Optimising Exercise Prescription in Patients with Intermittent Claudication: A United Kingdom Perspective

by

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A thesis submitted in partial fulfilment for the requirements for the degree of Doctor of Philosophy (via MPhil) at the University of Central Lancashire

September 2023

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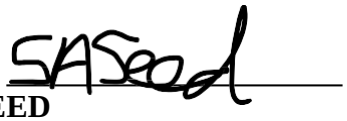
Signature of Candidate: 
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General Abstract

The National Institute for Health Care Excellence guidelines (NICE) recommend supervised exercise programmes (SEPs) as the first line of treatment for patients with intermittent claudication (IC). However, there are inconsistencies between guidelines regarding the optimal level of claudication pain prescribed. This thesis aimed to synthesis the current evidence in the literature and undertake a randomised control trial to understand which level of claudication pain was optimal in improving functional outcomes for patients with IC. In addition, it aimed to assess barriers, uptake and adherence to SEPs. Additional components of this thesis including a systematic review identifying how many studies had directly compared exercise prescription at differing levels of claudication pain on walking performance and a commentary highlighting the limitations of current guidance to clinicians and exercise professionals which could lead to variability in care.

Evidence from this thesis indicates that maximal claudication pain appears to elicit a larger benefit in treadmill related maximal walking distance compared to pain-free and moderate claudication pain, supporting the current NICE guidelines. However, at the time of submission we had not fully recruited and therefore results may be subject to change.

In addition, the evidence indicates that adherence to exercise in this clinical population is poor. Although, this was largely associated with non-PAD related health issues. Common barriers to attending the SEP included time and location of the class. Therefore, centres should engage with their patients to develop an effective accessible rehabilitation programme.

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Acknowledgments

I cannot express enough thanks to Dr Stefan Birkett for the continuous support throughout my PhD journey. For his tireless patience, enthusiasm, motivation, friendship and immense knowledge, I offer my sincere appreciation for believing in me and providing me with the opportunity to reach my true potential. He has guided me through this entire process, and I could not have imagined having a better supervisor and mentor.

I am most thankful to Amy Harwood and Jonathan Sinclair for their insightful comments, knowledge and invaluable help in preparing this thesis. I have greatly benefitted from their critical reviews and vision throughout my work.

I would also like to thank all the staff at Heartbeat NWCC for all the time they have invested in the research project. To Joanne Duff and Debbie Crossley for help with numerous assessments, the CEO Louise Bache for her endless support and all the BACPR Instructors for their patience and interest in allowing me to conduct the research trial.

Most importantly, to my family. I am greatly indebted to my mum, dad, sister and boyfriend for their keen interest in my academic achievements and always supporting me, I would not be who I am today without you. Jules your commitment, passion, nurturing nature and incredible nursing career inspired me from a young age to always look for opportunities to improve the treatment given to clinical populations.

This thesis is dedicated to my mum Julie Seed and my dad Andy Seed.

List of Publications

Published Contributions from this Thesis

Seed SA, Harwood AE, Sinclair J, et al. A Systematic Review of Exercise Prescription in Patients with Intermittent Claudication: Does Pain Matter? *Annals of Vascular Surgery*. DOI: 10.1016/j.avsg.2021.06.025.

Seed SA, Harwood AE, Sinclair J, et al. What is the correct level of claudication pain to prescribe? Universal inconsistency within guidelines, a painful issue. *Vascular*; 0: 17085381231155940. DOI: 10.1177/17085381231155940

Birkett ST, Sinclair J, **Seed SA**, et al. Effects of exercise prescribed at different levels of claudication pain on walking performance in patients with intermittent claudication: a protocol for a randomised controlled trial. *Ther Adv Cardiovasc Dis* 2022; 16: 17539447221108817. 2022/06/29. DOI: 10.1177/17539447221108817.

Full list of Publications

Seed SA, Harwood AE, Sinclair J, et al. A Systematic Review of Exercise Prescription in Patients with Intermittent Claudication: Does Pain Matter? *Annals of Vascular Surgery*. DOI: 10.1016/j.avsg.2021.06.025.

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Birkett ST, Sinclair J, **Seed SA**, et al. Effects of exercise prescribed at different levels of claudication pain on walking performance in patients with intermittent claudication: a protocol for a randomised controlled trial. *Ther Adv Cardiovasc Dis* 2022; 16: 17539447221108817. 2022/06/29. DOI: 10.1177/17539447221108817.

Waddell A, **Seed SA**, Broom DR, et al. Safety of home-based exercise for people with intermittent claudication: A systematic review. *Vascular Medicine*; 0: 1358863X211060388. DOI: 10.1177/1358863x211060388.

Whorlton-Jones E**, Seed S**, Waddell A, et al. Does the level of encouragement affect 6-minute walk test performance in patients with intermittent claudication? A protocol for a randomised multicentre controlled trial. DOI:10.54522/jvsgbi.2022.08

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Abbreviations

ABPI	Ankle Brachial Pressure Index
ACEI	Angiotensin-Converting Enzyme Inhibitors
ACSM	American College of Sports Medicine
AHA	American Heart Association
ARB	Angiotensin Receptor Blockers
BASES	British Association of Sport and Exercise Science
BACPR	British Association of Cardiac Rehabilitation and Prevention
BMI	Body Mass Index
BMT	Best Medical Treatment
BP	Blood Pressure
CHD	Coronary Heart Disease
CI	Confidence Interval
CLTI	Chronic Limb Threatening Ischemia
CO_2	Carbon Dioxide
CPET	Cardiopulmonary Exercise Testing
CR	Cardiac Rehabilitation
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
ECQ	Edinburgh Claudication Questionnaire
EQ-5D	EuroQol-5
ESC	European Society of Cardiology
EU	European Union
FCD	Functional Claudication Distance
FITT	Frequency Intensity Time Type
FMD	Flow Mediated Dilation
GS	Gardner-Skinner Protocol
GT	Graded-Exercise Test
HBEP	Home-based Exercise Programme
HIC	High Income Countries
HIIT	High Intensity Interval Training
HPS	Heart Protection Study
HR	Heart Rate
HRM	Heart Rate Max
IC	Intermittent Claudication
IDL	Intermediate-Density Lipoproteins
IRAS	Integrated Research Application System
LDL	Low-Density Lipoproteins
LMICS	Low-Income and Middle-Income Countries
LTHTR	Lancashire Teaching Hospitals Foundation Trust
MAX-P	Maximal Pain
MCID	Minimally Clinical Important Difference
MET	Metabolic Equivalent
MI	Myocardial Infarction
MOD-P	Moderate Pain
MWD	Maximal Walking Distance

MWT	Maximal Walking Time
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NRT	Nicotine Replacement Therapy
NVR	National Vascular Registry
NWCC	North-West Cardiac Care
O_2	Oxygen
PA	Physical Activity
PAD	Peripheral Artery Disease
PF	Pain-Free
PFWD	Pain-Free Walking Distance
PFWT	Pain-Free Walking Time
PTA	Percutaneous Angioplasty
PVI	Peripheral Vascular Intervention
QoL	Quality of Life
RCT	Randomised Control Trial
RER	Respiratory Exchange Ratio
SBP	Systolic Blood Pressure
SEP	Supervised Exercise Programme
SET	Supervised Exercise Therapy
SF-36	Short Form-36 Questionnaire
T2DM	Type 2 Diabetes Mellitus
TASC II	Inter-Society Consensus for the Management of Peripheral Artery Disease
TBPI	Toe Brachial Pressure Index
TOT	Time of Test
UK	United Kingdom
USA	United States of America
VascuQoL	Vascular Quality of Life Questionnaire
VLDL	Very Low-Density Lipoproteins
VO_{2peak}	Peak Oxygen Uptake
WA	Walking Advice
WBC	White Blood Cells
WHO	World Health Organisation
b	Mean difference between groups
d	Cohen's d
P-value	$P < 0.05$
1RM	1 Rep Max
6MWD	6 Minute Walk Distance
6MWT	6 Minute Walk Time
6-MWT	Six Minute Walk Test
95% CI	95% Confidence Interval

Chapter 1. Introduction

1.1 Rationale

Peripheral artery disease is an atherosclerotic condition of the lower extremity arteries, produced by the blockage of arteries supplying blood to the lower limbs, leading to end limb ischemia (Krishna et al., 2015). Classically, the disease produces a cramping sensation the leg and buttocks brought on during exertion and is relieved at rest, this is known as intermittent claudication (IC) (Ouriel, 2001). Supervised exercise programmes (SEP) are the first line of treatment for patients with intermittent claudication (IC) (NICE, 2012).

Despite the benefit of exercise, there lies inconsistencies between exercise prescription and guidelines regarding the optimal level of claudication pain for patients with IC and it remains unknown what that optimal level is (Treat-Jacobson et al., 2019). Previous research has suggested exercise should be performed at near-maximal levels of claudication pain (Gardner and Poehlman, 1995, Lane et al., 2017b, Fokkenrood et al., 2013b). Supporting this, a recent review with 305 patients found low-intensity exercise (walking without ischemic leg symptoms) was significantly less effective than high-intensity exercise (walking at a pace eliciting moderate to severe ischemic leg symptoms) for improving 6-minute walking distance (McDermott et al., 2021a).

However, a recent review found pain-free SEPs elicit similar improvements in functional outcomes than moderate-SEPs (Seed et al., 2021). Similarly, Parmenter et al (2015) found mild to moderate pain may yield optimal results (Parmenter et al., 2015). Recently, a review supported the provision of both high and low pain exercise on improvements in MWD and PFWD for patients with IC (Perks et al., 2021). Of the 14 studies used in the review, structured

low-pain exercise had a larger positive effect than structured high-pain exercise for MWD/T and PFWAD/T compared with a control group. Additionally, in a comparison of low-pain and high-pain, there was a large positive effect of low-pain on walking ability, with statistical significance on PFWA (Mean difference 1.50, CI 0.24 to 2.75) (Perks et al., 2021). The paper concluded structured low pain may have been overlooked due to the lack of literature. Only two studies have directly compared pain-free and moderate claudication pain on functional outcomes and quality of life (Mika et al., 2013, Novakovic et al., 2019). No trial has directly compared maximal claudication pain which is the current recommended guidelines (NICE, 2012). This indicates that further studies comparing the three levels of claudication pain would be of practical and clinical relevance.

1.2 Aims

This thesis aimed to design and implement a new NHS referral pathway and to create a specific SEP for patients with IC at Heartbeat Northwest Cardiac Centre. A further aim was to conduct an randomised control trial to optimise exercise prescription and uptake by comparing the effects of exercise prescribed at different levels of claudication (pain-free, moderate pain and maximal pain on:

1. Maximal and pain-free walking distance
2. Uptake and adherence
3. Enjoyment of the exercise intervention
4. Barriers and quality of life

Chapter 2. Review of Literature

2.1 Cardiovascular Disease

The World Health Association (WHO) defines cardiovascular disease (CVD) as “disorders of the heart and blood vessels” (WHO, 2017). These include coronary heart disease (CHD), peripheral artery disease (PAD), cerebrovascular disease, rheumatic heart disease, congenital heart disease and deep vein thrombosis (WHO, 2017). The World Heart Federation (2023) estimated the global death rate of CVD to be 20.5 million deaths in 2021, close to a third of all deaths globally (Federation, 2023). This has increased during the past decade by 12.5% (Collaborators, 2016). Changes in the prevalence of CVD are driven by population growth and an ageing population, this is most prevalent in countries of South and East Asia due to their large population growth (Joseph et al., 2017). In the United Kingdom it was estimated 29% of all deaths occurred from CVD, equating to a death rate of 176,000 people per year.

The European Heart Network (Wilkins et al., 2017) estimated that CVD cost the European Union (EU) economy €210 billion a year. Of this, 53% was due to direct health costs, 26% to productivity losses and 21% to the informal care of people with CVD. In 2015, CVD cost the health care systems of the EU just over €111 billion, 8% of the total health care expenditure in the EU. Of this 25% is due to the drugs spend and over 50% was accounted for inpatient hospital care.

Cardiovascular disease may cause acute events such as a myocardial infarction or a stroke which are the main causes of mortality (Foundation, 2020). The Framingham Heart Study identified major risk factors influencing the development of CVD (Mahmood et al., 2014). After being comprehensively evaluated these are now used in many risk models for CVD. From

this, a case-controlled study 'INTERHEART' (Yusuf et al., 2004) identified nine risk factors which account for >90% of the risk attributed to CVD, therefore their control or elimination would make a substantial reduction in the prevalence of CVD at a population level (Pencina et al., 2019). Indeed they are on the WHOs target for reduction by 2025 (WHO, 2017). The risk factors and health behaviours included are hypertension, dyslipidaemia, diabetes, obesity, smoking, alcohol, diet, and sedentary lifestyle (Timmis et al., 2019).

2.2 Peripheral Artery Disease

Peripheral artery disease is an atherosclerotic condition of the lower extremity arteries, produced by the blockage of arteries supplying blood to the lower limbs, leading to end limb ischemia (Krishna et al., 2015). Globally, 236 million people are living with the disease, equivalent to 5.56% of people aged 25 years or older (Song et al., 2019). It is associated with atherothrombosis of other vascular beds including the cardiovascular and cerebrovascular systems which interfere with exercise ability (Thiruvoipati et al., 2015). The disease can present on a wide spectrum from asymptomatic to symptomatic and critically life-threatening. Classically, the disease produces a cramping sensation the leg and buttocks brought on during exertion and is relieved at rest, this is known as intermittent claudication (IC) (Ouriel, 2001). In severe cases of symptomatic PAD, patients can develop chronic limb threatening ischaemia (CLTI) where patients present with ischaemic rest pain and non-healing wounds or gangrene (Nehler et al., 2014a).

Supervised exercise programmes (SEP) are the first line of treatment for patients with PAD, although provision is poor, and so is uptake and adherence (Lin et al., 2019a, Harwood et al., 2021). Perhaps this is due to patients being conscience of the discomfort and pain associated with walking and exercise (Lin et al., 2019a). Additional treatment involves reducing their

cardiovascular risk factor profile such as smoking cessation, weight management, antiplatelet therapy, statin therapy and the management of hypertension and diabetes (NICE, 2012). Further treatments include angioplasty, bypass surgery and in severe cases of CLTI, amputation. PAD is becoming more prevalent with advancing age and it is an independent predictor of cardiovascular morbidity and mortality (Golomb et al., 2006). As PAD shares risk factors with coronary artery disease and cerebrovascular disease this heightens the burden of cardiovascular disease on the population (Golomb et al., 2006).

2.2.1 Pathophysiology of Atherosclerosis

The pathophysiology of athero-thrombosis induced PAD is complex, involving a large number of cells, proteins and pathways (Krishna et al., 2015). Initially, atherosclerosis was considered a lipid storage disease, however it is now identified as an inflammatory disease (Badimon and Vilahur, 2014, Ross and Harker, 1976). The early stage in the development of atherosclerosis is endothelial dysfunction caused by an exposure to cardiovascular risk factors such as hypertension, diabetes, obesity, free radicals from cigarette smoking and high cholesterol (Ross, 1999). As a result of the injury, the endothelial dysfunction causes a compensatory response which alters the homeostatic properties of the endothelium and allows it to become more permeable (Ross, 1999). Consequently, allowing the low-density lipoproteins (LDL-C) to infiltrate the extracellular matrix, developing into targets for enzymatic and oxidative modifications (Badimon and Vilahur, 2014). LDL-C then becomes oxidised which stimulates the expression of adhesion molecules and attracts T-lymphocytes and monocytes to enter the intima (Nguyen et al., 2019) (figure 2.1).

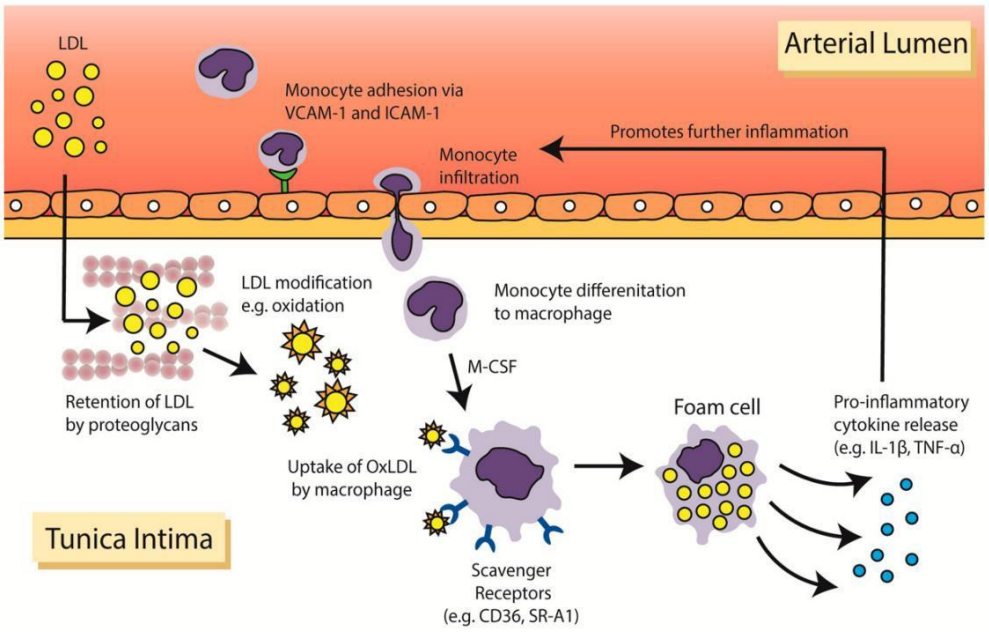


Figure 2.1. Infiltration of the low-density lipoprotein and formation of the macrophage foam cells in the arterial wall (Nguyen et al., 2019).

Once the monocyte become resident in the arterial intima, they mature into macrophages. The mononuclear phagocytes express scavenger receptors which allows them to ingest lipids, consequently becoming overloaded, hence foam cells are formed (Libby, 2012). Over time the foam cells accumulate which results in a build-up of 'fatty plaque'. The migration of the smooth muscle cells from the media to the intima occur due to macrophages releasing pro-inflammatory cytokines. These cells flourish under growth factors and produce an extracellular matrix including collagen which contributes to forming a thin fibrous cap over the atherosclerotic plaque (Libby et al., 2011). The macrophages and smooth muscle cells within atherosclerotic plaques over express a procoagulant tissue factor. The inflammatory mediator CD40 has been found a disease relevant activator of tissue factor expression. Therefore supporting that inflammation regulates the thrombogenicity of the plaque and the integrity of the fibrous cap (Libby, 2012). Due to their fragile nature, the fibrous cap continues to become overloaded with foam cells they are at increased risk of rupture. Once this occurs and the plaque

encounters blood, a cascade of events occurs resulting in platelet aggregation and adhesion, consequently forming a thrombus (Bentzon et al., 2014).

As a result of further platelet initiation, a platelet plug occurs. If it is attached to the vessel wall firmly it can progress and grow until it completely obstructs the lumen. However, if it becomes unstable it may detach and cause an acute thrombotic event. In severe cases flow limiting plaque stenosis results in IC (Meru et al., 2006b). In PAD, flow limiting plaques are a major contributor to IC and critical leg ischemia, with flow velocity at rest being recorded as low as 20cm/s in the femoral artery. This means for a stenosis to be significant at these velocities a diameter reduction of >90% would be required (Meru et al., 2006b). During exercise, femoral artery velocities may increase up to 150cm/s, therefore a stenosis of even 50% may cause significant pressure leading to inadequate oxygen delivery. Moreover, high shear stress in exercising may lead to platelet thrombosis (Meru et al., 2006b).

The mechanisms that lead up to IC in PAD patients are complex. These include skeletal muscle perfusion, reduced microcirculatory flow, reduced limb perfusion, systemic inflammation, vascular dysfunction and impaired angiogenesis (Hamburg and Creager, 2017). Therefore, it is critical for an enhanced understanding of the pathophysiology of the leg to develop therapeutic approaches (Hamburg and Creager, 2017).

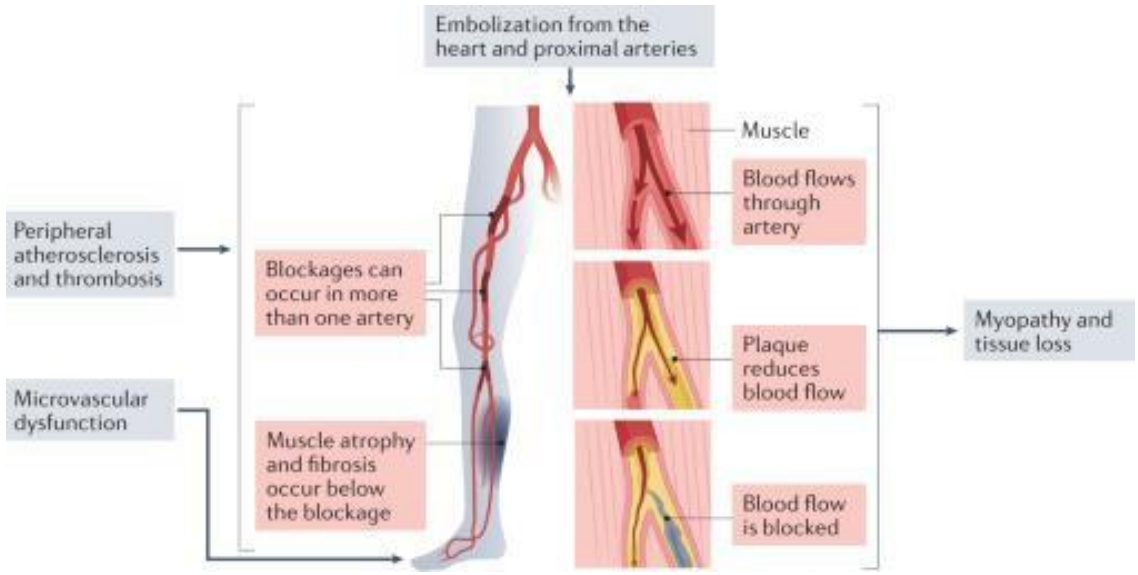


Figure 2.2. The pathophysiology of peripheral artery disease (Golledge, 2022).

2.2.2 Epidemiology and Prevalence

PAD is the third leading cause of atherosclerotic cardiovascular morbidity (Fowkes et al., 2013a). Globally, 236 million people are living with the disease, equivalent to 5.56% of people aged 25 years or older (Song et al., 2019). The prevalence of PAD is higher in high-income countries (HICs) at 65-69 years, however in low-income and middle-income countries (LMICS) PAD is most prevalent at a younger age (45-49 years). This may be due to a relatively lower life expectancy and a higher prevalence unhealthy behaviours in LMICs (Song et al., 2019). For example, out of 28 studies (16 HICs vs 12 LMICs) there was over 29,000 current smokers in LMICs compared to HICs (82,865 vs. 53,559). The incidence of PAD is higher in LMICS (72.91%) than HICS in younger people, however this is dependent on age. From the age of 50 years, there is higher prevalence in HICs than LMICS (Song et al., 2019). This could be due to environmental factors such as industrialisation, infection, dietary changes, lack of physical activity and poverty causing the development of PAD at a younger age in LMICS

(Fowkes et al., 2013b). Furthermore, hypertension, diabetes and simultaneous CVD has been associated with a higher risk of PAD in both HICs and LMICs (Song et al., 2019).

Interestingly, in HICs, the occurrence of PAD did not differ between sex. Up until the age of 75, the prevalence was lower in men than women. This may be due females presenting with other risk factors such as obesity and socioeconomic inequality which may be inherent for the disease mechanism (Song et al., 2019). This is contrary to previous belief that PAD is male dominant, which could be due to women being asymptomatic and only presenting with the disease when symptoms have worsened (Srivaratharajah and Abramson, 2018). Intriguingly, women have been reported to be disproportionally under-represented in RCTs for vascular disease (Vavra and Kibbe, 2009). In a review looking at trials on lower extremity revascularisation women presented 22.4% of participants, however as the Nationwide Inpatient Sample showed women represented 41.3% this highlighted women were underrepresented by ~50% (Hoel et al., 2009). Hence, this has provoked an increased enrolment of women on research trials to focus on strategy prevention (Srivaratharajah and Abramson, 2018). Therefore, the evidence base may not be reflected of women with PAD.

In 2015, the highest share of PAD cases was in the Western Pacific region (74.08 million cases) in contrary, the Eastern Mediterranean Region had the least cases (14.67 million cases) (Song et al., 2019). As the major risk factors, such as smoking and diabetes, are likely to considerably increase over the next 10 years more efforts need to focus on early diagnosis and prevention (Guariguata et al., 2014). Governments, particularly in LMICs, need to prioritise the awareness of PAD and fund the resources to manage it.

2.2.3 Established Cardiovascular Risk Factors

The development of PAD is multifactorial and includes both non-modifiable and modifiable risk factors (Shammas, 2007). The risk factors of PAD are similar to that of patients with coronary artery disease (Shammas, 2007) and are associated with the development and progression of the disease (Berger et al., 2013).

Table 2.1. Prevalence/classifications of Risk Factors

Risk Factor	**Prevalence / Classification**
Non-modifiable	
Age	Most prevalent in 65-69 years in HICs and 45-49 years in LMICs
Sex	Prevalence of PAD and CVD is higher in males than females
Ethnicity	African Americans and American Indians (in some countries) have an increased risk of PAD/CHD
Modifiable	
Smoking	Aim for completion of a smoking cessation programme
Hypertension	Blood pressure >140 mmHg systolic, >90 mmHg diastolic
Type 2 diabetes mellitus	Fasting plasma glucose >100 $mg{\cdot}dL^{-1}$ HbA1c >48 mmol/L (6.5%)
Dyslipidaemia	Total cholesterol >200 $mg{\cdot}dL^{-1}$ LDL-C >100 $mg{\cdot}dL^{-1}$ LDL >40 $mg{\cdot}dL^{-1}$ for patients at high risk of an ischaemic event
Obesity	Waist > 102cm in men and 88cm in women BMI $\geq$30 $kg{\cdot}m^{-2}$

HICS = High Income Countries; LMICs = Low-income and Middle-income countries; PAD = Peripheral Artery Disease; CVD = Cardiovascular Disease; mmHg = Millimetres of Mercury; CVD = Cardiovascular Disease; $mg{\cdot}dL^{-1}$, CHD = Coronary Heart Disease; LDL = Low Density Lipoprotein

2.2.4 Risk factors and PAD

2.2.4.1 Non-modifiable

2.2.4.1.1 Age

Peripheral artery disease is age related, with its incidence significantly increasing with age (Fowkes et al., 2017). The prevalence of PAD has been studied widely in the USA and Europe, however less so in low-income countries due to the lack of resources. A review of epidemiological studies in western countries found the prevalence was <1% in those aged <50 years, increasing to 6% in those aged >65 years (Norgren et al., 2007). The prevalence of PAD is sharply age-related, rising 10% among patients in their 60s and 70s (Criqui and Aboyans, 2015). By 2023, older people, defined as over 65 years, are set to make up 21.8% of the UKs population (Jarman, 2022). Given the ageing population, an upward trend of PAD is expected, which is likely to cause a large burden in the foreseeable future (Song et al., 2019).

2.2.4.1.2 Sex

It has been suggested the prevalence of PAD is slightly higher in men than women, particularly in the younger age groups, with the ratio of men to women being 1:2 and 2:1 in patients with IC (Norgren et al., 2007). However, despite the reported higher burden in men, research has highlighted women suffered a greater increase in morbidity and mortality between 1990 and 2010 (Sampson et al., 2014). A recent study from a nationwide sample discovered women with PAD who present to the hospital and have endovascular interventions are at a significantly higher risk of in-hospital morbidity and mortality than men. Furthermore, females had a significantly higher risk of major adverse cardiovascular events (Hassan et al., 2021). A reason for this could be explained due to females presenting at a later stage of the disease which may result in prolonged and more complex procedures which further complicates the risk (Hassan et al., 2021). Another possible mechanism is that females metabolise heparin, a common anticoagulant used during endovascular procedures, slower than males. As a consequence females were more likely to have postprocedural bleeding than males (Cheng et al., 2009).

Further, in 2012, the American Heart Association issued scientific statement ‘Call to action: Women and Peripheral Artery Disease” urging healthcare professionals to ensure PAD diagnosis is established promptly in women. This suggested women suffer the consequences as the same rate as men however major gaps in the knowledge exist (Hirsch et al., 2012). However, the prevalence of PAD between sexes continues to be an ongoing debate as some studies report it to be equally common in both sexes (FOWKES et al., 1991, Sigvant et al., 2007).

More recently, it has been identified sex differences could be related to the economic status of the country. A review suggested the prevalence of PAD was similar in men and women and increased consistently with age in high-income countries (Fowkes et al., 2013a). However in low-income and middle-income countries the prevalence of PAD was higher in women (6·31% [4·86–8·15%] of women aged 45–49 years) then men (2·89% [2·04–4·07%] at 45–49 years) and was more pronounced at younger ages (Fowkes et al., 2013a). It is clear governments and private sector in low-income and middle-income countries need to address economic consequences and devise optimal treatment and disease prevention.

2.2.4.1.3 Ethnicity

PAD prevalence has been reported to vary by ethnicity (Criqui et al., 2005a). Research suggests black ethnicity is a strong and independent risk factor for PAD, and is not associated with higher levels of diabetes, hypertension and body mass index (Criqui et al., 2005a). A study researching 2343 participants found 104 cases of PAD (4.4%) with black people having a higher prevalence than non-Hispanic whites (OR = 2.30, P<0.024) (Criqui et al., 2005b). Furthermore, the inclusion of other PAD risk factors did not change the effect of the black ethnicity on PAD (OR = 2.34, P<0.048). Following this finding, it has been suggested further

research into atherogenic, inflammatory and prothrombotic markers are needed to explain the large cases of PAD in black people as no objective data supports the assumption that the increased prevalence is due to an increased incidence of risk factors (Criqui et al., 2005a). A review analysed seven studies to pool ethnic-specific prevalence rates (Allison et al., 2007). They identified non-Hispanic whites contributed to the prevalence of PAD, however at an older age African Americans had a incidence rate two to three times higher (Allison et al., 2007). In women, there was an exponential increase in PAD cases in American Indians and African Americans which occurred a decade earlier than all other ethnicities (Allison et al., 2007). Studies in the United Kingdom have recognised PAD prevalence is lower in South Asians compared to other ethnic groups even though they have a greater risk of coronary artery disease (Premalatha et al., 2000). This could be explained by the high premature death rate of South Asians, therefore they do not live long enough to develop symptoms (Bennett et al., 2008). Furthermore, black Americans present with a greater ambulatory dysfunction, higher rate of mobility loss and a faster functional decline, non-Hispanic whites measured by serial walking tests (Rucker-Whitaker et al., 2004). Hence, the need for early and aggressive treatment to prevent disease progression (Rucker-Whitaker et al., 2004).

2.2.4.2 Modifiable

2.2.4.2.1 Smoking

Smoking is one of the key risk factors for the development and progression of PAD (Murabito et al., 1997), as it plays a strong aetiological role in the development of atherosclerosis (Minar and Schillinger, 2013). It is considered the most modifiable risk factor (Willigendael et al., 2004). Research into the relationship between smoking and PAD was recognised in 1911 when it was reported that IC was 3 times more common in smokers and 6 times more common in heavy smokers when compared to non-smokers (Willigendael et al., 2004). Following this, the

Edinburgh Artery Study (1999) studied 1592 men and women aged 55-74 with PAD for 5 years (Price et al., 1999). They found smoking was a stronger risk factor for PAD than for coronary artery disease and smoking 25 or more cigarettes a day increased the odds ratio of PAD by 7.3 times (Price et al., 1999). One study investigating in-hospital predictors of complications following a percutaneous intervention found smoking was a strong independent predictor for the risk of unplanned urgent revascularisation (Shammas and Dippel, 2005). Furthermore, research has concluded smoking appears to affect further risk in a dose-dependent fashion (Minar and Schillinger, 2013). Therefore if patients continue to smoke once they have developed PAD, it is expected their maximal walking distance will continue to decline and the progression of their disease may result in major amputation (Palfreyman et al., 2011). This is supported by the Edinburgh Artery Study which showed ex-smokers, who had stopped within 5 years, had less chance of developing PAD than current smokers. This highlights smoking cessation as an important first step in the treatment for PAD (Ratchford, 2017).

2.2.4.2.2 Hypertension

It is estimated that 35-52% of patients with PAD at presentation have hypertension, however the relationship between hypertension and PAD is less robust than above factors such as diabetes and smoking (Minar and Schillinger, 2013). That said, hypertension still remains an independent risk factor of PAD as identified by the Framingham Heart study where hypertension increased risk 2.5-to fourfold in men and women (Kannel and McGee, 1985). A study researching Chinese patients with hypertension found systolic blood pressure was an independent risk factor for a low ankle-brachial pressure index, ultimately associated with cardiovascular mortality (Luo et al., 2007). Furthermore, high blood pressure has been associated with increased risk of ischemic limb events (Fudim et al., 2020).

As well as the epidemiological associations, hypertension has been found to contribute to the process of atherosclerosis (Makin et al., 2001, Alexander, 1995). Research postulates that hypertension accelerates atherosclerosis as a result of the elevated pressure inducing oxidative stress on the arterial wall. Therefore, injury to the endothelium results in an activation of redox-sensitive mechanisms that recruit mononuclear leukocytes into the arterial wall, contributing to the build-up of a atherosclerotic plaque (Alexander, 1995). Consequently, the adequate treatment of hypertension is imperative and should be a principal primary objective (Hooi et al., 2001). The presence of cardiovascular disease risk is two-fold for each increment of 20mg in systolic blood pressure and 10mg in diastolic blood pressure (Lewington et al., 2002). Furthermore, research has identified every 10mg reduction in systolic blood pressure contributes to a 20% relative risk reduction for CHD and 13% reduction in all-cause mortality (Ettehad et al., 2016). Therefore, concluding intensified efforts to treat hypertension are justified (Mehler et al., 2003).

2.2.4.2.3 Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a powerful risk factor for PAD. Research has shown a 1% reduction in HbA_{1c} results in a 14% reduction in CVD (Stratton et al., 2000). Furthermore, the presence of HbA_{1c} has been associated with a significantly increased relative risk (1.28) of PAD (Muntner et al., 2005). Individuals with a HbA_{1C} >7.5% were more than five times as likely to develop IC compared to individuals with good glycaemic control (HbA_{1C} <6%). This highlights that efforts to improve an individuals' glycaemic control may substantially reduce the development of PAD. A survey with 2174 participants found T2DM was associated with nearly a threefold increased risk for developing PAD, behind smoking which presented the biggest risk in the analysis (Selvin and Erlinger, 2004). Furthermore, it is understood the presence of T2DM greatly increases the risk of PAD, as well as accelerating its course.

Therefore, patients become more susceptible to impaired functional status and ischaemic events (Thiruvoipati et al., 2015). Consequently, diabetic patients have a higher mortality and are more likely to die at a younger age (Jude et al., 2001).

The occurrence of PAD and T2DM is especially high in patients with CLTI, as more than 50% of patients diagnosed have diabetes (Dick et al., 2007). The presentation of the disease in diabetic patients is in distal arterial beds below the knee whereas other risk factors, such as smoking, are associated with more proximal PAD. Moreover, after endovascular revascularisation, T2DM increases the risk of all-cause death at 12 months and the likelihood of major amputation (Shammas et al., 2017). The difference in functional capacity with diabetic patients could be explained by diabetes-associated neuropathy which exacerbates symptom, as there is a higher prevalence of leg pain of exertion and so accelerates the progression of the disease (Dolan et al., 2002).

2.2.4.2.4 Dyslipidaemia

Lipid derangements have been related to an increased risk of PAD (Minar and Schillinger, 2013). A fasting cholesterol level greater than 7 mmol/L was associated with a doubling of the incidence of IC (Norgren et al., 2007). But, the ratio of total cholesterol to high density lipoprotein cholesterol (HDL) is an independent risk factor and the best significant predictor of PAD, as a lower concentration is found amongst patients (Aboyans et al., 2006). Further, one study emphasised the role of lipoprotein disturbances such as serum triglycerides, very low density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) are a significant risk factor of patients with PAD (Sentí et al., 1992). Importantly, the study suggested IDL abnormalities should be considered a vascular risk factor in normocholesterolemic and norm triglyceridemic patients (Sentí et al., 1992). Patients who smoked had an increased LDL

cholesterol and triglycerides and lower HDL concentrations compared with non-smokers. This further highlights the importance of smoking cessation for reducing PAD in patients.

