard method of evaluating exercise capacity in this patient population is the cardiopulmonary exercise test or symptom-limited exercise test with ECG monitoring (ERS Task Force et al., 2007). However, these laboratory-based assessments are impractical in relation to routine clinical practice. Thus, the ISWT, an externally paced maximal field exercise test, was selected as the method of exercise capacity evaluation as it is non-invasive, can be administered practically in a clinical setting, and the outcome of the test (distance walked) has been shown to correlate with the outcome of the symptom-limited exercise test ($\dot{V}O_{2peak}$) in CAD patients (Fowler et al., 2005). Moreover, this test possesses clinical relevance as it is routinely performed during CR programmes to assess baseline exercise capacity, determine appropriate exercise prescriptions, and evaluate changes in cardiorespiratory fitness (Price et al., 2016).

The protocol that was employed for the ISWT complied with guidelines for field walking tests that were published by the European Respiratory Society / American Thoracic Society (Holland et al., 2014). The test was performed on an unobstructed gymnasium floor. Participants were required to walk back and forth around two cones placed 10 metres (m) apart. The walking speed was externally paced, with signal beeps played on a compact disk (The Shuttle Walk Test, University Hospital of Leicester) occurring at regular intervals to indicate when the participant should turn around the cone to commence the next shuttle. The test initiated with a walking speed of 0.5 m per second (m/s), with speed increments of 0.17 m/s each minute for a maximum of 12 minutes. HR was measured continuously with a Polar HR monitor (Polar Electro Oy, Finland). Measurements of HR and RPE on the Borg scale were recorded each minute. The test terminated if the participant felt unwell (*i.e.* chest pain or dyspnoea) or when the participant was no longer capable of matching the pace (being more than 0.5 m from a cone when the beep sounded). Upon test completion, the quantity of completed shuttles was recorded and the total distance walked (m) was calculated. Repetition of the test to ensure familiarity was unnecessary as the participants had prior experience of the assessment.

3.4.1.2 Anthropometric Measurements

Prior to acquisition of anthropometric measurements, participants were asked to remove footwear and jackets/ coats. Height was measured using a stadiometer (Marsden, Rotherham, UK) to the nearest 0.1 centimetre (cm). Body weight was assessed using body weight scales (Salter, Kent, UK) to the nearest 0.1 kg. BMI (kg per m squared (kg/m^2)) was calculated by dividing body weight (kg) by the square of height (m). WC was evaluated using anthropometric tape measure (Seca, Birmingham, UK) to the nearest 0.1 cm in accordance with the National Health and Nutrition Examination Survey protocol, with the uppermost lateral border of the right ilium serving as the standardised anatomical measurement site (Centers for Disease Control and Prevention, 2016).

3.4.1.3 Resting Heart Rate

RHR was measured using a Polar HR monitor (Polar Electro Oy, Finland) whilst participants rested in a supine position. The measurement was performed for 3 minutes, with the lowest value over this period being recorded as the RHR in beats per minute (BPM).

3.4.1.4 Blood Pressure

SBP and diastolic blood pressure (DBP) (millimetres of mercury (mmHg)) were recorded using an automated, non-invasive device (Omron Automatic Blood Pressure Monitor, Omron Healthcare, Lake Forest IL) in accordance with National Institute for Health and Care Excellence clinical guidelines (National Institute For Health and Care Excellence, 2019). The participants were seated during the assessment. The cuff was applied to the upper region of the left arm, which was supported by a table. Three measurements interspersed with 1-minute rest intervals were obtained. The mean of these values was then calculated and recorded.

3.4.1.5 Brachial Flow-Mediated Dilatation

Brachial FMD is a widely utilised non-invasive, ultrasound-based method of evaluating endothelial function *in-vivo*. This assessment was chosen as it may represent a surrogate measure of coronary artery endothelial function (Takase et al., 1998; Broxterman et al., 2019), and may serve as a predictor of recurrent cardiovascular complications in CAD patients (Inaba et al., 2010; Maruhashi et al., 2018). The brachial FMD test involves an ultrasound evaluation of the vasodilatory response to reactive hyperaemia (stimulus for NO production) following a period of distal limb ischaemia (Rodriguez-Miguelez et al., 2016). The protocol that was utilised complied with technical guidelines (Rodriguez-Miguelez et al., 2016; Thijssen et al., 2019). Brachial FMD measurements were obtained at a similar time of day at each TP to account for diurnal variation. Prior to measurement acquisition, participants completed a questionnaire to supply information regarding potential confounding factors (see Appendix K). Information supplied by participants through the completion of the brachial FMD questionnaires indicated that the presence of potential confounding factors prior to measurement acquisition was uncommon (*i.e.*

consumption of a high-fat meal over the past 6 hours, consumption of caffeinated or alcoholic beverages over the past 12 hours, smoked or exposed to second-hand smoke over the past 12 hours, or participated in exercise over the past 24 hours). While the intake of secondary prevention medication could not be avoided, brachial FMD examination was performed at a consistent time following drug administration. Moreover, all female participants had experienced menopause. During the procedure, the participant was in a supine position on a clinical bed, with his/ her right arm extended laterally at approximately 80° of shoulder abduction, and the distal forearm secured in a vacuum-packed pillow to stabilise the arm during the measurement. A 5 cm forearm occlusion cuff (D.E. Hokanson, Bellevue, WA, USA) was attached immediately distal to the medial epicondyle. A LOGIQ ultrasound system (GE Healthcare, UK) with a 12-megahertz linear transducer was used to obtain a longitudinal B-mode image of the brachial artery between 2 to 10 cm above the antecubital fossa. The transducer was then secured in a stereotactic probe holder to maintain the image during the procedure. Subsequently, the image was optimised to ensure clear visualisation of the near and far walls of the endothelium by adjusting the gain, focal points, dynamic range, and harmonics. Anatomical landmarks (*i.e.* veins or fascial planes) were noted for reference during transducer placement at subsequent TPs. Duplex scanning in pulsed-wave Doppler mode was then activated with a large, centred sample volume and an insonation angle of 60°. When a satisfactory B-mode image and clear Doppler signal were determined, the ultrasound CINE loop was reset, and baseline data was recorded for 30 seconds (s) by Vascular Imager software (Version 6.0.3, Medical Imaging Applications, USA). The forearm occlusion cuff was then rapidly inflated with compressed air (E20 Rapid Cuff Inflator, AG101 Cuff Inflator Air Source, USA) to > 50 mmHg above SBP for 5 minutes to induce arterial occlusion. Data recording was initiated following 4 minutes and 30 s of forearm occlusion. The forearm occlusion cuff was deflated at 5 minutes, and data recording continued for 3 minutes. Data recording was terminated and saved following this period. ECG-based-gated analysis was not utilised as continuous data analysis of brachial diameter across the cardiac cycle has been shown to correlate with ECG-gated analysis and is more time efficient (Kizhakekuttu et al., 2010).

The data that was collected during the brachial FMD procedure was analysed using offline edge detection software (Brachial Analyser for Research Version 5.7.0,

Medical Imaging Applications, USA). Baseline diameter and blood flow velocity were represented by the average values over the 30-s collection period. 4-s averages were calculated for diameter and blood flow velocity values over the first 20 s post-cuff deflation, and 5-s averages for these values were calculated over the remainder of the post-cuff deflation collection period. Peak diameter (maximum dilation) was represented by the highest averaged interval over the post-cuff deflation collection period.

The brachial FMD response was represented by the maximum change in brachial artery diameter post-cuff deflation relative to the baseline brachial artery diameter. As such, the brachial FMD response was calculated in accordance with the following equation:

$$FMD\ (\%) = \left(\frac{Peak\ diameter - Baseline\ diameter)}{Baseline\ diameter} \right) \times\ 100$$

Shear stress is a primary stimulus for the brachial FMD response (Davies & Tripathi, 1993). As such, shear rate (area-under-the-curve (AUC) up to peak diameter) was considered as it represents the accumulated shear that contributed to the brachial FMD response (Corretti et al., 2002). This parameter was calculated in accordance with the trapezoidal rule, every 4-second interval over the first 20 s post-cuff deflation, and every 5-second interval over the remainder of the post-cuff deflation collection period (Harris et al., 2010).

Time-to-peak vasodilation (s) was represented by the mid-point of the highest averaged interval post-cuff deflation.

To potentially improve the sensitivity and reliability of the test, previous literature has suggested that the brachial FMD response should be normalised or allometrically scaled for shear stress and/ or baseline diameter to control for inter-individual variability (Padilla et al., 2008; Atkinson & Batterham, 2013). According to the current expert

consensus, there is uncertainty whether and how to appropriately correct the brachial FMD response for shear stress and/ or baseline diameters (Thijssen et al., 2019). However, given that baseline diameter is strongly and inversely related to FMD (Silber et al., 2005), brachial FMD data was allometrically scaled to baseline diameter in line with recommendations proposed by Atkinson & Batterham (2013). Allometric scaling is a statistical method of accounting for the relationship between baseline and peak diameter (Atkinson & Batterham, 2013). Nonetheless, allometrically scaled brachial FMD was similar to unadjusted brachial FMD data (see Table 3.1 and Table 3.2). As such, unadjusted brachial FMD data is presented in this thesis.

Table 3.1 Comparison of unadjusted and allometrically scaled brachial FMD data for the primary analysis of secondary outcome measures (brachial FMD data available for non-CR, $n = 2$; phase-III CR, $n = 15$).

Group	TP-1				TP-2			
	Unadjusted brachial FMD	Difference	*P* value [a]		Unadjusted brachial FMD	Difference	*P* value [a]	
	Allometrically scaled brachial FMD				Allometrically scaled brachial FMD			
Non-CR	3.30 (2.80, 3.80)	0.01	0.66		2.65 (2.30, 3.00)	0.05	0.66	
	3.29 (2.76, 3.81)				2.70 (2.30, 3.10)			
Phase-III CR	2.77 (0.47, 8.29)	0.00	0.23		4.92 (1.17, 12.70)	0.01	0.28	
	2.77 (0.47, 8.29)				4.91 (1.17, 12.70)			

Data presented as median (minimum, maximum); TP, Time Point; FMD, flow-mediated dilatation; CR, cardiac rehabilitation; [a], for Wilcoxon Signed Ranks Test.

Table 3.2 Comparison of unadjusted and allometrically scaled brachial FMD data for the sub-analysis of secondary outcome measures (brachial FMD data available for non-CR, $n = 1$; phase-III CR only, $n = 2$; phase-III & phase-IV CR, $n = 5$).

Group	TP-1			TP-2			TP-3		
	Unadjusted brachial FMD	Difference	P value [a]	Unadjusted brachial FMD	Difference	P value [a]	Unadjusted brachial FMD	Difference	P value [a]
	Allometrically scaled brachial FMD			Allometrically scaled brachial FMD			Allometrically scaled brachial FMD		
Non-CR	2.80 (2.80, 2.80)	0.04	-	2.30 (2.30, 2.30)	0.00	-	2.67 (2.67, 2.67)	0.00	-
	2.76 (2.76, 2.76)			2.30 (2.30, 2.30)			2.67 (2.67, 2.67)		
Phase-III CR only	2.20 (0.76, 3.63)	0.00	0.67	7.68 (4.55, 10.80)	0.01	0.18	5.89 (3.79, 7.99)	0.00	0.18
	2.20 (0.76, 3.63)			7.67 (4.55, 10.80)			5.89 (3.79, 7.99)		
Phase-III & phase-IV CR	1.56 (0.47, 8.29)	0.00	0.23	5.43 (1.17, 12.70)	0.00	0.69	6.94 (1.72, 15.76)	0.00	0.50
	1.56 (0.47, 8.29)			5.43 (1.17, 12.70)			6.94 (1.72, 15.76)		

Data presented as median (minimum, maximum); TP, Time Point; FMD, flow-mediated dilatation; CR, cardiac rehabilitation; [a], for Wilcoxon Signed Ranks Test; -, insufficient number (n) of cases ($n = 1$) for statistical analysis.

3.4.1.6 Arterial Stiffness

The Pulse Trace PCA 2 (Micro Medical, Rochester, UK) was used to assess arterial stiffness as it is a non-invasive, validated procedure (Chowienczyk et al., 1999; Millasseau et al., 2000), which possesses comparative value to the gold standard non-invasive carotid-femoral pulse wave velocity assessment of large artery stiffness (Millasseau et al., 2002). The Pulse Trace PCA 2 device (Micro Medical, Rochester, UK) utilises a photoplethysmography (measurement of infra-red light transmission through the finger) technique to record digital volume pulse (DVP) from a probe placed on an index finger. This measurement enables the reconstruction of the pulse wave curve, with the volume of the pulse wave (DVP) comprising two elements: a systolic component that represents the pulse wave transmission from the aorta to the digital arteries, and a diastolic component that signifies the pulse waves that have been reflected back towards the aorta. The timing of the diastolic component relative to the systolic component is determined by large artery stiffness, with stiff arteries causing an increased pulse propagation speed, which would result in the diastolic component arriving earlier in the cardiac cycle (Wood, 1998). The amplitude of the diastolic component relates to the magnitude of pulse wave reflection, which is primarily determined by the vascular tone of small arteries (Chowienczyk et al., 1999; Millasseau et al., 2002). The indices derived from DVP are stiffness index (SI) and reflective index (RI), which represent large artery stiffness and vascular tone of small arteries respectively (DeLoach & Townsend, 2008). SI (m/s) was calculated by dividing the height of a participant by the peak-to-peak time (time between systolic and diastolic peaks). RI (%) was defined as the diastolic peak expressed as a percentage of the systolic peak, which was calculated by dividing the height of the diastolic peak by the height of the systolic peak, and multiplying the result by 100% (DeLoach & Townsend, 2008).

The protocol for performing arterial stiffness measurements complied with methodological guidelines (Laurent et al., 2006). Arterial stiffness measurements were obtained at a similar time of day at each TP to account for diurnal variation. During the procedure, the participant was in a supine position on a clinical bed, with the measurement arm resting by his/ her side on the surface of the clinical bed. The probe was placed on the index finger of the non-dependent hand, whilst ensuring that there was no weight

bearing on the probe. The Pulse Trace PCA 2 unit (Micro Medical, Rochester, UK) was placed on a separate table to prevent movement artefacts during the procedure. The result of the arterial stiffness assessment was the average of three DVP measurements interspersed with 30-45-s intervals. If a typical waveform shape was absent or large fluctuations of the SI were detected (>15%), the Pulse Trace PCA 2 device (Micro Medical, Rochester, UK) reported the need to repeat the assessment.

3.4.1.7 International Physical Activity Questionnaire

The International Physical Activity Questionnaire (IPAQ) was used to assess the physical activity levels of the participants over the course of the study to account for the potential confounding influence of this variable. This internationally validated measurement tool is designed as a standardised self-report questionnaire that provides estimates of physical activity and inactivity within a population (Craig et al., 2003). Whilst subjective self-report measurements of physical activity may be influenced by recall or desirability bias (Sallis & Saelens, 2000; Adams et al., 2005), the IPAQ was chosen as it was more financially feasible and placed a lower level of burden upon the participants than objective measurements of physical activity, such as: accelerometers or pedometers. Participants were provided with the IPAQ (long-form), which comprised 27 questions that reflected on activities ≥ 10 minutes over the previous 7 days according to the following domains: 1) job-related physical activity; 2) transportation physical activity; 3) housework, house maintenance, and caring for family; 4) recreation, sport, and leisure-time physical activity; and 5) time spent sitting (see Appendix L). Each participant was asked to complete 1 IPAQ on week-1, week-8, and week-22 of the study. All IPAQ data was cleaned in accordance with the standardised IPAQ Scoring Protocol (The IPAQ Group, 2005), which involved converting responses to duration (time) from hours and minutes into minutes; excluding values of < 10 minutes of activity; and capping total weekly minutes for each of walking, moderate physical activity, and vigorous physical activity at a maximum of 3 hours per day or 21 hours per week. Data collected from the IPAQ were reported as total physical activity metabolic equivalent (MET)-minutes/ week (total walking MET-minutes/ week + total moderate physical activity MET-minutes/ week + total vigorous physical activity MET-minutes/ week). MET-minutes/ week were calculated with the following equation:

MET score of an activity $\times$ minutes performed $\times$ days performed per week

The following MET scores for activities were utilised (The IPAQ Group, 2005):

- Walking = 3.3 METs
- Cycle for transport = 6.0 METs
- Moderate activity at work = 4.0 METs
- Moderate activity yard chores = 4.0 METs
- Moderate activity inside chores = 3.0 METs
- Moderate activity in leisure = 4.0 METs
- Vigorous activity yard chores = 5.5 METs
- Vigorous activity at work = 8.0 METs
- Vigorous activity in leisure = 8.0 METs

3.4.1.8 Three-Day Estimated Food Records

The literature indicates that dietary intake may influence a number of the measurements obtained in Study 2, such as: inflammation, endothelial function, and SIRT-1 (Lopez-Garcia et al., 2004; Allard et al., 2009). Therefore, three-day estimated food records (3DEFRs) were included in the initial study protocol to obtain information regarding the dietary intake of participants over the course of the study. However, the ORECNI deemed methods of recording dietary intake an undue burden for participants. Consequently, 3DEFRs were removed from the study protocol in order to receive ethical approval. As such, failure to investigate dietary intake as a potential confounding variable is an acknowledged limitation of Study 2.

3.4.1.9 Haematological Measurement

The literature recommends a 12 hour fasting period for patients prior to blood sampling, which serves as an attempt to standardise inter-individual blood biochemistry (Simundic et al., 2014). However, fasting samples were not obtained for ethical reasons; blood was drawn from patients on days when they were routinely present on-site for CR attendance to limit participant burden, with a fasted state posing a risk of unsafe participation in the exercise sessions due to potential hypoglycaemic states. Venous blood collection (51.2 mL) was performed with participants in a supine position on a clinical bed. A disposable tourniquet was applied with appropriate restriction to the distal region of the humerus. Upon identification of a prominent antecubital vein, a 70% v/v isopropyl alcohol wipe was utilised to clean the venepuncture site. All blood samples were collected using the Vacutainer ™ method (Becton, Dickinson, Oxford, UK). Blood was collected in 4 mL dipotassium ethylene-diamine-tetra-acetic acid (K_2EDTA) vacutainers, which act as anticoagulants by sequestering calcium ions; 5 mL advanced serum separating tubes (SSTs), which result in the formation of a fibrin clot; and 5.2 mL buffered trisodium citrate Seditainer™ tubes, which facilitate a closed system for erythrocyte sedimentation rate (ESR) determination. Following venous blood collection, K_2EDTA vacutainers were immediately placed in a sample transport container (DISON, Henan, China) that possessed a temperature of 4°C. Advanced SSTs were allowed to clot at room temperature for a minimum of 30 minutes before being stored in the sample transport container (DISON, Henan, China). Seditainer™ tubes were analysed on-site (methods discussed in the "biochemical and molecular techniques" section) prior to storage in the sample transport container (DISON, Henan, China) for appropriate disposal at UU. All blood samples were transported to UU for processing and storage within 2 hours of collection.

Upon return to UU, K_2EDTA vacutainers and SSTs were centrifuged at 3500 rotations per minute (RPM) for 10 minutes. Subsequently, plasma and serum samples were aliquoted with a 1 mL pipette into 2 mL polypropylene (PP) micro tubes (SARSTEDT, Numbrecht, Germany), and stored immediately at -80°C until analysis (within 12 months). The literature suggests that analyte stability is higher in serum than in plasma (Boyanton & Blick, 2002). Thus, serum was used for analysis when either sample type could be utilised with efficacy. For the purpose of storing lymphocytes for messenger ribonucleic acid (mRNA) gene expression analysis, 3 mL of whole blood collected in K_2EDTA vacutainers was decanted onto 3 mL of Histopaque-1077 (Sigma-

Aldrich, Dorset, UK) in a 15 mL PP centrifuge tube (SARSTEDT, Numbrecht, Germany). Samples were then centrifuged at 4°C for 30 minutes at 3500 RPM. Subsequently, 1 mL of peripheral blood mononuclear cells was aspirated into a separate 15 mL PP centrifuge tube (SARSTEDT, Numbrecht, Germany) containing 10 mL of phosphate buffered saline (PBS) (Sigma-Aldrich, Dorset, UK), and centrifuged for 10 minutes at 3500 RPM to generate a cell pellet. The cell pellet was re-suspended in 800 microlitres (µL) Roswell Park Memorial Institute (RPMI)-1640 medium (Sigma-Aldrich, Dorset, UK), 100 µL fetal bovine serum (Sigma-Aldrich, Dorset, UK), and 100 µL dimethyl sulfoxide (DMSO) (Sigma-Aldrich, Dorset, UK) before being transferred to a 2 mL PP DNase/ RNase free micro tube (SARSTEDT, Numbrecht, Germany) for storage at -80°C.

3.4.1.10 Feasibility Assessments

The primary purpose of a pilot study is to test the feasibility of methods and procedures for future use on a larger scale and/ or to search for potential effects and associations that warrant further investigation in a larger study (Everitt, 2006). Thus, the feasibility assessments discussed in the following sections comprised an evaluation of the processes that are key to the success of a larger study (Thabane et al., 2010).

3.4.1.10.1 Recruitment Rate

Recruitment is characterised by the selection and enrollment of potential participants into a study (Gul & Ali, 2010). This process is vital to any trial that depends on the participation of humans, with a failure to recruit a sufficient number of participants potentially resulting in the premature termination of a research project due to the costs and methodological issues associated with a prolonged recruitment period (Grap & Munro, 2003). Conversely, efficient recruitment may result in adequate retention, an increased data set, and enable in-budget and in-time completion of a research project (Poston & Buescher, 2010; Jerosch-Herold et al., 2011). Therefore, recruitment rate was measured as it allowed the efficiency of the recruitment strategy to be assessed, with this information allowing the identification of potential issues and informing the required

duration of the recruitment period for a larger study (Moore et al., 2011). CR nurses maintained a record of the potential participants who were invited to participate in the study. This information was shared with the research team to calculate the recruitment rate, which was defined as the percentage of eligible patients who agreed to participated in the study, and the number of patients recruited per week over the recruitment period. The CR uptake rate was also calculated (*i.e.* the percentage of recruited patients who chose to participate in phase-III CR), which provided information regarding possible participant numbers across the groups in a larger study.

3.4.1.10.2 Drop-Out Rate

Drop-out consists of a reduction in the number of participants in a study as it progresses (*i.e.* withdrawal or loss to follow-up) (Nunan et al., 2018). The loss of participants during a research project may introduce attrition bias, which involves systematic differences in quantitative and qualitative characteristics between the study groups (Nunan et al., 2018). As such, drop-out rate was measured to obtain an estimate of potential rates of participant attrition in a larger study, which would provide information about the suitability of the study design and methodology for participants, and inform a future sample size calculation (Moore et al., 2011). Drop-out rate was expressed as the percentage of recruited participants who withdrew from the study, with this parameter being calculated overall and at each TP.

3.4.1.10.3 Adherence Rate

The literature suggests that the health benefits of exercise in CAD patients are dose-dependent (Curtis et al., 2010). As such, adherence rate to the supervised exercise sessions was measured. Participant completion of the supervised exercise sessions was routinely recorded by the CR nurses and phase-IV CR facilitators during the phase-III and phase-IV CR programmes, respectively. This information was shared with the research team to calculate the supervised exercise session adherence rate, which was defined as the percentage of prescribed exercise sessions that were completed.

3.4.1.10.4 Success Criteria

A pilot study should possess clearly defined *a priori* success criteria that are based on the feasibility assessments. These criteria serve as the basis for interpreting the results to ascertain if a larger study is feasible (Thabane et al., 2010). The following success criteria were used to determine if a future prospective cohort study was feasible: adequate recruitment rate (> 70% of eligible patients recruited), < 20% drop-out rate overall and at each TP for each group, completed > 80% of prescribed exercise sessions, and apparent changes in the secondary outcomes that warrant further investigation (*i.e.* an increase in SIRT-1 concentration following CR). The success criterion for recruitment rate was set at > 70% of eligible participants recruited as the research team deemed this result representative of an efficient recruitment strategy. With regard to drop-out rate, the success criterion of < 20% overall and at each TP for each group was chosen as a greater loss of participants may pose a serious threat to validity (Higgins et al., 2019). Finally, the research team agreed that the completion of > 80% of the prescribed exercise sessions represented a successful adherence rate, which was in line with Oliveira et al. (2015).

3.4.2 Data Collection for Study 3

Data collection for Study 3 is described in **Paper 3** (chapter 6).

3.5 Biochemical and Molecular Techniques

3.5.1 Erythrocyte Sedimentation Rate

ESR was measured as it is an inexpensive, clinically accepted indirect index of systemic inflammatory activity (Bray et al., 2016). This test reflects the rate of settling of erythrocytes in a vertically positioned tube containing whole blood following a 60-minute period, with the sedimentation rate being primarily influenced by the concentrations of acute-phase reactants, such as: fibrinogen and CRP (Bochen et al., 2011). ESR was assessed using the Seditainer™ method, which is a sealed vacuum extraction system that offers enhanced precision due to the controlled dilution of blood with anticoagulant-diluent solution, and possesses comparative value with the gold standard Westergren method (Patton et al., 1989). Moreover, this method enabled ESR to be determined

immediately after blood collection at the collaborating sites, which served as an attempt to increase the accuracy of the results. The Seditainer™ ESR system involved extracting 5.2 mL of blood into a Seditainer™ tube (Becton, Dickinson, Oxford, UK), which was subsequently placed vertically in a Seditainer™ manual stand (Becton, Dickinson, Oxford, UK). After 60 minutes, the ESR value was determined by using the linear scale on the Seditainer™ manual stand to measure the height of the erythrocyte-free plasma at the top of the Seditainer™ tube, with the result being recorded in millimetres per hour (mm/ h).

3.5.2 Serum Lipid Hydroperoxides

Lipid peroxidation is a common consequence of oxidative damage (Halliwell & Chirico, 1993). Lipid hydroperoxides (LOOH) are by-products of lipid peroxidation, and are primarily formed when polyunsaturated fatty acids undergo oxidation through radical or non-radical mechanisms (Villamena, 2016). Thus, serum LOOH were measured as an indirect marker of oxidative stress. The ferrous oxidation in xylenol orange (FOX)-1 assay was utilised to determine serum LOOH levels (Wolff, 1994). Theoretically, the presence of LOOH will result in the oxidation of ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}). LOOH concentration is then indirectly quantified by spectrophotometrically measuring the binding of Fe^{3+} to Fe^{3+}-sensitive xylenol orange (Wolff, 1994). A concentration of 0-5 micromoles per litre ($\mu M \cdot L^{-1}$) of H_2O_2 was used to create a standard curve, with all samples being read spectrophotometrically at an absorbance of 560 nanometres (nm). The FOX-1 reagent was prepared by combining 100 $\mu M \cdot l^{-1}$ xylenol orange, 250 $\mu M \cdot l^{-1}$ ammonium ferrous sulphate, 100 millimoles per litre ($mM \cdot L^{-1}$) sorbitol, and 25 $mM \cdot L^{-1}$ of sulphuric acid in a volumetric flask. High-performance liquid chromatography (HPLC)-grade water (Sigma-Aldrich, Dorset, UK) was added to the volumetric flask until the meniscus reached 100 mL. The volumetric flask was then stored in a dark room to avoid light exposure. After thawing, 50 μL of each serum aliquot was added to 950 μL of FOX-1 reagent in PP micro tubes (SARSTEDT, Numbrecht, Germany). A blank sample was formed by adding 50 μL of HPLC-grade water (Sigma-Aldrich, Dorset, UK) and 950 μL of FOX-1 reagent to a PP micro tube (SARSTEDT, Numbrecht, Germany). Samples were then vortexed and left to incubate for a 30-minute period at room temperature in a dark room. Subsequently, all samples were transferred to cuvettes for spectrophotometric

analysis (UV mini-1240 UV-Vis Spectrophotometer) at an absorbance of 560 nm. The blank sample was analysed first to determine the background absorbance, followed by the participant samples.

3.5.3 Ascorbyl Free Radical

Ascorbyl free radical ($A^{\bullet-}$) is generated via ascorbate oxidation, with most reactive species intrinsic to the biological milieu being capable of performing this reaction (Spasojeviä, 2011). Thus, $A^{\bullet-}$ levels are highly sensitive to the oxidative status of a biological system. Moreover, this free radical is relatively stable and possesses a long half-life (Buettner & Jurkiewicz, 1993). As such, $A^{\bullet-}$ concentration was measured as a direct marker of oxidative stress. Electron paramagnetic resonance (EPR) spectroscopy was used to assess $A^{\bullet-}$ levels as this method is an accurate and highly sensitive technique for detecting free radical species (Spasojeviä, 2011). $A^{\bullet-}$ concentration was quantified at room temperature using a Bruker EMX series X-band EPR spectrometer (Bruker, Karlsruhe, Germany). 1 mL of plasma was mixed with 1 mL of DMSO (Sigma-Aldrich, Dorset, UK) in a glass tube. Subsequently, 1 mL of the final solution was drawn into a sterile syringe and slowly flushed into an aqua X multiple bore cavity cell. The following spectrometer parameters were configured: frequency, 9.785 gigahertz; microwave power, 20 megawatts; modulation frequency, 100 kilohertz; and modulation amplitude, 1.194 G. All EPR spectra were subjected to 3 sweeps. Spectral parameters were filtered identically and analysed using WinEPR software (Version 3.2, Bruker WinEPR, Coventry, UK). $A^{\bullet-}$ levels were determined by the average spectral peak-to-trough line amplitude.

3.5.4 Lipid Soluble Antioxidants

Lipid soluble antioxidants (α-tocopherol, γ-tocopherol, α-carotene, β-carotene, lycopene, retinol, and xanthophyll) are exogenous antioxidants that interact synergistically with endogenous antioxidants to maintain or re-establish redox homeostasis (Bouayed & Bohn, 2010), with an increase in exogenous antioxidants promoting a greater endogenous antioxidant capacity and vice versa (Valko et al., 2007). The analysis of lipid soluble antioxidant concentrations as an index of antioxidant status via the simultaneous HPLC

assay of Thurnham et al. (1988) was planned. However, technical issues with the HPLC equipment precluded the generation of valid data. Thus, the measurement of lipid soluble antioxidants was not possible.

3.5.5 Sirtuin-1

The analysis of human body fluid (*i.e.* blood, urine, and saliva) proteome is a promising method of identifying possible protein markers for a disease (Kumar et al., 2013). Human serum proteins enter systemic circulation secondary to secretion and leakage from a variety of tissues (Taylor, 1969), with the concentrations of these proteins representing human physiological or pathological states (Anderson & Anderson, 2002; Thadikkaran et al., 2005). Indeed, a number of studies have measured circulating (serum or plasma) SIRT-1 protein concentration to delineate its potential to serve as a biomarker or therapeutic target in different physiological and pathological states, such as: ageing (Zhong et al., 2016), frailty (Kumar et al., 2014), obesity (Mariani et al., 2016), Alzheimer's disease (Kumar et al., 2013), and CAD (He et al., 2019). Thus, to support this growing body of evidence, SIRT-1 concentration was measured in serum by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer instructions (Elabscience®, ELISA kit catalog no. E-EL-H1546, USA). All reagents and samples were brought to room temperature prior to the initiation of the assay. 750 mL of wash buffer was prepared by diluting 30 mL of concentrated wash buffer with 720 mL of deionised water. The standard was centrifuged for 1-minute prior to 1 mL of reference standard and sample diluent being added. Subsequently, the standard was left to stand for 10 minutes before being gently inverted several times and thoroughly mixed with a pipette. This reconstitution produced a working solution of 20 nanograms per mL (ng/ mL). 500 µL of reference standard and sample diluent was then added to 7 PP micro tubes (SARSTEDT, Numbrecht, Germany). Afterwards, 500 µL of the 20 ng/ mL working solution was pipetted into the first PP micro tube and mixed to create a 10 ng/ mL working solution. A process of pipetting 500 µL of the solution from the former PP micro tube into the latter was performed until the 7th PP micro tube was reached. This final PP micro tube served as the blank standard. The concentration gradient of the standards was as follows: 10, 5, 2.5, 1.25, 0.63, 0.31, and 0 ng/ mL. 9600 µL working solutions of biotinylated detection antibody and concentrated avidin-horseradish peroxidase (HRP)

conjugate were prepared by diluting the respective 100 × concentrated reagents to 1 × working solutions with the corresponding diluents. 100 μL of each concentration of the standards was added in duplicate to the first two columns of the microplate. Subsequently, 100 μL of the samples were added in duplicate to the remaining wells. The microplate was then covered with a plate sealer and incubated for 90 minutes at 37 °C. Following the incubation period, the liquid was decanted from the wells. 100 μL of biotinylated detection antibody working solution was immediately added to each well. The microplate was then covered with a plate sealer and incubated for 60 minutes at 37 °C. Subsequently, the solution was decanted from the wells before adding 350 μL of wash buffer to each well. The microplate was then left to soak for 2 minutes. Following this period, the solution was decanted from the wells and the microplate was patted dry against clean absorbent paper. This wash step was repeated 3 times in total. After this wash phase, 100 μL of HRP conjugate working solution was added to each well. The microplate was then covered with a plate sealer and incubated for 30 minutes at 37 °C. The solution was then decanted from the wells and the wash process was repeated as previously described for 5 times in total. 90 μL of substrate reagent was then added to each well. The microplate was covered with a plate sealer and incubated for 15 minutes at 37 °C. Upon removal from the incubator, 50 μL of stop solution was added to each well in the same order as the substrate reagent. The optical density (OD) of each well was then determined spectrophotometrically with a microplate reader (EL 808, BioTek Instruments, USA) set at 450 nm. The average OD of the blank standard was subtracted from the average OD of the duplicate readings for each standard and sample. SIRT-1 concentration was then calculated using curve-fitting software (GraphPad Prism, Version 8, GraphPad Software, USA) with a 4-parameter logistic model ($R^2 = 0.9984$). Table 3.3 outlines the OD values of the standard curve, and Figure 3.1 displays the standard curve that was utilised for interpolation of SIRT-1 concentration. Intra-assay coefficient of variation (CV) was < 5%. Due to funding constraints, SIRT-1 concentration was solely measured in samples obtained at each TP.

Table 3.3 OD values of the SIRT-1 ELISA standard curve

Concentration (ng/mL)	10	5	2.5	1.25	0.63	0.31	0
OD	1.836	1.416	1.037	0.653	0.379	0.215	0.039
Corrected OD	1.797	1.377	0.998	0.614	0.34	0.176	-

ng/mL, nanograms per millilitre; OD, optical density
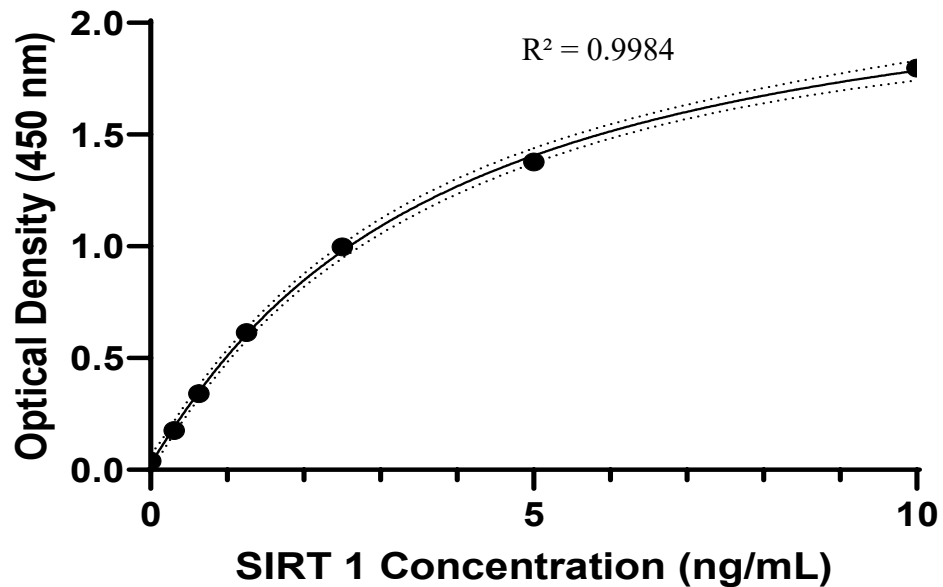
Figure 3.1 Standard curve (4-parameter logistic model) for interpolation of SIRT-1 concentration

nm, nanometres; ng/mL, nanograms per millilitre

3.5.6 Interleukin-6

IL-6 concentration was measured in serum by a Quantikine® HS sandwich ELISA according to the manufacturer instructions (R&D Systems, ELISA kit catalog no. HS600C, UK). IL-6 was measured as it is pro-inflammatory cytokine that fulfills a principal role in orchestrating atherogenesis (Tedgui & Mallat, 2006), and is a primary mediator of chronic systemic inflammation through the stimulation of acute-phase reactant synthesis (Gabay & Kushner, 1999). Indeed, serum IL-6 concentration has been

associated with all-cause and cardiovascular mortality in CAD patients (Su et al., 2013). All reagents and samples were brought to room temperature prior to the initiation of the assay. 1000 mL of wash buffer was prepared by adding 40 mL of wash buffer concentrate to 960 mL of deionised water. Substrate solution was prepared by mixing colour reagents A and B in equal volumes. 0.215 mL of streptavidin polymer-HRP (100×) was added to streptavidin polymer-HRP diluent to create a 1 × working solution. 1 mL of deionised water was added to the IL-6 HS standard before the solution was left to stand for 15 minutes. This reconstitution produced a working solution of 100 picograms per mL (pg/mL). The standard solution was gently agitated before dilutions were performed. 8 PP micro tubes (SARSTEDT, Numbrecht, Germany) were arranged. 900 µL of calibrator diluent RD5-4 was pipetted into the first PP micro tube, with 500 µL being pipetted into the remaining micro tubes. 100 µL of the 100 pg/mL working solution was pipetted into the first PP micro tube and mixed to create a 10 pg/mL working solution. A process of pipetting 500 µL of the solution from the former PP micro tube into the latter was performed until the 8th PP micro tube was reached. This final PP micro tube served as the blank standard. The concentration gradient of the standards was as follows: 10, 5, 2.5, 1.25, 0.625, 0.313, 0.156, and 0 pg/mL. 100 µL of assay diluent RD1W was added to each well of the microplate. 100 µL of each concentration of the standards was added in duplicate to the first two columns of the microplate. Subsequently, 100 µL of the samples was added in duplicate to the remaining wells. The microplate was then covered with a plate sealer and incubated for 120 minutes at room temperature on a horizontal orbital microplate shaker set at 500 RPM. Following the incubation period, the liquid was decanted from the wells. 400 µL of wash buffer was then added to each well, and the microplate was left to soak for 30 s. Following this period, the solution was decanted from the wells and the microplate was patted dry against clean absorbent paper. This wash step was performed for 4 times in total. After this wash phase, 200 µL of human IL-6 HS conjugate was added to each well. The microplate was then covered with a plate sealer and incubated for 60 minutes at room temperature on the horizontal orbital microplate shaker set at 500 RPM. The solution was then decanted from the wells and the wash process was repeated as previously described for 4 times in total. Subsequently, 200 µL of streptavidin polymer-HRP (1×) was added to each well. The microplate was then covered with a plate sealer and incubated for 30 minutes at room temperature on the horizontal orbital microplate shaker set at 500 RPM. The solution was then decanted from the wells and the wash process was repeated as previously described for 4 times in total.

200 µL of substrate solution was then added to each well. The microplate was then incubated for 30 minutes at room temperature whilst placed on the benchtop and covered with a box for protection from light. Subsequently, 50 µL of stop solution was added to each well in the same order as the substrate solution. The OD of each well was then determined spectrophotometrically with a microplate reader (EL 808, BioTek Instruments, USA) set at 450 nm. The average OD of the blank standard was subtracted from the average OD of the duplicate readings for each standard and sample. IL-6 concentration was then calculated using curve-fitting software (GraphPad Prism, Version 8, GraphPad Software, USA) with a 4-parameter logistic model ($R^2 = 0.9998$). Table 3.4 outlines the OD values of the standard curve, and Figure 3.2 displays the standard curve that was utilised for interpolation of IL-6 concentration. Intra-assay CV was < 5%. Due to funding constraints, IL-6 concentration was solely measured in samples obtained at each TP.

Table 3.4 OD values of the IL-6 ELISA standard curve

Concentration (pg/mL)	10	5	2.5	1.25	0.63	0.31	0.16	0
OD	2.49	1.427	0.807	0.438	0.255	0.155	0.115	0.048
Corrected OD	2.442	1.379	0.759	0.39	0.207	0.107	0.067	-

pg/mL, picograms per millilitre; OD, optical density
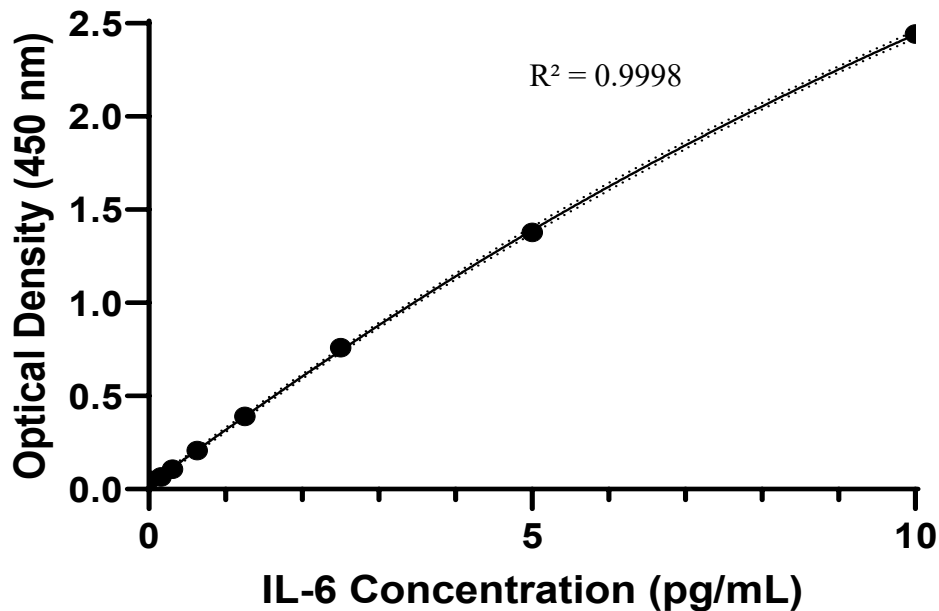
Figure 3.2 Standard curve (4-parameter logistic model) for interpolation of IL-6 concentration

nm, nanometres; pg/mL, picograms per millilitre

3.5.7 Interleukin-10

IL-10 concentration was measured in serum by a Quantikine® HS sandwich ELISA according to the manufacturer instructions (R&D Systems, ELISA kit catalog no. HS100C, UK). IL-10 was measured as it is an anti-inflammatory cytokine that may mitigate inflammation by modulating the pro-inflammatory cytokine response (Opal & DePalo, 2000). Moreover, elevated serum IL-10 concentration has been associated with a more favourable prognosis in CAD patients following ACS (Heeschen et al., 2003). All reagents and samples were brought to room temperature prior to the initiation of the assay. 1000 mL of wash buffer was prepared by adding 100 mL of wash buffer concentrate to 900 mL of deionised water. Substrate and amplifier solutions were prepared by thoroughly mixing the respective lyophilised solution with 6 mL of the corresponding diluent. 1.10 mL of calibrator diluent RD6-10 was added to the human IL-10 HS standard before the solution was left to stand for 15 minutes. This reconstitution produced a working solution of 500 pg/mL. The standard solution was gently agitated before

dilutions were performed. 8 PP micro tubes (SARSTEDT, Numbrecht, Germany) were arranged. 900 µL of calibrator diluent RD6-10 was pipetted into the first PP micro tube, with 500 µL being pipetted into the remaining micro tubes. 100 µL of the 500 pg/mL working solution was pipetted into the first PP micro tube and mixed to create a 50 pg/mL working solution. A process of pipetting 500 µL of the solution from the former PP micro tube into the latter was performed until the 8th PP micro tube was reached. This final PP micro tube served as the blank standard. The concentration gradient of the standards was as follows: 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78, and 0 pg/mL. 50 µL of assay diluent RD1-10 was added to each well of the microplate. 200 µL of each concentration of the standards was added in duplicate to the first two columns of the microplate. Subsequently, 200 µL of the samples was added in duplicate to the remaining wells. The microplate was then covered with a plate sealer and incubated for 120 minutes at room temperature on a horizontal orbital microplate shaker set at 500 RPM. Following the incubation period, the liquid was decanted from the wells. 400 µL of wash buffer was then added to each well, and the microplate was left to soak for 30 s. Following this period, the solution was decanted from the wells and the microplate was patted dry against clean absorbent paper. This wash step was performed for 6 times in total. After this wash phase, 200 µL of human IL-10 HS conjugate was added to each well. The microplate was then covered with a plate sealer and incubated for 120 minutes at room temperature on the horizontal orbital microplate shaker set at 500 RPM. The solution was then decanted from the wells and the wash process was repeated as previously described for 6 times in total. Subsequently, 50 µL of substrate solution was added to each well. The microplate was then covered with a plate sealer and incubated for 60 minutes at room temperature on the horizontal orbital microplate shaker set at 500 RPM. 50 µL of amplifier solution was then added to each well in the same order as the substrate solution. The microplate was then covered with a plate sealer and incubated for 30 minutes at room temperature on the horizontal orbital microplate shaker set at 500 RPM. Subsequently, 50 µL of stop solution was added to each well in the same order as the substrate solution. The OD of each well was then determined spectrophotometrically with a microplate reader (EL 808, BioTek Instruments, USA) set at 490 nm. The average OD of the blank standard was subtracted from the average OD of the duplicate readings for each standard and sample. IL-10 concentration was then calculated using curve-fitting software (GraphPad Prism, Version 8, GraphPad Software, USA) with a 4-parameter logistic model ($R^2 = 0.9985$). Table 3.5 outlines the OD values of the standard curve, and Figure 3.3 displays the standard curve

that was utilised for interpolation of IL-10 concentration. Intra-assay CV was < 5%. Due to funding constraints, IL-10 concentration was solely measured in samples obtained at each TP.

Table 3.5 OD values of the IL-10 ELISA standard curve

Concentration (pg/mL)	50	25	12.5	6.25	3.13	1.56	0.78	0
OD	2.053	1.180	0.617	0.280	0.146	0.077	0.042	0.02
Corrected OD	2.033	1.160	0.597	0.260	0.126	0.057	0.022	-

pg/mL, picograms per millilitre; OD, optical density
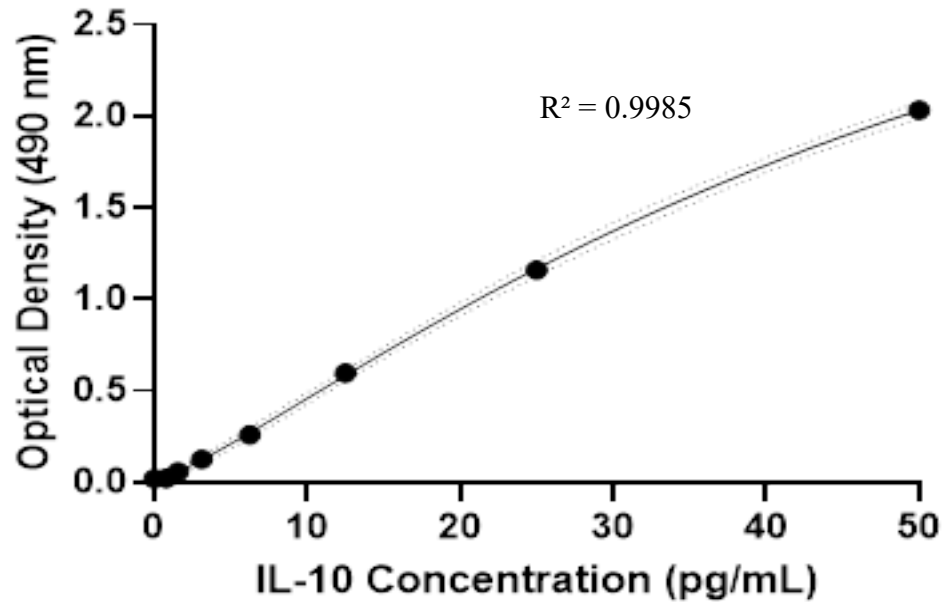
Figure 3.3 Standard curve (4-parameter logistic model) for interpolation of IL-10 concentration

nm, nanometres; pg/mL, picograms per millilitre

3.5.8 Lipid Panel

Lipid panel was measured as dyslipidaemia is a primary CVD risk factor for CAD development (Yusuf et al., 2004), with the potential to serve as a pathogenic driver of chronic inflammation (Munkhaugen et al., 2018). Lipid panel (TC, LDL-C, HDL-C, triglycerides (TG), TC/ HDL-C ratio, and non-HDL-C) was measured in serum at the BHSCT and SEHSCT as per routine clinical practice at TP-1 and TP-2. Informed consent was obtained from the participants for the CR nurses to provide the PhD researcher (GT) with the results of these measurements. The research team had planned to provide serum from the samples obtained at TP-3 to the laboratories at Ulster Hospital for the measurement of lipid panels as per the Service Level Agreement between Ulster University and the SEHSCT, which facilitated a discounted rate for laboratory services. However, despite numerous attempts, contact with the laboratories at Ulster Hospital to arrange this service could not be established. The research team surmise that the workload

at the laboratories at Ulster Hospital due to COVID-19 resulted in external requests being rejected. As such, lipid panel was solely measured at TP-1 and TP-2.

3.5.9 Messenger Ribonucleic Acid Gene Expression

The analysis of SIRT-1, IL-6, and IL-10 mRNA gene expression using a reverse transcription polymerase chain reaction technique was planned. However, performing these measurements was contingent on the acquisition of additional funding due to the expensive cost. Unfortunately, mRNA gene expression was not measured as the required funding was not obtained. Nevertheless, lymphocytes have been stored in case funding is received for future analysis.

3.6 Data Analysis

3.6.1 Data Analysis for Study 1

The methods employed for the statistical analysis of data in Study 1 are comprehensively discussed in **Paper 1** (chapter 4).

3.6.2 Data Analysis for Study 2

The literature suggests that pilot studies should focus on descriptive statistics and estimation rather than formal hypothesis testing (Lancaster et al., 2004). As such, descriptive statistics were performed in an attempt to identify trends that inform the development of future fully powered studies (Lee et al., 2014). The methods employed for the statistical analysis of data in Study 2 are comprehensively discussed in **Paper 2** (chapter 5).

The COVID-19 pandemic resulted in data collection terminating prematurely. Consequently, it was not possible to obtain the study measurements (secondary outcome measures) in 50% of the participants at TP-3, which resulted in unequal intra-group sample sizes across each TP. Thus, the primary analysis of secondary outcome measures comprised the data obtained at TP-1 and TP-2 from phase-III CR participants and patients who did not participate in CR (non-CR participants), with a sub-analysis comparing

groups of participants (group 1, non-CR; group 2, participated in phase-III CR only; and group 3, participated in phase-III and phase-IV CR) who completed each TP.

3.6.2.1 Inferential Statistics for Study 2

Study 2 was not formally powered to detect statistical significance. However, inferential statistics were performed on the secondary outcome measures for the purpose of research training. Statistical analysis was performed on all data with Statistical Product and Service Solutions (SPSS) statistical software (IBM, Surrey, UK, Version 25), with the level of significance set at $p < 0.05$. Data were assessed for normality using the Shapiro-Wilk test. Continuous data were reported as mean ± standard deviation (SD) for normally distributed data and as median (minimum, maximum) for skewed data. Discrete data were presented as absolute numbers and percentages. The equality of variances for normally and non-normally distributed data were verified with a parametric Levene's test and a non-parametric Levene's test ($p > 0.05$ for all), respectively. For the primary analysis of secondary outcome measures, differences in baseline continuous variables between the groups were analysed by a Student's independent t-test or Mann-Whitney U test, with the choice of test depending on data normality. A Fisher's exact test was used for the comparison of baseline categorical data. Within-group comparisons were performed with Student's paired t-test or Wilcoxon signed-rank test, and between-group comparisons at TP-2 were examined with Student's independent t-test or Mann-Whitney U test, as appropriate. Effect sizes were expressed by the correlation coefficient r (Cohen, 1988):

$$r = \sqrt{\frac{t^2}{t^2 + df}} \text{ for parametric tests or } r = \frac{z}{\sqrt{N}} \text{ for non-parametric tests.}$$

The calculation of a 95% CI for an effect size was based on Fisher-z transformation (Fisher, 1915). The magnitude of effect sizes was interpreted in accordance with Cohen's criteria for r: 0.1-0.3, small; 0.3-0.5, medium; 0.5-1.0, large (Cohen, 1988).

For the sub-analysis of secondary outcome measures, non-parametric tests were used as the small sample size of the non-CR group (number (n) < 3) precluded tests of normality. Differences in baseline variables between the groups were examined with a Kruskal-Wallis test for continuous data and a Fisher's exact test for categorical data. A

Friedman test was used to ascertain overall within-group differences between values measured across each TP. Following a significant main effect, Wilcoxon signed-rank tests were conducted to examine within-time differences. A Kruskal-Wallis test was utilised to analyse between-group differences at each TP, with Mann-Whitney U tests being used to explore any significant main effects. The familywise error rate for post-hoc tests was not controlled due to the low statistical power of the small sample size, with alpha adjustments potentially resulting in Type II errors (Nakagawa, 2004). Effect sizes were expressed by the correlation coefficient *r* (Cohen, 1988):

$$r = \frac{z}{\sqrt{N}}$$

The methods utilised to calculate 95% CIs and interpret the magnitude of effect sizes have been previously discussed. Spearman's correlation coefficient was performed to investigate the relationship between SIRT-1 concentration and the other secondary outcome measures at each TP for the phase-III & phase-IV CR group. The non-CR and phase-III CR only groups were excluded from this analysis due to insufficient sample sizes ($n < 7$) (Fowler et al., 2013). The results of the inferential statistics for Study 2 are presented in section 5.1.

3.6.2.2 Coefficient of Variation

The CV (%) was calculated using the following equation:

$$CV\ (\%) = \frac{Standard\ deviation}{Mean}\ x\ 100$$

3.6.3 Data Analysis for Study 3

Given the paucity of literature, Study 3 employed an exploratory approach to generate a rich understanding of the investigated phenomena by examining the views and opinions

of the participants. Reflexive thematic analysis was utilised to methodically identify, organise, and report patterns (themes) within the dataset. This method was selected due to its theoretical flexibility, well established guidelines for conducting the analysis, and usefulness for exploring an individual's experiences, perspectives, and opinions (Braun et al., 2019). In line with the exploratory nature of the study, an inductive orientation to identifying themes was implemented, which enabled the analysis to be freely guided by the data without trying to import ideas, concepts, or theories (Braun et al., 2019). An iterative approach was employed, whereby data analysis was performed after each interview. Recruitment terminated when the research team believed that data saturation had been achieved (Corbin & Strauss, 2014), whereby the collection of data from the tenth dyad did not necessarily add to the overall story. Thus, ten participants per group (patient and significant other) were recruited, which provided sufficient data for answering the research question as the identified themes were common across and within both patient and significant other data sets. The data sets for patients and significant others were analysed separately. Whilst this approach may have prevented an exploration of relationship dynamics (Taylor & De Vocht, 2011), it enabled the personal perceptions and perspectives of each group to be acknowledged, which was in line with the objective of Study 3.

The data-driven inductive thematic analysis was performed by two members of the research team (GT and Professor Ciara Hughes (CH)) and followed the recommendations of Braun and Clarke (2006). The *six-steps* of this method were not linear, with the analysis moving back and forward as it became more in-depth and nuanced. These *six-steps* of thematic analysis in relation to Study 3 are discussed below.

Step one: familiarisation with the data

The initial step involved GT and CH becoming immersed in the data by independently reading the transcripts multiple times to understand and appreciate the complexity of the content (Braun & Clarke, 2006). The audio-recordings were

transcribed verbatim by GT. The transcripts were then checked against the audio-recordings by GT before being sent to the participants for verification that the content accurately reflected their thoughts and feelings. The process of reading and re-reading the transcripts enabled GT and CH to become familiar with the large volume of data before progressing to *step two.*

Step two: generation of initial codes

This step involved GT and CH independently organising the data sets in a systematic manner by assigning codes to blocks of text that represented a coherent thought or idea (data extract). Coding was performed at both semantic and latent levels to capture explicit and implicit meaning, which facilitated an in-depth analysis of the data. For instance, participants often reported that they exercised for the purpose of improving their health, which resulted in the semantic code "health benefits". Moreover, participants stated that they were concerned about their health following the AMI, which contributed to the latent code "AMI- stimulus for improvements in health". All identified codes were agreed by consensus during a research team meeting to ensure rigour. Data analysis of the interview transcripts was aided by NVivo software (QSR International Pty Ltd. Version 12), which served as a platform to organise the data and manage the coding process.

Step three: identification of themes

At this step, GT and CH independently generated themes that represented meaningful patterns across the data sets by combining codes and further checking them against the data and other themes. For example, several codes were related to how the content of the CR programmes influenced participation in exercise, which resulted in the theme of "CR experience". The researchers (GT and CH) used note-taking and code descriptions to assist with the development of themes.

Step four: review themes

This step involved GT and CH discussing the themes through critical dialogue with another member of the research team who had also read the transcripts (Dr Iseult Wilson (IW)). At this stage, the research team determined that some of the themes developed in *step three* were slightly descriptive. For instance, GT had limited the data to themes that reflected the objectives of Study 3 (*i.e.* explicit factors that influence participation in CR and long-term exercise), which did not fully capture the complexity of the experiences and perspectives of the participants. Thus, there was a requirement to review, modify, and re-develop the themes. Through reflecting and critically discussing the content of the data sets with CH and IW, GT was able to generate new themes that provided a richer insight into the story of the data.

Step five: define themes

At this step, the themes were defined and named to ensure that the meaningful data was clearly and comprehensively captured. Moreover, it was important to ascertain overarching themes and how they relate to sub-themes to identify the essence of the story (Braun & Clarke, 2006). For example, it was apparent that several themes were related to "health benefits". These themes were merged into an overarching theme of "a need to improve health", which provided an in-depth account of the perspectives of the patients and significant others towards factors that influence participation in CR and long-term exercise. The overarching and sub-themes were defined and agreed by consensus between the research team (GT, CH, and IW).

Step six: write-up

Following the confirmation of the themes, the findings were written up by GT for dissemination in academic peer-reviewed journals and conferences. The write-up of the

results presented a coherent and interesting account of the data, with direct quotes from participants being included to enhance understanding and demonstrate the prevalence of themes (Braun and Clarke, 2006).

3.6.3.1 Reflexivity

As a concept, reflexivity represents the researcher's self-awareness of his/ her active role in the study, with an understanding that his/her position is not independent of the research project (Palaganas et al., 2017). As a process, reflexivity entails continuous introspection on the role of subjectivity during the research process (Parahoo, 2014), which constitutes a procedure through which researchers attempt to identify, examine, and comprehend how their values, social backgrounds, locations, and assumptions impact their research practice (Hesse-Biber, 2011). Thus, adopting a reflexive approach when performing qualitative research may enhance the rigour of the research process by facilitating an assessment of the influence of the researcher's preconceptions, assumptions, and experiences on the phenomena being investigated (Jootun et al., 2009).

In order to be reflexive, researchers should make their respective positions explicit when presenting qualitative research to contextualise the data collection and analysis processes (McNair et al., 2008). Prior to Study 3, the PhD researcher (GT) completed qualitative data collection and analysis training as he possessed an exclusive experience of quantitative research methodologies. As such, the position of the PhD researcher (GT) in Study 3 changed from a quantitative role to a qualitative stance. This transition between research paradigms was an insightful journey of professional development for the PhD researcher (GT). When preparing the first version of the semi-structured interview guide, the PhD researcher (GT) naturally employed quantitative research principles by shaping the questions in a deductive manner that tested the preconceptions that he had derived from the literature. However, feedback received from experienced supervisors (CH and IW) enabled the PhD researcher (GT) to recognise the importance of utilising an interview guide that comprised broad, open-ended questions to allow the participants to speak freely around the topics raised. If this understanding had not been developed, the explicit thoughts and feelings of the participants may not have been captured during the

interviews. The data collection period also served as a continuous learning experience for the PhD researcher (GT), which involved interviewing skills being further developed with each interview that was performed. During the early period of data collection, the PhD researcher (GT) encountered difficulties with encouraging participants to speak thoroughly about the key topics in the interview guide due to his inexperience with performing interviews. Upon reflecting on his performance after the first few interviews, the PhD researcher (GT) identified a need to overcome this challenge by focusing on probing more deeply. By actively practicing this skill in subsequent interviews, the confidence of the PhD researcher (GT) with conducting interviews increased, which was conducive to the collection of rich qualitative data.

The opinions and perceptions of researchers may affect the way in which data is perceived and subsequently presented (Creswell & Creswell, 2017). As such, a component of reflexivity involves researchers considering their personal interest in the topic being explored (Ramani et al., 2018). The research team were not involved with delivering CR or care to patients and had no prior experience in this area of CR research. However, the PhD researcher (GT) was familiar with the participants and the CR programmes that they attended, was acquainted with the nurses who delivered the CR programmes, possessed an academic understanding of the role of exercise in the secondary prevention of CAD, and was familiar with barriers and facilitators to CR and long-term exercise in CAD patients by virtue of reviewing the available literature in this field. Therefore, the position of the PhD researcher (GT) was that he approved of CAD patient engagement with CR and exercise training, with an understanding of potential factors that may influence participation. By reflexively acknowledging these aspects, the research team recognised the need to implement various measures that mitigate the influence of preconceptions on data collection in order to ensure rigour. To elaborate, the interview guide comprised broad, open-ended questions to allow the participants to speak freely around the topics raised. It was iteratively developed, which allowed the questions to be reframed in accordance with the matters discussed by the participants. In addition, the PhD researcher (GT) made every effort not to lead participants during interviews, and the transcripts were also checked with this in mind.

In the early stages of coding, the analysis performed by the PhD researcher (GT) was limited to the surface level of the data, with implicit meaning being overlooked. This issue is common amongst inexperienced qualitative researchers (Terry et al., 2017). However, by engaging with the feedback and guidance provided by experienced members of the research team (CH and IW), the PhD researcher (GT) developed an ability to perform a "deeper" level of analysis beyond the explicit meaning of the data, which contributed to the generation of findings that represented meaningful patterns with greater explanatory power. Given that the PhD researcher (GT) approved of CAD patient engagement with CR and exercise training, and possessed an understanding of potential factors that may influence participation, measures were taken to limit the influence of preconceptions during data analysis. The PhD researcher (GT) and a member of the research team (CH) actively searched for negative cases (evidence that contradicts, or appears to contradict the findings being developed) or statements that were different to their preconceptions (*i.e.* benefits of CR) over the course of data analysis. This process helped to illuminate the associations between the themes and sub-themes. Moreover, the PhD researcher (GT) and CH met to discuss the content of the interviews, consider the topics raised by the participants, and agree on the main findings by consensus with another member of the research team (IW). By doing so, the likelihood of individual preconceptions influencing the findings was reduced, which may have contributed to the generation of credible results.

3.7 Ethical Considerations

3.7.1 Informed Consent and Participant Autonomy

Informed consent involves a participant voluntarily entering a research project by providing written consent following the receipt of study information (Falagas et al., 2009). To achieve this, a minimum of one-week was allocated from the provision of PIS to the point of providing informed consent for both Study 2 and Study 3. This period constituted a "cooling-off" phase, which allowed the individuals to evaluate potential questions or uncertainties related to participation. This period also provided the individuals with time to consider their willingness to participate and circumvented a possible coerced decision from being made. Information regarding the purpose, protocol,

requirements, and benefits/ risks of participation was transparently discussed with potential participants by the PhD researcher (GT) prior to receiving informed consent. Each potential participant was given the opportunity to discuss any concerns or queries about participation before written informed consent was obtained. At the meetings with interested patients, and during contact from an individual who was interested in participating in an interview, all queries were thoroughly answered by the PhD researcher (GT). Informed consent was only obtained by the PhD researcher (GT) from individuals who clearly understood the study protocol and were willing to participate. A copy of the informed consent form was supplied to each participant, a copy was stored in a Trust Site File, and the original document was contained within a locked filling cabinet in a secure central data bank in the Institute of Nursing and Health Research at UU, Jordanstown. The participants were clearly informed by the PhD researcher (GT) that they could withdraw at any given moment throughout the study or stop an interview at any point without the requirement to provide reason.

3.7.2 Confidentiality

Confidentiality represents a requirement of the researcher to safeguard information about participants from unauthorized access, utilisation, disclosure, modification, loss, or theft (Kaiser, 2009). Thus, personal data associated with participants was stored in accordance with UU Code of Practice for Professional Integrity in the Conduct of Research. Participant information was anonymised using a coding system to maintain patient confidentiality, with this anonymised information being used in any database containing information about the study. Any information that may have been used to identify the participants, such as: consent forms, names of participants, or coding information was separated from the raw study data and stored in a separate locked filing cabinet within a secure central data bank at UU, Jordanstown as per the General Data Protection Regulation (2018). The electronic study data was stored on a password protected computer, and paper based data was stored in a locked filing cabinet that did not contain information that may have been used to identify the participants within a secure central data bank at UU, Jordanstown. Only members of the research team had access to the study data and participant personal information. The data from the research project will be stored at UU, Jordanstown for ten years in accordance with UU policy before the

information is shredded or erased. Only the research team will have access to the data during this time.

A Trust Site File comprising documents associated with this research project was maintained at each site. Copies of any study documentation associated with the participants were stored within the Trust Site File in a secure locked filing cabinet at the corresponding site.

The PhD researcher (GT) used participant personal contact information to arrange suitable times and locations to provide the study measurements at each TP. Additionally, participant personal contact information was used to arrange a suitable time and location for the interviews to be held, to send descriptive summaries of each interview discussion for confirmation of content, and to arrange a group-meeting with willing participants for a final confirmation of the interview findings. Participant personal contact information was only used for the purpose of this research project, and information regarding this matter was contained within the PIS, consent forms, and provided by the PhD researcher (GT) during the consenting process.

Patient blood samples were obtained, handled, and disposed of in accordance with the Human Tissue Authority regulations based on the policies enforced by the Human Tissue Act (2004). The PhD researcher (GT) who handled the blood samples completed Human Tissue Authority training to meet the requirements needed for safe tissue handling. Blood samples were clearly labelled and cross referenced with consent forms using appropriate coding to maintain participant confidentiality. The blood samples were stored in a Human Tissue Authority compliant freezer at -80 ºC at UU, Jordanstown in room 15C20. The storage of all blood samples was electronically recorded, which included documentation of the quantity and status of the samples during the analytical process. The blood samples were not used for any other purpose other than that required for the research project and were appropriately discarded immediately after analysis. No information that may identify the participants was associated with any study measurements, blood samples, interview transcriptions, or in academic publications.