Additionally, research suggests the importance of lipoprotein (a) as a significant marker on the progression of PAD, a genetically determined cholesterol rich plasma lipoprotein (Aboyans et al., 2006, Cheng et al., 1997). Lipoprotein (a) was first associated with myocardial infarctions and coronary artery disease (Kostner et al., 1981). However more recently, is has been shown to be an independent risk factor of early atherosclerosis (Cheng et al., 1997, Golledge et al., 2020).

2.2.4.2.5 Obesity

Obesity is defined by body mass index (BMI) of 30kg.m^{-2} or greater (Riebe et al., 2018). It is associated with a significant health care burden on society, with the rates of clinical complications increasing exponentially with a greater BMI (Flegal et al., 2005). An increase in weight has been linked to an increased risk of diabetes mellitus, hypertension and dyslipidaemia (Nguyen et al., 2011, Ludhwani and Wu, 2019). Furthermore, obesity is an independent risk factor of CVD (Poirier et al., 2006). A systematic review with 9319 patients concluded obesity was an independent risk factor for cardiovascular events in patients with PAD (Cronin et al., 2013). Likewise, a previous study analysed the association of obesity and IC with 60 PAD patients, 48 of whom were obese. They found obesity was independently predicted with the severity of PAD during a 24-month follow up (Golledge et al., 2007).

2.2.4.2.6 C-Reactive Protein

C- reactive protein (CRP) is a plasma protein which is produced in response to inflammation. In clinical populations such as PAD, CRP is said to be significantly increased as it plays a

casual role in the pathogenesis of atherosclerosis (Shankar et al., 2007). However, this is disputed as further research suggests CRP is a biomarker rather than a casual factor in atherosclerosis, suggesting more evidence is required (Ridker, 2016). To detect inflammation in the body, high-sensitivity assays (hs-CRP) can now detect CRP levels as low as 1 microgram per litre (mg/L) (Roberts, 2004). These tests are extremely beneficial as CRP has now emerged as a major cardiovascular risk factor and a strong predictor of CVD and future events (Ridker et al., 1997). One study associated elevated CRP levels with an 8-fold increase in CVD mortality (Ridker, 2003). Furthermore, research has concluded patients with a CRP over 10mg/L was correlated with an over 4% risk of developing a fatal CVD in 10 years (Cozlea et al., 2013). Intriguingly, higher levels of CRP have been associated with PAD patients free of other risk factors such as diabetes and hypertension, therefore suggesting the inflammatory mechanism related to atherosclerosis may be operative even among clinically healthy adults (Shankar et al., 2007).

The AHA and the Centre for Disease Control classifies hs-CRP levels classified hs-CRP levels <1 mg/L as low risk for future CVD events, 1-3 $mg{\cdot}L^{-1}$ moderate risk and >3 $mg{\cdot}L^{-1}$ high risk respectively (Ridker, 2003). A prospective data study highlighted the importance of CRP testing, as baseline levels of CRP predict future risk of developing symptomatic PAD (Ridker et al., 1998). Despite the depth of evidence, recommendations for the routine use of CRP in assessments for patients with CVD has yet to emerge in clinical guidelines (Bonaca and Morrow, 2008).

2.3 Clinical Presentation

Between 20% to 50% of patients are are asymptomatic (McDermott et al., 2008). Due to PAD patients having multiple co-morbidities, it can be difficult to differentiate between classic

claudication/ leg symptoms caused by PAD or those resulting from another medical condition (Lau et al., 2011).

2.3.1 Asymptomatic Disease

Asymptomatic PAD implies the absence of classic leg claudication symptoms (pain in the calf muscle brought on by exertion which is relieved at rest) however, may still present with measurable adverse cardiovascular outcomes and limb dysfunction. The classification of patients with asymptomatic PAD has implied that individuals have neither (a) limb ischemic symptoms or (b) other "symptomatic" consequences of systemic atherosclerosis (Hirsch et al., 2006a). Data from standardised questionnaires have demonstrated asymptomatic PAD is 2 to 5 times more prevalent than symptomatic PAD in the United States and Europe (Hirsch et al., 2006a). Approximately half of patients with PAD have not yet suffered a cardiovascular event, as their disease is unidentified (Norgren et al., 2007).

A longitudinal study found asymptomatic patients at baseline developed IC symptoms more often than normal subjects (Hooi et al., 2001). This can be expected since asymptomatic and symptomatic are atherosclerotic manifestations appearing at different time points. One study found patients who were asymptomatic and never develop leg symptoms have a greater functional impairment and pathophysiological findings such as a smaller calf muscle area and lower calf muscle density (McDermott et al., 2008). This could be explained due to asymptomatic patients walking at a slower speed to avoid ischemic leg symptoms. As a result, functional capacity will continue to decline leading to claudicants having a reduced quality of life (QoL) due to limited independence and mobility (Khaira et al., 1996). However, one study suggested the underlying progression of PAD is identical whether the patient has symptoms in the leg (Norgren et al., 2007). This agrees with previous studies which conclude symptom

development depends largely on the physical activity level of the patient (McDermott et al., 2008, Norgren et al., 2007).

2.3.2 Intermittent Claudication

Intermittent claudication (IC) is the most common symptom of PAD, defined as cramping, pain and fatigue in the legs and buttocks, brought on by exertion and relieved at rest (Rose, 1962). Claudication is derived from the Latin word 'claudicare' meaning 'to limp' and was associated with Roman emperor Claudius who was said to walk with a limp (Bick, 2003). PAD occurs due to atherosclerosis process and an inadequate blood supply, causing exercised induced ischaemia, leading to an oxygen supply and demand imbalance (Meru et al., 2006a). During exertion, the increase oxygen demand cannot be met due to the build-up of plaque in the arteries, therefore the muscle begins to work anaerobically. Subsequently, causing a cramping pain sensation effecting the lower limb. Although this pain is relieved at rest, the cycle of lactic acid build up continues to reoccurs on exercise (Meru et al., 2006a).

The definition of PAD was first determined by G.A Rose who aimed to determine the precise characteristics of the pain experienced by hospital patients with IC (Rose, 1962). From this definition was derived and a simple questionnaire created. Due to IC having well-delineated characteristics it was very suitable for diagnosis in surveys (Rose, 1962). The definition for IC was as follows:

"A leg pain with the following characteristics:

(1) Its site must include one or both calves.

(2) It must be provoked by either hurrying or walking uphill (or by walking on the level, for those who never attempt more).

(3) It must never start at rest.

(4) It must make the subject either stop or slacken pace.

(5) It must disappear on the majority of occasions in 10 minutes or less from the time when the subject stands still.

(6) It must never disappear while walking continues" (Rose, 1962)

Following this, the WHO/Rose questionnaire (figure 2.3) was developed.

SECTION C: INTERMITTENT CLAUDICATION

If an answer is recorded in a box marked *, no further questions need be asked.

	Yes	No		Office use
DO YOU GET PAIN IN EITHER LEG ON WALKING?	☐	☐*	53	☐
DOES THIS PAIN EVER BEGIN WHEN YOU ARE STANDING STILL OR SITTING?	☐*	☐	54	☐
IN WHAT PART OF YOUR LEG DO YOU FEEL IT?				
Pain includes calf/calves ☐ 1			55	☐
Pain does not include calf/calves ☐* 0				
If calves not mentioned, ask ANYWHERE ELSE?				
DO YOU GET IT WHEN YOU WALK UPHILL OR HURRY? Yes ☐ 1				
No ☐* 0			56	☐
Never hurries or walks uphill ☐ 2				
DO YOU GET IT WHEN YOU WALK AT AN ORDINARY PACE ON THE LEVEL?	☐	☐	57	☐
If *yes* to *either* of last two questions, ask				
DOES THE PAIN EVER DISAPPEAR WHILE YOU ARE STILL WALKING?	☐*	☐	58	☐
WHAT DO YOU DO IF YOU GET IT WHEN YOU ARE WALKING?			59	☐
Stop or slacken pace ☐ 1				
Carry on ☐* 0				

			Office use
WHAT HAPPENS TO IT IF YOU STAND STILL?			
Relieved ☐ 1		60	☐
Not relieved ☐* 0			
HOW SOON? 10 minutes or less ☐ 1		61	☐
More than 10 minutes ☐ 0			

CONCLUSION

			Office use
Effort pain: If *yes* to (a) 28 *or* (*b*) 29 *or* (*c*) 30 *and* 31		62	☐
If *no* to 24:	GRADE 1 ☐ 1		
If *yes* to 24:	GRADE 2 ☐ 2		
	NO ☐ 0		
"Possible infarction": If *yes* to 49:	YES ☐ 1	63	☐
If *no* to 49:	NO ☐ 0		
Intermittent claudication: If *10 minutes or less* to 61:	YES ☐	64	☐
If *no* to 57:	GRADE 1 ☐ 1		
If *yes* to 57:	GRADE 2 ☐ 2		
If *more than* 10 *minutes* to 61:	NO ☐ 0		

Figure 2.3 The WHO/Rose questionnaire. *Note*. From "Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962; 27: 645-658. 1962/01/01.

The WHO/Rose Questionnaire highlights that if an answer is recorded in a box marked * then no further questions need to be asked. Consequently, implying that if the patient indicates their pain does not include the calf/calves then the patient does not have IC (Rose, 1962). However, dependent on the site of the atherosclerosis will determine the site of claudication. This can vary from the buttock, thigh, and calf muscle and therefore may not just be present in the calf muscle (Tew, 2018). Therefore, even though the WHO/Rose Questionnaire was widely used and had a high specificity (90-100%), it is only moderately sensitive (60-68%) (Leng and Fowkes, 1992).

Hence, in 1992, the Edinburgh claudication questionnaire (ECQ) (figure 2.4) was developed to improve the specificity and sensitivity of the questionnaire (Leng and Fowkes, 1992). Although like the WHO/Rose questionnaire, there are some differences. The ECQ removed asking patients if they got the pain only in the calf. Instead, the questionnaire asks the patient to mark on a diagram where the pain is present. From this the claudication will be labelled *definite* or *atypical.* A *definite* claudicant is one who provides a positive response to the ECQ and indicates pain in the calf regardless of whether pain is also marked in other sites. A *atypical* claudicant provides a positive response to the ECQ however indicates pain in the thigh or buttock in the absence of calf pain (Leng and Fowkes, 1992). However, the diagnostic performance of the ECQ has recently been doubted (Ibeggazene et al., 2023). The outcome of 100 patients ECQs were compared to a clinical diagnosis of IC (i.e., ABPI and exercise treadmill test). Overall, the ECQ had a sensitivity of 46.8% (95% CI: 27–65%), accuracy of 53.0% (95% CI: 43–63%) and specificity of 63.2% (95% CI: 43–82%) (Ibeggazene et al., 2023). Therefore, the

distribution of the ECQ as a screen tool is questionable and there is a need for a new diagnostic tool for patients with IC.

APPENDIX B

The Edinburgh Claudication Questionnaire

(1) Do you get a pain or discomfort in your leg(s) when you walk? Yes ☐ No ☐ I am unable to walk ☐

If you answered "Yes" to question (1)—please answer the following questions. Otherwise you need not continue.

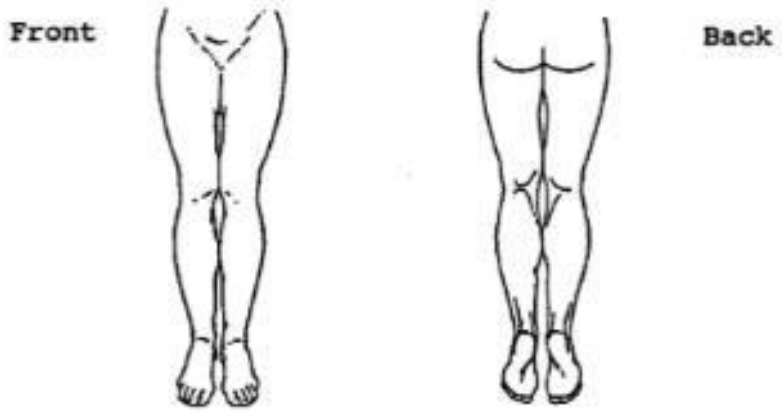
(2) Does this pain ever begin when you are standing still or sitting? Yes ☐ No ☐

(3) Do you get it if you walk uphill or hurry? Yes ☐ No ☐

(4) Do you get it when you walk at an ordinary pace on the level? Yes ☐ No ☐

(5) What happens to it if you stand still?
Usually continues more than 10 minutes ☐
Usually disappears in 10 minutes or less ☐

(6) Where do you get this pain or discomfort?
Mark the place(s) with "×" on the diagram below.



Definition of positive classification requires all of the following responses: "Yes" to (1), "No" to (2), "Yes" to (3), and "usually disappears in 10 minutes or less" to (5); grade 1 = "No" to (4) and grade 2 = "Yes" to (4). If these criteria are fulfilled, a **definite** claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of *atypical* claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain in the calf.

Figure 2.4. The Edinburgh Claudication Questionnaire. *Note*. From Leng GC and Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992; 45: 1101-1109. 1992/10/01. DOI: 10.1016/0895-4356(92)90150-l.

2.3.3 Chronic Limb Threatening Ischemia

Chronic limb threatening ischemia (CLTI) is internationally defined as any patient with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease (Norgren et al., 2007). CLTI is considered the end stage of PAD as it occurs after

chronic lack of blood supply, causing a cascade of pathophysiological events such as lesions and resting leg pain (Varu et al., 2010). A large prospective study on the incidence of CLTI found 220 new cases every year per million population (Rothwell et al., 2004). Figure 2.5 shows analysis of risk factors that have been associated with CLTI (Norgren et al., 2007).

Furthermore, a population-based study of incidence found the incidence of CLTI events was 22 per 100,000 per year (Howard et al., 2015). In patients with CLTI there was a significant risk of limb loss, 6.6% at a 1-year follow up and 43.4% at a 5-year follow up, though overall survival at 30 days remained high at 92.6% (Howard et al., 2015). Of the 202 patients reviewed 97.5% of patients had at least one risk factor, highlighting the multiple treatable risk factors (Howard et al., 2015, Norgren et al., 2007).

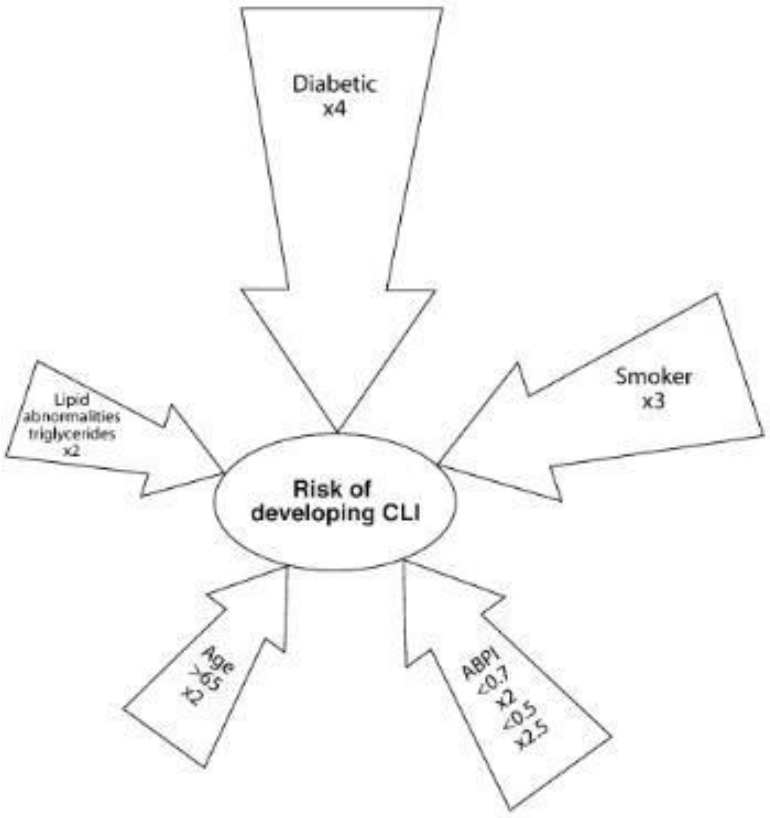


Figure 2.5. Approximate magnitude of the effect of risk factors on the development of critical limb ischemia in patients with peripheral arterial disease. *Note.* From Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Journal of Vascular Surgery* 2007; 45: S5-S67. DOI: 10.1016/j.jvs.2006.12.037.

Even though the majority of patients have long-standing claudication, 1-3% of patients presenting with CLTI have no prior warning symptoms (Falluji and Mukherjee, 2014). This could be due to other comorbidities such as diabetes which has led to neuropathy, masking the perception of claudication pain. Clinical tests such as ABPI can be used to diagnose CLTI. In patients with CLTI the ABPI is usually <0.5 and an ankle pressure of 50 to 70mmg HG for patients with ischemic ulcers (Falluji and Mukherjee, 2014). A toe brachial pressure index (TBPI) can be used to diagnose CLTI for patients with diabetes and falsely elevated ABPIs, a reading of <30mmHG for patients with rest pain and <50 mmHG in patients with non-healing ulcers would suggest CLTI (Falluji and Mukherjee, 2014).

2.3.5 PAD Classifications

The varied presentation for PAD has led to numerous classification systems throughout literature. Reproducible objective classification are crucial for clinical trials and baseline to clinical follow-up when looking at effective medical, surgical and endovascular treatments (Hardman et al., 2014). There are two major classifications for PAD. The Fontaine Classification (1954) (Fontaine, 1954) and the Rutherford Classification (1997) (Rutherford et al., 1997).

The Fontaine Classification (table 2.2) was the first to emerge from the European Society of Cardiovascular Surgery in 1952 (Fontaine, 1954). This classification grades patients on four stages, based solely on clinical symptoms without any objective tests. As this is subjective it is not routinely used in patient care (Hardman et al., 2014).

Table 2.2. The Fontaine Classification

Grade	**Symptoms**
Stage I	Asymptomatic, incomplete blood vessel obstruction
Stage II	Mild claudication pain in limb
Stage IIA	Claudication at a distance >200m
Stage IIB	Claudication at a distance <200m
Stage III	Rest pain, mostly in the feet
Stage IV	Necrosis and/or gangrene of the limb

The Rutherford classification was adapted in 1986 and revised in 1997 (table 2.3), classifying PAD into acute and chronic limb ischemia depending on the timing of symptom onset (Rutherford et al., 1997). Although Rutherford's chronic limb ischemia classification mostly resembles Fontaine's classification it has added objective non-invasive data (Hardman et al., 2014). The Rutherford classification is useful to reliably verify claudication onset by walking/treadmill tests. Treadmill tests incorporating pre and post exercise ABPIs enable differentiation between claudication from pseudo claudication in patients with exertional leg pain. Furthermore, using treadmill testing we are able to objectively document the magnitude of symptom limitation in patients with claudication and diagnose PAD with a normal resting ABPI but a reduced ABPI following exercise (Hardman et al., 2014).

Table 2.3. The Rutherford Classification for Chronic Limb Threatening Ischemia (Lee and Jung, 2013)

Grade	Category	Clinical description	Objective description
	0	Asymptomatic	Normal treadmill or reactive hyperemia test
I	1	Mild intermittent claudication	Treadmill exercise limited to 5 minutes; ankle pressure after exercise, 50 mmHg but at least 20 mmHg lower than at rest
I	2	Moderate intermittent claudication	Between Rutherford 1 and 3 disease
I	3	Severe intermittent claudication	Treadmill exercise limited to 5 minutes; ankle pressure after exercise, 50 mmHg
II	4	Ischemic rest pain	Resting ankle pressure, 40 mmHg and/or great toe pressure, 30 mmHg; pulse volume recording barely pulsatile or flat
III	5	Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure, 60 mmHg and/or great toe pressure, 30 mmHg; pulse volume recording barely pulsatile or flat
III	6	Major tissue loss: extending above transmetatarsal level, functional foot no longer salvageable	Resting ankle pressure, 60 mmHg and/or great toe pressure, 30 mmHg; pulse volume recording barely pulsatile or flat

Note. From Lee, S., & Jung, H. (2013). Hybrid Operation (Balloon, Stent Covered Stent and/with Bypass, Excise It!): When and How? *Korean Journal of Vascular and Endovascular Surgery*, *29*, 46. doi:10.5758/kjves.2013.29.2.46

2.4 Clinical Examinations

2.4.1 Clinical History

A consultation to examine a patient with PAD should begin with a comprehensive review of their past medical history and family history. This will check for previous cardiovascular events such as a myocardial infarction, cerebrovascular disease, and PAD to establish if there is a history of CVD. Following this, personal risk factors will then be examined including hypertension, hyperlipidaemia, prior CVD, kidney disease and dietary habits. Also, current and previous smoking habits should be estimated (Willigendael et al., 2004).

2.4.2 General Physical Examination

A general physical examination for patients should be conducted to show the nature of the atherosclerosis process. This includes blood pressure taken in both arms, heart rate, height and

weight. Pulmonary and cardiac examinations should be performed to assess cardiac manifestations of atherosclerosis, the risks of potential invasive or surgical treatment and arrhythmias responsible for blood clots (Wennberg, 2013). A blood test should also be taken for a full blood count, urea and electrolytes, lipid screening and HbA1c if diabetes has not been formally excluded (Bailey et al., 2014).

2.4.3 Peripheral Vascular Examination

Following a general examination, the focus will be on examining the extremities to look for signs of PAD. Initially there should be a skin inspection to note any temperature or skin colour change, cracking or fissures in the heel and differences between feet. Skin findings such as redness or elevated pallor are seen in patients with severe PAD (Wennberg, 2013). The toes and area between the toes should be examined for ulcers. Ulcers which are found on the tip of the toes and at the dorsal surface of the toe and are significantly irritating and painful are an indicator for PAD (Khan et al., 2006). Also slow growing toenails and scars indicating previous arterial or venous vascular surgery should be noted (Bailey et al., 2014). Hair loss is not a specific marker to PAD, however when it is associated with other symptoms it is a strong indicator. Capillary refill is an unreliable predictor of PAD as it can be influenced by external factors such as temperature, however delayed capillary refill or prolonged refill is an indicator of ischemia (Anderson et al., 2008).

Succeeding the initial assessment, palpitation of the arteries should be performed for all vascular patients (Wennberg, 2013, NICE, 2012). The femoral, popliteal, posterior tibial and dorsalis pedis pulses are assessed (Bailey et al., 2014). According to the American Heart Association/American College of Cardiology guidelines the palpitations are graded on a scale of 0 to 3, with 0 being absent, 1 reduced, 2 normal and 3 bounding (Hirsch et al., 2006b).

However, these gradings vary as the trans-Atlantic Inter-society Consensus suggest a different grading system (Norgren et al., 2007). Therefore, it is important that the clinician documents the scale used when examining the patient for understanding and future examination comparison. A sign of PAD is the absence of femoral pulses and abnormalities (Armstrong et al., 2010). Pulses should be assessed in both legs and abnormalities compared with symptoms to determine the location of the disease (Norgren et al., 2007). Upper examination will also take place including palpation of the radial, carotid, brachial and ulnar arteries. These will then be used to calculate ABPI.

2.4.4 Laboratory Testing

Laboratory testing for patients include blood tests and urine samples. The tests are useful for examining biological substances such as fasting glucose plasma, creatinine, lipid profiles and uric acid which could highlight the prevalence of risk factors such as high cholesterol and diabetes (Aboyans et al., 2018). Furthermore, they are useful for assessing the risk of progression and response to therapy (Cooke and Wilson, 2010). Should the patient need a revascularisation procedure an ultrasound, computed tomographic angiography or magnetic resonance angiography may be used to define the lower limb arterial system (Hinchliffe et al., 2020).

2.4.5 Ankle Brachial Pressure Index (ABPI)

ABPI should be taken, as per the National Institute of health and Care Excellence (NICE) guidelines (NICE, 2012). The patient should be in the supine position and resting. Systolic blood pressure should be recorded in both arms using an appropriately sized cuff (NICE, 2012), with the highest reading taken as the brachial pressure. A manual sphygmomanometer with an appropriately sized cuff should be placed on the ankle. The posterior tibial artery and dorsalis

pedis artery should be located using a doppler probe of suitable frequency (Bailey et al., 2014). The doppler signal should be recorded and monophasic, biphasic or triphasic. The ankle cuff should then be inflated to occlude the artery and slowly released. The return of the signal heard through the doppler indicates the systolic pressure of the arteries in the foot (Bailey et al., 2014). The highest of the two brachial pressures along with the highest of the two-foot pressures for each limb are used to calculate APBI (highest foot pressure/highest brachial pressure). The results are then interpretated using the NICE guidelines, with an ABPI <0.9 classed as abnormal.

Table 2.4 National Institute of Health and Care Excellence Interpretation of Ankle Brachial Pressure Index Results

Clinical Status	**Ankle Brachial Pressure Index**
Asymptomatic	>0.9 – 1.2
Intermittent Claudication	0.9-0.5
Critical Limb Ischemia	<0.5

An elevated high reading of >1.4 may be a sign of calcified vessels causing them to be incompressible (Tendera et al., 2011). This type of reading is most common in patients with diabetes and renal disease (Tummala and Scherbel, 2018). It is important to note that ABPI remains unchanged as a result as exercise. A large Cochrane review with moderate quality evidence found ABPI remained unchanged in 13 trials and 570 participants (MD 0.04, 95% CI 0.00 to 0.08) (Lane et al., 2017b). Therefore, ABPI should not be used to measure the success of an exercise intervention.

Comparable to ABPI, TBPI is used to confirm the diagnosis of PAD, particularly in people with diabetes or incompressible disease. This is the ratio of systolic blood pressure of the toe

to the higher amount of the arm pressures (Tummala and Scherbel, 2018). TBPI of less than <0.7 is classified as abnormal (Gerhard-Herman et al., 2017). However, little research has been done to clarify less than 0.7 as having PAD therefore this number is somewhat unreliable.

2.4.6 Exercise Testing

Treadmill exercise testing is known as the gold standard to objectively measure pain-free and maximal walking distance/time in patients with PAD (Gerhard-Herman et al., 2017, Nicolaï et al., 2009a, Birkett et al., 2021). There are two common treadmill testing protocols which are used for patients with PAD. The earliest treadmill test, established in the 1950s, was the constant-load treadmill test (CLT) (Hiatt et al., 1988). Following this, the graded treadmill test evolved and has now become widely adopted (Gardner et al., 1991b). Additionally, the 6-minute walk test (6MWT) is a common submaximal alternative measure to treadmill testing. The 6MWT is simple, valid and inexpensive, making it an option when a treadmill may not be readily available (McDermott et al., 2014a). The main outcomes of exercise testing are pain-free walking distance/time and maximal walking distance/time. These measurements are useful for measuring the severity of the disease and the success of an intervention, such as a SEP. The utility of any exercise test relies on sufficient implementation. Therefore, tests should be performed under reproducible and standardised conditions (Riebe et al., 2018) (Table 2.5).

Table 2.5. Requirements for Exercise Testing

1	The patient should not walk long distances to the testing laboratory (to avoid claudication) and should be rested before commencing the test
2	The patient should refrain from digesting food, alcohol, caffeine and tobacco within three hours of testing
3	The patient should wear comfortable clothes and appropriate shoes
4	Any timing device used to assess test duration should be hidden from the patient so as not to bias their performance
5	Familiarisation of all patients before the conduct of a formal test for analysis should be allowed. The patient should initiate the test by straddling the moving belt at 2 mph and start walking at that speed at time 0.
6	The patient should not hold onto the treadmill bars for support or off-loading because this will introduce variability to the test
7	The patient should continue to take their usual medication

Note. From Hiatt WR, Rogers RK and Brass EP. The Treadmill Is a Better Functional Test Than the 6-Minute Walk Test in Therapeutic Trials of Patients With Peripheral Artery Disease. *Circulation 2014*; 130: 69-78. DOI: doi:10.1161/CIRCULATIONAHA.113.007003.

2.4.6.1 Constant-load test

The constant-load treadmill test (CLT) is performed at a single work rate and was the earliest developed treadmill test to diagnose PAD (Hiatt et al., 2014). The protocol for CLT is usually 2mph and a gradient of 10% to 12% (Degischer et al., 2002). A meta-regression analysis of the CLT found the reliability of the test was dependent of the grade of the treadmill (Nicolaï et al., 2009b). As such a 12% gradient had a highest intra-class correlation coefficient than a gradient

at 10% (0.91 vs. 0.89). Therefore, when a CLT has to be used (if a treadmill which automatically adjusts its gradient is unavailable) the incline should be set at 12% (Nicolaï et al., 2009b). Furthermore, previous research found PAD patients who were tested twice per month for 4 months using the CLT had an improvement in MWD in month 0-1 and month 1-2 (Gardner et al., 1991b), which was not seen in the group using the graded exercise test. However, there was a familiarisation effect noticed in the CLT which was not apparent in the graded test, meaning three constant load tests were needed to occur to gain reliable results (Gardner et al., 1991b). It is suggested this protocol is not appropriate for an accurate assessment of functional impairment due to the broad symptoms which occur across PAD patients. For example, patients with mild PAD symptoms may be able to walk at a constant load for an extended period. In contrast, patients with severe PAD may not even be able to walk on a grade of 10% and therefore are unable to conduct the test (Hiatt et al., 2014). Nevertheless, CLT still remains a well-established protocol in several guidelines and research studies (Norgren et al., 2007, Aboyans et al., 2017).

2.4.6.2 Graded test

The Gardner-Skinner Protocol (GS) is a standardised graded exercise test (GT) commonly used for patients with PAD throughout rehabilitation programmes (Gardner et al., 1991b). The treadmill speed is held at a constant speed of 2mph (3.2kph) and starts at a gradient of 0% increasing 2% every 2 minutes. Research has concluded that progressive exercise testing allows for the severity of PAD to be better assessed as the clinical measures are more reliable through exercise and recovery (Gardner et al., 1991b).

A meta regression analysis assessing the reliability of treadmill testing in eight PAD studies concluded the GT had a significantly high reliability for MWD compared with the CLT

(Intraclass correlation coefficient 0.95 vs. 0.90) (Nicolaï et al., 2009b). Likewise, a clinical trial with 330 patients confirmed the reproducibility of the GT for absolute and initial walking distance (Labs et al., 1999). During the baseline run-in period patients took part in three graded-treadmill tests over a 2-week period. The study found excellent reproducibility in the reliability coefficient (RC), coefficient of variance (CV) and relative precision (RP) for absolute claudication distance (RC 0.952, CV 15.5%, RP 21.9%) and initial claudication distance (RC 0.820, CV 28.6%, RP 42.4%) (Labs et al., 1999). Likewise, a multicentre trial with 386 patients completed three baseline GT tests at least three days apart (Brass et al., 2007). Data confirmed the reproducibility of the GT and showed an intra-subject coefficient of variation (repeat testing of the same patient over a period of time) of 15%, independent of the baseline performance. These results confirm earlier research which demonstrated that a GT was superior and more reliable at assessing PAD severity than a CLT (coefficient of variation 32.1% vs. 12.6%) (Gardner et al., 1991b).

Furthermore, the GS is realistic and achievable for PAD patients as the protocol starts on 0% incline. This is likely to determine true walking distance as PAD patients will be used to walking on a flat ground. In contrast the CLT starts at a 12% incline, which may result in an inability for PAD patients to conduct the test as the steep incline may initiate a metabolic response which is beyond the patient's walking capacity. As a result, the test may be terminated earlier thus limiting the significance of the test. In contrast, the GS can be modified, and the speed can be reduced further to 0.5mph and increase by 0.5mph every 2 minutes until 2.0mph is reached, making it inclusive no matter the severity of the disease (Gardner et al., 1991b, Treat-Jacobson et al., 2019). Therefore, the GT is more reliable and takes into account the physiological limitations of patients with IC making it the gold standard for clinical practise and research trials (Hiatt et al., 2014).

2.4.6.3 6-Minute Walk Test

The 6-minute walk test (6MWT) which measures 6-minute walk distance (6MWD) is a relatively new but well-established outcome for patients with PAD (McDermott et al., 2021b). The submaximal test follows a standardised protocol were patients walk up and down a 100-foot hallway (30 metres) for six minutes. Patients should receive standardised instructions before the test which includes the goal to cover as much distance as possible (McDermott et al., 2009). The distance completed after six-minutes is then recorded. Evidence suggests that the 6MWT can used for clinical trials as it is representative of walking in daily life, inexpensive and a validated measure of walking which does not require any expensive equipment (McDermott et al., 2014b, McDermott et al., 2014a). Furthermore, the 6MWT can predict rates of all-cause and cardiovascular mortality and facilitates the progressive decline in walking endurance faced by PAD patients with IC (McDermott et al., 2008).

That said, it has been found 6MWD cannot be compared against treadmill walking distance such as MWD. A meta-analysis with 467 patients compared 6MWD and MWD (measured on a treadmill) at baseline and 6-months in response to a therapeutic intervention or control group (McDermott et al., 2020). At a 6-month follow-up, patients randomised to the control group significantly declined the 6MWD (-10.2m) but improved their MWD (+25.7m) (McDermott et al., 2020). Furthermore, those taking part in a treadmill exercise training, showed a greater improvement of 141.3m further in MWD on the treadmill than 6MWD. This highlights that the results of the tests cannot be used interchangeably. It has been hypothesised the difference in outcomes could be attributed to the graded treadmill test resulting in different physiological adaptations to a submaximal 6MWT (Hiatt et al., 2014). The use of 6MWT and GT are limited to single-site trials and should be used with caution on multi-centre trials (Hiatt et al., 2014).

That said, both tests add to the thorough assessment of functional walking capacity in patients with IC.

2.4.6.4 Cardiopulmonary Exercise Test

Cardiopulmonary exercise testing (CPET) allows a wide array of unique ventilatory gas exchange measurements and clinical information (Balady et al., 2010). A CPET test allows for the analysis of gas exchange at rest, during exercise and recovery and shows objective markers such as peak oxygen uptake (VO_{2peak}), the highest volume of oxygen uptake. This relies on individuals putting in their maximum volitional effort (Balady et al., 2010). To test if an individual has put in sufficient effort, the respiratory exchange ratio (RER) can be analysed to see the ratio of VCo_2 and VO_2. A peak RER of $\geq$1.10 and peak heart rate >85% age-predicted maximum is regard as an indication of excellent subject effort (Balady et al., 2010). Previous research has shown the importance of a metabolic equivalent (MET) increase (3.5 $ml.kg^{-1}.min^{-1}$) in $\dot{V}O_{2peak}$ as indicators for survival and test variables in patients with PAD (Leeper et al., 2013). Patients had an age-adjusted 20% reduction in cardiovascular mortality and an age-adjusted 17% reduction in total mortality with each additional MET (Leeper et al., 2013). This is higher than other clinical populations, such as cardiac rehabilitation, where each 1 $ml.kg^{-1}.min^{-1}$ increase in $\dot{V}O_{2peak}$ was associated with a 15% decrease in all-cause mortality (Keteyian et al., 2008). However, patients presenting with IC often stop the treadmill exercise test due to claudication pain rather than significant cardiopulmonary stress. As a result, VO_{2peak} will be significantly underestimated. As such research has highlighted the positive metabolic response of cycling compared to a GT as an alternative cardiopulmonary testing mortality in patients with IC (Tuner et al., 2008). Cycling could be preferable to a graded treadmill test when using CPET as it is better tolerated by patients and induces a greater cardiopulmonary response, such

as peak heart rate (treadmill, r = 0.94; cycle, r = 0.96) and metabolic response (Tuner et al., 2008).

2.5 Management

2.5.1 Primary Prevention

Primary prevention aims to prevent the occurrence of atherosclerotic disease developing, addressing risk factors such as high cholesterol and high blood pressure can lower the chances of being diagnosed with PAD (Palumbo and Melton III, 1995). The success of primary prevention has been emphasised in research looking at temporal trends of IC from 1950 to 1999. Baseline CVD measures allowed exploration of the differences in IC incidence related to primary prevention over time. The paper aimed to find if there was a decline in IC incidence among patients without CVD, suggesting primary prevention effects occurred (Murabito et al., 2005). The study found primary prevention efforts at modifying risk factors was significant as the incidence of IC declined significantly among people without prevalent CVD. This therefore shows the positive effect of modifying risk factors such as rates of smoking, statin and antiplatelet therapies can have on the effect of IC and consequently CVD (Murabito et al., 2005).

2.5.2 Secondary Prevention

Secondary prevention for patients with PAD focuses on preventing further cardiovascular diseases and early mortality (Hamburg and Balady, 2011a). Cardiovascular rehabilitation that includes exercise training is an important model for the secondary prevention of PAD. Table 2.6 highlights the benefits of secondary therapies which include a multifaceted exercise-based intervention (Hamburg and Balady, 2011a). Although, SEPs are the first line of treatment for PAD, a meta-analysis with 24 studies revealed only 23% of PAD patients entered a walking

programme as secondary prevention for their condition (Flu et al., 2010). Furthermore, NICE recommend offering all patients information, advice, support in relation to the cardiovascular risk factors (NICE, 2012, Hamburg and Balady, 2011a). This includes promoting information on smoking cessation, diet and weight management, lipid modification and statin therapy, antiplatelet therapy and the prevention, diagnosis and management of diabetes and high blood pressure.

Execution of secondary prevention is vital due the low implementation of guideline-based risk factor interventions in patients with PAD compared to other cardiovascular populations (Hamburg and Balady, 2011a). This has been revealed in previous research, where only 41% of PAD patients who underwent vascular surgery achieved the recommended guideline-based medication therapy. Even though the use of recommended therapies was associated with a reduction in 3-year mortality (Hoeks et al., 2009). Additionally, a meta-analysis including 30,000 PAD patients over a 9-year period highlighted the low application of secondary prevention for PAD patients. Contrary to the guidelines, only 45% of patients were prescribed lipid-lowering therapies and 63% where offered antiplatelet agents (Flu et al., 2010). Of the 762 current smokers, only 39% were offered smoking cessation (Flu et al., 2010). As there is an anticipated high cardiovascular risk in these populations, secondary prevention is vital (Hoeks et al., 2009).

The optimisation of secondary prevention can reduce the risk of further revascularisation for PAD patients, improve QoL and is cost-effective. Research suggests secondary prevention is expected to produce a cumulative relative risk reduction of around 75% (Flu et al., 2010). The reason for inappropriate secondary prevention is a combination of patient-related and physician related factors, consequently there is a need for an increased awareness of secondary prevention

for PAD through reimbursement, comprehensive risk factor prevention and a higher implementation of PAD screening (Flu et al., 2010).

Table 2.6. Secondary Treatment therapies available for patients with IC.

Lipid-lowering therapy	Treatment with statin for all PAD patients to target LDL cholesterol<100mg/dl
	Target LDL cholesterol < 70mg/dl for high risk patients
Hypertension Treatment	Treat to target blood pressure <140/90mmHg (<130/80mmHg for patients with diabetes or chronic kidney disease)
	Consider ACE inhibitor in hypertensive patients
	Use of beta-blockers is not contraindicated in PAD
Smoking Cessation	Provide comprehensive smoking intervention program
	Consider pharmacotherapy to support smoking cessation
Antiplatelet Therapy	Treat with aspirin 75–325mg or clopidogrel 75mg
	Treat with aspirin+thienopyridine in patients with acute coronary syndrome or coronary or peripheral stent

LDL = Low-density lipoprotein; ACE = Angiotensin converting enzyme. *Note*. From Hamburg NM and Balady GJ. Exercise Rehabilitation in Peripheral Artery Disease. *Circulation* 2011; 123: 87-97. DOI: doi:10.1161/CIRCULATIONAHA.109.881888.

2.5.3 Surgical interventions

Surgical interventions for patients with PAD include angioplasty/stenting and bypass surgery and graft types. According to the NICE guidelines, angioplasty for treating patients with IC should only be offered when advice on risk factors have been reinforced, a SEP has not led to satisfactory improvement in symptoms and imaging has confirmed angioplasty is suitable for that individual (NICE, 2012). Angioplasty involves widening a narrowed artery caused from atherosclerosis, a balloon catheter is passed through the narrowed legions and then inflated to a fixed size. The balloon is then collapsed and withdrawn. Stenting involves a mesh coil around the balloon that remains in place once the balloon is removed (Medical Advisory, 2010).

Overall, angioplasty has been found successful in PAD patients for improvements in functional outcomes such as MWD and QoL (Lindgren et al., 2018, Husmann et al., 2008). A study comparing angioplasty to best medical therapy found that patients who received revascularisation had a significant improvement in flow-mediated dilation (FMD) and ABPI compared to the control group (Husmann et al., 2008). Also, patients receiving angioplasty had a significant decrease in their white blood cells (WBCs) compared to baseline. This could be due to the revascularisation reducing oxidative stress which appears when the muscle continues to be ischemic, therefore reducing inflammatory markers such as WBCs (Husmann et al., 2008).

Even though SEP remains the first line of treatment, recently, research has evaluated the combination of endovascular revascularisation plus SEPs on effectiveness for patients with IC. A meta-analysis with over 2,983 patients with IC compared best medical treatment (BMT), versus SEP vs. percutaneous angioplasty (PTA) vs. PTA plus SEP (Saratzis et al., 2019). Overall the study found a significant difference in MWD over a 1-year follow up with an average gain of 110m 95% CI: 16 to 200 m; $p < 0.001$) on MWD when combining PTA with SEP compared to SEP alone and a gain of 290m compared with BMT (95% CI: 180 to 390 m; $p < 0.001$) (Saratzis et al., 2019). Likewise, the ERASE (Endovascular Revascularisation and Supervised Exercise) conducted a cost-effective analysis of 212 patients randomised to either a combination therapy (stenting and SEP) or SEP only (Fakhry et al., 2021). The study used cost-effective ratios from a healthcare and societal perspective. They concluded at 1-year follow-up the combination therapy was clinically and economically a more attractive approach than SEP alone, with a probability of being 87% and 95% cost-effective from the health care and societal perspective (Fakhry et al., 2021). This suggests, PTA combined with SEP may be an optimal strategy. Yet, the IRONIC trial (Invasive Revascularisation or Not in Intermittent

Claudication) compared revascularisation plus BMT plus supervised exercise therapy (SET) (revascularisation group) to BMT plus SET (non-revascularisation group). After 5 years, they found no differences in vascular QoL or treadmill walking distances between the two groups. The RCT concluded after 5-years revascularisation had lost its early benefit and was not a cost-effective treatment option ($13 098 versus $6965, *P*=0.02) (Djerf et al., 2020).

If angioplasty is unsuccessful or unsuitable and the imaging has been confirmed, bypass surgery may be offered to people with severe lifestyle-limiting IC (NICE, 2012). Bypass involves finding a path around the narrowed or blocked part of the artery. This uses one of the veins from the individual or a tube made from man-made or animal materials to bypass the blocked area, resulting in a new pathway for the blood to flow (Medical Advisory, 2010). A research trial comparing outcomes of patients with either a bypass or angioplasty (BASIL) trial found there was no statistical significance between the two treatments regarding amputation free survival and overall survival (Bradbury et al., 2010). Although, treatment success in both surgical intervention groups were arguably low (vein bypass 86% vs. balloon angioplasty 73%) (Bradbury et al., 2010). Further research is ongoing (BASIL-2) to compare the cost and clinical effectiveness of bypass vs stenting (Popplewell et al., 2016).

Major amputation is another surgical intervention, however should only be offered to people with CLTI after all revascularisation has been considered and discussed with a multidisciplinary team (NICE, 2012). PAD is one of the biggest causes of lower leg amputation, as the British Heart Foundation found 1-2% of patients with IC will undergo amputation within 5 years. In a recent analysis of US Medicare data from 2000 to 2008, out of three million PAD patients hospitalised, 186,338 underwent major amputation (Swaminathan et al., 2014). Of these patients, the mortality rate was nearly twice as high as patients who did

not undergo major leg amputation at 30 days (13.5% vs. 6.9%), 1 year (48.3% vs. 24.2%) and 3 years (70.9% vs. 43.2%) (Swaminathan et al., 2014). This accentuates the importance of increasing public awareness and standardising SEPs to prevent amputation.

2.5.4 Vascular Specific Pharmacological interventions

Treatment for patients with PAD are aimed to improve exercise performance and QoL, though there is debate over the effectiveness of vascular specific drugs for the treatment of IC. Cilostazol has antiplatelet and antithrombotic actions (Sallustio et al., 2010). It also acts on smooth muscle as a vasodilator and has been approved for the treatment of IC (D'Angelo et al.). The Inter-Society Consensus for the Management of Peripheral Artery Disease (TASC II) define cilostazol as having "the best overall evidence for treatment benefits in patients with claudication" (Norgren et al., 2007). A Cochrane review, with seven RCTs, found cilostazol (50 to 100mg twice daily) significantly improved initial and maximal walking distance in patients with stable to severe IC (Robless et al., 2008). Cilostazol was also associated with a greater improvement in walking performance and QoL compared to the placebo group (Regensteiner et al., 2002). Patients taking 100mg of cilostazol improved their MWD on the CLT by 40% (100 ± 143 m) compared with 20% (50 ± 127m) increase for the placebo. Likewise, patients taking 100mg bid of cilostazol using the CLT protocol also significantly improved their MWD compared to placebo (76%, 95 ± 272m vs. 20%, 27 ± 113m).

The most common side effect for cilostazol includes headaches, nausea and diarrhoea, though the analysis of the safety database of the drug showed no evidence towards cardiovascular morbidity or mortality (Chapman and Goa, 2003, Pratt, 2001). That said, the Scottish Medicines Consortium have limited the use of cilostazol, recommending that the drug has limited effects on QoL, physical function and pain and therefore should be stopped after 3

months if it is ineffective (Peach et al., 2012). Similarly, the use of the drug for patients with PAD and previous MI should be used with caution. A RCT identified patients with a preceding acute MI had a statistically higher heart rate and numerous arrhythmias when receiving cilostazol with a conventional antiplatelet regimen compared to patients on the conventional antiplatelet regimen alone (Lee et al., 2007b). Furthermore, the drug has been predominately studied in Asian populations, therefore the safety of the drug in a more diverse population still remains unclear (Rogers et al., 2015).

Pentoxifylline is a current drug to treat IC. It has properties to promote tissue oxygen concentration and decrease blood viscosity (Broderick et al., 2020). Though a recent review has demonstrated there is a lack of evidence to support the use of pentoxifylline with PAD patients. Out of 24 studies with 3377 participants, there was low-certainty evidence that pentoxifylline improves MWD, PFWD compared to a placebo and no evidence that it benefits QoL or ABPI (Broderick et al., 2020). When compared to cilostazol MWD was significantly higher in cilostazol than pentoxifylline (107m vs. 64m) (Dawson et al., 2000).

The NICE guidelines recommend considering naftidrofuryl oxalate or patients with IC. Naftidrofuryl oxalate is a vasoactive drug which relaxes the smooth muscle in the blood vessels causing dilation and an increased blood supply to the muscles (Stevens et al., 2012). However, they suggest this should only be considered if a SEP has not led to a satisfactory improvement and the person does not want to be considered for angioplasty or bypass surgery (NICE, 2012). Following 3-6 months of treatment, the effectiveness of naftidrofuryl oxalate should be considered and discontinued if there has been no symptomatic benefit. Though the use of vasoconstrictive drugs is controversial, a review including 1266 participants randomised to naftidrofuryl oxalate or placebo found that the medication had a clinically meaningful effect

when compared to placebo on improving walking distance of patients with IC (De Backer et al., 2009). The naftidrofuryl oxalate group walked 37% further than the placebo group and the patients responding to naftidrofuryl oxalate was 22% higher (and an improvement of more than 50%) when compared to the placebo (De Backer et al., 2009). A review and meta-analysis comparing naftidrofuryl oxalate, cilostazol and pentoxifylline using 26 RCTs found naftidrofuryl oxalate had the greatest effect on MWD (60% increase) and was the most effective vasoactive drug compared to cilostazol and pentoxifylline. Although there has been no long-term safety studies on naftidrofuryl oxalate (Stevens et al., 2012). Therefore, it has been considered new medicines would benefit from shared ownership or access to individual patient data for drug related RCTs to add to the existing knowledge.

2.5.5 Medications

2.5.5.1 Antiplatelet medication

Anti-platelet therapy is essential to treat symptomatic PAD (Aday and Gutierrez, 2020). A low dose of aspirin (325mg once daily) has been seen to reduce cardiovascular events such as a myocardial infarction in this patient group. The CAPRIE trial (Clopidogrel versus aspirin in patients at risk of ischemic events) published in 1996, highlighted a 23.8% risk reduction in vascular disease when a patient was put on clopidogrel, an antiplatelet, when compared to aspirin for patients with PAD (Hess et al., 2017). Therefore, further antiplatelet medications such as ticagrelor and vorapaxar have been commonly prescribed for patients with PAD. However, the benefit of dual antiplatelet therapy is less clear. The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance) found that dual antiplatelet therapy (clopidogrel and aspirin) did not result in a statistically significant reduction in the primary end point of major cardiovascular events when compared to aspirin and a placebo treatment (OR: 1.99; 95% CI, 1.69–2.34) (Hess et al., 2017).

Though, a trial comparing mono with dual antiplatelet therapy in endovascularly treated PAD patients found the use of dual antiplatelet therapy (clopidogrel and aspirin) had a significantly lower rate of target lesion revascularisation compared to a placebo patient (aspirin and placebo) at 6 months of therapy [2 (5%) vs. 8 (20%), p=0.04] (Strobl et al., 2013). However, there was no significant difference in target lesion revascularisation at 12 months [9 (25%) clopidogrel vs. 12 (32.4%) placebo, p=0.35], therefore concluding prolonged dual therapy should be an option for patients with a high risk of restenosis (Strobl et al., 2013).

More recently, there has been a large, randomised placebo-controlled trial of medication following revascularisation therapy, the VOYAGER study (Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularisation for Peripheral Artery Disease). This study found a low dose of rivaroxaban (2.5mg twice daily) plus aspirin was significant in reducing cardiovascular disease and limb events by approximately 15% (hazard ratio, 0.85, 95% confidence interval [CI], 0.76 to 0.96; P=0.009) (Bonaca et al., 2020). Therefore, the use on antiplatelet medication along with aspirin will continue to be distributed through PAD patients until more research has been identified (Aday and Gutierrez, 2020).

2.5.5.2 Lipid lowering therapy

Lipid lowering therapy has been proven efficient in the treatment of patients with PAD (Crismaru and Diaconu, 2015). High low-density lipoproteins in dyslipidaemia are a common risk factor of cardiovascular disease. Therefore, it is important to lower the mortality rates in patients by including lipid-lowering treatment (Crismaru and Diaconu, 2015). As the use of statins in this clinical population has been well researched, statins are recommended as part of European guidelines.

Multiple studies have taken place to look at the success of cholesterol-lowering therapy concerning the stabilisation of atherosclerotic lesions and the secondary prevention of cardiovascular disease. The largest study called the Heart Protection Study (HPS), demonstrated the benefits of PAD patients on cholesterol-lowering statin therapy (2007). The study compared PAD patients taking 40mg simvastatin daily to a placebo group over a 5-year period. The HPS found simvastatin was associated with a significant 22% reduction in the rate of a major vascular event (95% CI 15-29) and a 16% relative reduction in the rate of a first peripheral vascular event following randomisation (479 [4.7%] simvastatin vs 561 [5.5%] placebo).

Furthermore, a Cochrane review including 18 trials and 10,049 participants showed that lipid-lowering therapy significantly reduced the risk of total cardiovascular events (OR 0.74; CI 0.55 to 0.98). Furthermore simvastatin was seen as highly effective in people with blood cholesterol more than 3.5mmol/litre (Aung et al., 2007). Lipid lowering therapy has also shown to have a positive effect on functional outcomes such as maximal and pain-free walking distance. Although there was no significant change in ABPI (Aung et al., 2007). Whilst simvastatin is the most common statin for patients with PAD, atorvastatin has also been found effective to improve symptomatic PAD and pain-free walking distance (Moher et al., 2009). Likewise, pravastatin has shown to slow the progression of atherosclerosis in men over the age of 70 with coronary artery disease (de Groot et al., 1998).

Although statins have been found to be advantageous, it is recognised they may come with adverse side effects (i.e., muscle pain, headaches, dizziness) therefore the acceptance rate maybe low. A review understanding the attitudes of statins users found 60% of former statin

uses stopped taking the drug due to muscle pain and of the current users the primary reason for discontinuation was side effects (62%) (Cohen et al., 2012). However, trials have found adverse events do not occur more frequently in the statin group than the placebo group (Ridker et al., 2008). Furthermore, a trial randomised patients to a period of taking a placebo, statins or no treatment over a 12-month period. The intensity of the symptoms did not differ whether the patient was taking the placebo or statins, however they reported greater intensity of symptoms than when they were not taking treatment (Wood et al., 2020). This supports the thought that the side effects of statins could be 'nocebo' whereby effects are elicited by an inert substance (Penson and Banach, 2021).

Furthermore, lifestyle modification including exercise has been shown to lower triglyceride levels which can consequently reduce the risk of PAD. Exercise increases lipoprotein lipase activity with modest lowering of triglycerides in overweight and obese adults (Seip et al., 1997, Carroll and Dudfield, 2004). This can have a significant effect the reduction of CVD as a 1mmol/L increase in triglyceride levels results in an increased risk of CVD by 32% and 76% in males and females (Scherer and Nicholls, 2015).

2.5.5.3 Diabetic control

Diabetes mellitus (DM) is a major risk factor of PAD associated with accelerating the disease leading to an increase mortality and morbidity (Thiruvoipati et al., 2015). The NICE guidelines recommends that all patients with PAD should be offered advice, support and treatment on the prevention, diagnosis and management of PAD (NICE, 2012). A meta-analysis of 102 prospective studies found that DM, independent of any other risk factors, conferred a two-fold excess risk of vascular outcomes such as coronary heart disease and vascular deaths (Sarwar et al., 2010).

The management of DM for PAD patients is not much different from patients with general CVD (Cosentino et al., 2020). A trial reported the combination of rivaroxaban and aspirin in patients with atherosclerotic vascular disease had a significant reduction in CV death, stroke and MI (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). This combination therapy also showed a reduction of major limb amputation over a mean of 23 months (Eikelboom et al., 2017). Evidently, weight loss is the most significant diabetes control for patients with PAD, combined with medication this can reduce the risk of CVD, revascularisation and amputation.

The European Society of Cardiology (ESC) address that lifestyle changes, such as moderate-vigorous physical activity of 150 min/week, are key to prevent DM and the risk to cardiovascular disease associated with it. Exercise has been shown to increase HDL cholesterol concentrations (Couillard et al., 2001). This can have significant effect on the risk of CVD as a 1 $mg{\cdot}dL^{-1}$ increase in HDL decreases the risk of CVD by 2% in males and 3% in females (Gordon et al., 1989).

2.5.5.4 Hypertension control

Lowering of systolic blood pressure has been shown to reduce cardiovascular events (Aboyans et al., 2017). However, research on optimal blood pressure (BP) for patients with PAD is not very well researched and should be treated with caution. Lowering BP in patients with PAD could decrease perfusion to distal extremities and therefore intensify symptoms such as IC and rest pain (Itoga et al., 2018). A recent trial investigated the association of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with lower extremity PAD events. They found a U-shaped association with SBP and PAD. Particularly, SBP <120mmHg which was

associate with a 26% higher rate of lower extremity PAD whereas an SBP≥160mmHg was associated with a 21% higher rate of lower extremity event. Furthermore, a DBP of <70mmHg was associated with higher rates of PAD events, no difference was seen in a higher DBP (Itoga et al., 2018).

Similarly, research has confirmed the J-curve association which suggests a DBP less than 70mmHg and SBP of less than 120mmHg has been associated with a high risk of coronary events and deaths in high-risk patients (Vidal-Petiot et al., 2016, Bangalore et al., 2010). Likewise, these results have been seen in PAD studies (Itoga et al., 2018). An explanation for the observation of lower DBP and higher rate of PAD could relate to importance of lower extremity perfusion during diastole. During exercise DBP increases more in clinical populations than in healthy populations due to hypertension, as they have an inability to reduce total peripheral resistance. Therefore, in PAD patients, when systolic flow is limited due to the atherosclerosis process, perfusion becomes more dependent on DBP during exercise.

Drug therapy and a combination of non-pharmacological therapy is required to treat high BP. Non-pharmacological interventions such as a reduction in sodium intake to <100mmol/day, eating a diet rich in vegetables, fruit and low-fat dairy products have been shown to improve BP (Cosentino et al., 2020). Antihypertensive drugs such as diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are recommended for this clinical population. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial showed ACEIs and ARBs should be recommended for the secondary prevention of patients with PAD and CLTI (Yusuf et al., 2008).

2.5.6 Smoking cessation

Smoking is a major modifiable risk factors for patients with PAD and CVD. It is known that up to 80% of patients with PAD are current or former smokers (Smith et al., 1990). Furthermore, cigarette smoking increases the risk of having PAD by a 2-fold to 4-fold (Creager and Hamburg, 2022). Uniquely, patients with PAD are a highly motivated clinical population driven to quit smoking when given the knowledge that their claudication may improve and the need for invasive treatment and long term medication may be reduced (Ratchford and Black, 2011, Hennrikus et al., 2010b).

The 2018 American College of Cardiology have developed an ideal approach for the cessation treatment for PAD patients (figure 2.6) (Barua et al., 2018). This is based on "The 5 A's framework" (Ask, Assess, Advise, Assist, Arrange) which has been designed to engage clinical professionals to deliver effective treatment. Furthermore, health professionals push to keep smoking on the problem list because it can be lost or related as a lower priority issue. It is also important to keep high-quality education material for patients to provide out-of-clinic education (Ratchford and Black, 2011).

Behavioural therapy such as motivational interviewing and contact with a tobacco cessation coach can assess patients' barriers and beliefs around smoking, as well as setting goals to prepare patients for their quit date. Group support sessions can also be accessed through health systems, encouraging patients to spend time in a smoke-free setting. It is important to highlight any underlying conditions such as PAD which may be associated with pain and functional limitation that can be improved through quitting smoking (Barua et al., 2018). One behaviour programme specified to PAD patients showed an intensive intervention group here significantly more likely to remain abstinent at a 6 month follow up than a minimal intervention group (21.8% vs 6.8%) (Hennrikus et al., 2010a).

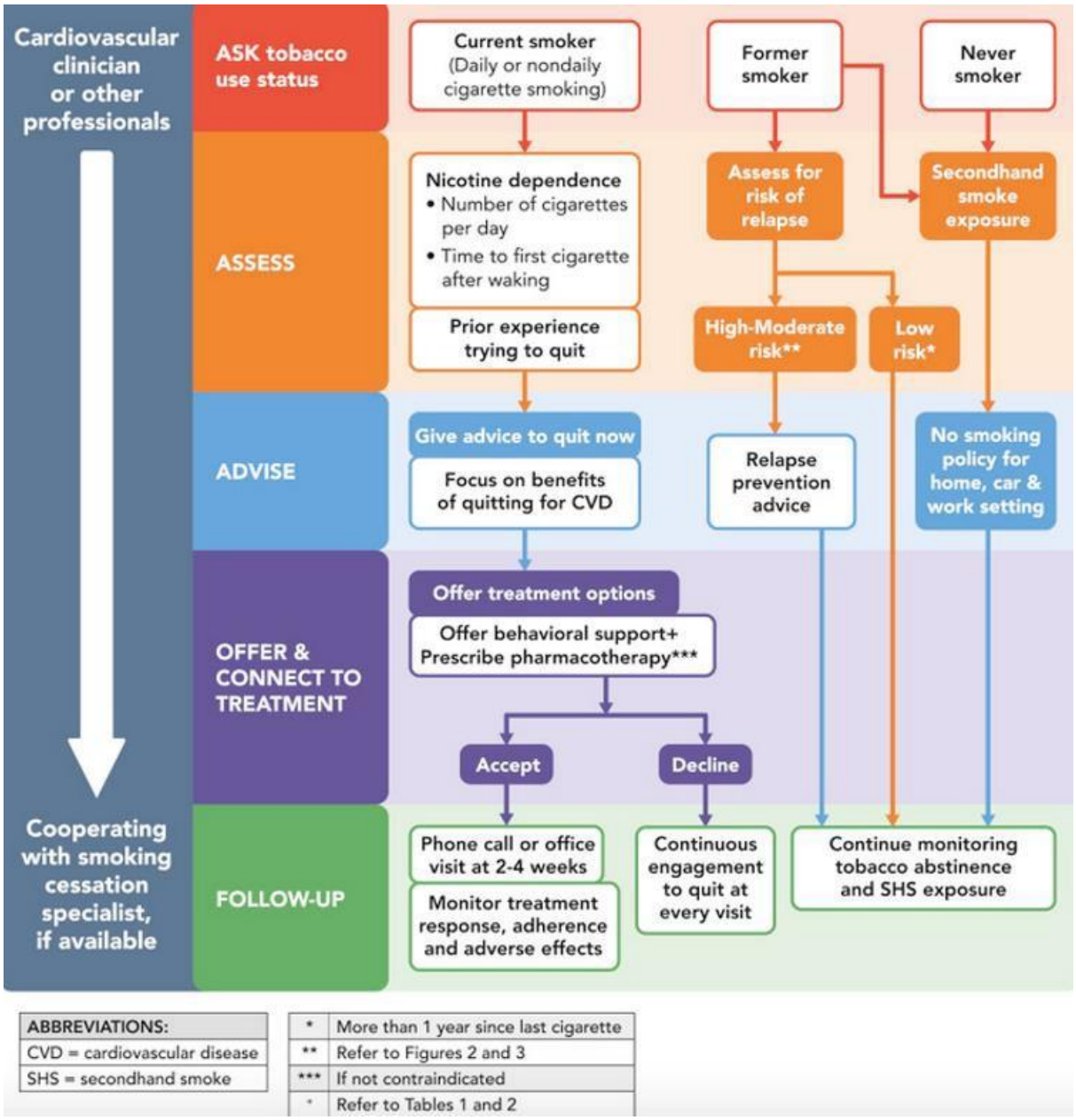


Figure 2.6. Pathway for Tobacco Cessation Treatment. *Note*. From Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2018; 72: 3332-3365. 2018/12/12. DOI: 10.1016/j.jacc.2018.10.027.(Barua et al., 2018)

Behavioural therapy combined with pharmacological treatment is the general care practice for patients with PAD. Nicotine replacement therapy (NRT) and bupropion have been approved for smoking cessation (Barua et al., 2018). NRT combined with bupropion has been shown to

be more effective than a placebo and is the preferred treatment if the patient has signs/symptoms of depression (Anthenelli et al., 2016).

PAD patients will need life-long support to maintain abstinence and deal with relapse (Hobbs and Bradbury, 2003). One study highlighted better cessation strategies are needed for patients with PAD. Among 1272 patients, 474 were active smokers. Of these, only 16% were referred to cessation and 11% were prescribed pharmacological treatment. Patients were shown to relapse early in treatment and 72% of all smokers continued to smoke after 12-months (Patel et al., 2018).

2.6 Quality of Life Outcomes

The role of physical activity for patients with IC is to relieve lower extremities symptoms and consequently improve their QoL. Objective measures such as pain-free walking distance and maximal walking distance are used to measure the success of SEPs. Patient reported outcomes are measured by generic and specific QoL questionnaires (Poku et al., 2016).

QoL is an important outcome measure for interventions designed to improve health, wellbeing, or both (Morgan et al., 2001). Although it is increasingly recognised that objective assessments of functional capacity and walking ability are important to determining disease severity, a qualitative approach should be used in conjunction with clinical outcomes (Nicolaï et al., 2009b). There are generic and disease specific QoL measures available for patients with PAD.

2.6.1 Short-Form 36 Questionnaire

The Short-Form 36 Questionnaire is an internationally recognised generic measure, which authors suggest should be a standard instrument in vascular studies (Morgan et al., 2001). A

recent review demonstrated that the SF-36, or variations of it, was the most used QoL measuring tool for patients with IC, used in 23 of 31 studies (Harwood et al., 2017d). Indeed, it has been extensively validated for assessing QoL in patients with PAD (Beattie et al., 1997). The SF-36 measures eight domains: physical, role and social functioning, mental health, patient health perceptions, vitality, bodily pain, and change in health through 36 questions. Each individual domain is transformed to a score of 0 to 100, with 100 being the best possible score (Mays et al., 2011). The scores can then be grouped into physical and mental component summary scores (Mays et al., 2011). Research suggests patients with IC reported the greatest influence on their QoL are aspects which relate to pain and physical limitations (Hicken et al., 2000). However, it has been recommended the SF-36 should be accompanied by a disease-specific measure (Garratt et al., 1993).

2.6.2 Vascular Quality of Life Questionnaire

The Kings College Hospital Vascular QoL questionnaire was developed and validated as an easily used disease-specific measure for patients with chronic limb ischemia (Morgan et al., 2001). The questionnaire was formulated as it was highlighted generic instruments were not sensitive to components of QoL relevant to vascular disease, specifically PAD. It is reliable, responsive and valid to within-patient change. Therefore, it can be used should the patient's condition improve or deteriorate and fulfils the requirements of an evaluative measure (Morgan et al., 2001). The questionnaire consists of 25 questions with five domains: pain, symptoms, activities, social and emotional. Each domain is scored out of seven with one being the worst score and seven being the best score. A total score can then be calculated for the whole questionnaire by adding all the scores and dividing by 25.

2.6.3 Barriers to Physical Activity Questionnaire

The Barriers to Physical Activity Questionnaire is a validated questionnaire divided into two questions to understand the personal and environmental barriers limiting a PAD patients taking part in physical activity (Barbosa et al., 2015b). Personal barriers include lack of knowledge, need for supervision, lack of time, other health reasons, financial reasons and barriers specific to IC (pain on exertion, need for rest and fear of falling). Environmental barriers include unfavourable weather, poor quality sidewalks, hilly terrain, shortness of space to exercise and barriers specific to IC (obstacles aggravating pain and no place to rest when experiencing pain). Each question is scored on a scale of 1-5 with 1 being never experiencing the limiting factor and 5 being always experiencing the limiting factor. Findings from this questionnaire are used to highlight exercise determinants of physical and environmental barriers to physical activity.

2.6.4 EuroQol-5 (EQ-5D) Dimension Questionnaire

The EQ-5D is an instrument which evaluates the generic QoL developed in Europe and widely used (Balestroni and Bertolotti, 2012). The health-related descriptive system contains one question for each of the five domains which include mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D questionnaire also has a Visual Analog Scale where patients can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status) (Balestroni and Bertolotti, 2012). Research has shown responses from the EQ-5D can be reliably used when measuring change in health related QoL (Badia et al., 2001) and has been proven to have clinically validity for patients with PAD when used alongside other questionnaires to provide a holistic assessment of the health related QoL (Issa et al., 2010, Vaidya et al., 2018).

2.6.5 Walking Impairment Questionnaire

The Walking Impairment Questionnaire was developed as a self-report tool to aid the clinical identification of walking ability in patients with PAD (Sagar et al., 2012). The questionnaire characterised walking speed, distance and symptoms limiting walking to evaluate the degree of walking impairment. The scores can be used to measure the efficacy of an exercise intervention in patients with PAD (Regensteiner et al., 1990). The measure is reported to be both reliable and valid (Coyne et al., 2003, Regensteiner et al., 1990). For each domain, the participant rates their ability to perform a task e.g., walking 300ft on a Likert 0-3 scale, with 0 indicating unable to do and 3 indicating no difficulty. The score for each task then gets multiplied by a prespecified weight for that task and the product of this equation is then divided by the maximal possible score. This is then multiplied by 100 to obtain a percentage with 0% indicating inability to perform the task and 100% indicating no difficulty at all with the tasks (Sagar et al., 2012, Regensteiner et al., 1990).

2.7 Physiological Outcomes

2.7.1 Pain-Free and Maximal Walking Distance

The gold standard measures of walking ability include pain-free (PFWD/T) and maximal walking distance or time (MWD/T) (Harwood et al., 2020). Pain-free walking distance is the distance walked when the onset of claudication pain occurs. Maximal walking distance/time is the distance at which the claudication pain is so severe the patient is forced to stop. It is important to note ‘maximal’ or ‘maximum’ should always be used in this outcome (Birkett et al., 2021). However, a recent review with sixty-four trials showed that fourteen terminologies were used to describe MWD (Birkett et al., 2021). A Cochrane review which has recently informed clinical guidelines only used studies which included MWD/MWT (Lane et al., 2017b). The distance covered during a 6-minute 30m walk test is an additional test to measure PFWD and MWD, 6-minute walk distance (6MWD) and is more reflective of normal every

day walking (Hiatt et al., 2014). If the distance walked on the treadmill is unavailable, then the qualified exercise professional conducting the test can convert the time into metres using the following equation: distance = speed [meters per second] x time [seconds].

Previous research has highlighted how both measures of PFWD and MWD are reliable and reproducible measures for patients with IC (Degischer et al., 2002, Labs et al., 1999, Gardner et al., 1991c, Zwierska et al., 2004). Although MWD implies patients should walk until they are forced to stop, this measure has said to be subjective depending on the psychology of the patient and the perception of pain (Watson et al., 1997). For example, this was highlighted in a study as two-thirds of patients in a research trial said they had to stop because of pain, however proceeded to immediately walk 15-45m to the rest room (Watson et al., 1997). Recently, research has also considered measuring a patients functional claudication distance (FCD), when the patient would prefer to stop walking, as it a more correspondent measure of everyday life (Kruidenier et al., 2009). Even though this is not widely used, it has been found a reliable and valid measure of determining functional capacity in trained patients with IC (Kruidenier et al., 2009). In a trial using 82 participants taking part in treadmill testing, FCD was a reliable and valid measure to determine functional impairment in patients with IC (Kruidenier et al., 2009). However, MWD was still the most reliable measurement during the treadmill test, in agreement with previous research (Gardner et al., 1991b, Labs et al., 1999) (Gardner et al., 1991c).

Although treadmill testing to measure for MWD allows for results to be accurate, reproducible and simple, some researchers argue the test remains protocol dependent, technically demanding, limited to laboratories and time-consuming (Faucheur et al., 2008). Furthermore, there are questions regarding the inaccuracy of the test and whether or not it is representative

of true living (Watson et al., 1997). For instance, the treadmill test does not account for difference in the nature of the terrain, length of stride, ambient temperatures and footwear (Watson et al., 1997). Should the initial assessment and assessment following the exercise programme use the same standardised protocol, this should allow for a valid and reliable comparison of results.

Research has demonstrated physical exercise to the level of severe claudication pain leads to an improvement in mitochondrial content post-training which is a contributing factor for training-induced performance improvements (Crowther et al., 2012). Therefore, participants in the maximal pain intervention see greater increase in their MWD due to an increase mitochondrion which increases their aerobic capacity and so delaying the onset of ischemia (Harwood et al., 2016, Crowther et al., 2012).

2.7.2 Minimal Clinically Important Difference

The minimal clinically important difference (MCID) represents the smallest threshold change in an outcome measure that a patient considers beneficial (Jaeschke et al., 1989a). The MCID has been estimate using PAD specific outcomes including a standardised treadmill test, 6MWT and the walking impairment questionnaire and SF-36 (Gardner et al., 2018). The MCIDs for MWT/MWD following a 3-month supervised exercise programme was 38 seconds (34m) for a small change, 95 seconds (85m) for a moderate change and 152 seconds (136m) for a large change (Gardner et al., 2018). MCIDs small, moderate and large changes in PFWT/PFWD were 35 (31m), 87 (78m) and 138 (123m) seconds. Similar MCIDs were found for a three-month home-based exercise intervention. Therefore, for an exercise intervention to elicit MCIDs in PAD patients they need to have an improvement of PFWD and MWD by up to 4

minutes, equivalent to working through two stages of the standardised Gardner-Skinner treadmill test (Gardner et al., 2018).

A recent trial observed meaningful changes in the 6MWT and the walking impairment questionnaire for patients with PAD over a longitudinal study at baseline and one year later. Out of 777 participants with PAD, the study found an 8-metre improvement in walking distance represents a small meaningful improvement in walking ability and a 20-metre improvement corresponds to a large meaningful change in people with PAD (McDermott et al., 2021b). Furthermore, a study explored the test-retest reliability and minimal detectable change in the 6MWT for patients with PAD. Of 102 patients with IC, the study demonstrated an improvement or deterioration in MWD ≥46m following an intervention would be required to be 95% confident that the change was significant (Sandberg et al., 2020).