Prior to the commencement of each interview, the PhD researcher (GT) informed the participant that information disclosed during the discussion would be kept confidential and that the audio-recordings shall be anonymised during transcription. The PhD researcher (GT) also instructed the participant to avoid specifically identifying another individual, or a hospital/ organisational establishment to maintain anonymity. If confidential information was accidentally disclosed by a participant during an interview, the PhD researcher (GT) excluded this information from the transcript. No identifiable information was transcribed from the audio-recordings of each interview. This was achieved during the transcription process by the PhD researcher (GT) replacing the participant's name with an anonymous code and not transcribing any personal information associated with any response. Therefore, the produced transcripts that were analysed contained no information that disclosed the identity of the participant, other individuals, or organisational establishments. The original audio-recordings of each interview were destroyed following transcription and analysis of data.

Interviews that had been arranged to take place in a participant's home carried the risk of being overheard by family members or the other participant of the dyad. To ensure confidentiality, the participant was offered the opportunity to schedule the interview for a time of day when family members were not present e.g. at work or school, or for the interview to be held in a location within the home that prevented other individuals from overhearing the conversation e.g. in a particular room/ floor of the house, or at a reasonable distance from family members/ the other participant of the dyad. An interview that was arranged at a venue other than the participant's home was held in private room at the chosen site to circumvent the discussion from being overheard and to allow confidentiality to maintained.

3.7.3 Non-Maleficence

No intentional harm should occur at any stage of the research process (Martela et al., 2018). The research team ensured that research project was conducted in compliance with the Declaration of Helsinki (2002) and the laws and regulations within the UK to ensure an optimal level of protection was offered to each participant.

3.7.3.1 Study 2

Appropriate emergency procedures were in place at each site where the study measurements were obtained to protect the safety and well-being of the participants. This included staff members who possessed basic life support training, along with access to medical equipment, such as: first aid kits and automated electronic defibrillators. Therefore, the study measurements were obtained at locations where a rapid response to an emergency was possible.

The demand on the participants was kept to a minimum. The minimum volume of blood sample (51.2 mL) required for laboratory analyses was obtained to minimise distress during this procedure. The blood samples were obtained in a spacious, ventilated, and well- lit room that was appropriate for safely performing blood draws at each site by a qualified phlebotomist (GT). Bruising and discomfort were minimised by applying pressure to the needle wound. Additionally, "white nail" pressure as per routine phlebotomy practice was applied to the needle wound for five minutes after the blood draw to prevent excessive bleeding.

All study measurement procedures were performed by the PhD researcher (GT) who possessed relevant training and experience. If a participant was unwilling to provide or continue with any study measurement, this was respected. The welfare of a participant was always prioritised over receiving or finishing a study measurement. At the pre- and post-phase-III CR programme assessments, the participants were routinely asked by CR nurses to complete an ISWT as per standard practice. Therefore, the participants were not asked to complete additional ISWTs by the PhD researcher (GT) at TP-1 and TP-2. Instead, the PhD researcher (GT) requested informed consent from participants to be provided with the results of SCMs.

The CR participants were present at their allocated sites to participate in the programmes at TP-1 and TP-2, which prevented any logistical demands being placed on these participants to provide the study measurements. Due to funding limitations, the

research team were incapable of reimbursing the participants for any travel costs incurred as a result of participation in this research project. Therefore, the PhD researcher (GT) ensured that all participants understood that there was no pressure to unsuitably commute to provide study measurements. The decision to be present at a determined site to provide study measurements was made by the participants, free from coercion.

3.7.3.2 Study 3

The PhD researcher (GT) received interview training and was aware of the necessary methods to relieve tension or insecurities that arose during the interviews. Potential participants were fully informed of the requirement to audio-record the interviews within the PIS and when being invited to take part in this component of the research project by the PhD researcher (GT). Concerned individuals were given the opportunity to discuss any apprehensions with the PhD researcher (GT) over a phone call. Interviews were only performed with those who were comfortable with the process of audio-recording.

Every attempt was made to ensure that the interview discussions did not cause distress for the participants. The topics discussed were not overly sensitive. However, patients were asked to speak about their conditions, along with the significant others being asked to speak about how the conditions of the patients had affected them. These topics carried the possibility of inducing participant distress. As such, a "distress management protocol" was established, which involved a break in the interview to give the participant an opportunity to take time out. Following the short break, if a participant remained upset, an opportunity to leave the room and step away from the interview would be provided. An upset participant would then be offered an opportunity to discuss any issues with a member of the research team. The participant would then be offered the option of either returning to or withdrawing from the interview. Appropriate arrangements would be made to ensure that the distressed participant is returned home safely. If the PhD researcher (GT) had noticed any concerning behaviour or statements from a participant during an interview, or had a support service been required, the individual would have been directed towards appropriate support mechanisms provided by the BHSCT or SEHSCT. Additionally, if poor professional practice had been identified during an interview, the

participant would have been provided with information regarding the patient's complaints procedure in accordance with National Health Service policy.

Each participant was offered the choice of determining a suitable time and venue for the interview to take place, such as: the participant's home, an UU campus, a BHSCT site, or Ulster Hospital. This allowed the interview to be conveniently scheduled for the participant and prevented excessive logistical demand. If an interview was arranged to take place at a participant's home, a series of "Lone Worker" guidelines were followed to ensure the safety of the PhD researcher (GT). The PhD researcher (GT) informed the Chief Investigator (CH) of the following details prior to attending a home visit to interview the participant: date, time, participant name, contact number of PhD researcher (GT), location of interview, and expected duration. This information was destroyed following confirmation that the PhD researcher had safely completed the interview.

Chapter 4

Systematic Review and Meta-Analysis (Paper 1)

4.0 Results of the Systematic Review and Meta-Analysis (Paper 1)

This chapter reports the findings of the systematic review and meta-analysis (**Paper 1**). This study has been published in the *Journal of Sports Sciences.*

4.1 Exercise and Inflammation in Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomised Trials

4.1.1 Introduction

CAD involves an attenuation of myocardial perfusion due to progressive intraluminal accumulation of fibrous atherosclerotic plaque within an epicardial coronary artery (Libby & Theroux, 2005). The ramifications of this may include: ACS comprising myocardial infarction and angina pectoris, impaired ventricular function, or heart failure (Libby et al., 2009; Santos-Gallego et al., 2014). Despite improvements in CVD science and medical care over the past few decades, CAD remains a leading cause of mortality throughout the world (Wang et al., 2016).

The global prevalence of CAD has provoked scientific investigations to elucidate the underlying pathophysiological mechanisms responsible for atherogenesis. As a consequence, it is becoming increasingly clear that low-grade chronic inflammation is implicated in each pathological stage of atherosclerotic development (Libby & Peter, 2012; Wong et al., 2012). Notably, Ridker et al. (2017) recently documented that the administration of canakinumab, a monoclonal antibody that targets the IL-1β innate immunity pathway, contributed to a significant reduction in hs-CRP and recurrent cardiovascular complications in CAD patients with previous myocardial infarction and a residual inflammatory response (hs-CRP > 2 mg/L) compared to placebo. Therefore, this investigation provided evidence of the benefits of targeting inflammatory pathways to improve clinical outcomes in high-risk CAD patients.

Exercise is an established therapeutic strategy for primary and secondary prevention of CAD (Haskell et al., 2007; Anderson et al., 2016; Alves et al., 2016; Piepoli et al., 2016). Interestingly, a meta-analysis performed by Swardfager et al. (2012) concluded that exercise may reduce inflammatory activity in CAD patients, as indicated by lower post-intervention values of CRP, fibrinogen, IL-6, and VCAM-1. As such, this conclusion suggests that exercise may induce an anti-inflammatory effect in CAD patients, which may partially represent a mechanism by which secondary prevention is conferred. However, the evidence produced by Swardfager et al. (2012) was generated by pooling randomised and non-randomised studies; the latter study design potentially

decreasing the validity of the results due to selection bias (Reeves et al., 2008). As such, this systematic review and meta-analysis will analyse randomised studies that investigated the effect of exercise on inflammatory biomarkers in CAD patients. Utilising this approach will provide a timely update to the evidence base by synthesising a rigorous examination of the capability of exercise to serve as an anti-inflammatory strategy in CAD.

4.2 Methods

The methodology implemented in this systematic review and meta-analysis adhered to guidelines presented in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011), and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations (Moher et al., 2009) (PROSPERO registration number: CRD42018105245).

4.2.1 Search Strategy

A computerised search of the following databases from inception to August 2019 was performed: MEDLINE, EMBASE, AMED, CINAHL, Cochrane Central Register of Controlled Trials, and SPORT Discus. To ensure a comprehensive search strategy was implemented, various search terms comprising Medical Subject Headings (MeSH), database specific subject headings, and key words were derived from four primary concepts: "coronary artery disease", "exercise", "inflammatory biomarker", and "randomised trial". The search strategy was limited to human trials and English publications. An example of the implemented search strategy for Cochrane Central Register of Controlled Trials is presented in ESM 1, Appendix A. To minimise the risk of introducing bias to this review, grey literature was sought from the following resources: Google Scholar, specialised databases (National Rehabilitation Information Centre, Physiotherapy Evidence Database, and the National Institute for Health Research Journals Library), and the International Clinical Trials Registry Platform. Hand searching of reference lists of articles and previous reviews was also performed to identify additional trials that were potentially eligible. All identified publications were read as either abstracts or full texts.

4.2.2 Inclusion and Exclusion Criteria

A protocol comprising inclusion and exclusion criteria was established to ascertain suitable studies for inclusion (see Table 4.1).

Table 4.1 Inclusion and exclusion protocol

Inclusion criteria	*Exclusion criteria*
• Report published in English • Randomised trial • In consideration of standard treatment, studies involving control groups that routinely received usual care (*i.e.,* pharmacological treatment and lifestyle recommendations) were included • Recruited only formally diagnosed coronary artery disease patients with history of a myocardial infarction, acute coronary syndrome, coronary revascularisation by percutaneous coronary intervention or coronary artery bypass graft, or $\geq$ 50% occlusion of at least one major coronary artery as confirmed by an angiogram • At least one inflammatory biomarker measured in blood (plasma or serum) before and after an exercise intervention (any form of aerobic, resistance training, or aerobic and resistance training combined) with a duration > 2-weeks, which may allow potential changes in inflammatory biomarkers to be representative of exercise induced physiological adaptation • Studies comprising exercise training in combination with a comprehensive cardiac rehabilitation programme (*i.e.,* lifestyle/ risk factor advice and psychosocial management) were included if the additional components of the programme were solely educational	• Studies were excluded if a co-intervention was reported (*i.e.,* provision of a hypocaloric diet or antioxidant/ vitamin supplement), to allow the results to potentially reflect an independent effect of exercise • Studies that recruited CAD patients with severe heart failure (New York Heart Association Class III or IV or left ventricular ejection fraction $\leq$ 30%) were excluded to standardise the severity of CAD in the included participants, along with the reduced exercise tolerance and increased inflammatory state associated with severe heart failure being potential confounding variables (Haykowsky et al., 2015; Arroyo-Espliguero et al., 2004)

4.2.3 Data Extraction

Data not reported in main text or tables were extracted from figures when possible. If available, data analysed using the intention-to-treat principles were preferentially extracted to mitigate bias and permit clinical relevance (Higgins et al., 2011). When insufficient information was reported by a study, a member of the review team (GT) contacted the authors to request any missing data. Two members of the review team (GT and CH) independently extracted the necessary data from each included study into a preformatted data collection form designed by the Cochrane Collaboration. Discrepancies were identified and discussed until disagreements were resolved by consensus (a third member of the review team (Mrs Jacqui Crawford (JC)) was consulted when necessary). The lead review author (GT) entered the data into tables and inserted a unified data set into Review Manager Version 5.3 for the completion of meta-analyses.

4.2.4 Quality Assessment

The reliability of the results provided by each trial was determined by conducting a risk of bias (ROB) assessment in accordance with guidelines presented in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). In accordance with Sveaas et al. (2017), the "blinding of participants and personnel" ROB item was excluded as such an approach is very difficult, if not impossible to utilise in studies that implemented an exercise intervention. When available, published *a priori* study protocols were used to supplement the assessment of ROB.

The quality of evidence for each outcome that was included in the post-intervention inflammatory biomarker value comparisons between exercise and control groups was rated in accordance with the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system (Balshem et al., 2011) (see Table 4.2). Three members (GT, CH, and JC) of the review team independently performed a ROB and GRADE assessment on the included studies to mitigate the influence of individual subjectivity during quality assessment; disagreements were discussed at a meeting until the final decisions were agreed by consensus.

Table 4.2 GRADE system guidelines for rating overall quality of evidence (Balshem et al., 2011)

GRADE Domain	Description
Study Limitations	The quality of evidence is downgraded by the existence of internal limitations such as: lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome measures, selective outcome reporting, or terminating early for benefit.
Inconsistency of Results	The quality of evidence is downgraded by the following criteria: wide variance of point estimates across studies, minimal or no overlap of confidence intervals, statistical tests for heterogeneity (χ^2) generate low P-values (≤ 0.1), or large I² values are documented.
Indirectness of Evidence	The quality of evidence is downgraded if interventions were not compared directly to one another, or if a restricted version of the main review question in terms of population, intervention, or outcomes was investigated.
Imprecision	The quality of the evidence is downgraded when studies included relatively few participants and thus had wide confidence intervals around the estimate of effect.
Publication Bias	The quality of the evidence is downgraded if a systematic under-estimation or an over-estimation of significant or non-significant intervention effects due to the selective publication of studies is suspected.

4.2.5 Statistical Analysis

A random-effects inverse variance model was used to calculate standardised mean differences SMDs with 95% CIs. In accordance with Swardfager et al. (2012), meta-analyses were conducted to facilitate post-intervention value comparisons between exercise and control groups (a negative SMD represents a lower value in the exercise group compared to control group). A random-effects inverse variance model was chosen due to anticipated clinical heterogeneity between studies, and SMD was calculated due to expected variance in outcome measurement methodology (Deeks et al., 2011). An SMD ≤ 0.4 was interpreted as a small effect size, between 0.5 and 0.7 was considered to be a medium effect size, and ≥ 0.8 was deemed a large effect size (Cohen, 1988). Data were pooled for meta-analyses when ≥ two studies measured the same outcome and data was available in a suitable format (mean ± SD). If studies reported data as median and range or interquartile range (IQR), the sample means ± SDs were estimated by utilising the formula proposed by Wan et al. (2014). Further, if mean ± standard error of the mean (SEM) was reported, the Review Manager Version 5.3 calculator resource was used to estimate SD. When a study implemented multiple exercise groups, the data for each group was entered separately as an independent data point. Additionally, the sample size of the control group was divided by the number of intervention groups to prevent a unit of analysis error (Deeks et al., 2011). A P value of ≤ 0.05 was considered statistically significant. Heterogeneity was investigated through inspection of I^2 and χ^2 test values; a P value of ≤ 0.1 for the χ^2 test or an I^2 value of ≥ 50% was considered to be indicative of substantial heterogeneity (Higgins et al., 2003). Sub-group analyses were performed using χ^2 heterogeneity statistics to investigate if the following variables influenced the magnitude of effect (SMD) or contributed to heterogeneity in the overall pooled results:

- Duration of exercise programme: < 12 weeks versus ≥ 12 weeks.
- Sessions per week: ≤ 3 compared to > 3.
- Exercise modality: aerobic interval exercise (AIE) versus continuous aerobic exercise (CAE) versus RT verses a combination of RT and cardiorespiratory exercise (AIE or CAE).
- Exercise alongside CR versus exercise only.

A statistically significant test for sub-group differences was considered as $P \leq 0.1$ (χ^2) (Deeks et al., 2011). Sensitivity analyses were performed to assess the robustness of the pooled results by removing the studies that reported data that required the estimation of mean ± SD from median and range or IQR, or SD from the SEM. Additionally, the influence of "outlying" data generated by one study (Giallauria et al., 2011) on the results of the post-intervention CRP value comparison was investigated. All meta-analyses were performed using Review Manager Version 5.3. Descriptive analyses were performed for studies and outcomes that could not be meta-analysed.

4.3 Results

4.3.1 Study Selection

A total of 8,290 articles were identified by various literature searches. The lead author (GT) performed the initial screening process, which entailed reading the titles and abstracts of articles to exclude irrelevant studies that did not meet the inclusion criteria. Following the initial screening process, a full text evaluation of thirty-three articles was independently performed by three members (GT, CH, and JC) of the review team to ascertain correlation with the inclusion criteria. Authors were contacted if any uncertainty existed surrounding the suitability of a particular study for inclusion. If no reply was provided, the study was excluded. A meeting was held between the three members (GT, CH, and JC) of the review team to discuss findings, until disagreements were agreed by consensus. Consequently, twenty-five randomised studies (Lee et al., 2006; Bilinska et al., 2010; Conraads et al., 2015; Fernandes et al., 2011; Hansen et al., 2011; Beckie et al., 2010; Lee et al., 2012; Lian et al., 2014; Madssen et al., 2014; Moholdt et al., 2012; Oliveira et al., 2015; Pedersen et al., 2016; Raygan et al., 2017; Ribeiro et al., 2012; Schumacher et al., 2006; Sixt et al., 2008; Theodorou et al., 2016; Toyama et al., 2012; Vona et al., 2009; Munk et al., 2011; Luk et al., 2012; Jalaly et al., 2015; Giallauria et al., 2011; El Missiri & Taher, 2016; Balen et al., 2008) were deemed appropriate for inclusion in this systematic review; ten (Pedersen et al., 2016; Raygan et al., 2017; Conraads et al., 2015; Hansen et al., 2011; Moholdt et al., 2012; Beckie et al., 2010; Lee et al., 2006; Toyama et al., 2012; El Missiri & Taher, 2016; Luk et al., 2012) of which were unsuitable for meta-analyses (see Figure 4.1 for PRISMA flow diagram depicting the study selection process).
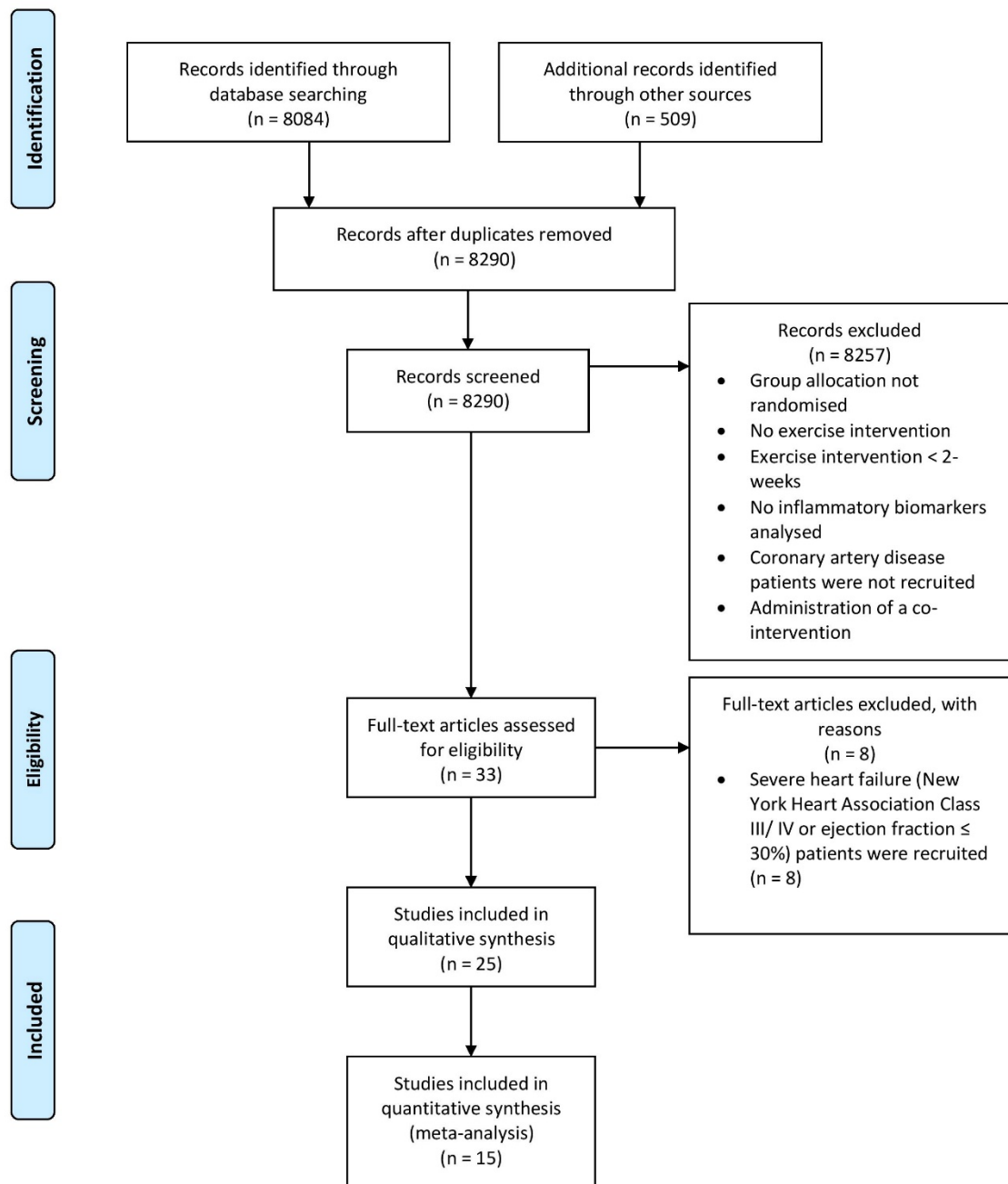
Figure 4.1 PRISMA flow diagram depicting the study selection process

4.3.2 Study Characteristics

The main study characteristics are presented in ESM 1, Tables S1, S2, S3, and S4 (see Appendix A). Studies were published between 2006 and 2017. Of the twenty-five randomised studies that were included, eighteen trials (Lian et al., 2014; Raygan et al., 2017; Bilinska et al., 2010; Fernandes et al., 2011; Ribeiro et al., 2012; Lee et al., 2012; Oliveira et al., 2015; Schumacher et al., 2006; Madssen et al., 2014; Sixt et al., 2008; Theodorou et al., 2016; Vona et al., 2009; Munk et al., 2011; Jalaly et al., 2015; Giallauria et al., 2011; Balen et al., 2008; Luk et al., 2012; El Missiri & Taher, 2016) randomised participants to an exercise intervention or control group, three studies (Conraads et al., 2015; Hansen et al., 2011; Moholdt et al., 2012) randomised participants to different forms of exercise, one study (Pedersen et al., 2016) randomised participants to an exercise intervention or low-energy diet, two studies (Beckie et al., 2010; Lee et al., 2006) randomised participants to different forms of CR, and one study (Toyama et al., 2012) randomised participants to a combination of exercise and a standard dose of rosuvastatin or atorvastatin treatment.

4.3.3 Participant Characteristics

Sample populations in the twenty-five included studies varied from 28 to 275 participants. Overall, the included studies provided results for 2105 (1426 exercising and 679 control) participants, of which, 73% were male (1527). The mean age of the participants was 59.9 ± 4.2 years (range: 51-68 years). The condition of CAD in the included participants encompassed: post- revascularisation (CABG/ PCI), post-myocardial infarction, stable angina pectoris, and ≥ 3 months after cardiovascular complication or revascularisation. Finally, participant baseline inflammatory biomarker concentrations varied from low to high across the included studies (See Appendix A, ESM 1, Tables S5.1 and S5.2 for participant baseline inflammatory biomarker concentrations).

4.3.4 Exercise Intervention Characteristics

A detailed description of the exercise intervention characteristics can be found in ESM 1, Tables S1, S2, S3, and S4 (See Appendix A). Each of the included studies implemented a cardiorespiratory (CAE and/ or AIE) intervention. Moreover, six of the included studies

(Beckie et al., 2010; Lee et al., 2006; Hansen et al., 2011; Theodorou et al., 2016; Vona et al., 2009; Luk et al., 2012) implemented a group that received a RT intervention alone or in combination with cardiorespiratory exercise. Across which, the utilised RT exercises (weights, resistance bands, resistance machines, and wall-pulleys) activated major muscle groups (upper and/ or lower body).

According to exercise intensity classifications published by the American College of Sports Medicine (Garber et al., 2011), eighteen of the included studies (Beckie et al., 2010; Bilinska et al., 2010; Conraads et al., 2015; Fernandes et al., 2011; Hansen et al., 2011; Lee et al., 2012; Madssen et al., 2014; Moholdt et al., 2012; Oliveira et al., 2015; Pedersen et al., 2016; Schumacher et al., 2006; Theodorou et al., 2016; Vona et al., 2009; Giallauria et al., 2011; Luk et al., 2012; El Missiri & Taher, 2016; Jalaly et al., 2015; Munk et al., 2011) prescribed a vigorous intensity for the cardiorespiratory exercise intervention, and the remaining seven studies (Lee et al., 2006; Lian et al., 2014; Raygan et al., 2017; Ribeiro et al., 2012; Sixt et al., 2008; Toyama et al., 2012; Balen et al., 2008) prescribed a moderate intensity. The prescribed RT intensity across two studies (Hansen et al., 2011; Theodorou et al., 2016) ranged from 60-65% of one-repetition maximum. Furthermore, one study (Vona et al., 2009) prescribed a RT intensity of 60% of maximum voluntary contraction, one study (Luk et al., 2012) described the RT intensity as being similar to that of the accompanying vigorous intensity cardiorespiratory exercise, and two studies (Beckie et al., 2010; Lee et al., 2006) did not report the prescribed RT intensity. Overall, mean exercise session duration was 38 ± 12 minutes (range: 15-75 minutes); mean exercise session frequency was 4 ± 1 sessions per week (range: 2-7 sessions per week); and mean exercise intervention period was 14 ± 10 weeks (range: 3-48 weeks).

4.3.5 Synthesis of Results

Ten studies were not included in any of the meta-analyses performed; seven of which did not implement a control group (Pedersen et al., 2016; Conraads et al., 2015; Hansen et al., 2011; Moholdt et al., 2012; Beckie et al., 2010; Lee et al., 2006; Toyama et al., 2012), El Missiri and Taher (2016) reported a baseline imbalance in CRP values, Luk et al. (2012) presented data in an inappropriate format (mean change ± SD), and Raygan et al. (2017) was the only study to report data for IL-33 and IL-35. Moreover, Oliveira et al. (2015) was excluded from the post-intervention CRP value comparison due to a baseline

imbalance in CRP concentrations. Summaries of the various meta-analyses that were performed are provided in ESM 2, Table S1 (see Appendix A).

4.3.5.1 Post-Intervention Inflammatory Biomarker Comparisons

The results of the post-intervention inflammatory biomarker comparisons between exercise and control groups are depicted in Figures 4.2(a), 4.2(b), 4.2(c), and 4.3. Very low qualities of evidence for significant medium and large beneficial effect sizes for exercise on CRP (SMD: -0.55 (95% CI: -0.93, -0.16), P= 0.005), fibrinogen (SMD: -0.52 (95% CI: -0.74, -0.29, P= <0.00001), and vWF (SMD: -1.57 (95% CI: -2.23, -0.92), P= <0.00001) were documented. However, between-study heterogeneity was substantial for CRP (I^2= 85%, χ^2 P= <0.00001) and vWF (I^2= 76%, χ^2 P= 0.007). Significant effect sizes were not documented for IL-6, IL-10, TNF-α, VCAM-1, ICAM-1, E-selectin, P-selectin, IL-8, and regulated on activation, normal T-cell expressed and secreted (RANTES).

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 CRP								
Balen et al. (2008)	5.67	4.67	30	13.33	6.23	30	7.5%	-1.37 [-1.94, -0.81]
Bilińska et al. (2010)	0.19	0.23	59	0.3	0.61	59	8.3%	-0.24 [-0.60, 0.13]
Fernandes et al. (2011)	1.5	2.59	15	1.5	1.85	19	7.0%	0.00 [-0.68, 0.68]
Giallauria et al. (2011)	3.9	1.8	37	13.4	3.9	38	7.0%	-3.08 [-3.76, -2.40]
Lee et al. (2012)	0.08	0.16	22	0.23	0.65	24	7.5%	-0.31 [-0.89, 0.28]
Lian et al. (2014) [Evening CAE]	2.36	0.79	64	3.2	0.86	39	8.1%	-1.02 [-1.44, -0.60]
Lian et al. (2014) [Morning CAE]	2.77	0.86	70	3.2	0.86	38	8.2%	-0.50 [-0.90, -0.10]
Madssen et al. (2014)	1.07	0.6	24	1.5	2.5	25	7.6%	-0.23 [-0.79, 0.33]
Ribeiro et al. (2012)	1.3	1.41	22	0.9	0.89	20	7.3%	0.33 [-0.28, 0.94]
Schumacher et al. (2006)	2.23	1.73	95	2.68	2.61	94	8.6%	-0.20 [-0.49, 0.08]
Sixt et al. (2008)	2.9	1.6	13	3.8	2.9	10	6.3%	-0.39 [-1.22, 0.45]
Theodorou et al. (2016) [AIE & RT]	0.28	0.62	15	0.4	0.85	5	5.5%	-0.17 [-1.18, 0.84]
Theodorou et al. (2016) [AIE]	0.28	0.54	15	0.4	0.85	5	5.5%	-0.18 [-1.20, 0.83]
Theodorou et al. (2016) [RT]	0.32	0.53	11	0.4	0.85	5	5.4%	-0.12 [-1.18, 0.94]
Subtotal (95% CI)			492			411	100.0%	-0.55 [-0.93, -0.16]

Heterogeneity: Tau² = 0.43; Chi² = 88.46, df = 13 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.79 (P = 0.005)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.2 Fibrinogen								
Balen et al. (2008)	4.3	1.2	30	5.3	1.8	30	15.2%	-0.65 [-1.17, -0.13]
Bilińska et al. (2010)	3.53	0.89	59	4.17	1.37	59	25.3%	-0.55 [-0.92, -0.18]
Lian et al. (2014) [Evening CAE]	0.93	0.19	89	1.08	0.19	49	25.9%	-0.79 [-1.15, -0.42]
Lian et al. (2014) [Morning CAE]	1.04	0.15	89	1.08	0.19	48	26.7%	-0.24 [-0.59, 0.11]
Sixt et al. (2008)	3.6	0.5	13	3.7	0.8	10	6.9%	-0.15 [-0.97, 0.68]
Subtotal (95% CI)			280			196	100.0%	-0.52 [-0.74, -0.29]

Heterogeneity: Tau² = 0.02; Chi² = 5.50, df = 4 (P = 0.24); I² = 27%
Test for overall effect: Z = 4.43 (P < 0.00001)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.3 vWF								
Munk et al. (2011)	99.9	61.2	18	173.2	146.4	18	24.5%	-0.64 [-1.31, 0.03]
Vona et al. (2009) [CAE & RT]	91	11	53	109	15	17	25.9%	-1.48 [-2.08, -0.87]
Vona et al. (2009) [CAE]	86	8.6	52	109	15	17	24.7%	-2.17 [-2.83, -1.51]
Vona et al. (2009) [RT]	87	9.4	54	109	15	16	24.9%	-2.00 [-2.65, -1.34]
Subtotal (95% CI)			177			68	100.0%	-1.57 [-2.23, -0.92]

Heterogeneity: Tau² = 0.34; Chi² = 12.26, df = 3 (P = 0.007); I² = 76%
Test for overall effect: Z = 4.71 (P < 0.00001)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.4 IL-6								
Bilińska et al. (2010)	2.25	1.61	59	2.77	2.27	59	24.2%	-0.26 [-0.62, 0.10]
Munk et al. (2011)	0.61	0.39	18	1.13	0.55	18	12.5%	-1.07 [-1.77, -0.36]
Oliveira et al. (2015)	1.2	0.77	44	1.53	1.77	42	21.5%	-0.24 [-0.67, 0.18]
Ribeiro et al. (2012)	3.1	2.15	20	3.3	1.41	18	14.2%	-0.11 [-0.74, 0.53]
Schumacher et al. (2006)	3.3	2.42	95	3.12	2.06	94	27.7%	0.08 [-0.21, 0.36]
Subtotal (95% CI)			236			231	100.0%	-0.24 [-0.55, 0.07]

Heterogeneity: Tau² = 0.07; Chi² = 9.57, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 1.54 (P = 0.12)

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.5 TNF-alpha								
Balen et al. (2008)	45.77	44.6	30	37.4	18.14	30	16.1%	0.24 [-0.27, 0.75]
Munk et al. (2011)	1.3	0.95	18	1.32	0.55	18	9.7%	-0.03 [-0.68, 0.63]
Oliveira et al. (2015)	7.4	3.16	44	7.83	3.84	42	23.2%	-0.12 [-0.54, 0.30]
Schumacher et al. (2006)	3.08	1.83	95	3.57	2.89	94	50.9%	-0.20 [-0.49, 0.08]
Subtotal (95% CI)			187			184	100.0%	-0.09 [-0.30, 0.11]

Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

-4 -2 0 2 4
Favours [Exercise]   Favours [Control]

Figure 4.2(a) Forest plots of post-intervention inflammatory biomarker value comparisons between exercise and control groups

SD, standard deviation; Std, standardised; IV, inverse variance; CI, confidence interval; CRP, C-reactive protein; vWF, von Willebrand factor; IL-6, interleukin-6; TNF-alpha, tumour necrosis factor-alpha; CAE, continuous aerobic exercise; AIE, aerobic interval exercise; RT, resistance training
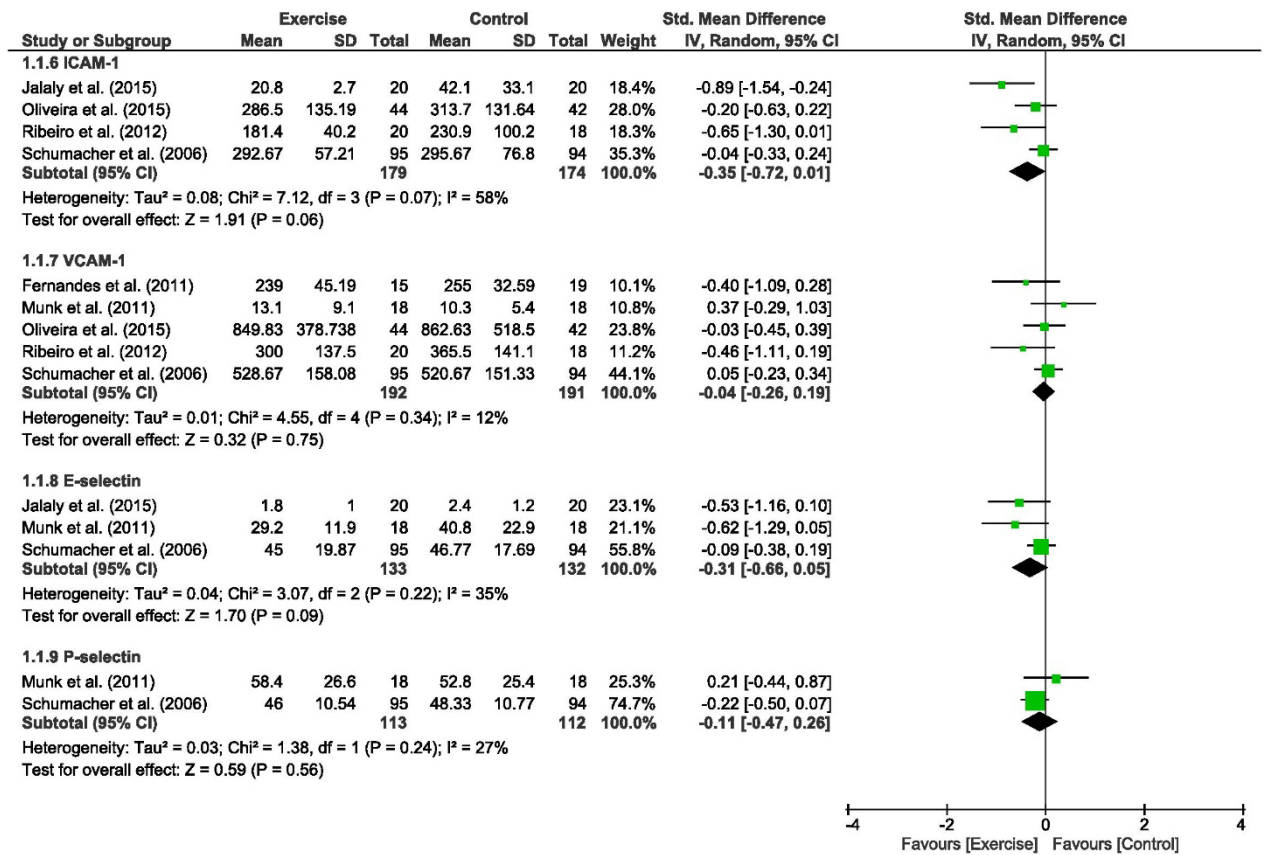
Figure 4.2(b) Forest plots of post-intervention inflammatory biomarker value comparisons between exercise and control groups

SD, standard deviation; Std, standardised; IV, inverse variance; CI, confidence interval; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.10 IL-8								
Balen et al. (2008)	8	3.66	30	13.4	8.56	30	53.2%	-0.81 [-1.34, -0.28]
Munk et al. (2011)	11.72	6.6	18	11.96	8.4	18	46.8%	-0.03 [-0.68, 0.62]
Subtotal (95% CI)			48			48	100.0%	-0.45 [-1.21, 0.32]
Heterogeneity: Tau² = 0.21; Chi² = 3.30, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 1.15 (P = 0.25)								
1.1.11 RANTES								
Munk et al. (2011)	1,378	173	18	1,316	228	18	40.2%	0.30 [-0.36, 0.96]
Oliveira et al. (2015)	52.63	37.4	44	63.07	37.23	42	59.8%	-0.28 [-0.70, 0.15]
Subtotal (95% CI)			62			60	100.0%	-0.05 [-0.60, 0.51]
Heterogeneity: Tau² = 0.09; Chi² = 2.09, df = 1 (P = 0.15); I² = 52%								
Test for overall effect: Z = 0.16 (P = 0.87)								

Figure 4.2(c) Forest plots of post-intervention inflammatory biomarker value comparisons between exercise and control groups

SD, standard deviation; Std, standardised; IV, inverse variance; CI, confidence interval; IL-8, interleukin-8; RANTES, regulated on activation, normal T-cell expressed and secreted

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 IL-10								
Balen et al. (2008)	4.07	2.02	30	3.67	3.11	30	27.3%	0.15 [-0.36, 0.66]
Munk et al. (2011)	1.93	1.6	18	1.62	1.06	18	16.3%	0.22 [-0.43, 0.88]
Oliveira et al. (2015)	8.47	5.75	44	9.7	7.68	42	39.1%	-0.18 [-0.60, 0.24]
Ribeiro et al. (2012)	7	8.15	20	6.7	4	18	17.3%	0.04 [-0.59, 0.68]
Subtotal (95% CI)			112			108	100.0%	0.01 [-0.25, 0.28]
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 3 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.11 (P = 0.91)								

Figure 4.3 Forest plot of post-intervention IL-10 value comparison between exercise and control groups

SD, standard deviation; Std, standardised; IV, inverse variance; CI, confidence interval; IL-10, interleukin-10

4.3.5.2 Descriptive Analyses

A summary of the results for each of the included studies is presented in ESM 1, Tables S1, S2, S3, and S4 (see Appendix A). Across the outcomes that could not be meta-analysed, beneficial within-exercise group changes were demonstrated for soluble tumour necrosis factor- alpha receptor 1 (TNF-α SR1) ($P< 0.001$) (Balen et al., 2008), chemokine (C-C motif) ligand 21 (CCL21) ($P< 0.05$) (Munk et al., 2011), and IL-35 ($P= 0.001$) (Raygan et al., 2017). Also, positive differences between exercise and control groups were observed for TNF-α SR1 ($P= 0.004$) (Balen et al., 2008), IL-35 ($P= 0.002$) (Raygan et al., 2017) and interferon gamma-induced protein 10 (IP-10) ($P= 0.03$) (Fernandes et al., 2011). No significant changes were reported within or between-groups for IL-33 (Raygan et al., 2017), monokine induced by gamma interferon (Mig) (Fernandes et al., 2011), MCP-1 (Munk et al., 2011), chemokine (C-C motif) ligand 19 (CCL19) (Munk et al., 2011), chemokine (C-X-C motif) ligand 16 (CXCL16) (Munk et al., 2011), CD40 ligand (CD40L) (Munk et al., 2011), and pentraxin 3 (PTX-3) (Munk et al., 2011).

In terms of the studies that were not included in the meta-analyses, eight trials (Conraads et al., 2015; Hansen et al., 2011; Moholdt et al., 2012; Pedersen et al., 2016; Beckie et al., 2010; Toyama et al., 2012; El Missiri & Taher, 2016; Luk et al., 2012) investigated the impact of exercise on CRP. Across which, beneficial within-exercise group changes were observed by four studies (Conraads et al., 2015; Beckie et al., 2010; Toyama et al., 2012; El Missiri & Taher, 2016), whilst no significant changes were reported by the other four studies (Hansen et al., 2011; Moholdt et al., 2012; Pedersen et al., 2016; Luk et al., 2012). Three trials (Hansen et al., 2011; Pedersen et al., 2016; Beckie et al., 2010) examined the effect of exercise on IL-6; one study (Beckie et al., 2010) documented beneficial within-exercise group changes, whilst the remaining two studies (Hansen et al., 2011; Pedersen et al., 2016) observed no significant changes. Two studies (Pedersen et al., 2016; Beckie et al., 2010) reported data regarding the influence of exercise on TNF-α. Beneficial within-exercise group changes were observed by one study (Beckie et al., 2010), whereas the other trial documented no significant changes (Pedersen et al., 2016). Finally, beneficial within-exercise group changes were reported for ICAM-1 (Beckie et al., 2010), fibrinogen (Lee et al., 2006), and vWF (Lee et al., 2006), whilst no significant changes were observed for IL-8 (Hansen et al., 2011) or P-selectin (Lee et al., 2006).

4.3.6 Quality Assessment

A summary of the ROB assessment for the twenty-five included studies is presented in Figure 4.4. Three studies (Lee et al., 2006; Moholdt et al., 2012; Pedersen et al., 2016) were rated as a low risk of bias for each domain. However, inadequate reporting of random sequence generation and allocation concealment decreased the reliability of the results across most of the included studies. The results for the quality of evidence assessment using the GRADE system are presented in ESM 2, Table S2 (see Appendix A). Issues pertaining to the before mentioned ROB study limitations, along with inconsistency of results, indirectness of evidence, and imprecision resulted in the overall quality of evidence ranging from very low to moderate for the inflammatory biomarkers included in the post-intervention value comparisons.

Figure 4.4 Review authors' judgements about each risk of bias item for each included study

4.3.7 Sub-Group Analyses

The results of the sub-group analyses are presented in ESM 3, Tables S1, S2, S3, and S4 (see Appendix A). Various statistically significant (χ^2 P $\leq$ 0.1) sub-group differences were detected (see Appendix A, ESM 4, Table S1 for summaries of the statistically significant sub-group differences). However, an uneven covariate (a limited or unbalanced number of studies and / or participants contributing to each sub-group) distribution rendered the results meaningless (Richardson et al., 2018). As such, the results of the statistically significant sub-group differences were not discussed in order to circumvent misleading conclusions.

4.3.8 Sensitivity Analyses

The results of the sensitivity analyses are presented in ESM 4, Tables S2 and S3 (see Appendix A). Removal of the six studies (Fernandes et al., 2011; Oliveira et al., 2015; Schumacher et al., 2006; Theodorou et al., 2016; Ribeiro et al., 2012; Balen et al., 2008) that presented data that necessitated the estimation of mean ± SD or SD from the corresponding meta-analyses precluded post-intervention value comparisons for IL-8, IL-10, TNF-α, P-selectin, and RANTES as < 2 studies were available for pooling. As such, the results of these meta-analyses should be interpreted with caution. Nevertheless, of the sensitivity analyses that could be performed, the results indicated that the inclusion of data that required the estimation of mean ± SD or SD did not substantially influence the directions and significance levels of the effect sizes, or substantially increase the between-study heterogeneity across the CRP, IL-6, and VCAM-1 meta-analyses (see Appendix A, ESM 4, Table S2). However, the removal of data that required the estimation of mean ± SD or SD resulted in significant medium beneficial effect sizes for exercise on ICAM-1 (before; SMD: -0.35 (95% CI: -0.72, 0.01), P= 0.06, after; SMD: -0.77 (95% CI: -1.23, -0.31), P= 0.001) and E-selectin (before; SMD: -0.31 (95% CI: -0.66, 0.05), P= 0.09, after; SMD: -0.57 (95% CI: -1.03, -0.11), P= 0.01). Moreover, the between-study heterogeneity was reduced for ICAM-1 (before: I²= 58%, χ^2 P= 0.07, after: I²= 0%, χ^2 P= 0.61) and E-selectin (before: I²= 35%, χ^2 P= 0.22, after: I²= 0%, χ^2 P= 0.85). Nonetheless, these results should be interpreted with caution due to the small sample sizes of the meta-analyses (ICAM: 40 exercise participants and 38 controls, E-selectin: 38 exercise participants and 38 controls).

The study performed by Giallauria et al. (2011) generated a noticeably larger beneficial effect size in comparison to the other pooled studies in the post-intervention CRP value comparison. Therefore, a sensitivity analysis was performed to ascertain the influence of this "outlying" data on the overall pooled results by removing Giallauria et al. (2011). Consequently, no major impact on the direction and significance level of the pooled effect size, or substantial change in between-study heterogeneity was documented (see Appendix A, ESM 4, Table S3).

4.3.9 Adverse Events, Withdrawals, and Exercise Session Compliance

A detailed report of adverse events, withdrawals, and exercise session compliance can be found in ESM 4, Table S4 (see Appendix A). Fourteen of the included studies (Bilinska et al., 2010; Conraads et al., 2015; Hansen et al., 2011; Madssen et al., 2014; Moholdt et al., 2012; Oliveira et al., 2015; Pedersen et al., 2016; Ribeiro et al., 2012; Schumacher et al., 2006; Theodorou et al., 2016; Vona et al., 2009; Balen et al., 2008; Giallauria et al., 2011; Munk et al., 2011) reported on adverse events. Exercise was safe; no adverse events during or as a result of exercise were reported. Across the included studies, the mean withdrawal rate was 5% (range: 0-22%). Information regarding participant compliance with the prescribed exercise sessions was reported by thirteen studies (Beckie et al., 2010; Conraads et al., 2015; Hansen et al., 2011; Lian et al., 2014; Madssen et al., 2014; Moholdt et al., 2012; Oliveira et al., 2015; Pedersen et al., 2016; Ribeiro et al., 2012; Vona et al., 2009; Giallauria et al., 2011; Luk et al., 2012; Munk et al., 2011). On average, the participants across these studies completed 88% (range: 60-100%) of the prescribed exercise sessions.

4.4 Discussion

The contribution of chronic inflammation to the development and progression of CAD is now well established (Libby, 2012; Wong et al., 2012). Interestingly, there is evidence to suggest that exercise may constitute a method of reducing inflammatory activity in this patient population (Swardfager et al., 2012), which potentially partially explains the secondary prevention induced by this intervention. As such, the purpose of this systematic review and meta-analysis was to provide a timely update to the literature by rigorously

examining the influence of exercise on various inflammatory biomarkers in CAD patients.

Twenty-five randomised studies comprising 2105 (1426 exercising and 679 controls) participants were reviewed. Saliently, an anti-inflammatory effect of exercise was documented, as indicated by significant beneficial effects on CRP, fibrinogen, and vWF. Moreover, the meta-analyses of inflammatory biomarkers that documented non-significant results generated SMDs that represented lower post-intervention values in the exercise groups compared to controls. Failure to reach significance for these inflammatory biomarker outcomes could be a result of wide confidence intervals due to small sample sizes.

The anti-inflammatory effects of exercise in CAD patients, as documented in this review, may lack generalisability in healthy populations. In particular, there is inconsistent evidence for an anti-inflammatory effect of exercise in healthy populations (Ford, 2002; Lin et al., 2015; Kelley & Kelley, 2006; Sloan et al., 2018; Fedewa et al., 2017). Therefore, the discrepancy between the results of this review and the evidence for an anti-inflammatory effect in healthy populations may be attributed to a more pronounced effect in CAD patients due to higher baseline levels of inflammatory activity (Al Shahi et al., 2015), or an amelioration of principal CVD risk factors that promote inflammation, such as: dyslipidaemia, hypertension, diabetes, and obesity (Libby et al., 2002; Pedersen, 2017). Whilst it was beyond the scope of this review to investigate these relationships, Swardfager et al. (2012) reported that elevated baseline CRP values and adverse lipid profiles were associated with greater reductions in CRP values in CAD patients. Moreover, a recent meta-analysis performed by Fedewa et al. (2017) demonstrated that exercise induced greater reductions in CRP when accompanied by a decrease in BMI in healthy and clinical populations. Besides improving CVD risk factors, exercise may also incite anti-inflammatory protection by directly modulating various overlapping signalling pathways associated with oxidative stress and inflammation (Sallam & Laher, 2016). However, the influence of exercise on these underlying mechanisms is poorly understood (Sallam & Laher, 2016), and is an area for future research.

4.4.1 Pro-inflammatory Cytokines

In accordance with the results of the meta-analysis performed by Swardfager et al. (2012), the post-intervention IL-6 and TNF-α value comparisons between exercise and control groups were not significantly different. Although, the paucity of data from studies that implemented a control group may account for these non-significant findings.

Regarding the studies that were not included in the meta-analyses, the evidence for a beneficial effect of exercise on pro-inflammatory cytokines was inconsistent. To elaborate, one study (Beckie et al., 2010) documented beneficial within-exercise group changes in IL-6 and TNF-α, whilst two studies reported no significant changes (Hansen et al., 2011; Pedersen et al., 2016). However, the trials performed by Hansen et al. (2011) and Pedersen et al. (2016) may have been underpowered to detect changes in IL-6 or TNF-α as sample size calculations based on pro-inflammatory cytokines were not performed. When considering the individual results of the included studies, Schumacher et al. (2006) recorded a significant inverse correlation between physical performance and levels of IL-6. Moreover, Munk et al. (2011) observed positive differences between exercise and control groups in IL-6, and Balen et al. (2008) documented beneficial differences between exercise and control groups in TNF-α SR1. As such, these findings potentially represent a positive effect of exercise on pro-inflammatory cytokines. Nevertheless, the results of this review failed to generate conclusive evidence that exercise significantly reduces pro-inflammatory cytokines. Therefore, further research regarding the effect of exercise on these inflammatory mediators is required.

4.4.2 Anti-inflammatory Cytokines

The meta-analyses performed in this review failed to demonstrate a beneficial effect of exercise on IL-10 concentrations, which may be attributed to the small number of pooled studies. Overall, the individual results of four (Ribeiro et al., 2012; Raygan et al., 2017; Balen et al., 2008; Munk et al., 2011) out of the five studies (Oliveira et al., 2015; Ribeiro et al., 2012; Raygan et al., 2017; Balen et al., 2008; Munk et al., 2011) that examined the effect of exercise on anti-inflammatory cytokines documented positive influences. Nevertheless, the paucity of evidence in this area precluded a robust evaluation. As such, further research into the effect of exercise on anti-inflammatory cytokines in CAD patients is required.

4.4.3 Acute-Phase Reactants

The results of this review documented a positive influence of exercise on acute-phase reactants; post-intervention CRP, fibrinogen, and vWF value comparisons documented very low qualities of evidence for significantly lower values in exercise groups compared to controls. However, the results of the CRP and vWF meta-analyses should be interpreted with caution as substantial between-study heterogeneity was identified. Moreover, the post-intervention vWF value comparison comprised two studies, which limits the validity of the result. Qualitatively, the findings of the trials that were not included in the meta-analyses support the quantitative results of this review; five (Conraads et al., 2015; Beckie et al., 2010; Toyama et al., 2012; El Missiri & Taher, 2016; Lee et al., 2006) out of the nine studies (Conraads et al., 2015; Hansen et al., 2011; Moholdt et al., 2012; Pedersen et al., 2016; Beckie et al., 2010; Toyama et al., 2012; El Missiri & Taher, 2016; Luk et al., 2012; Lee et al., 2006) that investigated the impact of exercise on acute-phase reactants reported beneficial within-exercise group changes. Altogether, the results of this review support the ability of exercise to reduce CRP, fibrinogen, and vWF in CAD patients. The correlation between these acute-phase reactants and adverse outcomes accentuates the potential importance of this finding (Danesh et al., 2004; Ridker et al., 2002; Kaptoge et al., 2010; Coppola et al., 2005, Thompson et al., 1995).

4.4.4 Adhesion Molecules

The meta-analyses failed to find significant post-intervention differences between exercise and control groups for VCAM-1, ICAM-1, P-selectin and E-selectin. Although, a positive effect of exercise on ICAM-1 approached statistical significance (P= 0.06). When considering the results of the studies individually, only three (Schumacher et al., 2006; Beckie et al., 2010; Jalaly et al., 2015) of the eight studies (Schumacher et al., 2006; Beckie et al., 2010; Fernandes et al., 2011; Oliveira et al., 2015; Ribeiro et al., 2012; Lee et al., 2006; Jalaly et al., 2015; Munk et al., 2011) that investigated the effect of exercise on adhesion molecules demonstrated a significant effect. However, two of these studies (Beckie et al., 2010; Schumacher et al., 2006) provided an exercise intervention alongside a comprehensive CR programme, which limits attributing these results to an independent effect of exercise. With regard to Ribeiro et al. (2012), no significant within-exercise group changes in the post-intervention levels of ICAM-1 and VCAM-1 were documented.

Yet, the post-intervention values of these adhesion molecules significantly increased in the control group, which resulted in significant between-group differences for changes in ICAM-1 and VCAM-1 levels. Interestingly, these results imply that exercise may supress deterioration in endothelial function. Collectively, the results of this review failed to demonstrate conclusive evidence for a beneficial effect of exercise on adhesion molecules. Nevertheless, the majority of studies possessed small sample sizes, which may account for the non-significant results. Also, the limited data for each adhesion molecule precluded a robust evaluation. Despite the equivocal effect of exercise on adhesion molecules, six studies (Vona et al., 2009; Lee et al., 2006; Conraads et al., 2015; Moholdt et al., 2012; Sixt et al., 2008; Luk et al., 2012) in this review demonstrated an improvement in endothelial function as measured via brachial FMD. The ability of exercise to stimulate an improvement in brachial FMD was also supported by a recent meta-analysis (Ashor et al., 2015). As such, studies should continue to explore the effect of exercise on adhesion molecules to further illuminate the exercise induced improvements in endothelial function.

4.4.5 Chemokines

The meta-analyses failed to find significant post-intervention differences between exercise and control groups for IL-8 and RANTES, which may be attributed to the small number of pooled studies. In terms of the qualitative analysis, the effect of exercise on chemokines was equivocal. To elaborate, across the included studies, no significant effects on post-intervention values of Mig, RANTES, CXCL16, CCL19, MCP-1, and CD40L were documented. However, two (Balen et al., 2008; Munk et al., 2011) out of the three studies (Balen et al., 2008; Munk et al., 2011; Hansen et al., 2011) that evaluated the impact of exercise on IL-8 observed significantly lower post-intervention values in exercise groups compared to controls. Moreover, Fernandes et al. (2011) demonstrated beneficial between-group differences in post-intervention IP-10 values, and Munk et al. (2011) recorded significant within-exercise group reductions in CCL21 levels. In particular, the results generated by Fernandes et al. (2011) are of interest as there is evidence to suggest that increased levels of IP-10 correlate with restenosis following PCI in CAD patients (Kawamura et al., 2003). Overall, the limited amount of evidence for the effect of exercise on chemokines prevented a valid evaluation. Moreover, the reviewed studies consisted of small sample sizes, which as mentioned before, may have precluded

the identification of significant results. Given the vital role of chemokines in orchestrating atherogenesis (Zernecke et al., 2008), and in acknowledgment of the qualitative findings, further research into the effect of exercise on chemokines is required.

4.4.6 Sub-Group Analyses

An uneven covariate distribution precluded valid sub-group analyses of the influence of exercise intervention characteristics on inflammatory biomarker changes. However, six of the included studies (Hansen et al., 2011; Conraads et al., 2015; Lee et al., 2006; Moholdt et al., 2012; Theodorou et al., 2016; Vona et al., 2009) compared the effects of different exercise modalities on inflammatory biomarkers. Across which, no statistically significant between-exercise group differences in post-intervention inflammatory biomarker values were seen.

The acute response to exercise involves the release of IL-6 from skeletal muscle cells, which serves as a stimulus for anti-inflammatory adaptation (Pedersen, 2017). Importantly, the intensity (Ostrowski et al., 2000) and duration of exercise (Pedersen, 2017), along with the involved muscle mass (Steensberg et al., 2000; Pedersen, 2017) determine the acute rise in IL-6. However, evidence regarding optimal exercise characteristics for inducing anti-inflammatory protection is equivocal. To elaborate, Hayashino et al. (2014) stated that longer exercise programmes and greater exercise session frequencies were associated with greater reductions in IL-6, albeit results from type 2 diabetes patients. In contrast, Swardfager et al. (2012) demonstrated that the duration of exercise programmes was not associated with a decrease in CRP in CAD patients. Moreover, Fedewa et al. (2017) concluded that duration, frequency, and mode of exercise were not associated with reductions in CRP in healthy and clinical populations. As such, further research to identify optimal exercise characteristics for reducing inflammation in CAD patients is necessary.

4.4.7 Strengths and Limitations

To our combined knowledge, this is the first systematic review and meta-analysis to exclusively evaluate randomised studies that investigated the effect of exercise on inflammatory biomarkers in CAD patients. The exclusion of studies that possessed

confounding variables, such as: the recruitment of CAD patients with severe heart failure (New York Heart Association (NYHA) Class III or IV or left ventricular ejection fraction (LVEF) $\leq$ 30%), or the provision of co-interventions (e.g. a hypocaloric diet or antioxidant/ vitamin supplement) to exercise increased the validity of the findings. Further strengths of this review include: a comprehensive literature search, evaluation of overall quality of evidence using the GRADE system, and the pooling of data for meta-analyses. Moreover, qualitative analyses of studies and outcomes that could not be meta-analysed were performed to circumvent the exclusion of valuable findings.

The exclusion of studies that recruited patients with severe heart failure (NYHA Class III or IV or LVEF $\leq$ 30%) limits extrapolating the results of this review to CAD patients with these deteriorated conditions. Whilst a comprehensive literature search was performed, the exclusion of studies that were not reported in English may have introduced publication bias. Nevertheless, this issue was not strongly suspected for any outcome as both negative and positive findings were reported by studies with varying sample sizes.

A further limitation involves the sub-group analyses of exercise intervention characteristics failing to provide a valid evaluation of potential sources of between-study heterogeneity. However, the level of between-study heterogeneity may also have been influenced by the following factors: population characteristics (*i.e.,* comorbidities) (Libby et al., 2002), diet (Lopez-Garcia et al., 2004), medication (Albert et al., 2001), natural recovery following cardiovascular complication/ surgical intervention (Saadeddin et al., 2002; Kushner et al., 1978), measurement medium (plasma or serum) (Parkitny et al., 2013), and methods employed for blood sample preparation and handling (Parkitny et al., 2013; Lundman et al., 2007; Gregersen et al. 2012).

With regard to study quality, inadequate reporting of random sequence generation and allocation concealment, along with imprecision as a result of small sample sizes decreased the reliability of the results across most of the included studies and limited the overall quality of evidence. As such, the results of this review should be interpreted with caution until further randomised studies with high methodological qualities and large sample sizes are conducted.

4.5 Conclusion

This systematic review and meta-analysis demonstrates that exercise reduces CRP, fibrinogen, and vWF concentrations in CAD patients. In addition, qualitative analyses identified evidence that supports a positive effect on these acute-phase reactants. However, current evidence surrounding the effect of exercise on anti-inflammatory cytokines, adhesion molecules, and chemokines is equivocal, which may be attributed to a paucity of research. Nevertheless, whilst the findings of this review support the ability of exercise to reduce inflammatory activity in CAD patients, various requirements for future research have been identified. Firstly, the quality of evidence for this area needs to be improved by further randomised studies with high methodological qualities and large sample sizes. Moreover, additional research into the effect of exercise on proximal mediators of inflammation and anti-inflammatory cytokines is required. In order for exercise to be utilised as an anti-inflammatory strategy in CAD, future studies should seek to identify optimal exercise characteristics for mitigating inflammation. Finally, to generate a comprehensive understanding of the anti-inflammatory effect of exercise, future research should explore the underlying molecular mechanisms that may be responsible for orchestrating an exercise induced reduction in inflammation.

Chapter 5

Pilot Prospective Cohort Study (Paper 2)

5.0 Results of Pilot Prospective Cohort Study (Paper 2)

The findings of the published systematic review and meta-analysis (**Paper 1**) supported an anti-inflammatory effect of exercise in CAD patients. As such, this section reports the results of a pilot prospective cohort study that investigated the feasibility of evaluating the effect of exercise (delivered as a CR programme) on molecular mechanisms that may mediate cardioprotective physiological adaptation in CAD patients. This study has been submitted for publication at the *Journal of Sports Sciences* (see Appendix M for evidence of submission). The ESM for **Paper 2** is presented in Appendix N.

5.1 Exercise and Cardioprotection in Coronary Artery Disease: A Pilot Prospective Cohort Study

5.1.1 Introduction

CAD is characterised by the development of fibrous atherosclerotic plaque in the coronary arteries (Hansson, 2005). This form of CVD may elicit myocardial ischaemia, with the clinical manifestations being ACS comprising unstable angina pectoris, AMI (NSTEMI or STEMI), or sudden cardiac death (Ambrose & Singh, 2015). Despite advances in CVD science and medical treatment, CAD remains a leading cause of mortality and morbidity worldwide (Naghavi et al., 2017).

Testament to sophisticated cellular biology investigations, chronic low-grade inflammation is now regarded as a primary pathogenic mechanism for atherosclerotic development and clinical sequalae (Ambrose & Bhullar, 2019; Bäck et al., 2019; Tabas et al., 2015; van Holten et al., 2013). Importantly, a recent meta-analysis demonstrated that exercise reduced inflammatory activity in CAD patients, as indicated by lower post-intervention CRP, fibrinogen, and vWF (Thompson et al., 2020). As such, the anti-inflammatory effect of exercise may represent a primary mechanism through which the secondary prevention of CAD is conferred. However, the molecular transducers that mediate the anti-inflammatory adaptations of exercise are yet to be fully elucidated.

SIRT-1 is a NAD^+ dependent enzyme that may represent a mechanism that underlies the cardioprotective effect of exercise (Suwa & Sakuma, 2013). This protein mediates the cellular response to exogenous stressors (*i.e.,* exercise), and is located in the nucleus and cytoplasm, with a primary function of catalysing deacetylation of histone

lysine residues, transcription factors, enzymes, cofactors, and structural proteins (Michan & Sinclair, 2007; Winnik et al., 2015). Saliently, an exercise-induced increase in SIRT-1 may ameliorate pathogenic states related to atherogenesis; studies in clinical populations (patients with low-back pain and heart failure patients) have observed an increase in SIRT-1 expression or activity following exercise, which was associated with a decrease in inflammation and/ or oxidative stress (Cheng et al., 2015; Corbi et al., 2019; Russomanno et al., 2017). In terms of CAD, one study explored the effect of exercise on SIRT-1 in post-CABG patients. Alavizadeh et al. (2018) documented an increase in SIRT-1 following an 8-week exercise programme comprising 3 sessions per week of either moderate-intensity aerobic training or combined training (moderate-intensity aerobic exercise and RT) in comparison to control, with no difference between the two exercise groups. However, the consequential impact on pathogenic states that are implicated in atherogenesis, such as: inflammation, oxidative stress, and endothelial dysfunction was not explored (Alavizadeh et al., 2018). Moreover, this study was not fully powered to detect statistically significant changes in SIRT-1 concentration (Alavizadeh et al., 2018), which limits data reliability (Faber & Fonseca, 2014).

To the best of our knowledge, the role of SIRT-1 in mediating the cardioprotective effects of exercise in CAD patients has not been explored. By doing so, the role of exercise in the rehabilitation of CAD patients may be further understood, and novel therapeutic targets for secondary prevention strategies may be identified. Thus, the primary objective of this pilot study was to assess the feasibility of performing a prospective cohort study by evaluating the rates of recruitment, drop-out, and adherence. Moreover, the secondary objective was to investigate if exercise (delivered as a CR programme) is associated with changes in SIRT-1, markers of atherogenesis

(inflammation, oxidative stress, endothelial function, and arterial stiffness), and SCMs in post-AMI patients.

5.2 Methods

The reporting of this study complies with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007). Aspects related to the pilot component of the study are in line with the Consolidated Standards of Reporting Trials (CONSORT) extension for pilot and feasibility trials, excluding items required for randomised studies (Eldridge et al., 2016). The PhD researcher (GT) recruited participants; collected participant demographics and clinical characteristics from medical records at TP-1; obtained the study measurements from participants at each TP; performed the laboratory analyses; and analysed the collected data.

5.2.1 Study Design

A multi-centre pilot prospective cohort study was conducted in post-AMI patients who had been invited to participate in phase-III CR at National Health Service sites in the UK. Ethical approval was obtained from ORECNI (reference number: 18/NI/0213), all procedures were conducted in accordance with the Declaration of Helsinki (2002), and the study was registered on ClinicalTrials.gov (identifier: NCT03907293).

5.2.2 Participants

Post-AMI patients were recruited as they represent the largest CAD patient group at CR programmes across the UK (British Heart Foundation, 2019b), which served as an attempt to improve the generalisability of the results. Recruitment of participants was performed from 1st July 2019 until 31st January 2020. The CR nurses at the collaborating sites reviewed the clinical records of patients who had been invited to phase-III CR, and subsequently invited potential participants to the study. Interested patients received an explanation of the study from a member of the research team (GT) at their corresponding hospital site. The inclusion and exclusion criteria are presented in Table 5.1. All participants provided written informed consent at their meeting for recruitment and autonomously decided whether to participate in phase-III and phase-IV CR.