2.8 Exercise Therapy for Intermittent Claudication

2.8.1 Unsupervised Exercise

Unsupervised exercise consists of simple 'go home and walk' advice provided by many sites once PAD patients are diagnosed and do not have access to a SEP (Al-Jundi et al., 2013). However, a review concluded unstructured recommendations for PAD patients are not efficacious (Mays et al., 2011). Furthermore, a study found an improvement of 210m in MWD when taking part in a SEP compared to walking advice. Researchers also detected a improvement in QoL favouring the SEP over walking advice (Hageman et al., 2018).

A review provided an overview of supervised versus non-supervised exercise. A total of 1002 patients with PAD where used in the review which found supervised exercise therapy to be significantly beneficial compared to non-supervised regimens (Fokkenrood et al., 2013b). Of

the 14 studies, with moderate to good quality evidence, SET showed a statistically significant improvement in MWD compared with non-supervised exercise regimen, with an overall effect size of 0.69 (95% CI 0.51 to 0.86) at 3-months and 0.48 (95% CI 0.32 to 0.64) at 6-months (Fokkenrood et al., 2013b). Therefore, SEPs following a structure should be provided for all symptomatic PAD patients.

2.8.2 Home-based Exercise Programmes

Home-based exercise programmes (HBEPs) are a convenient safe alternative to SEPs and unsupervised 'go home and walk' advice (Waddell et al., 2022). HBEPs remove potential barriers such as expense and having to travel to an exercise centre which is a burden for patients with limited mobility (McDermott and Polonsky, 2016). A recent review highlighted HBEPs are safe method of exercise for patients with IC as an all-cause complication rate of one event per 36,953 patient-hours. As such HBEPs need to be thoroughly investigated as an alternative exercise option for patients with PAD (Waddell et al., 2022).

HBEPs are a structured self-managed exercise programme with an appropriate intensity, frequency, duration and type of exercise. Monitoring of patients through logbooks, pedometers and physical activity monitors are a key element to HBEPs (Pymer et al., 2021). A Cochrane review compared SEPs to HBEP and walking advice (WA). Overall, SEPs was superior to HBEP and WA on MWD and PFWD. There was no statistical difference when comparing HBEPs to WA, however the mean difference between SEPs and WA was 210m compared to a difference of 120m between SEPs and HBEPs. The review did not find any difference in QoL parameters and self-reported functional impairment between SEPs and HBEPs, though there were small improvements in QoL favouring SEPs over WA (Hageman et al., 2018). That said, review and meta-analysis did find significant improvements in the WIQ and physical

functioning questionnaire when comparing HBEPs to basic exercise advice (Pymer et al., 2021). This suggests there is a benefit of HBEPs over WA given appropriate supervision (Hageman et al., 2018).

A recent large multicentre control trial (MOSAIC) of 190 adults with PAD were randomised to either a walking exercise behaviour change intervention or usual care (Bearne et al., 2022). Overall, the study highlighted how a home-based walking exercise intervention resulted in an improved walking distance at 3 months (352.9m at baseline to 380.6m at 3 months) compared to a placebo (369.6m at baseline to 372.1m at 3 months). However, the 27.7m difference in 6-minute walking distance following the intervention did not meet the threshold for small change (of 31m) in MCID in patients with PAD (McDermott et al., 2021b, Bearne et al., 2022). Possible reasons for a smaller effect size in this study could have been due to COVID-19 pandemic hindering patients walking plans or participants did not walk at a sufficient intensity to produce large improvements in 6-minute walking distance (McDermott et al., 2021b).

Little research exists on the optimal FITT principles for effective HBEPs. The American Heart Association offers vague advice, suggesting clinicians should prescribe an exercise regime similar to SEPs (Gerhard-Herman et al., 2017). A recent trial found HBEPs had high adherence and efficacious at improving claudication similar to SEPs when 12 weeks of intermittent walking to near maximal pain was prescribed 3 days per week (Gardner et al., 2011). Walking duration began at 20 minutes and progressively increased five minutes biweekly until 45 minutes was accomplished (Gardner et al., 2011). Likewise, a RCT with similar FITT principles (12 weeks, activity monitoring, patient education), but daily steps given based on steps per day, also found HBEPs can improve functional outcomes of patients with PAD (Duscha et al., 2018).

Furthermore, HBEPs appear more efficacious in increasingly daily ambulatory activity than SEPs (Gardner et al., 2011). This could be due to periodic meeting and feedback with clinicians which enhanced motivation and adherence to the programme. That said, a recent RCT, compared HBEPs wearing technology and telephone coaching compared to no exercise advice and found no difference between HBEPs and the control group (McDermott et al., 2018). Therefore, more research is needed to evaluate the components of HBEPs to maximise patient benefit (i.e., technology, FITT principle, on-site visits) (Harwood et al., 2020).

2.8.3 Supervised Exercise Programmes

SEPs are the first line of treatment for PAD patients, as recommended in national and international guidelines (Layden et al., 2012, Gerhard-Herman et al., 2017, American College of Sports et al., 2018, Tew et al., 2018). SEPs have been shown to be an effective low-risk, inexpensive option compared to other non-invasive therapies of alleviating symptoms of patient with IC (Lane et al., 2017b). SEPS have an exceptionally low all-cause complication rate of one event per 10,340 patient-hours, making then an assured safe form of treatment for PAD patients (Gommans et al., 2015).

A Cochrane review, utilising high quality evidence, showed an overall improvement in MWD and PFWD (120.36m and 82.11m) for patients taking part in a SEP when compared with a no exercise group (Lane et al., 2017b). Furthermore, one study discovered SEPs are superior to stent revascularisation for an improvement in treadmill walking performance for patients with aortoiliac PAD (Murphy et al., 2012). Likewise a meta-analysis including 25 RCTs of SEPs demonstrated that exercise was associated with a statistically significantly improvement in MWT and PFWD (Fakhry et al., 2012a).

Although the evidence of the benefits of SEPs are irrefutable, there are inconsistencies between different components of the programme. Frequency, intensity (claudication level during exercise), time of exercise session and type of exercise programme all vary between guidelines (Treat-Jacobson et al., 2019).

The optimal frequency of a SEP varies considerably within guidelines from 12 weeks (Gerhard-Herman et al., 2017, Tew et al., 2018, Riebe et al., 2018) to 6 months (Askew et al., 2014, Foundation, 2016). One study suggested a 3-month SEP as the most preferable and significant for patients with PAD. After 3-months the SEP can be replaced with a HBEP which has been shown as effective after 6-months (Gommans et al., 2014). Furthermore, many meta-analyses and a high-quality evidence Cochrane review have shown a large effect size after 3 months on a SEP during the treadmill test (Fokkenrood et al., 2013b, Fakhry et al., 2012a, Gommans et al., 2014, Lane et al., 2017b).

The duration of exercise session is similar between guidelines, recommending 30-60 minutes per session (NICE, 2012, Riebe et al., 2018, Norgren et al., 2007, Gerhard-Herman et al., 2017, Tew et al., 2018). Although little research has been done to verify the optimal session length of a SEP. An early meta-analysis found that a SEP lasting > 30 minutes vs 30 minutes or less was more beneficial on functional outcomes (Gardner and Poehlman, 1995). Though, more recently, research did not identify session duration as being independently associated with a change in MWD and PFWD (Fakhry et al., 2012a).

Although most guidelines highlight walking as the most beneficial form of exercise, adherence to walking can be difficult due to claudication pain therefore alternative modes of training have

been researched to a very limited extent (Bulmer and Coombes, 2004). A Cochrane review found that exercise such as cycling, upper arm ergometry and strength training had similar effects on walking distance to a supervised walking programme (Lauret et al., 2014). A recent review analysing 826 patients found that overall resistance training significantly improved constant/progressive treadmill test and 6MWT PFWD and MWD (Parmenter et al., 2020). Resistance training varied from 6 to 24 weeks, averaging 3 times a week. The review examined elements of the interventions which were associated with high improvements in walking ability and found high intensity resistance training (70-84% 1RM) and exercises focusing on the lower body to be the most effective (Parmenter et al., 2020). Large intervention effects were found in exercises focusing on the calf muscles, quadriceps, hamstrings and gluteals. Furthermore, high-intensity strength training (70-84% 1RM) was associated with a significant improvement in walking distance compared to moderate intensity (50-69% 1RM) and low intensity resistance training (30-49% 1RM) (mean ES = 0.66 vs 0.46 vs -0.21) (Parmenter et al., 2020). This is in agreement with previous research which found whole-body progressive high- intensity resistance training (80% 1RM) significantly improved 6-minute walking performance compared to low-intensity nonprogressive resistance training (30% 1RM) (Parmenter et al., 2013).

Alternatively, cycling is an attractive mode of exercise to study for PAD patients since it is relatively easy, inexpensive and a popular mode of transport. Although, an RCT with 42 patients randomised to cycling, treadmill or control found cycling training did not significantly improve walking performance, but it did significantly improve cycling performance (Sanderson et al., 2006). Whereas treadmill training significantly improved MWD and PFWD but did not improve cycling performance. Treadmill training had a significantly larger effect ($P < .05$) on MWT (240 ± 178 seconds) than cycling training had on maximal cycling time (93

± 98 seconds). These results could be explained by the location of the claudication in the lower limb. As claudication is most cited in the calf, perhaps this is leads to some suggestion why cycling may not be as beneficial for PAD patients. Although, 5 of the 15 cycling patients improved their walking performance and a previous study has found bicycle exercise training to significantly improve walking distances (Haga et al., 2020). Therefore, more research is needed before cycling is discarded as a mode of exercise (Sanderson et al., 2006).

Besides this, upper-limb exercise training such as arm ergometry has been shown to considerably improve walking performance. An RCT with 104 patients compared upper-limb aerobic exercise training with lower-limb aerobic training over a 24-week period. The results showed a statistical significance (all $P < .001$) in MWD for both the upper-limb exercise group (29% improvement) and the lower-limb exercise group (31% improvement) (Zwierska et al., 2005). This finding supports previous research which suggested upper-limb exercise could be a useful stimulus for improving or maintaining cardiorespiratory function in patients with severe PAD as they have a greater upper-limb strength (Zwierska et al., 2006, Walker et al., 2000). This highlights alternative modes of exercise could be an option should walking be inaccessible, however larger sample sizes ae needed to make more meaningful comparisons (Parmenter et al., 2013).

The intensity of an exercise programme is defined as working at a percentage of maximal workload attained during a treadmill test (Treat-Jacobson et al., 2019). A study by Gardner et al, found low-intensity exercise groups (40%) elicited similar changes in functional outcomes for patients with PAD compared with high-intensity exercise (80%) (Gardner et al., 2005). Thus, suggesting intensity of exercise may not be directly significant to a change in MWD and PFWD. Yet, a review suggested vigorous intensity training (70-90% HRMax) was superior to

moderate intensity training (40-60% HRMax) (Parmenter et al., 2015). Therefore, it is apparent more research is needed to find whether low-intensity or high-intensity exercise is more beneficial for patients with PAD.

Recently, a statement and infographic has been issued by British Association of Sport and Exercise Science (BASES) to improve the standardisation of SEPs (Tew et al., 2020, Tew, 2018). The recommendations include walking through the pain until strong levels of leg pain, 30–60-minute sessions and at least 3 sessions a week. The infographic also highlights the importance of resting until the pain has subsided before moving on to the next exercise (Tew et al., 2020). It is clear more research is needed to create a universal set of guidelines to promote the optimal benefits for PAD patients.

2.8.5 Adherence and Uptake to Supervised Exercise Programmes

Even though SEPs are the first line of treatment for patients with IC, uptake and adherence rates in this clinical population are poor (Harwood et al., 2016b, Lin et al., 2019a). Many patients who begin an exercise intervention fail to complete the programme. Hence, the clinical and cost effectiveness of SEPs for managing this disease may be lacking due to the poor recruitment and adherence to these sessions (Harwood et al., 2016b). A review with 4,012 patients aimed to find the uptake and adherence rates in patients with IC (Harwood et al., 2016b). They found that overall, only 1 in 3 patients screened were suitable and willing to undertake a SEP. Moreover, only 75.1% of patients were reported to have completed the SEP (Harwood et al., 2016b). The study found that lack of motivation was a major factor in poor adherence for PAD patients. Therefore, it is essential to improve the commitment in these

patients, which relies on trying to understand why these patients reject the opportunity to take part in SEPs.

A large proportion of patients who fail to complete SEPs have a significant number of comorbidities and risk factors preventing the commencement of exercise (Harwood et al., 2016b). This demonstrates that vascular patients may have lived an unhealthy lifestyle for a long time and perhaps are unable to see that they need to take responsibility for their health. Patients with IC are looking for a "quick fix" which leaves them uncompliant with an exercise intervention where the improvement may only occur after a number of weeks (Popplewell and Bradbury, 2014). Another commonly cited barriers to SEPs are time, no transport or inability to access public transport, financial limitations and work/family commitments (Harwood et al., 2021, Lin et al., 2019a).

A further point to note is the reluctance of health care professionals to promote the importance of SEPs (Popplewell and Bradbury, 2014). In 2021, an online survey was sent out to try and understand how SEPs in the UK where being implemented and how valued they were by clinicians, patients and commissioning groups. Ninety-three vascular units where identified and, of the 48 who responded, only 23 had access to a SEP (Harwood et al., 2021). Clinicians appeared to rate SEPs as slightly to very important, but the commissioning and funding bodies felt the SEPs were not at all to slightly important. As the commissioning bodies are responsible for execution of SEPs throughout hospitals, should they deem the SEPs not important, funding is going to be a major barrier to implement these programmes (Harwood et al., 2021).

Although more research is required to distinguish the poor uptake and levels of adherence in SEPs, patient resistance needs to be overcome to promote SEPs. Research alludes there needs

to be a reward for hospitals that run a successful SEP, as re-imbursement drives practise (Duwayri et al., 2021). Also, clinicians need to give time for SEPs and behavioural medical therapy to work before advising interventional therapies which are often not cost-effective and have little credibility against SEPs (Popplewell and Bradbury, 2014). As there is no current service evaluation or standardised framework, a record of uptake and adherence rates would be beneficial to ensure the effectiveness and quality of SEP delivery (Harwood et al., 2021).

2.9 Training Adaptions

2.9.1 Central Adaptations

Patients with IC are at a higher risk of further cardiovascular events; therefore, it is important to evaluate central adaptations that occur following SEPS. It is well documented that SEPs, involving high intensity interval training (HIIT), have a similar superior physical benefits in promoting an increase in maximal oxygen uptake in healthy and clinical populations such as coronary heart disease patients (Liou et al., 2016, Weston et al., 2014, Batacan et al., 2017). Furthermore, the use of HIIT in patients with IC has been found to have significant effects on $VO_{2peak.}$ A review looking at the effects of HIIT on patients with IC found significant effects of HIIT (8 week programme) compared to lower intensity exercise 6-month programme) on VO_{2peak} (16% vs 9%; $P < .05$) (Pymer et al., 2019). In contrast, a study compared a 12-week walking (until they reached level three or four on the claudication pain scale) SEP to a control group who were encouraged to walk regularly (Hodges et al., 2008). Although there was a significant improvement in MWD for the patients taking part in a SEP, there was no significant difference in peak oxygen consumption or peak cardiac output in either group. Furthermore, there was no significance of a decrease in heartrate between weeks 1 to 12. This suggests that SEPs may initially only promote peripheral adaptations as patients are limited due to the limitations of IC. However, once patients are able to walk further with the continuation of

SEPs, cardiovascular changes are likely to occur (Hodges et al., 2008). This has been shown in earlier research whereby treadmill training promoted a systemic response of a 17-beat reduction in HR, brought on by a physiological response to exercise. This demonstrates how training responses in these populations can occur at a given workload if they can overcome the pain barrier (Hiatt et al., 1994).

2.9.2 Peripheral Adaptations

Supervised exercise programmes play a significant role on peripheral adaptations for patients with IC as many papers have shown a significant increase in maximal walking distance following an exercise intervention (Lane et al., 2017a, Hodges et al., 2008, Gardner and Poehlman, 1995, Parmenter et al., 2011). Exercise promotes an increase in blood flow to the working limbs and to the coronary circulation. In healthy individuals these arteries dilate in response to an increase blood flow, however in patients with IC this may be limited due to the atherosclerosis (Hodges et al., 2008). Research suggest inflammatory status are related to the severity of the disease described by the patient (Silvestro et al., 2002a). Taking part in intermittent SEPs involving repetition on the exercising limbs, elicits an adaptive peripheral response which increases the responsiveness of nitric oxide synthase (Woodman et al., 1997). Consequently, there is an increase in the synthesis and release of nitric oxide, a vasodilator. This leads to an improvement of the endothelial function as the vessels ability to vasodilate is increased and more oxygen is available to the working muscle (Woodman et al., 1997). This may explain why there is an increase in walking ability following a SEP (Hambrecht et al., 1998).

Endothelial function can be measured via flow-mediated dilation (FMD) which is an independent predictor of PAD and is the gold standard assessment of endothelial function

(Brevetti et al., 2010, Harwood et al., 2015). It is thought, patients with PAD have a low FMD due to an inadequate bioavailability of nitric oxide, an endothelial-mediated dilator of the arteries (Haas et al., 2012). There has been a strong association between higher levels of physical activity (measured using a vertical accelerometer and a pedometer over 7 days) and FMD responsiveness in patients with PAD (Payvandi et al., 2009). Research has found FMD to significantly improve following an exercise programme from 4.81 to 7.97 ($p < 0.005$) (Januszek et al., 2014, Brendle et al., 2001). However, several studies have shown FMD in the calf was not significantly altered with SEPs (Parmenter et al., 2015, Parmenter et al., 2010). Likewise, unsupervised exercise programmes have been shown less ineffective at improving FMD, maybe due to patients being less compliant (Allen et al., 2010). Therefore, given the lack of data within patients with IC, it is difficult to conclude whether exercise provides a significant improvement of FMD for patients with IC.

A further adaptation to exercise is an increase capillarity density, brought on through angiogenesis (Brodal et al., 1977). Due to an increase in capillary density, surface area for diffusion of oxygen and CO_2 diffusion in the working muscle. This adaptation could play a significant role for patients with IC, who need to optimise the utilisation of oxygen being delivered to the affected leg (Sørlie and Myhre, 1978). Patients with PAD have been found to have a reduced capillary density in the gastrocnemius muscle compared to healthy individuals (Robbins et al., 2011). Yet, it has been found an increase in capillary density significantly correlates functional outcomes such as to MWD and PFWD (Robbins et al., 2011). Therefore, taking part in a SEP which induces an increase in capillary density for patients with IC could be a contributor to an increase tolerance in exercise performance due to an increase oxygen consumption (Haas et al., 2012).

A review found near maximal claudication pain was the most important factor to determine positive training adaptations during SEPs, as walking to maximal pain accounted for 55% and 40% improvement in PFWD and MWD (Gardner and Poehlman, 1995). However, some patients with IC are limited to how much they can walk, therefore questioning the effectiveness of SEPs to promote physiological adaptations in PAD patients (Haas et al., 2012). Furthermore, there has been debate whether exercising PAD patients to the point of pain causes an extensive inflammatory response, subsequently exacerbating their condition. A trial investigated exercising patients within tolerable levels of claudication pain (Cucato et al., 2013). The RCT randomised patients to a walking intervention prescribed at the HR of onset claudication pain (above the anaerobic threshold and >80% of the heart rate peak and VO2peak). Following the 12-weeks exercise intervention, the onset of claudication distance increased significantly (309m ± 153m to 413m ± 201m) and total walking distance also increased significantly (784m ± 182m to 1100m ± 236m) compared to the control group. Therefore, the paper supports suggestions that patients can exercise at an intensity to improve walking performance which does not require experiencing intolerable levels of ischemic leg pain (Cucato et al., 2013).

Evidence suggests there is a possibility that regular exercise will protect against chronic systemic low-grade inflammation and these benefits can be seen with PAD patients (Petersen and Pedersen, 2005). This long-term effect of exercise can be attributed to the anti-inflammatory response of exercise mediated by muscle-derived IL-6 (a receptor antagonist which stimulates the appearance of other anti-inflammatory cytokines and inhibits the production of proinflammatory cytokine TNF-a). As inflammatory markers are predictive of disease severity, morbidity and mortality, any reduction of these as a consequence of an exercise intervention should benefit PAD patients and the improvement of IC (Tisi and Shearman, 1998).

2.10 Optimal Level of Claudication Pain

Despite the therapeutic benefits of exercise, there are universal inconsistencies regarding the appropriate level of prescribed claudication pain. The advocated level of pain varies from maximal claudication pain to pain-free walking, and some guidelines do not even recommend a level of claudication pain to work towards. This will lead to major variability in care. As a result, some patients may receive sub-optimal care.

The level of claudication pain prescribed during a SEP is used as a guide to instruct patients when to stop exercising, however the prescribed level of claudication pain varies significantly The NICE, AHA, and BASES recommend exercising to maximal claudication pain (NICE, 2012, Gerhard-Herman et al., 2017, Tew et al., 2018). Whilst the ACSM and Exercise and Sports Science Australia suggest moderate pain is more beneficial (Riebe et al., 2018, Askew et al., 2014). Therefore, it remains unclear which claudication pain prescription is optimal for improving functional outcomes.

Previous research has suggested exercise should be performed at near-maximal levels of claudication pain (Gardner and Poehlman, 1995, Lane et al., 2017b, Fokkenrood et al., 2013b). Supporting this, a recent review with 305 patients found low-intensity exercise (walking without ischemic leg symptoms) was significantly less effective than high-intensity exercise (walking at a pace eliciting moderate to severe ischemic leg symptoms) for improving 6-minute walking distance (McDermott et al., 2021a).

However, a recent review found pain-free SEPs elicit similar improvements in functional outcomes than moderate-SEPs (Seed et al., 2021). Similarly, Parmenter et al (2015) found mild

to moderate pain may yield optimal results (Parmenter et al., 2015). Recently, a review supported the provision of both high and low pain exercise on improvements in MWD and PFWD for patients with IC (Perks et al., 2021). Of the 14 studies used in the review, structured low-pain exercise had a larger positive effect than structured high-pain exercise for MWD/T and PFWAD/T compared with a control group. Additionally, in a comparison of low-pain and high-pain, there was a large positive effect of low-pain on walking ability, with statistical significance on PFWA (Mean difference 1.50, CI 0.24 to 2.75) (Perks et al., 2021). The paper concluded structured low pain may have been overlooked due to the lack of literature.

We recently published a review aimed to compare interventions that had directly compared exercise prescription at differing levels of claudication pain (Seed et al., 2021). Out of 1,543 results, only two were retained for review. Interestingly, both studies used in the review compared pain-free SEPs to moderate SEPs, with no studies comparing to maximum pain which is the current national guidelines (NICE, 2012, Mika et al., 2013, Novakovic et al., 2019). The review concluded pain-free exercise may be as beneficial as exercise prescribed at moderate levels of claudication pain for improving walking outcomes. This is in agreement with an earlier review who concluded exercise to mild-moderate pain may yield optimal results (Parmenter et al., 2011). Mutually, both studies concluded that prescribing exercise at a lower level of claudication pain may be as beneficial for patients with IC and could possibly improve the current poor uptake and adherence rates (Parmenter et al., 2011).

Additionally, asking patients to walk to maximal claudication pain has been cited as a barrier to adherence in SEPs (Harwood et al., 2016b, Lin et al., 2019a). A review including 84 studies found groups taking part in a low pain exercise programme were 1.52 times more likely to complete the intervention than groups taking part in a high pain exercise (Lin et al., 2019a).

Adherence was also significantly higher in the low pain SEPs compared to the high pain SEPs (93.4% vs. 77.0%). Exercising to maximal pain may discourage patients from taking part in SEPs, as such research suggests promoting pain-free exercise may be more appropriate (Al-Jundi et al., 2013). A recent review has highlighted the benefits of lower intensity interventions and has suggested they may be a good starting point to promote long-term behaviour change (Parmenter et al., 2011). As SEPs are the first line of treatment for IC, exercise interventions need to provide larger emphasis on patient perspective. Therefore, allowing patients to work at a lower level of claudication pain may allow for greater success, leading to the completion of small goals causing a positive mind and as result a greater compliance and adherence to SEPs. Recently, a statement from the American Heart Association has recommended the need for further research to find the optimal level of claudication pain which will improve functional outcomes and patient adherence (Treat-Jacobson et al., 2019). No trial has directly compared the level of pain at different thresholds; pain-free; moderate intensity; maximal pain; despite a maximal pain prescription being recommended in most clinical guidelines (Birkett et al., 2022a).

This thesis aims to conduct a randomised control trial to optimise exercise prescription and uptake by comparing the effects of exercise prescribed at different levels of claudication (pain-free, moderate pain and maximal pain).

Chapter 3. A Systematic Review of Exercise Prescription in Patients with Intermittent Claudication: Does Pain Matter?

3.1 Introduction

Peripheral artery disease (PAD) is a chronic disease characterised by atherosclerotic lesions in the lower limbs, (Criqui and Aboyans, 2015) affecting over 236 million people worldwide (Fowkes et al., 2013a). A classic symptom of PAD is intermittent claudication (IC), characterised by reproducible cramping, ischaemic muscle pain, precipitated by exertion and relieved by rest (Meru et al., 2006b). This symptom arises due to the imbalance of oxygen supply and demand in the working muscles, secondary to atherosclerosis (Hamburg and Balady, 2011b). IC can reduce an individual's quality of life by significantly impairing walking ability and functional capacity (Pell, 1995, Barletta et al., 1996).

National and international guidelines (Aboyans et al., 2018, NICE, 2012) recommend supervised exercise programmes (SEP) as first line treatment for patients with IC and there is overwhelming evidence for the benefit of SEPs including improvements in maximal and pain-free walking distance (Hageman et al., 2018). Despite these benefits, recruitment and adherence rates are poor with only one third of patients eligible and willing to undertake a SEP (Harwood et al., 2016b, Lin et al., 2019b). One potential reason for this may be because of the exercise-related pain. Indeed, it has been demonstrated that completion rates were higher when exercise was performed at a low, rather than high, pain threshold (Galea et al., 2008, Gardner and Poehlman, 1995). Exercising to a high level of pain may have adverse effects, such as pro-inflammatory response and muscle catabolism (Delaney et al., 2014). Furthermore, limited evidence has also shown that exercising up to the point of onset or mild claudication pain improves walking ability (Fakhry et al., 2012a, Parmenter et al., 2011).

Despite this, current UK guidelines (NICE, 2012) recommend exercise to maximal claudication pain, with international guidelines and meta-analyses advocating that exercise should be performed at moderate to maximal pain to improve walking ability (Riebe et al., 2018). As such, conflicting evidence exists, with inconsistencies between guidelines as to what level of pain exercise is prescribed at. Therefore, it remains unclear which claudication pain prescription is optimal for improving functional outcomes. Furthermore, a recent scientific statement from the American Heart Association (Treat-Jacobson et al., 2019) recommended further research to consider the role of exercising at different pain levels as identifying the optimal pain-based prescription may improve patient adherence (Galea et al., 2008).

Therefore, the primary aim of this systematic review was to assess interventions that have directly compared exercise prescription at differing levels of claudication pain on walking performance in patients with IC. A secondary aim was to access the level of claudication pain on vascular function and quality of life (QoL).

3.2 Methods

This review adhered to the PRISMA guidelines (Parmenter et al., 2015) and was prospectively registered on PROSPERO (CRD42020213684).

3.2.1 Search Strategy and Inclusion Criteria

Potential studies were identified from database inception to 9th October 2020. The CENTRAL, MEDLINE, Embase and CINAHL databases were searched. Only full text articles published in the English language were included and duplicate articles were removed. Key search terms were developed by SS and reviewed by SB and AH. The search strategy combined key words

including “peripheral artery disease” [OR] “intermittent claudication” [AND] “pain free” [OR] “moderate pain” [OR] “maximal pain”. All titles and abstracts were independently screened by two assessors (SS and SB), and a third reviewer was consulted to discuss any disagreements (AH). Full text manuscripts of potentially eligible articles were then independently screened using the inclusion/exclusion criteria. Reference lists of full texts were also hand searched to make sure we had not missed any materials which were not found through the traditional searches (Mika et al., 2013, Novakovic et al., 2019). We included randomised control trials (RCTs) that employed any mode of prescribed structured exercise for the treatment of IC, comparing at least two different intensities of IC pain. Exercise interventions had to be ≥4 weeks in duration and studies that included patients with critical limb ischaemia or asymptomatic PAD were excluded. Studies were also excluded if patients were <18 years old or the programme used other interventions (e.g., surgery) in addition to exercise.

3.2.2 Data Extraction

Data was extracted and inputted into a Microsoft Excel database (Microsoft Excel, Redmond, USA). Data extraction included the primary outcome measure of maximal walking distance/time (MWD/T). MWT where reported was converted to MWD to allow between study comparison (walking time in seconds (s) x treadmill speed (m/s)). Other outcomes included pain-free walking distance/time (PFWD/T), recruitment and adherence, flow mediated dilation (FMD), ankle brachial pressure index (ABPI), and QoL data. Study characteristics such as sample size, intervention components and inclusion/exclusion criteria were also extracted to assess the quality of the study.

3.2.3 Risk of bias and Quality assessment

RCTs that met our inclusion criteria were assessed by two reviewers (SS and AH) for risk of bias using the Cochrane risk of bias tool (Sterne et al., 2019). Quality assessment was also performed using the physiotherapy evidence database (PEDro) scale (Maher et al., 2003). Points were awarded when a criterion was clearly satisfied generating an overall score of the study out of 10 (Table 3.2).

3.3 Results

The PRISMA flow diagram (Stovold et al., 2014) is shown in Figure 3.1. Our search generated 1,543 results and four full-text articles were retrieved after screening titles and abstracts. Two articles were then excluded (Gardner et al., 2005, Marko Novakovic et al., 2018) due to the exercise intensity prescription based on percentage of heart rate on maximal capacity. Two articles (Mika et al., 2013, Novakovic et al., 2019) were retained for the review.

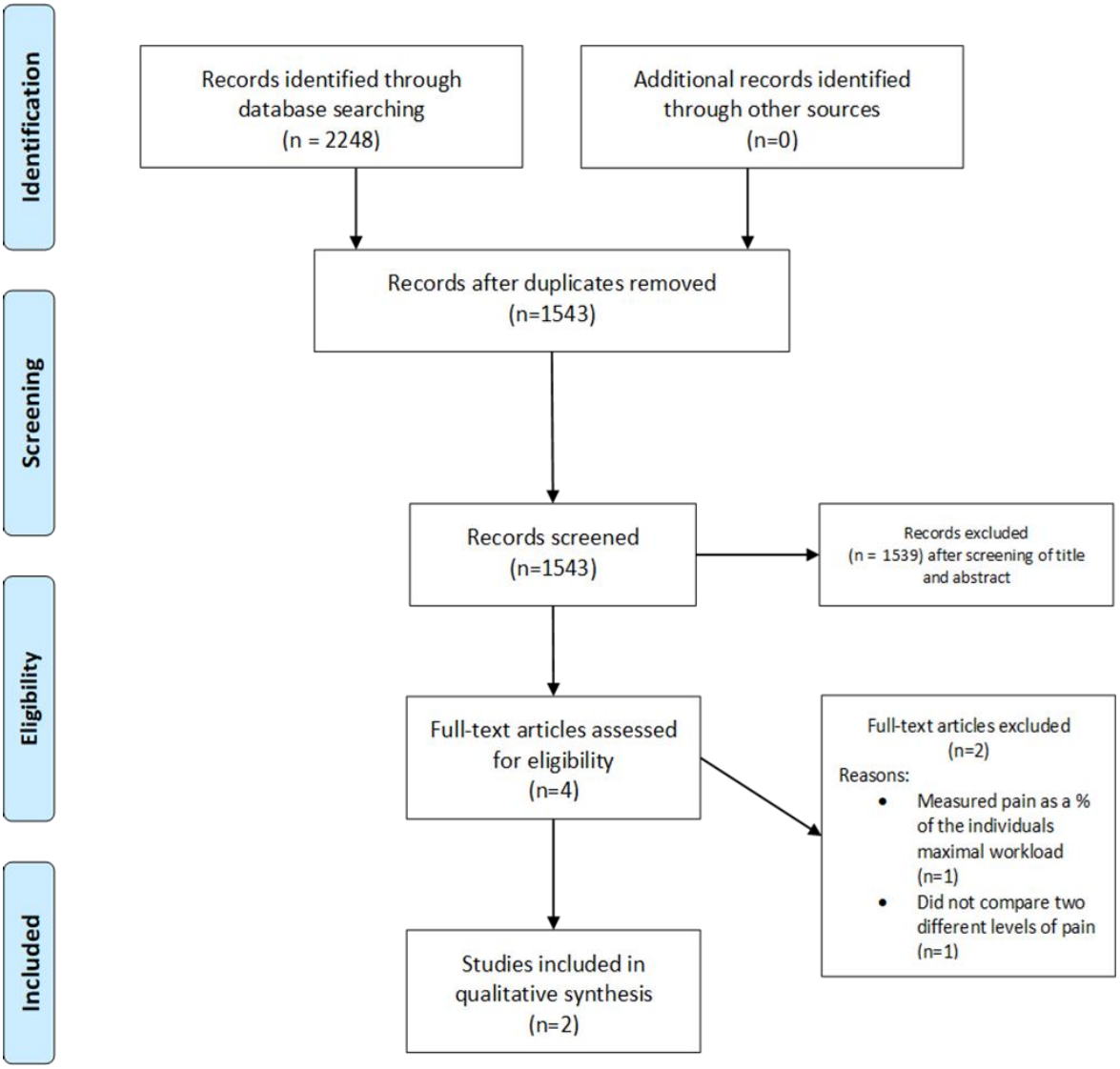


Figure 3.1. PRIMSA Flow Chart of Included Studies

3.3.1 Included Trials

The total number of patients included in the analysis was 81. Of those, 73 were allocated to a SEP and 8 were allocated to the control (non-exercise) group. Mika et al (2013) randomised 27 patients (59% males and 41% female, mean age of 64.8 ± 7.2) to the moderate-pain SEP group and 25 patients (64% males and 36% females, mean age of 65.2 ± 8.0) to the pain-free SEP group (Mika et al., 2013). Novakovic et al (2019) randomised 10 patients to the moderate-pain SEP group (60% male and 40% female, mean age 65.1 ± 7.6), 11 patients to the pain-free SEP

group (82% male and 18% female, mean age 65.6 ± 11.0) and 8 patients to the control group (75% male and 25% female ,mean age 62.0 ± 8.3) (Novakovic et al., 2019). Novakovic et al (2019) also used a control group that did not attend a SEP and was advised to continue with secondary preventative activities such as walking, as recommended by a vascular surgeon or other vascular medicine specialist (Novakovic et al., 2019). Medications included aspirin (acetylsalicylic acid), clopidogrel, β-blockade, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics and statins. MWD/T was measured using either a graded (Mika et al., 2013) or constant load treadmill protocol (Novakovic et al., 2019) and was determined as the point at which patients reached a level of 5 on the 1-5 pain scale, a continuous scale from 1 indicating no pain, the interval from 3 to 4 consistent with moderate to severe pain and 5 consistent with maximal unbearable pain (Parmenter et al., 2015). ABPI and FMD were measured via established techniques.

Treadmill walking was the mode of exercise for both interventions. Methods of exercise prescription differed between studies. Novakovic et al (2019) set the initial treadmill speed based on an intensity of 70% of predicted maximum heart rate (HR_{max}) with the gradient set at 0% (Novakovic et al., 2019). When heart rate during walking reduced to <65% HR_{max} the treadmill speed was increased by 0.3 km/h. For the moderate-pain SEP, patients walked until they reported a score of three to four on the five-point pain scale. For the pain-free SEP, patients walked up to two-thirds of their PFWD measured at baseline. Mika et al (2013*)* set the treadmill speed at 3.2 km/h and the grade was individually determined for each patient so that it would induce claudication pain within three to five minutes (Mika et al., 2013). The moderate-pain SEP group walked until they reported a score of four on the pain scale, whilst the pain-free SEP group stopped at the onset of claudication (a score of two on the pain scale).

SEP delivery varied between studies, one study used an exercise bike for active recovery to allow leg pain to subside (Novakovic et al., 2019), whilst the other allowed patients to rest until the claudication pain had abated (Mika et al., 2013). Training frequency and duration varied from two to three times per week for up to 35 to 60 minutes per session, for a period of 12 weeks. Study characteristics are shown in Table 3.1.

Table 3.1. Summary of findings

Study (country and design)	**Sample**	**Description of Intervention**	**Outcome measures, follow-up**	**Main findings**
Novakovic et al, 2019[21] (Slovenia) Randomised trial	Total *n* = 29. Patients with diagnosed PAD, Fontaine II classification. Patients with unstable CVD, hospitalisation (< 3 months) and any comorbidities were excluded.	Three groups – moderate-pain SEP, pain-free SEP and control group. 36 sessions – 2/3 times per week for 60 minutes, walking on a treadmill, followed by AR on an exercise bike	PFWD, MWD, ABPI, FMD, biomarkers, HRV and health related QoL, SF-36 questionnaire Measures performed twice at baseline and after the intervention (12 weeks)	Both moderate-pain and pain-free SEP improved walking capacity (Moderate; PFWD p = .005, MWD p = .005) (Pain-Free; PFWD p = .003, AWD p = .003) There were no improvement in PFWD and MWD with the control group The moderate pain SEP significantly improved FMD (p = .002) whereas the pain-free SEP did not. Neither condition significantly changed ABPI/HRV/biomarkers Moderate-pain SEP significantly improved the physical component

				summary but no change in the mental component summary of the SF-36
Mika et al, 2013 [20] (Poland) Randomised trial	Total *n* = 52. Patients with PAD, Fontaine II classification ABPI < 0.9, able to walk 150m without pain, Pharmacological treatment was stable within 6 months and remained unchanged. Patients with CHD < 1 year, unable to walk 3.2 km/h and any comorbidities were excluded.	Two groups – moderate-pain SEP group (n=27) Pain-free SEP group (n=25) 12 weeks, 3 sessions per week Began at 35 minutes, progressively increasing by by 5 min every 2 weeks until 60 mins was completed.	PFWT, MWT, ABPI, FMD, biomarkers Measures performed twice at baseline and after the intervention (12 weeks)	Both moderate-pain and pain-free SEP significantly improved PFWT and MWT(p <0.001) Both groups showed a significant increase in resting and post-exercise FMD (Pain-free; p<0.01, moderate; p<0.001) Significant ABPI change observed only in the moderate training group after 12 weeks (p<0.05) Neither condition significantly changed biomarkers

PAD, peripheral artery disease; CVD, cardiovascular disease; PFWD, pain-free walking distance; MWD, maximal walking distance; AR, Active Recovery; ABPI, ankle-brachial pressure index; FMD, flow mediated dilation; HRV, heart rate variability; QoL, quality of life; CHD, coronary heart disease; PFWT, pain-free walking time; MWT, maximal walking

3.3.2 Risk of Bias

Risk of bias is shown in Figure 3.2 and study quality in Table 3.2. The mean score on the PEDro scale was 6.5. One study stated that outcome assessors were blinded and an intention to treat analysis was not used in either study.

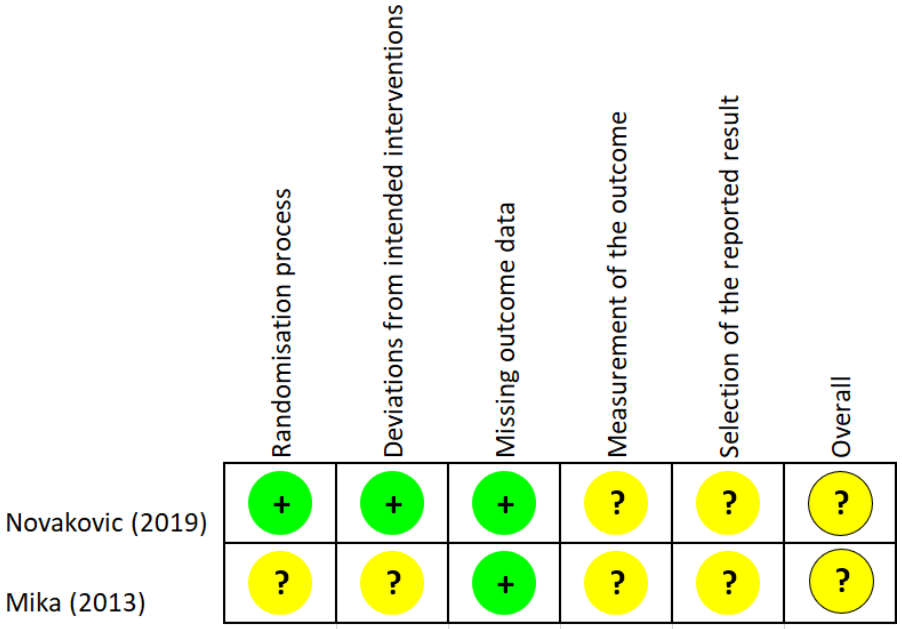


Figure 3.2. Risk of Bias using the Cochrane collaboration tool.

Table 3.2 Quality assessment of included trials according to a Physiotherapy Evidence Database (PEDro Scale)

PEDro Scale	Novakovic (2019)	Mika (2013)
Eligibility criteria specified	1	1
Random Allocation	1	1
Concealed Allocation	1	1
Baseline similarity	1	1
Blinding of all subjects	0	0
Blinding of the therapists	0	0
Blinding of assessors	0	1
Measure of one outcome at least 85% subjects	1	1
Intention to treat analysis used	0	0
Between-group comparison performed	1	1
Measures of variability	1	1
Total	7	8

0, No; 1, yes. Score out of 10

3.3.3 Walking Performance and Adherence

Maximal Walking Distance/Time (MWD/T)

One study reported MWD in meters (Novakovic et al., 2019) and one reported MWT in seconds (Mika et al., 2013). Novakovic et al (2019) found that the moderate-pain SEP group improved by 128% (median change 109m, range 85m to 194m, p <0.005) compared to baseline and the pain-free SEP group improved by 77% (median change 71m, range 92m to 163m, p <0.003) compared to baseline (Novakovic et al., 2019). There was no improvement in MWD for the control group compared to baseline. Mika et al (2013) found that the moderate-pain SEP group improved by 100% (mean change 440 ± 262 seconds, p <0.001, converted to 392 ± 233m) compared to baseline and the pain-free SEP group improved by 98% (mean change 479 ± 333 seconds, p <0.001, converted to 426 ± 296m) compared to baseline (Mika et al., 2013). There were no significant differences between the moderate-pain and pain-free SEP groups in either study, for improvements in MWD (Table 3.1).

Pain Free Walking Distance/Time (PFWD/T)

Novakovic et al (2019) found that PFWD improved by 114% (median change 57m, range 50m to 107m, p <.005) compared to baseline in the moderate-pain SEP group, and by 141% (median change 75m, range 53 to 128m, p <0.003) in the pain-free SEP group compared to baseline (Novakovic et al., 2019). There was no significant improvement in the control group. Mika et al (2013) found comparable results as PFWT improved by 119% (mean change 167 ± 158 seconds, p <0.001, converted to 149 ± 141m) compared to baseline in the moderate-pain SEP group and by 93% in the pain-free SEP group compared to baseline (mean change 157 ± 117 seconds, p <0.001, converted to 140 ± 104m) (Mika et al., 2013). There were no significant differences between the moderate-pain and pain-free SEP groups in either study, for improvements in PFWD (Table 3.1).

3.3.4 Quality of Life

QoL was considered in one study using the short-form 36 (Novakovic et al., 2019). Following the 12-week programme, the moderate-pain SEP group showed significant improvements in the physical component summary (p =0.004) but not the mental component summary. The moderate-pain SEP noted improvements in several physical single domains including physical functioning and bodily pain, whilst the pain-free SEP group had significant improvements in the single domains of physical role and bodily pain (Table 3.1).

3.3.5 Vascular Function

Flow Mediated Dilation

Both trials reported the effect of exercise on FMD, measured at the brachial artery. Novakovic et al (2019) found that the moderate-pain SEP group had a significant improvement in FMD compared to baseline , whilst the pain-free SEP group did not (4.4% to 8.0%; p =0.002 vs pain-free: 4.6% to 6.9%; p =0.066) (Novakovic et al., 2019). Mika et al (2013) found that both SEP groups had a significant improvement in FMD (moderate-pain: 4.59% to 6.27%; p <0.001 vs pain-free: 3.98% to 6.22%; p <0.001; Table 3.1) (Mika et al., 2013).

Ankle Brachial Pressure Index

Novakovic et al (2019) reported that neither SEP group had a significant improvement in ABPI (Novakovic et al., 2019). Mika et al (2013) however, reported a significant improvement in ABPI (0.06 ± 0.12 p <0.05) in the moderate-pain SEP group, but not the pain-free SEP group (Table 3.1) (Mika et al., 2013).

3.3.6 Adherence

Completion of the exercise interventions varied between studies, ranging from 80% (Novakovic et al., 2019) to 87% (Mika et al., 2013). Reasons for non-completion included surgery, ulcers, transportation problems, personal reasons and lost to follow-up. Only one study reported adherence rates which were similar between groups (93% vs 95%; p =0.645) (Novakovic et al., 2019).

3.4 Discussion

Current recommendations state that patients with IC should exercise at moderate to maximal pain to obtain optimal improvements in MWD, though evidence comparing different pain intensities is lacking (NICE, 2012, Riebe et al., 2018, Harwood et al., 2020). We aimed to consider the evidence for exercise prescribed at different levels of claudication pain. Whilst there were only two RCTs identified, the findings indicate that pain-free exercise may be as beneficial as exercise prescribed at moderate levels of claudication pain for improving walking performance. Importantly, neither study included a maximum pain SEP group.

3.4.1 Walking Performance and Adherence

Both studies showed significant improvements in walking performance, there was no statistical difference between training conditions, with similar improvements shown in the pain-free SEP group and the moderate-pain SEP group. This supports previous evidence that pain-free exercise improves walking performance to a similar extent as moderate-pain exercise (Fakhry et al., 2012a, Parmenter et al., 2011). Indeed, prescribing exercise to the point of strong pain has been described as behaviourally counterintuitive (Al-Jundi et al., 2013), however a recent study showed that exercise at a high pain threshold was significantly more effective at improving walking performance versus pain-free exercise (McDermott et al., 2021a). Despite this, no trial has directly compared a pain-free SEP, to a moderate-pain SEP and maximal-pain

SEP (Treat-Jacobson et al., 2019). Consequently, conclusions cannot be drawn as to which method provides the most effective outcomes. Further investigation is therefore warranted, which has the potential to inform future guidelines and clinical practice, as long as it is well-designed and adequately powered.

This further work is important, given that the level of pain prescribed can have a significant impact on patient adherence to SEPs (Abaraogu et al., 2018). Indeed, Harwood et al (2016) highlighted that SEP participation rates remain low, with claudication pain being a contributable factor (Harwood et al., 2016b). Likewise, a recent systematic review (Lin et al., 2019a) found that completion rates were significantly higher in those prescribed low claudication pain exercise (93.4% adherence) versus exercise prescribed to high pain (77.0% adherence). In addition, completion rates were higher in the low pain groups, with patients in these groups being 1.5 times more likely to complete the intervention. This is further supported by a recent study that found significantly lower levels of fidelity to the desired intensity when exercise was prescribed at maximal pain (McDermott et al., 2021a). Therefore, whilst low and moderate pain exercise may elicit similar improvements in walking, low pain exercise could encourage a higher compliance and be more likely to result in long lasting behaviour change.

One major concern with regards to exercise prescription is the inconsistency between guidelines. For instance, UK guidelines state that patients should exercise to the point of maximal pain, whereas the American College of Sports Medicine guidelines advocate exercising to the point of moderate pain (Riebe et al., 2018, NICE, 2012). Moreover, the American Heart Association guidelines state that patients should walk to moderate-maximal pain (Gerhard-Herman et al., 2017) whilst several other guidelines do not provide a specific recommendation (Norgren et al., 2007, Au et al., 2013). Consequently, this could cause

confusion for clinicians and exercise professionals, who may be unsure which guidelines to adhere to, leading to some patients receiving suboptimal care. These findings indicate that a universal and consistent guideline is required for exercise prescription in patients with IC.

3.4.2 Quality of Life

IC is strongly associated with reduced QoL (Raja et al., 2020), however only one study (Novakovic et al., 2019) in this review investigated the impact on QoL as a consequence of exercise prescribed at different pain thresholds. Exercise prescribed to moderate claudication pain led to improvements in the physical component summary of the SF-36, and several single domains including physical functioning and bodily pain, whilst pain-free exercise led to improvements in the single domains of role physical and bodily pain. Neither intervention found improvements in the mental component summary. These results are in agreement with previous studies, by which exercise training improved physical functioning and bodily pain (Guidon and McGee, 2010, Tsai et al., 2002). However there is a general paucity of data considering the effects of exercise training on QoL (Lane et al., 2017b). In addition, it is likely that the trials included in this review would be underpowered to detect meaningful change in QoL. Therefore, adequately powered trials that directly compare a pain-free SEP, a moderate-pain SEP, and a maximal-pain SEP are required to investigate if the level of pain is associated with changes in QoL.

3.4.3 Vascular Function

Increases in FMD may lead to improvements in walking performance (Coutinho et al., 2011). Mika et al (2013) demonstrated an improvement in FMD in both SEP groups (Mika et al., 2013). This supports previous findings which have shown an improvement in FMD following a SEP (Brendle et al., 2001, McDermott et al., 2009), although this finding is not consistent

across different studies (Delaney et al., 2015). In contrast, Novakovic et al (2019) only found a significant improvement in FMD in the moderate-pain SEP group, suggesting changes may be intensity driven, with exercise prescribed at higher pain thresholds providing an adequate stimulus for physiological adaptations (Novakovic et al., 2019). Indeed, this is supported by previous evidence, though even higher intensities (maximal claudication pain) may be needed to consistently elicit positive changes in FMD (Silvestro et al., 2002b). However, exercising to maximal pain may impair vascular function due to an increase oxidative stress which inactivates endothelium derived nitric oxide, thus exacerbating the condition (Silvestro et al., 2002b). However, this effect is relatively short lived with a gradual four-hour post-exercise recovery (Haas et al., 2012). Clearly, there are inconsistencies in the evidence as to which pain threshold is required to promote changes in FMD in patients with IC, with no trial directly comparing a pain-free SEP, a moderate-pain SEP and a maximal-pain SEP. This warrants further investigation.

Novakovic et al (2019) reported no change in ABPI in either SEP group and this finding is supported by a recent Cochrane review which found that SEPs do not elicit changes in ABPI (Novakovic et al., 2019, Lane et al., 2017b). In contrast, Mika et al (2013) found a significant change in ABPI in the moderate training group, but not the pain-free group, with the authors suggesting that the ischaemic stimulus from this level of pain was a contributing factor (Mika et al., 2013). However, there was a lack of correlation between walking performance and ABPI, increasing the possibility of this finding being due to a type I error.

3.5 Limitations

This review is not without limitations. Firstly, we were unable to directly compare pain-free and moderate exercise with exercise prescribed at a maximal pain threshold. Secondly, both

studies had an unclear risk of bias for a number of criteria and had small sample sizes, with only one adequately powered to detect change in MWD (Novakovic et al., 2019). Thirdly, both studies used treadmill walking as the form of exercise, meaning the results cannot be generalised to different forms of SEP such as a circuit format (Harwood et al., 2019). Finally, the studies adopted different claudication pain scales, as such the number that represents moderate (3/5 vs. 4/5) or severe (4/5 vs. 5/5) differs. Future studies should familiarise patients with the pain scale to enable accurate reporting.

3.6 Conclusions

Evidence suggests that pain-free SEPs and moderate-pain SEPs elicit similar improvements in walking performance for patients with IC. However, no trial has directly compared the level of pain at different thresholds; pain-free; moderate intensity; maximal pain; despite a maximal pain prescription being recommended in most clinical guidelines. Adequately powered RCTs are therefore required to compare all three pain thresholds, which may affect patient adherence to SEPs, and directly impact upon future exercise training guidelines in patients with IC.

3.7 Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Chapter 4. Establishing a Multi-Centre SEP for Patients with Peripheral Artery Disease in the Preston Network

4.1 Background

Initially, patients with peripheral artery disease (PAD) were advised to "go home and walk" as treatment for their intermittent claudication (IC). However, established randomised control trial (RCT) evidence began to emerge which supported the effectiveness of supervised exercise programme (SEP) for patients with IC. Such benefits included an increase in walking distance, physical function, balance and quality of life (Gardner et al., 2011, Bendermacher et al., 2007, McDermott et al., 2010). Therefore, in August 2012 the National Institute for Health and Care Excellence (NICE) recommended SEPs as the first line of treatment for patients with IC (NICE, 2012). The guidelines suggest 2-hours of exercise a week for a 3-month period encouraging patients to exercise to a point of maximal pain.

Although the NICE guidelines were introduced, a UK international survey in 2012 highlighted the lack of implementation for SEPs. Of the 378 responses amongst vascular surgeons using an online questionnaire, only 30.4% of the participants had access to a SEP (Makris et al., 2012). Despite the new recommendations, access remained similar to a survey in 2009 which showed that only 24% of British surgeons had access to a SEP (Shalhoub et al., 2009). Furthermore, another survey in 2017 suggested access to SEPs remained highly variable across the UK. Of the 89 responses received, only 41% of vascular surgeons had access to a SEP. Even though this is a 17% increase compared to the situation in 2009, local SEP access and provision still remained remarkably low (Harwood et al., 2017c). More recently, a survey with 48 vascular units found only 23 (48%) had access to an exercise programme. Of the 23, only 5 were meeting the dose recommendations in the UK NICE guidelines (Harwood et al., 2022).

Furthermore, the survey highlighted that although clinicians found them slightly to very important, they did not have the support from commissioning/funding bodies to develop them. Despite them being the recommended first line of treatment.

Supporting this, the latest report by the National Vascular Registry (NVR) showed that of the established 67 vascular units in the UK only 25 units (37%) have a pathway that included a SEP. The NVR was commissioned in 2013 by the Healthcare Quality Improvement Partnership as part of the National Clinical Audit and Patient Outcomes Programme. The aim is to measure the quality and outcomes of care for adult patients who undergo major vascular procedures in NHS hospitals, and to support vascular services to improve the quality of care for these patients (Waton S, 2022). This report along with the above survey by (Harwood et al., 2017c) highlights how patients are still not receiving access to the recommended first line of treatment (NICE, 2012).

Despite various recommendations from governing bodies, SEPs remain largely unavailable amongst the UK. Hence, patients may require surgery as an alternative treatment. In 2021, NHS Trusts submitted 5,817 (3,149 elective and 2,668 non-elective) bypass procedures to the NVR and 6,509 endovascular procedures (4,297 elective and 2,212 non-elective). However, of the patients who undergo surgery, it is understood the intervention and revascularisation has poor outcome at a 5-year follow-up. A recent study evaluated the association of early peripheral vascular intervention (PVI) for claudication with subsequent interventions (Sorber et al., 2023). Of the 187,442 patients identified with claudication during the study period, 6069 patients identified had undergone early PVI (within 6 months of a claudication diagnosis). After a 4.39-year follow-up, 22.5% of early PVI patients had undergone late PVI compared to 3.6% of those without early PVI ($P < 0.001$) (Sorber et al., 2023). This emphasises the importance of

providing access to a SEP as the first line of treatment to avoid patients having repeat and somewhat unsuccessful surgery.

If PAD remains untreated, it can possibly deteriorate and progress into critical limb threatening ischaemia (CLTI). A previous study of a US Medicare population found that 15% of patients presenting with PAD had CLTI (Nehler et al., 2014b). Of these patients, around 5-10% per year are at risk of having major amputation (Golledge, 2022). This emphasises the severity of PAD if left untreated and the burden on the NHS (Waton S, 2022).

4.2 Supervised Exercise Programme in the North-West

The North-West of England was amongst the 63% of vascular units in the UK having no referral pathway. Further, Lancashire Teaching Hospitals (Preston and Chorley) were in the top ten NHS trusts for the high volume of procedures in 2021. Given that there was no referral pathway in an area of high incidence, a SEP for patients with PAD was co-designed and implemented at Heartbeat Northwest Cardiac Care with referrals from Lancashire Teaching Hospitals NHS Foundation Trust (LTHFT).

As explained in the previous chapter, the optimal level of claudication pain for patients with IC is disputed within guidelines (NICE, 2012, Riebe et al., 2018, Gerhard-Herman et al., 2017). Therefore, the newly established SEP would be the centre for a RCT (Birkett et al., 2022a) to establish which level of claudication pain is optimal for patients with intermittent claudication. Patients would be randomised to either pain-free, moderate-pain or maximal claudication pain for a 6-month period and measured on functional outcomes and quality of life.

Heartbeat is a well-established cardiovascular prevention and rehabilitation charity in the Northwest providing services for 950 people weekly and has been running for over 40 years. Receiving PAD specific referrals would be a new pathway, therefore, a multidisciplinary team was created which included the Chief Executive Officer of Heartbeat, British Association of Cardiac Prevention and Rehabilitation Instructors, the vascular nurses and the vascular consultant at LTHFT, to design and implement a programme. The process and timeline of events which led to the development and initiation of the new SEP are outlined below (figure 4.1).

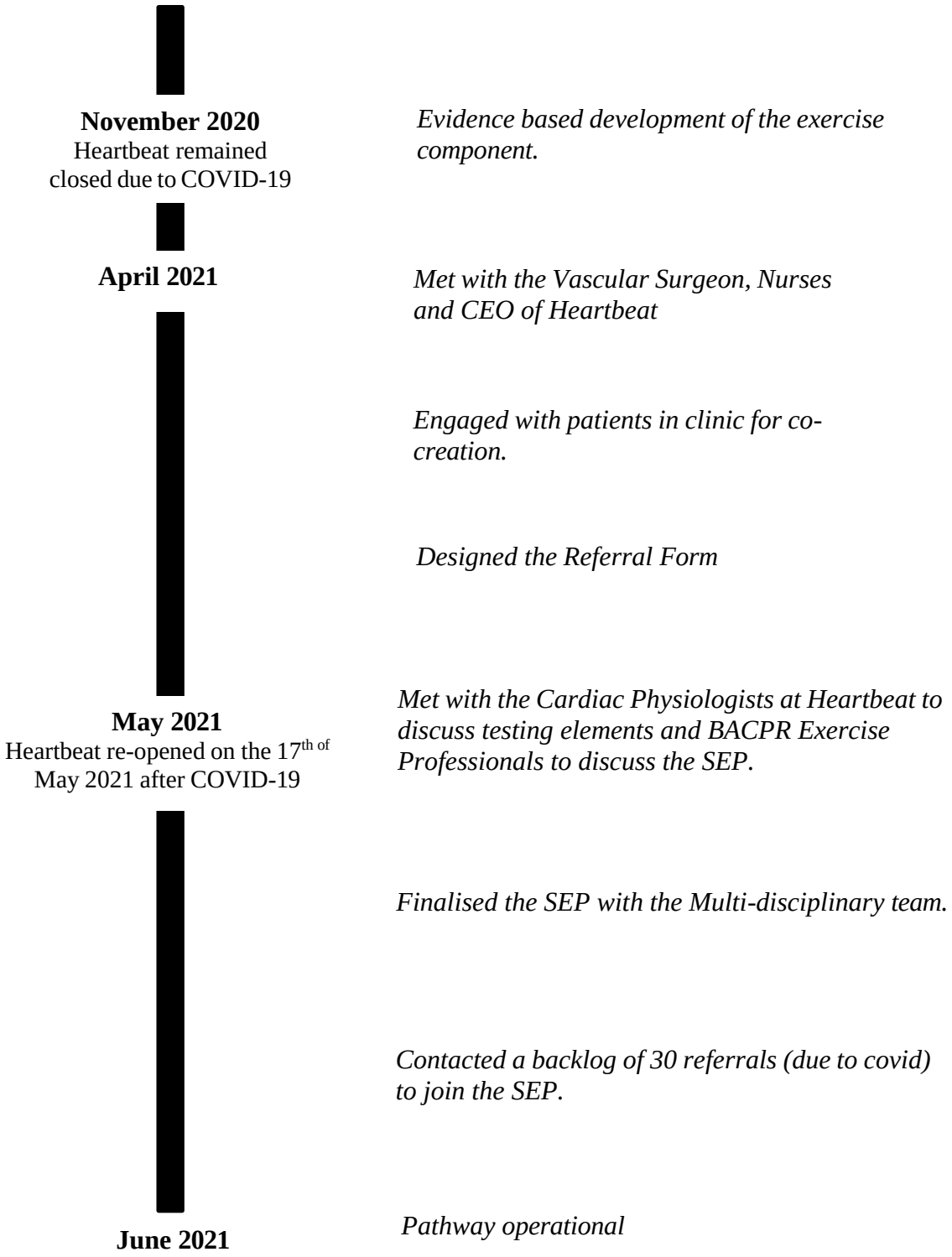


Figure 4.1. The Timeline of Developing a SEP

Below is a detailed explanation of the development of the SEP.

4.3 Evidence based Development of The Exercise Component

After reviewing the evidence of the systematic review in chapter 3, a SEP was identified which considered various levels of claudication pain was necessary to find the optimal level of exercise intensity. Though, Heartbeat, the centre for the RCT, did not facilitate or have any existing knowledge on exercise prescription for patients with PAD. Therefore, a specific weight-bearing circuit for patients with IC which would bring on their claudication pain and facilitate the specific research question was proposed (Harwood et al., 2019, Caldow et al., 2019b) This 6-station exercise circuit is shown in figure 4.2.

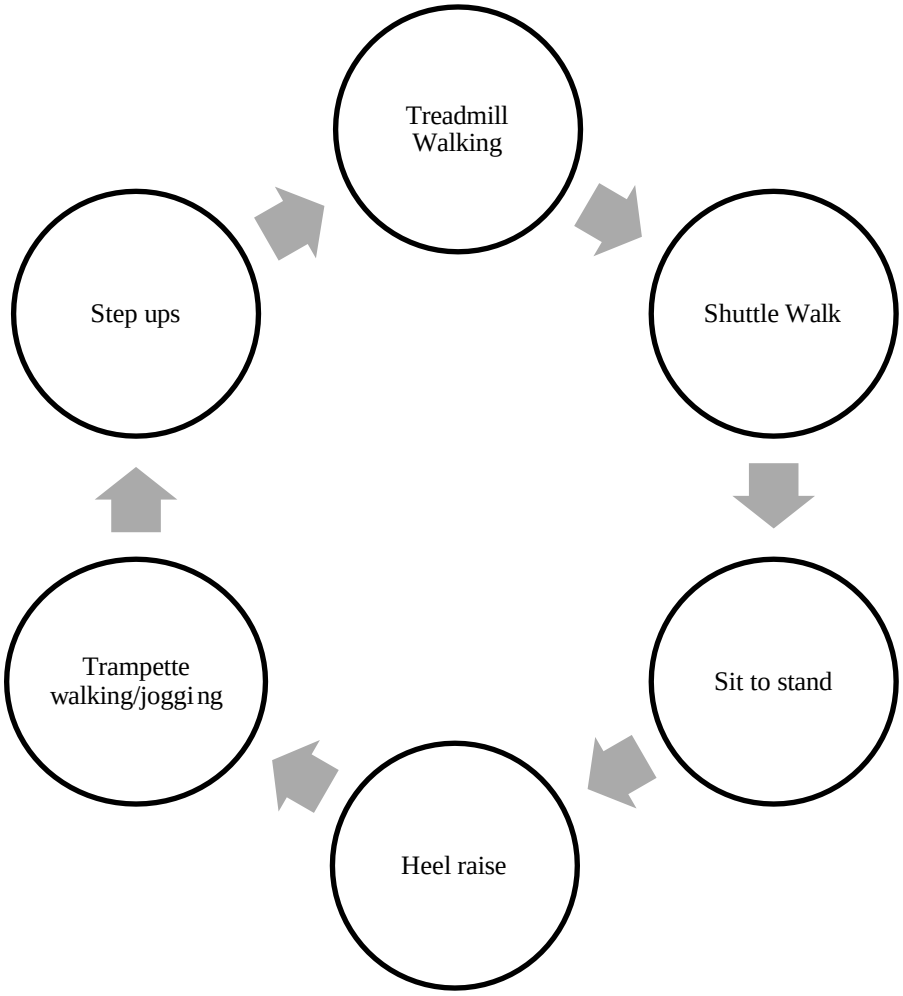


Figure 4.2. A 6-station exercise circuit.
Patients started off at one of the stations above and worked to the desired level of claudication pain they had been randomised to. Patients then rested and moved onto another station once the pain had subsided. The stations could be completed in any order. If the patient completed all stations before the end of the exercise session, they could do them again.

4.4 Meeting with the Vascular Surgeon, Nurses and CEO of Heartbeat

Following this, it was arranged that the research team would observe the vascular nurses to understand their current assessment process for PAD patients. This included PAD patients with a differing severity of disease for example leg ulcers and gangrene. During this time, the researcher also gained an understanding of the pre-operative assessment process. This led to a professional working relationship and the discussion of the new referral pathway to a third sector organisation which was a new initiative for that team.

Once the pathway was agreed the next step was the transfer of patient identifiable information, which had to consider the General Data Protection Regulation 2018. This required a copy of the referral form to be discussed at their Safety and Quality Governance meeting. At the meeting it was approved by the surgical directorate governance team. Alongside this, the main researcher had to complete their research passport, prior to commencing this RCT, which was submitted to the Head of Research Development at LTHFT for approval. Both approvals allowed the research to commence. The agreement was that the referral information would be sent from the vascular nurse's generic email to a generic email at Heartbeat. These conversations encouraging and the nurses were pleased to have a pathway to refer these patients especially considering long waiting times with the NHS.

Following the agreement for referrals it was important to ascertain the support of the CEO of Heartbeat regarding the initiation of the project. It was essential to discuss details of the SEP including class timings, equipment and availability of a BACPR Instructor to lead the exercise classes. An understanding of the main differences from the cardiac rehabilitation classes needed to be shared, for example the need for chairs in the gym to give the patients time to rest following leg pain. She confirmed that the different approach would be accommodated, and we agreed to undertake the classes on two days per week which would allow the availability of an instructor (Tuesday & Thursday 12.15 – 13.15pm).

4.5 Engaged with Patients in Clinic for Co-Creation

It was important to engage with the patients prior to the SEP commencing. Therefore, the researcher took the opportunity to speak to patients whilst visiting the vascular clinic and gather their views as it was important to assess the patient's perspective. During this time it was explained by the researcher why the research was important and the goal for their clinical population. The informal discussions were useful to gain an insight into the thoughts and feelings of patients living with the disease. Insight was gained into PAD caused an impairment to the individual's quality of life and even though the researcher sensed caution, they would be willing to take part in a SEP to try and improve their symptoms. To promote the SEP to patients the reseacher planned to make posters of patient feedback (chapter 7, figures 7.2 – 7.5) and a video to give small snapshots of how the class is delivered.

The next step was to gather the opinions of the professional team on the SEP and how to utilise the hour to achieve the best outcome for the patient, guiding the team to understand the need for specific weight bearing exercises. The design of the programme was discussed and they all agreed that the right proposal was in place to commence the classes.

4.6 Met with the Cardiac Physiologists at Heartbeat to discuss testing elements and BACPR Exercise Professionals to discuss the SEP.

It was important that I met with the BACPR instructors who would be instructing the exercise class. During this meeting, the trial methodology, the rationale and why the research needed to be undertaken was discussed. In the meeting also reviewed the layout of the circuit and the differences from the cardiac classes for example the need for chairs and the different exercise stations. It was important for them to understand this, as the trial included randomising patients to maximal pain, moderate pain and pain-free. Following this information there was a lot of apprehension due to the inequality of the exercise programme. They felt all patients should undertake the same level of exercise programme. It was reaffirmed that this was a research trial, and a randomised approach was necessary. By the conclusion of the meeting the instructors were fully onboard and excited to begin as they felt this was a different challenge.

The cardiac physiologists were an important part of the testing process, and it was important to engage their support as it would be a change to their normal testing protocol (Bruce Protocol). The testing required the Gardner-Skinner protocol, a specific treadmill test for patients with IC (Gardner et al., 1991c). For this professional group it is important when introducing new procedures to provide a reliable evidence base. The Gardner-Skinner protocol has a constant speed of 3kph and an increase of 2% every 2 minute which was programmed into the testing treadmill. A meta regression analysis confirmed the reliability of the Gardner- Skinner treadmill protocol for maximal walking distance in eight PAD studies (Nicolaï et al., 2009b). Furthermore, a clinical trial with 330 patients confirmed the reproducibility of the graded exercise test for maximal and pain-free walking distance (Labs et al., 1999). Following this evidence being presented, the cardiac physiologists were supportive of the new testing.

Following their request, it was agreed was that all patients would be fitted with an ECG whilst taking part in the treadmill test to abide by the risk assessment outlined in Heartbeats standard operating procedure.

In the initial stages of receiving the referral forms created by the registered nurses, information was missing, so a meeting was arranged to discuss minor changes to make the form more accurate with clinical information. For example, the importance to distinguish whether ankle brachial pressure index (ABPI) or toe brachial pressure index was being measured in the vascular assessment. Although all patients were offered the opportunity to take part in the SEP, only patients with ABPI could take part in the research trial. The importance of making sure there was a contact number on the referral form so the researcher could contact the patient having received the referral form was also emphasised. This meeting played a significant role in improving the quality of the referral pathway.

4.7 Finalised the SEP with the Multi-disciplinary team & contacted a backlog of 30 referrals (due to COVID) to join the SEP

In the early stages of initiating the SEP the researcher liaised with all members of the MDT to ensure that everyone was familiar with the pathway and the SEP. It is important to understand that much of the development of the pathway was undertaken during 2020/21 when COVID-19 restrictions were in place. Heartbeat had a delayed opening following the relaxation of the restrictions due to reducing the size of classes. This led to a backlog of over 30 referrals sent by the vascular nurses which impacted on the commencement of the SEP. A significant amount of time was spent ringing up each individual patient asking if they would like to take part in a

SEP explaining the benefits to their health. Many were apprehensive due to the COVID -19 restrictions.

4.8 Pathway Operational

After a long process designing, developing and implementing the SEP, we finally got the first couple of patients assessed and commenced the SEP. As the SEP progressed, we opened a second class at Preston and one at an external site in Chorley. As a novice researcher it was great to have set up a new referral pathway and SEP.

Chapter 5: The Effects of Exercise Prescribed at Different Levels of Claudication Pain on Walking Performance in Patients with Intermittent Claudication: A Randomised Control Trial

5.1 Introduction

Peripheral artery disease (PAD) is a chronic disease characterised by atherosclerotic lesions of the arteries in the lower limbs, resulting in a reduction of blood flow (Hiatt, 2001). As outlined in chapter 2, globally it is estimated 236 million people are living with PAD which increased by 24% from 2010 to 2015 (Song et al., 2019). The presentation and disease severity of PAD varies from mild to severe. A classic symptom of PAD is IC, characterised by an ischemic muscle pain which is precipitated on exertion and relieved at rest (Aboyans et al., 2018).

As mentioned in chapter 6, exercise therapy is the first line of treatment for patients with PAD, as recommend in national and international guidelines. Currently, patients are encouraged to take part in two hours of supervised exercise per week, working to the point of maximum claudication pain (Aboyans et al., 2018, NICE, 2012). It is well supported that exercise therapy plays a significant role in treatment for IC, whilst being cost-effective and costing less than a tenth of surgery (Lane et al., 2017b). Although, there remains inconsistencies between guidelines as to the optimal level of claudication pain.

However, as discussed in chapter 4, less than half of vascular units in the UK have access to a SEP and even when a programme is available, adherence rates are still low (Harwood et al., 2016b, Harwood et al., 2016a). Indeed, a lack of motivation due to the severity of claudication pain has been cited as a contributing barrier to withdrawing or not taking part in a SEP (Harwood et al., 2016b). Furthermore, research has shown exercise-induced pain and

prescribing exercise at a higher level of claudication pain can influence completion rates (Lin et al., 2019a, Barbosa et al., 2015b). When exercise is prescribed at higher levels of claudication pain, completion rates are lower, yet the current guidelines still advocate exercising to the point of maximal pain (McDermott et al., 2021a).