Table 5.1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Formally diagnosed CAD with evidence of STEMI or NSTEMI that was consistent with diagnostic criteria presented by Zipes et al. (2018)	• Unstable angina pectoris
• Over 18 years of age	• Uncontrolled cardiac arrhythmia
• Provision of informed consent	• Survivor of cardiac arrest or cardiogenic shock
• Ability to speak and write in English	• Any form of anaemia
• No hospital readmissions with unstable symptoms (e.g. chest pain, shortness of breath, discomfort, or nausea) during the previous 4 weeks	• Hepatic failure
• Willing to comply with study requirements	• Uncontrolled hypertension
	• History of Raynaud's phenomenon
	• Congenital or acquired physical abnormalities of both arms
	• Consumption of vitamins, herbal, testosterone, estrogen/ progesterone, or antioxidant supplements
	• Pregnant
	• History of any form of cancer
	• Current participation in a different research study

CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

Participants provided measurements at three TPs over the course of a 22-week study. TP-1 (week-1) and TP-2 (week-8) coincided with the first and final day of the phase-III CR programme, respectively. At TP-2, the CR nurses routinely offered the participants who completed the phase-III CR programme the opportunity to enter a phase-IV CR programme. The participants who agreed to participate in a phase-IV CR programme completed an additional 12 weeks of supervised exercise training at their routinely allocated site. TP-3 (week-22) coincided with the end of a phase-IV CR programme.

5.2.3 Description of Phase-III CR Programme Characteristics

Patients who agreed to participate in phase-III CR entered this programme approximately 2-4 weeks after AMI. The programme was delivered by CR nurses at centres that were certified for achieving national CR delivery standards (British Heart Foundation, 2019a). Supervised exercise training was the centrepiece of the phase-III CR programme (15-minute warm-up, 30 minutes of moderate-intensity circuit training, and a 15-minute cool-down). Patients alternated between aerobic exercise (*i.e.,* walking, cycle ergometer, and rowing machine) and RT (*i.e.,* body weight exercises, dumbbells, and machines) interspersed with periods of active recovery. Intensity was maintained between 40-70% of HRR and/or an RPE between 11-14 on the Borg scale. During active recovery periods, HRR and RPE levels dropped below the prescribed exercise intensity to provide patients with temporary respite. CR nurses continuously monitored HRR and RPE levels during the exercise sessions. The supervised exercise component was also supplemented with optimal pharmacological therapy, psychological support, and lifestyle advice. The phase-III CR programmes involved one session per week for eight weeks. Patients who refused

to participate in phase-III CR were discharged with standard secondary prevention medication.

5.2.3.1 Description of Phase-IV CR Programme Characteristics

Patients who agreed to participate in phase-IV CR were enrolled in this programme approximately two weeks after completing phase-III CR. This programme was facilitated by qualified exercise professionals at gyms or fitness centres in the private sector. All phase-IV CR centres complied with national service delivery guidelines (Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2015). Phase-IV CR involved one supervised exercise session per week for twelve weeks, with the exercise programme corresponding with phase-III CR. HRR and RPE levels during the exercise sessions were constantly monitored by the phase-IV CR facilitators. Patients who refused to participate in phase-IV CR did not receive a supervised exercise programme following phase-III CR completion.

5.2.4 Primary Outcome Measures

5.2.4.1 Recruitment Rate

The recruitment rate was defined as the percentage of eligible patients who agreed to participated in the study, and the number of patients recruited per week over the recruitment period. The CR uptake rate was also calculated (*i.e.,* the percentage of recruited patients who chose to participate in phase-III CR).

5.2.4.2 Drop-Out Rate

Drop-out rate was expressed as the percentage of recruited participants who withdrew from the study, with this parameter being calculated overall and at each TP.

5.2.4.3 Adherence Rate

The supervised exercise session adherence rate was defined as the percentage of prescribed exercise sessions that were completed during the phase-III and phase-IV CR programmes.

5.2.4.4 Success Criteria

The following success criteria were used to ascertain if a future prospective cohort study was feasible: adequate recruitment rate (> 70% of eligible patients recruited), < 20% drop-out rate overall and at each TP for each group, completed > 80% of prescribed exercise sessions, and apparent changes in the secondary outcomes that warrant further investigation (*i.e.,* an increase in SIRT-1 concentration following CR).

5.2.5 Secondary Outcome Measures

The secondary outcome measures comprised variables aligned to any prospective cohort study, with SIRT-1 serving as the primary outcome measure. All physiological measurements were obtained in a temperature controlled (22 °C - 24 ºC) environment prior to exercise (if applicable). Prior to study measurement acquisition, the participants

were required to rest in a seated position for approximately 20 minutes to achieve a haemodynamic steady state.

5.2.5.1 Standard Clinical Measurements

Height was measured using a stadiometer (Marsden, Rotherham, UK) to the nearest 0.1 cm. Body mass was assessed using scales (Salter, Kent, UK) to the nearest 0.1 kg. BMI was calculated by dividing mass (kg) by the square of height (m). WC was evaluated using an anthropometric tape measure (Seca, Birmingham, UK) to the nearest 0.1 cm at the uppermost lateral border of the right ilium (Centers for Disease Control and Prevention, 2016). Exercise capacity was measured with the ISWT in accordance with guidelines for field walking tests published by the European Respiratory Society / American Thoracic Society (Holland et al., 2014). Upon test completion, the quantity of completed shuttles was recorded and the total distance walked (m) was calculated.

5.2.5.2 Resting Haemodynamics

RHR was measured using a Polar telemetry HR monitor (Polar Electro Oy, Finland) while participants rested in a supine position. SBP and DBP were recorded using an automated, non-invasive device (Omron Automatic Blood Pressure Monitor, Omron Healthcare, Lake Forest IL). Three measurements interspersed with 1-minute rest intervals were obtained. The mean of these values was then calculated and recorded.

5.2.5.3 Endothelial Function

Brachial FMD was utilised to assess endothelial function, with measurements obtained at a similar time of day at each TP to account for diurnal variation. Brachial FMD was performed and analysed in accordance with technical guidelines (Thijssen et al., 2019). A LOGIQ ultrasound system (GE Healthcare, UK) with a 12-megahertz linear transducer was used to perform brachial FMD. Data was recorded by Vascular Imager software (Version 6.0.3, Medical Imaging Applications, USA) and analysed using offline edge detection software (Brachial Analyser for Research Version 5.7.0, Medical Imaging Applications, USA). Brachial FMD data is not available for the entire cohort due to logistical challenges (*i.e.,* insufficient space for equipment at site or impossible to physically transfer equipment to site).

5.2.5.4 Arterial Stiffness

Arterial stiffness was measured with a Pulse Trace PCA 2 device (Micro Medical, Rochester, UK), which utilises photoplethysmography to record digital volume pulse. The protocol for performing arterial stiffness measurements complied with methodological guidelines (Laurent, Cockcroft et al. 2006). Arterial stiffness measurements were obtained at a similar time of day at each TP to account for diurnal variation. SI (m/s) and RI (%) were recorded, which represent large artery stiffness and vascular tone of small arteries, respectively (DeLoach, Townsend 2008).

5.2.5.5 Physical Activity

The IPAQ (long form) was used to assess physical activity of participants over the course of the study. Participants were asked to complete the IPAQ on week-1, week-8, and week-

22. All IPAQ data was cleaned and analysed in accordance with the standardised IPAQ Scoring Protocol (The IPAQ Group, 2005). Data collected from the IPAQs were reported as total physical activity MET-minutes/ week.

5.2.5.6 Blood Sample Collection

Venous blood samples were collected using the Vacutainer ™ method (Becton, Dickinson, Oxford, UK) from a prominent forearm vein while participants rested in a supine position. All blood was centrifuged, aliquoted, and stored at -80°C until biochemical analysis (within 12 months).

5.2.5.7 Measurement of Erythrocyte Sedimentation Rate

ESR was measured as an indirect index of systemic inflammatory activity (Bray et al., 2016). The Seditainer™ method involved extracting 5.2 mL of blood into a Seditainer™ tube (Becton, Dickinson, Oxford, UK) and immediately placing it vertically in a Seditainer™ manual stand (Becton, Dickinson, Oxford, UK). After 60 minutes, the linear scale on the Seditainer™ manual stand was used to record ESR in mm/h.

5.2.5.8 Lipid Hydroperoxides

Serum LOOH were measured spectrophotometrically according to the method of Wolff (Wolff, 1994). FOX was utilised to quantify the oxidation of Fe^{2+} iron to Fe^{3+} iron ions, and the consequential binding of Fe^{3+} to the FOX-1 reagent. Sample absorbance was

determined by a UV spectrophotometer (UV mini-1240 Shimadzu, Mason Technologies, Ireland) at 560 nm.

5.2.5.9 Ascorbyl Free Radical

The $A^{\bullet-}$ was quantified at room temperature using EPR spectroscopy on a Bruker EMX spectrometer (Bruker, Karlsruhe, Germany) as described previously by Williamson et al. (2020).

5.2.5.10 SIRT-1, IL-6, and IL-10

The serum concentrations of SIRT- 1, IL-6, and IL-10 were measured by sandwich ELISA according to the manufacturer instructions (SIRT-1: Elabscience®, ELISA kit catalog no. E-EL-H1546, USA; IL-6: R&D Systems, ELISA kit catalog no. HS600C, UK; IL-10: R&D Systems, ELISA kit catalog no. HS100C, UK). All samples were run in duplicate. Intra-assay coefficient of variation was < 5% for each parameter. SIRT-1, IL-6, and IL-10 were only measured in samples obtained from participants at all three TPs.

5.2.5.11 Lipid Panel

A lipid panel (TC, LDL-C, HDL-C, TG, TC/ HDL-C ratio, and non-HDL-C) was measured in serum as per standard clinical chemistry at an accredited clinical biochemistry laboratory at TP-1 and TP-2. However, lipid panels were not measured at TP-3 due to COVID-19.

5.2.6 Statistical Analysis

Statistical analysis was performed on all data with SPSS statistical software (IBM, Surrey, UK, Version 25). Continuous data were reported as mean ± SD. Discrete data were presented as absolute numbers and percentages. Inferential statistics were not performed as this study was not formally powered to detect statistical significance. The primary and secondary outcome measures were reported with descriptive statistics. Within-group change scores for the secondary outcome measures were calculated by subtracting the baseline value from the outcome data at TP-2 and TP-3. Within and between-group effect sizes with 95% CIs were calculated using Cohen's d, with ≤ 0.4 interpreted as a small effect size, between 0.5 and 0.7 viewed as a medium effect size, and ≥ 0.8 deemed a large effect size (Cohen, 1988). Trends were reported and interpreted in accordance with MCID (if available) or CD (if available), which represent the smallest value that would make a beneficial difference to patients or that may change care (Jaeschke et al., 1989), and the change required for a true biological difference to be claimed (Fraser & Fogarty, 1989), respectively.

The primary analysis of secondary outcome measures comprised the data obtained at TP-1 and TP-2 from phase-III CR participants and non-CR participants, with a sub-analysis comparing groups of participants who completed each TP. The research team contacted the participants who were lost to follow-up due to COVID-19 to inquire if they had agreed to participate in phase-IV CR, and asked if they had intended to provide the study measurements at TP-3. This information was used to determine participant uptake to phase-IV CR and to calculate an estimate of drop-out rate at TP-3 for the primary outcome measures.

5.3 Results

5.3.1 Participant Flow

Figure 5.1 describes the flow of participants. Seventy-three eligible patients were invited to participate from 1st July 2019 until 31st January 2020; forty-five did not contact the research team to arrange a meeting for recruitment and twenty-eight provided consent to participate. Of the cohort, twenty-five patients enrolled in phase-III CR and three patients refused to partake in the programme. Twenty-one participants of the phase-III CR group provided the study measurements at TP-2, with four participants lost to follow-up (no show). All participants of the non-CR group ($n = 3$) supplied the study measurements at TP-2. Across the twenty-one participants of the phase-III CR group who provided the study measurements at TP-2, $n = 11$ patients agreed to take part in phase-IV CR and $n = 10$ patients refused to enter phase-IV CR but agreed to remain in the study. The follow-up period terminated prematurely on 18th March 2020 as the COVID-19 pandemic rendered in person data collection impossible. Consequently, seven participants of the phase-III CR only group, four participants who completed both phase-III and phase-IV CR, and one participant of the non-CR group were lost to follow-up at TP-3. Twelve participants completed all three TPs: phase-III & phase-IV CR group ($n = 7$), phase-III CR only group ($n = 3$), and non-CR group ($n = 2$). All recruited participants ($n = 28$) were included in the analysis of primary outcome measures. Four patients from the phase-III CR group were excluded from the analysis of secondary outcome measures as no study measurements were obtained at TP-2.
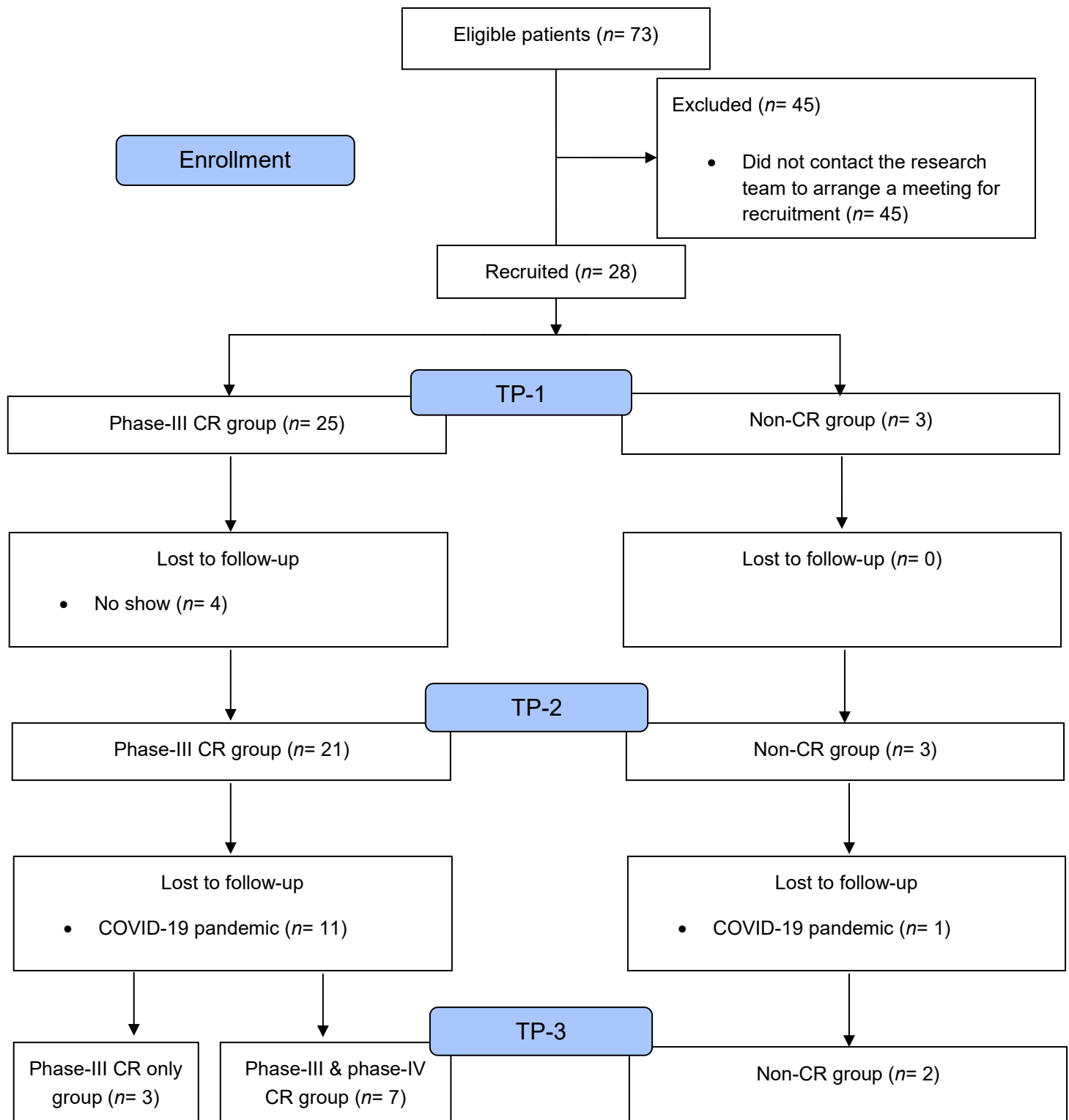
Figure 5.1 Participant flow diagram

CR, cardiac rehabilitation; TP, time point

5.3.2 Participant Characteristics

The participants were predominantly male (79%), and all were of white ethnicity. The mean sample age was 60.2 ± 10.5, with the proportion of NSTEMI (54%) being slightly higher than STEMI (46%). All participants received PCI. The most common CVD risk factors across the sample were family history of CAD (67%), hypertension (67%), and dyslipidaemia (83%). A minority of the participants possessed diabetes mellitus (17%) and were current smokers (21%). All participants were prescribed a form of secondary prevention medication, with the most prevalent being antiplatelets (100%), beta blockers (96%), and statins (100%). At baseline, all groups appeared to be similar regarding demographic variables, clinical characteristics, and secondary outcome measures (see Tables 5.2-5.9).

5.3.3 Primary Outcome Measures

The recruitment rate was 0.9 participants per week over a 30-week period, with 38.4% ($n = 28$) of the eligible patients ($n = 73$) recruited. Of the recruited participants, 89.3% ($n = 25$) enrolled in phase-III CR, with 54.2% ($n = 13$) of those who completed phase-III CR ($n = 24$) partaking in phase-IV CR. The overall drop-out rate was 17.9% ($n = 5$); 14.3% ($n = 4$) and 4.2% ($n = 1$) of participants withdrew from the study at TP-2 and TP-3, respectively. On average, participants of the phase-III CR group attended 90.0% ($n = 7.2$) of the prescribed exercise sessions ($n = 8$), with participants of the phase-III & phase-IV CR group completing 82.5% ($n = 9.9$) of the phase-IV CR exercise sessions ($n = 12$). Overall, the success criteria for drop-out rate and adherence rate were satisfied. However,

the success criterion regarding recruitment rate was not fulfilled (< 70% of eligible patients were recruited).

5.3.4 Analysis of Secondary Outcome Measures

The changes in variables from TP-1 to TP-2 indicate improvements in the secondary outcome measures following the completion of phase-III CR, whilst unfavourable changes and/ or smaller improvements were documented in the non-CR group at TP-2 (see Tables 5.4-5.6). In particular, the phase-III CR group displayed moderate (d between 0.5 and 0.7) or large ($d \geq 0.8$) improvements in exercise capacity (distance walked in ISWT increased by a MCID (70 m; (Houchen-Wolloff et al., 2015)), endothelial function (brachial FMD and brachial FMD absolute change), arterial stiffness (SI), physical activity, CVD risk factors (SBP, DBP, RHR, TC, and non-HDL-C), and oxidative stress (LOOH and $A^{\bullet -}$) from TP-1 to TP-2. Between-group differences at TP-2 were moderate or large for CVD risk factors (SBP, DBP, RHR, BMI, WC, TC, LDL-C, TG, and non-HDL-C), endothelial function (brachial FMD and brachial FMD absolute change), arterial stiffness (SI), exercise capacity (distance walked in the ISWT), physical activity, inflammation (ESR), and oxidative stress (LOOH and $A^{\bullet -}$).

5.3.4.1 Sub-Analysis of Secondary Outcome Measures

Values of the secondary outcome measures at each TP are presented in Tables 5.7-5.9 (see Appendix N, ESM 1, Table S1 and Table S2 for change scores and effect sizes). Figure 5.2 displays SIRT-1 concentration across the TPs for each group. Across the three groups, the changes in variables from TP-1 to TP-2 were similar to the trends identified

in the analysis of secondary outcome measures described in the section above, with the phase-III CR only and phase-III & phase-IV CR groups both demonstrating improvements in the secondary outcome measures following the completion of phase-III CR, whilst unfavourable changes and/ or smaller improvements were documented in the non-CR group at TP-2 (see Appendix N, ESM 1, Table S1).

The non-CR group displayed further moderate or large unfavourable changes in distance walked in ISWT, SIRT-1, ESR, and DBP from TP-2 to TP-3. Whilst the values of many parameters improved from TP-1 to TP-2 in the phase-III CR only group, unfavourable changes from TP-2 to TP-3 were seen for all parameters aside from additional small ($d \leq 0.4$) improvements in physical activity, IL-10, and LOOH (see Appendix N, ESM 1, Table S1). With regard to the phase-III & phase-IV CR group, improvements were seen at each TP for all parameters aside from shear rate, TTP vasodilation, and IL-10 (see Appendix N, ESM 1, Table S1). Namely, the differences at TP-3 between the phase-III & phase-IV CR group and the non-CR and phase-III CR only groups were moderate or large for CVD risk factors (DBP, RHR, BMI, and WC), exercise capacity (distance walked in ISWT), endothelial function (brachial FMD absolute change), arterial stiffness (SI), SIRT-1, inflammation (ESR and IL-6), and oxidative stress (LOOH and A$^{\bullet -}$).

Changes in physical activity, as measured by the patient reported IPAQ, from TP-1 to TP-3 were similar for the phase-III CR only and phase-III & phase-IV CR groups (see Appendix N, ESM 1, Table S1). However, the distance walked in ISWT increased from TP-1 to TP-2 in the phase-III CR only group, with the cessation of exercise resulting in this parameter decreasing to a value close to baseline at TP-3. In contrast, distance

walked in ISWT improved by a MCID (70 m; (Houchen-Wolloff et al., 2015)) at TP-2 and again at TP-3 for the phase-III & phase-IV CR group. The changes in LOOH at each TP in all groups across the primary and sub-analyses were below the CD value (28%) observed by Davison et al. (2012).

Table 5.2 Baseline demographic and clinical characteristics of participants (primary analysis of secondary outcome measures)

Variable	Non-CR	Phase-III CR
General features		
n	3	21
Age (years)	69.7 ± 10.6	58.8 ± 10.0
Male	2 (66.7%)	17 (81%)
White	3 (100%)	21 (100%)
STEMI	1 (33.3%)	10 (47.6%)
NSTEMI	2 (66.7%)	11 (52.4%)
PCI	3 (100%)	21 (100%)
CVD risk factors		
Family history	2 (66.7%)	14 (66.7%)
Diabetes mellitus	1 (33.3%)	3 (14.3%)
Hypertension	3 (100%)	13 (61.9%)
Dyslipidaemia	3 (100%)	17 (81%)
Obesity	1 (33.3%)	9 (42.9%)
Currently smoking	2 (66.7%)	3 (14.3%)
Prescribed medication		
Antiplatelets	3 (100%)	21 (100%)
Beta blockers	3 (100%)	20 (95.2%)
ACE inhibitors	1 (33.3%)	12 (57.1%)
Nitrates	1 (33.3%)	9 (42.9%)
Angiotensin II receptor antagonists	0 (0%)	2 (9.5%)
Statins	3 (100%)	21 (100%)
Biguanides	1 (33.3%)	3 (14.3%)

Data are mean ± standard deviation or number (%). CR, cardiac rehabilitation; *n*, number; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CVD, cardiovascular disease; and ACE, angiotensin-converting enzyme.

Table 5.3 Baseline demographic and clinical characteristics of participants (sub-analysis of secondary outcome measures)

Variable	Non-CR	Phase-III CR only	Phase-III & phase-IV CR
General features			
n	2	3	7
Age (years)	74.5 ± 9.2	52.0 ± 3.0	55.4 ± 12.1
Male	1 (50%)	3 (100%)	6 (85.7%)
White	2 (100%)	3 (100%)	7 (100%)
STEMI	1 (50%)	2 (66.7%)	2 (28.6%)
NSTEMI	1 (50%)	1 (33.3%)	5 (71.4%)
PCI	2 (100%)	3 (100%)	7 (100%)
CVD risk factors			
Family history	1 (50%)	1 (33.3%)	5 (71.4%)
Diabetes mellitus	0 (0%)	1 (33.3%)	1 (14.3%)
Hypertension	2 (100%)	2 (66.7%)	3 (42.9%)
Dyslipidaemia	2 (100%)	2 (66.7%)	5 (71.4%)
Obesity	1 (50%)	0 (0%)	5 (71.4%)
Currently smoking	1 (50%)	2 (66.7%)	3 (42.9%)
Prescribed medication			
Antiplatelets	2 (100%)	3 (100%)	7 (100%)
Beta blockers	2 (100%)	3 (100%)	7 (100%)
ACE inhibitors	1 (50%)	3 (100%)	5 (71.4%)
Nitrates	1 (50%)	3 (100%)	3 (42.9%)
Angiotensin II receptor antagonists	0 (0%)	0 (0%)	1 (14.3%)
Statins	2 (100%)	3 (100%)	7 (100%)
Biguanides	0 (0%)	1 (33.3%)	1 (14.3%)

Data are mean ± standard deviation or number (%). CR, cardiac rehabilitation; *n*, number; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CVD, cardiovascular disease; and ACE, angiotensin-converting enzyme.

Table 5.4 Values of secondary outcome measures, change scores, and effect sizes at Time Point 1 and Time Point 2 for SCMs (primary analysis of secondary outcome measures; non-CR, $n = 3$; phase-III CR, $n = 21$)

Variable	TP-1	TP-2	Change score	d (95% CI) Within-group [a]	Between-group [b]
Distance walked in ISWT (m)					
Non-CR	360 ± 79	343 ± 82	-17 ± 6	-0.2 (-1.8, 1.4)	1.4 (0.2, 2.7)
Phase-III CR	413 ± 107	492 ± 106	79 ± 45	0.7 (0.1, 1.4)	
SBP (mmHg)					
Non-CR	126 ± 15	138 ± 20	12 ± 19	0.7 (-1.0, 2.3)	-1.7 (-3.1, -0.4)
Phase-III CR	128 ± 17	119 ± 10	-9 ± 12	-0.7 (-1.3, -0.0)	
DBP (mmHg)					
Non-CR	82 ± 9	86 ± 8	4 ± 7	0.5 (-1.1, 2.1)	-1.4 (-2.6, -0.1)
Phase-III CR	81 ± 11	76 ± 8	-5 ± 7	-0.5 (-1.1, 0.1)	
RHR (beats/min)					
Non-CR	72 ± 3	75 ± 3	3 ± 3	1.0 (-0.7, 2.6)	-2.0 (-3.3, -0.6)
Phase-III CR	66 ± 8	62 ± 7	-4 ± 7	-0.5 (-1.1, 0.1)	
BMI (kg/m²)					
Non-CR	25.6 ± 5.9	26.0 ± 5.4	0.4 ± 0.7	0.1 (-1.5, 1.7)	0.8 (-0.5, 2.0)
Phase-III CR	30.0 ± 4.4	29.6 ± 4.6	-0.3 ± 0.8	-0.1 (-0.7, 0.5)	
WC (inches)					
Non-CR	35.5 ± 6.8	35.9 ± 6.3	0.3 ± 0.6	0.1 (-1.5, 1.7)	0.6 (-0.6, 1.9)
Phase-III CR	40.1 ± 5.0	39.4 ± 5.3	-0.7 ± 1.6	-0.1 (-0.7, 0.5)	
Total physical activity (MET-minutes/week)					
Non-CR	513 ± 38	499 ± 68	-14 ± 30	-0.3 (-1.9, 1.4)	8.3 (5.7, 11.0)
Phase-III CR	510 ± 58	1811 ± 164	1301 ± 169	10.6 (8.3, 12.9)	

TC (mmol/L)					
Non-CR	4.4 ± 2.0	4.7 ± 1.0	0.3 ± 2.2	0.2 (-1.4, 1.8)	-0.5 (-1.8, 0.7)
Phase-III CR	4.8 ± 1.5	4.0 ± 1.3	-0.8 ± 0.9	-0.6 (-1.2, 0.0)	
LDL-C (mmol/L)					
Non-CR	3.2 ± 0.9	3.1 ± 0.9	-0.1 ± 0.3	-0.1 (-1.7, 1.5)	-0.6 (-1.8, 0.6)
Phase-III CR	2.9 ± 1.3	2.4 ± 1.2	-0.6 ± 1.0	-0.4 (-1.0, 0.2)	
HDL-C (mmol/L)					
Non-CR	1.3 ± 0.3	1.1 ± 0.2	-0.1 ± 0.2	-0.8 (-2.4, 0.9)	0.3 (-0.9, 1.6)
Phase-III CR	1.1 ± 0.2	1.2 ± 0.3	0.1 ± 0.3	0.4 (-0.2, 1.0)	
TG (mmol/L)					
Non-CR	2.5 ± 2.0	2.2 ± 1.6	-0.3 ± 0.5	-0.2 (-1.8, 1.4)	-0.5 (-1.7, 0.7)
Phase-III CR	1.9 ± 1.9	1.7 ± 1.0	-0.3 ± 1.1	-0.1 (-0.7, 0.5)	
TC/HDL-C ratio					
Non-CR	4.5 ± 2.7	4.3 ± 1.1	-0.2 ± 2.3	-0.1 (-1.7, 1.5)	-0.4 (-1.6, 0.8)
Phase-III CR	4.7 ± 2.3	3.7 ± 1.6	-1.0 ± 1.8	-0.5 (-1.1, 0.1)	
Non-HDL-C (mmol/L)					
Non-CR	3.3 ± 2.2	3.6 ± 0.9	0.3 ± 2.3	0.2 (-1.4, 1.8)	-0.6 (-1.9, 0.6)
Phase-III CR	3.7 ± 1.6	2.8 ± 1.3	-0.9 ± 0.9	-0.6 (-1.2, 0.0)	

Data are mean ± standard deviation; TP, time point; *d*, Cohen's *d*; CI, confidence interval; %, percent; ISWT, incremental shuttle walk test; m, metres; CR, cardiac rehabilitation; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; cm, centimetres; MET-minutes/week, metabolic equivalent minutes per week mmol/L, millimoles per litre; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; [a], for TP-2 – TP-1; [b], for TP-2.

Table 5.5 Values of secondary outcome measures, change scores, and effect sizes at Time Point 1 and Time Point 2 for vascular measurements (primary analysis of secondary outcome measures; non-CR, $n = 3$; phase-III CR, $n = 21$)

Variable	TP-1	TP-2	Change score	d (95% CI)	
				Within-group [a]	Between-group [b]
Baseline diameter (cm) [c]					
Non-CR	0.45 ± 0.03	0.51 ± 0.13	0.06 ± 0.16	0.6 (-1.4, 2.6)	-1.2 (-2.7, 0.3)
Phase-III CR	0.41 ± 0.06	0.41 ± 0.08	-0.00 ± 0.05	0.0 (-0.7, 0.7)	
Peak diameter (cm) [c]					
Non-CR	0.47 ± 0.03	0.53 ± 0.14	0.06 ± 0.17	0.6 (-1.4, 2.6)	-1.2 (-2.7, 0.4)
Phase-III CR	0.42 ± 0.06	0.43 ± 0.08	0.01 ± 0.05	0.1 (-0.6, 0.9)	
Brachial FMD (%) [c]					
Non-CR	3.3 ± 0.7	2.7 ± 0.5	-0.7 ± 0.2	-1.0 (-3.1, 1.1)	0.8 (-0.7, 2.3)
Phase-III CR	2.9 ± 2.2	5.3 ± 3.2	2.4 ± 3.2	0.9 (0.1, 1.6)	
Brachial FMD absolute change (cm) [c]					
Non-CR	0.015 ± 0.004	0.013 ± 0.001	-0.002 ± 0.006	-0.7 (-2.7, 1.3)	0.7 (-0.8, 2.2)
Phase-III CR	0.012 ± 0.010	0.022 ± 0.014	0.010 ± 0.013	0.8 (0.1, 1.6)	
Shear rate (AUC) [c]					
Non-CR	23300.1 ± 19279.3	3167.9 ± 3287.0	-20132.2 ± 22566.3	-1.5 (-3.7, 0.7)	1.2 (-0.3, 2.8)
Phase-III CR	16318.1 ± 5721.1	16306.8 ± 10888.3	-11.2 ± 9125.3	-0.0 (-0.7, 0.7)	
TTP vasodilation (s) [c]					
Non-CR	68 ± 35	23 ± 13	-45 ± 48	-1.7 (-3.9, 0.6)	0.9 (-0.6, 2.4)
Phase-III CR	71 ± 31	52 ± 32	-19 ± 29	-0.6 (-1.4, 0.1)	
SI (m/s)					
Non-CR	15.2 ± 1.6	16.3 ± 2.2	1.1 ± 0.9	0.6 (-1.1, 2.2)	-2.1 (-3.4, -0.7)

Phase-III CR	14.2 ± 3.4	10.8 ± 2.7	-3.3 ± 2.3	-1.1 (-1.8, -0.5)	
RI (%)					
Non-CR	95.7 ± 10.1	90.3 ± 21.5	-5.3 ± 11.8	-0.3 (-1.9, 1.3)	-1.4 (-2.7, -0.1)
Phase-III CR	81.4 ± 8.7	76.0 ± 8.1	-5.5 ± 6.6	-0.6 (-1.3, -0.0)	

Data are mean ± standard deviation; TP, time point; *d*, Cohen's *d*; CI, confidence interval; %, percent; CR, cardiac rehabilitation; FMD, flow-mediated dilatation; AUC, area-under-the-curve; TTP, time-to-peak; s, seconds; SI, stiffness index; m/s, metres per second; RI, reflective index; [a], for TP-2 – TP-1; [b], for TP-2; [c], data available for sub-group (non-CR, *n* = 2 and phase-III CR, *n* = 15).

Table 5.6 Values of secondary outcome measures, change scores, and effect sizes at Time Point 1 and Time Point 2 for biochemical analyses (primary analysis of secondary outcome measures; non-CR, $n = 3$; phase-III CR, $n = 21$)

Variable	TP-1	TP-2	Change score	d (95% CI) Within-group [a]	Between-group [b]
ESR (mm/hr)					
Non-CR	15.3 ± 1.2	14.7 ± 2.1	-0.7 ± 1.5	-0.4 (-2.0, 1.3)	-1.5 (-2.8, -1.0)
Phase-III CR	15.1 ± 3.8	10.1 ± 3.2	-5.0 ± 3.4	-1.4 (-2.1, -0.7)	
LOOH (μmol/L)					
Non-CR	1.0 ± 0.1	1.2 ± 0.2	0.2 ± 0.1	1.3 (-0.5, 3.0)	-1.0 (-2.2, 0.2)
Phase-III CR	1.2 ± 0.2	1.0 ± 0.2	-0.2 ± 0.3	-1.0 (-1.6, -0.4)	
$A^{\bullet-}$ (a.u.) × 10 ^{4}					
Non-CR	9.8 ± 3.9	12.6 ± 5.3	2.8 ± 1.7	0.6 (-1.0, 2.3)	-1.0 (-2.3, 0.2)
Phase-III CR	15.9 ± 9.0	6.8 ± 5.7	-9.1 ± 8.8	-1.2 (-1.9, -0.6)	

Data are mean ± standard deviation; TP, time point; d, Cohen's d; CI, confidence interval; %, percent; CR, cardiac rehabilitation; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; LOOH, lipid hydroperoxides; μmol/L, micromoles per litre; $A^{\bullet-}$, ascorbyl free radical; a.u., arbitrary units; [a], for TP-2 – TP-1; [b], for TP-2.

Table 5.7 Values of secondary outcome measures at each Time Point for SCMs (sub-analysis of secondary outcome measures; non-CR, $n = 2$; phase-III CR only, $n = 3$; phase-III & phase-IV CR, $n = 7$)

Variable	TP-1	TP-2	TP-3
Distance walked in ISWT (m)			
Non-CR	405 ± 21	390 ± 14	365 ± 35
Phase-III CR only	333 ± 72	400 ± 56	330 ± 108
Phase-III & phase-IV CR	434 ± 124	510 ± 120	586 ± 93
SBP (mmHg)			
Non-CR	129 ± 20	130 ± 20	135 ± 20
Phase-III CR only	118 ± 3	117 ± 5	121 ± 9
Phase-III & phase-IV CR	128 ± 18	122 ± 12	120 ± 9
DBP (mmHg)			
Non-CR	79 ± 10	82 ± 1	84 ± 1
Phase-III CR only	73 ± 5	72 ± 8	81 ± 6
Phase-III & phase-IV CR	82 ± 13	79 ± 10	77 ± 7
RHR (beats/min)			
Non-CR	74 ± 4	75 ± 4.2	75 ± 1
Phase-III CR only	69 ± 8	62 ± 6	73 ± 2
Phase-III & phase-IV CR	68 ± 20	64 ± 9	62 ± 9
BMI (kg/m²)			
Non-CR	25.2 ± 8.3	25.4 ± 7.5	25.5 ± 6.7
Phase-III CR only	27.6 ± 2.1	27.1 ± 1.9	28.5 ± 2.4
Phase-III & phase-IV CR	32.7 ± 5.9	32.6 ± 6.0	31.9 ± 6.9

WC (inches)			
Non-CR	35.0 ± 9.5	35.1 ± 8.8	34.9 ± 7.6
Phase-III CR only	36.0 ± 0.9	35.3 ± 1.0	37.0 ± 1.4
Phase-III & phase-IV CR	41.8 ± 7.2	41.5 ± 7.4	40.2 ± 7.6
Total physical activity (MET-minutes/week)			
Non-CR	495 ± 28	466 ± 51	511 ± 46
Phase-III CR only	483 ± 93	1897 ± 101	1949 ± 132
Phase-III & phase-IV CR	501 ± 68	1792 ± 101	1946 ± 150

Data are mean ± standard deviation; TP, time point; ISWT, incremental shuttle walk test; m, metres; CR, cardiac rehabilitation; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; MET-minutes/week, metabolic equivalent minutes per week.

Table 5.8 Values of secondary outcome measures at each Time Point for vascular measurements (sub-analysis of secondary outcome measures; non-CR, n = 2; phase-III CR only, n = 3; phase-III & phase-IV CR, n = 7)

Variable	TP-1	TP-2	TP-3
Baseline diameter (cm) [a]			
Non-CR	0.43 ± 0.00	0.61 ± 0.00	0.45 ± 0.00
Phase-III CR only	0.42 ± 0.03	0.43 ± 0.05	0.38 ± 0.02
Phase-III & phase-IV CR	0.43 ± 0.02	0.43 ± 0.06	0.44 ± 0.07
Peak diameter (cm) [a]			
Non-CR	0.45 ± 0.00	0.62 ± 0.00	0.46 ± 0.00
Phase-III CR only	0.43 ± 0.04	0.46 ± 0.03	0.40 ± 0.01
Phase-III & phase-IV CR	0.44 ± 0.03	0.45 ± 0.06	0.47 ± 0.05
Brachial FMD (%) [a]			
Non-CR	2.8 ± 0.0	2.3 ± 0.0	2.7 ± 0.0
Phase-III CR only	2.2 ± 2.0	7.7 ± 4.4	5.9 ± 3.0
Phase-III & phase-IV CR	2.8 ± 3.2	5.3 ± 4.6	7.5 ± 5.4
Brachial FMD absolute change (cm) [a]			
Non-CR	0.012 ± 0.000	0.014 ± 0.000	0.012 ± 0.000
Phase-III CR only	0.010 ± 0.009	0.032 ± 0.016	0.022 ± 0.010
Phase-III & phase-IV CR	0.012 ± 0.014	0.022 ± 0.020	0.030 ± 0.018
Shear rate (AUC) [a]			
Non-CR	9667.6 ± 0.0	5492.2 ± 0.0	5687.9 ± 0.0
Phase-III CR only	14451.2 ± 2680.6	27850.5 ± 9937.9	15526.8 ± 14604.9
Phase-III & phase-IV CR	17458.5 ± 9379.8	14593.6 ± 13993.2	15543.6 ± 10739.0

TTP vasodilation (s) [a]			
Non-CR	43 ± 0	33 ± 0	38 ± 0
Phase-III CR only	85 ± 18	43 ± 7	70 ± 39
Phase-III & phase-IV CR	66 ± 42	66 ± 50	54 ± 36
SI (m/s)			
Non-CR	15.2 ± 2.3	15.8 ± 2.8	15.8 ± 2.2
Phase-III CR only	15.8 ± 1.2	11.9 ± 1.7	13.8 ± 1.7
Phase-III & phase-IV CR	12.2 ± 4.4	9.0 ± 2.8	7.6 ± 2.1
RI (%)			
Non-CR	95.0 ± 14.1	86.5 ± 29.0	86.5 ± 26.2
Phase-III CR only	76.3 ± 4.5	75.3 ± 5.5	81.0 ± 4.4
Phase-III & phase-IV CR	76.3 ± 7.4	73.9 ± 6.1	72.1 ± 6.0

Data are mean ± standard deviation; TP, time point; CR, cardiac rehabilitation; cm, centimetres; FMD, flow-mediated dilatation; %, percentage; AUC, area-under-the-curve; TTP, time-to-peak; s, seconds; SI, stiffness index; m/s, metres per second; RI, reflective index; [a], data available for sub-group (non-CR, $n = 1$; phase-III CR only, $n = 2$; phase-III and phase-IV CR, $n = 5$).

Table 5.9 Values of secondary outcome measures at each Time Point for biochemical analyses (sub-analysis of secondary outcome measures; non-CR, $n = 2$; phase-III CR only, $n = 3$; phase-III & phase-IV CR, $n = 7$)

Variable	TP-1	TP-2	TP-3
SIRT-1 (ng/mL)			
Non-CR	0.145 ± 0.001	0.140 ± 0.002	0.132 ± 0.002
Phase-III CR only	0.140 ± 0.006	0.195 ± 0.006	0.141 ± 0.009
Phase-III & phase-IV CR	0.134 ± 0.006	0.204 ± 0.011	0.271 ± 0.027
ESR (mm/hr)			
Non-CR	16.0 ± 0.0	15.5 ± 2.1	17.5 ± 3.5
Phase-III CR only	13.0 ± 4.4	9.3 ± 4.2	12.0 ± 3.6
Phase-III & phase-IV CR	13.1 ± 2.0	8.9 ± 2.2	6.6 ± 2.4
IL-6 (pg/mL)			
Non-CR	4.0 ± 1.4	4.1 ± 1.1	3.9 ± 1.2
Phase-III CR only	2.8 ± 1.8	2.8 ± 1.4	3.0 ± 1.4
Phase-III & phase-IV CR	2.6 ± 0.9	2.4 ± 0.8	2.1 ± 0.7
IL-10 (pg/mL)			
Non-CR	4.7 ± 0.6	4.5 ± 0.5	4.3 ± 0.6
Phase-III CR only	3.4 ± 1.1	3.5 ± 1.2	3.6 ± 1.4
Phase-III & phase-IV CR	3.1 ± 1.1	3.2 ± 1.2	3.2 ± 1.3
LOOH (µmol/L)			
Non-CR	1.0 ± 0.1	1.2 ± 0.3	1.2 ± 0.1
Phase-III CR only	1.1 ± 0.1	0.9 ± 0.3	0.8 ± 0.0
Phase-III & phase-IV CR	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1

$A^{\bullet-}$ (a.u.) $\times$ 10 ^{4}			
Non-CR	9.3 ± 5.4	12.6 ± 7.5	14.5 ± 8.5
Phase-III CR only	7.9 ± 3.5	5.5 ± 4.5	9.3 ± 1.7
Phase-III & phase-IV CR	21.1 ± 11.7	11.3 ± 6.0	4.6 ± 3.3

Data are mean ± standard deviation; TP, time point; CR, cardiac rehabilitation; SIRT-1, sirtuin-1; ng/mL, nanograms per millilitre; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; IL-6, interleukin-6; pg/mL, picograms per millilitre; IL-10, interleukin-10; LOOH, lipid hydroperoxides; μmol/L, micromoles per litre; $A^{\bullet-}$, ascorbyl free radical; a.u., arbitrary units.
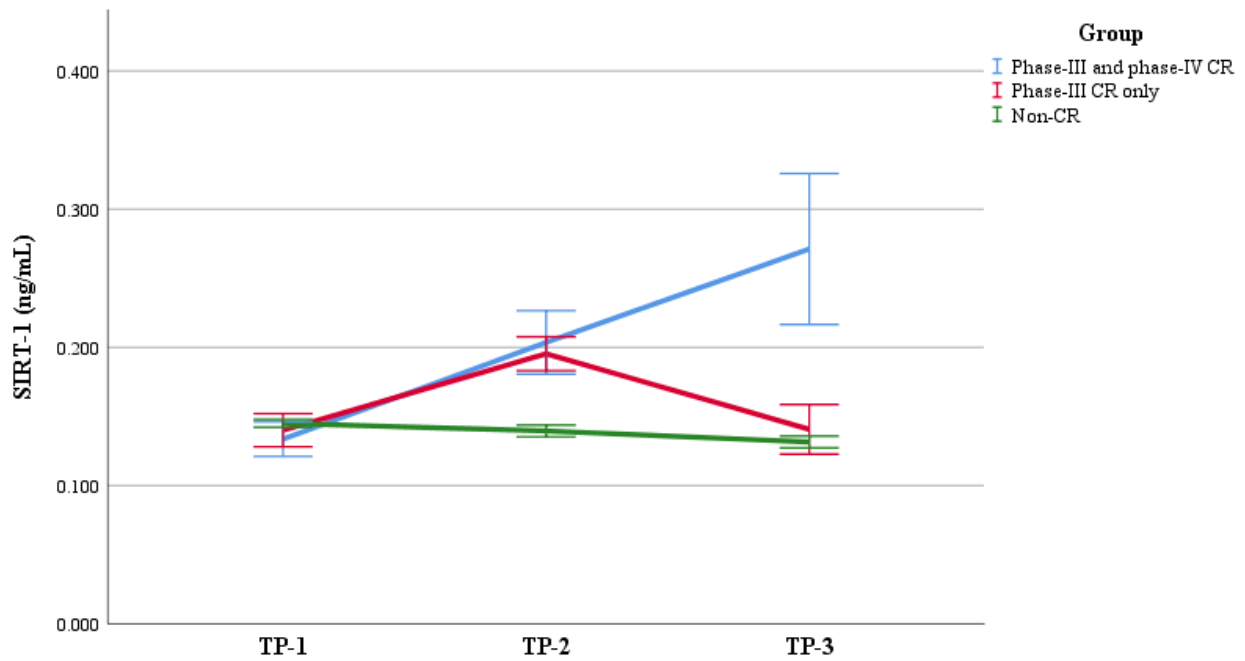
Figure 5.2 SIRT-1 concentration (ng/mL) across each Time Point

Data expressed as mean ± standard deviation; SIRT-1, sirtuin-1; ng/mL, nanograms per millilitre; TP, time point; and CR, cardiac rehabilitation.

5.3.5 Results of Inferential Statistics

Whilst Study 2 was not powered to detect statistical significance, inferential statistics were performed and presented as a component of this chapter to enable the PhD researcher to acquire an experience of conducting this form of data analysis. At baseline, all groups were statistically similar ($p > 0.05$ for all data) regarding demographic variables, clinical characteristics, and secondary outcome measures (see Appendix O, Tables 1, 2, 3, and 4).

5.3.5.1 Analysis of Secondary Outcome Measures

Twenty-four participants completed TP-1 and TP-2: phase-III CR group ($n = 21$) and non-CR group ($n = 3$). The results of the primary analysis of secondary outcome measures are presented in Appendix O, Table 3. A decrease in distanced walked in the ISWT (m) was found in the non-CR group ($p < 0.05$), with no significant within-group changes being seen in the other variables measured ($p > 0.05$ for all). Beneficial changes from TP-1 to TP-2 in distance walked in the ISWT (m), SBP, DBP, RHR, WC, brachial FMD, brachial FMD absolute change, time-to-peak vasodilation, arterial SI, RI, physical activity, ESR, LOOH, A$^{\bullet-}$, TC, LDL-C, TC/HDL-C ratio, and non-HDL-C were detected for the phase-III CR group ($p < 0.05$ for all). Between-group differences at TP-2 were observed for distance walked in ISWT (m), DBP, RHR, arterial SI, total physical activity level, and ESR ($p < 0.05$ for all). No significant within or between-group changes in the other variables measured were seen in the phase-III CR group ($p > 0.05$ for all; see Appendix O, Table 3).

5.3.5.2 Sub-Analysis of Secondary Outcome Measures

Twelve participants completed all three TPs: phase-III & phase-IV CR group ($n = 7$), phase-III CR only group ($n = 3$), and non-CR group ($n = 2$). The results of the sub-analysis of secondary outcome measures are presented in Appendix O, Table 4 (see Appendix O, Table 5 for effect sizes). No within-group changes in any of the variables measured were observed for the non-CR and phase-III CR only groups ($p > 0.05$ for all). However, beneficial changes in SIRT-1, distanced walked in ISWT (m), arterial SI, ESR, and A$^{\bullet-}$

were detected at each TP for the phase-III & phase-IV CR group ($p < 0.05$ at each TP for all). Favorable changes in WC, brachial FMD, and brachial FMD absolute change were identified after phase-IV CR in this group, as indicated by significant differences between TP-1 and TP-3 ($p < 0.05$ for all) and TP-2 and TP-3 ($p < 0.05$ for all), with no significant change between TP-1 and TP-2 ($p > 0.05$ for all). Moreover, physical activity increased after phase-III CR in the phase-III & phase-IV CR group as significant differences between TP-1 and TP-2 ($p > 0.05$) and TP-1 and TP-3 ($p > 0.05$) were seen, with no significant change between TP-2 and TP-3 ($p > 0.05$). The values of SIRT-1, distance walked in ISWT (m), arterial SI, and ESR in the phase-III & phase-IV CR group were significantly different from the non-CR and phase-III CR only groups at TP-3 ($p < 0.05$ for all), with arterial SI being significantly lower than the non-CR group at TP-2 ($p < 0.05$). No significant within or between-group changes in the other variables measured were seen in the phase-III & phase-IV CR group ($p > 0.05$ for all; see Appendix O, Table 4).

5.3.5.3 Correlation Analysis

Spearman's correlation coefficient revealed no relationships between SIRT-1 concentration and the other secondary outcome measures at each TP for the phase-III & phase-IV CR group ($p > 0.05$ for all; see Appendix O, Table 6). However, strong negative and positive correlations with SIRT-1 approached statistical significance for IL-6 at TP-3 ($r_s = -0.75$, $p = 0.052$; see Figure 5.3) and IL-10 at TP-1 ($r_s = 0.75$, $p = 0.052$; see Figure 5.4), respectively.
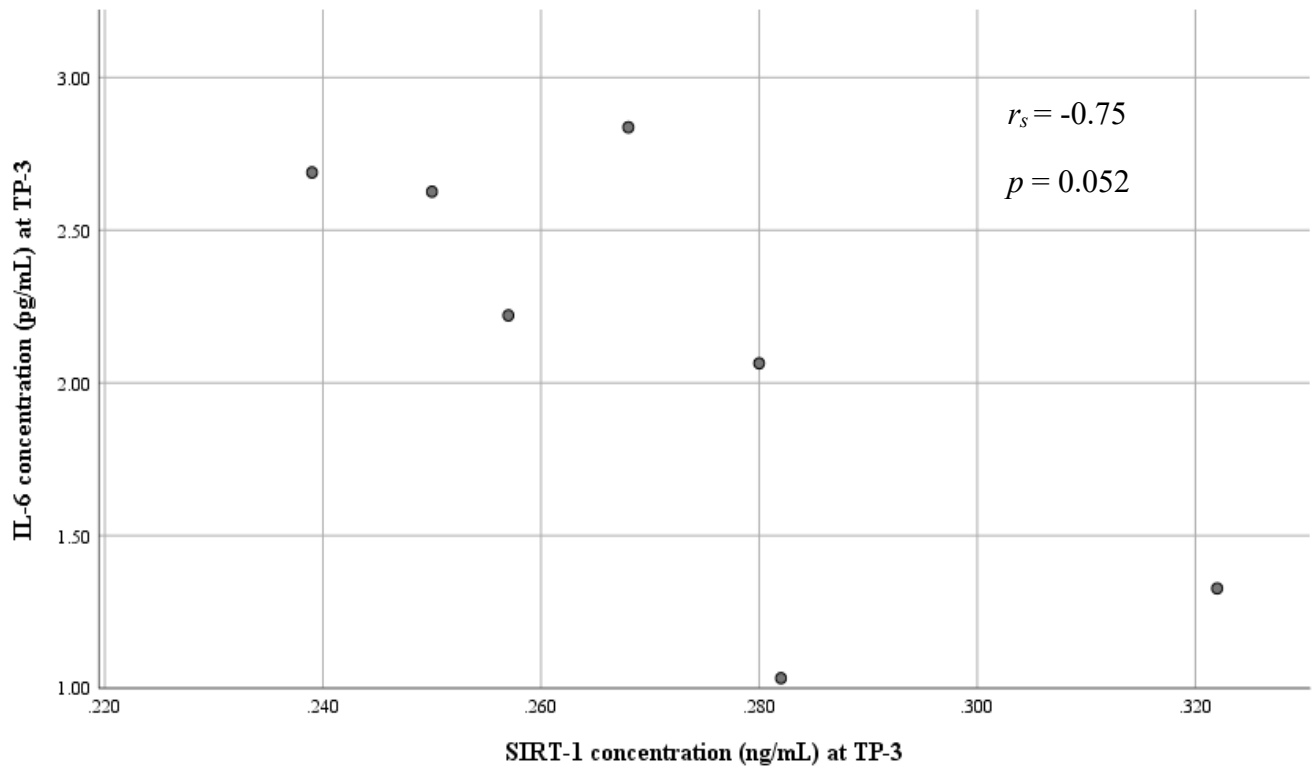
Figure 5.3 Relationship between SIRT-1 and IL-6 concentrations at TP-3

SIRT-1, sirtuin-1; ng/mL, nanograms per millilitre; TP, time point; IL-6, interleukin-6; pg/mL, picograms per millilitre; r_s, Spearman's correlation coefficient.
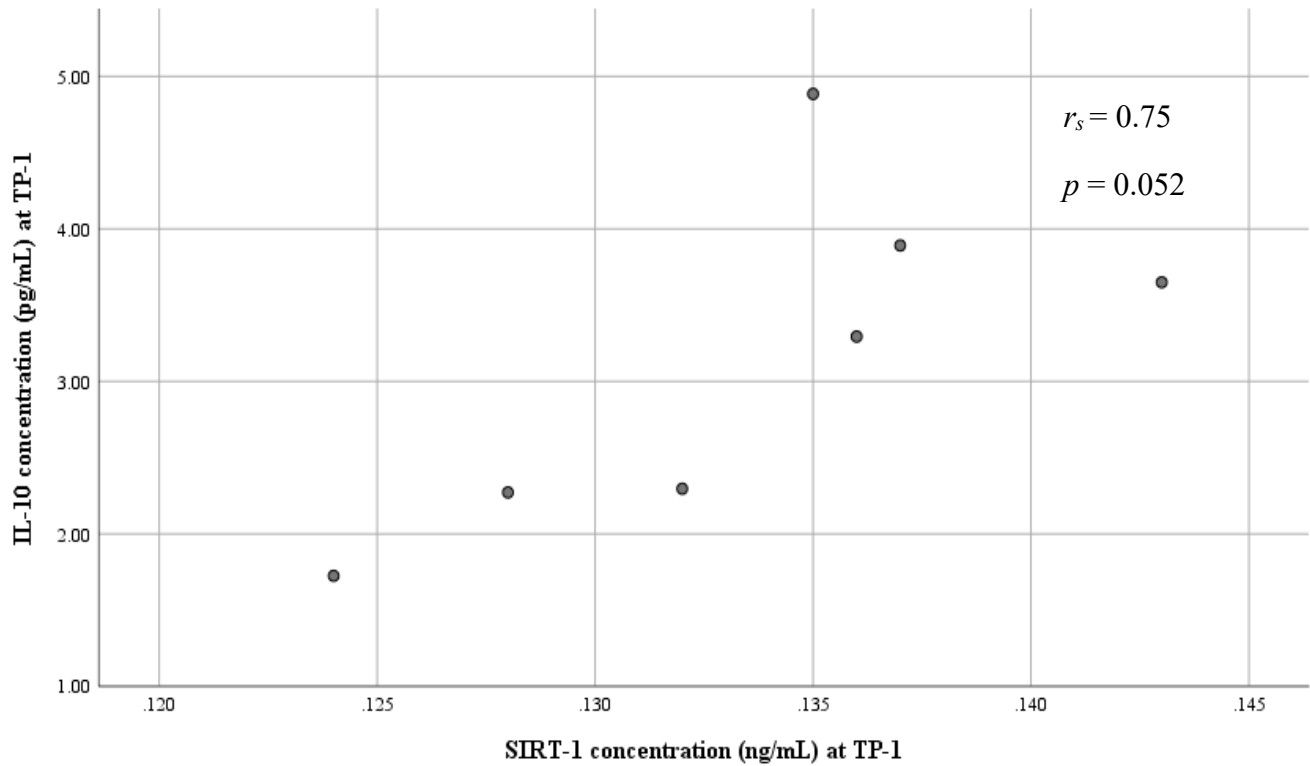
Figure 5.4 Relationship between SIRT-1 and IL-10 concentrations at TP-1

SIRT-1, sirtuin-1; ng/mL, nanograms per millilitre; TP, time point; IL-10, interleukin-10; pg/mL, picograms per millilitre; r_s, Spearman's correlation coefficient.

5.4 Discussion

The primary objective of this pilot study was to assess the feasibility of performing a future prospective cohort study in this area by evaluating the rates of recruitment, drop-out, and adherence. The success criteria for drop-out rate (< 20% overall and at each TP for each group) and adherence rate (completed > 80% of prescribed exercise sessions) were satisfied, which indicates that the study design and methodology were suitable for the participants. Although, the success criterion regarding recruitment rate was not fulfilled (< 70% of eligible patients were recruited).

The challenges of recruiting patients to clinical studies are recognised in the literature (Tramm et al., 2013). Indeed, similar trials that recruited participants from a CR population demonstrated recruitment rates (38% (Oliveira et al., 2015), 36% (Jørgensen et al., 2018), and 32% (Bilinska et al., 2010)) that were comparable to this pilot study (38%). Thus, in retrospect, the success criterion for recruitment rate may have been ambitious (> 70% of eligible patients recruited). The sole reason for non-participation was a failure by participants to contact the research team to arrange a meeting for recruitment, which suggests that the inclusion and exclusion criteria are appropriate for use in a future study as undue exclusivity was not an issue. Across the recruited participants, 25 (89%) patients agreed to participate in phase-III CR, with 13 (54%) of these individuals also involved in phase-IV CR. This uptake rate suggests that balanced numbers across CR groups (phase-III & phase-IV CR and phase-III CR only) may be attainable in the future prospective cohort study, which may increase the reliability of the corresponding between-group comparisons (Zimmerman, 1987).

In terms of the secondary outcome measures, there was a trend that involved improvements in the assessed parameters following the completion of phase-III CR, with unfavourable changes and/ or smaller improvements observed in the non-CR group at TP-2. Moreover, the completion of phase-IV CR often resulted in further amelioration of the secondary outcome measures. Saliently, the beneficial physiological adaptations induced by phase-III CR generally deteriorated at TP-3 in the phase-III CR only group, with the non-CR group typically demonstrating additional declines in the secondary outcome measures at TP-3. These findings highlight the importance of CAD patient participation in phase-III and phase-IV CR, along with adherence to long-term exercise. Indeed, a recent systematic review demonstrated that maintenance CR programmes following clinically supervised CR resulted in increased quality of life, functional capacity, and physical activity levels in CVD patients (Sánchez-Delgado et al., 2020). Moreover, results from large prospective cohort studies suggest an inverse relationship between physical activity and cardiovascular mortality rates in CAD patients (Lahtinen et al., 2018; Stewart et al., 2017; Biscaglia et al., 2019). However, CR programmes are underutilised by patients worldwide (Kotseva et al., 2013; Beatty et al., 2018; Turk-Adawi & Grace, 2015). In addition, the literature indicates that adherence to long-term exercise in CAD patients is poor (Kotseva et al., 2019; Blanchard et al., 2014; Sweet et al., 2011), with 66% of CAD patients across Europe being classified as sedentary (< 30 minutes of physical activity on five days per week) (Kotseva et al., 2019). Thus, effective strategies for promoting CAD patient participation in CR and long-term exercise are needed.

The beneficial effect of exercise on CVD risk factors and clinical parameters in CAD patients has been well documented in the literature (Taylor et al., 2006; Marzolini

et al., 2012; Liou et al., 2016). Indeed, a MCID (70 m; (Houchen-Wolloff et al., 2015)) in distance walked in ISWT was seen after both phase-III CR and phase-IV CR. Importantly, this parameter decreased at each TP for the non-CR group, with the phase-III CR only group experiencing a decrease in distance walked in ISWT from TP-2 to TP-3 that was proportionate to a MCID (70 m; (Houchen-Wolloff et al., 2015)). Interestingly, the phase-III CR only group experienced a decline in distance walked in ISWT despite demonstrating similar physical activity levels to the phase-III & phase-IV CR group at TP-2 and TP-3. This result may be explained by either the intensity of physical activity in the phase-III CR only group from TP-2 to TP-3 failing to exceed a threshold for improvements in exercise capacity, or inaccurate self-reporting of physical activity due to recall or desirability bias (Sallis & Saelens, 2000; Adams et al., 2005). Nonetheless, there is evidence to suggest that an increase in physical activity without improvements in cardiorespiratory fitness may not result in protection against CAD (Lakka et al., 1994), which emphasises the potential importance of the beneficial effect of phase-III and phase-IV CR participation on exercise capacity as observed in this study. The dose-response relationship between exercise and distance walked in ISWT that was identified is consistent with the findings of a meta-analysis that documented greater improvements in distance walked in ISWT in patients prescribed $n > 12$ exercise sessions compared with those receiving $n \leq 12$ exercise sessions at CR (Almodhy et al., 2016). The values of SBP, DBP, RHR, BMI, and WC also decreased after phase-III and phase-IV CR. In particular, the reduction in SBP following these CR programmes (-8 ± 11) approached the threshold (10 mmHg decrease in SBP) for a 20% reduction in the risk of major CVD events (Ettehad et al., 2016). Moreover, RHR in the phase-III & phase-IV CR group (62 ± 9) was lower than the non-CR (75 ± 1) and phase-III CR only (73 ± 2) groups at TP-3, which may have equated to a lower risk of cardiovascular mortality (Diaz et al., 2005). In the primary

analysis of secondary outcome measures, an improvement in lipid profile was seen following phase-III CR, with all parameters aside from HDL-C being lower in the phase-III CR group than the non-CR group at TP-2. Saliently, the phase-III CR group demonstrated a greater decrease in LDL-C at TP-2 than the non-CR group, which may result in a greater cardiovascular risk reduction (Navarese et al., 2018).

Through a complex interplay, systemic inflammation mediates numerous pathophysiological pathways that may contribute to CAD development, such as: oxidative stress (Kotur-Stevuljevic et al., 2007), endothelial dysfunction (Weiner et al., 2014), and arterial stiffness (van Bussel et al., 2011). Importantly, the literature indicates that CAD patients possess repressed SIRT-1, with concomitant up-regulation of inflammatory activity and oxidative stress (Breitenstein et al., 2013; Li et al., 2016; Hu et al., 2015; Chan et al., 2017). Moreover, low SIRT-1 has been associated with high-risk coronary plaques in asymptomatic CAD patients (He et al., 2019). Saliently, evidence regarding the protective effect of SIRT-1 in vascular biology suggests that this protein may serve as a target for CVD prevention and treatment (Yu et al., 2009).

The principal finding of this study was an increase in SIRT-1 following phase-III CR and phase-IV CR. This positive effect of exercise on SIRT-1 in CAD patients supports the results generated by Alavizadeh et al. (2018). To the best of our knowledge, previous literature has not compared the impact of different exercise programme durations on SIRT-1. Positive differences between exercise and control groups in SIRT-1 concentration have been detected by studies in CAD patients (Alavizadeh et al., 2018) and type II diabetes mellitus patients (Vizvari et al., 2018) following exercise programmes of a short duration (8 weeks). Whilst a rise in SIRT-1 was seen after phase-

III CR (8 weeks), the results of this study demonstrated an additional increase in SIRT-1 concentration following phase-IV CR at TP-3. These findings add to the literature by suggesting a beneficial effect of longer exercise programme durations (20 weeks) on SIRT-1. Nevertheless, future research in this area should seek to define optimal exercise programme characteristics for augmenting SIRT-1 levels.

The literature suggests that SIRT-1 plays a principal role in the regulation of inflammation through the modulation of NF-κβ transcriptional activity (Yeung et al., 2004; Cheng et al., 2015). Indeed, previous research has demonstrated an inverse relationship between SIRT-1 and pro-inflammatory cytokines in CAD patients (Babaee et al., 2020; Li et al., 2016). Whilst there is a paucity of evidence regarding the correlation between SIRT-1 and IL-10 in CAD patients, the literature indicates that SIRT-1 may stimulate IL-10 induction via control of peroxisome proliferator-activated receptor-gamma co-activator-1α transcriptional activity (Amat et al., 2009; Morari et al., 2010). Interestingly, ESR and IL-6 decreased after phase-III and phase-IV CR, with unfavourable changes or smaller improvements being seen in the non-CR and phase-III CR only groups from TP-1 to TP-3. Moreover, a small increase in IL-10 was observed in the phase-III & phase-IV CR group from TP-1 to TP-3, whilst a moderate decrease in the level of this parameter from TP-1 to TP-3 was observed in the non-CR group. This beneficial effect of exercise on systemic inflammatory activity in CAD patients is consistent with the findings of previous research (Thompson et al., 2020; Ribeiro et al., 2012).

Whilst data associated with redox balance following exercise programmes in CAD patient populations is sparse, a systematic review and meta-analysis performed by

de Sousa et al. (2017) concluded that pro-oxidant indicators decrease and antioxidant parameters increase in the general population (*i.e.,* healthy adults, obese individuals, type II diabetes mellitus patients, and CVD patients) after exercise training. In the current study, a large decrease in LOOH and $A^{\bullet-}$ from TP-1 to TP-3 was observed in the phase-III & phase-IV CR group, with a large increase in LOOH and a moderate rise in $A^{\bullet-}$ from TP-1 to TP-3 observed in the non-CR group. These changes in LOOH at each TP in all groups were below the CD value (28%) observed by Davison et al. (2012). However, the CD values generated by Davison et al. (2012) were obtained from apparently healthy male participants, which may limit generalisability to this study. To the best of our knowledge, no study has determined CD values for biomarkers of oxidants-antioxidants in a CAD patient population. Given that oxidative stress has been associated with risk of death in CAD patients (Patel et al., 2016), future research is needed in this area to determine the biological significance of exercise-induced changes in oxidative stress. Whilst the assessment of lipid soluble antioxidants was planned, technical issues precluded the generation of valid data. Nevertheless, given that dietary intake is the primary source of lipid soluble antioxidants (Bouayed & Bohn, 2010), the measurement of endogenous antioxidants may have allowed the effect of exercise on antioxidant status to be better examined; Russomanno et al. (2017) demonstrated that an exercise-induced increase in SIRT-1 activity resulted in augmented SOD and catalase activity in heart failure patients.

The literature suggests that the incidence of endothelial dysfunction predicts future CAD development (Maruhashi et al., 2013; Yoboah et al., 2009). In a dysfunctional state, the endothelium elicits a pro-atherogenic inflammatory phenotype (Gimbrone & García-Cardeña, 2016), which may promote arterial stiffening due to impaired functional

regulation of arterial elasticity secondary to diminished nitric oxide bioavailability and increased collagen synthesis (Nigam et al., 2003; Kinlay et al., 2001; Gonzalez-Santiago et al., 2002). Importantly, endothelial dysfunction and arterial stiffness have been associated with recurrent cardiovascular complications in CAD patients (Inaba et al., 2010; Maruhashi et al., 2018). SIRT-1 may ameliorate endothelial function and arterial stiffness by activating endothelial nitric oxide synthase in endothelial cells (Mattagajasingh et al., 2007); reducing inflammation via NF-κβ suppression (Yeung et al., 2004); and attenuating oxidative stress by mitigating nicotinamide adenine dinucleotide phosphate oxidase activation and inducing the expression of antioxidant enzymes (SOD and catalase) (Zarzuelo et al., 2013; Rahman et al., 2009; Conti et al., 2015; Ferrara et al., 2008). In the current study, improvements in endothelial function (brachial FMD) and arterial stiffness (SI and RI) were observed following phase-III and phase-IV CR, with unfavourable changes or smaller improvements being seen in the non-CR and phase-III CR only groups from TP-1 to TP-3. Saliently, brachial FMD at TP-3 in the phase-III & phase-IV CR group (7.5 ± 5.4) was higher than the non-CR (2.7 ± 0.0) and phase-III CR only (5.9 ± 3.0) groups. Interestingly, brachial FMD values > 7.1% have been associated with a lower risk of CVD events in CAD patients, albeit evidence from a Japanese cohort (Maruhashi et al., 2018). The positive effect of exercise on endothelial function and arterial stiffness in CAD patients, as documented in this study, is consistent with the findings of previous research (Pattyn et al., 2018; Zhang et al., 2018).

Several factors must be considered before moving forward to the future prospective cohort study. Firstly, the success criterion for recruitment rate was not satisfied, thus, amendments to the recruitment strategy are warranted in order to circumvent issues with recruitment. Moreover, only 3 (11%) patients who refused to

participate in phase-III CR were recruited. Discussions with the collaborating CR nurses indicated that the overall recruitment rate may be improved by implementing a recruitment strategy that involves a member of the research team being present at clinical departments to discuss the study with potential participants in person. Nonetheless, participation in CR is affected by a variety of intrinsic and extrinsic factors; a recent systematic review of quantitative studies performed by Resurrección et al. (2019) illuminated the complexity of this decision by identifying sixty-three factors associated with barriers to participation in CR, which were divided into the following five categories: intrapersonal factors (*i.e.*, older age, female gender, low socioeconomic status, comorbidities, depressive symptoms, low-self efficacy for managing disease, and poor perceived benefit of CR), interpersonal factors (*i.e.*, unmarried, unemployed or retired, and low social and practical support), clinical factors (*i.e.*, smoker, higher BMI, poor functional capacity, uncontrolled cholesterol levels, diabetes mellitus, previous history of CVD, and disease severity), logistical factors (*i.e.*, longer travel times, being a non-driver, lack of transport, and living in a rural or geographically inaccessible area), and healthcare system factors (*i.e.*, lack of referral to CR and low strength of endorsement from physicians). These factors may also serve as barriers to the recruitment of non-CR patients. Indeed, according to the CR nurses, this patient population is typically unreceptive to participation in research projects due to personal circumstances (*i.e.,* lack of transport) and/ or inherent attitudes (*i.e.,* depressive symptoms). As such, financial incentives may be required for the recruitment of non-CR patients to the future prospective cohort study. Moreover, in the case of poor recruitment, the level of participant burden could be reduced by solely examining changes in SIRT-1 levels, which may enhance recruitment as blood samples could be collected during routine appointments. Collectively, the beforementioned amendments to the recruitment strategy

will be implemented in the future prospective cohort study and should be considered when designing future trials in this area.

Process evaluation was not included in the feasibility assessments as all centres delivered a CR programme that complied with Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) guidelines (2015), with each of the sites being certified for achieving national CR delivery standards (British Heart Foundation, 2019a). Nonetheless, a future study that assesses the consistency of CR delivery (*i.e.,* compliance with ACPICR guidelines, methods used for obtaining SCMs, and delivery quality) across BHSCT and SEHSCT sites may be useful for informing the design of the future prospective cohort study (*i.e.,* suitability of examining the effect of CR programmes on study outcome measures).

The results of the secondary outcome measures support the examination of the relationship between SIRT-1 and markers of atherogenesis (inflammation, oxidative stress, endothelial function, and arterial stiffness) following exercise in CAD patients. However, financial constraints restricted the measurement of SIRT-1, IL-6, and IL-10 to a small sub-group of the sample ($n = 12$), which potentially limits the reliability of the results. Nonetheless, additional funding has been secured for completing the biochemical analyses in the remaining samples. Data from which will be used to increase the accuracy of a sample size calculation based on a primary outcome of change in SIRT-1 for the future prospective study. Altogether, strategies for addressing potential issues with recruitment have been identified. Moreover, the reliability of the data for a sample size calculation based on change in SIRT-1 will be improved. Thus, a future prospective cohort study has been deemed feasible with minor amendment (recruitment strategy). The

findings reported will inform the protocol of this study. Future research in this area bears the potential to elucidate the molecular mechanisms that mediate exercise-induced cardioprotection, which may enhance CAD secondary prevention strategies by identifying novel therapeutic targets (*i.e.,* biomarkers or drug targets).

5.4.1 Strengths and Limitations

To the best of our knowledge, this is the first clinical study to assess the feasibility of investigating the mechanisms that may mediate the cardioprotective effects of exercise in CAD patients. The structure of the CR programmes was not altered, which allowed the results to potentially represent the effect of the routinely delivered programmes. Moreover, the prospective cohort study design did not involve any active attempts to prevent participant withdrawal. The beforementioned actions may have enabled the generation of clinically representative data. Groups of patients who completed exercise programmes of different durations were compared, which allowed the impact of exercise programme duration to be assessed. Additionally, the cardioprotective effect of exercise was comprehensively assessed by obtaining a series of physiological measurements related to the pathophysiology of atherosclerosis. However, several limitations should be considered when interpreting results. Firstly, this study was not powered to detect statistically significant changes in the secondary outcome measures. Thus, the preliminary evidence generated must be examined by a future fully powered study before definitive conclusions can be made. The COVID-19 pandemic precluded the acquisition of study measurements in 50% of the participants at TP-3, with the small sample size resulting in imprecise results for the secondary outcome measures as indicated by wide CIs around the effect size estimates. Moreover, funding constraints restricted the

measurement of SIRT-1, IL-6, and IL-10 to a small sub-group of the sample ($n = 12$), which potentially limits the reliability of the results. Finally, the frequency of supervised exercise sessions at the CR programmes was low (1 per week). As such, the positive changes in SIRT-1, as documented in the phase-III & phase-IV CR group, may also have been influenced by dietary intake (Allard et al., 2009), physical activity, or medication (*i.e.* statins) (Ota et al., 2010). Future research should seek to account for these confounding variables to ascertain the independent effect of exercise on SIRT-1.

5.5 Conclusion

This pilot study has demonstrated that a future fully powered prospective cohort study that investigates the molecular transducers that mediate the exercise-induced cardioprotective adaptations in CAD patients is feasible with minor amendment (recruitment strategy). In addition, a beneficial effect of exercise on SIRT 1 in CAD patients was observed, with positive changes in physiological states related to atherogenesis also being detected (inflammation, oxidative stress, endothelial function, and arterial stiffness). Fully powered studies should seek to build upon this preliminary evidence. Progress in this area bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.,* biomarkers or drug targets).

Chapter 6

Qualitative Investigation (Paper 3)

6.0 Findings of the Qualitative Investigation (Paper 3)

The results of Study 1 and Study 2 potentially support a beneficial effect of exercise on the health of CAD patients. However, the participation rates of CAD patients in CR and long-term exercise are poor worldwide (Blanchard et al., 2014; Turk-Adawi & Grace, 2015; Beatty et al., 2018), which may prevent this patient population from availing of optimal secondary prevention strategies. Therefore, more work is needed to understand the factors that influence CAD patient participation in CR and long-term exercise. This section presents the findings of a qualitative investigation that explored the factors that influence CR participation and long-term exercise adherence from the perspectives of CAD patients and their significant others. This study has been submitted for publication at *Disability and Rehabilitation* (see Appendix P for evidence of submission). The Supplemental Online Material for **Paper 3** is presented in Appendix Q.

6.1 "Why would you not listen? It is like being given the winning lottery numbers and deciding not to take them": semi-structured interviews with post-acute myocardial infarction patients and their significant others exploring factors that influence participation in cardiac rehabilitation and long-term exercise training

6.1.1 Introduction

CAD is a leading cause of mortality and morbidity worldwide (Naghavi et al., 2017). This form of CVD may result in myocardial ischaemia secondary to diminished myocardial perfusion (Hansson, 2005). The clinical manifestations are ACS comprising unstable angina pectoris, AMI (NSTEMI or STEMI), or sudden cardiac death (Ambrose & Singh, 2015). Importantly, an increased survival rate following AMI has contributed to a residual population of CAD patients at risk of suffering recurrent cardiovascular complications (Koch et al., 2015; Smolina et al., 2012). As such, effective secondary prevention strategies are imperative for improving long-term prognosis of CAD patients (Briffa et al., 2009; Bata et al., 2006).

CR represents a principal secondary prevention strategy (Piepoli et al., 2016; Knuuti et al., 2019). This programme serves as a method of delivering evidence-based management in order to alleviate the psychological and physiological ramifications of CVD (Dalal et al., 2015). Supervised exercise training is the primary component of CR, with these sessions being supplemented with optimal pharmacological therapy, psychological support (*i.e.,* stress management), and lifestyle advice (National Institute For Health and Care Excellence, 2013; British Association for Cardiovascular Prevention and Rehabilitation; 2017; Piepoli et al., 2014). Whilst CR services may vary across the globe (Supervia et al., 2019), the standard structure of this programme in the UK consists of four phases (Bethell et al., 2009) (see Table 6.1). In terms of prognostic benefit, participation in CR has been associated with a reduction in mortality and morbidity in CAD patients (Anderson et al., 2016; Abell et al., 2017; Anderson et al., 2017; Rauch et al., 2016; Kabboul et al., 2018). Importantly, the results of a recent network meta-analysis highlighted the centrality of exercise training as the key component of CR by identifying beneficial effects on the risk of all-cause mortality, risk of total-AMI, and risk of fatal-

AMI (Kabboul et al., 2018), which emphasises the important role of exercise in the secondary prevention of CAD. Not surprisingly, CR is a Class 1 level A recommendation in clinical guidelines for this patient population (Knuuti et al., 2019; Piepoli et al., 2016).

Despite the clinical benefits, CR programmes are underutilised by patients worldwide (Kotseva et al., 2013; Beatty et al., 2018; Turk-Adawi & Grace, 2015). This poor participation in CR is detrimental as many eligible patients may fail to receive optimal secondary prevention strategies and the guidance required to implement positive lifestyle adjustments (*i.e.,* long-term exercise training). Indeed, the literature indicates that a large majority of CAD patients across Europe lead an unhealthy lifestyle (smoking, not adhering to dietary guidelines, and sedentary behaviour) (Kotseva et al., 2019). In addition, of those patients who participate in CR, many may experience difficulties with long-term maintenance of exercise training following programme completion (Blanchard et al., 2014; Sweet et al., 2011). Notably, without sustained adherence to exercise, the cardioprotective physiological adaptations induced by CR may be lost (Theodorou et al., 2016; Vona et al., 2009).

Participation in CR is affected by a variety of intrinsic and extrinsic factors; a recent systematic review of quantitative studies performed by Resurrección et al. (2019) illuminated the complexity of this decision by identifying sixty-three factors associated with barriers to participation in CR, which were divided into the following five categories: intrapersonal factors (*i.e.,* older age, female gender, low socioeconomic status, comorbidities, depressive symptoms, low-self efficacy for managing disease, and poor perceived benefit of CR), interpersonal factors (*i.e.,* unmarried, unemployed or retired, and low social and practical support), clinical factors (*i.e.*, smoker, higher BMI, poor functional capacity, uncontrolled cholesterol levels, diabetes mellitus, previous history of CVD, and disease severity), logistical factors (*i.e.,* longer travel times, being a non-driver, lack of transport, and living in a rural or geographically inaccessible area), and healthcare system factors (*i.e.,* lack of referral to CR and low strength of endorsement from physicians). Given the evidence to support the prognostic benefit of CR (Anderson et al., 2016; Abell et al., 2017; Anderson et al., 2017; Rauch et al., 2016; Kabboul et al., 2018)

and long-term exercise training in CAD patients (Lahtinen et al., 2018; Stewart et al., 2017; Biscaglia et al., 2019), identifying methods of promoting participation may result in a reduced burden of CAD by improving CVD risk profiles, with concomitant societal and economic benefits through lower rates of premature mortality, fewer hospital readmissions, and improved quality of life (De Gruyter et al., 2016). To assist with the development of these strategies, more work is needed to identify and understand the factors that influence participation in CR and adherence to long-term exercise training in CAD patients.

Qualitative research methods are utilised to develop a better understanding of complex, subjective processes by enabling key knowledge holders to share their personal experiences and perceptions (Hennink et al., 2020). Systematic reviews of qualitative studies conducted by Clark et al. (2012) and Campkin et al. (2017) concluded that social support (*i.e.*, offering advice and exercising with the patient) from significant others (*i.e.,* spouses, family members, or personal friends) was an integral factor for promoting participation in CR and adherence to long-term exercise training in CAD patients, with recent qualitative studies corroborating this finding (Rouleau et al., 2018; Sweet et al., 2019; Hanna et al., 2020). Indeed, the role of the significant other during the rehabilitation process has received increasing attention; significant others are inherently positioned to be affected by the patients' disease (*i.e.,* emotional distress) (Son et al., 2013); CAD patients and their spouses often share similar dietary intakes, physical activity levels, and CVD risk factors (Macken et al., 2000; Yates et al., 2015); CAD patients have reported that the quality of their recovery was dependent on the level of social support received from family and friends (Pryor et al., 2014); and frequent contact with friends and relatives has been associated with greater medication adherence (Mondesir et al., 2018). Thus, the dyad may influence each other when coping with CAD.

Whilst patient enrollment in CR and participation in long-term exercise training may be influenced by significant others (Clark et al., 2012; Campkin et al., 2017), the studies in this area have primarily focused on the perspective of the patient (Rouleau et al., 2018; Sweet al., 2019; Hanna et al., 2020). Therefore, the aim of this study was to

investigate the factors influencing participation in CR programmes and long-term exercise training from the perspectives of both CAD patients and their significant others. This novel qualitative knowledge may generate a deeper understanding of barriers and facilitators to CR enrollment and long-term exercise training, which may guide the development of interventions to promote CAD patient participation.

6.2 Methods

The reporting of data in this study adhered to the standards for reporting qualitative research (O'Brien et al., 2014). Ethical approval was obtained from ORECNI (reference number: 18/NI/0213). All participants included in the study provided informed consent. Anonymity and confidentiality were ensured by removing identifying information from transcripts and limiting access to participant data to the research team. This study was registered on ClinicalTrials.gov (identifier: NCT03907293).

6.2.1 Description of CR Programme

Table 6.1 provides a description of the structure of the phase-III and phase-IV CR programmes that were delivered. All CR centres complied with national service guidelines (British Association for Cardiovascular Prevention and Rehabilitation, 2017).

Table 6.1 Standard structure of CR in the UK (Bethell et al., 2009)

Phase	Description
I	Prescription of secondary prevention medication and invitation to participate in phase-III CR.
II	Period of recovery at home prior to the initiation of phase-III CR; education regarding healthy living and encouragement to increase physical activity levels are also provided.
III	A comprehensive CR programme is delivered by a multidisciplinary team to supervised groups in outpatient hospital clinics or community centres. A course of supervised, graduated exercise training is the centrepiece, which often comprises 20 – 60 minutes of moderate-intensity circuit training. The supervised exercise component is also supplemented by optimal pharmacological therapy, psychological support, and lifestyle advice. The programmes typically involve weekly attendance at group sessions for approximately 8-weeks. Prior to being discharged from the programme, strategies for long-term compliance with exercise and healthy lifestyle adjustments would be discussed, and patients would be offered an opportunity to enter a phase-IV CR programme.
IV	Phase-IV constitutes the lifelong maintenance of positive lifestyle habits (*i.e.,* long-term exercise training). To assist with this, phase-IV CR programmes are facilitated by qualified exercise instructors at fitness centres and gyms in the private sector. This programme is typically 12-weeks in duration, and serves as a continuation of supervised exercise training for patients in a community setting. Patients usually attend one supervised group-based exercise session per week, with the form of exercise being similar to phase-III CR. Upon completion, patients are informed of appropriate exercise-maintenance schemes that are available within their local communities.

CR, cardiac rehabilitation

6.2.2 Participants and Recruitment

This study involved post-AMI patients referred to phase-III CR programmes at the BHSCT or SEHSCT in NI. The centres that facilitated the phase-III CR programmes were certified for achieving national CR delivery standards (British Heart Foundation, 2019a). Following the completion of phase-III CR, patients were routinely offered an opportunity to participate in phase-IV CR programmes held at local fitness centres and gyms. A convenience sampling method was utilised for recruitment of participants to this study. The selection strategy is presented in Table 6.2. Post-AMI patients recruited to a pilot prospective cohort study being conducted by the research team (not yet published) were invited to take part in an interview. Patients who enrolled in CR were invited to participate in this qualitative study following programme completion, whilst the patients who refused CR were invited during their participation in the quantitative study. Interested patients received a verbal explanation of the study protocol and were supplied with PIS. Each interested patient was asked to invite a significant other (*i.e.,* a family member, spouse, or close friend) who was primarily involved throughout the rehabilitation period to participate in this study. The PIS informed the individuals to consider their willingness to participate for a "cooling-off" period of at least 1-week before independently contacting the researcher (GT). The "cooling-off" period allowed the individuals to evaluate potential questions or uncertainties related to participation and provided the individuals with time to consider their willingness to participate to circumvent a possible coerced decision from being made. Upon contact, any questions were answered and if the potential participant was happy to continue, a suitable time and venue for the interview to take place was arranged, such as: the participant's home or a clinical site. Informed consent was received from the individuals before the interviews were performed. Recruitment terminated when the research team believed that data saturation had been achieved, whereby the collection of additional data did not necessarily add to the overall story (Corbin & Strauss, 2014). Ten participants per group (patient and significant other) were recruited, which provided sufficient data for answering the research question as the identified themes were common across and within both patient and significant other data sets. This sample size was in line with recommendations by Braun and Clarke (2013) for a study of this type and scope.

Table 6.2 Selection strategy

Patient	Significant other
Declined or agreed to participate in a phase-III CR programme or phase-IV CR programme.	Nominated by the patient and willing to participate.
Sufficient English language skills to understand and participate in an interview discussion.	Impacted or involved throughout the rehabilitation period.
Over 18 years of age.	Sufficient English language skills to understand and participate in an interview discussion.
Identified significant other provides informed consent to participate in the study.	Over 18 years of age.
	Patient provides informed consent to participate in the study.

CR, cardiac rehabilitation

6.2.3 Data Collection

6.2.3.1 Sample Characteristics

Sample characteristics were recorded to set the evidence in context. Information regarding CR participation and clinical characteristics (*i.e.,* form of AMI suffered and intervention received) of patients were obtained from the data recorded during the quantitative study. Prior to a semi-structured interview, gender, age, race, and relation of each participant were recorded.

6.2.3.2 Semi-Structured Interviews

The researcher (GT) facilitated individual semi-structured interviews with patients and their significant others in a private room at a time and location that was suitable for them. Following the completion of 10 (5 dyads) semi-structured in-person interviews, the COVID-19 pandemic resulted in the remainder of data collection comprising semi-structured telephone interviews (10 interviews, 5 dyads). Semi-structured interviews were chosen over other methods of qualitative data collection (*i.e.,* focus groups) to facilitate a comprehensive exploration of an individual's personal perspective, attitude, and feelings towards the phenomena being investigated (Taylor et al., 2015). Patients and significant others were interviewed separately to prevent the data that were captured from being influenced by the presence of the other participant, and to offer a private space to discuss potentially sensitive topics (Taylor & De Vocht, 2011). A semi-structured interview guide shaped by relevant literature was developed (Sweet et al., 2019; Rouleau et al., 2018), which contained open-ended questions that reflected the objectives of the study (see Appendix Q, Supplemental Online Material 1, Tables 1 and 2).

The semi-structured interview guide aimed to explore the factors that influence participation in CR and long-term exercise by stimulating discussions related to the impact of an AMI, knowledge of exercise, influence of significant others, CR experience, and health management. In addition, participants were asked to define and discuss the purpose of phase-III and phase-IV CR to investigate if level of understanding influenced participation. Whilst a semi-structured interview guide was used, there was flexibility for the participants to speak freely around the matters raised. Probes were solely utilised to

elicit additional information when required (Fylan, 2005). To avoid leading or influencing a participant during a semi-structured interview, the researcher (GT) sustained a neutral demeanor by withholding personal beliefs or attitudes that may affect the participant's responses, suspending judgement, and controlling non-verbal behaviour (Darawsheh & Stanley, 2014). As the semi-structured interviews progressed, the interview guide was iteratively developed by reframing the questions / probes as necessary in accordance with the matters discussed by the participants, which ensured an opportunity to explore the phenomenon in greater depth. All semi-structured interviews were audio recorded, then transcribed verbatim by the researcher (GT), and verified by the participants. Pseudonyms were assigned to participants to safeguard anonymity. Two periods (..) in a quote from a participant represent a pause in speech.

6.2.4 Data Analysis

Given the paucity of literature, this qualitative study employed an exploratory approach to generate a rich understanding of the investigated phenomena by examining the views and opinions of the participants. Reflexive thematic analysis was utilised to methodically identify, organise, and report patterns (themes) within the dataset. This method was selected due to its theoretical flexibility in conjunction with well established guidelines for conducting the analysis (Braun et al., 2019). In line with the exploratory nature of the study, an inductive orientation to identifying themes was implemented, which enabled the analysis to be freely guided by the data without trying to import ideas, concepts, or theories (Braun & Clarke, 2006).

Whilst an inductive approach was utilised, the data analysis was inevitably shaped by the subjectivities and theoretical lenses of the researchers involved (GT, CH, and IW). Thus, researchers should make their respective positions explicit when presenting qualitative research to contextualise the data collection and analysis processes (McNair et al., 2008). A critical realist epistemological approach was adopted, whereby the impossibility of understanding objects except under particular descriptions is acknowledged (Bhaskar, 1978). This epistemological approach enabled the generation of rich descriptions of individual experience in a relatively under-researched field. For transparency, the research team were not involved with delivering CR or care to patients and had no prior experience in this area of CR research. However, GT was familiar with

the participants and the CR programmes that they attended, was acquainted with the nurses who delivered the CR programmes, and possessed an academic understanding of the role of exercise in the secondary prevention of CAD. Therefore, GT's position was that he approved of CAD patient participation in CR and exercise training. Moreover, GT was familiar with barriers and facilitators to CR and long-term exercise in CAD patients by virtue of reviewing the available literature in this field.

Data analysis of the interview transcripts was facilitated by NVivo software (QSR International Pty Ltd. Version 12). An iterative approach was employed, whereby data analysis was performed after each interview. The data-driven inductive thematic analysis was performed by two members of the research team (GT and CH) and followed the recommendations of Braun and Clarke (2019). Initially, both researchers (GT and CH) became familiar with the data by independently reading the transcripts multiple times. Subsequently, the researchers (GT and CH) independently assigned codes to blocks of text that represented a coherent thought or idea (data extract). Coding was performed at both semantic and latent levels to facilitate an in-depth analysis of the data. All identified codes were agreed by consensus during a research team meeting. Themes that represented meaningful patterns were then generated by combining codes and further checking them against the data set and other themes, initially by individual researchers (GT and CH), and then agreed by consensus with another member of the research team who had also read the transcripts (IW). Several of the initial codes became sub-themes of overarching themes. Both researchers (GT and CH) collectively reviewed and checked the full set of potential themes against the data set to determine if important ideas were missing. Moreover, the themes were defined and named to ensure that the meaningful data was clearly and comprehensively captured, with all decisions being agreed by consensus between the research team (GT, CH, and IW).

Qualitative findings are generated at the intersection between the data and a researcher's subjective interpretation (Parahoo, 2014). Thus, in order to ensure rigour, the research team attempted to confirm the credibility of their interpretation of the participants' responses by seeking validation of the data by the interviewees (Parahoo, 2014). The participants were sent descriptive summaries of the qualitative analysis and asked to contact the research team if they disagreed with any of the findings. In addition, the research team invited the participants to a virtual group meeting following the initial

analysis to discuss the themes/ sub-themes and seek agreement of content. The purpose of these respondent validation exercises was to check if the qualitative findings accurately and credibly reflected the thoughts, feelings, and experiences of the participants.

6.2.4.1 Reflexivity

Reflexivity relates to the assessment of the influence of the researcher's preconceptions, assumptions, and experiences on the phenomena being investigated (Jootun et al., 2009). Various measures were implemented to ensure rigour by mitigating the influence of preconceptions on data collection and analysis. Firstly, the interview guide comprised broad, open-ended questions to allow the participants to speak freely around the topics raised. It was then iteratively developed, which allowed the questions to be reframed in accordance with the matters discussed by the participants. GT made every effort not to lead participants during interviews, and the transcripts were also checked with this in mind. Finally, throughout data collection and analysis, GT and CH actively searched for negative cases or statements that were different to their preconceptions (*i.e.,* benefits of CR), and met to discuss the content of the interviews, consider the topics raised by the participants, and agree on the main findings by consensus with another member of the research team (IW).

6.3 Results

In total, 10 patients and 10 significant others were interviewed. The characteristics of the participants are presented in Table 6.3. Interview duration ranged from 28-81 minutes (median, 49.5 minutes).

Table 6.3 Participant characteristics

N (%) or Median (range)				
	CAD patients (*n* = 10)		Significant others (*n* = 10)	
Age (years)	64 (37-77)		56 (29-87)	
Gender (% male)	80		40	
Race (% white)	100		100	
Form of AMI suffered	STEMI	4	N/A	
	NSTEMI	6		
Reperfusion therapy	PCI	10	N/A	
	CABG	0		
CR participation	DNA	0	N/A	
	Phase-III	10		
	Phase-IV	10		
Relation to patient	N/A		Mother	1
			Wife	4
			Unmarried partner	1
			Brother	2
			Son	2

CAD, coronary artery disease; *n,* number; %, percentage; N/A, not applicable; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CR, cardiac rehabilitation; and DNA, did not attend.

6.3.1 Qualitative Findings

The overarching theme from the data was a perceived need to improve health, with the participants viewing health benefits as the principal motive for participating in CR and long-term exercise training: "Improving my health was the most important reason for deciding to take part in the cardiac rehabilitation programmes and exercise" (Samuel, STEMI patient, 72 years old). Three further themes were identified: motivation, extrinsic influences, and CR experience (see Table 6.4). These themes captured the underlying elements of the participants' decision to take part in CR and long-term exercise training for the purpose of health improvements. All themes were similar across patients and significant others.

Table 6.4 Themes and sub-themes associated with participation in CR and long-term exercise training

Overarching theme	
A need to improve health	
Themes	**Sub-themes**
Motivation	Emotional response to AMI
	Contact with specialist staff
	Education
	Social opportunities
Extrinsic influences	Weather conditions
	Trusting the referral from a healthcare professional
	Significant others' understanding of the "supporter" role post-AMI
CR experience	Comprehension of the health benefits of exercise post-AMI
	Self-belief

AMI, acute myocardial infarction; CR, cardiac rehabilitation; and CAD, coronary artery disease.

6.3.1.1 Motivation

The experience of an AMI encouraged participants to improve their health by partaking in CR and long-term exercise. Several sub-themes that represent motivating factors were identified.

6.3.1.1.1 Emotional Response to AMI

Patients frequently stated that their AMI was a traumatic event: "Oh gosh it was frightening [AMI], the crushing chest pain, up the neck, and in my jaw. The minute that happened I was frightened, I realised that I could not put this down to anything else.. this is something serious" (Anna, NSTEMI patient, 57 years old). The traumatic experience of the AMI resulted in the patients becoming worried about the condition of their health: "The period of time after a heart attack can be emotionally overwhelming because you are concerned about your health" (Derrick, NSTEMI patient, 70 years old). This acknowledgement was often a driving force behind the patients' decisions to participate in the CR programmes and long-term exercise training, which served as an attempt to prevent a recurrent AMI and the consequential psychological distress: "I wanted to do whatever I could to avoid the distress of another heart attack, so I decided to take part in the cardiac rehabilitation programmes and exercise as much as possible to improve my health" (Frank, STEMI patient, 65 years old).

The psychological ramifications of the cardiovascular complication were not limited to the patients. Many significant others described the patients' AMI as an emotionally distressing incident due to concern about the health of the patients. This experience often encouraged the significant others to overcome feelings of anxiety and worry as they were determined to provide the patients with the support that was needed to improve their health: "I was shaken-up and worried about Robert's health after his heart attack, but a stronger side of me came out. I realised that I had to be strong in order to help Robert get better" (Lisa, significant other (unmarried partner), 50 years old). Beyond being concerned about the patients, the AMI also drew the attention of the significant others towards their own health. The cardiovascular complication that was suffered by the patients served as a "wake-up" call for many of the significant others by

emphasising the relationship between exercise and health: "When something like a heart attack happens, you realise the importance of exercising regularly in order to maintain your health" (Kathryn, significant other (wife), 51 years old). This realisation motivated significant others to exercise in an attempt to circumvent future cardiovascular complications: "Thinking about Paul's heart attack encourages me to exercise for health reasons as I don't want to suffer one [AMI]" (Noah, significant other (brother), 60 years old).

6.3.1.1.2 Contact with Specialist Staff

The acquisition of care from specialist CR nurses encouraged patients to participate in phase-III CR: "A reason why I decided to take part was in order to receive help and guidance from specialist nurses who knew what to do for me" (Robert, STEMI patient, 52 years old). This contact served as a method for patients to receive confirmation that they were recovering adequately from their AMI: "I thought about the opportunity to have my health monitored by the nurses to make sure that I was recovering properly. I thought that this service would provide me with reassurance that I was okay" (Brian, NSTEMI patient, 37 years old). Across the specialist services provided, receiving supervision from a knowledgeable professional during a structured exercise programme was a key attraction to phase-III and phase-IV CR. Patients anticipated that this service would accommodate a safe environment for becoming familiar with a beneficial exercise modality for their condition: "The structured design of the exercise sessions was also a reason as I knew that the form of exercise would be beneficial for my health, and it would also allow me to become familiar with what form of exercise has to be done in order for my health to improve" (Robert, STEMI patient, 52 years old). Significant others shared this opinion, with supervision by specialist staff being deemed a principal component of the CR programmes as it ensured the safety and guidance of patients during the exercise sessions: "I think that the supervised element of the programme was very important as it made sure that patients were exercising safely and taught them about what type of exercise was suitable for improving their [patients] health" (Noah, significant other (brother), 60 years old).

6.3.1.1.3 Education

Patients highlighted a requirement to receive information regarding their condition post-AMI. The educational component of the phase-III CR programme was viewed as a method of achieving this guidance: "I also decided to go to the phase-III cardiac rehabilitation programme because of the educational sessions. I knew that I would receive the information needed to improve my lifestyle during these talks" (Brian, NSTEMI patient, 37 years old). Additionally, significant others acknowledged that patients decided to participate in phase-IV CR in order to receive additional support with exercise: "Derrick was uncertain about exercising on his own after the phase-III [CR] programme. Derrick saw the phase-IV [CR] programme as a method of getting more support with knowing how to exercise after phase-III [CR]" (June, significant other (wife), 70 years old).

6.3.1.1.4 Social Opportunities

Patients frequently mentioned that social elements influenced their decision to participate in phase-III and phase-IV CR. There was a sense that the CR programmes would foster a social environment that promotes camaraderie, which in turn, would motivate patients to exercise and they could also experience emotional relief through confiding in their peers: "The social elements of the cardiac rehabilitation programmes encouraged me to take part as I would be able to speak to patients in a similar position to me each week about medical conditions and well-being. I also thought that the group-based environment would be inspiring as I would see other patients exercising to improve their health" (Thomas, NSTEMI patient, 52 years old). On a similar note, patients and significant others stated that group-based exercise classes would assist with long-term exercise adherence through enhanced enjoyment and a feeling of accountability: "I undoubtedly prefer a group-based environment for exercise. The social aspect of this allows me to enjoy the exercise, and the peer-pressure or accountability factor definitely helps.. social benefits and enjoyment are my primary reasons for taking part in long-term exercise.. the health benefits are a plus" (William, NSTEMI patient, 77 years old) and "I think that exercising in a group-based environment would have social benefits, as you could develop friendships with other active people who motivate you to continue exercising" (Kathryn, significant other (wife), 51 years old).

6.3.1.2 Extrinsic Influences

Factors that influenced the decision to engage in CR and long-term exercise extended beyond the participants' intrinsic perception to a broader, extrinsic context. Three sub-themes related to extrinsic influences were recognised.

6.3.1.2.1 Weather Conditions

For the majority of participants, the weather conditions determined the suitability of exercising outdoors: "I enjoy walking outside, that form of exercise makes me feel better as I like to experience the fresh air and sights, so if the weather is poor, then that might stop me from going out for a walk" (Carol, NSTEMI patient, 63 years old) and "I also believe that Anna will do more walking whenever the weather improves" (Eleanor, significant other (mother), 87 years old).

6.3.1.2.2 Trusting the Referral from a Healthcare Professional

With a desire for their health to improve post-AMI, both the patients and their significant others valued and trusted the guidance from healthcare professionals. Indeed, receiving a positive recommendation to participate from a healthcare professional during the referral process was often considered an indisputable reason to enroll in phase-III CR: "When I was in hospital the cardiac nurse discussed and invited me to the phase-III [CR] programme. My consultant also encouraged me to attend the [phase-III CR] programme. I valued this advice that was given by medical professionals as they would only do so for justified reasons, with your health and recovery being prioritised. Why would you not listen? It is like being given the winning lottery numbers and deciding not to take them" (Thomas, NSTEMI patient, 52 years old). This attitude extended to the acquisition of a referral to phase-IV CR, with patients feeling compelled to participate by virtue of the CR nurses' suggestion: "A nurse even told me about the phase-IV [CR] programme before I started phase-III [CR], so I had my decision to attend phase-IV [CR] made at the beginning of the phase-III [CR] programme.. I thought, I will definitely be going to that" (Anna, NSTEMI patient, 57 years old).

All patients mentioned that they had received a description of the elements of the CR programmes during the referral process. Although, a few patients suggested that receiving more information regarding the positive effect of CR on health may enhance uptake, with insights into the experiences of CR graduates supplementing this knowledge: "I think patients would be more likely to take part [in CR programmes] if they understood how the cardiac rehabilitation programmes would improve their health. I believe that having someone explain their experience of the programmes and how the programmes affected their health would encourage patients to take part as they would be inspired to make the same recovery" (Derrick, NSTEMI patient, 70 years old).

6.3.1.2.3 Significant Others' Understanding of the "Supporter" Role Post-AMI

Significant others cared deeply about the wellbeing of the patients, with a commitment to safeguarding the health of patients through a fear of losing them. Importantly, patients consistently discussed the importance of social support from significant others, with numerous patients claiming that it constituted a primary reason for their recovery: "Ian was determined to help me recover after my heart attack. He called at my house to speak to me about any concerns that I had and offered to help with anything that had to be done around the house. I really appreciated this support. I don't think I would have recovered without it" (Carol, NSTEMI patient, 63 years old). However, patients commonly stated that they independently decided to participate in phase-III and phase-IV CR as their significant others possessed a poor understanding of the purpose and structure of the programmes: "I decided to take part in the cardiac rehabilitation programmes by myself as Violet didn't receive any information about them, so she wouldn't have been able to help with my decision because she didn't know anything about the programmes" (Frank, STEMI patient, 65 years old). Nevertheless, it was generally believed that the provision of information regarding the CR programmes to significant others would empower them with the knowledge to support patients with their decision to participate: "I think significant others could help patients to take part in cardiac rehabilitation programmes if they [significant others] had a better understanding of what is being offered. This would allow them [significant others] to advise or encourage patients to take part" (Thomas, NSTEMI patient, 52 years old). Significant others also reported a lack of knowledge regarding the role of exercise post-AMI, which resulted in them offering a "wrapping in cotton wool" form of protection by attempting to discourage the patients from being

active due to concerns about exercise-induced cardiovascular complications. In turn, patients relayed the lifestyle education they received at the phase-III CR programme to significant others. The realisation that exercise induced health benefits post-AMI frequently encouraged significant others to support the patients with remaining active: "At the beginning, I thought that exercise was bad for Brian's heart. I was afraid that he would exert himself too much, so I told him to slow down and to stop being active. Brian then told me that exercise was beneficial for his health after a heart attack, which was the information that he received at the phase-III cardiac rehabilitation programme. I then changed my attitude about Brian being active and tried to support him with taking part in exercise by offering to do it with him" (Michael, significant other (brother), 37 years old).

6.3.1.3 CR Experience

The decision to partake in long-term exercise was an evolving process, influenced by ongoing experience and observation during CR participation. Two sub-themes related to CR experience were identified: comprehension of the health benefits of exercise post-AMI, and self-belief.

6.3.1.3.1 Comprehension of the Health Benefits of Exercise Post-AMI

Following the completion of phase-III and phase-IV CR, patients had developed an appreciation for the capacity of exercise to enhance their health, with many patients now accepting exercise as an essential component of their lifestyle. The lifestyle education received at phase-III CR enabled both patients and their significant others to develop an understanding of the cardioprotective effect of exercise post-AMI. This knowledge served as motivation for long-term exercise adherence in order to circumvent recurrent cardiovascular complications: "It [phase-III CR] changed my attitude about exercise. I didn't think about the health benefits of exercise before my heart attack. The educational talks taught me about how important exercise is for maintaining good health and stopping another heart attack. I am now determined to exercise regularly to improve my health and stop another heart attack.. I believe that it [exercise] is something that I have to do for my health. I think about exercise in the same way as my medication, it [exercise] has to be done each day to stay healthy" (Paul, STEMI patient, 64 years old). In addition to the comprehension of the role of exercise post-AMI, the physical perception of health

improvements promoted adherence to exercise: "I think that Robert's experience of his health improving because of exercising after a heart attack has provided him with motivation to participate in long-term exercise training" (Lisa, significant other (unmarried partner), 50 years old).

6.3.1.3.2 Self-Belief

The CR period exerted an upward spiralling effect on the self-belief of patients in their ability to exercise. By trusting the referral from the healthcare professional, patients engaged in the CR programmes for the purpose of improving their health. These programmes enabled patients to assimilate knowledge about how to exercise effectively post-AMI, with physical perceptions of improvements in health serving as tangible verification of the benefits of doing so. These experiences positively reinforced the belief of patients in their capacity to exercise, with confidence in this ability being gradually developed over the course of the phase-III and phase-IV CR programmes. With this newly found confidence, patients believed that were capable of adhering to long-term exercise training, and pushed back when significant others suggested for them to rest or "slow down". Saliently, this behaviour was indicative of "higher-order" learning (Anderson & Bloom, 2001), with the patients applying their knowledge of the role of exercise post-AMI through committing to long-term participation and sharing this understanding with their significant others: "Thomas could see the improvements in his health and wellbeing, the guidance and exercise during the cardiac rehabilitation programmes lifted him from a state of feeling vulnerable to a state of positivity and confidence. Thomas now believes that he is capable of exercising in a way that will improve his health over the long-term" (Kathryn, significant other (wife), 51 years old). Moreover, patients and significant others also claimed that performing an exercise modality that was enjoyable would enhance self-belief, which would serve as an incentive for long-term adherence: "I think that the most important factor is your attitude, you must have an interest and enjoy exercise to commit to it over the long-term. Finding forms of exercise that you enjoy and feel comfortable doing can help with this" (Robert, STEMI patient, 52 years old).

6.4 Discussion

The overarching theme was a need to improve health. Following the patients' AMI, both members of each dyad recognised the importance of improving their health for the purpose of circumventing future cardiovascular complications, with health benefits serving as the primary reason for participating in CR and long-term exercise. Aspects related to motivation, extrinsic influences, and CR experience underpinned these decisions. Interestingly, we identified a link between the factors identified in this study and each element of the Theoretical Domains Framework (TDF). The TDF is a comprehensive, integrative framework of behavior change theories (Cane et al., 2012), which has been shown to effectively determine theoretical constructs for exercise maintenance (Amireault et al., 2013). Saliently, as both patients and their significant others reported factors related to the TDF, the findings of this study underscore the relevance of these theoretical domains for CR participation and long-term exercise adherence.

The emotional response to an AMI by patients and their significant others appeared to serve as a principal motivating factor for engaging in CR and exercise adherence to obtain an improvement in health. This finding relates to the *emotion* domain of the TDF, whereby an individual attempts to manage a personally significant event through a complex reaction pattern comprising experiential, behavioural, and physiological elements (Cane et al., 2012). Importantly, the literature suggests that cardiac events are a psychologically distressing experience, which may be perceived as an existential threat that results in the transformation of the patients' priorities and perspectives in life (Simonÿ et al., 2015). Indeed, Holder et al. (2015) showed that an increased awareness of mortality following a cardiac event encouraged CAD patients to implement healthy lifestyle changes. However, to the best of our knowledge, this is the first qualitative study to clearly report that this impact extends to the significant others, with the emotional distress also triggering a determination to support the CAD patients with their recovery. These findings emphasise the important role of significant others during the post-AMI period. Although, there is also literature to suggest that the emotional response by CAD patients to a cardiac event may serve as a barrier to participation in CR, with some individuals choosing to live in the present, thereby disregarding their health in the future and the personal relevance of CR or exercise by extension (Bäck et al., 2017). Thus, this inconsistent influence of emotional distress on CR participation and exercise following a cardiovascular complication warrants additional investigation, with the

perspectives of significant others also being further explored. Nonetheless, healthcare professionals may promote participation in CR by advising CAD patients to derive motivation to improve their health from the emotional response to a cardiac complication.

Motivation to improve health was not limited to inherent emotional responses to an AMI. The patients considered the potential benefits of CR for their health when deciding to enroll, which comprised receiving care from specialist staff, education regarding their condition, support with exercise in a safe environment, and social opportunities that would foster inspiration and peer-support. These anticipated benefits served as external sources of motivation to participate in CR, and represented multiple domains of the TDF, such as: *memory, attention, and decision processes*; *social / professional role and identity; intentions; and social influences* (Cane et al., 2012). In addition, it is worth acknowledging that "anticipated benefits" are consistent with established theories of health behaviour change, which assert that favourable attitudes about a certain behaviour (Theory of Planned Behaviour) (Ajzen, 1991) or expectations for positive outcomes (Health Action Process Approach) (Schwarzer et al., 2011) promote the execution of a target behaviour.

Importantly, there is evidence to suggest that the quality of the referral process and the patients' interpretation of the strength of the recommendation may be variable (Rouleau et al., 2018). In this study, the patients suggested that receiving more information about the health benefits of CR during the referral process may improve uptake, with insights into the experiences of CR graduates supplementing the strength of the recommendation. As such, to promote participation in CR, healthcare professionals should raise awareness of health literacy during the referral process by discussing the health benefits of CR and harnessing social influences by including CR graduates (*i.e.,* testimonies or peer-to-peer discussions). To assist with this practice, research departments at hospital sites or local universities should offer educational sessions on the current scientific evidence regarding the cardioprotective effects of CR and long-term exercise to CR facilitators, which may empower these healthcare professionals with the knowledge required to optimally discuss the associated health benefits with patients during the CR referral process.

The importance of social support post-AMI was frequently discussed by the respondents, with patients attributing elements of practical (*i.e.,* physical assistance with daily tasks), informational (*i.e.,* reminders about medication), and emotional (*i.e.,* confiding in each other about concerns or worries) support from significant others as primary reasons for their recovery. Whilst previous research has identified social support from spouses and family members as a factor that influences participation in CR and exercise maintenance (Campkin et al., 2017; Clark et al., 2012), the findings of this study indicate that significant others receive insufficient information regarding the purpose of CR and long-term exercise. This deficiency in information rendered some significant others incapable of assisting the patients with their decision to participate in phase-III and phase-IV CR. Moreover, a deep concern about the wellbeing of patients coupled with a poor comprehension of the health benefits of exercise post-AMI often resulted in the significant others attempting to discourage the patients from being active due to concerns about exercise-induced cardiovascular complications. Saliently, this perspective was revised after the patients supplied information regarding the lifestyle education received at phase-III CR, with significant others developing a supportive attitude towards long-term exercise post-AMI (*i.e.,* offering to exercise with the patient). Indeed, previous research has demonstrated a poor supply of information to significant others/ caregivers of CAD patients (Jackson et al., 2011), stroke survivors (Pindus et al., 2018), and cancer patients (McCarthy, 2011). Importantly, in the UK, the standards and core components for CR published by the British Association for Cardiovascular Prevention and Rehabilitation recommend for significant others to be invited to participate in CR activities (*i.e.,* educational sessions) whenever possible, and for patients and their significant others to play an active role in the educative process (British Association for Cardiovascular Prevention and Rehabilitation, 2017). As such, the information deficiency for significant others may be attributed to a practice that is based on the individualised view of the patient, irrespective of the context and influence of significant others (Gannik, 2002). Moreover, the delivery of CR services is a complex process (Fernandez et al., 2011). Therefore, time constraints and/ or existing workloads for CR staff may also impede the provision of information to significant others, with evidence to suggest that communication between healthcare professionals, cardiac patients, and significant others is problematic (*i.e.,* lack of empathy, lack of respect, use of medical terminology, giving ambiguous messages, and misunderstanding) during patient education (Farahani et al., 2011). Nonetheless, there is a paucity of research regarding the challenges or barriers that

are faced by healthcare professionals when supplying significant others with information related to CR and long-term exercise. Future research in this area may identify methods of assisting healthcare professionals with the provision of information regarding the health benefits and purpose of CR and long-term exercise to significant others. Altogether, investigations of CR participation and long-term exercise adherence should select a theory that captures dimensions of *social influence* (*i.e.,* TDF (Cane et al., 2012)). Practically, healthcare professionals should attempt to include significant others in the referral process for CR. This approach may prevent the influential role of significant others post-AMI from being overlooked or neglected by ensuring they are empowered with the knowledge (*i.e.,* health benefits of exercise) required to promote patient participation in CR and long-term exercise.

In line with previous research (Sweet et al., 2019; Martin & Woods, 2012; Thow et al., 2008), establishing a link between exercise and health benefits post-AMI encourages long-term exercise participation, which relates to the *beliefs about consequences* and *reinforcement* domains of the TDF (Cane et al., 2012). However, the current study adds depth to the literature by delineating how the experiences of phase-III and phase-IV CR participation influence the development of this association. The respondents reported that participation in these CR programmes conferred knowledge and a physical perception of the health benefits of exercise post-AMI. Collectively, these experiences enabled patients to become confident in their ability to exercise effectively, which motivated them to embrace long-term exercise for the purpose of health benefits. These findings represent multiple domains of the TDF, such as: *belief about capabilities*, *skills*, *knowledge*, *optimism, goals, and behavioural regulation* (Cane et al., 2012). Thus, CR facilitators should ensure that patients develop these key behavioural skills (*i.e.,* providing assistance with establishing exercise goals or an association between exercise and health benefits for ill-health avoidance), which may promote long-term exercise participation. However, there is a paucity of research regarding the level of understanding (*i.e.,* comprehension of suitable exercise modalities, session frequency, session duration, and exercise intensity) required for long-term exercise participation in CAD patients. The elucidation of this topic may identify methods of enhancing CR delivery to ensure patients are equipped with the necessary knowledge for long-term exercise adherence.

The affective experiences that individuals associate with exercise are key determinants of participation (Ekkekakis & Petruzzello, 1999) and adherence (Williams, 2008). Indeed, the respondents reported that positive emotions (*i.e.,* improved mood) encouraged them to exercise, with appealing exercise modalities fostering adherence through enhanced enjoyment. This observation regarding the influence of emotions on long-term exercise participation is consistent with previous literature (Campkin et al., 2017; Sweet et al., 2019). As such, CR facilitators should encourage patients to acknowledge their positive experiences during exercise and assist with the identification of an enjoyable exercise modality. By doing so, patients may associate positive affective experiences with exercise, which may be conducive to long-term adherence.

6.4.1 Strengths and Limitations

Rigour of the study was enhanced by three members of the research team (GT, CH, and IW) agreeing on all decisions pertaining to data analysis by consensus, which contributed to the generation of meaningful patterns with greater explanatory power through the consideration of multiple individual perspectives. Sufficient data were obtained for answering the research question as the identified themes were common across and within both patient and significant other data sets. Good practice was adhered to through the research team iteratively developing the interview guide as the semi-structured interviews progressed, and offering the participants an opportunity to comment on the findings through the provision of descriptive summaries and an invitation to a virtual group meeting. In terms of conducting the semi-structured interviews, the patients and significant others were interviewed separately to prevent coercion or the presence of an individual influencing the response of the other person. Additionally, the significant others were not limited to intimate partners, which allowed other relationships to be acknowledged (*i.e.,* mother-daughter or brother-brother dyads). However, several limitations should be considered when interpreting the results. Firstly, the majority of participants did not confirm receipt of the descriptive summaries and invitation to the virtual group meeting, with no individuals agreeing to partake in the latter. Technological requirements and/ or conditions related to the COVID-19 pandemic may have deterred participation in the beforementioned member checking activities. Nevertheless, participant verification of the findings following the analysis was not achieved. Secondly, the participants were a convenience-based sample from two Health and Social Care Trusts

in NI, which may limit generalisability to other locations. However, the convenience sampling method was pragmatically chosen due to the time constraints that were imposed by the PhD research project, and in consideration of the possibility of generating rich qualitative data by virtue of the level of familiarity between the researcher and the sample population (Koerber & McMichael, 2008). Additionally, the sample comprised only English speakers and all participants were white. The inclusion of a more diverse sample in terms of language and race may have resulted in the identification of additional themes. Only two female patients agreed to participate, and all patients had participated in phase-III and phase-IV CR. Therefore, future research should consider exploring the perspectives of female patients and their significant others, and attempt to capture the opinions of patients who refused to participate in CR and/ or long-term exercise and their significant others, which may add valuable perspectives on the current topic. Given that patients who rejected CR refused to participate in this study, future research that aims to capture the opinions and experiences of this patient group should consider forms of data collection that carry a low level of participant burden (*i.e.,* questionnaires), which may encourage participation. The requirement to perform a number of interviews via telephone calls due to the COVID-19 pandemic may have partially diminished the richness of data collected (Johnson et al., 2019). Finally, the duration of the interviews increased as data collection progressed, which potentially represents a gradual improvement in the interviewing skills of the PhD researcher (GT). Thus, the richness of data collection may have been reduced in the initial interviews. In retrospect, it may have been beneficial for the PhD researcher (GT) to perform a number of practice interviews prior to data collection to circumvent this issue.

6.5 Conclusion

The qualitative findings of this study reveal how an AMI collectively impacts the attitudes and beliefs of patients and their significant others in relation to CR participation, long-term exercise, and health. Health benefits served as the primary reason for participating in CR and long-term exercise, with aspects related to motivation, extrinsic influences, and CR experience underpinning these decisions. Importantly, the factors reported by patients and significant others were consistent with the TDF, which suggests that multiple theoretical constructs are associated with participation in CR and long-term exercise. Altogether, the study of CAD patient enrollment in CR and adherence to long-term

exercise remains crucial due to the poor participation rates. Future research should seek to define and test strategies of enhancing patient participation in CR and long-term exercise that incorporate comprehensive theoretical frameworks (*i.e.,* TDF) to capture the full scope of influencing factors, with particular attention being paid to the *social influence* of significant others.

Chapter 7

Discussion and Conclusion

7.0 Discussion and Conclusion

The work presented in this thesis aimed to further scientific understanding of the role of exercise in the secondary prevention of CAD. Whilst the overarching theme was associated with physiological mechanisms, qualitative knowledge regarding the factors that influence CR participation and long-term exercise training was also sought. In Study 1, the capacity of exercise to serve as an anti-inflammatory strategy in CAD patients was examined by performing a systematic review and meta-analysis of randomised trials. The second study comprised an assessment of the feasibility of investigating the molecular mechanisms that may mediate exercise-induced anti-inflammatory physiological adaptations in CAD patients. Finally, Study 3 outlined the factors that influence CR participation and adherence to long-term exercise training by exploring the experiences and perspectives of CAD patients and their significant others. The following section summarises and discusses the overall findings of this body of work, examines the contribution to the literature, considers the strengths and limitations of the work, provides recommendations for future research, and concludes the thesis.

7.1 Discussion of Findings

7.1.1 Anti-Inflammatory Effect of Exercise

The literature suggests that CVD events frequently occur in CAD patients despite contemporary evidence-based secondary prevention therapies (*i.e.* achieving guideline-based recommended levels of LDL-C) (Baigent, 2005). As such, novel strategies may be required to adequately diminish this residual cardiovascular risk, with current efforts focusing on the identification of methods of addressing systemic inflammation (Lawler et al., 2020). Indeed, correlations between plasma or serum levels of inflammatory mediators (*i.e.* IL-6, CRP, and fibrinogen) and cardiovascular complications have been observed in CAD patients (Coppola et al., 2005; Kaptoge et al., 2010; Kälsch et al., 2020), with the results of CANTOS supporting the clinical benefits of IL-1β pharmacological inhibition (Ridker et al., 2017). Despite the beneficial effect of secondary prevention medication (*i.e.* statins) on inflammatory activity (Ridker et al., 2005), chronic low-grade inflammation (hs-CRP values $\geq$ 2 mg/L) is prevalent in post-AMI and/ or post-

revascularisation CAD patient populations without concomitant inflammatory diseases (*i.e.* inflammatory arthritis, inflammatory bowel disease, and connective tissue diseases) (Munkhaugen et al., 2018). Therefore, addressing systemic inflammation may constitute a novel therapeutic strategy for optimising secondary prevention in CAD patients (Ruparelia & Choudhury, 2020). As such, research in this field is currently exploring anti-inflammatory therapies for targeting inflammatory pathways (primarily IL-1β/ IL-6), and attempting to detect optimal inflammatory biomarkers for identifying CAD patients with residual inflammatory risk who may benefit from anti-inflammatory therapy, with hs-CRP and IL-6 showing promise (Lawler et al., 2020). Progress in this area may result in the incorporation of anti-inflammatory treatment into routine clinical practice for the secondary prevention of CAD. Nonetheless, whilst dysregulated inflammation is central to atherogenesis, the pharmacological inhibition of immune pathways may mitigate physiological protection against infection and wound healing; significantly more deaths from infection or sepsis were documented in the canakinumab group compared to placebo in CANTOS (Ridker et al., 2017). As such, attention has been directed towards identifying safe and cost-effective methods of inducing anti-inflammatory protection in CAD patients (Baylis et al., 2017; Lawler et al., 2020).

Reductions in inflammatory factors (CRP, fibrinogen, and ICAM-1) substantially contribute to the inverse association between physical activity and CAD risk (Mora et al., 2007). Moreover, there is evidence to suggest that the optimisation of lifestyle factors ($\geq$ 1.5 hours per week of physical activity, healthy diet (Mediterranean diet score > 12 points), and smoking cessation) may allow CAD patients with residual inflammatory burden to achieve an hs-CRP value < 2 mg/L (Blaum et al., 2019). Thus, the implementation of positive lifestyle changes in CAD patients may constitute a safe and cost-effective form of anti-inflammatory therapy. In particular, a meta-analysis of 23 studies performed by Swardfager et al. (2012) demonstrated that exercise reduces inflammatory activity in CAD patients, as indicated by lower post-intervention values of CRP, fibrinogen, IL-6, and VCAM-1. However, the methodological limitations of this review reduced the validity of the evidence for this effect. Thus, the published systematic review and meta-analysis in section 4.0 furthered the literature in this area by providing a robust examination of the influence of exercise on inflammation in CAD patients, which was achieved by exclusively including randomised studies to decrease the likelihood of

potential biases (*i.e.* selection bias), excluding studies that possessed confounding variables to facilitate an assessment of the independent effect of exercise, comprehensively searching for relevant literature to minimise the possibility of publication bias, assessing the overall quality of evidence using the GRADE system, and conducting quantitative and qualitative analyses to prevent the exclusion of valuable findings. These methodological characteristics enabled the aim of rigorously evaluating the capability of exercise to serve as an anti-inflammatory strategy in CAD patients to be achieved for Study 1.

The findings of Study 1 support an anti-inflammatory effect of exercise in CAD patients, as indicated by quantitative and qualitative evidence that supports a reduction in CRP, fibrinogen, and vWF post-intervention. Whilst this finding is consistent with the results of the previous review in this area (Swardfager et al., 2012), Study 1 adds to the literature by demonstrating a beneficial effect of exercise on acute-phase reactants in randomised studies. Importantly, acute-phase reactants may play a direct pathophysiological role in the development and progression of atherogenesis by promoting endothelial dysfunction (Pasceri et al., 2000), foam cell formation (Zwaka et al., 2001), pro-inflammatory cytokine production (Ballou & Lozanski, 1992), and thrombus formation (Reinhart, 2003). Indeed, acute-phase reactants (CRP, fibrinogen, and vWF) have been associated with adverse outcomes in CAD patients (Thompson et al., 1995; Ridker et al., 2002; Danesh et al., 2004; Coppola et al., 2005; Kaptoge et al., 2010), which accentuates the potential importance of the evidence generated by Study 1 that supports a positive effect of exercise on these inflammatory mediators in CAD patients. Finally, as acute-phase reactants are a marker of systemic inflammation, a decrease in these proteins may represent a reduction in chronic inflammation (Haidari et al., 2001), which potentially supports the ability of exercise to serve as an anti-inflammatory strategy in CAD patients.

Proximal mediators of inflammation (*i.e.* IL-6, TNF-α, ICAM-1, and IL-8) assume a pivotal role in orchestrating local and systemic inflammatory processes that drive atherosclerotic development (Soeki & Sata, 2016), with anti-inflammatory cytokines (*i.e.* IL-10, IL-33, and IL-35) countering atherogenesis by modulating the

inflammatory response (Lisinski & Furie, 2002; Miller, 2011). However, Study 2 concluded that current evidence surrounding the effect of exercise on pro-inflammatory cytokines, anti-inflammatory cytokines, adhesion molecules, and chemokines in CAD patients is equivocal. This observation is consistent with the results of the meta-analysis performed by Swardfager et al. (2012), which found no significant differences in post-intervention values of IL-6, TNF-α, VCAM-1, and ICAM-1 between exercise and control groups. Although, the meta-analyses of inflammatory biomarkers that documented non-significant results in Study 1 generated SMDs that represented lower post-intervention values in the exercise groups compared to controls, with small sample sizes due to a paucity of research potentially precluding statistical significance. Thus, future randomised studies should examine the effect of exercise on proximal mediators of inflammation and anti-inflammatory cytokines to fully elucidate the anti-inflammatory effect of this intervention.

Several statistically significant differences were documented in the sub-group analysis of exercise programme characteristics that was performed in Study 1. Namely, exercise programmes < 12 weeks in duration with > 3 sessions per week elicited greater reductions in vWF and IL-8 than exercise programmes comprising ≤ 3 sessions per week for ≥ 12 weeks, which suggests that exercise session frequency was more influential than exercise programme duration for inducing decreases in the beforementioned inflammatory mediators. Moreover, continuous aerobic exercise appeared to be the most effective modality for stimulating reductions in vWF and IL-8. However, an uneven covariate (a limited or unbalanced number of studies and/or participants contributing to each sub-group) distribution precluded definitive conclusions regarding optimal exercise programme characteristics for reducing inflammation in CAD patients (Richardson et al., 2018). Nonetheless, the literature suggests that the acute release of IL-6 from skeletal muscle cells in response to exercise serves as a stimulus for anti-inflammatory adaptation (Pedersen, 2017); it should be noted that when derived from skeletal muscle, IL-6 exerts a paradoxical anti-inflammatory rather than pro-inflammatory effect (Steensberg et al., 2003). Saliently, the magnitude of the acute increase in IL-6 is contingent on the intensity and duration of exercise (Ostrowski et al., 2000; Pedersen, 2017), in conjunction with the involved muscle mass (Steensberg et al., 2000; Pedersen, 2017). However, the impact of exercise programme characteristics on reductions in inflammation has been inconsistent

across different populations, with longer exercise programme durations and greater exercise session frequencies contributing to greater decreases in IL-6 in type 2 diabetes mellitus patients (Hayashino et al., 2014); exercise programme duration was not associated with CRP reductions in CAD patients (Swardfager et al., 2012); and duration, frequency and exercise modality did not influence reductions in CRP in healthy and clinical populations (Fedewa et al., 2017). Therefore, the form of exercise programme that elicits the greatest reductions in inflammation is not currently clear, with the anti-inflammatory response to exercise training potentially depending on level of cardiorespiratory fitness (Lavie et al., 2011), disease progression (Bruning & Sturek, 2015), levels of inflammatory activity (Swardfager et al., 2012), or amelioration of CVD risk factors (*i.e.* BMI or lipid profiles) (Swardfager et al., 2012; Fedewa et al., 2017; Pedersen, 2017). Nonetheless, in order for exercise to serve as an effective anti-inflammatory strategy in CAD patients, future research should seek to identify optimal exercise programme characteristics for alleviating systemic inflammation.

The reliability of the results and overall quality of evidence for the trials included in Study 1 were reduced by inadequate reporting of random sequence generation and allocation concealment, along with imprecision due to small sample sizes. Thus, the results of Study 1 should be interpreted with caution until the quality of evidence is improved by further randomised studies with high methodological qualities and large sample sizes. Nevertheless, the identification of areas for future research in Study 1 has highlighted the work that is required for the quality of evidence in this area to improve and the anti-inflammatory effect of exercise to be further elucidated, which if addressed by future studies, may result in exercise being utilised as a substitute for or an adjunct to anti-inflammatory pharmacological treatment in future clinical practice related to the secondary prevention of CAD.

7.1.2 Cardioprotective Molecular Mechanisms

The anti-inflammatory effect of exercise, as demonstrated in Study 1, may represent a primary mechanism through which the secondary prevention of CAD is conferred. However, the molecular transducers that orchestrate the anti-inflammatory adaptations of

exercise are yet to be fully elucidated. Thus, Study 2 comprised a pilot prospective cohort study that assessed the feasibility of investigating the molecular mechanisms that may mediate exercise-induced cardioprotective physiological adaptations in CAD patients.

In terms of the secondary outcome measures, the principal finding of Study 2 involved the identification of a trend that was indicative of a dose-response relationship, with most values of the assessed parameters demonstrating improvements at each TP in the phase-III & phase-IV CR group. Importantly, unfavourable changes and/ or smaller improvements were observed in the non-CR group at each TP, with the phase-III CR only group experiencing a deterioration in the physiological measurements at TP-3. Indeed, the literature indicates that the health benefits of exercise in CAD patients are dose-dependent (Curtis et al., 2010), with this assertion being supported by evidence for an inverse relationship between physical activity and cardiovascular mortality rates in CAD patients (Biscaglia et al., 2019). Moreover, a decline in exercise-induced cardioprotective physiological adaptation (*i.e.* endothelial function, lipid profile, and inflammation status) following the cessation of a training stimulus (detraining) has been documented in the literature (Vona et al., 2009; Theodorou et al., 2016). However, Study 2 identified a reduction in SIRT-1 in the phase-III CR only group at TP-3, which adds to the literature by demonstrating that the level of this protein decreases as a result of detraining. Moreover, improvements in SIRT-1 at each TP in the phase-III & phase-IV CR group were identified. Whilst previous research has documented increases in SIRT-1 following exercise programmes of a short duration (4-8 weeks) in healthy and clinical populations (Gurd et al., 2010; Cheng et al., 2015; Russomanno et al., 2017; Alavizadeh et al., 2018; Vizvari et al., 2018; Corbi et al., 2019), the findings of Study 2 offer a novel contribution to the literature by suggesting a beneficial effect of longer exercise programme durations (20 weeks) on SIRT-1. Nevertheless, whilst Study 2 identified a positive effect of 1 session per week of moderate-intensity circuit training (alternating between aerobic exercise and RT interspersed with periods of active recovery) on SIRT-1 after 8 and 20 weeks, other studies have observed increases in SIRT-1 following different exercise modalities (*i.e.* aerobic exercise, combined training (aerobic exercise and RT), muscle stretching, and interval training), intensities (moderate and high), frequencies (3-5 sessions per week), and programme durations (4-8 weeks) in healthy and clinical populations (Gurd et al., 2010; Cheng et al., 2015; Russomanno et al., 2017; Alavizadeh

et al., 2018; Vizvari et al., 2018; Corbi et al., 2019). As such, future research in this area should seek to define optimal exercise programme characteristics for augmenting SIRT-1 levels. Collectively, the beforementioned findings of Study 2 reinforce the importance of CAD patient participation in phase-III and phase-IV CR, along with long-term exercise for the purpose of improvements in health.

A number of beneficial changes in CVD risk factors/ clinical parameters were seen following exercise in Study 2. The positive effect of exercise on these parameters has been well documented in the literature (Taylor et al., 2006; Marzolini et al., 2012; Liou et al., 2016). In particular, repressed levels of SIRT-1 have been demonstrated in CAD patients (Breitenstein et al., 2013; Hu et al., 2015; Li et al., 2016; Chan et al., 2017), with low gene expression of SIRT-1 being associated with CVD risk factors, such as: obesity (Peeters et al., 2008), type II diabetes mellitus (Han et al., 2015), hypertension (Shimoyama et al., 2011), and dyslipidaemia (Shimoyama et al., 2012). The literature suggests that CVD risk factors may impair the function of nicotinamide phosphoribosyltransferase, which would lead to a reduction in SIRT-1 expression and activity secondary to decreased cellular NAD^+ content (de Kreutzenberg et al., 2010). Moreover, CVD risk factors may result in the downregulation of SIRT-1 due to an increase in inflammation and ROS production (de Kreutzenberg et al., 2010; Hu et al., 2015). However, an increase in SIRT-1 may ameliorate CVD risk factors by positively regulating many transcription factors related to key metabolic, inflammatory, and cardiovascular processes (Winnik et al., 2015). Indeed, SIRT-1 activation has been shown to improve insulin sensitivity, blood glucose levels, lipid profiles, fat mobilisation in adipocytes, and blood pressure (Picard et al., 2004; Milne et al., 2007; Libri et al., 2012). Therefore, future research should examine the relationships between SIRT-1 and CVD risk factors following an exercise programme, which may allow the molecular mechanisms that mediate exercise-induced improvements in SIRT-1 and CVD risk profiles to be elucidated.