In chapter 3, the systematic review found pain-free exercise as beneficial as moderate pain (Seed et al., 2021). Similarly, previous research suggests mild or pain-free exercise improves walking ability (Parmenter et al., 2011, Mika et al., 2013, Fakhry et al., 2012a). Considering all the evidence, it remains unclear which level of claudication pain is optimal for improving functional outcomes whilst increasing uptake and adherence. Supporting this, a recent statement from the American Heart Association suggested there needed to be a randomised control trial (RCT) investigating the effects of exercise prescribed at the differing levels of claudication pain (Treat-Jacobson et al., 2019).

5.2 Aim

There are inconsistencies within guidelines as to what is the optimal level of claudication pain to exercise too. In addition, the systematic review performed in chapter three highlighted that no study has compared all three levels of claudication pain on functional outcomes (PF, MOD-P and MAX-P). Therefore, the aim of this study was to directly compare the effects of exercise prescribed at different levels of claudication (pain-free [PF], moderate pain [MOD-P] and maximal pain [MAX-P]) on clinically relevant functional outcomes.

5.3 Methods

5.3.1 Trial Setting

Data collection took place at Heartbeat NWCC charity programme. As discussed in chapter 4, a new referral pathway and SEP was set up to facilitate patients with IC. Originally patients attended the SEP exclusively at the Preston site, however as the number referrals grew, classes opened across Lancashire including Clayton Green (Chorley).

5.3.2 Participants

Ethical approval for this randomised controlled trial was approved by the NHS Northwest–Preston Research Ethics Committee (20/NW/0401) on 10 December 2020 and the University of Central Lancashire granted approval at the HEALTH Ethics Review in March 2021 (reference number: HEALTH0162) (appendix A). Participant recruitment commenced in June 2021 and will remain ongoing to achieve the full sample size of 57 participants. For the purpose of this doctoral thesis, data collection was ceased on 1st August 2023 and a total of 30 participants were recruited and randomised to 24-weeks of a SEP working to either pain-free, moderate-pain or maximal claudication pain.

5.3.3 Participant Eligibility

Participants recently diagnosed with IC by a vascular surgeon or vascular specialist nurse and referred for our SEP were appropriate to enroll on this study. The study inclusion and exclusion criteria are shown in table 5.1.

Table 5.1. Study Inclusion and Exclusion Criteria

Inclusion	Exclusion
Resting ankle brachial pressure index (ABPI) <0.9	Those who have critical limb threatening ischemia (rest pain and/or tissue loss)
Able to walk unaided	Unable to provide consent

>18 years old	Those undergoing active cancer treatment
English speaking and able to follow exercise instructions	Those presenting with any significant comorbidities or contraindications to exercise testing or training in accordance to the American College of Sports Medicine
Able to provide informed consent	Unstable/uncontrolled coronary heart disease

5.3.4 Withdrawal of Participation

Participants were free to withdraw at any time and did not have to give a reason for doing so. If the participant exhibited any of the exclusion criteria or lost the capacity to consent after enrolment on the study, they were withdrawn.

5.4 Outcome Measures

The primary outcome was to assess the changes in maximal walking distance at 12 and 24 weeks. The secondary outcomes were to access pain-free walking distance, acceptability, enjoyment of the exercise intervention and barriers and quality of life.

5.5 Study Design

Once participants were referred, they were contacted via phone call by a cardiac physiologist or a member of the research team which included verbal information of the SEP and a brief discussion of the study. Eligible participants were offered the opportunity to participate in the study and received a participant information sheet (PIS) (appendix B), sent via the post, detailing the study aims and testing procedures. A subsequent phone call (at least 48 hours later) from the research team confirmed those who wished to participate and answered any

outstanding questions they may have regarding the study procedure. Participants who enrolled in the study were then invited to Heartbeat NWCC to undergo their baseline assessment. Participants were asked to wear suitable comfortable clothing, bring water and a list of up-to-date medication. They were then randomly allocated 24 weeks of PF, MOD-P or MAX -P, which was generated by the trial statistician and concealed in an opaque envelope for each participant. Outcomes were measured at baseline (visit 1), 12 weeks (visit 2) and at 24 weeks (visit 3). Visit two was to allow for the results to be comparable to the current NICE guidelines of 12 weeks (NICE, 2012). Study flow chart is represented in figure 5.1.

5.5.1 Randomisation

Each participant received a concealed opaque envelope which contained the level of claudication pain they were going to be randomised to for the research trial (PF, MOD-P or MAX-P). The random allocation sequence was generated by the trial statistician using a computer program random number generator. All measures completed at baseline were repeated at 12 and 24 weeks.

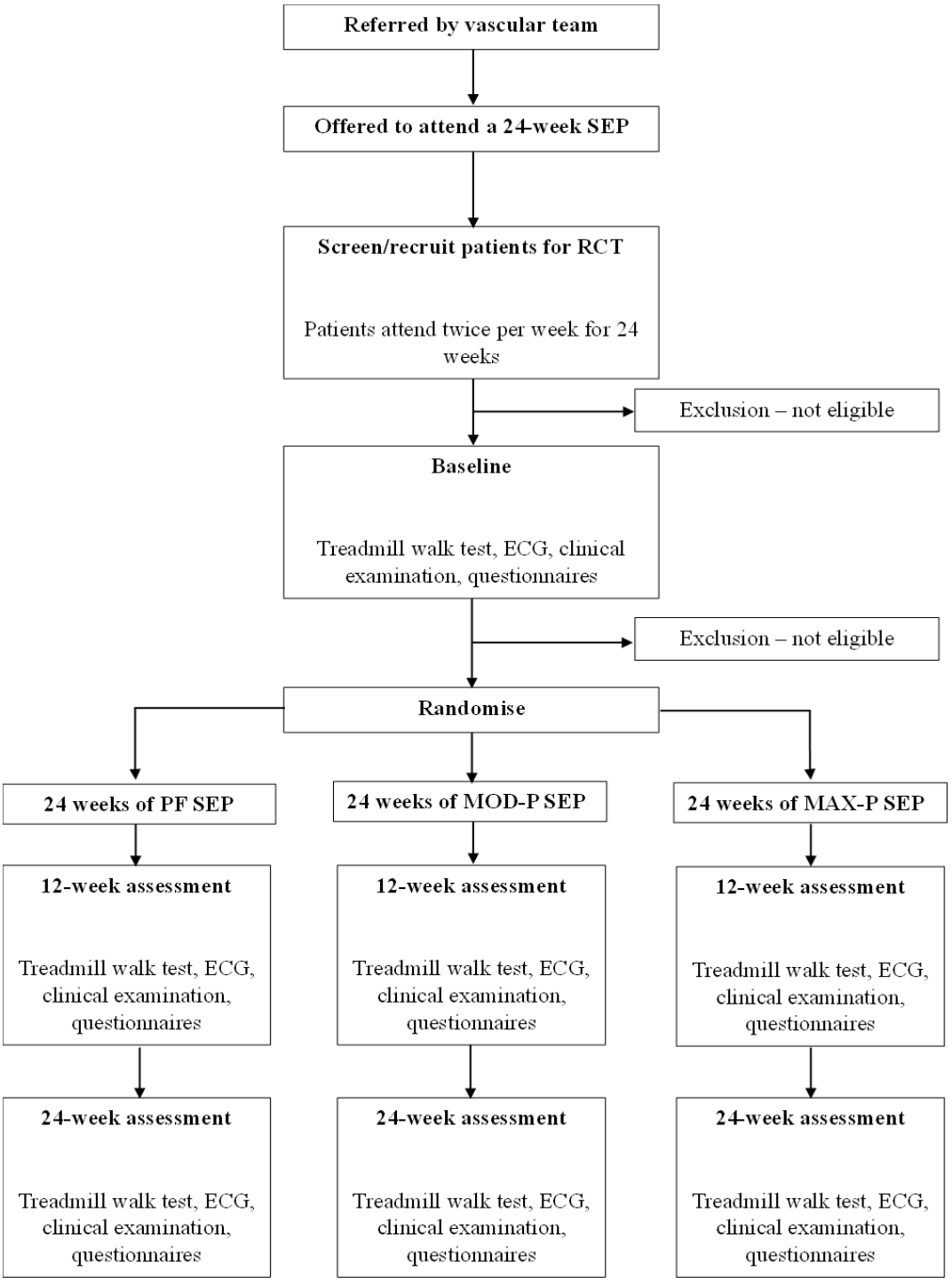


Figure 5.1. Study Flowchart

5.6 Baseline Assessment

5.6.1 Clinical Examination

At the baseline assessment, participants were greeted by the researcher and informed consent was obtained (appendix C). Then participants were asked questions regarding their symptoms of IC, past medical history and medications which were noted in their case-report form (appendix D). Height was recorded to the nearest 0.1cm using a free-standing stadiometer (Seca, Vogel & Halke Hamburg) head level and heels together. Body mass (kg) was measured to one decimal point using scales (Seca, Vogel & Halke Hamburg). Body mass index (BMI) was calculated by dividing body weight in (kg) by height in meters squared and presented as kg/m^2. Waist and hip circumference were measured using a tape measure (XENICAL orlistat). Waist to hip ratio was measured by dividing the measurement of the waist by the measurement of the hip. Resting blood pressure was measured after 15 minutes of rest (supine) using an (SunTech Tango M2) blood pressure monitor. Resting heart rate was measured via a 12-lead ECG using the Welch Allyn CardioPerfect software.

5.6.2 Gardner-Skinner Treadmill Test

Each participant completed the graded Gardner-Skinner treadmill walking test which was performed by the researcher and the cardiac physiologist. This test remains at a constant speed of 3.2km/hr and the incline starts at 0% and increases 2% every 2 minutes (Gardner et al., 1991a). The test has been found reliable and superior in assessing PAD severity (Labs et al., 1999, Brass et al., 2007). The test followed the requirements for exercise testing as explained in chapter 2, table 2.5 (page 48). During the test participants were fitted with an ECG to adhere to the risk assessment outlined in Heartbeats standard operating procedure. Participants were asked to report their level of claudication pain using the Intermittent Claudication Rating Scale (figure 5.2, page 125) which was fixed on the treadmill display. Participants were asked to report when they first felt claudication pain in their legs (level 1 on the pain scale) this was recorded as their pain-free walking time. Following this, participants continued walking until

they could not walk any further (level 4 on the pain scale), this was recorded as their maximal walking time. These times were then converted into distance using the equation: distance = speed x time.

E.g. Treadmill Speed: 3.2km/hr = 0.88889m/s

Maximal walking time: 2.35 mins = 155 seconds

Distance = Speed x Time

Distance = 0.88889 x 155

Distance = 138m

5.6.3 Quality of life Questionnaires

Following this, participants were given several quality of life (QoL) questionnaires to complete. The Short-Form-36 and the EuroQol-5 (EQ-5D) Dimension Questionnaire were to assess generic factors. The Walking Impairment Questionnaire (WIQ) assessed the perceived impact of claudication and the Kings College vascular QoL, a 24-item questionnaire assessed five domains barriers (pain, symptoms, activities, social and emotional) (Morgan et al., 2001). A questionnaire assessing personal and environmental factors to physical activity for participants with PAD was given based on a study by (Barbosa et al., 2015b). This was a five-point ordinal scale (never, seldom, sometimes, frequently, always) used to access the limiting factor of each barrier (Cornelis et al., 2018).

5.7 Trial Intervention

As mentioned in chapter 4, the SEP consisted of a validated circuit designed to elicit IC pain (Caldow et al., 2019a, Harwood et al., 2019) (Figure 6.2, page 119). The duration of the SEP was 60 minutes, including a 10 minute warm-up and cooldown (ACPICR, 2015). Participants exercised at each station until they reached the desired level of claudication pain within 3-5

minutes. In the pain-free group, the pain may have occurred earlier (e.g., 30 seconds). Following this, participants were advised to rest either standing or seated until the pain subsided to zero. They then moved onto the next station. The 0-4 scale to rate claudication pain was adopted (Figure 5.2). Participants in the PF group ceased exercise at the onset of claudication (1 on the rating scale), the MOD-P group stopped once moderate pain was achieved (2 on the rating scale) and MAX-P group until maximal pain was achieved (4 on the rating scale). The SEP was run by a British Association of Cardiac Prevention and Rehabilitation Exercise Professional as discussed earlier in chapter 4. Participants were regarded a completer if they had achieved a minimum of 80% of sessions (38 of 48). Following completion of the SEP, semi-structured interviews were conducted to coincide with the 24-week assessment (chapter 7).

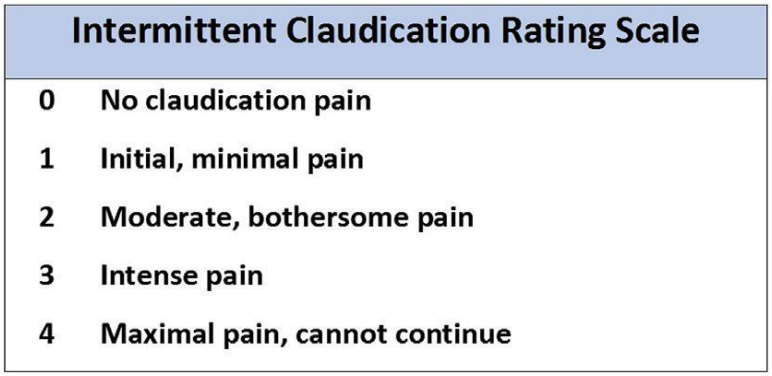


Figure 5.2. The Intermittent Claudication rating scale which will be used by the participants to grade claudication pain during the exercise intervention. Taken from ACCPVR Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs (2013)

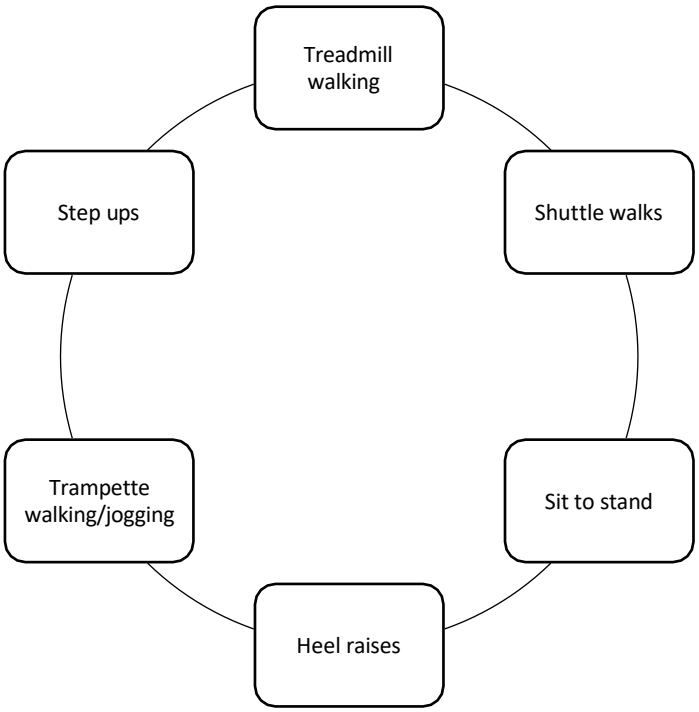


Figure 5.3. Visual representation of the PAD specific exercise circuit

5.8 Statistics and Data Analysis

All continuous experimental variables are presented as means and standard deviations. All exploratory analysis of the intervention-based data were performed on an intention to treat basis. To determine the effects of the intervention on all the outcome measures, differences in the changes from baseline to 12 weeks, baseline to 24 weeks and 12 to 24 weeks between the three groups were examined using linear mixed effect models with group modelled as a fixed factor and random intercepts by participants adopted. For linear mixed effect models, the presented data is the mean difference *(b)* between groups in change from baseline to 12 weeks, baseline to 24 weeks and 12 to 24 weeks and 95% confidence intervals are presented.

Effect sizes were calculated for the changes from baseline to 12 weeks, 12 weeks and 24 weeks and baseline to 24 weeks between the two groups, using Cohen's d, in accordance with

McGough, & Faraone, Cohen's d values were interpreted as 0.2=small, 0.5=medium, and 0.8=large (Cohen, 1977). A negative cohen's d value shows the direction of the change score between groups. The change scores are negative when the reductions in each parameter are greater at 12/24 weeks compared to baseline. Data was inputted into SPSS by a single investigator (SS) who had overall responsibility for the data quality. All analyses were conducted using SPSS v28 (IBM, SPSS), and statistical significance for all analyses was accepted as the $P \leq 0.05$ level. All data is summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline (Moher et al., 2010).

As the trial is not yet fully recruited any inferential statistics undertaken at this stage should be considered exploratory.

5.9 Results

5.9.1 Participant Recruitment

Between June 2021 and May 2023, 105 participants with IC were referred to the SEP at Heartbeat and screened for the study. Of these, 86% (90/105) were eligible to take part in the SEP and 33% consented to participate (30/90) in the research trial (Figure 6.4). The main reasons for exclusion were participants presenting with significant co-morbidities to exercise such as chronic obstructive pulmonary disease, undergoing cancer treatment and being unable to measure ABPI. Out of the 67% (60/90) who declined the SEP, 22 participants still wanted to take part in the SEP but did not want to take part in the research. The most common reason for declining the research trial included commitment and apprehension towards a 24-week programme. Therefore although there was only 30 patients who took part in the research trial the SEP had around 52 patients enrolled to take part in exercise twice a week.

Of the 30 participants, ten participants completed at least one session but withdrew or data collection was stopped before the 12-week assessment. Three participants withdrew due to acute illness (unrelated to the study), three participants withdrew due to developing back pain which was possibly related to study intervention (or existing medical problems) and two participants withdrew due to mental unrelated health. Following the 12-week assessment, two participants were unable to complete the intervention, their 12-week data was used in the statistical analysis. One participant was diagnosed with stage four cancer, one participant withdrew with mental health. A further two participants had their final assessment booked after the data cut-off date for this thesis. As such 16 participants (53%) completed the SEP. Of these, 15 completed the follow-up qualitative interview (Figure 5.4).

5.9.2 Participant Characteristics

Baseline characteristics of all recruited participants (n = 30) are shown in table in table 5.2. Patient medication classifications are shown in table 5.3 and risk factors and the presentation of symptoms in table 5.4.

Table 5.2. Baseline Characteristics

Variables	**Pain-Free (n = 9)**	**Moderate-Pain (n = 13)**	**Maximal Pain (n = 8)**
Males (% sex)	7 (78)	10 (77)	4 (50)
Age (years)	74 ± 4.8	70 ± 7.7	66 ± 7.6
Height (cm)	168 ± 5.3	171.7 ± 9.1	165.9 ± 6.3
Weight (kg)	81 ± 9.5	81.5 ± 14.7	82.3 ± 22.5
BMI (kg/m^2)	28.9 ± 3.21	27.6 ± 4.5	29.7 ± 7.5
Waist-to-hip ratio	1.0 ± .04	1.0 ± .07	0.9 ± 0.1
Systolic Blood Pressure (mmHg)	157.7 ± 15.2	163 ± 14.9	152 ± 17.0
Diastolic Blood Pressure	85.7 ± 8.5	87.6 ± 10.7	84.4 ± 11.1
Resting heart rate (bpm)	69.6 ± 27.7	70.5 ± 14.4	76.0 ± 20.2
ABPI R Leg	0.5 ± 0.2	0.7 ± 0.3	0.7 ± 0.2
ABPI L Leg	0.5 ± 0.3	0.7 ± 0.3	0.7 ± 0.2

cm = centimetres; kg = kilogram; BMI = body mass index; mmHg = millimetres of mercury; bpm = beats per minutes; APBI = ankle brachial pressure index; R = right; L = left

Table 5.3. Participant Medications Classifications

Medications	**Pain-Free (n = 9)**	**Moderate-Pain (n = 13)**	**Maximal Pain (n = 8)**
Aspirin (%)	n=3 (33)	n=6 (46)	n=4 (50)
Antiplatelet (%)	n=7 (78)	n=8 (62)	n=5 (63)
Diuretic (%)	n=4 (44)	n=0 (0)	n=2 (25)
ACE Inhibitor (%)	n=3 (33)	n=3 (23)	n=2 (25)
Statin (%)	n=8 (89)	n=12 (92)	n=7 (88)
Calcium Channel Blocker (%)	n=6 (67)	n=2 (15)	n=3 (38)
Naftidrofuryl Oxalate (%)	n=1 (11)	n=2 (15)	n=2 (25)
Beta Blocker (%)	n=3 (33)	n=4 (31)	n=3 (38)
Post-Menopausal (%)	n=0 (0)	n=0 (0)	n=0 (0)

ACE = Angiotensin-converting enzyme

Table 5.4. Risk Factors and Symptoms

Risk Factors	**Pain-Free (n = 9)**	**Moderate-Pain (n = 13)**	**Maximal Pain (n = 8)**
Non-smoker (%)	n=1 (11)	n=2 (15)	n=1 (13)
Current smoker (%)	n=1 (11)	n=2 (15)	n=0 (0)
Ex-smoker (%)	n=7 (78)	n=9 (70)	n=7 (87)
Hypertension (%)	n=8 (89)	n=8 (53)	n=4 (50)
Diabetic Type I (%)	n=0 (0)	n=1 (7)	n=1 (13)
Diabetic Type II (%)	n=5 (56)	n=11 (85)	n=3 (38)
Hyperlipidemia (%)	n=7 (78)	n=9 (69)	n=5 (63)
Coronary Heart Disease (%)	n=4 (44)	n=3 (23)	n=1 (13)
Family History of PAD (%)	n=3 (33)	n=7 (54)	n=4 (50)
Symptoms			
Weakness in the leg/feet	n=0 (0)	n=6 (46)	n=3 (38)
Hair loss	n=0 (0)	n=1 (8)	n=1 (13)
Ingrowing Toenail	n=1 (11)	n=3 (23)	n=0 (0)

PAD = peripheral artery disease

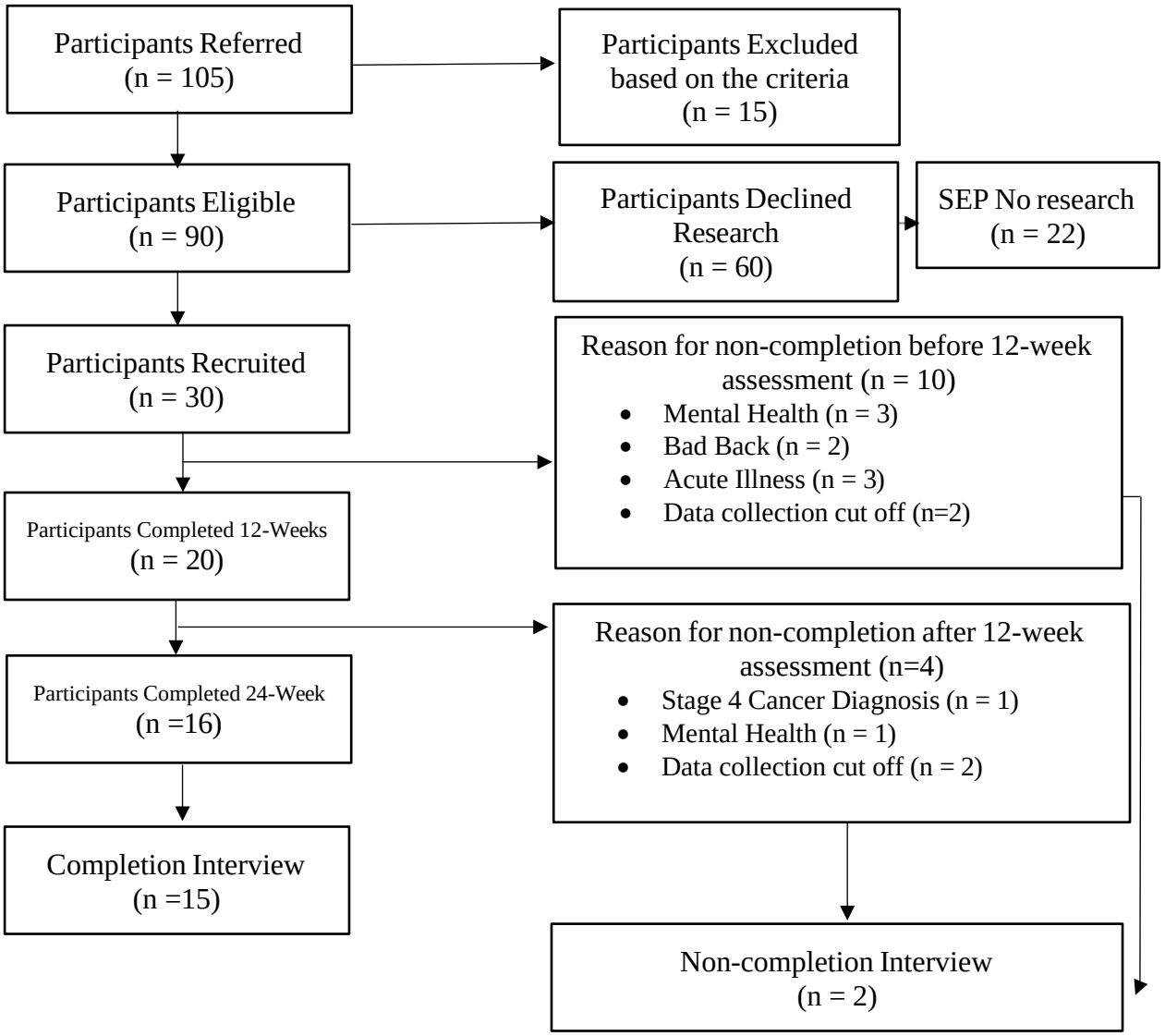


Figure 5.4. Participant Study Flowchart

5.9.3 Changes in Maximal Walking Distance (MWD)

Intention to treat analysis showed there was no statistically significant differences in MWD between pain-free to moderate pain from baseline-12 weeks, 12-24 and baseline to 24 weeks (Table 5.5). Intention to treat analysis showed there was no statistically significant differences in MWD between pain-free to maximal pain from baseline-12 weeks, 12-24 weeks and baseline to 24 weeks (Table 5.5). Intention to treat analysis showed there was no statistically significant

differences in MWD between moderate to maximal pain from baseline-12, 12-24 weeks and baseline to 24 weeks (Table 5.5).

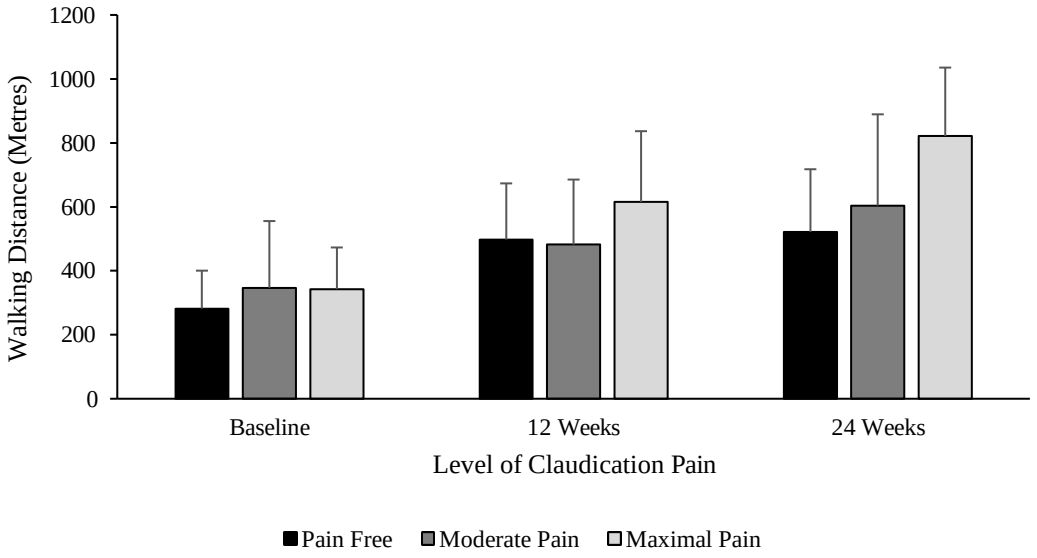


Figure 5.5. Maximal walking distance between at each timepoint for pain-free, moderate-pain and maximal-pain. Error bars are 1 standard deviation.

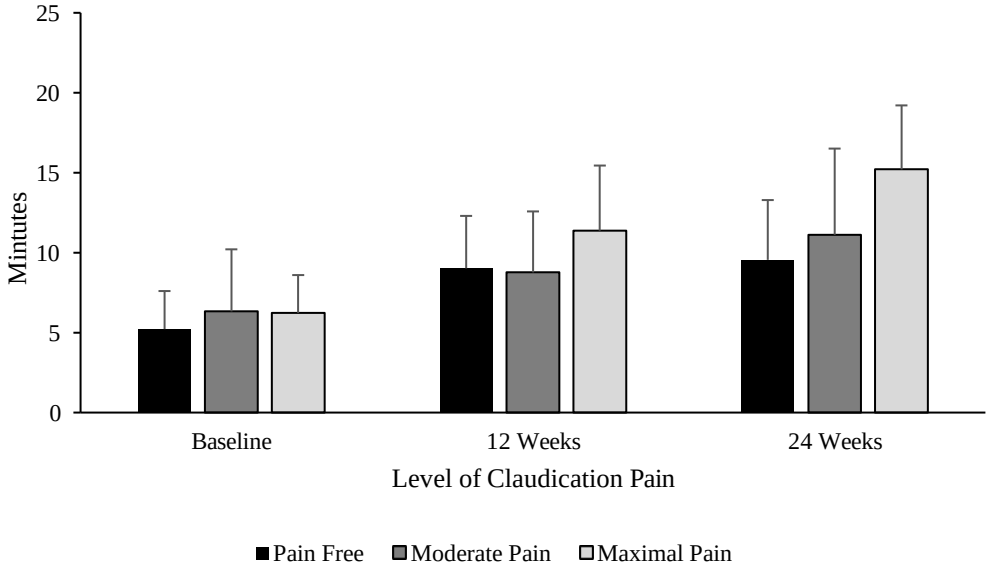


Figure 5.6. Time of test at each timepoint for pain-free, moderate-pain and maximal-pain. Error bars are 1 standard deviation.

5.9.4 Pain Free Walking Distance (PFWD)

In the pain-free SEP PFWD improved from baseline to 12 weeks but decreased from 12-24 weeks. Intention to treat analysis showed there was no statistically significant differences in PFWD between pain-free to moderate pain from baseline-12 weeks, 12-24 and baseline to 24 weeks (Table 5.5). Intention to treat analysis showed there was no statistically significant differences in PFWD between pain-free to maximal pain from baseline-12 weeks, 12-24 weeks and baseline to 24 weeks (Table 5.5). Intention to treat analysis showed there was no statistically significant differences in PFWD between moderate to maximal pain from baseline-12 weeks, 12-24 weeks and baseline to 24 (Table 5.5). Figure 5.8 shows the individual scores for PFWD and MWD for each group across the three timepoints.

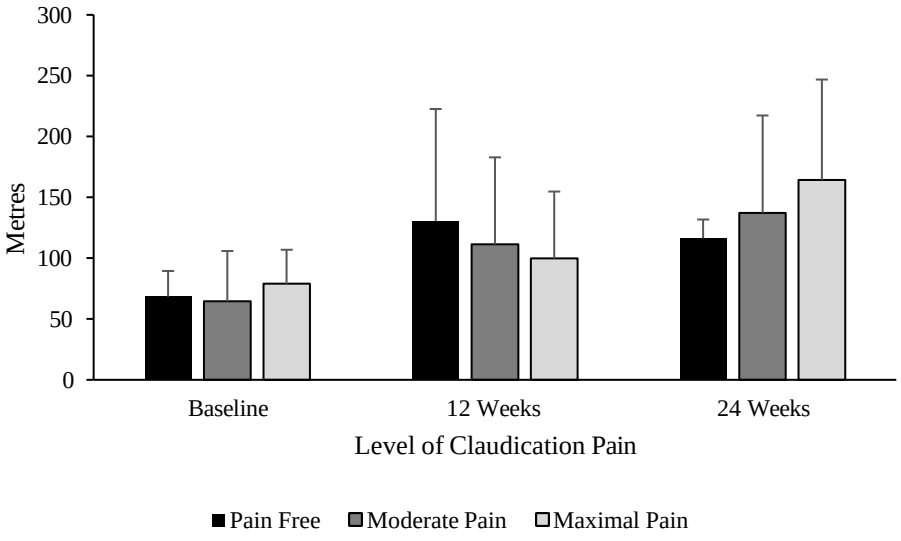


Figure 5.7. PFWD at each timepoint for PF, MOD-P and MAX-P

5.9.5 Minimally clinical important difference (MCID)

The MCID was measured using previous PAD specific research which was estimated following a supervised exercise programme for symptomatic patients with PAD (Gardner et al., 2018). For MWD the maximal claudication pain intervention showed a large MCID change compared

to PF at BL-24 weeks and 12-24 weeks (202.19m and 138.85m). There was also a small change favouring MAX-P at BL to 12 weeks (56.77m). When comparing MOD-P to MAX-P at BL-12 weeks 12-24 weeks there was a moderate change between groups for MCID favouring MAX-P (137.28m and 112.90m) and a large change in MCID favouring MAX-P against MOD-P at BL-24 weeks (168.97m). Only a small change was found from BL-12 favouring PF against MOD-P (80.51m) with no changes found at BL-24 or 12-24.

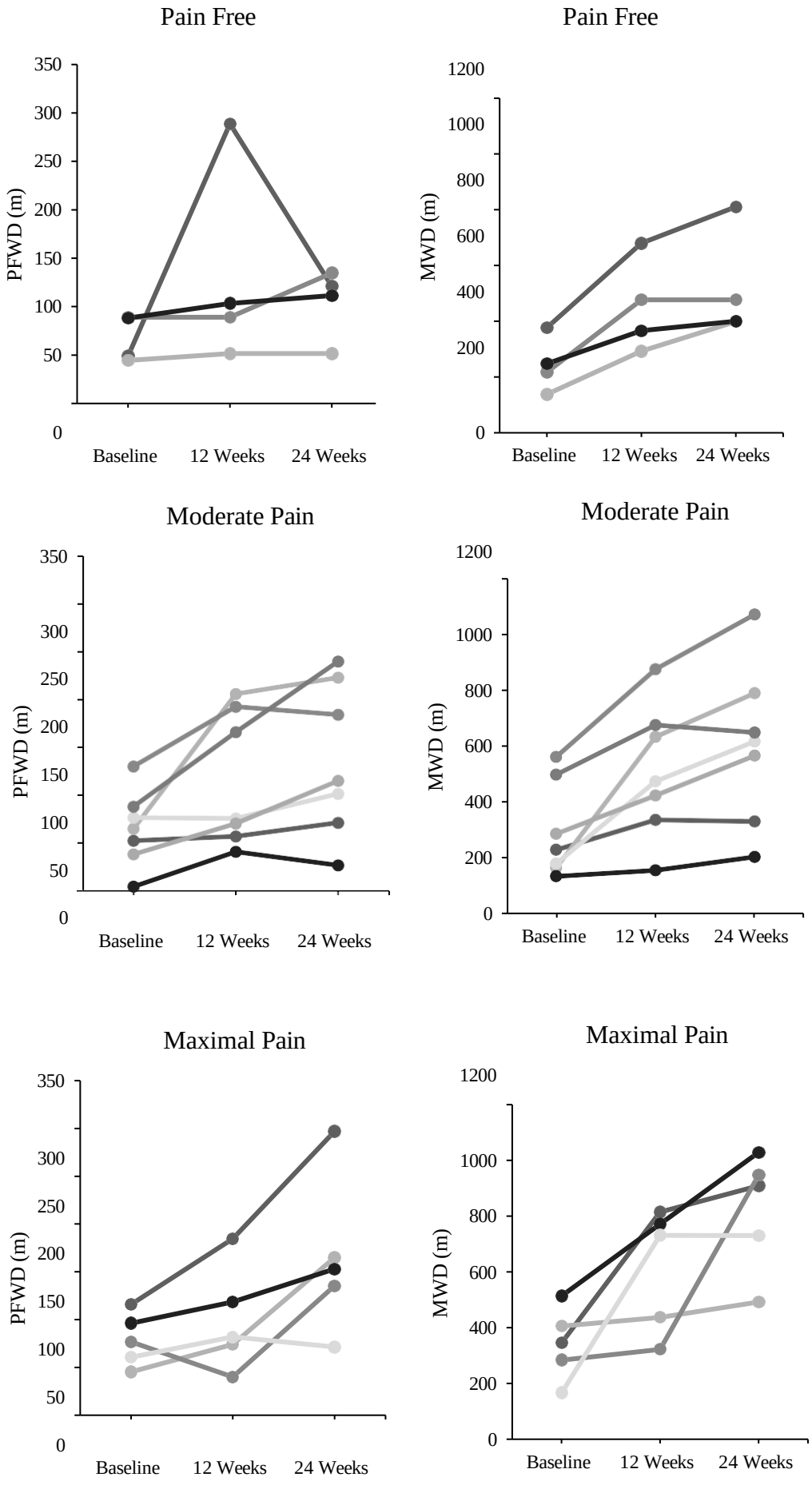


Figure 5.8 Individual scores for changes in PFWD and MWD at baseline, 12 and 24 weeks. This figure only shows data for the 16 participants who completed the whole 24 weeks.