Traditional CVD risk factors (*i.e.* dyslipidaemia, obesity, and physical inactivity) are principal pathogenic drivers of systemic inflammation (Munkhaugen et al., 2018; Blaum et al., 2019). Thus, exercise may indirectly reduce inflammation by ameliorating

CVD risk factors (Swardfager et al., 2012; Fedewa et al., 2017), with an increase in SIRT-1 potentially representing a mediating mechanism (previously discussed). Nonetheless, the literature suggests that SIRT-1 also assumes a pivotal role in the direct regulation of inflammation through the modulation of NF-κβ transcriptional activity (Yeung et al., 2004). Indeed, an inverse relationship between SIRT-1 and pro-inflammatory cytokines in CAD patients has been observed (Li et al., 2016; Babaee et al., 2020). However, there is a paucity of evidence regarding the association between SIRT-1 and IL-10 in CAD patients. Although, the literature indicates that SIRT-1 may stimulate IL-10 induction via control of peroxisome proliferator-activated receptor-gamma co-activator-1α transcriptional activity (Amat et al., 2009; Morari et al., 2010). Interestingly, ESR and IL-6 decreased after phase-III and phase-IV CR, with unfavourable changes or smaller improvements being seen in the non-CR and phase-III CR only groups from TP-1 to TP-3. Moreover, a small increase in IL-10 was observed in the phase-III & phase-IV CR group from TP-1 to TP-3, whilst a moderate decrease in the level of this parameter from TP-1 to TP-3 was observed in the non-CR group. These findings are consistent with previous research that demonstrated a beneficial effect of exercise on IL-6, IL-10, and ESR in CAD patients (Bilinska et al., 2010; Ribeiro et al., 2012). Whilst ESR constituted an indirect index of systemic inflammatory activity (Bray et al., 2016), the measurement of CRP or hs-CRP in Study 2 may have allowed a more specific assessment of the association between SIRT-1 and chronic inflammation. Moreover, the measurement of mRNA gene expression for inflammatory mediators and NF-κβ may have enabled further elucidation of the molecular pathway of interest as SIRT-1 modulates transcriptional activity. Indeed, there is evidence to suggest that exercise induces favourable changes in mRNA gene expression of inflammatory cytokines, SIRT-1, and NF-κβ activity in patients with low back pain (Cheng et al., 2015). As such, the inclusion of these measurements will be considered for the future prospective cohort study.

The literature indicates that CAD patients possess repressed levels of SIRT-1, with concomitant up-regulation of inflammatory activity and oxidative stress (Breitenstein et al., 2013; Hu et al., 2015; Li et al., 2016; Chan et al., 2017). These pathogenic states may elicit a deleterious effect on vascular function by promoting endothelial dysfunction and arterial stiffening (van Bussel et al., 2011; Weiner et al., 2014), which may contribute to recurrent cardiovascular complications in CAD patients

(Inaba et al., 2010; Maruhashi et al., 2018). Interestingly, SIRT-1 may alleviate endothelial dysfunction and arterial stiffness by activating eNOS in endothelial cells (Mattagajasingh et al., 2007); reducing inflammation by inhibiting NF-κβ activation (Yeung et al., 2004); attenuating oxidative stress by mitigating NAD(P)H oxidase activation and inducing the expression of antioxidant enzymes (SOD and catalase) (Ferrara et al., 2008; Rahman et al., 2009; Zarzuelo et al., 2013; Conti et al., 2015); and countering pathogenic arterial remodelling through the inhibition of collagen deposition, neointima formation, and endothelial senescence (Man et al., 2019). In Study 2, improvements in endothelial function (brachial FMD and brachial FMD absolute change) and arterial stiffness (SI) were seen in the phase-III & phase-IV CR group at each TP. These positive effects of exercise on endothelial function and arterial stiffness in CAD patients are consistent with the results of previous research (Pattyn et al., 2018; Zhang et al., 2018). In particular, the literature suggests that exercise may induce favourable arterial remodelling, which involves functional changes (*i.e.* endothelial function) preceding structural adaptations (*i.e.* increased arterial diameter) (Green et al., 2017). Importantly, there is a paucity of research regarding the time-course of exercise induced changes in arterial function and remodelling in CAD patients, with some evidence to suggest that structural adaptations are less likely to occur in patients with cardiovascular risk and/or disease (Green et al., 2017). Thus, future research should explore this area to further elucidate the effect of exercise on vascular health in CAD patients. In addition, small changes in shear rate were seen in the phase-III & phase-IV CR and phase-III CR only groups from TP-1 to TP-3, with a decrease (effect size unavailable) in this parameter observed in the non-CR group from TP-1 to TP-3. Importantly, shear rate potentially represents a marker of peripheral microvascular function as reactive hyperaemia may be dependent on maximal forearm resistance (Mitchell et al., 2004; Anderson et al., 2011; Alexander et al., 2020). Thus, the results of Study 2 may suggest that exercise did not substantially influence microvascular function. However, Borges et al. (2018) demonstrated that six months of high frequency (> 2 sessions per week) combined training (moderate-intensity aerobic exercise and RT) was superior to low frequency (≤ 2 sessions per week) combined training (previously described) in improving microvascular function (skin microvascular reactivity) in CAD patients. Therefore, the exercise frequency (1 session per week) of Study 2 may have been insufficient for stimulating improvements in microvascular function. Nonetheless, additional studies are needed as a paucity of research has directly investigated the effect of exercise on

microvascular function in CAD patients. In terms of oxidative stress, large decreases in LOOH and $A^{\bullet-}$ from TP-1 to TP-3 were observed in the phase-III & phase-IV CR group. These changes may be representative of an exercise-induced reduction in systemic oxidative stress, with the decrease in LOOH being of particular interest as lipid peroxidation is a principal event during atherogenesis (Kutuk & Basaga, 2003). Indeed, previous research has identified a beneficial effect of exercise on oxidative stress in CAD patients (de Sousa et al., 2017; Taty et al., 2018). However, the inability to measure lipid soluble antioxidants represents a limitation of Study 2. This data may have further elucidated the effect of exercise on redox balance. For instance, a decrease in lipid peroxidation may be aligned to an increase in lipid soluble antioxidant capacity; the propagation phase of lipid peroxidation produces the α-tocopherol radical through the reduction of lipid peroxyl radicals by α-tocopherol, with consequential reductions in α-tocopherol concentration and $A^{\bullet-}$ generation secondary to the recycling of α-tocopherol radicals during the univalent oxidation of ascorbate (Young & Woodside, 2001). Moreover, lipid peroxidation may result in decreases in lycopene and α-carotene as these lipid soluble antioxidants hold an affinity for peroxyl radical intermediates (Young & Woodside, 2001).

It should be noted that the endothelial function and arterial stiffness measurements of Study 2 provided data primarily related to the vascular health of large arteries. A more global assessment of arterial function would have included microvascular function (*i.e.* laser doppler techniques) and carotid/ femoral ultrasound of intima-media thickness. The former test, although not possible due to equipment constraints, may have supplemented the assessment of macrovascular function (brachial FMD) by evaluating endothelial function in the microcirculation (*i.e.* arterioles, venules, and capillaries). Saliently, due to shared mechanisms of vascular damage (*i.e.* inflammation and oxidative stress), microvascular dysfunction often precedes or coexists with macrovascular impairment (Krentz et al., 2009). Indeed, impaired microvascular function has been identified in CAD patients compared to healthy subjects (Borges et al., 2016), and this vascular perturbation has been associated with increased risk of CAD mortality (Liew et al., 2011). Moreover, there is evidence to suggest that individuals with reduced plasma levels of SIRT-1 during childhood exhibit premature microvascular dysfunction during early adulthood (Rodriguez-Miguelez et al., 2020), which further supports the role SIRT-1 in the

pathophysiology of CVD. With regard to carotid/ femoral ultrasound of intima-media thickness, this measurement may have generated information related to subclinical atherosclerosis and arterial remodeling (structural changes). In addition, funding and time constraints (during testing of participants) precluded incorporating an assessment of endothelium-independent dilatation (vasodilatory response to exogenous NO doners (*i.e.* glyceryl trinitrate)) into the brachial FMD measurements. This is a limitation of Study 2 as the data generated may have complemented the assessment of endothelium-dependent dilatation by reflecting vascular structure and smooth muscle cell function (Alexander et al., 2020). Finally, given that SIRT-1 may induce the expression of antioxidant enzymes (*i.e.* SOD and catalase) (Russomanno et al., 2017), the quantification of these endogenous antioxidants may have allowed the effect of exercise and SIRT-1 on redox balance to be better examined. Collectively, future research in this area should consider integrating the beforementioned assessments, which may allow the generation of more precise information related to the cardioprotective mechanisms mediated by SIRT-1 following exercise.

Seminal research established an association between the SIRT family and longevity in lower organisms (Kaeberlein et al., 1999). Since then, there has been a focus on elucidating the mechanisms through which SIRT-1 may improve health (Winnik et al., 2015). Consequently, low expression/ and or dysregulation of SIRT-1 has been correlated with vascular dysfunction and overt CVD (Breitenstein et al., 2011; Winnik et al., 2015). Moreover, low serum concentrations of SIRT-1 have been associated with high-risk coronary plaques in asymptomatic CAD patients (He et al., 2019). Conversely, an increase in SIRT-1 may elicit cardioprotective effects by alleviating principal pathogenic states that drive atherogenesis, such as: inflammation (Yeung et al., 2004), oxidative stress (Russomanno et al., 2017), endothelial dysfunction (Mattagajasingh et al., 2007), and arterial stiffness (Man et al., 2019). Indeed, current research is investigating the clinical applications of pharmacological modulators of SIRT-1 by virtue of the potential anti-atherosclerotic effects of SIRT-1 activation (Sosnowska et al., 2017; D'Onofrio et al., 2018; Chen et al., 2020). As such, developing a deeper understanding of the links between SIRT-1 and the cellular mechanisms implicated in the development of CAD is a prime scientific endeavour of the upcoming years (D'Onofrio et al., 2018).

Given that SIRT-1 appears to be responsive to exercise, as demonstrated in Study 2, this intervention may serve as a tool for elucidating the cardioprotective signalling pathways that are modulated by SIRT-1 in CAD patients. Thus, future fully powered studies should seek to build upon the preliminary evidence generated by Study 2. Importantly, the findings of Study 2 suggest that a future prospective cohort study in this area is feasible with minor amendment (recruitment strategy). The study design and methodology were suitable for the participants, as indicated by the success criteria for drop-out rate (< 20% overall and at each TP for each group) and adherence rate (completed > 80% of prescribed exercise sessions) being satisfied. Additionally, the uptake rate to phase-IV CR (54%) suggests that balanced numbers across CR groups (phase-III & phase-IV CR and phase-III CR only) may be attainable in the future prospective cohort study, which may increase the reliability of the corresponding between-group comparisons (Zimmerman, 1987). However, the success criterion regarding recruitment rate was not fulfilled (< 70% of eligible patients were recruited). Moreover, only 3 (11%) patients who refused to participate in phase-III CR were recruited. Therefore, amendments to the recruitment strategy had to be identified before considering moving forward to the future prospective cohort study. Firstly, discussions with the collaborating CR nurses identified a potential method of improving the overall recruitment rate, which involves implementing a recruitment strategy that consists of a member of the research team being present at clinical departments to discuss the study with potential participants in person. Secondly, given that the recruitment of non-CR participants may be affected by the complex barriers to participation in CR (Resurrección et al., 2019), financial incentives may be required for the recruitment of this patient population. Finally, in the case of poor recruitment, the level of participant burden could be reduced by solely examining changes in SIRT-1 levels, which may enhance recruitment as blood samples could be collected during routine appointments. Collectively, strategies for addressing potential issues with recruitment in a future prospective cohort study have been identified. Moreover, the reliability of the data for a sample size calculation based on change in SIRT-1 will be improved as additional funding has been secured for completing the biochemical analyses in the samples that could not be analysed during the PhD research project due to financial constraints. Saliently, the advancement of scientific knowledge can be conceptualised as an iterative process, whereby future studies aim to overcome the limitations or further the findings of previous research. This iterative process enables scientific knowledge to continuously evolve, with

attention being placed on emerging areas of interest (Thagard, 2007). Indeed, the findings of the pilot prospective cohort study will inform a funding application for a future prospective cohort study, which will be performed by the PhD researcher (GT) as postdoctoral work. Progress in this area bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets).

7.1.3 Factors Influencing Participation in Cardiac Rehabilitation and Long-Term Exercise

Socioeconomic growth has resulted in the global development of an "obesogenic" environment that is contributing to an increased prevalence of principal CVD risk factors, such as: diabetes mellitus (Cho et al., 2018), hypertension (Zhou et al., 2017), obesity (Mozaffarian et al., 2011; Lakerveld et al., 2018), and physical inactivity (Guthold et al., 2018). As such, hospitalisation rates for CAD are increasing across Europe (Bhatnagar et al., 2016; Townsend et al., 2016), and the prevalence of CAD is continuing to rise in developing countries (Sanchis-Gomar et al., 2016). Thus, the substantial worldwide incidence of CAD coupled with the high risk of recurrent cardiovascular events has placed an emphasis on effective secondary prevention strategies for improving long-term prognosis of CAD patients (Briffa et al., 2011; Smolina et al., 2012).

CR is the cornerstone of secondary prevention strategies, with exercise serving as the primary component (BACPR, 2017). Considerable evidence supports the ability of CR and long-term exercise to improve long-term prognosis in CAD patients (Dibben et al., 2018; Biscaglia et al., 2019). However, despite the clinical benefits, CR programmes are underutilised by patients worldwide (Kotseva et al., 2013; Turk-Adawi & Grace, 2015; Beatty et al., 2018). In addition, the literature indicates that adherence to long-term exercise in CAD patients is poor (Sweet et al., 2011; Blanchard et al., 2014; Kotseva et al., 2019), with 66% of CAD patients across Europe being classified as sedentary (< 30 minutes of physical activity on five days per week) (Kotseva et al., 2019). Importantly, the National Health Service Long Term Plan has set an objective of achieving an 85%

uptake to CR in the UK by 2028 by scaling up and improving the marketing of CR programmes, which may prevent up to 23,000 premature deaths and 50,000 hospital readmissions over 10 years (National Health Service England, 2019). However, the NACR report asserted that reaching this uptake target will require significant innovation and funding, and highlighted a requirement to identify methods of increasing the recruitment of post-AMI CAD patients to CR in particular (British Heart Foundation, 2019b).

Whilst the results of Study 1 and Study 2 potentially support a beneficial effect of exercise on the health of CAD patients, more work is needed to identify and understand the factors that influence participation in CR and adherence to long-term exercise training in CAD patients. By doing so, methods of promoting participation in these interventions may be developed, which could result in a reduced burden of CAD by improving CVD risk profiles, with concomitant societal and economic benefits through lower rates of premature mortality, fewer hospital readmissions, and improved quality of life (De Gruyter et al., 2016). Importantly, recent qualitative evidence suggests that patient enrollment in CR and participation in long-term exercise training may be influenced by significant others (Clark et al., 2012; Campkin et al., 2017). However, the studies in this area have primarily focused on the perspective of the patient (Rouleau et al., 2018; Sweet et al., 2019; Hanna et al., 2020). Therefore, Study 3 aimed to generate novel qualitative knowledge regarding the factors that influence participation in CR and long-term exercise by investigating the perspectives and experiences of both CAD patients and their significant others.

The overarching theme of Study 3 was a need to improve health. Following the patients' AMI, both members of each dyad recognised the importance of improving their health for the purpose of circumventing future cardiovascular complications, with health benefits serving as the primary reason for participating in CR and long-term exercise. Importantly, aspects related to motivation, extrinsic influences, and CR experience underpinned these decisions. Sufficient data were obtained for answering the research question as the identified themes were common across and within both patient and significant other data sets (Braun & Clarke, 2013). The qualitative evidence generated by

Study 3 enhances understanding of the factors that influence CAD patient participation in CR and long-term exercise training, and adds to a growing body of literature regarding the important role that significant others play post-AMI (Clark et al., 2012; Son et al., 2013; Yates et al., 2015; Campkin et al., 2017; Mondesir et al., 2018). Importantly, a link between the factors identified in Study 3 and each element of the TDF was identified. The TDF is a comprehensive theoretical integrative framework related to behavior change (see Table 7.1) (Cane et al., 2012), which has been shown to effectively determine theoretical constructs for exercise maintenance (Amireault et al., 2013). As such, the TDF provides a multi-theoretical perspective to assist with the understanding of behaviour change, which may render it a suitable framework for determining the theoretical factors that influence participation in CR and long-term exercise for CAD patients. To the best of my knowledge, this is the first study to demonstrate both CAD patients and their significant others reporting factors related to the TDF (*i.e. emotion*, *social influence*, *beliefs about consequences*, and *reinforcement*), which underscores the relevance of these theoretical domains for CR participation and long-term exercise adherence.

Table 7.1 Theoretical domains of the TDF (Cane et al., 2012)

Domain	Definition
Skills (physical, cognitive, and interpersonal)	An ability acquired via practice
Knowledge	An awareness of the existence of something
Memory, attention, and decision processes	The capacity to retain information, selectively focus on elements of the environment, and select between two or more alternatives
Behavioural regulation	Anything aimed at managing or altering objectively observed or measured actions
Social / professional role and identity	A coherent set of behaviours and presented personal qualities of an individual in a social or work environment
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Optimism	A belief that things will happen for the best or that objectives will be attained
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Intentions	A conscious decision to execute a behaviour or a determination to act in a specific way
Goals	Mental representations of outcomes that an individual aspires to achieve
Reinforcement	Increasing the possibility of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus

Emotion	Attempts to manage a personally significant event through a complex reaction pattern comprising experiential, behavioural, and physiological elements
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour
Social influences	Interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours

The literature suggests that an increased awareness of mortality following a cardiac event encourages CAD patients to implement healthy lifestyle changes (Holder al., 2015). Saliently, a novel finding of Study 3 involved clearly reporting that the emotional response to an AMI by patients and their significant others appeared to serve as a principal motivating factor for engaging in CR and exercise adherence to obtain an improvement in health, which relates to the *emotion* domain of the TDF. Thus, healthcare professionals may promote participation in CR by advising CAD patients to derive motivation to improve their health from the emotional response to a cardiac complication. In addition, future investigations of CR and long-term exercise participation should be mindful to select a theory that includes dimensions of the emotional response to a cardiac complication.

A deep concern about the health of the patients triggered a determination in significant others to support the CAD patients with their recovery. Importantly, patients attributed elements of practical (*i.e.* physical assistance with daily tasks), informational (*i.e.* reminders about medication), and emotional (*i.e.* confiding in each other about concerns or worries) support from significant others as primary reasons for their recovery. These findings highlight the influential position of significant others during the rehabilitation period. Whilst previous research has identified social support from spouses and family members as a factor that influences patient participation in CR and exercise maintenance (Clark et al., 2012; Campkin et al., 2017), a principal finding of Study 3 was related to significant others receiving insufficient information regarding the purpose of CR and long-term exercise. This information deficiency rendered some significant others incapable of assisting the patients with their decision to participate in phase-III and phase-IV CR. Moreover, a poor comprehension of the health benefits of exercise post-AMI often resulted in the significant others attempting to discourage the patients from being active due to concerns about exercise-induced cardiovascular complications. Indeed, a poor supply of information to significant others/ caregivers of CAD patients has been demonstrated in the literature (Jackson et al., 2011). Nonetheless, the standards and core components for CR in the UK recommend for significant others to be invited to participate in CR activities (*i.e.* educational sessions) whenever possible, and for patients and their significant others to play an active role in the educative process (BACPR, 2017). Therefore, the information deficiency for significant others, as documented in Study 3,

may be attributed to a practice that is based on the individualised view of the patient, irrespective of the context and influence of significant others (Gannik, 2002). Moreover, the complexities of CR delivery (*i.e.* time constraints, existing workloads for CR staff, or communication barriers) may impede the provision of information to significant others (Farahani et al., 2011). Nonetheless, there is a paucity of research regarding the challenges or barriers that are faced by healthcare professionals when supplying significant others with information related to CR and long-term exercise. Future research in this area may enable healthcare professionals to include significant others in the referral process for CR, which may prevent the influential role of significant others post-AMI from being overlooked or neglected by ensuring they are empowered with the knowledge (*i.e.* health benefits of exercise) required to promote patient participation in CR and long-term exercise. Collectively, future investigations should select a theory that captures dimensions of *social influence* (*i.e.* TDF).

Several of the identified themes echoed previous research in this field, such as: health benefits constituting a principal reason for CR and long-term exercise participation (Rouleau et al., 2018; Sweet et al., 2019), anticipated benefits of CR participation (*i.e.* care from specialist staff, education, and social opportunities) (Cooper et al., 2005; Bäck et al., 2017; Rouleau et al., 2018), climatic conditions (Campkin et al., 2017), referral from a healthcare professional (Neubeck et al., 2012), and positive influence of emotions (*i.e.* improved mood) on long-term exercise participation (Sweet et al., 2019). Nonetheless, these findings enhance the literature as they were reported by both patients and their significant others, with a link to numerous domains of the TDF being identified, such as: *memory, attention, and decision processes*; *social / professional role and identity; intentions; and social influences* (Cane et al., 2012). Importantly, this observation suggests that multiple theoretical constructs are associated with participation in CR and long-term exercise. Thus, future work in this area should incorporate comprehensive theoretical frameworks (*i.e.* TDF) to capture the full scope of influencing factors, with particular attention being paid to the *social influence* of significant others.

Altogether, the study of CAD patient enrollment in CR and adherence to long-term exercise remains crucial due to the poor participation rates. Recent systematic reviews have concluded that interventions (*i.e.* contact from a healthcare professional, physical activity intervention, or cognitive-behavioural intervention) may increase patient participation in CR and long-term exercise; however, additional research is needed to improve the quality of evidence (de Araújo Pio et al., 2019; Graham et al., 2020). The factors identified in Study 3 may inform methods of promoting patient participation in CR and long-term exercise, such as: encouraging patients to derive motivation to improve their health from the emotional response to an AMI, supplying more information about the health benefits during the referral process, providing patients with insights into the experiences of CR graduates, fostering positive affective experiences with exercise by assisting with the identification of an enjoyable exercise modality, and empowering significant others with knowledge regarding the purpose of CR and long-term exercise. Importantly, there is a paucity of research regarding the effect of these suggested interventions, with the inclusion of significant others in particular being overlooked (de Araújo Pio et al., 2019; Graham et al., 2020). As such, future research should seek to define and test novel strategies of improving patient participation in CR and long-term exercise that acknowledge the factors identified in this study.

7.2 Overall Strengths and Limitations of the Thesis

Each of the studies possessed certain strengths and limitations as discussed in the preceding chapters. Overall, appropriate study designs and methods were utilised to answer the research questions in a valid manner, with results being reported in line with official guidelines for the purpose of transparency. The work presented within this thesis offers a significant contribution to the literature by furthering scientific understanding in novel areas related to the secondary prevention of CAD, which may stimulate and inform future research that potentially carries implications for clinical practice and patients. Nonetheless, several limitations should be recognised. The sample size of Study 2 was small, which decreased the reliability of the results and may have prevented statistical significance in a number of the inferential statistics performed. In addition, the participants of Study 3 were a convenience-based sample from two Health and Social Care Trusts in NI, which may limit generalisability to other locations. The

implementation of purposeful sampling in Study 3 may have enabled the inclusion of individuals who represent the widest variety of perspectives possible within the scope of the research question (*i.e.* phase-III & phase-IV CR patients, phase-III CR only patients, and non-CR patients). However, the financial and time constraints of a PhD research project precluded this approach, and may have contributed to the small sample size of Study 2 due to a restricted recruitment period. Finally, the beforementioned constraints also prevented the findings of Study 3 from being used to define and test a strategy of promoting patient participation in CR and long-term exercise in an additional study. Nonetheless, the inclusion of Study 3 contributed to balanced research training as an experience of quantitative and qualitative research paradigms was obtained. Altogether, the limitations of the work performed have been acknowledged and discussed throughout this thesis, which may inform future research that seeks to improve the quality of evidence generated.

7.3 Recommendations for Future Research

The findings of Study 1 demonstrated an anti-inflammatory effect of exercise in CAD patients. However, these results should be interpreted with caution until the quality of evidence is improved. Nevertheless, the identification of areas for future research in Study 1 has highlighted the work that is required for the quality of evidence in this area to increase and the anti-inflammatory effect of exercise to be further elucidated, which include: (1) additional randomised studies with high methodological qualities and large sample sizes; (2) further research into the effect of exercise on proximal mediators of inflammation and anti-inflammatory cytokines; (3) the identification of optimal exercise characteristics for mitigating inflammation; and (4) an exploration of the underlying molecular mechanisms that may be responsible for orchestrating an exercise-induced reduction in inflammation. Progress in these areas may result in exercise being utilised as a substitute for or an adjunct to anti-inflammatory pharmacological treatment in future clinical practice related to the secondary prevention of CAD.

The outcome of Study 2 resulted in a future prospective cohort study being deemed feasible with minor amendment (recruitment strategy). Moreover, preliminary evidence for a beneficial effect of exercise on SIRT-1 in CAD patients was generated. Whilst a funding application will be completed for the PhD researcher (GT) to perform the future prospective cohort study as postdoctoral work, several areas for future research have been identified: (1) the preliminary evidence generated by Study 2 must be examined by future fully powered studies before definitive conclusions can be made; (2) future research in this area should seek to account for confounding variables (*i.e.* physical activity, dietary intake, and medication) to assess the independent effect of exercise on SIRT-1; (3) studies should seek to define optimal exercise programme characteristics for augmenting SIRT-1 levels; and (4) to elucidate the molecular mechanisms that may mediate exercise-induced cardioprotection, future research should examine the relationships between SIRT-1, inflammatory activity, redox balance, endothelial function, and arterial stiffness following exercise in CAD patients. The advancement of scientific knowledge in these areas bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets).

The qualitative evidence generated by Study 3 enhances understanding of the factors that influence CAD patient enrollment in CR and participation in long-term exercise training. Nonetheless, a number of recommendations for future research have been determined: (1) future research in this area should seek to define and test novel strategies of improving patient participation in CR and long-term exercise that incorporate comprehensive theoretical frameworks (*i.e.* TDF) to capture the full scope of influencing factors, with particular attention being paid to the *social influence* of significant others; (2) the influence of emotional distress on participation in CR and long-term exercise following a cardiovascular complication warrants additional investigation, with the perspectives of significant others on this factor also being further explored; (3) future research should identify methods of assisting healthcare professionals with the provision of information regarding the health benefits and purpose of CR and long-term exercise to significant others, which may empower these individuals with the knowledge required to promote patient participation; (4) to enhance CR delivery, future studies

should elucidate the level of understanding (*i.e.* comprehension of suitable exercise modalities, session frequency, session duration, and exercise intensity) required for long-term exercise participation in CAD patients; and (5) future research should consider exploring the perspectives of female patients and their significant others, and attempt to capture the opinions of patients who refused to participate in CR and/ or long-term exercise and their significant others, which may add valuable perspectives on the current topic. Progress in these areas may contribute to the development of methods of promoting participation in CR and long-term exercise.

7.4 Clinical Implications of the Findings

CVD events frequently occur in CAD patients despite contemporary evidence-based secondary prevention therapies (*i.e.* achieving guideline-based recommended levels of LDL-C) (Baigent, 2005). Thus, current efforts are focusing on the identification of methods of addressing systemic inflammation in CAD patients in order to eliminate this residual risk (Lawler et al., 2020). The findings of Study 1 demonstrated an anti-inflammatory effect of exercise in CAD patients, as indicated by quantitative and qualitative evidence that supports a beneficial effect of exercise on acute-phase reactants (CRP, fibrinogen, and vWF). However, the quality of evidence for this area needs to be improved by further randomised studies with high methodological qualities and large sample sizes before a definitive conclusion regarding the capacity of exercise to serve as an anti-inflammatory strategy can be made. Nonetheless, the areas for future research identified by Study 1 may stimulate progress that results in exercise being utilised as a substitute for or an adjunct to anti-inflammatory pharmacological treatment in future clinical practice related to the secondary prevention of CAD.

The molecular transducers that orchestrate the cardioprotective adaptations of exercise are yet to be fully elucidated. The outcome of Study 2 resulted in a future prospective cohort study in this area being deemed feasible with minor amendment (recruitment strategy). Moreover, preliminary evidence for a beneficial effect of exercise on SIRT-1 in CAD patients was generated, with positive changes in physiological states related to atherogenesis also being detected (inflammation, oxidative stress, endothelial

function, and arterial stiffness). The findings of Study 2 will inform a funding application for the future prospective cohort study, which will be performed by the PhD researcher (GT) as postdoctoral work. Progress in this area bears the potential to further elucidate the pathophysiology of CAD, improve scientific understanding regarding the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets).

Despite the clinical benefits, CAD patient participation rates in CR and long-term exercise are poor worldwide (Blanchard et al., 2014; Turk-Adawi & Grace, 2015; Beatty et al., 2018). As such, many CAD patients are failing to receive optimal secondary prevention strategies. The qualitative evidence generated by Study 3 enhances understanding of the factors that influence CAD patient participation in CR and long-term exercise training by identifying a link between the factors reported by participants and each element of the TDF. This finding may inform future interventions on the theoretical variables to target in order to promote CAD patient participation in CR and long-term exercise. In addition, the results of Study 3 identified potential changes to clinical practice that may encourage participation in these interventions, such as: encouraging patients to derive motivation to improve their health from the emotional response to an AMI, supplying more information about the health benefits during the referral process, providing patients with insights into the experiences of CR graduates, fostering positive affective experiences with exercise by assisting with the identification of an enjoyable exercise modality, and empowering significant others with knowledge regarding the purpose of CR and long-term exercise. Overall, achieving greater CAD patient participation in CR and long-term exercise may reduce the burden of this disease by improving CVD risk profiles, with concomitant societal and economic benefits through lower rates of premature mortality, fewer hospital readmissions, and improved quality of life (De Gruyter et al., 2016).

7.5 Conclusion

The work in this thesis has enhanced scientific understanding of the role of exercise in the secondary prevention of CAD. The results of Study 1 suggest that exercise may

alleviate inflammation in this patient population, and offer future directions for the quality of evidence in this area to improve and the capacity of exercise to serve as an anti-inflammatory strategy in CAD patients to be further elucidated. The outcome of Study 2 generated preliminary evidence for a molecular mechanism that may mediate the cardioprotective effects of exercise, which may stimulate research that bears the potential to illuminate the pathophysiology of CAD, improve scientific understanding of the role of exercise in the rehabilitation of CAD patients, and identify novel therapeutic targets for secondary prevention strategies (*i.e.* biomarkers or pharmacological targets). Finally, whilst the beforementioned studies potentially support a beneficial effect of exercise on the health of CAD patients, the participation rates of this patient population in CR and long-term exercise are poor. Thus, the novel qualitative findings of Study 3 may inform future strategies to promote patient enrollment in these interventions.

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Appendix A. Electronic Supplementary Material for **Paper 1**

Exercise and Inflammation in Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomised Trials.

Journal Name: Journal of Sports Sciences

Electronic Supplementary Material (ESM) 1

ESM 1, Appendix S1. Example search strategy for Cochrane Central Register of Controlled Trials.

Concept 1: Coronary artery disease

#1   MeSH descriptor: [Coronary Artery Disease] explode all trees

#2   MeSH descriptor: [Myocardial Ischemia] explode all trees

#3   MeSH descriptor: [Heart Diseases] explode all trees

#4   MeSH descriptor: [Cardiovascular Diseases] explode all trees

#5   MeSH descriptor: [Acute Coronary Syndrome] explode all trees

#6   MeSH descriptor: [Myocardial Infarction] explode all trees

#7   MeSH descriptor: [Angina Pectoris] explode all trees

#8   MeSH descriptor: [Coronary Artery Bypass] explode all trees

#9   MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees

#10   MeSH descriptor: [Angioplasty, Balloon, Coronary] explode all trees

11   Key words: "coronary artery disease" or CAD or "coronary arteriosclerosis" or coronary heart disease* or isch*mic heart disease or myocardial isch*mia or "cardiovascular disease" or CVD or "acute coronary syndrome" or "myocardial infarction" or "angina pectoris" or "coronary artery bypass" or "percutaneous coronary intervention" or "angioplasty, balloon, coronary" or "coronary angioplasty"

Concept 2: Exercise

#12   MeSH descriptor: [Exercise] explode all trees

#13   MeSH descriptor: [Exercise Therapy] explode all trees

#14   MeSH descriptor: [Cardiac Rehabilitation] explode all trees

#15   MeSH descriptor: [Physical Conditioning, Human] explode all trees

#16   MeSH descriptor: [Physical Exertion] explode all trees

#17   MeSH descriptor: [Physical Fitness] explode all trees

#18   Key words: exercise* or "exercise therapy" or "cardiac rehabilitation" or "physical activity" or "physical conditioning" or "physical exertion" or "physical fitness" or "physical training" or training or aerobic* or "endurance training" or interval* or resistance* or "muscle strengthening" or "weight lifting" or circuit* or "combined training"

Concept 3: Inflammatory biomarker

#19   MeSH descriptor: [Inflammation] explode all trees

#20   MeSH descriptor: [Inflammation Mediators] explode all trees

#21   MeSH descriptor: [Biomarkers] explode all trees

#22   MeSH descriptor: [Acute-Phase Proteins] explode all trees

#23   MeSH descriptor: [von Willebrand Factor] explode all trees

#24   MeSH descriptor: [Cytokines] explode all trees

#25   MeSH descriptor: [Monokines] explode all trees

#26   MeSH descriptor: [Adipokines] explode all trees

#27   MeSH descriptor: [Interleukins] explode all trees

#28   MeSH descriptor: [Interferons] explode all trees

#29   MeSH descriptor: [Chemokines] explode all trees

#30   MeSH descriptor: [Cell Adhesion Molecules] explode all trees

#31   MeSH descriptor: [Matrix Metalloproteinases] explode all trees

#32   MeSH descriptor: [Platelet Activating Factor] explode all trees

#33   MeSH descriptor: [Peroxidases] explode all trees

#34   MeSH descriptor: [Phospholipases] explode all trees

#35   MeSH descriptor: [Transforming Growth Factors] explode all trees

#36   Key words: inflammation* or "inflammation mediators" or biomarker* or "inflammatory biomarker" or "biological marker" or cytokine* or interferon* or "interferon-gamma" or interleukin* or chemokine* or monokine* or adipokine* or adipocytokine* or "acute-phase proteins" or "acute-phase reactants" or "c-reactive protein" or CRP or fibrinogen or "serum amyloid A" or SAA or "soluble CD40 ligand" or IL-* or tum*r necrosis factor* or TNF* or "cell adhesion molecules" or intercellular adhesion molecule* or ICAM* or vascular cell adhesion molecule* or VCAM* or "E-selectin" or "P-selectin" or selectin* or "platelet activating factor" or PAF* or monocyte chemoattractant protein* or MCP* or fractalkine or myeloid-related protein* or MRP* or myeloperoxidase* or lysophosphatidylcholines or peroxidase or phospholipase* or lipoprotein phospholipase* or LP-PLA or pentraxin* or PTX* or "matrix metalloproteinases" or MMP* or "vonWillebrand Factor" or vWF or "transforming growth factors" or TGF*

Concept 4: Randomised trials

#37   MeSH descriptor: [Random allocation] explode all trees

#38   Key words: randomi?ed trial

Combinations

#39   {OR #1- #11} (Concept 1)

#40   {OR #12- #18} (Concept 2)

#41   {OR #19- #36} (Concept 3)

#42   #37 OR #38   (Concept 4)

#43   #39 AND #40 AND #41 AND #42

Limits

Trials option checked.

ESM 1, Table S1. Characteristics of the included studies that evaluated the effect of an exercise intervention on pro/ anti-inflammatory cytokines in coronary artery disease patients.

Author	Study duration	Subjects	Groups	N (male)	Age (y)	Modality	Intensity	Duration (minutes)	Frequency (sessions per week)	Sample times	IL-6	IL-10	TNF-α	TNF-α SR1	IL-33	IL-35
Balen et al. (2008)	3-weeks	AMI CAD patients	Exercise[a]	30 (21)	59± 9	W/ C	50-60% VO2peak	75	5	Baseline and week-3		↑(0.018)	→*	↓ (<0.001) **		
			Control	30 (23)	61± 10	-	-	-	-							
Beckie et al. (2010)	12-weeks	MetS CAD patients	Exercise[a]	39 (0)	61.6± 10	W/ C/ Ro/ RT	60-85% HRmax	35-45	3	Baseline and week-12	↓ (<0.05)		→			
			Exercise[a,b]	48 (0)	61.6± 10	W/ C/ Ro/ RT	60-85% HRmax	35-45	3			↓ (<0.05)	↓ (<0.05)			
Bilińska et al. (2010)	6-weeks	CABG CAD patients	Exercise	59 (59)	53.9± 5.0	IT- C, 4-min bouts with 2-min rest	70-80% HRmax	60	3	Baseline and week-6	↓ (<0.02)					
			Control	59 (59)	54.1± 5.8	-	-	-	-							
Hansen et al. (2011)	7-weeks	CAD patients	Exercise	25 (23)	58.9 ± 7.2	C/ W/ AC	65% VO2peak	40	3	Baseline and week-7	→					
			Exercise	22 (21)	60.4 ± 8.9	C/ W/ AC & RT (2 sets of 12-20 reps, 30-sec rest between sets)	65% VO2peak & 65% 1RM	40	3		→					

Study	Duration	Population	Group	N (n)	Age	Type	Intensity	Time (min)	Freq	Assessment	Outcome 1	Outcome 2	Outcome 3	Outcome 4
Munk et al. (2011)	6-months	CAD patients	Exercise	18 (16)	59.5± 10	IT- C/ R, 4-min bouts with 3-min active rest	80-90% HR$_{max}$ (60-70% during active rest)	60	3	Baseline and 6-months	↓ (<0.05)**	↑(<0.05)	→	
			Control	18 (14)	60.7± 9	-	-	-	-					
Oliveira et al. (2015)	8-weeks	CAD patients	Exercise[a]	44 (38)	55± 10.7	C/ R	70-85% HR$_{max}$	30	3	Baseline and week-8	→	→	→	
			Control	42 (34)	58.5± 10.7	-	-	-	-					
Pedersen et al. (2016)	12-weeks	CAD patients	Exercise	30 (NS)	NS	IT- C, 1-4 min bouts with 1-3 min active rest	85-90% VO2peak	28	3	Baseline and week-12	→[c]		→[c]	
			LED	34 (NS)	NS	-	-	-	-					
Raygan et al. (2017)	12-weeks	CAD patients	Exercise	21 (21)	58.5± 7.9	R	50-65% HR$_{max}$	40	3	Baseline and week-12			→	↑(0.001)**
			Control	23 (23)	64.78± 12.21	-	-	-	-					
Ribeiro et al. (2012)	8-weeks	AMI CAD patients	Exercise	20 (18)	54.3± 10.8	C/ R	65-75% HR$_{max}$	35	3	Baseline and week-8	→	↑(0.009)**		
			Control	18 (13)	57± 7.6	-	-	-	-					

Schumacher et al. (2006)	6-months	CAD patients	Exercise[a]	95 (78)	54± 8	DET	11-15 on the Borg scale	20	2	Baseline and 6-months	↓(<0.001)***	↓(0.021)***
			Control	94 (80)	55± 8	-	-	-	-			

Data for age presented as mean ± standard deviation, [a], exercise intervention provided alongside a comprehensive cardiac rehabilitation programme i.e. lifestyle & risk factor education, optimisation of standard pharmacological treatment, and psychosocial management; [b], motivationally enhanced gender-specific cardiac rehabilitation; [c], result of group that only received an exercise intervention; ↓ (p value), significant decrease is present in exercise group; ↑ (p value), significant increase is present in exercise group; →, no significant change is present in exercise group; *, significant decrease observed in control group; **, significant change compared to control group; ***, significant decrease is also present in control group; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumour necrosis factor- alpha; TNF-α SR1, soluble tumour necrosis factor- alpha receptor 1; IL-33, interleukin-33; IL-35, interleukin-35; N, number; y, years; CAD, coronary artery disease; CABG, coronary artery bypass graft; MetS, metabolic syndrome; AMI, acute myocardial infarction; C, cycling; IT, interval training; W, walking; Ro, rowing; RT, resistance training; LED, low energy diet (800-1000 kcal/day for 8-10 weeks, followed by a weight maintenance diet); DET, dynamic endurance training (aerobic exercises using arms and legs; no further information provided by authors); 1RM, 1 repetition maximum; AC, arm cranking; VO_{2peak}, peak oxygen consumption; R, running; HR_{max}, maximum heart rate; and NS, not stated

ESM 1, Table S2. Characteristics of the included studies that evaluated the effect of an exercise intervention on acute-phase reactants in coronary artery disease patients.

Author	Study duration	Subjects	Groups	N (male)	Age (y)	Modality	Intensity	Duration (minutes)	Frequency (sessions per week)	Sample times	CRP	Fibrinogen	vWF	PTX-3
Balen et al. (2008)	3-weeks	AMI CAD patients	Exercise[a]	30 (21)	59± 9	W/ C	50-60% VO_{2peak}	75	5	Baseline and week-3	↓(<0.001)*	↓(<0.001)*		
			Control	30 (23)	61± 10	-	-	-	-					
Beckie et al. (2010)	12-weeks	MetS CAD patients	Exercise[a]	39 (0)	61.6± 10	W/ C/ Ro/ RT	60-85% HR_{max}	35-45	3	Baseline and week-12	↓(<0.05)			
			Exercise[a,b]	48 (0)	61.6± 10	W/ C/ Ro/ RT	60-85% HR_{max}	35-45	3		↓(<0.05)			
Bilińska et al. (2010)	6-weeks	CABG CAD patients	Exercise	59 (59)	53.9± 5.0	IT- C, 4-min bouts with 2-min rest	70-80% HR_{max}	60	3	Baseline and week-6	↓(<0.05)	↓ (<0.01)*		
			Control	59 (59)	54.1± 5.8	-	-	-	-					
Conraads et al. (2015)	12-weeks	CAD patients	Exercise	85 (81)	NS	IT- C, 4-min bouts with 3-min active rest	90-95% HR_{peak} (50-70% during active rest)	25	3	Baseline and week-12	↓(<0.05)			
			Exercise	89 (80)	NS	C	70-75% HR_{peak}	37	3		↓(<0.05)			
El Missiri and Taher (2016)	12-weeks	CAD patients	Exercise[a]	40 (33)	50.7± 5.4	W/ R	65-85% HR_{max}	15-40	2	Baseline and week-12	↓(0.0006)*			
			Control	40 (28)	52.5± 5.4	-	-	-	-					

Study	Duration	Population	Group	n (n)	Age	Mode	Intensity	Duration (min)	Freq	Assessment			
Fernandes et al. (2011)	16-weeks	CAD patients	Exercise	15 (4)	60.7± 6.7	C	THR between VAT and RCP	40	3	Baseline and week-16	→		
			Control	19 (9)	59.5± 7.3	-	-	-	-				
Giallauria et al. (2011)	6-months	AMI CAD patients	Exercise[a]	37 (28)	61± 7	C	60-70% VO_{2peak}	40	3	Baseline and 6-months	↓(<0.0001)*		
			Control	38 (32)	60± 8	-	-	-	-				
Hansen et al. (2011)	7-weeks	CAD patients	Exercise	25 (23)	58.9 ± 7.2	C/ W/ AC	65% VO_{2peak}	40	3	Baseline and week-7	→		
			Exercise	22 (21)	60.4 ± 8.9	C/ W/ AC & RT (2 sets of 12-20 reps, 30-sec rest between sets)	65% VO_{2peak} & 65% 1RM	40	3		→		
Lee et al. (2006)	12-weeks	CAD patients	Exercise[a]	40 (NS)	59± 11	C/ R/ W/ RT/ O	65-75% HR_{max}	30-40	2	Baseline and week-12		↓(<0.001)	↓(<0.001)
			Exercise[c]	41 (NS)	59± 11	NS	"Moderately intense activity"	≥ 15	7			↓(0.003)	↓(0.001)
			Control	20 (NS)	59± 11	-	-	-	-				
Lee et al. (2012)	12-weeks	AMI CAD patients	Exercise[a]	22 (NS)	NS	W	40-80% HRR	30	5	Baseline and week-12	↓(<0.05)		
			Control	24 (NS)	NS	-	-	-	-				

Study	Duration	Population	Group	N (n)	Age	Type	Intensity	Duration (min)	Frequency	Assessment	Outcome 1	Outcome 2
Lian et al. (2014)	12-weeks	CAD patients	Morning Exercise	89 (64)	64.9± 9	W	2.5 miles/hour	≥ 30	≥ 5	Baseline and week-12	↓(<0.001)*[d]	↓(0.030)
			Evening Exercise	89 (69)	62± 10	W	2.5 miles/hour	≥ 30	≥ 5		↓(<0.001)**[d]	↓(<0.001)**
			Control	97 (68)	61± 10	-	-	-	-			
Luk et al. (2012)	8-weeks	CAD patients	Exercise[a]	32 (24)	67.7± 9	W/ R/ RT/ O	80% HRmax	50	3	Baseline and week-8	→	
			Control	32 (24)	66.6± 7.9	-	-	-	-			
Madssen et al. (2014)	12-months	CAD patients	Exercise	24 (18)	64.4 (47-78)	IT- W/ R/ C/ O, 4-min bouts with 3-min active rest	85-95% HRmax (70% during active rest)	28	3	Baseline and 12 months	→	
			Control	25 (18)	58.5 (42-71)	-	-	-	-			
Moholdt et al. (2012)	12-weeks	AMI CAD patients	Exercise	59 (49)	57.7 ± 9.3	W/ R/ O	"Exercise vigorously"	35	3	Baseline and week-12	→	
			Exercise	30 (25)	56.7 ± 10.4	IT- W/ R, 4-min bouts with 3-min active rest	85-95% HRmax (70% during active rest)	25	3		→	
Munk et al. (2011)	6-months	CAD patients	Exercise	18 (16)	59.5± 10	IT- C/ R, 4-min bouts with 3-min active rest	80-90% HRmax (60-70% during active rest)	60	3	Baseline and 6-months	→***	→
			Control	18 (14)	60.7± 9	-	-	-	-			

Study	Duration	Population	Group	N (n)	Age	Type	Intensity	Duration	Frequency	Time points	Outcome	
Oliveira et al. (2015)	8-weeks	AMI CAD patients	Exercise[a]	44 (38)	55± 10.7	C/ R	70-85% HR_{max}	30	3	Baseline and week-8	→	
			Control	42 (34)	58.5± 10.7	-	-	-	-			
Pedersen et al. (2016)	12-weeks	CAD patients	Exercise	30 (NS)	NS	IT- C, 1-4 min bouts with 1-3 min active rest	85-90% $VO2_{peak}$	28	3	Baseline and week-12	→[e]	
			LED	34 (NS)	NS	-	-	-	-			
Ribeiro et al. (2012)	8-weeks	AMI CAD patients	Exercise	20 (18)	54.3± 10.8	C/ R	65-75% HR_{max}	35	3	Baseline and week-8	→	
			Control	18 (13)	57± 7.6	-	-	-	-			
Schumacher et al. (2006)	6-months	CAD patients	Exercise[a]	95 (78)	54± 8	DET	11-15 on the Borg scale	20	2	Baseline and 6-months	↓(<0.001)****	
			Control	94 (80)	55± 8	-	-	-	-			
Sixt et al. (2008)	4-weeks	IGT CAD patients	Exercise	13 (10)	64± 6	C	70% HR_{max}	Week 1: 15, six times per day; Weeks 2-4: 30 per day	7	Baseline and week-4	→[e]	→[e]
			Rosiglitazone	11 (11)	62± 6	-	-	-	-			
			Control	10 (7)	64± 6	-	-	-	-			

Study	Duration	Population	Group	N (n)	Age	Mode	Intensity	Duration	Freq	Timepoints	Outcome
Theodorou et al. (2016)	8-months	CAD patients	Exercise	15 (15)	61± 7	IT- R/ C, 10-min bouts with 6-min rest	60-85% HR$_{max}$	64	3	Baseline, month-4, and month-8	↓(<0.05)
			Exercise	11 (11)	62± 8	RT- Circuit, 2 sets of 8 exercises (12-15 reps)	60% 1RM	Approx. 30	3		↓(<0.05)
			Exercise	15 (15)	64± 6	IT- R/ C, 10-min bouts with 6-min rest & RT- Circuit, 1 set of 8 exercises (12-15 reps)	60-85% HR$_{max}$ & 60% 1RM	Approx. 47	3		↓(<0.05)
			Control	15 (15)	64± 8	-	-	-	-		
Toyama et al. (2012)	20-weeks	CAD patients	Exercise[f]	14 (9)	68 ± 10	C/ W	VAT/ 12-13 on the Borg scale	30	7	Baseline and week-20	↓(0.001)[h]
			Exercise[g]	14 (12)	67 ± 13	C/ W	VAT/ 12-13 on the Borg scale	30	7		

Vona et al. (2009)	4-weeks	AMI CAD patients	Exercise	52 (39)	56± 6	C	75% HR$_{peak}$	40	4	Baseline and week-4	↓(<0.01)
			Exercise	54 (39)	57± 8	RT- Circuit, 4 sets of 10 exercises (10-12 reps)	60% MVC	Approx. 40	4		↓(<0.01)
			Exercise	53 (40)	55± 9	C & RT-Circuit, 4 sets of 10 exercises (10-12 reps)	75% HR$_{peak}$ & 60% MVC	40	4 (2 C & 2 RT)		↓(<0.01)
			Control	50 (37)	58± 7	-	-	-	-		

Data for age presented as mean ± standard deviation or median (interquartile range), [a], exercise intervention provided alongside a comprehensive cardiac rehabilitation programme i.e. lifestyle & risk factor education, optimisation of standard pharmacological treatment, and psychosocial management; [b], motivationally enhanced gender-specific cardiac rehabilitation; [c], home-based cardiac rehabilitation (Heart Manual); [d], result of sub-analysis (211 participants); [e], result of group that only received an exercise intervention; [f], in combination with Atorvastatin prescribed at a standard dose; [g], in combination with Rosuvastatin prescribed at a standard dose; [h], data only available for the result of both exercise groups combined; ↓ (p value), significant decrease is present in exercise group; →, no significant change is present in exercise group; *, significant change compared to control group; **, significant change compared to control group and morning exercise group; ***, significant increase observed in control group; ****, significant decrease is also present in control group; CRP, C-reactive protein; vWF, von Willebrand factor; PTX-3, pentraxin 3; N, number; y, years; MetS, metabolic syndrome; CAD, coronary artery disease; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; IGT, impaired glucose tolerance; NS, not stated; C, cycling; LED, low energy diet (800-1000 kcal/day for 8-10 weeks, followed by a weight maintenance diet); W, walking; Ro, rowing; R, running; RT, resistance training; AC, arm cranking; IT, interval training; O, other (i.e. rowing, stepping, arm ergometry, mobility, uphill walking, or body weight exercises); DET, dynamic endurance training (aerobic exercises using arms and legs; no further information provided by authors); HR$_{max}$, maximum heart rate; HR$_{peak}$, peak heart rate; HRR, heart rate reserve; THR, target heart rate; VAT, ventilatory anaerobic threshold; RCP, respiratory compensation point; VO$_{2peak}$, peak oxygen consumption; 1RM, 1 repetition maximum; and MVC, maximum voluntary contraction

ESM 1, Table S3. Characteristics of the included studies that evaluated the effect of an exercise intervention on chemokines in coronary artery disease patients.

Author	Study duration	Subjects	Groups	N (male)	Age (y)	Modality	Intensity	Duration (minutes)	Frequency (sessions per week)	Sample times	IP-10	Mig	RANTES	IL-8	CXCL 16	CCL 21	CCL 19	MCP-1	CD40L
Balen et al. (2008)	3-weeks	AMI CAD patients	Exercise a	30 (21)	59± 9	W/ C	50-60% VO2peak	75	5	Baseline and week-3				↓(<0.001)*					
			Control	30 (23)	61± 10	-	-	-	-										
Fernandes et al. (2011)	16-weeks	CAD patients	Exercise	15 (4)	60.7 ±6.7	C	THR between VAT and RCP	40	3	Baseline and week-16	↓(<0.05)*	→							
			Control	19 (9)	59.5 ±7.3	-	-	-	-										
Hansen et al. (2011)	7-weeks	CAD patients	Exercise	25 (23)	58.9 ± 7.2	C/ W/ AC	65% VO2peak	40	3	Baseline and week-7			→						
			Exercise	22 (21)	60.4 ± 8.9	C/ W/ AC & RT (2 sets of 12-20 reps, 30-sec rest between sets)	65% VO2peak & 65% 1RM	40	3				→						
Munk et al. (2011)	6-months	CAD patients	Exercise	18 (16)	59.5 ± 10	IT- C/ R, 4-min bouts with 3-min active rest	80-90% HRmax (60-70% during active rest)	60	3	Baseline and 6-months			→	↓(<0.001)*	→	↓(<0.05)	→	→	→
			Control	18 (14)	60.7 ± 9	-	-	-	-										

Oliveira et al. (2015)	8-weeks	AMI CAD patients	Exercise [a]	44 (38)	55± 10.7	C/ R	70-85% HR_{max}	30	3	Baseline and week-8	→
			Control	42 (34)	58.5 ±10.7	-	-	-	-		

Data for age presented as mean ± standard deviation; [a], exercise intervention provided alongside a comprehensive cardiac rehabilitation programme i.e. lifestyle & risk factor education, optimisation of standard pharmacological treatment, and psychosocial management; ↓ (*p* value), significant decrease is present in exercise group; →, no significant change is present in exercise group; *, significantly lower compared to control group; IP-10, interferon-gamma induced protein 10; Mig, monokine induced by interferon-gamma; RANTES, regulated on activation, normal T cell expressed and secreted; IL-8, interleukin-8; CXCL16, chemokine (C-X-C motif) ligand 16; CCL21, chemokine (C-C motif) ligand 21; CCL19, chemokine (C-C motif) ligand 19; MCP-1, monocyte chemoattractant protein 1; CD40L, CD40 ligand; N, number; y, years; AMI, acute myocardial infarction; CAD, coronary artery disease; C, cycling; W, walking; AC, arm cranking; RT, resistance training; R, running; IT, interval training; THR, target heart rate; VAT, ventilatory anaerobic threshold; RCP, respiratory compensation point; VO_{2peak}, peak oxygen consumption; 1RM, 1 repetition maximum; and HR_{max}, maximum heart rate

ESM 1, Table S4. Characteristics of the included studies that evaluated the effect of an exercise intervention on adhesion molecules in coronary artery disease patients.

Author	Study duration	Subjects	Groups	N (male)	Age (y)	Modality	Intensity	Duration (minutes)	Frequency (sessions per week)	Sample times	VCAM-1	ICAM-1	P-selectin	E-selectin
Beckie et al. (2010)	12-weeks	MetS CAD patients	Exercise[a]	39 (0)	61.6±10	W/ C/ Ro/ RT	60-85% HR$_{max}$	35-45	3	Baseline and week-12				→
			Exercise[a,b]	48 (0)	61.6±10	W/ C/ Ro/ RT	60-85% HR$_{max}$	35-45	3			↓ (<0.05)*		
Fernandes et al. (2011)	16-weeks	CAD patients	Exercise	15 (4)	60.7±6.7	C	THR between VAT and RCP	40	3	Baseline and week-16	→			
			Control	19 (9)	59.5±7.3	-	-	-	-					
Jalaly et al. (2015)	12-weeks	SAP CAD patients	Exercise	20 (11)	NS	R	40-60% HRR	20-30	2	Baseline and week-12		↓ (0.001)		↓ (0.001)
			Control	20 (11)	NS	-	-	-	-					
Lee et al. (2006)	12-weeks	CAD patients	Exercise[a]	40 (NS)	59±11	C/ R/ W/ RT/ O	65-75% HR$_{max}$	30-40	2	Baseline and week-12			→	
			Exercise[c]	41 (NS)	59±11	NS	"Moderately intense activity"	≥ 15	7				→	
			Control	20 (NS)	59±11	-	-	-	-					
Munk et al. (2011)	6-months	CAD patients	Exercise	18 (16)	59.5±10	IT- C/ R, 4-min bouts with 3-min active rest	80-90% HR$_{max}$ (60-70% during active rest)	60	3	Baseline and 6-months	↑(<0.05)		→	↑(<0.05)**
			Control	18 (14)	60.7±9	-	-	-	-					

Study	Duration	Population	Group	N (n)	Age	Type	Intensity	Min	Freq	Assessment				
Oliveira et al. (2015)	8-weeks	AMI CAD patients	Exercise[a]	44 (38)	55± 10.7	C/ R	70-85% HR$_{max}$	30	3	Baseline and week-8	→	→		
			Control	42 (34)	58.5± 10.7	-	-	-	-					
Ribeiro et al. (2012)	8-weeks	AMI CAD patients	Exercise	20 (18)	54.3± 10.8	C/ R	65-75% HR$_{max}$	35	3	Baseline and week-8	→ **	→ **		
			Control	18 (13)	57±7.6	-	-	-	-					
Schumacher et al. (2006)	6-months	CAD patients	Exercise[a]	95 (78)	54± 8	DET	11-15 on the Borg scale	20	2	Baseline and 6-months	↓(<0.001)***	↓(0.029)	→	→
			Control	94 (80)	55± 8	-	-	-	-					

Data for age presented as mean ± standard deviation; [a], exercise intervention provided alongside a comprehensive cardiac rehabilitation programme i.e. lifestyle & risk factor education, optimisation of standard pharmacological treatment, and psychosocial management; [b], motivationally enhanced gender-specific cardiac rehabilitation; [c], home-based cardiac rehabilitation (Heart Manual); ↓ (p value), significant decrease is present in exercise group; →, no significant change is present in exercise group; ↑ (p value), significant increase is present in exercise group; *, significant reduction compared to other exercise group; **, significant increase is present in control group; ***, significant decrease is also present in control group; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; N, number; y, years; CAD, coronary artery disease; SAP, stable angina pectoris; MetS, metabolic syndrome; HRR, heart rate reserve; NS, not stated; AMI, acute myocardial infarction; W, walking; C, cycling; Ro, rowing; RT, resistance training; R, running; O, other (i.e. rowing, stepping, arm ergometry, mobility, uphill walking, or bodyweight exercises); IT, interval training; DET, dynamic endurance training (aerobic exercises using arms and legs; no further information provided by authors); THR, target heart rate; VAT, ventilatory anaerobic threshold; RCP, respiratory compensation point; and HR$_{max}$, maximum heart rate

ESM 1, Table S5.1. Participant baseline inflammatory biomarker concentrations.

Author	Groups (N)	IL-6	IL-10	TNF-α	IL-33	IL-35	CRP	Fibrinogen	vWF	IP-10	Mig	RANTES	IL-8	VCAM-1	ICAM-1	E-selectin	P-selectin
Balen et al. (2008)	Exercise (30)	-	2.9 (2.4-4.6) (pg/mL)	50 (27-60.1) (pg/mL)	-	-	13.5 (5-19) (mg/L)	5.4±1.7 (g/L)	-	-	-	-	11.6 (8.1-15.1) (pg/mL)	-	-	-	-
	Control (30)	-	3 (2.2-5.3) (pg/mL)	44.9 (27.5-56.3) (pg/mL)	-	-	16.5 (7-25) (mg/L)	6±1.4 (g/L)	-	-	-	-	13.3 (9-18.4) (pg/mL)	-	-	-	-
Beckie et al. (2010)	Exercise (39)	17±45 (pg/mL)	-	12±31 (pg/mL)	-	-	6±9 (mg/L)	-	-	-	-	-	-	-	179±81 (pg/mL)	-	-
	Exercise (48)	18±48 (pg/mL)	-	8.5±9 (pg/mL)	-	-	6±8 (mg/L)	-	-	-	-	-	-	-	228.5±134 (pg/mL)	-	-
Bilińska et al. (2010)	Exercise (59)	3.11±2.52 (pg/mL)	-	-	-	-	0.39±0.47 (mg/L)	3.84±1.35 (g/L)	-	-	-	-	-	-	-	-	-
	Control (59)	2.69±1.79 (pg/mL)	-	-	-	-	0.24±0.27 (mg/L)	4.08±1.17 (g/L)	-	-	-	-	-	-	-	-	-
Conraads et al. (2015)	Exercise (85)	-	-	-	-	-	0.21±0.44 (mg/L)	-	-	-	-	-	-	-	-	-	-
	Exercise (89)	-	-	-	-	-	0.24±0.57 (mg/L)	-	-	-	-	-	-	-	-	-	-
El Missiri and Taher (2016)	Exercise (40)	-	-	-	-	-	2.36 (0.63-10.6) (mg/L)*	-	-	-	-	-	-	-	-	-	-
	Control (40)	-	-	-	-	-	1.68 (0.57-10.1) (mg/L)*	-	-	-	-	-	-	-	-	-	-

Study	Group (n)														
Fernandes et al. (2011)	Exercise (15)	-	-	-	-	-	2 (3.8) (mg/L)	-	-	99 (30) (ng/mL)	351 (50) (pg/mL)	236 (60) (pg/mL)	-	-	-	-
	Control (19)	-	-	-	-	-	1 (1.8) (mg/L)	-	-	120 (22) (ng/mL)	384 (71) (pg/mL)	230 (50) (pg/mL)	-	-	-	-
Giallauria et al. (2011)	Exercise (37)	-	-	-	-	-	18.6±8.4 (mg/L)	-	-	-	-	-	-	-	-	-
	Control (38)	-	-	-	-	-	16.2±7.3 (mg/L)	-	-	-	-	-	-	-	-	-
Hansen et al. (2011)	Exercise (25)	3.2±1.6 (pg/mL)	-	-	-	-	0.5±0.4 (mg/dL)	-	-	-	-	-	4±1.8 (pg/mL)	-	-	-
	Exercise (22)	3.2±1.4 (pg/mL)	-	-	-	-	0.5±0.6 (mg/dL)	-	-	-	-	-	4.1±1.6 (pg/mL)	-	-	-
Jalaly et al. (2015)	Exercise (20)	-	-	-	-	-	-	-	-	-	-	-	-	65.5±39.7 (ng/mL)	3.2±1.5 (ng/mL)	-
	Control (20)	-	-	-	-	-	-	-	-	-	-	-	-	56.1±36 (ng/mL)	2.7±1.3 (ng/mL)	-
Lee et al. (2006)	Exercise (40)	-	-	-	-	-	3.28±0.7 (g/L)	201±61 (IU/dL)	-	-	-	-	-	-	-	82 (72-92) (ng/mL)
	Exercise (41)	-	-	-	-	-	3.21±0.9 (g/L)	182±56 (IU/dL)	-	-	-	-	-	-	-	80 (75-95) (ng/mL)
	Control (20)	-	-	-	-	-	2.9±0.8 (g/L)	198±46 (IU/dL)	-	-	-	-	-	-	-	77 (66-87) (ng/mL)

Study	Group (n)																	
Lee et al. (2012)	Exercise (22)	-	-	-	-	-	0.37 ±0.66 (mg/dL)	-	-	-	-	-	-	-	-	-	-	-
	Control (24)	-	-	-	-	-	0.31 ±0.31 (mg/dL)	-	-	-	-	-	-	-	-	-	-	-
Lian et al. (2014)	Morning Exercise (89)	-	-	-	-	-	3.51 ±1.11 (mg/L)	1.08±0.19 (g/L)	-	-	-	-	-	-	-	-	-	-
	Evening Exercise (89)	-	-	-	-	-	3.52 ±0.89 (mg/L)	1.09±0.21 (g/L)	-	-	-	-	-	-	-	-	-	-
	Control (97)	-	-	-	-	-	3.49 ±1.11 (mg/L)[a]	1.07±0.22 (g/L)	-	-	-	-	-	-	-	-	-	-
Luk et al. (2012)	Exercise (32)	-	-	-	-	-	1.24±2.2 (mg/L)	-	-	-	-	-	-	-	-	-	-	-
	Control (32)	-	-	-	-	-	1.47±2.26 (mg/L)	-	-	-	-	-	-	-	-	-	-	-
Madssen et al. (2014)	Exercise (24)	-	-	-	-	-	1.09 ±0.9 (mg/L)	-	-	-	-	-	-	-	-	-	-	-
	Control (25)	-	-	-	-	-	1.2±0.9 (mg/L)	-	-	-	-	-	-	-	-	-	-	-
Moholdt et al. (2012)	Exercise (59)	-	-	-	-	-	2.2±2.8 (mg/L)	-	-	-	-	-	-	-	-	-	-	-
	Exercise (30)	-	-	-	-	-	2.3±2.6 (mg/L)	-	-	-	-	-	-	-	-	-	-	-

Study	Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Munk et al. (2011)	Exercise (18)	1±0.68 (pg/mL)	1.46±1.36 (pg/mL)	1.12±0.37 (pg/mL)	-	-	-	-	83.1±53.8 (%)	-	-	1300±152 (pg/mL)	17.3±8.9 (pg/mL)	9.2±5.6 (ng/mL)	-	25.2±10.4 (ng/mL)	47.2±19.3 (ng/mL)
	Control (18)	1.15±1.48 (pg/mL)	1.52±0.86 (pg/mL)	1.26±0.48 (pg/mL)	-	-	-	-	116.7±69.4 (%)	-	-	1283±186 (pg/mL)	4.3±8.6 (pg/mL)	12.2±6.6 (ng/mL)	-	30.5±15.6 (ng/mL)	50.2±28 (ng/mL)
Oliveira et al. (2015)	Exercise (44)	1.5 (0.9-2) (pg/mL)	7.7 (4.9-14.7) (pg/mL)	7.9 (5.9-10) (pg/mL)	-	-	1.3 (0.5-2.4) (mg/L)*	-	-	-	-	48.6 (30.6-81.4) (ng/mL)	-	946.9 (650.1-1261.8) (ng/mL)	270.6 (226.3-349.8) (ng/mL)	-	-
	Control (42)	1.2 (0.8-2.3) (pg/mL)	6.3 (4.4-11.7) (pg/mL)	7.5 (5.3-10.2) (pg/mL)	-	-	1.8 (0.8-3.3) (mg/L)*	-	-	-	-	49.6 (40.1-86.2) (ng/mL)	-	915.3 (569.2-1376.8) (ng/mL)	282.7 (229.3-385.3) (ng/mL)	-	-
Pedersen et al. (2016)	Exercise (30)	NS	-	5.68±1.24 (pg/mL)	-	-	1.72±3.06 (mg/L)	-	-	-	-	-	-	-	-	-	-
	LED (34)	NS	-	5.32±1.26 (pg/mL)	-	-	1.28±2.49 (mg/L)	-	-	-	-	-	-	-	-	-	-
Raygan et al. (2017)	Exercise (21)	-	-	-	89.69±43.75 (pg/mL)	41.53±23.87 (pg/mL)	-	-	-	-	-	-	-	-	-	-	-
	Control (23)	-	-	-	75.04±29 (pg/mL)	51.33±22.89 (pg/mL)	-	-	-	-	-	-	-	-	-	-	-

Study	Group																
Ribeiro et al. (2012)	Exercise (20)	3.1 (3.7) (pg/mL)	5.8 (5.5) (pg/mL)	-	-	-	1.1 (1.7) (mg/L)	-	-	-	-	-	-	273.4 ±78.4 (ng/mL)	174±48 (ng/mL)	-	-
	Control (18)	3.9 (4.5) (pg/mL)	7.3 (5.1) (pg/mL)	-	-	-	0.9 (1.2) (mg/L)	-	-	-	-	-	-	271.4 ±105.2 (ng/mL)	195.9 ±70.2 (ng/mL)	-	-
Schumacher et al. (2006)	Exercise (95)	3.93 (2.22-8.11) (pg/mL)	-	3.34 (2.34-5.31) (pg/mL)	-	-	5.91 (2.99-14.32) (µg/mL)	-	-	-	-	-	-	618 (526-732) (ng/mL)	305 (251-361) (ng/mL)	40.4 (30-58.8) (ng/mL)	44.4 (37.2-52.8) (ng/mL)
	Control (94)	4.51 (2.85-8.13) (pg/mL)	-	4.12 (2.76-5.64) (pg/mL)	-	-	5.33 (2.59-10.64) (µg/mL)	-	-	-	-	-	-	608 (494-740) (ng/mL)	298 (241-370) (ng/mL)	44.4 (30.7-58.6) (ng/mL)	44 (38.1-57.7) (ng/mL)
Sixt et al. (2008)	Exercise (13)	-	-	-	-	-	3.1±1.4 (mg/dL)	3.3±1.2 (mg/dL)	-	-	-	-	-	-	-	-	-
	Rosiglitazone (11)	-	-	-	-	-	3.7±2.3 (mg/dL)	3.0±1.3 (mg/dL)	-	-	-	-	-	-	-	-	-
	Control (10)	-	-	-	-	-	5.5±4.4 (mg/dL)	3.9±0.6 (mg/dL)	-	-	-	-	-	-	-	-	-
Theodorou et al. (2016)	Exercise (15)	-	-	-	-	-	0.33 ±0.58 (mg/dL)	-	-	-	-	-	-	-	-	-	-
	Exercise (11)	-	-	-	-	-	0.36 ±0.56 (mg/dL)	-	-	-	-	-	-	-	-	-	-
	Exercise (15)	-	-	-	-	-	0.34 ±0.66 (mg/dL)	-	-	-	-	-	-	-	-	-	-
	Control (15)	-	-	-	-	-	0.39 ±0.89 (mg/dL)	-	-	-	-	-	-	-	-	-	-

Toyama et al. (2012)	Exercise (14)	-	-	-	-	-	1430 (264-2478) (ng/mL) [b]	-	-	-	-	-	-	-	-	-	-
	Exercise (14)	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-
Vona et al. (2009)	Exercise (52)	-	-	-	-	-	-	-	102 ±12 (%)	-	-	-	-	-	-	-	-
	Exercise (54)	-	-	-	-	-	-	-	105 ±15 (%)	-	-	-	-	-	-	-	-
	Exercise (53)	-	-	-	-	-	-	-	108 ±11 (%)	-	-	-	-	-	-	-	-
	Control (50)	-	-	-	-	-	-	-	109 ±14 (%)	-	-	-	-	-	-	-	-

Data are presented as mean ± standard deviation, median (25th-75th percentile), or median (interquartile range); [a], estimated from data presented in a graph; [b], data only available for both exercise groups combined; *, significantly different baseline levels; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumour necrosis factor-alpha; IL-33, interleukin-33; IL-35, interleukin-35; CRP, C-reactive protein; vWF, von Willebrand factor; IP-10, interferon-gamma induced protein 10; Mig, monokine induced by interferon-gamma; RANTES, regulated on activation, normal T cell expressed and secreted; IL-8, interleukin-8; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; N, number; -, not measured; NS, not stated; pg/mL, picograms per millilitre; mg/L, milligrams per litre; g/L, grams per litre; ng/mL, nanograms per millilitre; mg/dL, milligrams per decilitre; IU/dL, international units per decilitre; μg/mL, micrograms per millilitre; and %, percentage

ESM 1, Table S5.2. Participant baseline inflammatory biomarker concentrations.

Author	Groups (N)	TNF-α SR1	PTX-3	CD40L	CXCL16	CCL21	CCL19	MCP-1
Balen et al. (2008)	Exercise (30)	1403 (1287-1751) (pg/mL)	-	-	-	-	-	-
	Control (30)	1553 (1267-2174) (pg/mL)	-	-	-	-	-	-
Beckie et al. (2010)	Exercise (39)	-	-	-	-	-	-	-
	Exercise (48)	-	-	-	-	-	-	-
Bilińska et al. (2010)	Exercise (59)	-	-	-	-	-	-	-
	Control (59)	-	-	-	-	-	-	-
Conraads et al. (2015)	Exercise (85)	-	-	-	-	-	-	-
	Exercise (89)	-	-	-	-	-	-	-
El Missiri and Taher (2016)	Exercise (40)	-	-	-	-	-	-	-
	Control (40)	-	-	-	-	-	-	-
Fernandes et al. (2011)	Exercise (15)	-	-	-	-	-	-	-
	Control (19)	-	-	-	-	-	-	-
Giallauria et al. (2011)	Exercise (37)	-	-	-	-	-	-	-
	Control (38)	-	-	-	-	-	-	-
Hansen et al. (2011)	Exercise (25)	-	-	-	-	-	-	-
	Exercise (22)	-	-	-	-	-	-	-

Study	Group							
Jalaly et al. (2015)	Exercise (20)	-	-	-	-	-	-	-
	Control (20)	-	-	-	-	-	-	-
Lee et al. (2006)	Exercise (40)	-	-	-	-	-	-	-
	Exercise (41)	-	-	-	-	-	-	-
	Control (20)	-	-	-	-	-	-	-
Lee et al. (2012)	Exercise (22)	-	-	-	-	-	-	-
	Control (24)	-	-	-	-	-	-	-
Lian et al. (2014)	Morning Exercise (89)	-	-	-	-	-	-	-
	Evening Exercise (89)	-	-	-	-	-	-	-
	Control (97)	-	-	-	-	-	-	-
Luk et al. (2012)	Exercise (32)	-	-	-	-	-	-	-
	Control (32)	-	-	-	-	-	-	-
Madssen et al. (2014)	Exercise (24)	-	-	-	-	-	-	-
	Control (25)	-	-	-	-	-	-	-
Moholdt et al. (2012)	Exercise (59)	-	-	-	-	-	-	-
	Exercise (30)	-	-	-	-	-	-	-
Munk et al. (2011)	Exercise (18)	-	5.01±2.58 (ng/mL)	2.22±1.64 (ng/mL)	434±69.1 (ng/mL)	277±211 (pg/mL)	123.8±86.6 (pg/mL)	191.3±73.8 (pg/mL)
	Control (18)	-	3.44±1.5 (ng/mL)	2.01±1.64 (ng/mL)	453.3±124 (ng/mL)	248±151 (pg/mL)	173.9±151.4 (pg/mL)	223.6±111 (pg/mL)

Oliveira et al. (2015)	Exercise (44)	-	-	-	-	-	-	-
	Control (42)	-	-	-	-	-	-	-
Pedersen et al. (2016)	Exercise (30)	-	-	-	-	-	-	-
	LED (34)	-	-	-	-	-	-	-
Raygan et al. (2017)	Exercise (21)	-	-	-	-	-	-	-
	Control (23)	-	-	-	-	-	-	-
Ribeiro et al. (2012)	Exercise (20)	-	-	-	-	-	-	-
	Control (18)	-	-	-	-	-	-	-
Schumacher et al. (2006)	Exercise (95)	-	-	-	-	-	-	-
	Control (94)	-	-	-	-	-	-	-
Sixt et al. (2008)	Exercise (13)	-	-	-	-	-	-	-
	Rosiglitazone (11)	-	-	-	-	-	-	-
	Control (10)	-	-	-	-	-	-	-
Theodorou et al. (2016)	Exercise (15)	-	-	-	-	-	-	-
	Exercise (11)	-	-	-	-	-	-	-
	Exercise (15)	-	-	-	-	-	-	-
	Control (15)	-	-	-	-	-	-	-

Toyama et al. (2012)	Exercise (14)	-	-	-	-	-	-	-
	Exercise (14)	-	-	-	-	-	-	-
Vona et al. (2009)	Exercise (52)	-	-	-	-	-	-	-
	Exercise (54)	-	-	-	-	-	-	-
	Exercise (53)	-	-	-	-	-	-	-
	Control (50)	-	-	-	-	-	-	-

Data are presented as mean ± standard deviation or median (25th-75th percentile); TNF-α SR1, soluble tumour necrosis factor- alpha receptor 1; PTX-3, pentraxin 3; CD40L, CD40 ligand; CXCL16, chemokine (C-X-C motif) ligand 16; CCL21, chemokine (C-C motif) ligand 21; CCL19, chemokine (C-C motif) ligand 19; MCP-1, monocyte chemoattractant protein 1; N, number; -, not measured; pg/mL, picograms per millilitre; and ng/mL, nanograms per millilitre

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ESM 2

ESM 2, Table S1. Summary of results for meta-analyses of post-intervention inflammatory biomarker value comparisons between exercise and control groups.

Outcome Measurement	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	P value*	Heterogeneity $I^{2\,b}$	χ^2 (P value)**
C-reactive protein	11	492	411	-0.55 (-0.93, -0.16)	0.005	85%	<0.00001
Fibrinogen	4	280	196	-0.52 (-0.74, -0.29)	<0.00001	27%	0.24
von Willebrand factor	2	177	68	-1.57 (-2.23, -0.92)	<0.00001	76%	0.007
Interleukin-6	5	236	231	-0.24 (-0.55, 0.07)	0.12	58%	0.05
Interleukin-10	4	112	108	0.01 (-0.25, 0.28)	0.91	0%	0.69
Tumour necrosis factor-alpha	4	187	184	-0.09 (-0.30, 0.11)	0.36	0%	0.51
Vascular cell adhesion molecule-1	5	192	191	-0.04 (-0.26, 0.19)	0.75	12%	0.34
Intercellular adhesion molecule-1	4	179	174	-0.35 (-0.72, 0.01)	0.06	58%	0.07
E-selectin	3	133	132	-0.31 (-0.66, 0.05)	0.09	35%	0.22
P-selectin	2	113	112	-0.11 (-0.47, 0.26)	0.56	27%	0.24
Interleukin-8	2	48	48	-0.45 (-1.21, 0.32)	0.25	70%	0.07
Regulated on activation, normal T-cell expressed and secreted	2	62	60	-0.05 (-0.60, 0.51)	0.87	52%	0.15

Key: [a] A negative SMD represents a lower value in the exercise group compared to control group post-intervention, [b] ≥ 50% represents substantial heterogeneity, * P ≤ 0.05 represents statistical significance, **= P ≤ 0.1 represents substantial heterogeneity, *SMD* standardised mean difference, *CI* confidence interval

ESM 2, Table S2. Quality of evidence assessment using the GRADE system.

Outcome Measurement	Number of Studies (Participants)	Study Limitations (ROB)	Inconsistency of Results	Indirectness of Evidence	Imprecision	Publication Bias	Overall Quality of Evidence
Interleukin-6	5 (467) Start score= 4	No concern	-1: Substantial heterogeneity documented[a]	-1: 1 study included a restricted study population[b]	-1: CI crosses zero (-0.55, 0.07)	No concern	Final score= 1 Very low
Interleukin-10	4 (220) Start score= 4	No concern	No concern	No concern	-1: CI crosses zero (-0.25, 0.28)	No concern	Final score= 3 Moderate
Tumour necrosis factor- alpha	4 (371) Start score= 4	No concern	No concern	No concern	-1: CI crosses zero (-0.30, 0.11)	No concern	Final score= 3 Moderate
C-reactive protein	11 (903) Start score= 4	-1: 6 Studies rated as an unclear ROB for random sequence generation. 8 studies rated as an unclear ROB for allocation concealment.	-1: Substantial heterogeneity documented[a]	No concern	-1: Wide CI documented (-0.93, -0.16)	No concern	Final score= 1 Very low
Fibrinogen	4 (476) Start score= 4	-1: 2 studies rated as an unclear ROB for random sequence generation. 4 studies rated as an unclear ROB for allocation concealment.	No concern	-1: 2 studies included a restricted study population[c]	-1: Wide CI documented (-0.74, -0.29)	No concern	Final score= 1 Very low
von Willebrand factor	2 (245) Start score= 4	No concern	-1: Substantial heterogeneity documented[a]	-1: 1 study included a restricted study population[d]	-1: Wide CI documented (-2.23, -0.92)	No concern	Final score= 1 Very low

Vascular cell adhesion molecule-1	5 (383) Start score= 4	No concern	No concern	No concern	-1: CI crosses zero (-0.26, 0.19)	No concern	Final score= 3 Moderate
Intercellular adhesion molecule-1	4 (353) Start score= 4	No concern	-1: Substantial heterogeneity documented[a]	No concern	-1: CI crosses zero (-0.72, 0.01)	No concern	Final score= 2 Low
Interleukin-8	2 (96) Start score= 4	No concern	-1: Substantial heterogeneity documented[a]	No concern	-1: CI crosses zero (-1.21, 0.32)	No concern	Final score= 2 Low
E-selectin	3 (265) Start score= 4	No concern	No concern	No concern	-1: CI crosses zero (-0.66, 0.05)	No concern	Final score= 3 Moderate
P-selectin	2 (225) Start score= 4	No concern	No concern	No concern	-1: CI crosses zero (-0.47, 0.26)	No concern	Final score= 3 Moderate
Regulated on activation, normal T-cell expressed and secreted	2 (122) Start score= 4	No concern	-1: Substantial heterogeneity documented[a]	No concern	-1: CI crosses zero (-0.60, 0.51)	No concern	Final score= 2 Low

[a], χ^2 $p \leq 0.1$ or $I^2 \geq 50\%$; [b], Bilińska et al. (2010) included only male patients, and excluded patients with diabetes mellitus, hypercholesterolemia, and current smokers; limited generalisability to a standard coronary artery disease (CAD) population; [c], Bilińska et al. (2010), see [a]; Sixt et al. (2008) excluded patients with diabetes mellitus and current smokers; limited generalisability to a standard CAD population; ROB, risk of bias; CI, confidence interval; and [d], Vona et al. (2009) excluded patients with diabetes mellitus, hypertension, and current smokers; limited generalisability to a standard CAD population.

Exercise and Inflammation in Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomised Trials.

Journal Name: Journal of Sports Sciences

ESM 3

ESM 3, Table S1. Results of post-intervention value comparisons: sub-group analysis of the duration of exercise programme (< 12-weeks versus ≥ 12-weeks).

Outcome Measurement	Sub-group	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	Heterogeneity (I^2)	P value	Test for Sub-group Differences (χ^2 Heterogeneity Statistics) P value*	I^2
C-reactive protein	< 12-weeks	4	124	119	-0.42 (-1.10, 0.27)	83%	0.23	0.67	0%
	≥ 12-weeks	7	368	292	-0.60 (-1.10, -0.10)	87%	0.02		
Fibrinogen	< 12-weeks	3	102	99	-0.53 (-0.81, -0.25)	0%	0.0002	0.95	0%
	≥ 12-weeks	1[b]	178	97	-0.51 (-1.04, 0.02)	78%	0.06		
von Willebrand factor	< 12-weeks	1[b]	159	50	-1.86 (-2.28, -1.44)	22%	<0.00001	0.002	89.1%
	≥ 12-weeks	1	18	18	-0.64 (-1.31, 0.03)	Not applicable	0.06		
Interleukin-6	< 12-weeks	3	123	119	-0.23 (-0.48, 0.02)	0%	0.07	0.71	0%
	≥ 12-weeks	2	113	112	-0.45 (-1.57, 0.67)	89%	0.43		
Interleukin-10	< 12-weeks	3	94	90	-0.03 (-0.32, 0.26)	0%	0.86	0.50	0%
	≥ 12-weeks	1	18	18	0.22 (-0.43, 0.88)	Not applicable	0.50		
Tumour necrosis factor-alpha	< 12-weeks	2	74	72	0.03 (-0.32, 0.38)	14%	0.86	0.36	0%
	≥ 12-weeks	2	113	112	-0.17 (-0.44, 0.09)	0%	0.19		
Vascular cell adhesion molecule-1	< 12-weeks	2	64	60	-0.17 (-0.57, 0.23)	17%	0.40	0.44	0%
	≥ 12-weeks	3	128	131	0.03 (-0.29, 0.35)	22%	0.86		

					SMD (95% CI)[a]	I^2	p	p	I^2
Intercellular adhesion molecule-1	< 12-weeks	2	64	60	-0.35 (-0.77, 0.06)	20%	0.09		
	≥ 12-weeks	2	115	114	-0.41 (-1.23, 0.41)	81%	0.32	0.90	0%
E-selectin	< 12-weeks	0	0	0	Not estimable	Not applicable	Not applicable	Not applicable	Not applicable
	≥ 12-weeks	3	133	132	-0.31 (-0.66, 0.05)	35%	0.09		
P-selectin	< 12-weeks	0	0	0	Not estimable	Not applicable	Not applicable	Not applicable	Not applicable
	≥ 12-weeks	2	113	112	-0.11 (-0.47, 0.26)	27%	0.56		
Interleukin-8	< 12-weeks	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003	0.07	69.7%
	≥ 12-weeks	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93		
Regulated on activation, normal T-cell expressed and secreted	< 12-weeks	1	44	42	-0.28 (-0.70, 0.15)	Not applicable	0.20	0.15	52.1%
	≥ 12-weeks	1	18	18	0.30 (-0.36, 0.96)	Not applicable	0.37		

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; [b], multiple independent data points; *, $p \leq 0.1$ represents statistical significance; SMD, standardised mean difference; and CI, confidence interval

ESM 3, Table S2. Results of post-intervention value comparisons: sub-group analysis of the exercise sessions per week (≤ 3 compared to > 3).

Outcome Measurement	Sub-group	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	Heterogeneity (I^2)	P value	Test for Sub-group Differences (χ^2 Heterogeneity Statistics)	
								P value*	I^2
C-reactive protein	≤ 3 sessions per week	7	293	270	-0.44 (-1.01, 0.13)	89%	0.13	0.39	0%
	> 3 sessions per week	4	199	141	-0.74 (-1.13, -0.35)	63%	0.0002		
Fibrinogen	≤ 3 sessions per week	1	59	59	-0.55 (-0.92, -0.18)	Not applicable	0.003	0.83	0%
	> 3 sessions per week	3	221	137	-0.50 (-0.81, -0.18)	45%	0.002		
von Willebrand factor	≤ 3 sessions per week	1	18	18	-0.64 (-1.31, 0.03)	Not applicable	0.06	0.002	89.1%
	> 3 sessions per week	1[b]	159	50	-1.86 (-2.28, -1.44)	22%	<0.00001		
Interleukin-6	≤ 3 sessions per week	5	236	231	-0.24 (-0.55, 0.07)	58%	0.12	Not applicable	Not applicable
	> 3 sessions per week	0	0	0	Not estimable	Not applicable	Not applicable		
Interleukin-10	≤ 3 sessions per week	3	82	78	-0.04 (-0.35, 0.27)	0%	0.82	0.54	0%
	> 3 sessions per week	1	30	30	0.15 (-0.36, 0.66)	Not applicable	0.56		
Tumour necrosis factor-alpha	≤ 3 sessions per week	3	157	154	-0.16 (-0.38, 0.06)	0%	0.16	0.16	50.4%
	> 3 sessions per week	1	30	30	0.24 (-0.27, 0.75)	Not applicable	0.35		

Marker	Sessions	Studies	Exercise	Control	SMD (95% CI)[a]	I^2	p-value		
Vascular cell adhesion molecule-1	≤ 3 sessions per week	5	192	191	-0.04 (-0.26, 0.19)	12%	0.75	Not applicable	Not applicable
	> 3 sessions per week	0	0	0	Not estimable	Not applicable	Not applicable		
Intercellular adhesion molecule-1	≤ 3 sessions per week	4	179	174	-0.35 (-0.72, 0.01)	58%	0.06	Not applicable	Not applicable
	> 3 sessions per week	0	0	0	Not estimable	Not applicable	Not applicable		
E-selectin	≤ 3 sessions per week	3	133	132	-0.31 (-0.66, 0.05)	35%	0.09	Not applicable	Not applicable
	> 3 sessions per week	0	0	0	Not estimable	Not applicable	Not applicable		
P-selectin	≤ 3 sessions per week	2	113	112	-0.11 (-0.47, 0.26)	27%	0.56	Not applicable	Not applicable
	> 3 sessions per week	0	0	0	Not estimable	Not applicable	Not applicable		
Interleukin-8	≤ 3 sessions per week	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93	0.07	69.7%
	> 3 sessions per week	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003		
Regulated on activation, normal T-cell expressed and secreted	≤ 3 sessions per week	2	62	60	-0.05 (-0.60, 0.51)	52%	0.87	Not applicable	Not applicable
	> 3 sessions per week	0	0	0	Not estimable	Not applicable	Not applicable		

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; [b], multiple independent data points; *, $p \leq 0.1$ represents statistical significance; SMD, standardised mean difference; and CI, confidence interval

ESM 3, Table S3. Results of post-intervention value comparisons: sub-group analysis of the exercise modality.

Outcome Measurement	Sub-group	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	Heterogeneity (I²)	P value	Test for Sub-group Differences (χ² Heterogeneity Statistics)	
								P value*	I²
C-reactive protein	AIE	3	98	89	-0.23 (-0.52, 0.06)	0%	0.12		
	CAE	8	368	312	-0.72 (-1.26, -0.17)	90%	0.010	0.45	0%
	RT	1	11	5	-0.12 (-1.18, 0.94)	Not applicable	0.83		
	RT & cardiorespiratory exercise	1	15	5	-0.17 (-1.18, 0.84)	Not applicable	0.74		
Fibrinogen	AIE	1	59	59	-0.55 (-0.92, -0.18)	Not applicable	0.003		
	CAE	3	221	137	-0.50 (-0.81, -0.18)	45%	0.002	0.83	0%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
von Willebrand factor	AIE	1	18	18	-0.64 (-1.31, 0.03)	Not applicable	0.06		
	CAE	1	52	17	-2.17 (-2.83, -1.51)	Not applicable	<0.00001	0.007	75.5%
	RT	1	54	16	-2.00 (-2.65, -1.34)	Not applicable	<0.00001		
	RT & cardiorespiratory exercise	1	53	17	-1.48 (-2.08, -0.87)	Not applicable	<0.00001		

Interleukin-6	AIE	2	77	77	-0.61 (-1.38, 0.17)	75%	0.13		
	CAE	3	159	154	-0.03 (-0.25, 0.19)	0%	0.79	0.16	48.3%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
Interleukin-10	AIE	1	18	18	0.22 (-0.43, 0.88)	Not applicable	0.50		
	CAE	3	94	90	-0.03 (-0.32, 0.26)	0%	0.86	0.50	0%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
Tumour necrosis factor- alpha	AIE	1	18	18	-0.03 (-0.68, 0.63)	Not applicable	0.94		
	CAE	3	169	166	-0.09 (-0.33, 0.14)	11%	0.43	0.85	0%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
Vascular cell adhesion molecule-1	AIE	1	18	18	0.37 (-0.29, 1.03)	Not applicable	0.28		
	CAE	4	174	173	-0.07 (-0.28, 0.15)	2%	0.53	0.22	33.8%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
Intercellular adhesion molecule-1	AIE	0	0	0	Not estimable	Not applicable	Not applicable		
	CAE	4	179	174	-0.35 (-0.72, 0.01)	58%	0.06	Not applicable	Not applicable
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		

					SMD (95% CI)		p-value		
E-selectin	AIE	1	18	18	-0.62 (-1.29, 0.05)	Not applicable	0.07		
	CAE	2	115	114	-0.22 (-0.61, 0.17)	35%	0.27	0.31	3.6%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
P-selectin	AIE	1	18	18	0.21 (-0.44, 0.87)	Not applicable	0.53		
	CAE	1	95	94	-0.22 (-0.50, 0.07)	Not applicable	0.14	0.24	27.5%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
Interleukin-8	AIE	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93		
	CAE	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003	0.07	69.7%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		
Regulated on activation, normal T-cell expressed and secreted	AIE	1	18	18	0.30 (-0.36, 0.96)	Not applicable	0.37		
	CAE	1	44	42	-0.28 (-0.70, 0.15)	Not applicable	0.20	0.15	52.1%
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; *, $p \leq 0.1$ represents statistical significance; SMD, standardised mean difference; CI, confidence interval; AIE, aerobic interval exercise; CAE, continuous aerobic exercise; and RT, resistance training

ESM 3, Table S4. Results of post-intervention value comparisons: sub-group analysis of exercise alongside cardiac rehabilitation versus exercise only.

Outcome Measurement	Sub-group	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	Heterogeneity (I^2)	P value	Test for Sub-group Differences (χ^2 Heterogeneity Statistics)	
								P value*	I^2
C-reactive protein	Exercise alongside CR	4	184	186	-1.22 (-2.40, -0.04)	95%	0.04	0.14	54.3%
	Exercise only	7	308	225	-0.31 (-0.57, -0.04)	47%	0.02		
Fibrinogen	Exercise alongside CR	1	30	30	-0.65 (-1.17, -0.13)	Not applicable	0.02	0.60	0%
	Exercise only	3	250	166	-0.49 (-0.77, -0.21)	43%	0.0006		
von Willebrand factor	Exercise alongside CR	0	0	0	Not estimable	Not applicable	Not applicable	Not applicable	Not applicable
	Exercise only	2	177	68	-1.57 (-2.23, -0.92)	76%	<0.00001		
Interleukin-6	Exercise alongside CR	2	139	136	-0.04 (-0.35, 0.26)	34%	0.79	0.19	42.0%
	Exercise only	3	97	95	-0.43 (-0.93, 0.06)	58%	0.09		
Interleukin-10	Exercise alongside CR	2	74	72	-0.04 (-0.37, 0.28)	0%	0.79	0.54	0%
	Exercise only	2	38	36	0.13 (-0.33, 0.59)	0%	0.57		
Tumour necrosis factor-alpha	Exercise alongside CR	3	169	166	-0.09 (-0.33, 0.14)	11%	0.43	0.85	0%
	Exercise only	1	18	18	-0.03 (-0.68, 0.63)	Not applicable	0.94		

					SMD (95% CI)[a]	I^2	p-value*	p-value*	I^2
Vascular cell adhesion molecule-1	Exercise alongside CR	2	139	136	0.03 (-0.21, 0.26)	0%	0.83	0.51	0%
	Exercise only	3	53	55	-0.17 (-0.69, 0.36)	47%	0.54		
Intercellular adhesion molecule-1	Exercise alongside CR	2	139	136	-0.09 (-0.33, 0.14)	0%	0.44	0.01	84.6%
	Exercise only	2	40	38	-0.77 (-1.23, -0.31)	0%	0.001		
E-selectin	Exercise alongside CR	1	95	94	-0.09 (-0.38, 0.19)	Not applicable	0.52	0.08	67.0%
	Exercise only	2	38	38	-0.57 (-1.03, -0.11)	0%	0.01		
P-selectin	Exercise alongside CR	1	95	94	-0.22 (-0.50, 0.07)	Not applicable	0.14	0.24	27.5%
	Exercise only	1	18	18	0.21 (-0.44, 0.87)	Not applicable	0.53		
Interleukin-8	Exercise alongside CR	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003	0.07	69.7%
	Exercise only	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93		
Regulated on activation, normal T-cell expressed and secreted	Exercise alongside CR	1	44	42	-0.28 (-0.70, 0.15)	Not applicable	0.20	0.15	52.1%
	Exercise only	1	18	18	0.30 (-0.36, 0.96)	Not applicable	0.37		

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; *, $p \leq 0.1$ represents statistical significance; SMD, standardised mean difference; CI, confidence interval; and CR, cardiac rehabilitation

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ESM 4

ESM 4, Table S1. Summary of statistically significant tests for sub-group differences (post-intervention value comparisons).

Outcome Measurement	Sub-group	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	Heterogeneity (I^2)	P value	Test for Sub-group Differences (χ^2 Heterogeneity Statistics)	
								P value*	I^2
von Willebrand factor	< 12-weeks	1[b]	159	50	-1.86 (-2.28, -1.44)	22%	<0.00001	0.002	89.1%
	≥ 12-weeks	1	18	18	-0.64 (-1.31, 0.03)	Not applicable	0.06		
Interleukin-8	< 12-weeks	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003	0.07	69.7%
	≥ 12-weeks	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93		
von Willebrand factor	≤ 3 sessions per week	1	18	18	-0.64 (-1.31, 0.03)	Not applicable	0.06	0.002	89.1%
	> 3 sessions per week	1[b]	159	50	-1.86 (-2.28, -1.44)	22%	<0.00001		
Interleukin-8	≤ 3 sessions per week	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93	0.07	69.7%
	> 3 sessions per week	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003		
von Willebrand factor	AIE	1	18	18	-0.64 (-1.31, 0.03)	Not applicable	0.06	0.007	75.5%
	CAE	1	52	17	-2.17 (-2.83, -1.51)	Not applicable	<0.00001		
	RT	1	54	16	-2.00 (-2.65, -1.34)	Not applicable	<0.00001		
	RT & cardiorespiratory exercise	1	53	17	-1.48 (-2.08, -0.87)	Not applicable	<0.00001		
Interleukin-8	AIE	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93	0.07	69.7%
	CAE	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003		
	RT	0	0	0	Not estimable	Not applicable	Not applicable		
	RT & cardiorespiratory exercise	0	0	0	Not estimable	Not applicable	Not applicable		

					SMD (95% CI)[a]	I^2	p		
Intercellular adhesion molecule-1	Exercise alongside CR	2	139	136	-0.09 (-0.33, 0.14)	0%	0.44	0.01	84.6%
	Exercise only	2	40	38	-0.77 (-1.23, -0.31)	0%	0.001		
E-selectin	Exercise alongside CR	1	95	94	-0.09 (-0.38, 0.19)	Not applicable	0.52	0.08	67.0%
	Exercise only	2	38	38	-0.57 (-1.03, -0.11)	0%	0.01		
Interleukin-8	Exercise alongside CR	1	30	30	-0.81 (-1.34, -0.28)	Not applicable	0.003	0.07	69.7%
	Exercise only	1	18	18	-0.03 (-0.68, 0.62)	Not applicable	0.93		

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; [b], multiple independent data points; *, $p \leq 0.1$ represents statistical significance; SMD, standardised mean difference; CI, confidence interval; AIE, aerobic interval exercise; CAE, continuous aerobic exercise; RT, resistance training; and CR, cardiac rehabilitation

ESM 4, Table S2. Summary of results for sensitivity analysis of post-intervention inflammatory biomarker value comparisons between exercise and control groups following the removal of studies that reported data that required the estimation of mean ± standard deviation (SD) or SD.

Outcome Measurement	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	P value*	Heterogeneity	
						I^2 [b]	χ^2 (P value)**
C-reactive protein	6[c]	289	233	-0.81 (-1.42, -0.19)	0.01	90%	< 0.00001
Interleukin-6	2[d]	77	77	-0.61 (-1.38, 0.17)	0.13	75%	0.05
Intercellular adhesion molecule-1	2[e]	40	38	-0.77 (-1.23, -0.31)	0.001	0%	0.61
Vascular cell adhesion molecule-1	2[f]	38	36	-0.05 (-0.86, 0.76)	0.90	68%	0.08
E-selectin	2[g]	38	38	-0.57 (-1.03, -0.11)	0.01	0%	0.85

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; [b], ≥ 50% represents substantial heterogeneity; [c], 5 studies removed from the primary meta-analysis: Balen et al. (2008), Fernandes et al. (2011), Ribeiro et al. (2012), Schumacher et al. (2006), and Theodorou et al. (2016); [d], 3 studies removed from the primary meta-analysis: Oliveira et al. (2015), Ribeiro et al. (2012), and Schumacher et al. (2006); [e], 2 studies removed from primary meta-analysis: Oliveira et al. (2015) and Schumacher et al. (2006); [f], 3 studies removed from the primary meta-analysis: Fernandes et al. (2011), Oliveira et al. (2015), and Schumacher et al. (2006); [g], 1 study removed from the primary meta-analysis: Schumacher et al. (2006); *, $p \leq 0.05$ represents statistical significance; **, $p \leq 0.1$ represents substantial heterogeneity; SMD, standardised mean difference; and CI, confidence interval

ESM 4, Table S3. Summary of results for sensitivity analysis of post-intervention C-reactive protein value comparison between exercise and control groups following the removal of Giallauria et al. (2011).

Outcome Measurement	Number of Studies	Number of Participants (Exercise)	Number of Participants (Control)	SMD (95% CI)[a]	P value*	Heterogeneity	
						$I^{2\,b}$	χ^2 (P value)**
C-reactive protein	10	455	373	-0.38 (-0.62, -0.13)	0.003	60%	0.003

[a], a negative SMD represents a lower value in the exercise group compared to control group post-intervention; [b], $\geq 50\%$ represents substantial heterogeneity; *, $p \leq 0.05$ represents statistical significance; **, $p \leq 0.1$ represents substantial heterogeneity; SMD, standardised mean difference; and CI, confidence interval

ESM 4, Table S4. Information regarding adverse events, withdrawals, and exercise session compliance for the included studies.

Author	Subjects	Groups	N (male)	Adverse Events	Withdrawals	Compliance
Balen et al. (2008)	AMI CAD patients	Exercise	30 (21)	No adverse events occured	No withdrawals occurred	NS
		Control	30 (23)	No adverse events occurred	No withdrawals occurred	-
Beckie et al. (2010)	MetS CAD patients	Exercise	39 (0)	NS	4 withdrawals: -Lack of compliance	Attended a mean of 28 ± 13 (78%) of the 36 prescribed exercise sessions
		Exercise	48 (0)	NS	No withdrawals occurred	Attended a mean of 33 ± 9 (92%) of the 36 prescribed exercise sessions
Bilińska et al. (2010)	CABG CAD patients	Exercise	59 (59)	No adverse effects occurred	1 withdrawal: - Commuting problems	NS
		Control	59 (59)	No adverse effects occurred	1 withdrawal: - Commuting problems	-
Conraads et al. (2015)	CAD patients	Exercise	85 (81)	No adverse events were reported during the exercise sessions.	15 withdrawals: - Work (n=3) - Familial/ social circumstances (n=3) - No longer interested (n=1) - Lack of compliance (n=3) - Disappearance (n=1) - Medical reasons (n=4) Intention-to-treat analysis (including withdrawals) was performed for primary outcome measure (VO2$_{peak}$)	Attended 35.7 ± 1.1 of the 36 prescribed exercise sessions.
		Exercise	89 (80)	No adverse events were reported during the exercise sessions.	11 withdrawals: - Work (n=3) - Familial/ social circumstances (n=1)	Attended 35.6 ± 1.5 of the 36 prescribed exercise sessions.

				1 patient had an AMI, 24-hours after the final training session, after which PCI was performed.	- No longer interested (n=2) - Lack of compliance (n=2) - Medical reasons (n=3)	
				2 patients had a significant ST-depression during the cardiopulmonary exercise test at week-6 and underwent PCI.	Intention-to-treat analysis (withdrawals included) was performed for primary outcome measure (VO_{2peak})	
El Missiri and Taher (2016)	CAD patients	Exercise	40 (33)	NS	No withdrawals occurred	NS
		Control	40 (28)	NS	No withdrawals occurred	-
Fernandes et al. (2011)	CAD patients	Exercise	15 (4)	NS	6 withdrawals: - Difficulty in maintaining the routine of going to the exercise sessions (n=3) - Tiredness provoked by exercise (n=2) - Change of job location (n=1) Intention-to-treat analysis performed (withdrawals included)	NS
		Control	19 (9)	NS	No withdrawals occurred	-
Giallauria et al. (2011)	AMI CAD patients	Exercise	37 (28)	No adverse events occurred	No withdrawals occurred	Attended 86% of the prescribed exercise sessions
		Control	38 (32)	No adverse events occurred	No withdrawals occurred	-
Hansen et al. (2011)	CAD patients	Exercise	25 (23)	No orthopaedic injuries occurred within the rehabilitation facility	5 withdrawals: - Did not follow prescription (n=1) - Re-stenosis (n =1) - Injury outside centre (n=1) - Lost to follow-up (n=2)	Attended 18 ± 2.1 exercise sessions over 6-weeks ($\geq$ 90% of overall sessions)
		Exercise	22 (21)	No orthopaedic injuries occurred within the rehabilitation facility	8 withdrawals: - Did not follow prescription (n=2) - Re-stenosis (n=1) - Infection with fever (n =2) - Lost to follow-up (n =1) - Pneumonia (n=1)	Attended 18.8 ± 2.3 exercise sessions over 6-weeks ($\geq$ 90% of overall sessions)

					- Cardiac re-event (n=1)	
Jalaly et al. (2015)	SAP CAD patients	Exercise	20 (11)	NS	No withdrawals occurred	NS
		Control	20 (11)	NS	No withdrawals occurred	-
Lee et al. (2006)	CAD patients	Exercise	40 (NS)	NS	No withdrawals occurred	NS
		Exercise	41 (NS)	NS	No withdrawals occurred	NS
		Control	20 (NS)	NS	No withdrawals occurred	NS
Lee et al. (2012)	AMI CAD patients	Exercise	22 (NS)	NS	No withdrawals occurred	NS
		Control	24 (NS)	NS	No withdrawals occurred	NS
Lian et al. (2014)	CAD patients	Morning Exercise	89 (64)	NS	21 withdrawals: - Did not meet the intervention criteria (n=6) - Out of touch (n=6) - Other reasons (n=9)	Completed ≥ 85% of the walking programme (those who did not were excluded from analysis)
		Evening Exercise	89 (69)	NS	21 withdrawals: - Did not meet the intervention criteria (n=5) - Out of touch (n=9) - Other reasons (n=7)	Completed ≥ 85% of the walking programme (those who did not were excluded from analysis)
		Control	97 (68)	NS	13 withdrawals: - Out of touch (n=7) - Personal circumstance (n=6)	-
Luk et al. (2012)	CAD patients	Exercise	32 (24)	NS	No withdrawals	Attended 94% of the prescribed exercise sessions
		Control	32 (24)	NS	No withdrawals	-

Madssen et al. (2014)	CAD patients	Exercise	24 (18)	No adverse events experienced during maximum exercise testing or training sessions 1 patient was diagnosed with a duodenal ulcer and atrial fibrillation 1 patient was diagnosed with chronic lymphatic leukaemia	No withdrawals occurred	On average, participants attended 7.8 of the 8 supervised exercise sessions ⅓ of participants reported that they complied with the prescribed home exercise programme (3 exercise sessions per week)
		Control	25 (18)	1 patient experienced a tibia fracture 1 patient underwent surgical treatment for breast carcinoma	No withdrawals occurred	-
Moholdt et al. (2012)	AMI CAD patients	Exercise	59 (49)	No major complications or cardiac events associated with the study protocol occurred.	13 withdrawals: - ≤ 17 exercise sessions (n=7) -Acute gastrointestinal bleeding (n=1) -Angina pectoris (n=1) -Bronchitis (n=1) -Knee surgery (n=1) -Low back pain (n=1) -Psychiatric disease (n=1) Intention-to-treat analysis (including withdrawals) was performed for primary outcome measure (VO_{2peak})	Attended 19.1 ± 4 of the 24 prescribed exercise sessions Participants who completed ≤ 17 exercise sessions were not included in analysis
		Exercise	30 (25)	No major complications or cardiac events associated with the study protocol occurred	5 withdrawals: - ≤ 17 exercise sessions (n=1) -Pancreatitis (n=1) -Angina pectoris (n=1) -Intermittent claudication (n=1) -Gastroenteritis (n=1) Intention-to-treat analysis (including withdrawals) was performed for primary outcome measure (VO_{2peak})	Attended 20.4 ± 5 of the 24 prescribed exercise sessions Participants who completed ≤ 17 exercise sessions were not included in analysis

Munk et al. (2011)	CAD patients	Exercise	18 (16)	No adverse events occurred	2 withdrawals: - Excluded from analysis due to unstable angina	Attended ≥ 90% of the prescribed exercise sessions
		Control	18 (14)	No adverse events occurred	2 withdrawals: - Excluded from analysis due to unstable angina	-
Oliveira et al. (2015)	AMI CAD patients	Exercise	44 (38)	No adverse events occurred	5 withdrawals: - Lost to follow-up (n=2) - Acute inflammatory process (n=3) Intention-to-treat analysis (on the basis of assigned treatment) was performed	41 participants attended ≥ 80% of the prescribed exercise sessions
		Control	42 (34)	No adverse events occurred	5 withdrawals: - Lost to follow-up (n=2) - Acute inflammatory process (n=3) Intention-to-treat analysis (on the basis of assigned treatment) was performed	-
Pedersen et al. (2016)	CAD patients	Exercise	30 (NS)	No serious adverse events occurred	5 withdrawals: - Time (n=3) - Gout (n=1) - Stopped statin (n=1) Intention-to-treat analysis (all participants (regardless of adherence) who were examined at 12-weeks included) was performed	25 participants attended ≥ 60% of the prescribed exercise sessions, and attended ≥ 50% of the prescribed exercise sessions during the final 2-weeks of the study
		LED	34 (NS)	No serious adverse events occurred Side effects: - Dizziness (n=10)	1 withdrawal: - Examination	29 participants achieved ≥ 5% weight loss

				- Headaches (n=9) - Obstipation (n=9) - Fatigue (n=7)		Intention-to-treat analysis (all participants (regardless of adherence) who were examined at 12-weeks included) was performed	
Raygan et al. (2017)	CAD patients	Exercise	21 (21)		NS	No withdrawals occurred	NS
		Control	23 (23)		NS	No withdrawals occurred	NS
Ribeiro et al. (2012)	AMI CAD patients	Exercise	20 (18)		NS	2 withdrawals: - Did not complete ≥ 80% of the prescribed exercise sessions (n=2)	Attended 24 ± 0.67 of the 24 prescribed exercise sessions
		Control	18 (13)	1 patient died during the study; cause of death was not reported		2 withdrawals: - Death (n=1) - Declined to participate in the final assessment without any particular reason (n=1)	-
Schumacher et al. (2006)	CAD patients	Exercise	95 (78)	1 patient died during the study; cause of death was not reported		3 withdrawals: - Death (n=1) - Non-compliance (n=2)	NS
		Control	94 (80)		NS	5 withdrawals: - Non-compliance (n=5)	-
Sixt et al. (2008)	IGT CAD patients	Exercise	13 (10)		NS	No withdrawals occurred	NS
		Rosiglitazone	11 (11)		NS	No withdrawals occurred	-
		Control	10 (7)		NS	No withdrawals occurred	-

Theodorou et al. (2016)	CAD patients	Exercise	15 (15)	NS	No withdrawals occurred	NS
		Exercise	11 (11)	1 patient suffered a muscle injury; no information provided to ascertain if exercise was the cause	4 withdrawals: - Personal reasons (n=2) - Muscle injury (n=1) - Did not perform more than 10% of the prescribed exercise sessions (n=1)	NS
		Exercise	15 (15)	NS	No withdrawals occurred	NS
		Control	15 (15)	NS	No withdrawals occurred	-
Toyama et al. (2012)	CAD patients	Exercise	14 (9)	NS	No withdrawals occurred	NS
		Exercise	14 (12)	NS	No withdrawals occurred	NS
Vona et al. (2009)	AMI CAD patients	Exercise	52 (39)	No adverse events occurred	6 withdrawals: - Change in medication (n=6)	Attended 92 ± 3% of the 16 prescribed exercise sessions
		Exercise	54 (39)	No adverse events occurred	3 withdrawals: - Change in medication (n=3)	Attended 95 ± 2% of the 16 prescribed exercise sessions
		Exercise	53 (40)	No adverse events occurred	4 withdrawals: - Change in medication (n=4)	Attended 94 ± 4% of the 16 prescribed exercise sessions
		Control	50 (37)	No adverse events occurred	6 withdrawals: - Change in medication (n=6)	-

Data are presented as mean ± standard deviation; N, number; MetS, metabolic syndrome; CAD, coronary artery disease; CABG, coronary artery bypass graft; AMI, acute myocardial infarction; SAP, stable angina pectoris; LED, low energy diet (800-1000 kcal/day for 8-10 weeks, followed by a weight maintenance diet); IGT, impaired glucose tolerance; PCI, percutaneous coronary intervention; VO_{2peak}, peak oxygen consumption; NS, not stated; and -, not applicable

UNIVERSITY OF ULSTER   **RESEARCH GOVERNANCE**

RG3   Filter Committee Report Form

Project Title	Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others
Chief Investigator	Dr Ciara Hughes
Filter Committee	Nursing and Health Research

This form should be completed by Filter Committees for all research project applications in categories A to D (*for categories A, B, and D the University's own application form – RG1a and RG1b – will have been submitted; for category C, the national, or ORECNI, application form will have been submitted).

Where substantial changes are required the Filter Committee should return an application to the Chief Investigator for clarification/amendment; the Filter Committee can reject an application if it is thought to be unethical, inappropriate, incomplete or not valid/viable.

Only when satisfied that its requirements have been met in full and any amendments are complete, the Filter Committee should make one of the following recommendations:

The research proposal is complete, of an appropriate standard and is in

- category A and the study may proceed*   ☐

- category B and the study must be submitted to the University's Research Ethics Committee** Please indicate briefly the reason(s) for this categorisation   ☐

- category C and the study must be submitted for external review along with the necessary supporting materials from the Research Governance Section***   ☒

- category D and the study must be submitted to the University's Research Ethics Committee**   ☐

Signed: *George Kernohan* Date: 24 Oct. 18   *Chair of Filter Committee*

*The application form and this assessment should now be returned to the Chief Investigator. The Filter Committee should retain a copy of the complete set of forms.

** The application form and this assessment should now be returned to the Chief Investigator so that he/she can submit the application to the UUREC via the Research Governance section. The Filter Committee should retain a copy of the complete set of forms for their own records.

*** The application form and this assessment should now be returned to the Chief Investigator so that he/she can prepare for application to an external committee. The Filter Committee should retain a copy of the complete set of forms for their own records.

For all categories, details of the application and review outcome should be minuted using the agreed format and forwarded to the Research Governance section

Please complete the following

The application should be accompanied by an appropriate and favourable Peer Review Report Form (if not, the Filter Committee should be prepared to address this as part of its review). Please comment on the peer review (include whether or not there is evidence that the comments of the peer reviewers have been addressed).

Peer review of the proposal was completed, filter committee reviewed an earlier version and concerns raised have been addressed. Given further refinement, there are no outstanding issues of serious ethical concern.

Please provide an assessment of all component parts of the application, including questionnaires, interview schedules or outline areas for group discussion/unstructured interviews.

The study design is appropriate for the study.

Please comment on the consent form and information sheet, in particular the level of language and accessibility.

The revised documentation provides adequate clarity as requested by the Committee

Please comment on the qualifications of the Chief and other Investigators.

The CI has an appropriate skill set and with the proposed local investigators, we have a team that is well placed to oversee the clinical aspects of this project.

Please comment on the risks present in conducting the study and whether or not they have been addressed.

Although quite complicated, committee did not find any serious risk associated with the study protocol.

Please indicate whether or not the ethical issues have been identified and addressed.

Issues have been addressed and the benefit in new knowledge to be gained outweighs any possible harm or inconvenience associated with data collection. There is no serious injustice or potential duty of care arising from the study that have not been addressed

Please comment on whether or not the subjects are appropriate to the study and the inclusion/exclusion criteria have been identified and listed

Appropriate subjects have been identified with suitable inclusion and exclusion criteria.

HSC Business Services Organisation

Office for Research Ethics Committees
Northern Ireland
(ORECNI)

Customer Care & Performance Directorate
Lissue Industrial Estate West
5 Rathdown Walk
Moira Road
Lisburn
BT28 2RF
Tel: 028 95361407
www.orecni.hscni.net
Health & Social Care Research Ethics Committee A (HSC REC A)

05 December 2018

Dr Ciara Hughes
Room: 01B118, School of Health Sciences,
Ulster University, Jordanstown,
Shore road, Newtownabbey, Co. Antrim.
BT37 0QB

Dear Dr Hughes

Study Title:	**Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.**
REC reference:	**18/NI/0213**
Protocol number:	**N/A**
IRAS project ID:	**256290**

The Research Ethics Committee reviewed the above application at the meeting held on 27 November 2018. Thank you for your availability to attend the meeting.

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to Dr Alastair Walker, Acting Chair.

Further information or clarification required

The Committee would be content to give a favourable opinion of the application, subject to receiving a complete response to a request for the following information:

1. The Committee requested amendments to the Participant Information Sheets (PIS) as follows:

   - Please include a paragraph in the PIS(s) to explain how limits of disclosure would be dealt with and reported (related to poor practice / criminal activity).

- Please update wording 'ethical approval for this study has been obtained from the Office of Research Ethics Committee' under the heading 'Has an ethical committee approved this study?' to read; 'this study has received a favourable opinion from Health and Social Care Research Ethics Committee A (HSC REC A)'.
- Reference to Data Protection (1998) legislation should be replaced with the 'General Data Protection Regulation (GDPR)' applicable from 25 May 2018. The HRA, on behalf of the UK, has published recommended transparency wording for use to ensure that participant information is compliant with the GDPR. Further information is available at the following link: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Ms Tamla Meredith, HSC REC A Manager.

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. Please refer to the guidance in IRAS for instructions on how to submit a response to provisional opinion electronically.

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. **A response should be submitted by no later than 04 January 2019.**

Extract of the meeting minutes

The Committee welcomed Mr Gareth Thompson, PhD Student, to the meeting by telephone and thanked him for his availability to accept the second telephone call (in the initial call made by the Committee, apologies was tendered as it had been explained that proceedings were behind schedule and a request to make a later call was made. It was acknowledged at that time that you would not be available for the later call but that Mr Gareth Thompson would be.

The Committee conveyed to Mr Thompson that comments from the previous unfavourable application had been taken on board and thanked him for the hard work undertaken, in relation to the application under review, to address concerns that had been raised.

The Committee informed Mr Thompson that there was an observer in attendance and asked if they he had any objection. Mr Thompson confirmed that he had no objection to the observer being present.

<u>**Recruitment arrangements and access to health information, and fair participant selection**</u>

The Committee conveyed to Mr Thompson that it acknowledged that there would be no reimbursement of travel expenses to participants as highlighted in the PIS. Members asked Mr Thompson for the total amount of funding allocated to study as this was not completed in the application. *Mr Thompson advised that the study was PhD funded however that he was not aware of the detail of this but that the information could be obtained if required.* The Committee queried if the funding would be used to pay for the study measurements and if this was the reason that travel would not be covered. *Mr Thompson agreed with this and advised that he did not know what the funding covered but that there was a costing document available and that he could advise that participant travel expenses would not be covered.* The Committee asked if lack of reimbursement could

potentially affect participation i.e people may decline to take part. *He agreed however reiterated that travel costs would not be made.*

In discussion, after the telephone call ended, the Committee agreed that it did not require any further information in relation to funding or non-reimbursement of travel costs associated with the study. This was because potential participants would now be made aware of this as it was included in the PIS.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

Members noted that the Participant information sheet did not explain how limits of disclosure would be dealt with or the reporting structure for same. It was agreed that it should be made clear to participants that any information divulged which related to poor practice or criminal activity in the course of the research would necessitate disclosure.

It was noted that reference to Data Protection (1998) legislation in the Participant Information Sheets should be replaced with The General Data Protection Regulation (GDPR) applicable from 25 May 2018.

The Committee asked Mr Thompson if the post interview group meeting was necessary given that a summary of the discussion during their interview was to be sent to participants. *He confirmed it was and explained that the purpose was to introduce rigor and discuss themes and also to confirm that analysis was reflective of discussion. Mr Thompson again confirmed that there would be no reimbursement of travel expenses.*

Members conveyed to Mr Thompson that it was not clear why DNA analysis was not mentioned in the Participant Information Sheet or Consent Form. *Mr Thompson referred to inflammatory biomarkers and confirmed that there would be no identification of health concerns that participants would be concerned about.*

The Committee thanked Mr Thompson for this availability to attend the meeting by telephone and the call was terminated. .

Informed consent process and the adequacy and completeness of participant information

The Committee noted that the title in the Participant Information Sheet(s) in the previous application given unfavourable opinion did not reflect the qualitative component of the study. Members were content that this had been addressed adequately in the application under review and that the two arms of the study were clearly detailed.

However, in its review of the Participant Information Sheets, the Committee requested amendments as follows:
- A paragraph should be included in the PIS to explain how limits of disclosure would be dealt with and reported (related to poor practice / criminal activity).
- Wording, *'ethical approval for this study has been obtained from the Office of Research Ethics Committee'* under the heading *'has an ethical committee approved this study?'* should be updated to read; 'this study has received a favourable opinion from Health and Social Care Research Ethics Committee A (HSC REC A)'.
- Reference to 'Data Protection (1998) legislation' should be replaced with The General Data Protection Regulation (GDPR) applicable from 25 May 2018. The HRA, on behalf of the UK, has published recommended transparency wording for use to ensure that participant information is compliant with the GDPR (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/).

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Covering letter on headed paper [Cover letter for study protocol]	Version 4	16 October 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of indemnity]		16 July 2018
Interview schedules or topic guides for participants [Interview guide]	Version 4	05 October 2018
IRAS Application Form [IRAS_Form_08112018]		08 November 2018
IRAS Checklist XML [Checklist_08112018]		08 November 2018
IRAS Checklist XML [Checklist_22112018]		22 November 2018
Letter from sponsor [Sponsor letter]		07 November 2018
Letters of invitation to participant [Letter of invitation]	Version 4	05 October 2018
Non-validated questionnaire [Screening questionnaire for cardiac rehabilitation nurses]	Version 1	10 October 2018
Non-validated questionnaire [Screening questionnaire]	Version 4	10 October 2018
Non-validated questionnaire [BFMD questionnaire]	Version 4	10 October 2018
Other [Flow diagram to accompany PIS for patients who have chosen to take part in a phase-III CR programme]	Version 4	05 October 2018
Other [Flow diagram to accompany PIS for patients who have chosen not to take part in a phase-III CR programme]	Version 4	05 October 2018
Other [Record of Potential Participants who have been Provided with Participant Information Sheets by Cardiac Rehabilitation Nurses]	Version 1	10 October 2018
Other [Record of Study Participants who have been Provided with Participant Information Sheets for the Interview Component of the Study]	Version 1	10 October 2018
Other [Cover letter for new application]	Version 1	23 October 2018
Other [HSC REC A unfavourable opinion letter]		03 October 2018
Other [Rebuttal to Concerns Raised by HSC REC A.]	Version 1	18 October 2018
Other [Lone Worker Policy]		18 September 2017
Participant consent form [Consent form for pilot study]	Version 4	05 October 2018
Participant consent form [Consent form for patients- Interview component of study]	Version 4	05 October 2018
Participant consent form [Consent form for significant other- Interview component of study]	Version 4	05 October 2018
Participant information sheet (PIS) [Patients who have chosen to take part in a phase-III CR programme]	Version 4	05 October 2018
Participant information sheet (PIS) [Patients who have chosen not to take part in a phase-III CR programme]	Version 4	05 October 2018
Participant information sheet (PIS) [PIS for patients- Interview component of study]	Version 4	05 October 2018
Participant information sheet (PIS) [PIS for significant other- Interview component of study]	Version 4	05 October 2018

Referee's report or other scientific critique report [University of Ulster Filter Committee Report Form- Previous application]		23 June 2018
Referee's report or other scientific critique report [University of Ulster- Research Governance]	Version 3	17 May 2018
Referee's report or other scientific critique report [University of Ulster Filter Committee Report Form- Update for new application]		24 October 2018
Research protocol or project proposal [Study Protocol]	Version 4	05 October 2018
Summary CV for Chief Investigator (CI) [CV for CI]	1	27 June 2018
Summary CV for student [CV for Student]	1	26 June 2018
Summary CV for supervisor (student research) [CV for Supervisor]	1	26 June 2018
Summary CV for supervisor (student research) [CV for Supervisor]	1	26 June 2018
Summary CV for supervisor (student research) [CV for Supervisor]	1	26 June 2018
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only) [Evidence of indemnity]		16 July 2018
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Study Flow Diagram]	Version 4	16 October 2018
Validated questionnaire [IPAQ]	Version 3	17 May 2018
Validated questionnaire [IPAQ for elderly]	Version 3	17 May 2018

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Committee Member Dr Helen Harty stated that she had worked with the Chief Investigator for the study but that she had no involvement in the study under review.

Statement of compliance

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

18/NI/0213	**Please quote this number on all correspondence**

Yours sincerely

Tamla Meredith

Tamla Meredith
HSC REC A Committee Manager

Email: RECA@hscni.net

Enclosure: List of names and professions of members who were present at the meeting

Copy to: *Mr Nick Curry, Ulster University*
Alison Murphy, Belfast Health & Social Care Trust

HSC REC A
Attendance at Committee meeting on 27 November 2018

Committee Members:

Name	Profession	Present	Notes
Ms Margaret Brady	Deputy Chief Education Welfare Officer Operations	Yes	
Ms Marie Fenton	Guardian Ad Litem, Social Worker	Yes	
Dr Helen Harty	Clinical Vacillator / Trainer	Yes	
Mrs Julie Howse	Barrister (non practising)	No	
Dr Lorna Lawther	Registered Midwife	Yes	
Mrs Kathryn Logue	Barrister In Independent Practice	No	
Mr Godfrey Madill	Project Manager	Yes	
Ms Rejina Mariam Verghis	Junior Biostatistician	No	
Dr Toni McAloon	Nurse Lecturer	No	
Mr Niall McSperrin	Solicitor	Yes	
Mr Barry Mimnagh	Pharmacist	Yes	
Dr Andrew Moriarty	Cardiologist	Yes	
Dr Charles Mullan	Consultant Radiologist	No	
Dr Mary Murphy	Registered Nurse	Yes	
Mr Patrick Ryan	Retired Civil Servant	No	
Professor Mahendra Varma	Consultant Physician in charge of Cardiology and Diabetic Services (Retired)	No	
Dr Alastair Walker	Retired Head of Education Services, CCEA	Yes	Acting Chair (Chair of meeting 27.11.2018)

Also in attendance:

Name	Position (or reason for attending)
Ms Tamla Meredith	REC Manager ORECNI

IRAS id 256290 REC Ref 18-NI-0213 – REC Provisional Opinion Letter

HSC **Business Services Organisation**

Office for Research Ethics Committees Northern Ireland (ORECNI)

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Tel: 028 95361407
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Health & Social Care Research Ethics Committee A (HSC REC A)

13 December 2018

Dr Ciara Hughes
Room: 01B118, School of Health Sciences,
Ulster University, Jordanstown,
Shore road, Newtownabbey, Co. Antrim.
BT37 0QB

Dear Dr Hughes

Study title:	**Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.**
REC reference:	**18/NI/0213**
Protocol number:	**N/A**
IRAS project ID:	**256290**

Thank you for correspondence of 11 December 2018, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Acting Chair, Dr Alastair Walker.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

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

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

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

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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

Ethical review of research sites

NHS sites

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

IRAS id 256290 REC Ref 18/NI/0213 – REC Favourable Opinion Letter

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering letter on headed paper [Cover letter for study protocol]	Version 4	16 October 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of indemnity]		16 July 2018
Interview schedules or topic guides for participants [Interview guide]	Version 4	05 October 2018
IRAS Application Form [IRAS_Form_08112018]		08 November 2018
IRAS Checklist XML [Checklist_08112018]		08 November 2018
IRAS Checklist XML [Checklist_22112018]		22 November 2018
IRAS Checklist XML [Checklist_11122018]		11 December 2018
Letter from sponsor [Sponsor letter]		07 November 2018
Letters of invitation to participant [Letter of invitation]	Version 4	05 October 2018
Non-validated questionnaire [Screening questionnaire for cardiac rehabilitation nurses]	Version 1	10 October 2018
Non-validated questionnaire [Screening questionnaire]	Version 4	10 October 2018
Non-validated questionnaire [BFMD questionnaire]	Version 4	10 October 2018
Other [Flow diagram to accompany PIS for patients who have chosen to take part in a phase-III CR programme]	Version 4	05 October 2018
Other [Flow diagram to accompany PIS for patients who have chosen not to take part in a phase-III CR programme]	Version 4	05 October 2018
Other [Record of Potential Participants who have been Provided with Participant Information Sheets by Cardiac Rehabilitation Nurses]	Version 1	10 October 2018
Other [Record of Study Participants who have been Provided with Participant Information Sheets for the Interview Component of the Study]	Version 1	10 October 2018
Other [Cover letter for new application]	Version 1	23 October 2018
Other [HSC REC A unfavourable opinion letter]		03 October 2018
Other [Rebuttal to Concerns Raised by HSC REC A.]	Version 1	18 October 2018
Other [Lone Worker Policy]		18 September 2017
Other [Cover letter for requested amendments]	Version 1	07 December 2018
Participant consent form [Consent form for pilot study]	Version 4	05 October 2018
Participant consent form [Consent form for patients- Interview component of study]	Version 4	05 October 2018
Participant consent form [Consent form for significant other- Interview component of study]	Version 4	05 October 2018
Participant information sheet (PIS) [Patients who have chosen to take part in a phase-III CR programme]	Version 5	07 December 2018
Participant information sheet (PIS) [Patients who have chosen not to take part in a phase-III CR programme]	Version 5	07 December 2018
Participant information sheet (PIS) [PIS for patients- Interview component of study]	Version 5	07 December 2018
Participant information sheet (PIS) [PIS for significant other- Interview component of study]	Version 5	07 December 2018
Referee's report or other scientific critique report [University of Ulster- Research Governance]	Version 3	17 May 2018
Referee's report or other scientific critique report [University of		23 June 2018

Ulster Filter Committee Report Form- Previous application]			
Referee's report or other scientific critique report [University of Ulster Filter Committee Report Form- Update for new application]		24 October 2018	
Research protocol or project proposal [Study Protocol]	Version 4	05 October 2018	
Summary CV for Chief Investigator (CI) [CV for CI]	1	27 June 2018	
Summary CV for student [CV for Student]	1	26 June 2018	
Summary CV for supervisor (student research) [CV for Supervisor]	1	26 June 2018	
Summary CV for supervisor (student research) [CV for Supervisor]	1	26 June 2018	
Summary CV for supervisor (student research) [CV for Supervisor]	1	26 June 2018	
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only) [Evidence of indemnity]		16 July 2018	
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Study Flow Diagram]	Version 4	16 October 2018	
Validated questionnaire [IPAQ]	Version 3	17 May 2018	
Validated questionnaire [IPAQ for elderly]	Version 3	17 May 2018	

Statement of compliance

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

After ethical review

Reporting requirements

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

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

User feedback

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

HRA training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

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

Yours sincerely

[signature]

pp Dr Alastair Walker
Acting Chair

Email: RECA@hscni.net

Enclosure: *"After ethical review – guidance for researchers"*

Copy to: *Mr Nick Curry, Ulster University*
                    Ms Alison Murphy, Belfast Health & Social Care Trust
                    Mr Gareth Thompson, PhD Student, Ulster University

Belfast Health and Social Care Trust

caring supporting improving together

22/02/2019

Dr Ciara Hughes
Room: 01B118, School of Health Sciences,
Ulster University, Jordanstown,
Shore road, Newtownabbey, Co. Antrim.
BT37 0QB

Dear Dr Hughes

Study Title: Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.
HSC Trust Ref: 18123CH-AS (Please quote this in all future correspondence)

IRAS Ref: 256290

I am pleased to advise that Belfast HSC Trust has given final Research Governance Permission for the above project to commence. Permission is granted for the duration of the project to 02/12/2019 .

The following documents have been approved for use in the project:

Document	Version
Protocol	V4 05/10/2018
Interview Guide	V4 05/10/2018
Letter of Invitation	V4 05/10/2018
Screening Questionnaire for Cardiac Rehab Nurses	V1 10/10/2018
Screening Questionnaire	V4 10/10/2018
BFMD Questionnaire	V4 10/10/2018
Flow Diagram to accompany PIS for patients who have chosen to take part in a phase-III CR programme	V4 05/10/2018
Flow Diagram to accompany PIS for patients who have not chosen to	V4 05/10/2018

Research Office, 2nd Floor King Edward Building, Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA

V1.0

Date: 08/02/2010

take part in a phase-III CR programme	
Record of Potential Participants who have been provided with PIS's for the Interview Component of the study	V1 10/10/2018
Lone Worker Policy	18/09/2018
Cover Letter for Requested amendments	V1 07/12/2018
Consent form for pilot study	V4 05/10/2018
Consent form for patients – interview component of study	V4 05/10/2018
Consent form for significant other – interview component of study	V4 05/10/2018
PIS: Patients who have chosen to take part in a phase-III programme	V5 07/12/2018
PIS: Patients who have chosen not to take part in a phase-III programme	V5 07/12/2018
PIS: Patients – Interview component of the study	V5 07/12/2018
PIS: Significant Other – Interview component of the study	V5 07/12/2018
Study Flow Diagram	V4 16/10/2018
IPAQ Questionnaire	V3 17/05/2018
IPAQ for elderly	V3 17/05/2018

The following personnel have been approved to work on the study at this Trust:

Name	Indemnity Provided by
Ms Lisa Spratt	BHSCT
Ms Paula Mainie	BHSCT
Ms Heather Hanna	BHSCT
Ms Cheryl Guiney	GLL
Mr Gareth Thompson	UU

Permission is granted subject to the attached conditions and I would ask you to please ensure that all members of the research team are familiar with these. Failure to abide by these conditions will invalidate permission and may result in the cessation of the research.