Table 5.5. Statistical analysis of the changes between groups on MWD, PFWD and TOT

Outcome	Baseline – 12 Weeks					Baseline – 24 Weeks					12 – 24 Weeks				
	b	95% CI		*P*-value	*d*	*b*	95% CI		*P*-value	*d*	*b*	95% CI		*P*-value	*d*
PF VS MOD-P															
PFWD	15.40	-63.99	94.79	0.68	0.23	-23.65	-95.04	47.74	0.47	-0.47	-38.74	-129.39	51.92	0.36	-0.61
MWD	80.51	-128.55	289.57	0.42	0.46	-33.22	-301.77	234.73	0.79	-0.18	-25.45	-137.75	86.85	0.62	-0.32
TOT	1.36	-2.50	5.21	0.46	0.42	-0.74	-5.68	4.19	0.74	-0.21	-0.49	-2.61	1.63	0.62	-0.33
PF VS MAX-P															
PFWD	41.38	-69.85	152.60	0.42	0.54	-36.76	-118.69	45.17	0.32	-0.71	-81.43	-203.95	41.08	0.16	-1.05
MWD	-56.77	-320.43	206.89	0.63	-0.31	-202.19	-498.58	94.20	0.15	-1.08	-138.85	-448.32	171.63	0.33	-0.71
TOT	-1.34	-6.09	3.41	0.53	-0.41	-3.95	-9.32	1.42	0.13	-1.17	-2.47	-8.14	3.19	0.34	-0.69
MOD VS MAX-P															
PFWD	25.95	-24.0	76.05	0.28	0.61	-13.11	-94.61	68.38	0.73	-0.21	-42.70	-95.00	9.60	0.10	-1.07
MWD	-137.28	-395.71	121.14	0.27	-0.63	-168.97	-456.20	118.26	0.22	-0.77	-112.90	-339.42	113.62	0.29	-0.65
TOT	-2.70	-7.46	2.07	0.24	-0.67	-3.21	-8.51	2.09	0.21	-0.79	-1.99	-6.13	2.16	0.31	-0.63

b=mean difference between groups in change from baseline to 12 weeks, baseline to 24 weeks and 12 – 24 weeks, 95% CI=confidence intervals of the mean difference and d=Cohen's d. PFWD = Pain free walking distance; MWD = Maximal walking distance; TOT = Time of test; n = number of participants.

5.9.6 Quality of Life

VascuQol

Four questionnaires were used in this study. The symptom scores category in the VascuQol demonstrated a significant improvement in MOD-P group compared to the MAX-P group at 12-24 weeks (b = 0.86, 95% CI: 0.18-1.54; *P*=0.02; d=1.64). No other statistically significant differences (*P*>0.05) in the VascuQol were found between the PF, MOD-P and MAX-P groups during the three timepoints (Table 5.6). The VascuQol total score did not significantly improved between groups at any timepoints following a supervised exercise programme (table 5.7).

SF-36

There was a statistically significant improvement in the general health domain in the MOD-P group compared to the MAX-P group from baseline to 12 weeks. Physical component summary was significantly improved in the MOD-P group compared to the MAX-P group from baseline to 12 weeks. No other statistically significant differences (*P*>0.05) in the SF-36 were found between the PF, MOD-P and MAX-P groups during the three timepoints (Table 5.9).

WIQ, EQ-5D-5L and Barriers to Physical Activity Questionnaire

WIQ and the EQ-5D-5L demonstrated no significant differences between the changes in PF, MOD-P and MAX-P groups during the three timepoints (Table 5.11 and 5.13). Mean changes were calculated for each personal and environmental factor in the barriers to physical activity questionnaire (figure 5.9 and figure 5.10) The most prevalent personal barrier was pain with exertion and the most prevalent environmental barrier was hilly terrain. These barriers remained high at baseline, 12 and 24 weeks.

Table 5.6. Summary of changes in VascuQoL measures at Baseline, 12 Weeks and 24 Weeks. Values are means ± standard deviation.

VascuQoL Variable	Pain-Free			Moderate-Pain			Maximal-Pain		
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**
VascuQoL Total	4.90 ± 0.78	5.58 ± 0.59	5.81 ± 0.35	4.70 ±1.04	5.03 ± 1.05	5.41 ± 1.16	4.58 ± 1.12	5.14 ± 1.08	5.12 ± 0.90
VascuQoL Pain	4.40 ± 0.45	5.25 ± 0.87	5.56 ± 0.38	4.15 ± 0.94	4.53 ± 1.08	4.93 ± 1.19	4.05 ± 1.30	4.30 ± 1.39	4.35 ±1.41
VascuQoL Social	4.70 ± 2.02	5.60 ± 0.96	6.19 ± 0.75	4.68 ± 1.74	4.94 ±1.51	5.64 ± 1.14	5.20 ±1.44	5.80 ± 1.15	5.60 ± 0.96
VascuQoL Activities	4.45 ± 0.86	5.10 ± 0.88	5.32 ± 0.55	4.14 ± 1.04	4.57 ± 1.07	5.02 ± 1.36	4.20 ± 1.26	4.75 ± 1.38	4.85 ± 1.00
VascuQoL Symptom	5.80 ± 0.27	5.95 ± 0.27	6.19 ± 0.24	5.45 ± 0.99	5.19 ± 1.06	5.71 ± 0.88	5.30 ± 1.02	5.50 ± 0.73	5.25 ± 1.10
VascuQoL Emotional	5.23 ± 1.13	6.08 ± 0.63	6.21 ± 0.76	5.20 ± 1.40	5.78 ± 1.23	5.90 ± 1.26	4.74 ± 1.40	5.66 ± 0.94	5.66 ± 0.92

Values are means ± standard deviation

Table 5.7. Statistical analysis of the changes between groups of VascuQoL Questionnaire

PF VS MOD-P															
VascuQoL	Baseline – 12 Weeks					Baseline – 24 Weeks					12 – 24 Weeks				
Variable	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*
Overall	0.24	-0.45	0.94	0.46	0.43	0.12	-1.12	1.35	0.83	0.14	-0.29	-1.00	0.42	0.38	-0.58
Pain	0.35	-0.51	1.21	0.40	0.49	0.29	-0.94	1.53	0.60	0.34	-0.16	-1.03	0.71	0.69	-0.26
Social	0.37	-1.22	1.96	0.62	0.29	0.41	-2.28	3.10	0.74	0.22	-0.16	-2.00	1.68	0.85	-0.12
Activities	0.14	-0.72	1.00	0.73	0.20	-0.27	-1.76	1.22	0.69	-0.26	-0.41	-1.49	0.67	0.41	-0.54
Symptom	0.32	-0.67	1.31	0.50	0.39	0.09	-0.98	1.16	0.85	0.12	-0.48	-1.09	0.13	0.11	-1.12
Emotional	0.20	-0.79	1.20	0.66	0.25	0.39	-1.25	2.04	0.60	0.34	-0.15	-0.96	0.66	0.68	-0.26
PF VS MAX-P															
Overall	0.13	-0.74	1.00	0.74	0.22	0.47	-0.91	1.85	0.44	0.55	0.17	-0.94	1.27	0.73	0.24
Pain	0.60	-0.07	1.27	0.07	1.30	0.89	-0.10	1.88	0.07	1.42	0.08	-1.35	1.50	0.90	0.08
Social	0.30	-1.91	2.51	0.76	0.20	1.48	-1.63	4.58	0.30	0.75	0.83	-1.29	2.94	0.39	0.62
Activities	0.10	-0.83	1.04	0.80	0.16	0.17	-1.30	1.63	0.80	0.18	0.02	-1.24	1.29	0.97	0.03
Symptom	-0.05	-0.60	0.50	0.84	-0.13	0.43	-0.47	1.32	0.30	0.75	0.38	-0.28	1.03	0.22	0.91
Emotional	-0.06	-1.57	1.46	0.93	-0.06	0.34	-1.94	2.61	0.74	0.24	0.07	-1.36	1.50	0.91	0.08
MOD VS MAX-P															

Overall	-0.12	-0.70	0.46	0.67	-0.24	0.36	-0.41	1.12	0.33	0.61	0.46	-0.03	0.94	0.06	1.23
Pain	0.25	-0.54	1.04	0.51	0.38	0.59	-0.62	1.81	0.30	0.64	0.24	-0.82	1.30	0.63	0.29
Social	-0.07	-1.77	1.63	0.93	-0.05	1.06	-1.00	3.13	0.28	0.67	0.99	-0.27	2.24	0.11	1.03
Activities	-0.03	-0.69	0.62	0.91	-0.06	0.44	-0.54	1.41	0.34	0.58	0.43	-0.17	1.03	0.14	0.94
Symptom	-0.37	-1.34	0.61	0.43	-0.46	0.34	-0.65	1.32	0.47	0.44	***0.86***	***0.18***	***1.54***	***0.02***	***1.64***
Emotional	-0.26	-1.19	0.66	0.55	-0.35	-0.06	-1.21	1.10	0.92	-0.06	0.22	-0.52	0.96	0.52	0.39

Bold text = significant difference in the changes from 12 to 24 weeks between moderate and maximal pain. b=mean difference between groups in change from baseline to 12 weeks, baseline to 24 weeks and 12 – 24 weeks, 95% CI=confidence intervals of the mean difference and d=Cohen's d

Table 5.8. Summary of changes in SF-36 measures at Baseline, 12 Weeks and 24 Weeks. Values are means ± standard deviation

SF-36 Variable	Pain-Free			Moderate-Pain			Maximal-Pain		
	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks
SF-36 PF	39.55 ± 9.63	43.76 ± 8.60	46.06 ± 4.42	36.87 ± 8.26	40.32 ± 7.66	37.31 ± 7.80	37.64 ± 7.11	39.74 ± 10.47	41.72 ± 1188
SF-36 RP	38.74 ± 12.13	48.17 ± 6.55	45.93 ± 10.21	35.82 ± 9.71	44.18 ± 9.90	43.36 ± 9.21	37.84 ± 13.99	42.34 ± 12.76	41.96 ± 20.35
SF-36 BP	43.29 ± 4.92	45.15 ± 7.63	42.74 ± 8.91	38.65 ± 10.59	40.23 ± 9.56	40.11 ± 9.16	42.65 ± 15.52	39.18 ± 708	37.85 ± 5.39
SF-36 GH	39.78 ± 10.23	41.11 ± 7.26	39.76 ± 4.50	40.54 ± 6.83	42.14 ± 7.65	40.89 ± 7.97	39.11 ± 12.93	36.73 ± 13.12	37.52 ± 10.59
SF-36 VIT	41.91 ± 5.40	44.08 ± 7.33	48.89 ± 3.74	46.96 ± 8.68	51.61 ± 7.57	50.48 ± 8.35	40.72 ± 12.07	46.06 ± 12.32	37.57 ± 13.65
SF-36 SF	47.31 ± 10.64	49.32 ± 5.72	44.81 ± 8.68	41.30 ± 13.33	47.31 ± 10.64	47.31 ± 7.09	45.31 ± 10.98	48.32 ± 7.44	45.83 ± 19.91
SF-36 RE	39.46 ± 14.01	44.33 ± 7.63	45.73 ± 12.39	41.88 ± 11.12	47.27 ± 11.82	45.23 ± 10.33	46.42 ± 6.70	54.08 ± 3.12	52.97 ± 15.08
SF-36 MH	48.78 ± 13.13	50.35 ± 6.77	51.52 ± 9.88	49.04 ± 7.51	51.74 ± 8.87	48.63 ± 7.91	51.91 ± 9.18	56.10 ± 4.53	61.97 ± 8.17
SF-36 PCS	39.02 ± 7.06	43.80 ± 6.75	42.53 ± 4.58	35.24 ± 9.70	38.99 ± 7.81	38.13 ± 7.56	35.47 ± 12.03	33.98 ± 12.92	32.40 ± 10.77
SF-36 MCS	46.80 ± 12.95	48.40 ± 4.63	49.50 ± 10.60	48.98 ± 7.97	53.34 ± 6.65	51.49 ± 5.75	51.16 ± 7.38	57.92 ± 2.73	52.57 ± 7.23

Values are means ± standard deviation. SF-36 = Short Form-36; PF = Physical Function; RP = Role Physical; BP = Bodily Pain; GH = General Health; VIT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; PCS = Physical Summary Component; MCS = Mental Component Summary.

Table 5.9. Statistical analysis of the changes between groups for the SF-36

PF VS MOD-P															
SF-36	Baseline – 12 Weeks					Baseline – 24 Weeks					12 – 24 Weeks				
Variable	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*
SF-36 PF	-0.26	-8.61	8.09	0.95	-0.04	3.07	-8.42	14.56	0.56	0.38	1.98	-7.25	11.21	0.64	0.30
SF-36 RP	-0.79	-13.03	11.44	0.89	-0.08	-0.56	-18.53	17.41	0.95	-0.04	-1.04	-15.52	13.44	0.87	-0.10
SF-36 BP	-1.59	-10.47	7.29	0.70	-0.22	-2.35	-13.23	8.53	0.64	-0.31	-3.23	-10.14	3.68	0.32	-0.66
SF-36 GH	-0.78	-5.16	3.60	0.71	-0.22	1.82	-10.53	14.16	0.75	0.21	1.21	-9.94	12.36	0.81	0.15
SF-36 VIT	-3.76	-9.48	1.95	0.18	-0.80	-1.17	-11.44	9.11	0.80	-0.16	2.48	-8.73	13.68	0.63	0.31
SF-36 SF	-5.79	-19.12	7.54	0.36	-0.53	-7.88	-23.90	8.15	0.30	-0.70	-7.16	-25.78	11.45	0.41	-0.55
SF-36 RE	-2.10	-20.80	16.59	0.81	-0.14	3.46	-18.80	25.73	0.73	0.22	5.85	-11.76	23.45	0.47	0.47
SF-36 MH	-1.92	-15.51	11.67	0.76	-0.17	3.08	-14.07	20.24	0.69	0.26	2.90	-1.99	7.78	0.21	0.84
SF-36 PCS	-0.33	-6.69	6.03	0.91	-0.06	-0.51	-13.19	12.18	0.93	-0.06	-1.88	-10.84	7.08	0.65	-0.30
SF-36 MCS	-3.95	-15.99	8.08	0.49	-0.40	0.18	-16.27	16.63	0.98	0.02	2.57	-7.23	12.37	0.57	0.37
PF VS MAX-P															
SF-36 PF	2.11	-6.82	11.04	0.60	0.35	1.18	-12.96	15.31	0.85	0.13	-2.46	-14.51	9.58	0.64	-0.32
SF-36 RP	4.94	-10.28	20.16	0.48	0.47	6.55	-21.51	34.62	0.60	0.37	-1.31	-20.67	18.05	0.88	-0.11
SF-36 BP	5.33	-7.84	18.49	0.38	0.59	6.30	-10.88	23.48	0.42	0.58	-0.70	-11.43	10.04	0.88	-0.10

SF-36 GH	3.71	-1.97	9.39	0.17	0.95	5.51	-10.08	21.11	0.43	0.56	0.28	-13.57	14.14	0.96	0.03
SF-36 VIT	-3.17	-8.23	1.89	0.19	-0.92	8.34	-8.23	24.91	0.27	0.80	10.97	-7.63	29.56	0.21	0.94
SF-36 SF	-1.00	-14.29	12.28	0.87	-0.11	-0.52	-26.98	25.93	0.96	-0.03	-2.53	-30.29	25.23	0.84	-0.14
SF-36 RE	-2.79	-13.86	8.28	0.58	-0.37	3.89	-25.43	33.21	0.76	0.21	5.46	-15.88	26.80	0.56	0.41
SF-36 MH	-2.61	-20.83	15.61	0.75	-0.21	-5.48	-27.28	16.31	0.57	-0.40	-5.22	-16.34	5.89	0.30	-0.75
SF-36 PCS	6.27	-0.29	12.84	0.06	1.39	7.64	-5.13	20.41	0.20	0.95	-0.45	-10.96	10.06	0.92	-0.07
SF-36 MCS	-5.16	-19.27	8.95	0.42	-0.53	3.84	-21.65	29.33	0.73	0.24	7.29	-5.07	19.66	0.21	0.94

MOD VS MAX-P

SF-36 PF	2.37	-4.45	9.19	0.46	0.42	-1.89	-9.94	6.15	0.61	-0.31	-4.44	-10.81	1.92	0.15	-0.91
SF-36 RP	5.74	-2.15	13.62	0.14	0.88	7.11	-8.50	22.72	0.33	0.59	-0.27	-17.13	16.60	0.97	-0.02
SF-36 BP	6.92	-2.61	16.45	0.14	0.88	8.65	-2.34	19.64	0.11	1.03	2.53	-2.66	7.72	0.30	0.64
SF-36 GH	***4.49***	***0.88***	***8.11***	***0.02***	***1.51***	*3.70*	-7.46	14.85	0.48	0.43	-0.92	-10.75	8.90	0.84	-0.12
SF-36 VIT	0.59	-5.00	6.19	0.82	0.13	9.51	-2.66	21.68	0.11	1.02	8.49	-4.79	21.77	0.19	0.83
SF-36 SF	4.79	-5.97	15.55	0.35	0.54	7.35	-12.83	27.53	0.44	0.48	4.63	-16.36	25.63	0.63	0.29
SF-36 RE	-0.69	-18.55	17.18	0.94	-0.05	0.43	-17.76	18.61	0.96	0.03	-0.38	-18.41	17.64	0.96	-0.03
SF-36 MH	-0.70	-10.02	8.63	0.87	-0.09	-8.57	-19.57	2.44	0.11	-1.02	-8.12	-16.50	0.26	0.06	-1.26
SF-36 PCS	***6.60***	***0.87***	***12.33***	***0.03***	***1.40***	*8.15*	-0.71	17.01	0.07	1.20	1.43	-3.97	6.83	0.57	0.35
SF-36 MCS	-1.21	-10.66	8.24	0.79	-0.16	3.66	-8.54	15.87	0.52	0.39	4.73	-5.39	14.84	0.32	0.61

Bold text = significant difference in the changes from 12 to 24 weeks between moderate and maximal pain. b=mean difference between groups in change from baseline to 12 weeks, baseline to 24 weeks and 12 – 24 weeks, 95% CI=confidence intervals of the mean difference and d=Cohen's d. SF-36 = Short Form-36; PF = Physical Function; RP = Role Physical; BP = Bodily Pain; GH = General Health; VIT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; PCS = Physical Summary Component; MCS = Mental Component Summary.

Table 5.10. Summary of changes in WIQ measures at Baseline, 12 Weeks and 24 Weeks

Walking Impairment Questionnaire	**Pain-Free**			**Moderate-Pain**			**Maximal-Pain**		
	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks
Overall Score	40.02 ± 23.32	53.65 ± 20.22	56.33 ± 3.54	34.04 ± 20.01	39.96 ± 19.49	38.25 ± 25.70	46.09 ± 27.12	52.42 ± 25.80	49.31 ± 16.89
Distance	40.15 ± 28.64	55.96 ± 33.43	65.91 ± 10.11	22.46 ± 21.41	34.48 ± 29.55	32.44 ± 29.18	35.53 ± 40.24	43.20 ± 33.44	45.04 ± 31.12
Speed	31.01 ± 22.84	46.09 ± 19.59	57.25 ± 11.44	25.22 ± 22.30	27.38 ± 15.57	27.54 ± 24.54	39.42 ± 23.36	50.73 ± 32.62	42.90 ± 23.89
Stairs	48.89 ± 31.77	58.89 ± 18.26	45.84 ± 19.45	54.45 ± 34.24	58.02 ± 33.00	54.76 ± 32.93	63.33 ± 23.76	63.33 ± 13.94	60.00 ± 11.38
Distance x Speed	35.58 ± 24.56	51.03 ± 24.93	61.58 ± 7.72	23.84 ± 17.81	30.93 ± 19.54	29.99 ± 26.30	37.47 ± 31.21	46.96 ± 32.62	43.95 ± 27.34

Values are means ± standard deviation

Table 5.11. Statistical analysis of the changes between groups for the Walking Impairment Questionnaire

PF VS MOD-P															
WIQ	Baseline – 12 Weeks					Baseline – 24 Weeks					12 – 24 Weeks				
Variable	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*
Overall	5.67	-9.75	21.08	0.44	0.45	5.19	-19.23	29.60	0.64	0.30	-4.74	-21.38	11.90	0.54	-0.40
Distance	3.38	-18.93	25.70	0.75	0.18	15.80	-15.70	47.31	0.29	0.71	-1.26	-32.07	29.56	0.93	-0.06
Speed	10.40	-7.98	28.78	0.24	0.69	11.08	-11.70	33.86	0.30	0.69	-0.05	-24.11	24.01	1.00	0.00
Stairs	3.21	-25.98	32.40	0.82	0.13	-11.30	-61.55	38.94	0.62	-0.32	-12.89	-45.10	19.31	0.39	-0.57
D X S	6.90	-7.90	21.70	0.33	0.57	13.44	-11.84	38.72	0.26	0.75	-0.66	-19.77	18.46	0.94	-0.05
PF VS MAX-P															
Overall	7.30	-9.58	24.19	0.35	0.63	8.28	-21.28	37.84	0.53	0.44	-1.13	-24.29	22.02	0.91	-0.08
Distance	8.14	-20.50	36.78	0.53	0.41	13.69	-29.74	57.12	0.48	0.50	-2.54	-47.62	42.53	0.90	-0.09
Speed	3.77	-19.41	26.95	0.72	0.24	17.54	-2.47	37.55	0.08	1.39	11.09	-14.92	37.09	0.35	0.68
Stairs	-6.38	-72.83	60.06	0.83	-0.15	-11.94	-46.86	22.98	0.45	-0.54	6.79	-14.34	27.92	0.50	0.39
D X S	10.00	-29.98	49.98	0.58	0.37	-6.38	-72.83	60.06	0.83	-0.15	-11.94	-46.86	22.98	0.45	-0.54
MOD VS MAX-P															
Overall	1.64	-12.16	15.44	0.80	0.14	3.09	-14.24	20.42	0.70	0.23	3.60	-13.59	20.80	0.65	0.27

Distance	4.76	-14.02	23.53	0.59	0.31	-2.11	-21.86	17.64	0.82	-0.14	-1.28	-26.90	24.33	0.91	-0.07
Speed	-6.38	-21.46	8.19	0.35	-0.54	6.46	-12.70	25.61	0.47	0.44	11.14	-11.56	33.84	0.30	0.64
Stairs	6.79	-14.34	27.92	0.50	0.39	4.92	-32.22	42.06	0.77	0.17	0.95	-28.30	30.20	0.94	0.04
D X S	-0.94	-13.22	11.34	0.87	-0.09	2.19	-14.35	18.74	0.77	0.17	4.95	-15.82	25.71	0.61	0.31

Bold text = significant difference in the changes from 12 to 24 weeks between moderate and maximal pain. D X S=distance x speed, b=mean difference between groups in change from baseline to 12 weeks, baseline to 24 weeks and 12 – 24 weeks, 95% CI=confidence intervals of the mean difference and d=Cohen's d

Table 5.12. Summary of changes in EQ-5D-5L measures at Baseline, 12 Weeks and 24 Weeks

EQ-5D-5L	**Pain-Free**			**Moderate-Pain**			**Maximal-Pain**		
	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks	Baseline	12 Weeks	24 Weeks
Overall Score	64.00 ± 16.73	61.00 ± 11.40	70.00 ± 0.00	56.60 ± 20.42	65.56 ± 18.62	68.43 ± 21.42	59.00 ± 23.02	62.00 ± 16.43	63.00 ± 21.68
Index Score	0.33 ± 0.15	0.23 ± 0.14	0.22 ± 0.19	0.41 ± 0.28	0.27 ± 0.20	0.34 ± 0.31	0.31 ± 0.17	0.20 ± 0.12	0.35 ± 0.14

Values are means ± standard deviation

Table 5.13. Statistical analysis of the changes between groups for the EQ-5D-5L

PF VS MOD-P														
EQ-5D-5L	Baseline – 12 Weeks					Baseline – 24 Weeks					12 – 24 Weeks				
	b	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*	*b*	95% CI		P-value	*d*
Overall	-14.11	-32.24	4.01	0.12	-0.95	-1.64	-15.23	11.94	0.79	-0.17	6.04	-6.09	18.16	0.29	0.71
Index	0.08	-0.14	0.29	0.46	0.43	-0.04	-0.30	0.21	0.72	-0.22	-0.11	-0.24	0.03	0.11	-1.04
PF VS MAX-P															
Overall	-6.00	-31.31	19.31	0.60	-0.35	8.50	-33.23	50.23	0.65	0.32	7.75	-27.66	43.16	0.62	0.35
Index	0.01	-0.29	0.31	0.94	0.05	-0.14	-0.63	0.34	0.50	-0.53	-0.17	-0.39	0.06	0.12	-1.31
MOD VS MAX-P															
Overall	8.11	-4.63	20.85	0.19	0.77	10.14	-19.38	39.67	0.46	0.45	1.71	-21.29	24.72	0.87	0.10
Index	-0.07	0.46	-0.26	0.12	-0.46	-0.10	0.52	-0.44	0.24	-0.47	-0.06	0.52	-0.26	0.14	-0.47

Bold text = significant difference in the changes from 12 to 24 weeks between moderate and maximal pain. b=mean difference between groups in change from baseline to 12 weeks, baseline to 24 weeks and 12 – 24 weeks, 95% CI=confidence intervals of the mean difference and d=Cohen's d

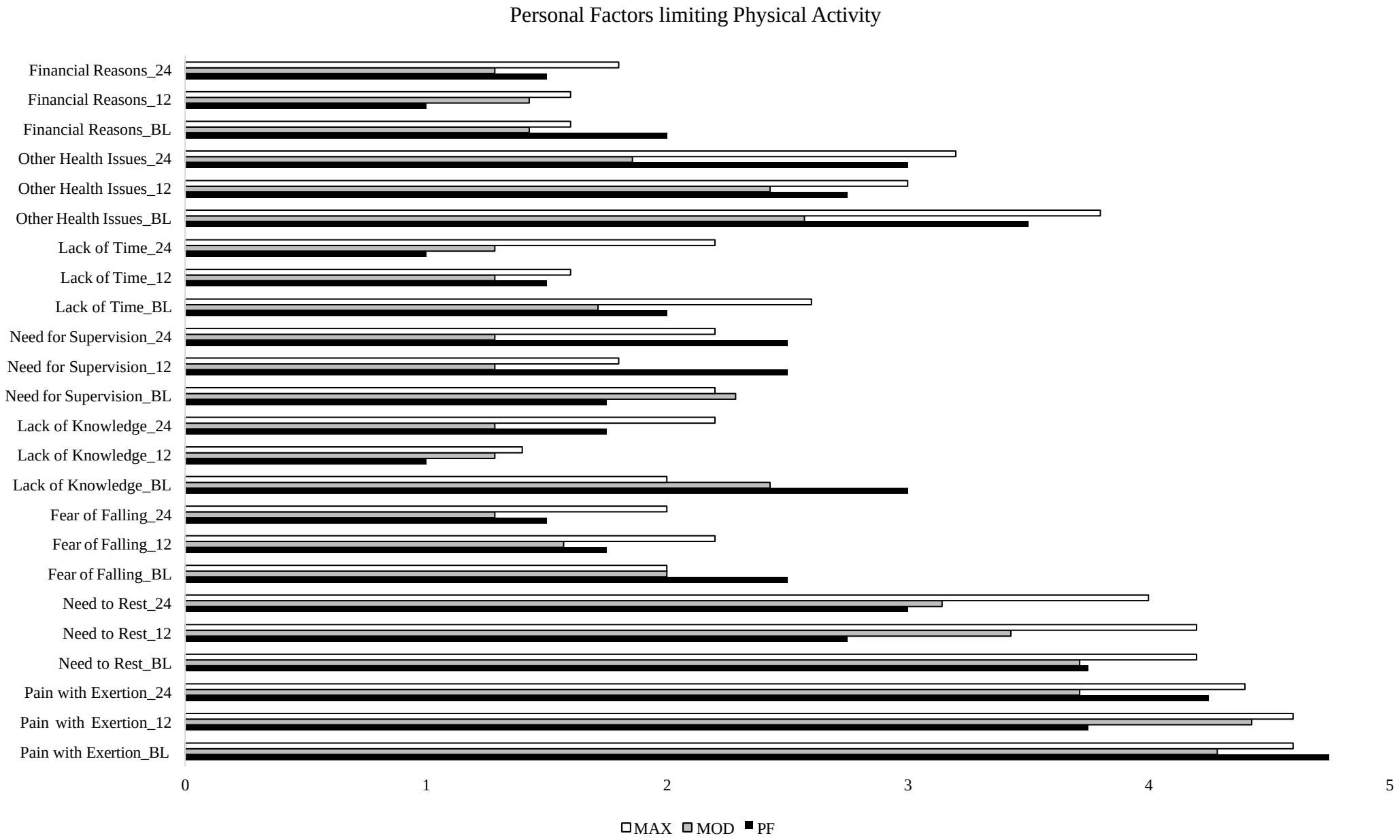


Figure 5.9 Mean Personal Factors limiting Physical Activity
1 = Never; 2 = Seldom; 3 = Sometimes; 4 = Frequently; 5 = Always

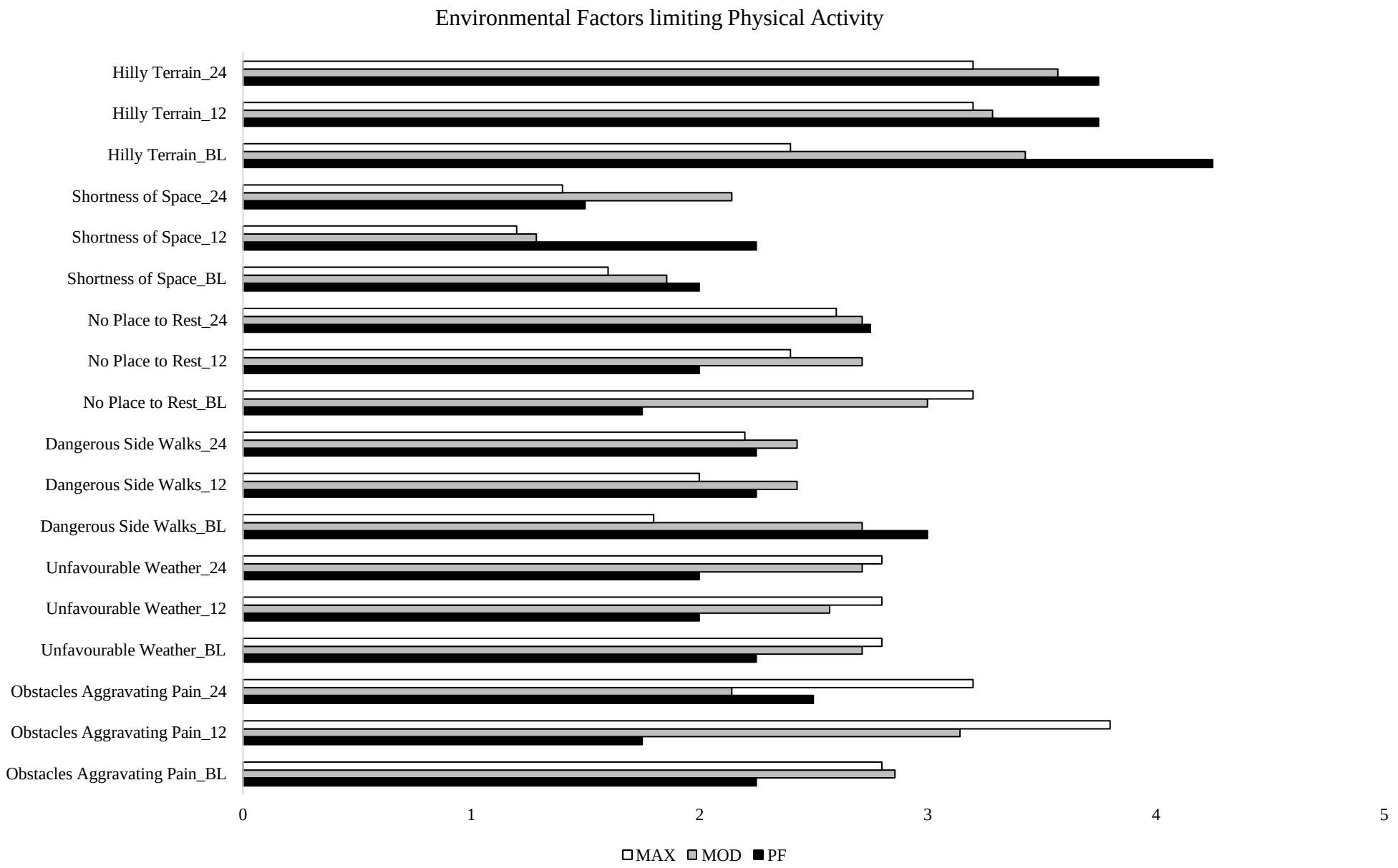


Figure 5.10 Mean Environmental Factors limiting Physical Activity
1 = Never; 2 = Seldom; 3 = Sometimes; 4 = Frequently; 5 = Always

5.10 Discussion

The primary aim of this chapter was to directly compare the effects of exercise prescribed at different levels of claudication (pain-free, moderate pain and maximal pain) on functional outcomes following a 24-week SEP in patients with IC. Patients were asked to attend a SEP at Heartbeat which took place on a Tuesday and Thursday 12:15-13:15pm/13:30-14:30pm. The layout of the exercise intervention, designed specifically to bring on claudication pain, is documented in figure 5.3. Whilst SEPs are the first line of treatment for patients with IC and functional outcomes, there lies inconsistencies between the optimal level of claudication pain for patients with PAD. To our knowledge no study has directly compared three levels of claudication as demonstrated in chapter 3. Yet, the need for identifying the optimal level of claudication pain for participants with IC has been highlighted as a recommended research area within the NICE guidelines and in a recent statement scientific statement by the American Heart Association (Treat-Jacobson et al., 2019, NICE, 2012). The primary aim and objective were to understand which level of claudication pain was most beneficial for patients with IC, so exercise interventions and guidelines could be tailored accordingly.

5.10.1 Walking Performance Indicators

Maximal walking distance (MWD) has been highlighted as a reliable and reproducible method to measure improvement for patients with IC (Labs et al., 1999, Gardner et al., 1991c). Likewise, from a patient perspective they are most interested in improvements in their MWD as it reflects improvements in function outcomes such as being able to walk to the shops or play with grandchildren etc (chapter 7). It is important to treat the results from this study with caution as the values are all exploratory and therefore are not powered to definitively draw conclusions.

Although maximal claudication pain elicited the largest increase in MWD (figure 5.8, page 144), there was no significant differences between the changes in walking distance between groups. These results suggest that although maximal pain is recommended by NICE, potentially moderate or pain-free could be as efficacious. This finding agrees with the systematic review in chapter 3 and previous research which found moderate pain to be as beneficial as pain-free (Parmenter et al., 2013, Mika et al., 2013). Furthermore, this finding is in accordance with a recently published systematic review which showed structured low-pain exercise had a larger positive effect than structured high-pain exercise on MWD and PFWD compared with usual-care control. In an analysis of structured low-pain versus high-pain exercise, there was a large positive effect which was in favour of low-pain exercise on MWD and PFWD, although this was only significant for PFWD (Perks et al., 2022). However, we are unable to definitively draw conclusions as we did not do a non-inferiority or superiority trial and so did not complete the relevant statistics.