I wish you every success with your project.

Yours sincerely,

PP *Angela Lorem*

Professor Ian Young
R&D Director

CC
Lisa Spratt
Gareth Thompson
Karen Hodgen

Conditions of Permission

Research Governance permission is issued provided the researcher(s) involved adhere to and abide by the conditions below.

- The researcher(s) must adhere strictly to the research protocol.
- There must be no changes to the research protocol or approved study documentation without the prior consent of the Trust, the Research Ethics Committee and, where applicable, the MHRA.
- There must be no changes in research staff without prior consent of the Trust.
- The Research Office should be informed if the Chief Investigator or Principal Investigator(CI/PI) is unable to continue to fulfil his/her duties as CI/PI for any reason such as long term absence, change in employment etc.
- There must be no increase in the resources required without prior consent of the Trust.
- Researcher(s) must report all untoward incidents and serious adverse events to the Trust.
- Any concerns in relation to the research protocol must be reported to the Trust.
- Researcher(s) must adhere to good research practice principles in line with the ICH Good Clinical Practice (GCP) guidelines.
- Researcher(s) must adhere to the Trust's Research & Development Standard Operating Procedures (available from the Research Office on request)
- On request, researcher(s) must make their research project available to Trust appointed monitors.
- The lead researcher must make an annual report to the Research Office for the duration of the project.
- The lead researcher should inform the Research Office on completion or termination of the project. Completion reports must be sent to the Research Office, Research Ethics Committee and, if applicable, MHRA.

Date: 16.05.2019

Dr Ciara Hughes
Ulster University
Room: 01B118, School of Health Sciences,
Ulster University, Jordanstown,
Shore road, Newtownabbey, Co. Antrim.
BT37OQB

By email to: cm.hughes@ulster.ac.uk

Dear Dr Hughes

Study Title: Effect of a CR programme on Molecular Mechanisms. Version 4.
HSC Trust Ref: SET.18.35
IRAS Ref: 256290

I am pleased to advise that SEHSCT has given Research Governance Permission for the above project to commence until 02/12/2019.

The following documents have been approved for use in the project at this Trust:

Document	Version	Date
Protocol	5	11/02/2019
Screening questionnaire	2	21/02/2019
PIS- taking part in Phase III CRP	6	25/02/2019
Flow diagram to accompany PIS- taking part in Phase III CRP	5	25/02/2019
PIS- not taking part in Phase III CRP	6	25/02/2019
Flow diagram to accompany PIS- not taking part in Phase III CRP	5	25/02/2019
Record of provision of PIS	2	21/02/2019
Invitation letter	5	25/02/2019
Screening questionnaire	5	20/02/2019
DCF Arterial stiffness	1	04/02/2019
DCF ESR	1	04/02/2019
DCF ISWT	1	04/02/2019
DCF standard measurements	1	04/02/2019
DEF clinical characteristics	1	04/02/2019
DEF standard clinical measurements	1	04/02/2019
BMFD Questionnaire	5	21/02/2019
IPAQ for middle aged adults	4	20/02/2019
IPAQ for the elderly	4	20/02/2019
PIS- interview component (patient)	6	25/02/2019
PIS- interview component (significant other)	6	25/02/2019
Interview guide	4	05/10/2018
Study flow diagram	4	16/10/2018
Consent form-pilot	4	05/10/2018
Consent form- interview component (patient)	4	05/10/2018
Consent form- interview component (significant other)	4	05/10/2018

Permission is granted subject to the attached conditions which I would ask you to please ensure that all members of the research team make themselves familiar. Failure to abide by these conditions will invalidate permission and may result in the cessation of the research.

I wish you every success with your project.

Yours sincerely,

Mr Paul Carlin
Research Manager

Copy to: Maureen Morrison, Raymond Gamble, Nick Curry, Gareth Thompson,

Conditions of Permission

Research Governance permission is issued provided the researcher(s) involved adhere to and abide by the conditions below.

- The researcher(s) must adhere strictly to the research protocol.
- There must be no changes to the research protocol or approved study documentation without the prior consent of the Trust, and where applicable, the Research Ethics Committee and the MHRA.
- There must be no changes in research staff without prior consent of the Trust.
- The Research Office should be informed if the Chief Investigator or Principal Investigator(CI/PI) is unable to continue to fulfil his/her duties as CI/PI for any reason such as long term absence, change in employment etc.
- There must be no increase in the resources required without prior consent of the Trust.
- Researcher(s) must report all untoward incidents and serious adverse events to the Trust.
- Any concerns in relation to the research protocol must be reported to the Trust.
- Researcher(s) must adhere to good research practice principles in line with the ICH Good Clinical Practice (GCP) guidelines.
- Researcher(s) must adhere to the Trust's Research & Development Standard Operating Procedures (available from the Research Office on request)
- On request, researcher(s) must make their research project available to Trust appointed monitors.
- The lead researcher must make an annual report to the Research Office for the duration of the project.
- The lead researcher should inform the Research Office on completion or termination of the project.   Completion reports must be sent to the Research Office an, if applicable, Research Ethics Committee and MHRA.

Appendix B (vi). Minor amendment approval (BHSCT).

Belfast Health and Social Care Trust
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Dear Dr Hughes

☐

IRAS Project ID:	256290
Trust Reference:	1823CH-AS
Short Study Title:	Effect of a CR programme on Molecular Mechanisms. Version 4.
Sponsor Amendment Reference Number:	2
Sponsor Amendment Date:	16/09/2019
Amendment Type:	Non Substantial
Amendment Categorisation:	A
Implementation Date:	23/10/2019

I am pleased to advise that the Belfast Health & Social Care Trust has no objection to the implementation of the above amendment at this site, following receipt of regulatory authorisations and/ or ethical opinion, if required.

Please contact me if you require any further information or have any queries.

Regards
Rosaleen

Rosaleen Donaghy
Research Assistant
R & D Office
Room 2006
2nd Floor, King Edward Building
Royal Victoria Hospital
Grosvenor Road
Belfast

South Eastern Health
and Social Care Trust

Subject: Amendment Acknowledgement

Date: 25 Oct 2019

Dr Ciara Hughes
Ulster University
Room: 01B118, School of Health Sciences,
Ulster University, Jordanstown,
Shore road, Newtownabbey, Co. Antrim. BT37OQB

Email to: cm.hughes@ulster.ac.uk

Dear Dr Hughes,

Study title	Effect of a CR programme on Molecular Mechanisms V4
Amendment number	NSA02
Amendment date	16/09/2019
IRAS project ID	256290

Thank you for the notification of amendment for the above study, the Trust has received the following documents:

Document	Version	Date
Notification of Non-Substantial Amendment	NSA2	16/09/2019
Protocol	V6	16/09/2019

SEHSCT cannot permit the study recruitment period to extend beyond the original date of 02/12/2019 due to contracted obligations to another project. However follow-up activity on participants recruited prior to this date may continue at site until 01/07/2020.

Yours sincerely

Paul Carlin
Research Manager
Research and Development

Copy to: Maureen Morrison
                Raymond Gamble
                Nick Curry
                Gareth Thompson

Appendix C. Screening questionnaire for potential participants.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

<u>**Note:**</u> To be completed by cardiac rehabilitation nurses who are members of the research team.
<u>**Instructions:**</u> Please use this screening questionnaire (tick relevant answer) when reviewing the clinical records of patients to identify potential participants whose medical conditions meet the study inclusion criteria.

Completed by (please insert your name): _____

Site: _____

Date: _____

Patient Initials: _____

Patient Health and Social Care Number: _____

Is the patient over 18 years of age?
- ○ Yes
- ○ No

Does the patient possess formally diagnosed coronary artery disease with evidence* of an ST-elevated or non-ST elevated myocardial infarction?
- ○ Yes
- ○ No

* Evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, and the detection of a rise and / or fall in cardiac biomarker values (preferably cardiac troponin), with at least one value above the 99th percentile upper reference limit, along with at least one of the following:

- Symptoms of ischaemia, such as: extreme fatigue, breathlessness, chest pain, and heart palpitations.
- New or presumed new significant ST-segment-T wave changes or new left bundle branch block.
- Development of pathological Q waves on the electrocardiogram.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography.

No evidence of the patient being readmitted to hospital with unstable symptoms (e.g. chest pain, shortness of breath, discomfort, or nausea) during the previous 4-weeks?
- ○ Yes
- ○ No

The patient is not currently diagnosed with unstable angina pectoris?
- ○ Yes
- ○ No

No history or evidence of a cardiac arrest or cardiogenic shock?
- ○ Yes
- ○ No

The patient is not currently diagnosed with uncontrolled hypertension (resting systolic measurement > 180 mm Hg and / or diastolic measurement > 100 mm Hg)?
- ○ Yes
- ○ No

The patient is not currently diagnosed with uncontrolled cardiac arrhythmia (presence of complex arrythmia despite medication or treatment)?
- ○ Yes
- ○ No

The patient is not currently diagnosed with any form of anaemia (haemoglobin < 90 grams/litre)?
- ○ Yes
- ○ No

No history or evidence of hepatic failure?
- ○ Yes
- ○ No

No history of / not currently diagnosed with any form of cancer?
- ○ Yes
- ○ No

If the answer is <u>YES</u> to each question, the patient is eligible for invitation to the study. Please provide the potential participant with the participant information sheets at his/her pre-phase III CR programme assessment. Conversely, if the potential participant has chosen not to take part in a phase-III CR programme, please post the participant information sheets to him/her.

Please store this document in the Trust Site File

Dr Ciara Hughes
Room 01B118
School of Health Sciences
Ulster University
Jordanstown
Shore Road
Newtownabbey
BT37 0QB

Letter of Invitation

Dear Sir or Madam,

Following your referral to participate in a phase-III cardiac rehabilitation (CR) programme with the Belfast Health and Social Care Trust or South Eastern Health and Social Care Trust, I would like to invite you to participate in a research study being conducted by Ulster University.

Recent research has suggested that the exercise part of a phase-III and phase-IV CR programme may activate certain protein molecules that improve the function of blood vessels (arteries) throughout the body. Arteries that are able to function well will allow blood to effectively circulate around the body. These changes could be a reason why phase-III and phase-IV CR programmes improve the health of patients who have suffered a heart attack. However, very little is known about the protein molecules that may cause these changes. Therefore, an aim of this study is to investigate the effect of a phase-III and phase-IV CR programme on protein molecules that may improve the function of arteries.

If you agree to take part in our study, we may invite you to take part in a one-to-one interview with a member of our research team. The purpose of this interview will be to listen to the reasons why you agreed or declined to take part in a phase-III or phase-IV CR programme. If you choose to take part in an interview, we would also ask you to identify a significant other (a partner/spouse, family member or close friend) who is willing to participate in a separate one-to-one interview with a member of our research team. The purpose of this interview will be to listen to your significant other's opinion of why you agreed or declined to take part in a phase-III or phase-IV CR programme.

I have enclosed information sheets that contain further details for you to consider. Please note that participation in this study is entirely voluntary. If you choose to participate, the care you receive and structure of the phase-III and phase-IV CR programmes will remain unchanged. The same circumstances apply if you choose not to participate.

Yours faithfully,

Dr Ciara Hughes

Please Note: If you have received these information sheets in the post, the research team from Ulster University has not accessed or been provided with your personal information. These information sheets were posted to you by cardiac rehabilitation nurses from the Belfast Health and Social Care Trust or South Eastern Health and Social Care Trust.

**Participant Information Sheets for Patients who have chosen to Participate in a Phase-III
Cardiac Rehabilitation Programme: Pilot Study.**

Project Title:
*Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial
Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR
Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

You are being invited to take part in a research study, which is part of a PhD project at Ulster
University (UU). Before you decide whether or not to take part, it is important that you
understand what the research is for, and what you will be asked to do. Please read the following
information and do not hesitate to ask any questions about anything that might not be clear to
you. Please ensure that you are happy before you make your decision. Thank you for taking the
time to consider this invitation.

What is the purpose of this study?
Exercise is an important part of a phase-III and phase-IV CR programme. Recent research has
stated that exercise may improve the health of a patient who has suffered a heart attack by
activating protein molecules that improve the function of blood vessels (arteries) throughout
the body. However, very little is known about the protein molecules that cause this
improvement. Therefore, an aim of this study is to investigate the effect of a phase-III and
phase-IV CR programme on protein molecules that may improve artery function. By doing so, it
may better our understanding of how exercise improves the health of a patient who has
suffered a heart attack, and possibly emphasise the effectiveness of a phase-III and phase-IV CR
programme.

The other aim of our study is to understand the reasons why patients agreed or declined to take
part in a phase-III or phase-IV CR programme. We would also like to explore a significant other's
(a patient's partner/spouse, family member or close friend) view towards why the patient made
his/her decision. To do this, we will have to perform one-to-one interviews with a certain
amount of participants to receive the information that we need. Therefore, if you agree to
participate in our study, we may invite you to take part in a one-to-one interview with the PhD
researcher (Mr Gareth Thompson (GT)). If you choose to take part in an interview, we would
also ask you to identify a significant other who is willing to participate in a separate one-to-one
interview with the PhD researcher (GT).

Who is eligible to take part in this study?
You have been invited to take part in this study as you have recently suffered a heart attack, and
have chosen to participate in a phase-III CR programme that will be run by the Belfast Health
and Social Care Trust (BHSCT) or South Eastern Health and Social Care Trust (SEHSCT). You will
be eligible to take part in this study if you intend to take part in the supervised group exercise
sessions.

Do I have to take part?
You are under no obligation to take part in this study. If you agree to participate, you can
change your mind at any time and withdraw from this study without giving a reason.
Withdrawing from this study will not influence your standard of care or your participation in the

phase-III or phase-IV CR programme. If you do withdraw, we will keep any measurements or data that you have already given us up to that point to analyse.

What does this study involve if I agree to take part? (Please see attached: "Study Flow Diagram" for visual aid)

We will ask you to provide study measurements at three "Time Points" over a 22-week period. Time Point 1 (week-1) and Time Point 2 (week-8) will be on the first and final day of the phase-III CR programme at your allocated site where the programme is being held. At Time Point 2, cardiac rehabilitation nurses will routinely offer you the opportunity to complete 12-weeks of additional supervised exercise by entering a phase-IV CR programme. Time Point 3 (week-22) will be on the last day of the phase-IV CR programme at your allocated site where the programme is being held. If you do not take part in the phase-IV CR programme, we will ask you to provide the final study measurements at a time and location that is convenient for yourself, such as: a BHSCT site, Ulster Hospital, or an UU campus.

At each Time Point, we will ask to use an ultrasound device and a small fingertip probe to evaluate how well your arteries are functioning. You will be asked to complete a short questionnaire before these procedures are performed to obtain information on lifestyle factors that may affect the results of the measurements. These procedures are not invasive and will last no longer than 15 minutes.

You will also be asked to provide a blood sample (51.2 millilitres (ml)), which will be drawn from a forearm vein. The blood samples will be analysed to evaluate the proteins that may improve the function of your arteries.

At Time point 3, we will ask to obtain a measurement of blood pressure, resting heart rate, weight, height, and waist circumference. These measurements will be recorded either by the phase-IV CR programme facilitator or by the PhD researcher (GT) in a quiet room. You will then be asked to perform an Incremental Shuttle Walk Test (ISWT) to evaluate how well you can exercise. This test will involve you walking back and forth along an unobstructed corridor or gymnasium floor in time with a "bleep" played from an audio-recording. This test will finish when you can no longer keep up with the "bleep". To ensure that this test is performed safely, we would ask for you to ensure that a light meal is consumed 1-2 hours before the test takes place. Also, we will request for you to wear comfortable clothing and appropriate footwear for walking. If you have stable angina, we will ask for you to bring your prescribed medication (e.g. sublingual nitroglycerin) to the test in case you experience chest pain whilst exercising.

The study measurement procedures will be completed by the PhD researcher (GT) who has obtained the relevant training to safely perform each test.

We will ask you to self-complete an International Physical Activity Questionnaire (IPAQ) at each time point. Each IPAQ will involve you answering questions about your level of physical activity over the past week by ticking boxes. These forms will allow us to evaluate if your level of physical activity throughout the study affected the study measurements.

When may you and your significant other be invited to participate in the interview part of this study?

If we have not completed all of the interviews that we need, we will ask for your informed consent to invite you to participate in the interview part of this study. If you give us informed

Effect of a CR Programme on Molecular Mechanisms: Participant Information Sheets for Patients who have chosen to Participate in a Phase-III CR Programme: Pilot Study. Version 6- 25/02/19.

consent, we will provide you with further information about this part of the study, and supply participant information sheets and consent forms for yourself and your significant other at Time Point 3. You will then be asked to identify a significant other e.g. a partner/spouse, family member or close friend who has been impacted or involved the most by your heart attack and during your recovery period. If the chosen individual is interested in participating, you will be asked to give your significant other his/her participant information sheets and consent form.

For us to obtain the information that we need, we have to conduct interviews with patients and their significant others. Therefore, you and your significant other must both be willing to participate in an interview in order to be included in the interview part of this study. If you and your significant other are willing to take part in an interview, the participant information sheets will request for each person to contact the PhD researcher (GT) to arrange a suitable time and location for his/her interview to be held, such as: his/her home, an UU campus, Ulster Hospital, or a BHSCT site.

What will the interview part of this study involve if my significant other and I agree to take part?
You and your significant other would take part in separate one-to-one interviews with the PhD researcher (GT). Each interview is expected to last around 40-60 minutes, and will take place in a quiet, private room at a time and location that is convenient for you and your significant other. During your interview, you will be asked questions about the following topics: your opinion of a phase-III and phase-IV CR programme, reasons why you agreed or declined to attend, and your opinion of exercise. During your significant other's interview, he/she will be asked questions about the following topics: opinion of a phase-III and phase-IV CR programme, reasons why he/she believes you agreed or declined to attend, and his/her opinion of exercise.

Each interview will be audio-recorded to help us understand the reasons why you made your decision. The responses provided during the interviews will be anonymised to ensure that each participant's thoughts and feelings are kept confidential.

What if you change your mind and decide not to take part in the phase-III CR programme or phase-IV CR programme?
It is completely fine for you to change your mind and not take part in the phase-III CR programme or phase-IV CR programme at any point. If you do change your mind, but would like to remain a participant in this study, we would continue to ask for you to provide the study measurements at the three Time Points.

Would you be willing to allow us to access the results of your standard clinical measurements and medical notes?
We will ask you to provide us with informed consent to access the results of your standard clinical measurements including: ISWT results, blood pressure, resting heart rate, height, weight, and routine blood tests to supplement our study measurements. Also, we will ask you to provide us with informed consent to access your medical notes to obtain information about what type of heart attack you had, conditions you have been diagnosed with, treatment you have received, and the medication that you have been prescribed. This information will help us understand the results of your study measurements.

What will happen to the blood samples?

Blood samples that have been provided for this study will be handled in accordance with the Human Tissue Authority (HTA) regulations that are based on the policies enforced by the Human Tissue Act (2004). Your blood samples will be clearly labeled with a unique code to prevent the display of any personal information that may be used to identify you. The blood samples will be stored in an HTA compliant freezer at UU, Jordanstown until analyses are performed in the research laboratory. The blood samples will not be used for any purpose other than that required for this study, and will be destroyed immediately after analyses have been performed in accordance with UU Health and Safety guidelines.

What are the potential benefits or risks for participants?
By participating in this study, you will provide valuable information that may help to advance research within this area. Any bruising or discomfort you experience during the blood draws will be minimised by applying pressure to the needle wound. During the ultrasound procedure, you may feel a temporary "pins and needles" sensation in your hand during the inflation of a blood pressure cuff. However, this feeling will disappear when the cuff has been released after 5 minutes.

All study measurements shall be taken within a suitable area with appropriate medical/ first aid support being readily available. Any study measurement will be stopped if you feel uncomfortable. If you decide not to take part in the phase-IV CR programme, we will ask you to travel to a site to provide the final study measurements at Time Point 3. Therefore, we will ask you to provide informed consent for us to use your personal contact details (e.g. telephone/ mobile number or email address) to arrange a suitable time and location for you to provide the study measurements at Time Point 3. Due to funding limitations, we will not be able to pay you for the cost of this travel. Therefore, we would like to state that you will be under no pressure to unsuitably travel to provide the study measurements; the decision to do so will be completely your own. Also, your participation in this study will not be affected if you choose not to be invited to take part in an interview. The decision to participate in the interview part of this study will be completely your own.

What if something goes wrong?
It is unlikely that something will go wrong during this study. However, if any issues or problems arise, UU has Research Ethics and Governance procedures in place for reporting, investigating, recording, and handling adverse events. Any complaints will be taken seriously. If you have any concerns please contact Dr Ciara Hughes (CH), Chief Investigator for this study (contact details below). In each instance, the Chief Investigator (CH) will report a concern or complaint to the appropriate authority, and every effort will be made to ensure a satisfactory resolution. Further information regarding UU Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Will the data collected during this study be kept confidential?
All data will be held securely and treated in the strictest confidence in compliance with the General Data Protection Regulation (2018). Your personal information will be anonymised using a coding system to prevent the study data from being traced or used to identify you. The electronic study data will be stored on a password protected computer, and paper based data will be stored in a secure central data bank at UU. Only members of the research team will have access to study data. Due to legal requirements, regulatory inspectors may request access to your personal data during the study to verify or cross check data during an audit. The study data will be erased or shredded after 10 years of storage in accordance with UU policy.

If you inform the research team of any information related to poor practice (e.g. misconduct of a health care provider) or criminal activity during the course of this study, the research team will be required to report these matters to an appropriate authority. Issues associated with poor practice would be reported in accordance with the BHSCT or SEHSCT complaints procedure. Matters related to criminal activity would be reported to the relevant law enforcement agency.

Has an ethical committee approved this study?
This study has received a favourable opinion from the Health and Social Care Research Ethics Committee A, the BHSCT Research Governance Committee, and the SEHSCT Research Governance Committee. This process ensures that this study will protect your safety, rights, well-being, and dignity.

Who will carry out this research?
Dr Ciara Hughes (Chief investigator), Mr Gareth Thompson (PhD researcher), Prof Gareth Davison, and Mrs Jacqui Crawford. Each member of this research team is based at UU. Funding for this study has been obtained from the Department of Economy Studentship.

What will happen to the results of this study?
The results from this study shall be analysed, written up as part of a PhD thesis, and potentially published as a paper in a scientific journal. Any information that may identify you will be removed prior to publication. If you would like to be informed of the results of this study, please feel free to contact any member of the research team (contact details below) after the study has been completed.

Who do I speak to if I have any questions?
Please feel free to contact the PhD researcher (GT- contact details below) if you have any questions or queries. If you would like to receive independent advice about participating in this study from an individual who is not a member of the research team, please contact Mr Nick Curry (contact details below).

What next?
If you are interested in participating in our study, please contact the PhD researcher (GT- contact details below) who will provide you with details surrounding a time and location for a meeting with the research team. A thorough explanation of the study shall be given at this meeting, and any questions or queries shall be answered. The research team will then ask you to complete a screening questionnaire to ensure that you are eligible to participate. If you are willing and eligible to participate following the meeting, you will be asked to provide informed consent by signing a consent form, and be recruited to our study.

Contact details:
- Mr Gareth Thompson, PhD Researcher
- Phone: 07714198795
- Email: Thompson-G7@ulster.ac.uk

- Dr Ciara Hughes, Senior Lecturer Clinical Physiology
- Phone: +44 (0)2890366227
- Email: cm.hughes@ulster.ac.uk

- Mr Nick Curry, Head of Research Governance, Ulster University
- Phone: +44(0)2890366629
- Email: n.curry@ulster.ac.uk

Flow Diagram that Depicts the Protocol of the Pilot Study for Patients who have chosen to Participate in a Phase-III Cardiac Rehabilitation Programme.

If you are interested in participating in this study, we ask that you contact the PhD researcher (Mr Gareth Thompson (GT) - see attached participant information sheets for contact details) who will invite you to a meeting with the research team.

This meeting will be held on the first day of the phase-III cardiac rehabilitation (CR) programme at your allocated site where the programme is being held.

The research team will provide you with a thorough explanation of the study and answer any questions at the meeting. If you are willing to participate, you will be asked to complete a screening questionnaire to check if you meet the participant inclusion criteria for this study. If you are eligible and willing to participate, you will then be asked to provide written informed consent by signing a consent form and be recruited to the study. If we have not completed all of the interviews that we need, we will also ask for your informed consent to invite you to participate in the interview part of this study.

After the meeting, you will be asked to provide the measurements of artery function in a quiet room (Time Point 1- week-1).

You will be asked to provide a blood sample (51.2 ml).

You will then be given the International Physical Activity Questionnaires (IPAQs).

Time Point 2 (week-8) will be on the final day of the phase-III CR programme at your allocated site where the programme is being held.

The study measurements will follow the same procedures and order as the study measurements that were obtained at Time Point 1.

The PhD researcher (GT) will collect the IPAQs that have been completed up until this point from you.

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You will be routinely offered the opportunity to enter a phase-IV CR programme by the cardiac rehabilitation nurses.

↓

Time Point 3 (week-22) will be on the final day of the phase-IV CR programme.

↓

If you have taken part in the phase-IV CR programme, you will be asked to provide the final study measurements on the last day of the phase-IV CR programme at your allocated site where the programme is being held. If you have not taken part in the phase-IV CR programme, you will be asked to provide the final study measurements at a time and location that is convenient for yourself, such as: a Belfast Health and Social Care Trust (BHSCT) site, Ulster Hospital, or an Ulster University (UU) campus.

↓

The final study measurements will be obtained following the same procedures and order as the study measurements that were taken at Time Point 1 and Time Point 2.

↓

At this Time Point, you will also be asked to provide the following measurements: blood pressure, resting heart rate, height, weight, waist circumference, and asked to complete an Incremental Shuttle Walk Test.

↓

The PhD researcher (GT) will collect the IPAQs that have been completed up until this point from you.

↓

If you provided us with informed consent to be invited to the interview part of this study, we will then give you further details about what the interview will involve. If you are interested in taking part, you will be supplied with participant information sheets and consent forms for yourself and your significant other (partner/spouse, family member or close friend).

↓

If you and your significant other are willing to participate in an interview, the participant information sheets will request for each person to contact the PhD researcher (GT) to arrange a suitable time and location for his/her interview to be held, such as: his/her home, an UU campus, Ulster Hospital, or a BHSCT site.

↓

The study measurements will be analysed by the PhD researcher (GT) in a research laboratory at UU.

↓

A summary sheet of the study findings will be sent to you by the research team when the study has been completed if you have requested to be informed of the study results.

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Dr Ciara Hughes
Room 01B118
School of Health Sciences
Ulster University
Jordanstown
Shore Road
Newtownabbey
BT37 0QB

Letter of Invitation

Dear Sir or Madam,

Following your referral to participate in a phase-III cardiac rehabilitation (CR) programme with the Belfast Health and Social Care Trust or South Eastern Health and Social Care Trust, I would like to invite you to participate in a research study being conducted by Ulster University.

Recent research has suggested that the exercise part of a phase-III and phase-IV CR programme may activate certain protein molecules that improve the function of blood vessels (arteries) throughout the body. Arteries that are able to function well will allow blood to effectively circulate around the body. These changes could be a reason why phase-III and phase-IV CR programmes improve the health of patients who have suffered a heart attack. However, very little is known about the protein molecules that may cause these changes. Therefore, an aim of this study is to investigate the effect of a phase-III and phase-IV CR programme on protein molecules that may improve the function of arteries.

If you agree to take part in our study, we may invite you to take part in a one-to-one interview with a member of our research team. The purpose of this interview will be to listen to the reasons why you agreed or declined to take part in a phase-III or phase-IV CR programme. If you choose to take part in an interview, we would also ask you to identify a significant other (a partner/spouse, family member or close friend) who is willing to participate in a separate one-to-one interview with a member of our research team. The purpose of this interview will be to listen to your significant other's opinion of why you agreed or declined to take part in a phase-III or phase-IV CR programme.

I have enclosed information sheets that contain further details for you to consider. Please note that participation in this study is entirely voluntary. If you choose to participate, the care you receive and structure of the phase-III and phase-IV CR programmes will remain unchanged. The same circumstances apply if you choose not to participate.

Yours faithfully,

Dr Ciara Hughes

Please Note: If you have received these information sheets in the post, the research team from Ulster University has not accessed or been provided with your personal information. These information sheets were posted to you by cardiac rehabilitation nurses from the Belfast Health and Social Care Trust or South Eastern Health and Social Care Trust.

Participant Information Sheets for Patients who have chosen not to Participate in a Phase-III Cardiac Rehabilitation Programme: Pilot Study.

Project Title:
Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.

You are being invited to take part in a research study, which is part of a PhD project at Ulster University (UU). Before you decide whether or not to take part, it is important that you understand what the research is for, and what you will be asked to do. Please read the following information and do not hesitate to ask any questions about anything that might not be clear to you. Please ensure that you are happy before you make your decision. Thank you for taking the time to consider this invitation.

What is the purpose of this study?
Exercise is an important part of a phase-III and phase-IV CR programme. Recent research has stated that exercise may improve the health of a patient who has suffered a heart attack by activating protein molecules that improve the function of blood vessels (arteries) throughout the body. However, very little is known about the protein molecules that cause this improvement. Therefore, an aim of this study is to investigate the effect of a phase-III and phase-IV CR programme on protein molecules that may improve artery function. By doing so, it may better our understanding of how exercise improves the health of a patient who has suffered a heart attack, and possibly emphasise the effectiveness of a phase-III and phase-IV CR programme.

The other aim of our study is to understand the reasons why patients agreed or declined to take part in a phase-III or phase-IV CR programme. We would also like to explore a significant other's (a patient's partner/spouse, family member or close friend) view towards why the patient made his/her decision. To do this, we will have to perform one-to-one interviews with a certain amount of participants to receive the information that we need. Therefore, if you agree to participate in our study, we may invite you to take part in a one-to-one interview with the PhD researcher (Mr Gareth Thompson (GT)). If you choose to take part in an interview, we would also ask you to identify a significant other who is willing to participate in a separate one-to-one interview with the PhD researcher (GT).

Who is eligible to take part in this study?
You have been invited to take part in this research study as you have recently suffered a heart attack, and have chosen not to participate in a phase-III CR programme that will be run by the Belfast Health and Social Care Trust (BHSCT) or South Eastern Health and Social Care Trust (SEHSCT). We would like to compare the function of your arteries and the protein molecules within your blood samples to those from people who have participated in a phase-III and phase-IV CR programme.

Do I have to take part?
You are under no obligation to take part in this research study. If you agree to participate, you can change your mind at any time and withdraw from this study without giving a reason. Withdrawing from this study will not influence the standard of care you receive. If you do

withdraw, we will keep any measurements or data that you have already given us up to that point to analyse.

What does this study involve if I agree to take part? (Please see attached: "Study Flow Diagram" for visual aid)

We will ask you to provide study measurements at three "Time Points" over a 22-week period. Time Point 1 (week-1), Time Point 2 (week-8), and Time Point 3 (week-22) will each be at a time and location that is convenient for yourself, such as: a BHSCT site, Ulster Hospital, or an UU campus. The study measurements that you provide will be compared to a group of participants who have taken part in a phase-III and phase-IV CR programme.

At each Time Point, we will ask to obtain a measurement of blood pressure, resting heart rate, weight, height, and waist circumference in a quiet room. We will then ask to use an ultrasound device and a small fingertip probe to evaluate how well your arteries are functioning. You will be asked to complete a short questionnaire before these procedures are performed to obtain information on lifestyle factors that may affect the results of the measurements. These procedures are not invasive and will last no longer than 15 minutes.

You will be asked to provide a blood sample (51.2 millilitres (ml)), which will be drawn from a forearm vein. The blood samples will be analysed to evaluate the proteins that may improve the function of your arteries.

You will then be asked to perform an Incremental Shuttle Walk Test to evaluate how well you can exercise. This test will involve you walking back and forth along an unobstructed corridor or gymnasium floor in time with a "bleep" played from an audio-recording. This test will finish when you can no longer keep up with the "bleep". To ensure that this test is performed safely, we would ask for you to ensure that a light meal is consumed 1-2 hours before the test takes place. Also, we will request for you to wear comfortable clothing and appropriate footwear for walking. If you have stable angina, we will ask for you to bring your prescribed medication (e.g. sublingual nitroglycerin) to the test in case you experience chest pain whilst exercising.

The study measurement procedures will be completed by the PhD researcher (GT) who has obtained the relevant training to safely perform each test.

We will ask you to self-complete an International Physical Activity Questionnaire (IPAQ) at each time point. Each IPAQ will involve you answering questions about your level of physical activity over the past week by ticking boxes. These forms will allow us to evaluate if your level of physical activity throughout the study affected the study measurements.

When may you and your significant other be invited to participate in the interview part of this study?

If we have not completed all of the interviews that we need, we will ask for your informed consent to invite you to participate in the interview part of this study. If you give us informed consent, we will provide you with further information about this part of the study, and supply participant information sheets and consent forms for yourself and your significant other at Time Point 2. You will then be asked to identify a significant other e.g. a partner/spouse, family member or close friend who has been impacted or involved the most by your heart attack and during your recovery period. If the chosen individual is interested in participating, you will be asked to give your significant other his/her participant information sheets and consent form.

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For us to obtain the information that we need, we have to conduct interviews with patients and their significant others. Therefore, you and your significant other must both be willing to participate in an interview in order to be included in the interview part of this study. If you and your significant other are willing to take part in an interview, the participant information sheets will request for each person to contact the PhD researcher (GT) to arrange a suitable time and location for his/her interview to be held, such as: his/her home, an UU campus, Ulster Hospital, or a BHSCT site.

What will the interview part of this study involve if my significant other and I agree to take part?

You and your significant other would take part in separate one-to-one interviews with the PhD researcher (GT). Each interview is expected to last around 40-60 minutes, and will take place in a quiet, private room at a time and location that is convenient for you and your significant other. During your interview, you will be asked questions about the following topics: your opinion of a phase-III CR programme, reasons why you chose not to attend, and your opinion of exercise. During your significant other's interview, he/she will be asked questions about the following topics: opinion of a phase-III CR programme, reasons why he/she believes you chose not to attend, and his/her opinion of exercise.

Each interview will be audio-recorded to help us understand the reasons why you made your decision. The responses provided during the interviews will be anonymised to ensure that each participant's thoughts and feelings are kept confidential.

What if you change your mind and decide to take part in the phase-III CR programme?

It is completely fine for you to change your mind and take part in the phase-III CR programme at any point. If you do change your mind, but would like to remain a participant in this study, we would continue to ask for you to provide the study measurements at the three Time Points.

Would you be willing to allow us to access the results of your standard clinical measurements and medical notes?

We will ask you to provide us with informed consent to access the results of your standard clinical measurements i.e. routine blood tests to supplement our study measurements. Also, we will ask you to provide us with informed consent to access your medical notes to obtain information about what type of heart attack you had, conditions you have been diagnosed with, treatment you have received, and the medication that you have been prescribed. This information will help us understand the results of your study measurements.

What will happen to the blood samples?

Blood samples that have been provided for this study will be handled in accordance with the Human Tissue Authority (HTA) regulations that are based on the policies enforced by the Human Tissue Act (2004). Your blood samples will be clearly labeled with a unique code to prevent the display of any personal information that may be used to identify you. The blood samples will be stored in a HTA compliant freezer at UU, Jordanstown until analyses are performed in the research laboratory. The blood samples will not be used for any purpose other than that required for this study, and will be destroyed immediately after analyses have been performed in accordance with UU Health and Safety guidelines.

What are the potential benefits or risks for participants?

By participating in this study, you will provide valuable information that may help to advance research within this area. Any bruising or discomfort you experience during the blood draws will be minimised by applying pressure to the needle wound. During the ultrasound procedure, you may feel a temporary "pins and needles" sensation in your hand during the inflation of a blood pressure cuff. However, this feeling will disappear when the cuff has been released after 5 minutes.

All study measurements shall be taken within a suitable area with appropriate medical/ first aid support being readily available. Any study measurement will be stopped if you feel uncomfortable. We will ask you to provide informed consent for us to use your personal contact details (e.g. telephone/ mobile number or email address) to arrange a suitable time and location for you to provide the study measurements at each Time Point. Due to funding limitations, we will not be able to pay you for the cost of this travel. Therefore, we would like to state that you will be under no pressure to unsuitably travel to provide the study measurements; the decision to do so will be completely your own. Also, your participation in this study will not be affected if you choose not to be invited to take part in an interview. The decision to participate in the interview part of this study will be completely your own.

What if something goes wrong?
It is unlikely that something will go wrong during this study. However, if any issues or problems arise, UU has Research Ethics and Governance procedures in place for reporting, investigating, recording, and handling adverse events. Any complaints will be taken seriously. If you have any concerns please contact Dr Ciara Hughes (CH), Chief Investigator for this study (contact details below). In each instance, the Chief Investigator (CH) will report a concern or complaint to the appropriate authority, and every effort will be made to ensure a satisfactory resolution. Further information regarding UU Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Will the data collected during this study be kept confidential?
All data will be held securely and treated in the strictest confidence in compliance with the General Data Protection Regulation (2018). Your personal information will be anonymised using a coding system to prevent the study data from being traced or used to identify you. The electronic study data will be stored on a password protected computer, and paper based data will be stored in a secure central data bank at UU. Only members of the research team will have access to study data. Due to legal requirements, regulatory inspectors may request access to your personal data during the study to verify or cross check data during an audit. The study data will be erased or shredded after 10 years of storage in accordance with UU policy.

If you inform the research team of any information related to poor practice (e.g. misconduct of a health care provider) or criminal activity during the course of this study, the research team will be required to report these matters to an appropriate authority. Issues associated with poor practice would be reported in accordance with the BHSCT or SEHSCT complaints procedure. Matters related to criminal activity would be reported to the relevant law enforcement agency.

Has an ethical committee approved this study?
This study has received a favourable opinion from the Health and Social Care Research Ethics Committee A, the BHSCT Research Governance Committee, and the SEHSCT Research Governance Committee. This process ensures that this study will protect your safety, rights, well-being, and dignity.

Effect of a CR Programme on Molecular Mechanisms: Participant Information Sheets for Patients who have chosen not to Participate in a Phase-III CR Programme: Pilot Study. Version 6- 25/02/19.

Who will carry out this research?
Dr Ciara Hughes (Chief investigator), Mr Gareth Thompson (PhD researcher), Prof Gareth Davison, and Mrs Jacqui Crawford. Each member of this research team is based at UU. Funding for this study has been obtained from the Department of Economy Studentship.

What will happen to the results of this study?
The results from this study shall be analysed, written up as part of a PhD thesis, and potentially published as a paper in a scientific journal. Any information that may identify you will be removed prior to publication. If you would like to be informed of the results of this study, please feel free to contact any member of the research team (contact details below) after the study has been completed.

Who do I speak to if I have any questions?
Please feel free to contact the PhD researcher (GT- contact details below) if you have any questions or queries. If you would like to receive independent advice about participating in this study from an individual who is not a member of the research team, please contact Mr Nick Curry (contact details below).

What next?
If you are interested in participating in our study, please contact the PhD researcher (GT- contact details below) who will provide you with details surrounding a time and location for a meeting with the research team. A thorough explanation of the study shall be given at this meeting, and any questions or queries shall be answered. The research team will then ask you to complete a screening questionnaire to ensure that you are eligible to participate. If you are willing and eligible to participate following the meeting, you will be asked to provide informed consent by signing a consent form, and be recruited to our study.

Contact details:

- Mr Gareth Thompson, PhD Researcher
- Phone: 07714198795
- Email: Thompson-G7@ulster.ac.uk

- Dr Ciara Hughes, Senior Lecturer Clinical Physiology
- Phone: +44 (0)2890366227
- Email: cm.hughes@ulster.ac.uk

- Mr Nick Curry, Head of Research Governance, Ulster University
- Phone: +44(0)2890366629
- Email: n.curry@ulster.ac.uk

Effect of a CR Programme on Molecular Mechanisms: Participant Information Sheets for Patients who have chosen not to Participate in a Phase-III CR Programme: Pilot Study. Version 6- 25/02/19.

Flow Diagram that Depicts the Protocol of the Pilot Study for Patients who have chosen not to Participate in a Phase-III Cardiac Rehabilitation Programme.

If you are interested in participating in this study, we ask that you contact the PhD researcher (Mr Gareth Thompson (GT) - see attached participant information sheets for contact details) who will invite you to a meeting with the research team.

⬇

This meeting will be held at a time and location that is convenient for you, such as: a Belfast Health and Social Care Trust (BHSCT) site, Ulster Hospital, or an Ulster University (UU) campus.

⬇

The research team will provide you with a thorough explanation of the study and answer any questions at the meeting. If you are willing to participate, you will be asked to complete a screening questionnaire to check if you meet the participant inclusion criteria for this study. If you are eligible and willing to participate, you will then be asked to provide written informed consent by signing a consent form and be recruited to the study. If we have not completed all of the interviews that we need, we will also ask for your informed consent to invite you to participate in the interview part of this study.

⬇

After the meeting, you will be asked to provide the following measurements: blood pressure, resting heart rate, height, weight, and waist circumference in a quiet room (Time Point 1- week-1).

⬇

You will be asked to provide the measurements of artery function.

⬇

You will be asked to provide a blood sample (51.2 ml).

⬇

You will then be asked to perform an Incremental Shuttle Walk Test on an unobstructed corridor or gymnasium floor.

⬇

You will then be given the International Physical Activity Questionnaires (IPAQs).

⬇

Time Point 2 (week-8) will be at a time and location that is convenient for you, such as: a BHSCT site, Ulster Hospital, or an UU campus.

⬇

Effect of a CR Programme on Molecular Mechanisms: Flow Diagram that Depicts the Protocol of the Pilot Study for Patients who have chosen not to Participate in a Phase-III CR Programme. Version 5- 25/02/19.

The study measurements will follow the same procedures and order as the study measurements that were obtained at Time Point 1.

The PhD researcher (GT) will collect the IPAQs that have been completed up until this point from you.

If you provided us with informed consent to be invited to the interview part of this study, we will then give you further details about what the interview will involve. If you are interested in taking part, you will be supplied with participant information sheets and consent forms for yourself and your significant other (partner/spouse, family member or close friend).

If you and your significant other are willing to participate in an interview, the participant information sheets will request for each person to contact the PhD researcher (GT) to arrange a suitable time and location for his/her interview to be held, such as: his/her home, an UU campus, Ulster Hospital, or a BHSCT site.

Time Point 3 (week-22) will be at a time and location that is convenient for you, such as: a BHSCT site, Ulster Hospital, or an UU campus.

The final study measurements will be obtained following the same procedures and order as the study measurements that were taken at Time Point 1 and Time Point 2.

The PhD researcher (GT) will collect the IPAQs that have been completed up until this point from you.

The study measurements will be analysed by the PhD researcher (GT) in a research laboratory at UU.

A summary sheet of the study findings will be sent to you by the research team when the study has been completed if you have requested to be informed of the study results.

Effect of a CR Programme on Molecular Mechanisms: Flow Diagram that Depicts the Protocol of the Pilot Study for Patients who have chosen not to Participate in a Phase-III CR Programme. Version 5-25/02/19.

Appendix E. Record of PIS provision.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Note: To be completed by cardiac rehabilitation nurses who are members of the research team.
Instructions: Please record the relevant details of potential participants who have been provided with participant information sheets.

Completed by (please insert your name): _____

Site:
_____

Please store this document in the Trust Site File

Patient Initials	Patient Health and Social Care Number	Site	Provision Date	Method of Provision (Please Circle)	Date of First Phase-III CR Programme Session (If Applicable)	Location of First Phase-III CR Programme Session (If Applicable)
				At Assessment *OR* by Post		
				At Assessment *OR* by Post		
				At Assessment *OR* by Post		
				At Assessment *OR* by Post		

Effect of a CR Programme on Molecular Mechanisms: Record of Potential Participants who have been Provided with Participant Information Sheets by Cardiac Rehabilitation Nurses. Version 2- 21/02/19.

				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		
				At Assessment *OR* **by Post**		

Effect of a CR Programme on Molecular Mechanisms: Record of Potential Participants who have been Provided with Participant Information Sheets by Cardiac Rehabilitation Nurses. Version 2- 21/02/19.

Appendix F. Final screening questionnaire.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Note: This form must be completed by a potential participant before informed consent is obtained.
Instructions for participant: Please provide a response for each of the following questions.

All information contained herein will be treated as confidential.

Patient Initials:

_____

Are you able to speak and write in English? (Please tick)
- Yes
- No

Have you been readmitted to hospital during the past 4-weeks with unstable symptoms (e.g. chest pain, shortness of breath, discomfort, or nausea)? (Please tick)
- Yes
- No

Do you have any of the following conditions? (Please tick)
- Periods of a body part turning white or blue along with numbness and pain (Raynaud's phenomenon)
- Physical abnormalities of both arms
- I do not have any of the mentioned conditions

Are you currently pregnant? (Please tick)
- Yes
- No
- Not applicable

Are you currently consuming any of the following supplements? (Please tick)
- Anti-oxidant or vitamin supplements
- Herbal supplements
- Testosterone, estrogen, or progesterone (hormone) supplements
- I am not consuming any of the mentioned supplements

If you have agreed to participate in a phase-III CR programme, do you intend to take part in the supervised group exercise sessions? (Please tick)
- Yes
- No
- Not applicable

Are you currently participating in a different research study?
- Yes
- No

Effect of a CR Programme on Molecular Mechanisms: Screening Questionnaire: Pilot Study. Version 5- 20/02/19.

Note: This section is to be completed by the PhD researcher (Mr Gareth Thompson).

Is the potential participant eligible to participate in this study?
- ○ **Yes**
- ○ **No**
- ○ *IF NO*, **please provide reason:**

_____

_____

_____

Date: _____

Signature: _____

Effect of a CR Programme on Molecular Mechanisms: Screening Questionnaire: Pilot Study. Version 5- 20/02/19.

Appendix G. Consent form for participants: Pilot Study
(Note: one copy for participant, one copy for Trust Site File, and one copy for researcher)

Title of study: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Chief Investigator: Dr Ciara Hughes   **Please initial**

I confirm that I have been given and have read and understood
the information sheets for the above study, and have asked and   [   ]
received answers to any questions raised.

I understand that the research team will ask me to provide study
measurements at three "Time Points" over a period of 22-weeks, and   [   ]
that the decision to do so will be completely my own.

I understand that if I choose to withdraw from the study any information
or data that I have provided up until that point will be retained by the   [   ]
research team for analysis.

I confirm that I give permission for the research team to access the results   [   ]
of my standard clinical measurements and routine blood tests,
and access my medical notes to obtain the stated information.

I confirm that I give permission for the research team to use my
personal contact information to contact me for only the purpose of   [   ]
the study.

I confirm that I give permission for the research team to approach and invite me [   ]
to participate in the interview part of this study.

I understand the nature and risks associated with blood draws,   [   ]
and I confirm and consent for blood collection and storage of the
stated amounts.

I understand that my participation is voluntary, and that I am free
to withdraw at any time without giving a reason, and without my   [   ]
rights or standard of care being affected in any way.

I understand that the researchers will hold all information and data
collected securely and in confidence, and that all efforts will be made
to ensure that I cannot be identified as a participant in the study   [   ]
(except as might be required by law), and I give permission
for the researchers to hold relevant anonymised personal data.

I agree to take part in the above study.   [   ]

Name of participant (please print)	Signature	Date (dd/mm/yyyy)

Name of researcher (please print)	Signature	Date (dd/mm/yyyy)

Please retain this copy for your own records

Further information regarding Ulster University Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Effect of a CR Programme on Molecular Mechanisms: Consent Form: Pilot Study. Version 4-05/10/18.

Appendix H (i). Clinical characteristics data extraction form.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Note: To be used by the research student (Mr Gareth Thompson) when extracting the relevant clinical characteristic information from the medical records of participants.

Participant ID: _____

Patient Site: _____

Date: _____

Age: _____

Gender: _____

Form of myocardial infarction suffered: _____

- **Details:** _____

_____

_____

_____

Co-morbidities:

- **Details:** _____

_____

_____

_____

Surgical Intervention Received:

- **Details:** _____

Effect of a CR Programme on Molecular Mechanisms: Clinical Characteristics of Participants- Data Extraction Form. Version 1- 04/02/19.

_____

_____

_____

Prescribed Medication:

- **Details:** _____

_____

_____

_____

Effect of a CR Programme on Molecular Mechanisms: Clinical Characteristics of Participants- Data Extraction Form. Version 1- 04/02/19.

Appendix H (ii). SCMs data extraction form.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Note: To be used by the research student (Mr Gareth Thompson) when recording the results of routine standard clinical measurements that were obtained from study participants by the CR nurses/ phase-IV CR facilitators.

Participant ID: _____

Patient Site: _____

Date: _____

Time Point: _____

Location: _____

Results of Standard Clinical Measurements:

Functional Exercise Capacity:

-   **Testing Method:** _____

-   **Pre-test Heart Rate:** _____

-   **Pre-test Blood pressure:** _____

-   **1-minute Post-test Heart Rate:** _____

-   **1-minute Post-test Blood Pressure:** _____

-   **Total Recovery Heart Rate and Blood Pressure:** _____

-   **Total Recovery Time:** _____

-   **Test End Point (70% HRR):** _____

Effect of a CR Programme on Molecular Mechanisms: Standard Clinical Measurements- Data Extraction Form. Version 1- 04/02/19.

- **Duration of Test: _____**

- **Outcome: _____**

Blood Pressure:

- **Testing method: _____**

- **Outcome: _____**

Resting Heart Rate:

- **Outcome: _____**

Weight:

- **Outcome: _____**

Height:

- **Outcome: _____**

Body Mass Index:

- **Outcome: _____**

Waist Circumference:

- **Outcome: _____**

Oxygen Saturation:

- **Outcome: _____**

Routine Blood Tests:

- **Outcome: _____**

_____

_____

_____

Attendance at CR sessions: _____

Effect of a CR Programme on Molecular Mechanisms: Standard Clinical Measurements- Data Extraction Form. Version 1- 04/02/19.

Appendix I (i). Patient PIS: Interview component.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

You are being invited to take part in a research study, which is part of a PhD project at Ulster University (UU). Before you decide whether or not to take part, it is important that you understand what the research is for, and what you will be asked to do. Please read the following information and do not hesitate to ask any questions about anything that might not be clear to you. Please ensure that you are happy before you make your decision. Thank you for taking the time to consider this invitation.

What is the purpose of the interview part of this study?
We would like to understand the reasons why patients agreed or declined to take part in a phase-III or phase-IV CR programme. We would also like to explore a significant other's (a patient's partner/spouse, family member or close friend) view towards why the patient made his/her decision. Therefore, we hope to carry out one-to-one interviews with patients who have agreed or declined to take part in a phase-III or phase-IV CR programme, and separate one-to-one interviews with their chosen significant other. Each interview will involve a one-to-one discussion between a participant and the PhD researcher (Mr Gareth Thompson (GT)). During an interview, a participant will be asked questions by the PhD researcher (GT), and encouraged to discuss each answer.

Who is eligible to participate in the interview part of this study?
You have been invited to participate in an interview as you have recently agreed or declined to participate in a phase-III or phase-IV CR programme run by the Belfast Health and Social Care Trust (BHSCT) or South Eastern Health and Social Care Trust (SEHSCT). Your chosen significant other must also agree to take part in an interview in order for you both to be eligible to participate in the interview part of this study.

Do I have to take part?
You are under no obligation to take part in the interview part of this study. If you choose to participate, you can change your mind at any time, and withdraw at any moment without giving a reason. Withdrawing from the interview part of this study will not influence your standard of care or your current participation in our study. If you do decide to withdraw, all of the information that you have provided during your interview will be withdrawn.

What does the interview part of this study involve if I agree to take part?
If you decide to participate, you will be asked to identify a significant other e.g. a partner/spouse, family member or close friend who has been impacted or involved the most by your heart attack and during your recovery period. If the chosen individual is willing to participate, we will ask you to provide him/her with the significant other participant information sheets and consent form that were given to you by the PhD researcher (GT).

For us to obtain the information that we need, we have to conduct interviews with patients and their significant others. Therefore, you and your significant other must both be willing to participate in an interview in order to be included in the interview part of this study. Likewise, if

you or your significant other withdraws from the interview part of this study after completing an interview, the information provided during each person's interview will be withdrawn.

If you and your significant other are willing to participate, we will invite you both to take part in separate one-to-one interviews with the PhD researcher (GT). Each interview is expected to last around 40-60 minutes. You will be offered the opportunity to arrange a suitable time and location for your interview to be held, such as: your home, an UU campus, Ulster Hospital, or a BHSCT site.

Your interview will be held in a quiet, private room at the time and location you have chosen. During your interview, you will be asked questions about the following topics: your opinion of a phase-III or phase-IV CR programme, reasons why you agreed or declined to attend, and your opinion of exercise. The PhD researcher (GT) will take notes of the key points made during this discussion, and your interview will be audio-recorded to help us understand the reasons why you made your decision. The responses that you provide during your interview will be anonymised to ensure that your thoughts and feelings are kept confidential.

After the information that was discussed during your interview has been analysed, you will be sent a summary of the discussion and asked to confirm if it accurately reflects your response to each question. If a particular point is identified in interviews with other participants, we may ask to arrange an additional short interview with you to obtain your opinion of this matter. Again, this interview would be held at a time and location that is suitable for you. Once we have completed all of the interviews that we need, we will invite you to attend a one-off group meeting with the research team and other participants who took part in an interview. This meeting will be held at a time and location that is suitable for each participant who is willing to attend, such as: an UU campus, Ulster Hospital, or a BHSCT site. During the meeting, we will ask the participants to confirm if our findings accurately reflect their thoughts and feelings.

What are the potential benefits or risks for participants?
By participating in the interview part of this study, you will provide valuable information that may help to advance research within this area. You will be able to arrange a suitable time and location for your interview to be held e.g. in a quiet, private room at your home. This would prevent you from having to travel to a location to participate in your interview. However, you may prefer for your interview to be held at a different location e.g. in a quiet, private room at an UU campus, Ulster Hospital, or a BHSCT site. In this case, you will be asked to travel to the chosen venue and spend around an hour of your time completing your interview, which may be an inconvenience to you. Also, due to funding limitations, we will not be able to pay you any cost of travel.

The questions that you will be asked during your interview will not be sensitive. However, if you become upset during your interview for any particular reason e.g. when speaking about a negative experience, we will offer you details of organisations that may be able to provide support for these issues if you desire. Your interview will be audio-recorded to help us understand the reasons why you made your decision. If you are uncomfortable with this process, please contact the PhD researcher (GT - contact details below) who will provide you with further information regarding this matter.

We will ask you to provide informed consent for us to use your personal contact details (e.g. telephone/ mobile number or email address) to possibly arrange an additional short interview,

send you a descriptive summary of your interview discussion, and invite you to a one-off group meeting with the research team and other willing participants who took part in an interview. Each of these requests will not be compulsory and the decision to do so will be completely your own.

What if something goes wrong?
It is unlikely that something will go wrong during the interview part of this study. However, if any issues or problems arise, UU has Research Ethics and Governance procedures in place for reporting, investigating, recording, and handling adverse events. Any complaints will be taken seriously. If you have any concerns please contact Dr Ciara Hughes (CH), Chief Investigator for this study (contact details below). In each instance, the Chief Investigator (CH) will report a concern or complaint to the appropriate authority, and every effort will be made to ensure a satisfactory resolution. Further information regarding UU Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Will the data collected during the interview part of this study be kept confidential?
All data will be held securely and treated in the strictest confidence in compliance with the General Data Protection Regulation (2018). Your personal information will be anonymised using a coding system to prevent the data from being traced or used to identify you. The electronic study data will be stored on a password protected computer, and paper-based data will be stored in a secure central data bank at UU. Only members of the research team will have access to study data and audio-recordings. Due to legal requirements, regulatory inspectors may request access to your personal data during the study to verify or cross check data during an audit. The study data will be erased or shredded after 10 years of storage in accordance with UU policy. During the transcription of the audio-recording of your interview, your name will be replaced by an anonymous code e.g. P1, P2 etc. Therefore, no information that may disclose your identity will be associated with any reports or publications associated with the interview part of this study. The audio-recording of your interview will be destroyed following the transcription and analysis of data.

If you discuss any information related to poor practice (e.g. misconduct of a health care provider) or criminal activity during your interview, the research team will be required to report these matters to an appropriate authority. Issues associated with poor practice would be reported in accordance with the BHSCT or SEHSCT complaints procedure. Matters related to criminal activity would be reported to the relevant law enforcement agency.

Has an ethical committee approved the interview part of this study?
The interview part of this study has received a favourable opinion from the Health and Social Care Research Ethics Committee A, the BHSCT Research Governance Committee, and the SEHSCT Research Governance Committee. This process ensures that the interview part of this study will protect your safety, rights, well-being, and dignity.

Who will carry out this research?
Dr Ciara Hughes (Chief Investigator), Mr Gareth Thompson (PhD researcher), Prof Gareth Davison, Mrs Jacqui Crawford, and Dr Iseult Wilson. Each member of this research team is based at UU. Funding for the interview part of this study has been obtained from the Department for Economy Studentship.

What will happen to the results of the interview part of this study?

The results from the interview part of this study shall be analysed, written up as part of a PhD thesis, and potentially published as a paper in a scientific journal. Any information that may identify you will be removed prior to publication. If you would like to be informed of the results, please feel free to contact any member of the research team (contact details below) after the interview part of this study has been completed.

Who do I speak to if I have any questions?

Please feel free to contact the PhD researcher (GT- contact details below) if you have any questions or queries. If you would like to receive independent advice about participating in this study from an individual who is not a member of the research team, please contact Mr Nick Curry (contact details below).

What next?

If you are interested in participating in the interview part of this study, please consider your willingness to participate for one week. After this period, if you are still willing to participate, please contact the PhD researcher (GT- contact details below) who will provide you with further details about the interview part of this study, and answer any questions or queries that you may have. During this contact, if you are willing to participate, you will be able to arrange a suitable time and location for your interview to be held. You will also be asked to bring the attached "consent form" to your interview to complete in the presence of the PhD researcher (GT).

Contact details:

- Mr Gareth Thompson, PhD
  Researcher
- Phone: 07714198795
- Email: Thompson-G7@ulster.ac.uk

- Dr Ciara Hughes, Senior Lecturer
  Clinical Physiology
- Phone: +44 (0)2890366227
- Email: cm.hughes@ulster.ac.uk

- Mr Nick Curry, Head of Research
  Governance, Ulster University
- Phone: +44(0)2890366629
- Email: n.curry@ulster.ac.uk

Appendix I (ii). Significant Other PIS: Interview component.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

You are being invited to take part in a research study, which is part of a PhD project at Ulster University (UU). Before you decide whether or not to take part, it is important that you understand what the research is for, and what you will be asked to do. Please read the following information and do not hesitate to ask any questions about anything that might not be clear to you. Make sure that you are happy before you make your decision. Thank you for taking the time to consider this invitation.

What is the purpose of the interview part of this study?
We would like to understand the reasons why patients agreed or declined to take part in a phase-III or phase-IV CR programme. We would also like to explore a significant other's (a patient's partner/spouse, family member or close friend) view towards why the patient made his/her decision. Therefore, we hope to carry out one-to-one interviews with patients who have agreed or declined to take part in a phase-III or phase-IV CR programme, and separate one-to-one interviews with their chosen significant other. Each interview will involve a one-to-one discussion between a participant and the PhD researcher (Mr Gareth Thompson (GT)). During an interview, a participant will be asked questions by the PhD researcher (GT), and encouraged to discuss each answer.

Who is eligible to participate in the interview part of this study?
You have been invited to participate in an interview as the patient has identified you as his/her significant other (e.g. a partner/spouse, family member or close friend who has been impacted or involved the most by his/her heart attack and during his/her recovery period). You must be over 18 years of age, and be able to speak and write in English to participate in the interview. The patient who identified you must also agree to take part in an interview in order for you both to be eligible to participate in the interview part of this study.

Do I have to take part?
You are under no obligation to take part in the interview part of this study. If you choose to participate, you can change your mind at any time, and withdraw at any moment without giving a reason. If you do decide to withdraw, all of the information that you have provided during your interview will be withdrawn.

What does the interview part of this study involve if I agree to take part?
For us to obtain the information that we need, we have to conduct interviews with patients and their significant others. Therefore, you and the patient must both be willing to participate in an interview in order to be included in the interview part of this study. Likewise, if you or the patient withdraws from the interview part of this study after completing an interview, the information provided during each person's interview will be withdrawn.

If you and the patient are willing to participate, we will invite you both to take part in separate one-to-one interviews with the PhD researcher (GT). Each interview is expected to last around 40-60 minutes. You will be offered the opportunity to arrange a suitable time and location for

your interview to be held, such as: your home, an UU campus, Ulster Hospital, or a Belfast Health and Social Care Trust (BHSCT) site.

Your interview will be held in a quiet, private room at the time and location you have chosen. During your interview, you will be asked questions about the following topics: your opinion of a phase-III or phase-IV CR programme, reasons why you believe the patient agreed or declined to attend, and your opinion of exercise. The PhD researcher (GT) will take notes of the key points made during this discussion, and your interview will be audio-recorded to help us understand the reasons why the patient made his/her decision. The responses that you provide during your interview will be anonymised to ensure that your thoughts and feelings are kept confidential.

After the information that was discussed during your interview has been analysed, you will be sent a summary of the discussion and asked to confirm if it accurately reflects your response to each question. If a particular point is identified in interviews with other participants, we may ask to arrange an additional short interview with you to obtain your opinion of this matter. Again, this interview would be held at a time and location that is suitable for you. Once we have completed all of the interviews that we need, we will invite you to attend a one-off group meeting with the research team and other participants who took part in an interview. This meeting will be held at a time and location that is suitable for each participant who is willing to attend, such as: an UU campus, Ulster Hospital, or a BHSCT site. During the meeting, we will ask the participants to confirm if our findings accurately reflect their thoughts and feelings.

What are the potential benefits or risks for participants?
By participating in the interview part of this study, you will provide valuable information that may help to advance research within this area. You will be able to arrange a suitable time and location for your interview to be held e.g. in a quiet, private room at your home. This would prevent you from having to travel to a location to participate in your interview. However, you may prefer for your interview to be held at a different location e.g. in a quiet, private room at an UU campus, Ulster Hospital, or a BHSCT site. In this case, you will be asked to travel to the chosen venue and spend around an hour of your time completing your interview, which may be an inconvenience to you. Also, due to funding limitations, we will not be able to pay you any cost of travel.

The questions that you will be asked during your interview will not be sensitive. However, if you become upset during your interview for any particular reason e.g. when speaking about a negative experience, we will offer you details of organisations that may be able to provide support for these issues if you desire. Your interview will be audio-recorded to help us understand the reasons why the patient made his/her decision. If you are uncomfortable with this process, please contact the PhD researcher (GT - contact details below) who will provide you with further information regarding this matter.

We will ask you to provide informed consent for us to use your personal contact details (e.g. telephone/ mobile number or email address) to possibly arrange an additional short interview, send you a descriptive summary of your interview discussion, and invite you to a one-off group meeting with the research team and other willing participants who took part in an interview. Each of these requests will not be compulsory and the decision to do so will be completely your own.

What if something goes wrong?

Effect of a CR Programme on Molecular Mechanisms: Significant Other Participant Information Sheets: Interview Component of Study. Version 6- 25/02/19.

It is unlikely that something will go wrong during the interview part of this study. However, if any issues or problems arise, UU has Research Ethics and Governance procedures in place for reporting, investigating, recording, and handling adverse events. Any complaints will be taken seriously. If you have any concerns please contact Dr Ciara Hughes (CH), Chief Investigator for this study (contact details below). In each instance, the Chief Investigator (CH) will report a concern or complaint to the appropriate authority, and every effort will be made to ensure a satisfactory resolution. Further information regarding UU Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Will the data collected during the interview part of this study be kept confidential?
All data will be held securely and treated in the strictest confidence in compliance with the General Data Protection Regulation (2018). Your personal information will be anonymised using a coding system to prevent the data from being traced or used to identify you. The electronic study data will be stored on a password protected computer, and paper-based data will be stored in a secure central data bank at UU. Only members of the research team will have access to study data and audio-recordings. Due to legal requirements, regulatory inspectors may request access to your personal data during the study to verify or cross check data during an audit. The study data will be erased or shredded after 10 years of storage in accordance with UU policy. During the transcription of the audio-recording of your interview, your name will be replaced by an anonymous code e.g. S1, S2 etc. Therefore, no information that may disclose your identity will be associated with any reports or publications associated with the interview part of this study. The audio-recording of your interview will be destroyed following the transcription and analysis of data.

If you discuss any information related to poor practice (e.g. misconduct of a health care provider) or criminal activity during your interview, the research team will be required to report these matters to an appropriate authority. Issues associated with poor practice would be reported in accordance with the BHSCT or South Eastern Health and Social Care Trust (SEHSCT) complaints procedure. Matters related to criminal activity would be reported to the relevant law enforcement agency.

Has an ethical committee approved the interview part of this study?
The interview part of this study has received a favourable opinion from the Health and Social Care Research Ethics Committee A, the BHSCT Research Governance Committee, and the SEHSCT Research Governance Committee. This process ensures that the interview part of this study will protect your safety, rights, well-being, and dignity.

Who will carry out this research?
Dr Ciara Hughes (Chief Investigator), Mr Gareth Thompson (PhD researcher), Prof Gareth Davison, Mrs Jacqui Crawford, and Dr Iseult Wilson. Each member of this research team is based at UU. Funding for the interview part of this study has been obtained from the Department for Economy Studentship.

What will happen to the results of the interview part of this study?
The results from the interview part of this study shall be analysed, written up as part of a PhD thesis, and potentially published as a paper in a scientific journal. Any information that may identify you will be removed prior to publication. If you would like to be informed of the results,

please feel free to contact any member of the research team (contact details below) after the interview part of this study has been completed.

Who do I speak to if I have any questions?
Please feel free to contact the PhD researcher (GT- contact details below) if you have any questions or queries. If you would like to receive independent advice about participating in this study from an individual who is not a member of the research team, please contact Mr Nick Curry (contact details below).

What next?
If you are interested in participating in the interview part of this study, please consider your willingness to participate for one week. After this period, if you are still willing to participate, please contact the PhD researcher (GT- contact details below) who will provide you with further details about the interview part of this study, and answer any questions or queries that you may have. During this contact, if you are willing to participate, you will be able to arrange a suitable time and location for your interview to be held. You will also be asked to bring the attached "consent form" to your interview to complete in the presence of the PhD researcher (GT).

Contact details:

- Mr Gareth Thompson, PhD Researcher
- Phone: 07714198795
- Email: Thompson-G7@ulster.ac.uk

- Dr Ciara Hughes, Senior Lecturer Clinical Physiology
- Phone: +44 (0)2890366227
- Email: cm.hughes@ulster.ac.uk

- Mr Nick Curry, Head of Research Governance, Ulster University
- Phone: +44(0)2890366629
- Email: n.curry@ulster.ac.uk

Appendix J (i): Consent form for patients: Interview component.
(Note: one copy for participant, one copy for Trust Site File, and one copy for researcher)

Title of study: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Chief Investigator: Dr Ciara Hughes   **Please initial**

I confirm that I have been given and have read and understood

the information sheet for the interview part of this study, and have asked   [   ]
and received answers to any questions raised.

I confirm that I give permission for the research team to audio-   [   ]
record the interview for only the purpose of the interview part of this study.

I confirm that I give permission for the research team to use my
personal contact information to contact me for only the purpose of   [   ]
the interview part of this study.

I understand that my participation is voluntary, and that I am free
to withdraw at any time without giving a reason, and without my   [   ]
rights or standard of care being affected in any way.

I understand that if I choose to withdraw from the interview part of this study,
the data provided by me and my significant other during the interviews will be   [   ]
withdrawn. In addition, I understand that if my elected significant other withdraws,
I will also be withdrawn.

I understand that the researchers will hold all information and data
collected securely and in confidence, and that all efforts will be made
to ensure that I cannot be identified as a participant in the interview part of this   [   ]
study (except as might be required by law), and I give permission
for the researchers to hold relevant anonymised personal data.

I agree to take part in the interview part of the above study.   [   ]

Name of participant (please print)	Signature	Date (dd/mm/yyyy)

Effect of a CR Programme on Molecular Mechanisms: Patient Consent Form: Interview Component of Study. Version 4- 05/10/18.

Name of researcher (please print)   Signature   Date (dd/mm/yyyy)

Please retain this copy for your own records.

Further information regarding Ulster University Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Appendix J (ii). Consent form for Significant Others: Interview component.
(Note: one copy for participant, one copy for Trust Site File, and one copy for researcher)

Title of study: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

Chief Investigator: Dr Ciara Hughes   **Please initial**

I confirm that I have been given and have read and understood

the information sheet for the interview part of this study, and have asked   [   ]
and received answers to any questions raised.

I confirm that I give permission for the research team to audio-   [   ]
record the interview for only the purpose of the interview part of this study.

I confirm that I give permission for the research team to use my
personal contact information to contact me for only the purpose of   [   ]
the interview part of this study.

I understand that my participation is voluntary, and that I am free
to withdraw at any time without giving a reason, and without my   [   ]
rights being affected in any way.

I understand that if I choose to withdraw from the interview part of this study,
the data provided by me and the patient during the interviews will be withdrawn.   [   ]
In addition, I understand that if the patient withdraws, I will also be withdrawn.

I understand that the researchers will hold all information and data
collected securely and in confidence, and that all efforts will be made
to ensure that I cannot be identified as a participant in the interview part of this   [   ]
study (except as might be required by law), and I give permission
for the researchers to hold relevant anonymised personal data.

I agree to take part in the interview part of the above study.   [   ]

Name of participant (please print)	Signature	Date (dd/mm/yyyy)
Name of researcher (please print)	Signature	Date (dd/mm/yyyy)

Please retain this copy for your own records.

Further information regarding Ulster University Research Ethics and Governance policies and procedures can be found at: https://www.ulster.ac.uk/research/our-research/research-integrity

Appendix K. Brachial FMD questionnaire.

Project Title: *Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.*

<u>**Note:**</u> This form must be completed by the participant prior to the commencement of the procedure.
<u>**Instructions for participant:**</u> Please provide a response for each of the following questions.

All information contained herein will be treated as confidential.

Participant ID: _____

Age: _____

With what gender do you identify? (Please tick)
- ○ Male
- ○ Female
- ○ Other **(Please specify)** _____

Race (Please tick):
- ○ White
- ○ Black African
- ○ Black Caribbean
- ○ Chinese
- ○ Filipino
- ○ Indian
- ○ Irish Traveller
- ○ Mixed Ethnic Group
- ○ Pakistani
- ○ Bangladeshi
- ○ Not assigned/ not known
- ○ Other **(Please specify)** _____

Have you consumed any form of painkiller medication (i.e. paracetamol or aspirin) over the past three days? (Please tick)
- ○ Yes
- ○ No
- ○ **If *YES*** was answered, please specify what medication was consumed, and when it was last taken:

_____

Could you please state when you last consumed the medication that has been prescribed for your condition?

_____

Could you please briefly state what food you have eaten over the past 6 hours?

_____

_____

_____

_____

Have you drunk any beverages that may contain caffeine or alcohol over the past 12 hours? (Please tick)
- ○ Coffee
- ○ Tea
- ○ Energy drinks (such as: Red Bull, Monster Energy, Rockstar, or Lucozade)
- ○ Fizzy drinks (such as: Coca-Cola, Pepsi, Mountain Dew, or Fanta)
- ○ Any form of alcoholic beverage
- ○ Not applicable
- ○ *If YES,* please roughly state when you last consumed this beverage, and how much you drank:

_____

Do you smoke cigarettes or any other form of tobacco? (Please tick)
- ○ Yes
- ○ No
- ○ *If YES*, have you smoked during the past 12 hours? **(Please circle)** __YES__ or __NO__
- ○ *If NO*, have you been exposed to second hand smoke during the past 12 hours? **(Please circle)** __YES__ or __NO__ __AND__ Are you an ex-smoker who has quit? **(Please circle)** __YES__ or __NO__

Have you participated in any form of exercise over the past 12 hours? (Please tick)
- ○ Yes
- ○ No
- ○ *If YES*, please state what form of exercise it was, when it was completed, and for how long:

_____

_____

_____

Have you gone through menopause? (Please tick) *(Please note: this question has been asked due to hormone changes within the female body that may influence artery function)*

- ○ Yes
- ○ No
- ○ Not applicable
- ○ Not willing to answer
- ○ *If NO*, please state how many weeks/ days it has been since the first day of your period this month:

Project Title:
Effect of a Cardiac Rehabilitation (CR) Programme on Protein Molecules Associated with Arterial Function, and an Exploration of Reasons for Agreeing or Declining to Participate in a CR Programme: Interviews with Coronary Artery Disease Patients and their Significant Others.

Participant ID: _____

Instructions for Participant:

Please complete one International Physical Activity Questionnaire (IPAQ) on week-1, week-8, and week-22. The PhD researcher (Mr Gareth Thompson) will collect the completed IPAQs from you before the provision of study measurements at Time Point 2 and Time Point 3.

Please record the date of when you completed this IPAQ: _____

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT (October 2002)

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an *International Physical Activity Prevalence Study* is in progress. For further information see the IPAQ website.

More Information
More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1.   Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No ➡ *Skip to PART 2: TRANSPORTATION*

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2.   During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity ➡ *Skip to question 4*

Effect of a CR Programme on Molecular Mechanisms: International Physical Activity Questionnaire-Middle Aged Adults. Version 4- 20/02/19.

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity ➡ *Skip to question 6*

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking ➡ *Skip to PART 2: TRANSPORTATION*

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle ➤ *Skip to question 10*

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place ➤ *Skip to question 12*

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place ➤ *Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY*

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14.   Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard ➡ ***Skip to question 16***

15.   How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16.   Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard ➡ ***Skip to question 18***

17.   How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18.   Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

Effect of a CR Programme on Molecular Mechanisms: International Physical Activity Questionnaire-Middle Aged Adults. Version 4- 20/02/19.

☐ No moderate activity inside home ➡ *Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY*

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time ➡ *Skip to question 22*

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time ➡ *Skip to question 24*

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time ➡ *Skip to PART 5: TIME SPENT SITTING*

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

Appendix M. Evidence for submission of **Paper 2** for publication.

Journal of Sports Sciences

Exercise and Cardioprotection in Coronary Artery Disease: A Pilot Prospective Cohort Study.
--Manuscript Draft--

Full Title:	Exercise and Cardioprotection in Coronary Artery Disease: A Pilot Prospective Cohort Study.
Manuscript Number:	RJSP-2020-2739
Article Type:	Original Manuscript
Keywords:	exercise; inflammation; molecular mechanisms; coronary artery disease; pilot prospective cohort study
Abstract:	Sirtuin-1 (SIRT-1) may represent a mechanism that orchestrates the cardioprotective effect of exercise. The primary objective of this pilot study was to assess the feasibility of performing a prospective cohort study. A multi-centre pilot prospective cohort study was conducted in post-acute myocardial infarction patients who were invited to phase-III cardiac rehabilitation (CR) at National Health Service sites in the United Kingdom. Participants provided measurements at three Time Points (TPs; 22 weeks) over the course of phase-III and phase-IV CR (ClinicalTrials.gov: NCT03907293). Twenty-eight (n = 28) patients were recruited, with n = 12 providing measurements at each TP. The success criteria for drop-out rate and adherence rate were satisfied. However, the success criterion regarding recruitment rate was not fulfilled. Preliminary evidence for a beneficial effect of exercise on SIRT-1 in CAD patients was generated, with positive changes in physiological states related to atherogenesis also detected (inflammation, oxidative stress, endothelial function, and arterial stiffness). Collectively, a prospective cohort study is feasible with minor amendment (recruitment strategy). Our data helps to improve scientific understanding of the role of exercise in the secondary prevention of CAD.
Order of Authors:	Gareth Thompson, BSc.
	Gareth W. Davison
	Jacqui Crawford
	Ciara M. Hughes

Appendix N. Electronic Supplementary Material for **Paper 2**

Exercise and Cardioprotection in Coronary Artery Disease: A Pilot Prospective Cohort Study.

Journal Name: Journal of Sports Sciences

Electronic Supplementary Material (ESM) 1

ESM 1, Table S1. Within-group change scores and effect sizes for the secondary outcome measures (sub-analysis of secondary outcome measures; non-CR, n = 2; phase-III CR only, n = 3; phase-III & phase-IV CR, n = 7).

Variable	Non-CR			Phase-III CR only			Phase-III & phase-IV CR		
	TP-3 – TP-1	TP-2 – TP-1	TP-3 – TP-2	TP-3 – TP-1	TP-2 – TP-1	TP-3 – TP-2	TP-3 – TP-1	TP-2 – TP-1	TP-3 – TP-2
	d (95% CI)	*d* (95% CI)	*d* (95% CI)	*d* (95% CI)	*d* (95% CI)	*d* (95% CI)	*d* (95% CI)	*d* (95% CI)	*d* (95% CI)
Distance walked in ISWT (m)	-40 ± 14	-15 ± 7	-25 ± 21	-3 ± 40	67 ± 25	-70 ± 53	151 ± 45	76 ± 26	76 ± 37
	-1.4 (-3.5, -0.8)	-0.8 (-2.9, 1.21)	-0.9 (-3.0, 1.1)	-0.0 (-1.6, 1.6)	1.0 (-0.7, 2.7)	-0.8 (-2.5, 0.9)	1.4 (0.2, 2.5)	0.6 (-0.5, 1.7)	0.7 (-0.4, 1.8)
SBP (mmHg)	6 ± 0	1 ± 0	5 ± 0	3 ± 8	-1 ± 3	4 ± 5	-8 ± 11	-6 ± 10	-2 ± 7
	0.3 (-1.7, 2.3)	0.1 (-1.9, 2.0)	0.3 (-1.7, 2.2)	0.5 (-1.1, 2.1)	-0.2 (-1.8, 1.4)	0.6 (-1.1, 2.2)	-0.6 (-1.7, 0.5)	-0.4 (-1.5, 0.7)	-0.2 (-1.3, 0.8)
DBP (mmHg)	5 ± 11	3 ± 9	2 ± 1	9 ± 8	-1 ± 3	10 ± 9	-5 ± 6	-3 ± 9	-2 ± 5
	0.6 (-1.4, 2.7)	0.4 (-1.6, 2.3)	2.9 (0.1, 5.6)	1.6 (-0.3, 3.4)	-0.2 (-1.8, 1.4)	1.4 (-0.4, 3.2)	-0.5 (-1.5, 0.6)	-0.3 (-1.3, 0.8)	-0.2 (-1.3, 0.8)
RHR (beats/ min)	2 ± 2	2 ± 1	0 ± 3	3 ± 8	-8 ± 13	11 ± 7	-6 ± 7	-3 ± 7	-2 ± 8
	0.6 (-1.4, 2.6)	0.4 (-1.6, 2.4)	0.0 (-2.0, 2.0)	0.6 (-1.0, 2.2)	-1.1 (-2.8, 0.6)	2.5 (0.3, 4.6)	-0.6 (-1.7, 0.5)	-0.4 (-1.4, 0.7)	-0.2 (-1.3, 0.8)
BMI (kg/m²)	0.3 ± 1.6	0.2 ± 0.8	0.1 ± 0.8	0.9 ± 0.4	-0.5 ± 0.2	1.4 ± 0.5	-0.8 ± 1.8	-0.0 ± 0.4	-0.8 ± 1.7
	0.0 (-1.9, 2.0)	0.0 (-1.9, 2.0)	0.0 (-1.9, 2.0)	0.4 (-1.2, 2.0)	-0.3 (-1.9, 1.4)	0.6 (-1.0, 2.3)	-0.1 (-1.2, 0.9)	-0.0 (-1.1, 1.0)	-0.1 (-1.2, 0.9)
WC (inches)	-0.2 ± 1.9	0.1 ± 0.7	-0.3 ± 1.2	1.0 ± 0.5	-0.7 ± 0.1	1.7 ± 0.4	-1.6 ± 0.8	-0.3 ± 0.5	-1.3 ± 0.8
	-0.0 (-2.0, 1.9)	0.0 (-1.9, 2.0)	-0.0 (-2.0, 1.9)	0.9 (-0.8, 2.5)	-0.7 (-2.4, 0.9)	1.4 (-0.4, 3.2)	-0.2 (-1.3, 0.8)	-0.0 (-1.1, 1.0)	-0.2 (-1.2, 0.9)
	0.02 ± 0.00	0.18 ± 0.00	-0.16 ± 0.00	-0.04 ± 0.01	0.01 ± 0.01	-0.05 ± 0.02	0.01 ± 0.08	0.00 ± 0.07	0.01 ± 0.06

Baseline diameter (cm) [a]	-	-	-	-1.6 (-3.8, 0.7)	0.2 (-1.7, 2.2)	-1.3 (-3.5, 0.8)	0.2 (-1.0, 1.4)	0.0 (-1.2, 1.2)	0.2 (-1.1, 1.4)
Peak diameter (cm) [a]	0.02 ± 0.00	0.18 ± 0.00	-0.16 ± 0.00	-0.03 ± 0.03	0.04 ± 0.01	-0.06 ± 0.02	0.03 ± 0.07	0.01 ± 0.06	0.02 ± 0.06
	-	-	-	-1.0 (-3.1, 1.1)	0.8 (-1.2, 2.9)	-2.7 (-5.4, 0.0)	0.7 (-0.6, 2.0)	0.2 (-1.0, 1.5)	0.4 (-0.9, 1.6)
Brachial FMD (%) [a]	-0.1 ± 0.0	-0.5 ± 0.0	0.37 ± 0.0	3.7 ± 5.0	5.5 ± 6.4	-1.8 ± 1.4	4.7 ± 3.5	2.5 ± 2.8	2.1 ± 1.1
	-	-	-	1.5 (-0.8, 3.7)	1.6 (-0.6, 3.9)	-0.5 (-2.5, 1.5)	1.1 (-0.3, 2.4)	0.6 (-0.6, 1.9)	0.4 (-0.8, 1.7)
Brachial FMD absolute change (cm) [a]	0.00 ± 0.0	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.02	0.02 ± 0.02	-0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
	-	-	-	1.3 (-0.9, 3.4)	1.7 (-0.6, 4.0)	-0.8 (-2.8, 1.3)	1.1 (-0.2, 2.4)	0.6 (-0.7, 1.8)	0.4 (-0.8, 1.7)
Shear rate (AUC) [a]	-3979.7 ± 0.0	-4175.4 ± 0.0	195.7 ± 0.0	1075.6 ± 11924.3	13399.3 ± 7257.3	-12323.7 ± 4667.0	-1914.9 ± 10940.6	-2864.8 ± 7163.3	949.9 ± 10886.5
	-	-	-	0.1 (-1.9, 2.1)	1.8 (-0.5, 4.2)	-1.0 (-3.1, 1.1)	-0.2 (-1.4, 1.1)	-0.2 (-1.5, 1.0)	0.1 (-1.2, 1.3)
TTP vasodilation (s) [a]	-5 ± 0	-10 ± 0	5 ± 0	-15 ± 57	-43 ± 11	28 ± 46	-12 ± 69	0 ± 38	-12 ± 73
	-	-	-	-0.5 (-2.5, 1.5)	-3.2 (-6.1, -0.2)	1.0 (-1.1, 3.1)	-0.3 (-1.6, 0.9)	0.0 (-1.2, 1.2)	-0.3 (-1.5, 1.0)
SI (m/s)	0.7 ± 0.1	0.6 ± 0.5	0.1 ± 0.6	-1.9 ± 0.5	-3.9 ± 2.1	2.0 ± 2.5	-4.6 ± 3.3	-3.1 ± 3.2	-1.4 ± 1.4

	0.3 (-1.7, 2.2)	0.2 (-1.7, 2.2)	0.0 (-2.0, 2.0)	-1.4 (-3.1, 0.4)	-2.7 (-4.8, -0.5)	1.1 (-0.6, 2.8)	-1.3 (-2.5, -0.2)	-0.9 (-2.0, 0.2)	-0.6 (-1.6, 0.5)
RI (%)	-8.5 ± 12.0	-8.5 ± 14.8	0.0 ± 2.8	4.7 ± 1.5	-1.0 ± 4.6	5.7 ± 3.1	-4.1 ± 7.4	-2.4 ± 6.8	-1.7 ± 1.4
	-0.4 (-2.4, 1.6)	-0.4 (-2.4, 1.6)	0.0 (-2.0, 2.0)	1.1 (-0.7, 2.8)	-0.2 (-1.8, 1.4)	1.1 (-0.6, 2.9)	-0.6 (-1.7, 0.4)	-0.4 (-1.4, 0.7)	-0.3 (-1.4, 0.8)
Total physical activity (MET-minutes/week)	16 ± 18	-29 ± 23	45 ± 5	1466 ± 198	1414 ± 148	52 ± 217	1445 ± 160	1291 ± 120	154 ± 138
	0.4 (-1.6, 2.4)	-0.7 (-2.7, 1.3)	0.9 (-1.1, 3.0)	12.8 (5.4, 20.3)	14.6 (6.2, 23.0)	0.4 (-1.2, 2.1)	12.5 (7.7, 17.2)	15.0 (9.3, 20.6)	1.2 (0.1, 2.3)
SIRT-1 (ng/mL)	-0.01 ± 0.00	-0.01 ± 0.00	-0.01 ± 0.00	0.00 ± 0.01	0.06 ± 0.01	-0.05 ± 0.01	0.14 ± 0.03	0.07 ± 0.01	0.07 ± 0.03
	-8.2 (-14.2, -2.2)	-3.2 (-6.1, -0.2)	-4.0 (-7.4, -0.6)	0.1 (-1.5, 1.7)	9.2 (3.7, 14.6)	-7.1 (-11.4, -2.8)	7.0 (4.2, 9.8)	7.9 (4.8, 11.0)	3.3 (1.7, 4.8)
ESR (mm/hr)	1.5 ± 3.5	-0.5 ± 2.1	2.0 ± 1.4	-1.0 ± 1.7	-3.7 ± 1.5	2.7 ± 0.6	-6.6 ± 1.1	-4.3 ± 1.6	-2.3 ± 2.0
	0.6 (-1.4, 2.6)	-0.3 (-2.3, 1.6)	0.7 (-1.3, 2.7)	-0.2 (-1.9, 1.4)	-0.9 (-2.5, 0.8)	0.7 (-1.0, 2.3)	-2.9 (-4.5, -1.4)	-2.0 (-3.3, -0.7)	-1.0 (-2.1, 0.1)
IL-6 (pg/mL)	-0.05 ± 0.17	0.11 ± 0.24	-0.17 ± 0.07	0.25 ± 0.43	0.05 ± 0.45	0.20 ± 0.14	-0.51 ± 0.53	-0.26 ± 0.39	-0.25 ± 0.30
	-0.1 (-2.0, 1.9)	0.1 (-1.9, 2.0)	-0.2 (-2.1, 1.8)	0.1 (-1.5, 1.7)	0.0 (-1.6, 1.6)	0.1 (-1.5, 1.7)	-0.6 (-1.7, 0.5)	-0.2 (-1.3, 0.8)	-0.4 (-1.5, 0.7)
IL-10 (pg/mL)	-0.45 ± 0.01	-0.21 ± 0.13	-0.24 ± 0.14	0.17 ± 0.38	0.15 ± 0.26	0.02 ± 0.20	0.03 ± 0.29	0.05 ± 0.11	-0.02 ± 0.22
	-0.7 (-2.7, 1.3)	-0.4 (-2.3, 1.6)	-0.4 (-2.3, 1.6)	0.2 (-1.4, 1.8)	0.1 (-1.5, 1.7)	0.1 (-1.5, 1.7)	0.1 (-1.0, 1.1)	0.1 (-1.0, 1.1)	0.0 (-1.0, 1.0)
LOOH (µmol/L)	0.19 ± 0.02	0.20 ± 0.20	-0.02 ± 0.22	-0.29 ± 0.16	-0.16 ± 0.25	-0.13 ± 0.23	-0.09 ± 0.11	-0.06 ± 0.08	-0.03 ± 0.08
	2.0 (-0.4, 4.4)	0.9 (-1.2, 3.0)	0.0 (-2.0, 2.0)	-4.2 (-7.1, -1.4)	-0.9 (-2.6, 0.8)	-0.4 (-2.1, 1.2)	-1.0 (-2.1, 0.1)	-1.0 (-2.1, 0.1)	0.0 (-1.0, 1.0)
	5.2 ± 3.2	3.3 ± 2.1	1.9 ± 1.1	1.5 ± 3.2	-2.4 ± 3.6	3.8 ± 2.9	-16.5 ± 13.7	-9.8 ± 11.3	-6.7 ± 6.1

A•− (a.u.) × 10^4	0.7 (-1.3, 2.8)	0.5 (-1.5, 2.5)	0.2 (-1.7, 2.2)	0.5 (-1.1, 2.1)	-0.6 (-2.2, 1.0)	1.1 (-0.6, 2.8)	-1.9 (-3.2, -0.7)	-1.1 (-2.2, 0.1)	-1.4 (-2.6, -0.2)

Data are mean ± standard deviation; TP, time point; ISWT, incremental shuttle walk test; m, metres; CR, cardiac rehabilitation; d, Cohen's d; CI, confidence interval; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; cm, centimetres; -, not applicable (insufficient number (n) of cases (n = 1)); FMD, flow-mediated dilatation; %, percentage; AUC, area-under-the-curve; TTP, time-to-peak; s, seconds; SI, stiffness index; m/s, metres per second; RI, reflective index; MET-minutes/week, metabolic equivalent minutes per week; SIRT-1, sirtuin-1; ng/mL, nanograms per millilitre; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; IL-6, interleukin-6; pg/mL, picograms per millilitre; IL-10, interleukin-10; LOOH, lipid hydroperoxides; μmol/L, micromoles per litre; A•−, ascorbyl free radical; a.u., arbitrary units; [a], data available for sub-group (non-CR, n = 1; phase-III CR only, n = 2; phase-III & phase-IV CR, n = 5).

ESM 1, Table S2. Between-group effect sizes for the secondary outcome measures (sub-analysis of secondary outcome measures; non-CR, $n = 2$; phase-III CR only, $n = 3$; phase-III & phase-IV CR, $n = 7$).

Variable	TP-2			TP-3		
	Non-CR and phase-III CR only	Non-CR and phase-III & phase-IV CR	Phase-III CR only and phase-III & phase-IV CR	Non-CR and phase-III CR only	Non-CR and phase-III & phase-IV CR	Phase-III CR only and phase-III & phase-IV CR
Distance walked in ISWT (m)	0.2 (-1.6, 2.0)	1.1 (-0.6, 2.7)	1.0 (-0.4, 2.4)	-0.4 (-2.2, 1.4)	2.5 (0.6, 4.5)	2.6 (0.9, 4.4)
SBP (mmHg)	-1.1 (-3.0, 0.82)	-0.6 (-2.2, 1.0)	0.5 (-0.9, 1.9)	-1.0 (-2.9, 0.9)	-1.3 (-3.0, 0.3)	-0.1 (-1.5, 1.2)
DBP (mmHg)	-1.6 (-3.6, 0.4)	-0.3 (-1.9, 1.3)	0.8 (-0.6, 2.2)	-0.4 (-2.3, 1.4)	-1.0 (-2.6, 0.7)	-0.6 (-2.0, 0.8)
RHR (beats/ min)	-2.4 (-4.8, -0.1)	-1.3 (-3.0, 0.4)	0.3 (-1.0, 1.7)	-1.2 (-3.2, 0.7)	-1.6 (-3.3, 0.2)	-1.4 (-2.8, 0.1)
BMI (kg/m²)	0.4 (-1.4, 2.2)	1.2 (-0.5, 2.8)	1.0 (-0.4, 2.5)	0.7 (-1.1, 2.5)	0.9 (-0.7, 2.6)	0.6 (-0.8, 1.9)
WC (inches)	0.0 (-1.8, 1.8)	0.8 (-0.8, 2.5)	1.0 (-0.5, 2.4)	0.5 (-1.3, 2.3)	0.7 (-0.9, 2.3)	0.5 (-0.9, 1.9)
Baseline diameter (cm) [a]	-3.6 (-7.4, 0.2)	-3.0 (-5.7, -0.3)	0.0 (-1.6, 1.6)	-3.5 (-7.2, 0.2)	-0.1 (-2.3, 2.0)	0.9 (-0.8, 2.7)
Peak diameter (cm) [a]	-5.3 (-10.2, -0.4)	-2.8 (-5.5, -0.2)	-0.2 (-1.8, 1.5)	-6.0 (-11.4, -0.6)	0.2 (-2.0, 2.4)	1.6 (-0.3, 3.4)

Brachial FMD (%) [a]	1.2 (-1.4, 3.8)	0.7 (-1.5, 2.8)	-0.5 (-2.2, 1.1)	1.1 (-1.5, 3.6)	0.9 (-1.3, 3.1)	0.3 (-1.3, 2.0)
Brachial FMD absolute change (cm) [a]	1.1 (-1.4, 3.7)	0.4 (-1.8, 2.6)	-0.5 (-2.2, 1.1)	1.0 (-1.5, 3.5)	1.0 (-1.2, 3.2)	0.5 (-1.2, 2.1)
Shear rate (AUC) [a]	2.3 (-0.8, 5.3)	0.7 (-1.5, 2.8)	-1.0 (-2.7, 0.7)	0.7 (-1.8, 3.1)	0.9 (-1.3, 3.1)	0.0 (-1.6, 1.6)
TTP vasodilation (s) [a]	1.4 (-1.2, 4.1)	0.7 (-1.5, 2.9)	0.5 (-1.1, 2.2)	0.8 (-1.7, 3.3)	0.5 (-1.7, 2.6)	-0.4 (-2.1, 1.2)
SI (m/s)	-1.8 (-3.9, 0.3)	-2.4 (-4.4, -0.5)	-1.1 (-2.6, 0.3)	-1.1 (-3.0, 0.8)	-3.9 (-6.3, -1.5)	-3.1 (-5.0, -1.2)
RI (%)	-0.6 (-2.5, 1.2)	-1.0 (-2.7, 0.6)	-0.2 (-1.6, 1.1)	-0.4 (-2.2, 1.4)	-1.3 (-2.9, 0.4)	-1.6 (-3.1, -0.1)
Total physical activity (MET-minutes/week)	16.4 (6.1, 26.7)	13.8 (7.3, 20.4)	-1.0 (-2.5, 0.4)	13.0 (4.7, 21.2)	10.3 (5.3, 15.3)	-0.0 (-1.4, 1.3)
SIRT-1 (ng/mL)	10.9 (3.9, 17.9)	6.3 (3.0, 9.6)	0.9 (-0.5, 2.3)	1.2 (-0.7, 3.2)	5.6 (2.5, 8.6)	5.5 (2.7, 8.2)
ESR (mm/hr)	-1.7 (-3.8, 0.4)	-3.0 (-5.1, -0.9)	-0.1 (-1.5, 1.2)	-1.5 (-3.6, 0.5)	-4.2 (-6.7, -1.7)	-2.0 (-3.6, -0.4)
IL-6 (pg/mL)	-1.0 (-2.9, 0.9)	-2.0 (-3.8, -0.2)	-0.4 (-1.8, 1.0)	-0.7 (-2.5, 1.2)	-2.3 (-4.2, -0.4)	-1.0 (-2.4, 0.4)

IL-10 (pg/mL)	-1.0 (-2.9, 0.9)	-1.2 (-2.8, 0.5)	-0.3 (-1.6, 1.1)	-0.6 (-2.4, 1.2)	-0.9 (-2.5, 0.7)	-0.3 (-1.7, 1.1)
LOOH (µmol/L)	-1.0 (-2.9, 0.9)	-1.4 (-3.1, 0.3)	0.6 (-0.8, 2.0)	-6.9 (-11.6, -2.3)	-2.0 (-3.8, -0.2)	2.3 (0.6, 4.0)
$A^{\bullet -}$ (a.u.) $\times 10^4$	-1.3 (-3.2, 0.7)	-0.2 (-1.8, 1.4)	1.0 (-0.4, 2.4)	-1.0 (-2.9, 0.9)	-2.2 (-4.1, -0.4)	-1.6 (-3.1, -0.1)

Data are Cohen's *d* (95% confidence interval); TP, time point; ISWT, incremental shuttle walk test; m, metres; CR, cardiac rehabilitation; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; cm, centimetres; FMD, flow-mediated dilatation; %, percentage; AUC, area-under-the-curve; TTP, time-to-peak; s, seconds; SI, stiffness index; m/s, metres per second; RI, reflective index; MET-minutes/week, metabolic equivalent minutes per week; SIRT-1, sirtuin-1; ng/mL, nanograms per millilitre; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; IL-6, interleukin-6; pg/mL, picograms per millilitre; IL-10, interleukin-10; LOOH, lipid hydroperoxides; µmol/L, micromoles per litre; $A^{\bullet -}$, ascorbyl free radical; a.u., arbitrary units; mmol/L, millimoles per litre; [a], data available for sub-group (non-CR, *n* = 1; phase-III CR only, *n* = 2; phase-III & phase-IV CR, *n* = 5).

Appendix O. Results of inferential statistics for **Paper 2**.

Table 1. Baseline demographic and clinical characteristics of participants (primary analysis of secondary outcome measures).

Variable	Non-CR	Phase-III CR	*P* value
General features			
n	3	21	-
Age (years)	69.7 ± 10.6	58.8 ± 10.0	0.10
Male	2 (66.7%)	17 (81%)	0.52
White	3 (100%)	21 (100%)	1.0
STEMI	1 (33.3%)	10 (47.6%)	1.0
NSTEMI	2 (66.7%)	11 (52.4%)	1.0
PCI	3 (100%)	21 (100%)	1.0
CVD risk factors			
Family history	2 (66.7%)	14 (66.7%)	1.0
Diabetes mellitus	1 (33.3%)	3 (14.3%)	0.44
Hypertension	3 (100%)	13 (61.9%)	0.53
Dyslipidaemia	3 (100%)	17 (81%)	1.0
Obesity	1 (33.3%)	9 (42.9%)	1.0
Currently smoking	2 (66.7%)	3 (14.3%)	0.10
Prescribed medication			
Antiplatelets	3 (100%)	21 (100%)	1.0
Beta blockers	3 (100%)	20 (95.2%)	1.0
ACE inhibitors	1 (33.3%)	12 (57.1%)	0.58
Nitrates	1 (33.3%)	9 (42.9%)	1.0
Angiotensin II receptor antagonists	0 (0%)	2 (9.5%)	1.0
Statins	3 (100%)	21 (100%)	1.0
Biguanides	1 (33.3%)	3 (14.3%)	0.44

Data are mean ± standard deviation or number (%). CR, cardiac rehabilitation; *n*, number; -, not applicable; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CVD, cardiovascular disease; and ACE, angiotensin-converting enzyme.

Table 2. Baseline demographic and clinical characteristics of participants (sub-analysis of secondary outcome measures).

Variable	Non-CR	Phase-III CR only	Phase-III & phase-IV CR	*P* value
General features				
n	2	3	7	-
Age (years)	75 (68, 81)	52 (49, 55)	57 (37, 77)	0.12
Male	1 (50%)	3 (100%)	6 (85.7%)	0.36
White	2 (100%)	3 (100%)	7 (100%)	1.0
STEMI	1 (50%)	2 (66.7%)	2 (28.6%)	0.74
NSTEMI	1 (50%)	1 (33.3%)	5 (71.4%)	0.74
PCI	2 (100%)	3 (100%)	7 (100%)	1.0
CVD risk factors				
Family history	1 (50%)	1 (33.3%)	5 (71.4%)	0.74
Diabetes mellitus	0 (0%)	1 (33.3%)	1 (14.3%)	1.0
Hypertension	2 (100%)	2 (66.7%)	3 (42.9%)	0.58
Dyslipidaemia	2 (100%)	2 (66.7%)	5 (71.4%)	1.0
Obesity	1 (50%)	0 (0%)	5 (71.4%)	0.18
Currently smoking	1 (50%)	2 (66.7%)	3 (42.9%)	1.0
Prescribed medication				
Antiplatelets	2 (100%)	3 (100%)	7 (100%)	1.0
Beta blockers	2 (100%)	3 (100%)	7 (100%)	1.0
ACE inhibitors	1 (50%)	3 (100%)	5 (71.4%)	0.71
Nitrates	1 (50%)	3 (100%)	3 (42.9%)	0.31
Angiotensin II receptor antagonists	0 (0%)	0 (0%)	1 (14.3%)	1.0
Statins	2 (100%)	3 (100%)	7 (100%)	1.0
Biguanides	0 (0%)	1 (33.3%)	1 (14.3%)	1.0

Data are median (minimum, maximum) or number (%). CR, cardiac rehabilitation; *n*, number; -, not applicable; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CVD, cardiovascular disease; and ACE, angiotensin-converting enzyme.

Table 3. Values of secondary outcomes at Time Point 1 and Time Point 2 (primary analysis of secondary outcome measures; non-CR, $n = 3$; phase-III CR, $n = 21$).

Variable	TP-1	TP-2	*P* value [a]	*r* (95% CI) [b]	*P* value [c]	*r* (95% CI) [d]
Distance walked in ISWT (m)						
Non-CR	360 ± 79	343 ± 81	0.038	0.96 (0.67, 0.99)	0.031	0.44 (0.05, 0.72)
Phase-III CR	413 ± 107	492 ± 106	0.000	0.88 (0.79, 0.93)		
SBP (mmHg)						
Non-CR	121 (115, 143)	144 (116, 155)	0.102	-0.67 (-0.96, 0.31)	0.073	-0.37 (-0.67, 0.04)
Phase-III CR	126 (103, 166)	118 (106, 142)	0.001	-0.52 (-0.71, -0.26)		
DBP (mmHg)						
Non-CR	82 ± 9	86 ± 8	0.408	0.59 (-0.43, 0.95)	0.038	0.43 (0.03, 0.71)
Phase-III CR	81 ± 11	76 ± 8	0.008	0.55 (0.30, 0.73)		
RHR (beats/min)						
Non-CR	72 ± 3	75 ± 3	0.188	0.81 (-0.00, 0.98)	0.004	0.57 (0.22, 0.79)
Phase-III CR	66 ± 8	62 ± 7	0.015	0.51 (0.24, 0.70)		
BMI (kg/m²)						
Non-CR	26.5 (19.3, 31.1)	27.3 (20.1, 30.7)	0.276	-0.44 (-0.92, 0.58)	0.458	-0.15 (-0.52, 0.27)
Phase-III CR	29.6 (24.5, 44.8)	28.9 (23.8, 45.3)	0.081	-0.27 (-0.53, 0.04)		
WC (inches)						
Non-CR	36.6 (28.3, 41.7)	37.4 (28.9, 41.3)	0.285	-0.44 (-0.92, 0.58)	0.570	-0.12 (-0.50, 0.30)
Phase-III CR	39.0 (35.4, 57.9)	38.4 (34.0, 57.9)	0.015	-0.38 (-0.61, -0.09)		
Baseline diameter (cm) [e]						
Non-CR	0.454 (0.434, 0.473)	0.514 (0.419, 0.609)	0.655	-0.22 (-0.97, 0.94)	0.263	-0.27 (-0.66, 0.24)
Phase-III CR	0.426 (0.272, 0.470)	0.419 (0.232, 0.514)	0.887	-0.03 (-0.39, 0.33)		

Peak diameter (cm) [e]						
Non-CR	0.469 (0.446, 0.491)	0.528 (0.432, 0.623)	0.655	-0.22 (-0.97, 0.94)	0.371	-0.22 (-0.63, 0.29)
Phase-III CR	0.433 (0.282, 0.489)	0.452 (0.235, 0.520)	0.495	-0.12 (-0.46, 0.25)		
Brachial FMD (%) [e]						
Non-CR	3.30 (2.80, 3.80)	2.65 (2.30, 3.00)	0.180	-0.67 (-0.99, 0.82)	0.233	-0.29 (-0.68, 0.22)
Phase-III CR	2.77 (0.47, 8.29)	4.92 (1.17, 12.70)	0.015	-0.45 (-0.70, -0.11)		
Brachial FMD absolute change (cm) [e]						
Non-CR	0.015 (0.012, 0.018)	0.013 (0.012, 0.014)	0.655	-0.22 (-0.97, 0.94)	0.296	-0.25 (-0.65, 0.26)
Phase-III CR	0.010 (0.002, 0.036)	0.020 (0.003, 0.056)	0.014	-0.45 (-0.70, -0.11)		
Shear rate (AUC) [e]						
Non-CR	23300.1 (9667.6, 36932.6)	3167.9 (843.6, 5492.2)	0.180	-0.67 (-0.99, 0.82)	0.053	-0.47 (-0.78, 0.01)
Phase-III CR	16346.7 (3352.5, 28778.3)	16832.2 (1139.7, 35227.1)	0.776	-0.05 (-0.40, 0.32)		
TTP vasodilation (s) [e]						
Non-CR	68 (43, 93)	23 (14, 33)	0.180	-0.67 (-0.99, 0.82)	0.154	-0.35 (-0.71, 0.16)
Phase-III CR	68 (11, 113)	38 (11, 108)	0.023	-0.41 (-0.67, -0.06)		
SI (m/s)						
Non-CR	15.30 (13.53, 16.80)	17.40 (13.76, 17.78)	0.109	-0.65 (-0.96, 0.34)	0.013	-0.51 (-0.76, -0.14)
Phase-III CR	15.36 (5.69, 17.80)	11.03 (5.70, 15.18)	0.000	-0.61 (-0.77, -0.38)		
RI (%)						
Non-CR	97.0 (85.0, 105.0)	98.0 (66.0, 107.0)	1.000	0.00 (-0.81, 0.81)	0.294	-0.21 (-0.57, 0.21)
Phase-III CR	81.0 (67.0, 93.0)	76.0 (56.0, 87.0)	0.002	-0.47 (-0.68, -0.19)		
Total physical activity (MET-minutes/week)						
Non-CR	513 (475, 550)	502 (430, 565)	0.593	-0.22 (-0.88, 0.72)	0.006	-0.56 (-0.79, -0.20)
Phase-III CR	523 (410, 590)	1856 (1234, 2001)	0.000	-0.62 (-0.78, -0.39)		

ESR (mm/hr)						
Non-CR	16.0 (14.0, 16.0)	14.0 (13.0, 17.0)	0.414	-0.33 (-0.90, 0.66)	0.048	-0.40 (-0.69, 0.00)
Phase-III CR	15.0 (10.0, 24.0)	10.0 (5.0, 15.0)	0.000	-0.62 (-0.78, -0.39)		
LOOH (µmol/L)						
Non-CR	1.0 ± 0.10	1.18 ± 0.24	0.171	0.69 (-0.28, 0.96)	0.115	0.33 (-0.08, 0.65)
Phase-III CR	1.19 ± 0.17	0.98 ± 0.19	0.001	0.64 (0.42, 0.79)		
$A^{\bullet-}$ *(a.u.)* $\times 10^{4}$						
Non-CR	10.7 (5.5, 13.1)	12.6 (7.3, 17.9)	0.109	-0.65 (-0.96, 0.34)	0.089	-0.35 (-0.66, 0.06)
Phase-III CR	13.2 (4.1, 35.7)	5.2 (1.0, 22.5)	0.000	-0.62 (-0.78, -0.39)		
TC (mmol/L)						
Non-CR	3.40 (3.10, 6.70)	4.90 (3.70, 5.60)	0.593	-0.22 (-0.88, 0.72)	0.238	-0.24 (-0.59, 0.18)
Phase-III CR	4.40 (2.30, 9.00)	3.90 (2.40, 7.60)	0.002	-0.47 (-0.68, -0.19)		
LDL-C (mmol/L)						
Non-CR	3.10 (2.31, 4.20)	3.40 (2.10, 3.90)	0.785	-0.11 (-0.85, 0.77)	0.176	-0.28 (-0.61, 0.14)
Phase-III CR	2.62 (0.90, 5.72)	1.92 (0.80, 6.10)	0.014	-0.38 (-0.61, -0.09)		
HDL-C (mmol/L)						
Non-CR	1.27 ± 0.34	1.13 ± 0.19	0.259	0.74 (-0.18, 0.97)	0.804	0.05 (-0.36, 0.44)
Phase-III CR	1.08 ± 0.20	1.17 ± 0.25	0.152	0.32 (-0.13, 0.66)		
TG (mmol/L)						
Non-CR	2.85 (0.30, 4.23)	2.80 (0.41, 3.33)	0.593	-0.22 (-0.88, 0.72)	0.458	-0.15 (-0.52, 0.27)
Phase-III CR	1.41 (0.34, 9.55)	1.53 (0.36, 5.38)	0.681	-0.06 (-0.36, 0.25)		
TC/HDL-C ratio						
Non-CR	4.17 (1.94, 7.27)	4.30 (3.20, 5.30)	0.655	-0.18 (-0.87, 0.74)	0.138	-0.30 (-0.63, 0.12)
Phase-III CR	4.39 (2.09, 11.62)	2.99 (1.70, 7.33)	0.001	-0.51 (-0.70, -0.24)		
Non-HDL-C (mmol/L)						
Non-CR	2.60 (1.50, 5.80)	4.0 (2.60, 4.30)	1.0	0 (-0.81, 0.81)	0.190	-0.27 (-0.61, 0.15)

Phase-III CR	3.50 (1.20, 8.10)	2.50 (1.10, 6.40)	0.011	-0.39 (-0.62, -0.10)	

Data are mean ± standard deviation or median (minimum, maximum). TP, time point; *r*, Pearson correlation coefficient; %, percent; CI, confidence interval; ISWT, incremental shuttle walk test; m, metres; CR, cardiac rehabilitation; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; cm, centimetres; FMD, flow-mediated dilatation; AUC, area-under-the-curve; TTP, time-to-peak; s, seconds; SI, stiffness index; m/s, metres per second; RI, reflective index; MET-minutes/week, metabolic equivalent minutes per week; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; LOOH, lipid hydroperoxides; μmol/L, micromoles per litre; A$^{\bullet-}$, ascorbyl free radical; a.u., arbitrary units; mmol/L, millimoles per litre; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; [a], for Student's paired t-test or Wilcoxon signed-rank test; [b], effect size for within-group comparisons; [c], for between-group comparisons at TP-2 with Student's independent t-test or Mann-Whitney U test; [d], effect size for between-group comparisons at TP-2; [e], data available for sub-group (non-CR, number (*n*) = 2 and phase-III CR, *n* = 15).

Table 4. Values of secondary outcomes at each Time Point (sub-analysis of secondary outcome measures; non-CR, $n = 2$; phase-III CR only, $n = 3$; phase-III and phase-IV CR, $n = 7$).

Variable	TP-1	TP-2	TP-3	*P* value [a]
Distance walked in ISWT (m)				
Non-CR	405 (390, 420)	390 (380, 400)	365 (340, 390)	0.135
Phase-III CR only	370 (250, 380)	410 (340, 450)	360 (210, 420)	0.97
Phase-III & phase-IV CR	420 (250, 630)	490 (350, 700) *	580 (440, 730) **, [b]	0.001
SBP (mmHg)				
Non-CR	129 (115, 143)	130 (116, 144)	135 (121, 149)	0.135
Phase-III CR only	119 (114, 120)	118 (111, 121)	119 (113, 131)	0.368
Phase-III & phase-IV CR	126 (103, 150)	121 (108, 142)	118 (109, 131)	0.066
DBP (mmHg)				
Non-CR	79 (72, 86)	82 (81, 82)	84 (83,84)	0.607
Phase-III CR only	75 (67, 76)	75 (63, 76)	80 (76, 88)	0.223
Phase-III & phase-IV CR	85 (57, 98)	77 (70,97)	78 (65, 87)	0.096
RHR (beats/min)				
Non-CR	74 (71, 76)	75 (72, 78)	75 (74, 76)	0.368
Phase-III CR only	66 (64, 78)	61 (56, 68)	72 (71, 75)	0.264
Phase-III & phase-IV CR	70 (53, 83)	67 (51, 73)	61 (52, 77)	0.236
BMI (kg/m²)				
Non-CR	25.2 (19.3, 31.1)	25.4 (20.1, 30.7)	25.5 (20.7, 30.2)	1.0
Phase-III CR only	27.6 (25.5, 29.6)	27.3 (25.1, 28.9)	28.7 (26, 30.8)	0.051
Phase-III & phase-IV CR	30.5 (27, 44.8)	30.4 (27.2, 45.3)	29.7 (26.3, 46.7)	0.368
WC (inches)				

Non-CR	35.0 (28.3, 41.7)	35.1 (28.9, 41.3)	34.9 (29.5, 40.2)	1.0
Phase-III CR only	35.6 (35.4, 37.1)	34.9 (34.6, 36.5)	36.2 (36.2, 38.6)	0.052
Phase-III & phase-IV CR	39.6 (36.6, 57.9)	39.8 (35.8, 57.9)	37.8 (34.3, 57.1) **	0.002
Baseline diameter (cm) [c]				
Non-CR	0.434 (0.434, 0.434)	0.609 (0.609, 0.609)	0.449 (0.449, 0.449)	-
Phase-III CR only	0.418 (0.394, 0.441)	0.430 (0.398, 0.462)	0.380 (0.363, 0.396)	0.135
Phase-III & phase-IV CR	0.434 (0.392, 0.452)	0.441 (0.350, 0.514)	0.432 (0.368, 0.524)	1.0
Peak diameter (cm) [c]				
Non-CR	0.446 (0.446, 0.446)	0.623 (0.623, 0.623)	0.461 (0.461, 0.461)	-
Phase-III CR only	0.427 (0.397, 0.457)	0.462, 0.441, 0.483)	0.402 (0.392, 0.411)	0.135
Phase-III & phase-IV CR	0.455, 0.404, 0.470)	0.470 (0.369, 0.520)	0.462 (0.414, 0.533)	0.549
Brachial FMD (%) [c]				
Non-CR	2.80 (2.80, 2.80)	2.30 (2.30, 2.30)	2.67 (2.67, 2.67)	-
Phase-III CR only	2.20 (0.76, 3.63)	7.68 (4.55, 10.80)	5.89 (3.79, 7.99)	0.135
Phase-III & phase-IV CR	1.56 (0.47, 8.29)	5.43 (1.17, 12.70)	6.94 (1.72, 15.76) **	0.015
Brachial FMD absolute change (cm) [c]				
Non-CR	0.012 (0.012, 0.012)	0.014 (0.014, 0.014)	0.012 (0.012, 0.012)	-
Phase-III CR only	0.010 (0.003, 0.016)	0.032 (0.021, 0.043)	0.022 (0.015, 0.029)	0.223
Phase-III & phase-IV CR	0.007 (0.002, 0.036)	0.019 (0.006, 0.056)	0.030 (0.009, 0.058) **	0.015
Shear rate (AUC) [c]				
Non-CR	9667.6 (9667.6, 9667.6)	5492.2 (5492.2, 5492.2)	5687.9 (5687.9, 5687.9)	-
Phase-III CR only	14451.2 (12555.8, 16346.7)	27850.5 (20823.4, 34877.7)	15526.8 (5199.7, 25854.0)	0.223
Phase-III & phase-IV CR	19077.9 (3352.5, 28778.3)	16832.2 (1139.7, 35227.1)	14256.0 (2793.9, 30908.5)	0.549
TTP vasodilation (s) [c]				
Non-CR	43 (43, 43)	33 (33, 33)	38 (38, 38)	-
Phase-III CR only	85 (73, 98)	43 (38, 48)	70.0 (43, 98)	0.607
Phase-III & phase-IV CR	58 (11, 113)	98 (11, 108)	43 (10, 103)	0.331

SI (m/s)				
Non-CR	15.17 (13.53, 16.80)	15.77 (13.76, 17.78)	15.82 (14.25, 17.39)	0.223
Phase-III CR only	16.30 (14.35, 16.60)	12.11 (10.00, 13.47)	14.64 (11.87, 15.00)	0.097
Phase-III & phase-IV CR	11.17 (5.69, 17.80)	8.87 (5.70, 13.49) *, d	6.99 (5.09, 11.06) **, b	0.002
RI (%)				
Non-CR	95.0 (85.0, 105.0)	86.5 (66.0, 107.0)	86.5 (68.0, 105.0)	0.867
Phase-III CR only	76.0 (72.0, 81.0)	75.0 (70.0, 81.0)	79.0 (78.0, 86.0)	0.086
Phase-III & phase-IV CR	74.0 (67.0, 89.0)	76.0 (66.0, 81.0)	74.0 (65.0, 78.0)	0.156
Total physical activity (MET-minutes/week)				
Non-CR	495 (475, 514)	466 (430, 502)	511 (478, 543)	0.135
Phase-III CR only	440 (420, 590)	1890 (1800, 2001)	1894 (1854, 2100)	0.097
Phase-III & phase-IV CR	497 (410, 580)	1823 (1645, 1924) *	1995 (1785, 2200) *	0.005
SIRT-1 (ng/mL)				
Non-CR	0.145 (0.144, 0.146)	0.140 (0.138, 0.141)	0.132 (0.130, 0.133)	0.135
Phase-III CR only	0.140 (0.134, 0.146)	0.194 (0.190, 0.202)	0.136 (0.135, 0.151)	0.097
Phase-III & phase-IV CR	0.135 (0.124, 0.143)	0.201 (0.191, 0.224) *	0.268 (0.239, 0.322) **, b	0.001
ESR (mm/hr)				
Non-CR	16.0 (16.0, 16.0)	15.5 (14.0, 17.0)	17.5 (15.0, 20.0)	0.607
Phase-III CR only	11.0 (10.0, 18.0)	8.0 (6.0, 14.0)	11.0 (9.0, 16.0)	0.097
Phase-III & phase-IV CR	13.0 (10.0, 16.0)	9.0 (7.0, 13.0) *	6.0 (4.0, 11.0) **, b	0.002
IL-6 (pg/mL)				
Non-CR	3.95 (2.99, 4.91)	4.06 (3.28, 4.85)	3.90 (3.06, 4.74)	0.607
Phase-III CR only	2.15 (1.34, 4.77)	2.07 (1.89, 4.45)	2.43 (2.00, 4.57)	0.264
Phase-III & phase-IV CR	2.84 (1.05, 3.72)	2.63 (1.15, 3.38)	2.22 (1.03, 2.84)	0.067
IL-10 (pg/mL)				
Non-CR	4.74 (4.31, 5.16)	4.52 (4.19, 4.85)	4.29 (3.86, 4.72)	0.135
Phase-III CR only	3.98 (2.15, 4.05)	3.90 (2.26, 4.48)	3.99 (2.05, 4.66)	0.717

Phase-III & phase-IV CR	3.29 (1.73, 4.89)	3.46 (1.78, 4.96)	3.64 (1.70, 5.15)	0.203
LOOH (µmol/L)				
Non-CR	0.99 (0.89, 1.08)	1.19 (0.95, 1.42)	1.17 (1.09, 1.25)	0.223
Phase-III CR only	1.01 (0.98, 1.23)	0.97 (0.64, 1.14)	0.77 (0.76, 0.82)	0.264
Phase-III & phase-IV CR	1.13 (0.94, 1.22)	1.04 (0.80, 1.20)	0.94 (0.76, 1.15)	0.060
$A^{\bullet-}$ *(a.u.)* $\times 10^{4}$				
Non-CR	9.3 (5.5, 13.1)	12.6 (7.3, 17.9)	14.5 (8.4, 20.5)	0.135
Phase-III CR only	8.6 (4.1, 10.9)	3.8 (2.1, 10.6)	9.2 (7.7, 11.1)	0.097
Phase-III & phase-IV CR	16.5 (7.7, 35.7)	10.6 (4.7, 22.5) *	5.0 (1.2, 9.7) **	0.001

Data are median (minimum, maximum). TP, time point; ISWT, incremental shuttle walk test; m, metres; CR, cardiac rehabilitation; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; cm, centimetres; -, insufficient number (n) of cases (n = 1) for statistical analysis; FMD, flow-mediated dilatation; %, percentage; AUC, area-under-the-curve; TTP, time-to-peak; s, seconds; SI, stiffness index; m/s, metres per second; RI, reflective index; MET-minutes/week, metabolic equivalent minutes per week; SIRT-1, sirtuin-1; ng/Ml, nanograms per millilitre; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; IL-6, interleukin-6; pg/Ml, picograms per millilitre; IL-10, interleukin-10; LOOH, lipid hydroperoxides; µmol/L, micromoles per litre; $A^{\bullet-}$, ascorbyl free radical; a.u., arbitrary units; *, significantly different from TP-1 ($p < 0.05$ for Wilcoxon signed-rank test); **, significantly different from TP-1 and TP-2 ($p < 0.05$ for Wilcoxon signed-rank test); [a], for Friedman test; [b], significantly different from non-CR and phase-III CR only groups at TP-3 ($p < 0.05$ for

Mann-Whitney U test); [c], data available for sub-group (non-CR, $n = 1$; phase-III CR only, $n = 2$; phase-III and phase-IV CR, $n = 5$); [d],

significantly different from non-CR group at TP-2 ($p < 0.05$ for Mann-Whitney U test).

Table 5. Effect sizes (*r*) for post-hoc tests performed in sub-analysis of secondary outcome measures.

Group	Sample size (*n*)	Parameter	Comparison	Test	*P* value	Z	*r* (95% CI)
Phase-III and phase-IV CR	7	Distance walked (m) in ISWT	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.017	-2.384	-0.64 (-0.87, -0.17)
Phase-III and phase-IV CR	7	Distance walked (m) in ISWT	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.371	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	Distance walked (m) in ISWT	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.371	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	Waist circumference	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.176	-1.355	-0.36 (-0.75, 0.21)
Phase-III and phase-IV CR	7	Waist circumference	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	Waist circumference	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.371	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	5	Brachial FMD (%)	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.138	-1.483	-0.47 (-0.85, 0.23)
Phase-III and phase-IV CR	5	Brachial FMD (%)	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.043	-2.023	-0.64 (-0.90, -0.02)
Phase-III and phase-IV CR	5	Brachial FMD (%)	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.043	-2.023	-0.64 (-0.90, -0.02)
Phase-III and phase-IV CR	5	Brachial FMD absolute change	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.136	-1.490	-0.47 (-0.85, 0.23)
Phase-III and phase-IV CR	5	Brachial FMD absolute change	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.042	-2.032	-0.64 (-0.90, -0.02)
Phase-III and phase-IV CR	5	Brachial FMD absolute change	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.043	-2.023	-0.64 (-0.90, -0.02)
Phase-III and phase-IV CR	7	SI	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.028	-2.197	-0.59 (-0.85, -0.09)

Group	N	Outcome	Timepoints	Test	p	z	Effect size (95% CI)
Phase-III and phase-IV CR	7	SI	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	SI	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	Total physical activity	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	Total physical activity	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.176	-1.352	-0.36 (-0.75, 0.21)
Phase-III and phase-IV CR	7	Total physical activity	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	SIRT-1	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	SIRT-1	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.371	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	SIRT-1	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and Phase-IV CR	7	ESR	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.017	-2.379	-0.64 (-0.87, -0.17)
Phase-III and phase-IV CR	7	ESR	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.034	-2.120	-0.57 (-0.85, -0.06)
Phase-III and phase-IV CR	7	ESR	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.016	-2.414	-0.65 (-0.88, -0.18)
Phase-III and phase-IV CR	7	$A^{\bullet-}$	TP-1 and TP-2	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	$A^{\bullet-}$	TP-2 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
Phase-III and phase-IV CR	7	$A^{\bullet-}$	TP-1 and TP-3	Within-time differences with Wilcoxin-signed rank test	0.018	-2.366	-0.63 (-0.87, -0.15)
-	5	Distance walked (m) in ISWT at TP-3	Non-CR and phase-III CR only	Between-group differences with Mann-Whitney U test	1.0	0.000	0 (-0.88, 0.88)

-	9	Distance walked (m) in ISWT at TP-3	Non-CR and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.04	-2.049	-0.68 (-0.93, -0.03)
-	10	Distance walked (m) in ISWT at TP-3	Phase-III CR only and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.017	-2.393	-0.76 (-0.94, -0.25)
-	5	SI at TP-2	Non-CR and phase-III CR only	Between-group differences with Mann-Whitney U test	0.083	-1.732	-0.77 (-0.98, 0.35)
-	9	SI at TP-2	Non-CR and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.04	-2.049	-0.68 (-0.93, -0.03)
-	10	SI at TP-2	Phase-III CR only and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.138	-1.481	-0.47 (-0.85, 0.23)
-	5	SI at TP-3	Non-CR and phase-III CR only	Between-group differences with Mann-Whitney U test	0.564	-0.577	-0.26 (-0.93, 0.81)
-	9	SI at TP-3	Non-CR and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.04	-2.058	-0.69 (-0.93, -0.05)
-	10	SI at TP-3	Phase-III CR only and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.016	-2.400	-0.76 (-0.94, -0.25)
-	5	ESR at TP-3	Non-CR and phase-III CR only	Between-group differences with Mann-Whitney U test	0.248	-1.155	-0.52 (-0.96, 0.67)

	n				p	z	r (CI)
-	9	ESR at TP-3	Non-CR and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.04	-2.058	-0.69 (-0.93, -0.05)
-	10	ESR at TP-3	Phase-III CR only and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.039	-2.064	-0.65 (-0.91, -0.04)
-	5	SIRT-1 at TP-3	Non-CR and phase-III CR only	Between-group differences with Mann-Whitney U test	0.083	-1.732	-0.77 (-0.98, 0.35)
-	9	SIRT-1 at TP-3	Non-CR and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.04	-2.049	-0.68 (-0.93, -0.03)
-	10	SIRT-1 at TP-3	Phase-III CR only and phase-III & phase-IV CR	Between-group differences with Mann-Whitney U test	0.017	-2.393	-0.76 (-0.94, -0.25)

n, number; r, Pearson correlation coefficient; %, percent; CI, confidence interval; CR, cardiac rehabilitation; m, metres; ISWT, Incremental Shuttle Walk Test; TP, time point; FMD, flow-mediated dilatation; SI, stiffness index; SIRT-1, sirtuin-1; ESR, erythrocyte sedimentation rate; A$^{\bullet-}$, ascorbyl free radical; -, not applicable.

Table 6. Spearman's rank-order correlation investigating the relationship between sirtuin-1 concentration and the other secondary outcome measures at each time point for the phase-III and phase-IV cardiac rehabilitation group.

Variable	TP-1		TP-2		TP-3	
	r_s	*P value* [a]	r_s	*P value* [a]	r_s	*P value* [a]
Distance walked in ISWT (m)	0.04	0.939	0.32	0.482	0.38	0.403
SBP (mmHg)	-0.32	0.482	-0.25	0.589	-0.34	0.452
DBP (mmHg)	-0.07	0.879	-0.67	0.102	-0.04	0.939
RHR (beats/min)	-0.38	0.403	-0.65	0.115	-0.54	0.215
BMI (kg/m²)	-0.11	0.819	-0.54	0.215	-0.46	0.294
WC (inches)	-0.36	0.432	-0.31	0.504	-0.32	0.478
SI (m/s)	-0.21	0.645	-0.07	0.879	-0.07	0.878
RI (%)	-0.56	0.192	-0.50	0.253	-0.42	0.350
Total physical activity (MET-minutes/week)	0.00	1.000	0.25	0.589	0.29	0.535
ESR (mm/hr)	-0.20	0.670	-0.21	0.658	-0.25	0.585
IL-6 (pg/mL)	-0.25	0.589	-0.46	0.294	-0.75	0.052
IL-10 (pg/mL)	0.75	0.052	-0.14	0.760	0.57	0.180
LOOH (µmol/L)	-0.29	0.535	-0.07	0.879	-0.65	0.115
$A^{\bullet-}$ (a.u.) $\times 10^4$	-0.36	0.432	-0.64	0.119	-0.64	0.119
TC (mmol/L)	-0.57	0.180	-0.29	0.535	-	-
LDL-C (mmol/L)	-0.64	0.119	-0.50	0.253	-	-
HDL-C (mmol/L)	0.65	0.115	0.36	0.427	-	-
TG (mmol/L)	-0.64	0.119	-0.79	0.702	-	-
TC/HDL-C ratio	-0.68	0.094	-0.54	0.215	-	-

Non-HDL-C (mmol/L)	-0.64	0.119	-0.21	0.645	-	-

Data not available for endothelial function parameters (number < 7). r_s, Spearman's correlation coefficient; ISWT, incremental shuttle walk test; m, metres; SBP, systolic blood pressure; mmHg, millimetres of mercury; DBP, diastolic blood pressure; RHR, resting heart rate; beats/min, beats per minute; BMI, body mass index; kg/m², kilograms per metres squared; WC, waist circumference; cm, centimetres; SI, stiffness index; m/s, metres per second; RI, reflective index; %, percentage; MET-minutes/week, metabolic equivalent minutes per week; ESR, erythrocyte sedimentation rate; mm/hr, millimetres per hour; IL-6, interleukin-6; pg/mL, picograms per millilitre; IL-10, interleukin-10; LOOH, lipid hydroperoxides; μmol/L, micromoles per litre; A•⁻, ascorbyl free radical; a.u., arbitrary units; mmol/L, millimoles per litre; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; [a], for Spearman's correlation coefficient between sirtuin-1 concentration (nanograms per millilitre) and other secondary outcome variable; -, data not available as measurement was not possible.

Appendix P. Evidence for submission of **Paper 3** for publication.

"Why would you not listen? It is like being given the winning lottery numbers and deciding not to take them": semi-structured interviews with post-acute myocardial infarction patients and their significant others exploring factors that influence participation in cardiac rehabilitation and long-term exercise training

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Appendix Q. Supplemental Online Material for **Paper 3**.

"Why would you not listen? It is like being given the winning lottery numbers and deciding not to take them": semi-structured interviews with post-acute myocardial infarction patients and their significant others exploring factors that influence participation in cardiac rehabilitation and long-term exercise training

Journal Name: Disability and Rehabilitation

Supplemental Online Material 1

Table 1. Interview guide for patients.

Ice-breaker Question	Probes
• **Can you tell me how you felt after your heart attack?**	• Reasons • Symptoms • Impact on significant other
Transition Questions	*Probes*
• **What do you understand about the word "exercise"?**	• Exercise and your condition • Long-term exercise training • Barriers • Facilitators
• **Some people have told us that close family members and friends make a difference to them. What does (name of significant other) think of long-term exercise training after a heart attack?**	• Opinion / attitude • Influence of significant other
• **Could you please give me a definition of a phase-III CR programme, and tell me what you think the purpose of this intervention is?**	• Experience during the phase-III CR programme • Reasons for attending • Relation to condition • Who it is for • Benefits • Risks • Opinion / influence of significant other
• **Could you please give me a definition of a phase-IV CR programme, and tell me what you think the purpose of this intervention is?**	• Relation to condition • Who it is for

	• Benefits
	• Risks
	• Opinion / influence of significant other
• **Could you tell me the reasons why you chose to attend a phase-IV CR programme?**	• Experiences during the phase-III CR programme
	• Knowledge of benefits
	• What would help participation
	• Opinion / influence of significant other
• **Some people have told us that having a heart attack makes them think about their health, and some people also think about the changes they might have to make. Have you thought about how you will manage your health from now on?**	• Lifestyle changes (work, diet, social life etc.)
	• Exercise
	• Influence of significant other
	• Barriers
	• Facilitators
	• Influence of phase-III and phase-IV CR programme participation
Ending Question	
• **Is there anything else that we haven't talked about today that you would like to add?**	

Table 2. Interview guide for significant others.

Ice-breaker Question	Probes
• **Can you tell me how you felt after (patient's name) suffered a heart attack?**	• Reasons • Patient's symptoms • Reaction • Involvement in recovery
Transition Questions	*Probes*
• **What do you understand about the word "exercise"?**	• Exercise and patient's condition • Long-term exercise training • Barriers • Facilitators
• **Some people who have suffered a heart attack have told us that close family members and friends make a difference to them. What do you think of long-term exercise training after a heart attack?**	• Perspective • Involvement
• **Could you please give me a definition of a phase-III CR programme, and tell me what you think the purpose of this intervention is?**	• Patient's experience during the phase-III CR programme • Reasons for patient attending • Involvement with decision • Relation to patient's condition • Who it is for • Benefits

	• Risks
• **Could you please give me a definition of a phase-IV CR programme, and tell me what you think the purpose of this intervention is?**	• Relation to patient's condition • Who it is for • Benefits • Risks • Involvement with decision
• **Could you tell me the reasons why you think the patient chose to attend a phase-IV CR programme?**	• Patient's experience during the phase-III CR programme • Involvement with decision • Feelings towards decision • Knowledge of benefits • What would help participation
• **Some people have told us that having a heart attack makes them think about their health, and some people also think about the changes they might have to make. Have you thought about how (patient's name) will manage his/ her health from now on?**	• Support from family members or friends • Lifestyle changes (work, diet, social life etc.) • Exercise • Barriers • Facilitators • Influence of patient's participation in the phase-III and phase-IV CR programmes
Ending Question	
• **Is there anything else that we haven't talked about today that you would like to add?**	