An explanation why there were no significant differences between conditions in this study could be due to the repeated bouts of ischemic reperfusion. Previous evidence suggests that an extensive inflammatory cascade can be induced when exercising to maximal claudication pain which may have a detrimental effect on the endothelium and the muscle and so consequently intensify their condition (Tisi and Shearman, 1998, Delaney et al., 2014). Likewise, one study found that patients who took part in 12-week SEP exercising to unbearable claudication pain had an increased calpin activity, a calcium dependent protease which can cause morphological damage to skeletal muscle. The study concluded repeated ischaemic reperfusion can lead to a catabolic muscle wasting state, potentially through activation of the calpain system (Delaney et al., 2014). Likewise, a review suggested acute responses to demanding exercise for patients with PAD could aggregate muscle injury which could exacerbate the inflammatory risk profile

that already exists in patients with PAD and cause an ischaemic reperfusion injury (Tisi and Shearman, 1998).

However, findings confirmed a large effect size in the maximal pain group in relation to the pain-free intervention from baseline to 24 weeks (1.07) and a medium effect size from 12-24 weeks (0.71). Likewise, a medium effect size favoured maximal pain against moderate pain at 12-24 weeks and baseline to 24 weeks (0.65 and 0.77). As the effect size is independent of the sample size, these findings imply the practical significance of maximal claudication pain for patients with IC compared to moderate and pain-free.

Also, although there were no significant differences between the changes of walking distance between groups as analysed by the traditional statistical probability (p-values), it is important for clinicians to include more clinically meaningful information (e.g., MCID) to determine if the treatment will be beneficial or harmful to their patients (Gardner et al., 2018). As indicated in previous research, a non-significant outcome does not automatically imply the treatment was not clinically effective. In this study the small sample size and measurement variability could have statistically influenced the results (Page, 2014).

The MCID represents the smallest threshold change in an outcome measure that a patient considers beneficial (Jaeschke et al., 1989b). Recent research has estimated the MCID for small, moderate and large changes in outcome measures for symptomatic PAD patients who have completed a SEP (Gardner et al., 2018). Interestingly, all MCID changes for MWD favoured exercising to maximal claudication pain. Specifically, there was a large and moderate effect of MAX-P against PF even though there was no statistical significance. If this is the case, these findings disagree with the research stated above which show PF and MOD-P just as

effective (Mika et al., 2013, Parmenter et al., 2011). Yet this finding supports the current guidelines (NICE, 2012).

Numerous studies suggest that repeated bouts of exercise, which promote a trained condition for patients with PAD, temper the inflammatory response to exercise, leading to a lessened inflammatory state (Hiatt et al., 1996). This study used six specific weight bearing exercises which promoted claudication pain during each station. This repeated bout of ischaemic pain brought on by weight bearing exercises could explain why the maximal claudication group saw a large MCID compared to pain-free and moderate who did not meet the ischaemic threshold. Likewise, studies have demonstrated that exercising at maximal claudication pain leads to an improvement in mitochondrial content post-training which is a contributing factor for training-induced performance improvements (Crowther et al., 2012). Therefore, participants in the maximal pain intervention may have seen a greater increase in their MWD due to an increase mitochondrion which increases their aerobic capacity and so delaying the onset of ischemia (Harwood et al., 2016a, Crowther et al., 2012).

Furthermore, another possibility for the large MCID found in maximal claudication pain in this study could have been due to changes in lower limb architecture which support lower limb blood flow when participants work to pain. A previous study has shown increased capillary density of the gastrocnemius muscle following a 12-week SEP where patients were asked to work to near maximal claudication pain (Duscha et al., 2011). Finally, one SEP whereby participants worked to moderate claudication pain twice a week for 6 months found significant increases the presence of endothelial progenitor cells and decreases asymmetric dimethylarginine. Endothelial progenitor cell is important for angiogenesis, and asymmetric

dimethylarginine is an inhibitor to nitric oxide (a vasodilator). Therefore, the SEP provided an increase in the availability for blood flow to the working muscle (Schlager et al., 2011).

Likewise, the higher MCID found in the maximal claudication intervention could have been due to a reduction in endothelium-derived inflammatory markers. Previous research suggests an 8-week maximal pain SEP leads to reduced inflammation markers (Saetre et al., 2011). E-selectin and ICAM-1 are two of the most endothelium specific adhesion molecules on leukocytes and endothelial cells which contribute to the process of inflammation. Following 8-weeks SEP working at maximal claudication pain there was significant reductions in plasma levels of the specific endothelium-derived inflammatory markers (Saetre et al., 2011)

Despite large clinically meaningful changes in MWD, there was also a small change in the MCID for PFWD. Interestingly, at 12 weeks there was a small change favouring PF against MAX-P. This was unexpected given the results of the MCID changes for MWD favouring MAX-P. These results may be explained by the nature of PFWD being subjective and relying on the participant to tell the investigator when the pain starts. This factor could have been influenced by patient motivation and wanting to walk further before admitting to getting pain. During each treadmill test the investigator and author of this thesis reiterated the importance of the participant telling the investigator as soon as they felt claudication pain whilst on the treadmill.

5.10.2 Quality of Life Indicators

Alongside improvements in functional outcomes, a treatment aim for patients with IC is to improve their QoL. Previous research assessing QoL following an exercise intervention have demonstrated significant improvements (Novaković et al., 2018, Lee et al., 2007a, Lane et al.,

2017a). Although QoL is assessed, many studies fail to report all the domains. A systematic review in 2017 demonstrated 24% of questionnaires across 31 studies were missing at least one domain, particularly within the SF-36 (Harwood et al., 2017d). This is similar to the results from a Cochrane review were only two studies fully reported all domains for QoL (Lane et al., 2017b).

This study has demonstrated a significant improvement in only one of the nine domains of the SF36 questionnaire and one of the component summaries (general health and physical component summary (PCS)). General health and the PCS were demonstrated a significant result for moderate versus maximal pain from baseline to 12 weeks. This is different from previous RCT which all report an improvement in the physical and mental component summary following a SEP (Gardner et al., 2002, Zwierska et al., 2005, McDermott and Polonsky, 2016). That said, it is difficult to draw accurate comparisons between previous research as each exercise trial uses a variety of exercise modality and intensity. Also, as the SF-36 has a semi-ordinal scoring system, participant motivation and wanting to impress the investigator may have influenced the participants scoring. However, if all participants had this mindset, we would be unlikely to see a change between groups. Interestingly in this study, participants in the moderate pain group had an improvement in their PCS compared to maximal pain. This is in agreement with a previous study whereby the moderate training group improved their PCS (Novaković et al., 2018). Perhaps this is due to participants in the moderate claudication pain intervention not having to push through the pain as much and therefore feel better physically.

Result from the disease specific VascuQol demonstrated a significant improvement in the symptom domain for the moderate training group compared to the maximal training group from weeks 12-24. Other domains and the total VascuQol score were not affected at any timepoint

between groups. This may be due to the study being underpowered to detect change. As mentioned above it is difficult to compare this to other studies to identify consistencies due to the variation across SEPs in other studies (e.g., frequency, intensity, time and type). Also, not all domains are reported in studies (Harwood et al., 2017d).

The WIQ is highly validated for its responses regarding walking speed and endurance following interventions such as SEPs for patients with IC (Regensteiner et al., 1990). That said, it appears the WIQ is the least utilised in the literature. Results from the WIQ showed no statistically significant changes between groups at any timepoints for all categories (overall, distance, speed, stairs). This could have been due to the small sample size and not powered to detect change. Previous research has found WIQ scores to be significantly higher in all three domains following a 3-month exercise intervention, although this study had a much larger sample size of 91 participants (Nicolaï et al., 2009b). Furthermore, the study suggests the WIQ can be used as an alternative to treadmill testing in determining the effect of treatment in patients with IC (Nicolaï et al., 2009a). The WIQ is a walking ability measure for a heterogenous group of patients, although it has been suggested future research is necessary to see whether WIQ scores can be used to predict important outcomes such as the progression of PAD to rest pain and gangrene (McDermott et al., 1998).

Results from the EQ-5D-5L showed no statistical difference between groups for the three timepoints for the overall score and index score. The EQ-5D-5L is a generic measure of health status for five aspects of health mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each status is coded from 1-5. An index value can be calculated by applying a formula that attaches a value to each level in each dimension. The index value is calculated by deducting appropriate weights from 1, the value for good health. Previous

research has highlighted negative impact of PAD on health related QoL with low scores for EQ-5D-5L (Vaidya et al., 2018). The study also used the SF-36 and suggested both measurements behaved in a consistent manner (Vaidya et al., 2018). Likewise, a study found less severe claudication pain were significantly related to better HRQoL, therefore clinicians should find a way of managing symptoms to improve functional status (Kim et al., 2021).

The barriers to physical activity questionnaire highlight potential personal and environmental barriers to be limiting an individual's physical activity from 1-5 (1 never and 5 always). Results from this questionnaire are displayed in figures 5.9 and 5.10 (page 159 and 160). Pain with exertion and the need to rest because of leg pain are the most prevalent personal barriers, this is in accordance with previous studies (Barbosa et al., 2015b, Galea et al., 2008). The limiting factors of pain with exertion and need to rest remained high throughout the 24-week intervention. This perhaps suggests that although a participants functional outcome improves throughout a SEP intervention, their perception of pain and the influence of it on their daily lives remains high. Therefore, incorporating a psychological intervention alongside a SEP could encourage participants to change their beliefs and perceptions around fear related movement pain (Duscha et al., 2018).

The most prevalent environmental barrier to physical activity in participants was hilly terrain and obstacles that aggregate the pain (figure 5.10). This is in agreement with a previous study which found the presence of obstacles such as hills and stairs to be the most common environmental barrier (Barbosa et al., 2015b). Interestingly, shortness of space was not rated highly as a barrier to physically activity (1-2 = never/seldom) by patients. This is important as a previous study has revealed having space such as parks within 500m of home increases the likelihood of being physically active by a factor of 2.2 (Foster et al., 2004). Perhaps the patients

did not find this a limiting factor because they attend a SEP and therefore have access to space to exercise. If this is the case, then increasing the number of SEPs available for patients with PAD may improve the physical activity levels for patients of this clinical population.

Future studies should use a combination of general and disease specific questionnaires. In this study there was five QoL questionnaires to complete which was time consuming. From a participant perspective a reduced number of questionnaires would have lessened the time the participant spent at each visit, and they may be more likely to take their time and complete the questionnaire properly.

5.10.3 Adherence

Exercise is the recommended treatment for patients with IC, though it is only effective if patients actively choose to participate in SEPs. Despite the evidence favouring SEPs, uptake and adherence in this clinical population are recognised as being far too low (Lin et al., 2019a, Lane et al., 2017b). The findings of this study reinforce this, with a 33% uptake and 53% adherence rate to the SEP. Interestingly, the highest level of dropout was in the pain-free group (4 participants), compared to a drop out of three participants in both the moderate and maximal pain intervention. However, reason for these dropouts were largely related to non-PAD related health issues (mental health/cancer diagnosis/acute illness and bad back). These findings are similar to previous systematic review which analysed 84 studies and found non-PAD/coronary artery disease health issues to be one of the highest reasons for non-completion of a SEP (18.4%) for a SEP (Lin et al., 2019b).

Unexpectedly, no patients in this study dropped out due to the level of claudication pain. However, it is important to take into consideration the trial is yet to be fully recruited. As such,

there is likely to be selection-bias as the participants who have agreed to the exercise intervention are more likely to complete it. Due to this, the sample and target population may differ in significant ways, limiting the availability to generalise the findings. That said, previous research has highlighted that the level of claudication pain can significantly impact a patients adherence to a SEP (Abaraogu et al., 2018). Indeed, previous studies have highlighted how participation rates and completion rates remain low, with the level of pain being a contributing factor (Harwood et al., 2016b, Lin et al., 2019a). This could be explained by the stress experienced by the individual patient to reach maximal pain which may be overwhelming. This can be counterproductive as the intolerable discomfort may reduce the compliance of the programme (Haas et al., 2012).

A reason why the level of claudication pain was not a contributing factor to drop out in this study could perhaps be due the social interaction and relationships created between like-minded participants in the SEP. Previous research suggests participants with IC rely on attitudinal, behavioural control and social normative cues to develop physical activity intentions (Galea et al., 2008). Therefore, although participants in this SEP may have found exercising to maximal pain challenging, their beliefs and social interaction with others in the class may have reinforced the importance of taking part and adhering to the SEP.

Previous research has encouraged low pain to promote a higher adherence and completion rate (Lin et al., 2019a, Harwood et al., 2016b). Likewise, it has been suggested that placing emphasis on tempering intensity of the training bouts, for example walking until the onset of pain may result in a more successful exercise programme (Haas et al., 2012). Even though this may not provide for an optimal stimulus, it can enhance exercise performance. This improvement in walking can eventually turn into a moderate intensity and permit extended

walking which can in turn create a greater benefit. However, this study suggested the level of pain was not a contributing factor to adherence. As such, the study suggests more attention should be given to the social environment and atmosphere in the SEP. The theory of planned behaviour suggests individuals use information around them to make informed decisions about whether to perform a behaviour (Ajzen, 1985). Therefore, it is important each participant receives specific, consistent and clear information whilst being surrounded by like-minded people with the same attitudes and believes. This could improve the adherence and uptake.

5.10.4 Recruitment and Uptake

In the two-year period 105 patients were referred and screened for the inclusion into this study. Of the 90 eligible to take part in the SEP, 67% declined to participate. This finding is similar to a systematic review where every 1 in 3 screened IC patients were willing to take part (Harwood et al., 2016b). Of the 30 participants recruited in this study, only 53% completed the programme. This study forms part of a larger RCT which is fully powered at 57 participants (10% attrition). Despite our best efforts, this number was not attainable for the timeline of this thesis and data collection is ongoing to achieve this.

The primary reason for patients not up taking to the SEP was due to the location of the class and the timing of the session. In addition, Heartbeat NWCC which received the referrals from Lancashire Teaching Hospitals Foundation Trust only provides classes at two locations, Preston and Chorley. Therefore, patients would often suggest they could not attend as they would be having to catch two buses to reach this city centre location from towns further afield (e.g., Penwortham and Longton). Although the accessibility to SEPs in other Heartbeat locations has been highlighted previously, this is not yet in place. The qualitative views and

opinions in chapter 7, along with the recruitment and uptake data in this study will enable the development of SEPs for patients with IC.

Besides amending the time and location of the classes, it is important that the referral process from the NHS trust to the exercise professionals is streamlined and efficient. During this study the clinical vascular lead was contacted to discuss changing the referral process, so data was not replicated and making sure all referral forms where completed fully with no missing data. In some cases, during this study, referral forms were sent missing a contact number which delayed recruitment as time was spent contacting the vascular nurses for this missing information. Likewise medical professionals may need educating on the importance of SEP as they provide the initial patient contact and SEP promotion.

Furthermore, clinicians need to allow for support to be given to the participant on a social level. As discussed in the next chapter, research highlights that social support from family members, friends and peers is a strong influencer for adherence to exercise interventions and encourages consistent behaviour change (Morgan et al., 2016). Therefore, it would be advantageous to allow time before/after the class for patients to socialise and discuss their symptoms. Likewise, a clinic could be established which allows current class members to discuss their experiences with new potential participants, who may be apprehensive about initiating the SEP.

5.10.5 Methodological Considerations

There were a few methodological considerations during the development and implementation of this study. Firstly, the trial was a RCT which was powered to 57 participants, conducting a RCT allowed for all three levels of pain to be investigated. A RCT was the most effective way to compare the three levels of claudication pain for patients with IC. However, due to the large

sample size and slow recruitment/uptake the results were unascertainable for this PhD thesis. Therefore, we have used an exploratory analysis which has identified rather than validated the most significant level of claudication pain. Furthermore, due to the trial being an RCT there was apprehension between exercise professionals as to whether it was ethical to allow some patients to work at pain-free or moderate claudication pain which was not the recommended guidelines. However, after explaining the evidence and need for the RCT they agreed this was needed.

It is important to note that the intervention lasted for 24-weeks, this duration does not represent a typical UK PAD SEP which is recommended for 12-weeks (NICE, 2012). That said, all groups achieved a large MCID from baseline to 24 weeks for MWD. For PFWD, pain-free and moderate pain groups achieved a small change in MCID, and the maximal pain group achieved a moderate change in MCID. Therefore, a 24-week SEP appears to be beneficial for PAD patients. Although, it is well known the completion for 12-week SEPs is already low. Therefore, it is likely that a 24-week SEP will result in a higher dropout.

5.11 Limitations

This study is not without limitations. The major limitation to this study was the recruitment and large number of participants declining the research trial. Due to COVID-19 the trial was delayed and data collection could not commence for several months due to the national lockdown. Once the trial did begin, participants were still extremely cautious of attending the research trial. This could have been due to participants, in the previous months, being advised to ‘stay home’ and not be in close contact with other individuals. Consequently, recruitment in the early stages was extremely slow. Furthermore, the vascular nurses responsible of referring patients into the SEP were transferred (for a month) to other wards in the hospital to help with the effects of COVID-

19 which slowed the referral process. As a result, participant uptake and sample size were limited, although it forms part of a much larger multi-centered RCT. Therefore, the exploratory analysis for predictive level of claudication pain should be interpreted with caution. Also exercise interventions tend to attract motivated individuals who clearly understand the nature of the proposed intervention and benefit of the SEP for their IC. As such, those who agreed to participate in the SEP are likely to be a subgroup of claudicants with a high level of motivation or willingness to change. Yet patients who perhaps may benefit most from this intervention exclude themselves and decline the SEP.

Secondly, the SEP was specifically designed with weight-bearing exercises to bring on claudication pain within 3-5 minutes, therefore limiting the generalisability to other SEP programmes which may include resistance training and upper body exercises. Therefore, future studies should include a variety of recommended exercises.

Thirdly, the author of this thesis was responsible for the study recruitment, patient testing and SEP supervision. This could have unwittingly created some investigator bias in the study. However, participants were unaware of the outcome of their baseline and 12-week test until their final visit, therefore not influenced by the result. In addition, the researcher attended all treadmill tests. This could have created subject bias as the participants may have consciously acted a certain way due to the presence of the researcher. That said, the testing was accompanied by two cardiac physiologists to ensure validity and reliability.

Finally, the research was a single-centre design with patients recruited from one geographical area in the North-West of England. Therefore, the trial is considered to have inferior external 167 validity. Although, allowing for a single-centre design allowed for the simple logistical organisation of this PhD project and guaranteed the consistency of the SEP under investigation.

5.1 Conclusions

SEPs are the recommended first line of treatment for patients with IC. There have been several reports of various levels of claudication pain which led to an improvement in functional outcomes following the programme. This study has identified that a maximal claudication pain intervention seems to elicit a larger benefit in treadmill related MWD compared to pain-free and moderate claudication pain. Perhaps, once the RCT is fully powered (57 participants) there could be statistical significance between groups.

Chapter 6. What is the correct level of claudication pain to prescribe? Universal inconsistency within guidelines, a painful issue

6.1 Background

Peripheral artery disease (PAD) is an atherosclerotic cardiovascular condition affecting the lower limbs. A classic symptom of PAD is intermittent claudication (IC), which precipitates on exertion and is relieved with rest (Fowkes et al., 2013a). Supervised exercise programmes (SEPs) are first line treatments for patients with IC (Lane et al., 2017b, Riebe et al., 2018). Despite the benefits of exercise, there are inconsistencies between guidelines regarding the recommended level of prescribed claudication pain. The aim of this commentary is to highlight the limitations of current guidance which will lead to variability in care.

The National Institute of Health and Care Excellence (NICE) (Layden et al., 2012), American Heart Association (Gerhard-Herman et al., 2017) and British Association of Sport and Exercise Sciences (Tew et al., 2018) recommend exercising to maximal claudication pain. Supporting this, an early meta-analysis showed walking to near maximal pain to be most beneficial at improving maximal walking and pain-free walking distances. Indicating that greater amounts of ischemia induced may produce greater hemodynamic and metabolic adaptations (Gardner and Poehlman, 1995). Metabolic adaptions are a biological response that reduces energy expenditure in response to starvation (Singer, 2004). Exercise training in PAD patients has demonstrated to increase arteriogenesis and angiogenesis with vessels enlargement and remodelling which is activated by a more efficient nitric oxide production and growth factors released (DE MARCHI, 2013). Furthermore, high-intensity walking, eliciting moderate-severe ischemic leg symptoms was superior to low-intensity without ischemic leg symptoms (McDermott et al., 2021a).

Conversely, the American College of Sports Medicine (Riebe et al., 2018) and Exercise and Sports Science Australia (Askew et al., 2014) suggest moderate pain is most beneficial. A systematic review suggested mild to moderate claudication pain yields optimal results in walking distance and cardiorespiratory fitness when compared to moderate-to-maximum pain (Parmenter et al., 2015). The conclusions were in line with the Vascular Disease Foundation and the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines in that lower limb exercise should be performed to a threshold of mild-moderate pain (Foundation, 2016).

As explained in chapter 3, despite the inconsistencies aforementioned, alarmingly several guidelines do not report a level of claudication pain to work towards (Aboyans et al., 2018), whilst others suggest working at a speed and gradient that induces claudication pain within 3-5 minutes, without specifying the intensity of the pain (Norgren et al., 2007) (Table 6.1). As such, clinicians are not provided with clear guidance. A major issue is that guidelines are not fully inclusive of the evidence, as they do not consider pain-free exercise. A meta-analysis showed significant improvements in absolute and initial walking distance without inducing claudication pain (Parmenter et al., 2011). A recent systematic review also suggests pain-free SEPs elicit similar improvements in walking performance and functional outcomes compared to moderate-pain.

The missed consideration of pain-free SEPs and high claudication pain prescription may lead to poor uptake, as high claudication pain has been commonly cited as a barrier to exercise adherence and uptake of SEPs (Harwood et al., 2016b, Lin et al., 2019a). Indeed, patients taking part in a low pain SEP where 1.52 times more likely to complete the SEP than those in the high

pain SEP (Lin et al., 2019a). As SEPs are the first line of treatment for patients with PAD, guidelines must ensure greater participation occurs, consequently patient ability and preference should be considered so it is tolerable and beneficial for all patients (Harwood et al., 2020).

In conclusion, there are inconsistencies regarding the recommended level of claudication pain for clinicians to prescribe (Table 6.1). Furthermore, there is no consideration for the evidence base regarding pain-free exercise. It is clear there is a need for a universal set of guidelines that consider optimising patient outcomes as well as uptake and adherence in relation to claudication pain. No research has directly compared maximal, pain-free and moderate claudication pain, however trials are underway (Birkett et al., 2022b).

Table 6.1. Guideline Recommendations for Exercise

Recommendation	Frequency	Level of Claudication Pain	Type	Time	Duration	Progression	Supervision	Location	Supplementary Exercises
Guideline									
NICE (2012)(Layden et al., 2012, NICE, 2012, Foundation, 2016)	2 x per week	Maximal pain	Walking	2 hours/week	3 months	Not reported	Supervised	Not reported	Not reported
AHA/ACC(Gerhard-Herman et al., 2017) (2016)	3 x per week	Maximum-moderate pain	Intermittent walking	30-45 mins per session, with a warm up and cool down	Minimum of 12 weeks	Not reported	Supervised by a qualified healthcare professional	Hospital/outpatient facility	Not reported
ESC (2017)(Aboyans et al., 2018)	Not reported	Not reported	Walking	Minimum of 3 hours/week	At least 3 months	Not reported	Supervised	Not reported	Cycling, strength training and upper-arm ergometry
TASC II (2017)(Norgren et al., 2007)	3 x per week	Speed and grade that induces claudication within 3-5 minutes	Intermittent treadmill walking	30 mins increasing to 60 mins	Not reported	Increase speed/grade if the patient can walk for more than 10 minutes	Not reported	Not reported	Not reported
RACGP (2013)(Au et al., 2013)	3-5 days per week	Pain	Intermittent walking	30 mins increasing to 60 mins	Not reported	Not reported	Supervised	Not reported	Not reported

ACSM(American College of Sports et al., 2018)	3-5 days per week	Moderate pain	Walking	30-45 mins	12 weeks	May progress to 60 minutes	Supervised	Not reported	Arm and leg ergometry
VDF & AACVPR (2016)(Foundation, 2016)	3 days per week	Mild-moderate pain	Treadmill walking	1hr per session	12-24 weeks	Increase the grade if the patient can walk for more than 8 minutes	Supervised	Not reported	Not reported
BASES (2018)(Tew et al., 2018)	≥ 3 days per weeks	Near-maximum leg pain	Walking	45-60 mins	At least 3 months	Increase walking by 5 mins each week	Supervised	Hospital or community based physiotherapy clinics/community exercise facilities	Upper/ lower ergometry and resistance exercises
ESSA (2013)(Askew et al., 2014)	3 days per week	Moderate intensity	Walking and other forms of aerobic such as cycling/arm cranking	40 mins of aerobic activity	6 months	Progress from moderate intensity to vigorous as tolerate for other aerobic exercises	Supervised	Not reported	Cycling/Arm Ergometry

NICE; National Institute for Health and Care Excellence, ACSM; American College of Sports Medicine, ESC; European Society of Cardiology, TASC II; Trans-Atlantic Inter-Society Consensus, RACGP; Royal Australian College of General Practitioners, AHA; American Heart Association, ACC; American College of Cardiology, VDF, Vascular Disease Foundation; AACVPR, American Association of Cardiovascular and Pulmonary Rehabilitation, BASES; British Association of Sport and Exercise Science, ESSA; Exercise and Sports Science Australia

Chapter 7: Exploring Experiences of a Supervised Exercise Programme for patients with Intermittent Claudication: A Qualitative Study

7.1 Introduction

The previous chapters of this thesis have focused on quantitatively justifying the effectiveness of SEPs prescribed at different levels of claudication pain. However, uptake and adherence in this clinical population remain poor (demonstrated by a high drop-out rate in this RCT) and a previous systematic review highlighted only 1 in 3 patients screened were willing to undertake a SEP (Harwood et al., 2016b). As such it is important to consider patient experiences of the SEP and investigate if there is an effect of the differing levels of claudication pain on uptake and adherence (Lin et al., 2019a, Harwood et al., 2017b). By conducting semi-structured interviews, patient perspective, rather than the investigator's interpretations, can be explored. Through using a combination of quantitative and qualitative data, a degree of comprehensiveness can be achieved to generate a greater in-depth understanding of SEPs with IC populations (Verhoef and Casebeer, 1997).

7.2 Aims and Objectives

This study aimed to explore:

1. Participant experience of the supervised exercise programme
2. How easy or difficult they found it
3. Their enjoyment of the programme and whether they would undertake it again
4. Any problems/barriers of the programme
5. Potential ways of improving the programme
6. Reasons for non-completion (if applicable)

This was achieved via semi-structured interviews with a subset of participants who were involved in the previous RCT (chapter 5). The main objective was to explore participant experiences and understand in greater detail why participants took part, why they dropped out and ways to improve current SEP.

7.3 Method and Design

7.3.1 Interview

Participants who were screened to take part in the above RCT were eligible to take part in this study. The interview was outlined in the PIS (appendix B) and consent form of the RCT (appendix C). Participants consented if they would be willing to participate in an interview following the completion of the 24-week programme. All interviews were conducted by SS who previously gained experience from watching clinical psychology interviews within the School of Sport and Health Sciences at the University of Central Lancashire (UCLan).

The interviews followed a pre-determined set of open questions but based on the response of the individual, follow up questions were asked. All interviews were face-to-face in a private room within Heartbeat NWCC. They were recorded using a voice memos software and transcribed anonymously. The interviews were saved and stored on a password protected laptop in a password protected word document file. Prior to the interview, participants were told they did not have to answer any questions which they were uncomfortable with. Furthermore, confidentiality and anonymity of their answers were reiterated. Each participant was made aware of this and had their identity protected using pseudonym and removing any identifying information. Although the data would be reviewed by members of the research team (i.e., supervisors), assessed by external collaborators and maybe published/disseminated at conferences, all this data would remain completely anonymous.

7.3.2 Interview Structure

The interview process involved a number of stages:

- *Introduction*
  - Introduce self
  - Explain: Nature & purpose of research
  - Who the research is for
  - Introduce audio recorder
  - Stress confidentiality
- *Background*
  - Household composition
  - Employment status and details
  - Spare time activities / hobbies
- *IF COMPLETED THE PROGRAMME: Experience of the exercise programme*
  - Overall, what did you think of the programme?
  - How did you find it? Was it easy, hard or somewhere in-between?
  - Why did you choose to participate?
  - What parts of the programme did you enjoy?
  - What parts of the programme did you dislike?
  - Would you complete the programme again?
  - What impact did the programme have on your symptoms of intermittent claudication?
- *IF DROPPED OUT: Experience of the exercise programme*
  - Overall, what did you think of the programme?
  - How did you find it? Was it easy, hard or somewhere in-between?

- Why did you choose to participate?
- What parts of the programme did you enjoy?
- What parts of the programme did you dislike?
- Why did you not complete the programme? Any barriers?
- What could we have done to prevent you from leaving the programme?
- What impact did the programme have on your symptoms of intermittent claudication?

- *All Participants: Potential barriers*
  - Do you think there would be any reasons, i.e. Money, Cost, Travel, Group, Emotional, Social why you would not take part in the programme again?
  - Why do you think other people do / do not take part in the programme?
  - Potential ways of improving the service
  - What could we do to encourage more people to take part in the exercise programme?
  - If you were promoting it, how would you do it and which elements would you highlight as most important?
  - What would you do to improve the current service? For example; time / location / provision / group sessions / type of exercise.
  - Is there anything else you would like to add?

- *Potential ways of improving the service*
  - How could we encourage more people to take part?
  - Anything else they would like to add

7.3.3 Participants

As previously detailed above, participants who were screened for the RCT were invited to take part in this study. Semi-structured interviews were conducted in two groups of participants:

Group one: Participants who completed the SEP. These interviews consisted of asking the participants about their experiences of the programme, why they chose to participate, whether they would be willing to undertake the programme again and the impact of the SEP on their symptoms of IC. Completers were coded as "C", e.g., a 71-year-old female completer would be abbreviated as (Female C, 71).

Group two: Participants who initially agreed to take part in the SEP but discontinued after taking part in at least one session. These interviews delved into how the participants found the SEP, any barriers that contributed to withdrawal and anything the research team could have done to prevent them from leaving the programme. This group where classed as the non-completers. Non-completers were coded as "NC", e.g., a 71-year-old female non-completer would be abbreviated as (Female NC, 71).

7.3.4 Sample Size

The sample size for qualitative interviews was based on the data reaching thematic saturation. This is where there are no new themes or categories arising from the data. Therefore, there was no pre-specified sample size, the aim was to complete interviews until saturation was reached. Previous research has found saturation can be occur with twelve interviews, although early basic themes can be present in as early as six interviews (Guest et al., 2006). Consequently, we aimed for six in each category to achieve saturation.

7.3.5 Data Analysis

Data was analysed using the Braun Clarke six stages of thematic analysis (Braun and Clarke, 2006). The data was transcribed by SS on Microsoft Word before being read and revised to note down initial ideas in the data set which were reoccurring in the transcripts. These initial

ideas were labelled codes, which emerged from the data collection and not a pre-existing framework. Therefore, taking an inductive approach.

Once the initial codes were identified, they were interpreted and synthesised into sub-themes. To ensure the coding theme was accurate, it was reviewed by a Health Psychologist at Heartbeat NWCC who was competent and had extensive experience analysing qualitative data after recently gaining her PhD (Table 7.1). Feedback was provided ahead of generating the final themes. Following this, four major themes were actively generated from the data set. Data was analysed using Microsoft Word.

Table 7.1. Coding Table

Initial code	Codes/Interpretation/Sub themes	Actively Generated Themes
Instructor relationship	Social Communication	
Comfortable environment	Social Communication	
Friendly atmosphere	Friendship	**The Importance of Social Interaction and Support**
Made friends in the class	Friendship	
Group environment	Friendship	
Willingness to take part again	Knowledge sharing /co learning	
Want to help others with the condition	Knowledge sharing /co learning	
Other people same condition	Knowledge sharing /co learning	
Increased knowledge and understanding of the condition	Education	
Apprehension to join a gym environment	Reluctance and Dedication	**Contributors to Physical and Mental Well-being**
Felt like this was the last chance	Reluctance and Dedication	
Commitment to themselves and the gym	Reluctance and Dedication	
Sad to drop out of the research – health reasons	Reluctance and Dedication	
Seeing an improvement in symptoms	Improvement in symptoms	
Increase habitual activity	Improvement in daily life	
Monitor improvement at home	Improvement in daily life	
Improvement in confidence	Mental health	
Mental barriers	Mental health	
Value for money	Physical barriers	**Programme Facilitators and Barriers**
Transport issues if no car	Physical barriers	
Time of day – earlier?	Physical barriers	
Good location	Physical barriers	
Gym environment (music, fun, enjoyment)	Programme layout	
Introduce upper body exercise?	Programme layout	
Boredom – same 6 exercises	Programme layout	
Programme promotion	Face to face interaction / Increase knowledge	**Awareness to Promote the SEP**
Open days	Face to face interaction	
Posters	Patient feedback/Increase publicity	
TV advertising	Patient feedback/Increase publicity	
Leaflets	Patient feedback/Increase publicity	

7.4 Results

7.4.1 Recruitment

Of the 16 participants who completed the SEP 15 completed the interview. All nine participants who withdrew from the programme were invited for interview, with two agreeing to participate. Although plentiful information had been gathered from those who had completed the programme, it is possible that new data could have emerged in from those who withdrew from the programme had more agreed to take part in the interviews. However, due to many people withdrawing due to further mental/physical health issues, recruitment for this group was minimal.

The mean interview length was 15 minutes and 07 seconds (range; 8 minutes and 44 seconds to 27 minutes and 34 seconds).

7.4.2 Participants

All interviews were conducted in person at Heartbeat NWCC in a private office and gave written and verbal consent to take part. Of the 17 participants interviewed, 35% of participants were female. For the withdrawers, the mean age was 78 ± 3.5 years and 50% of participants were male. For the completers, the mean age was 69 ± 9 and 67% of participants were male. This sample is representative of a typical PAD population as the prevalence is higher in men than women (as discussed in chapter 2) (Song et al., 2019).

7.4.3 Thematic Analysis

Four major themes were actively generated from the data analysis, with multiple sub themes within these. These are presented in table 7.2.

Table 7.2. Themes and Sub-themes

Themes	Sub-theme
The Importance of Social Interaction and Support	Social Communication & Friendship
	Knowledge sharing and co-learning
Contributors to Physical and Mental Well-being	Reluctance & Dedication
	Improvement in Symptoms and Daily Life
	Overcoming Mental Barriers
Programme Facilitators and Barriers	Physical barriers
	Exercise Programme Structure
Awareness to Promote the SEP	Face to face Interaction
	Patient Feedback & Increased Publicity

7.4.4 Theme 1 – The Importance of Social Interaction and Support

Throughout the interviews, the participants described social aspects of the programme as being positive contributors to their experience. Specifically, enjoyment of the social environment and having the opportunity to give and receive support were seen as important. This has been encapsulated in social communication and friendship and knowledge sharing and co-learning.

7.4.4.1 Sub theme 1a. – Social Communication and Friendship

The majority of participants who engaged in the SEP described enjoying the social environment. For example, a class member reported that the class was “very sociable and people are very friendly” (Female C, 74). This was supported by a male who highlighted humour as a notable element of the social environment by saying “the social interaction with everybody was quite a laugh” (Male C, 77). Furthermore, several participants explained deriving enjoyment from expanding their social horizons in the class. For example, one patient

stated, “meeting new people I wouldn’t normally do” (Male C, 60), whilst another patient described the class as having “a really good group and mix of people” (Male C, 51). Some participants described the class as an afternoon out “it’s like a trip out for a few hours” (Female C, 74) and others explained how it was nice to have a social interaction after the COVID-19 restrictions, “it’s the social side of it because at the moment or last couple of years since covid started we have not been going out” (Male C, 82). Likewise, the two participants who were unable to complete the SEP emphasised their positive experiences with the other class members, “the group were funny, they were good” (Male NC, 74) and “I have loved all the people they are all different characters” (Female NC, 81).

Several class members had a pre-conceived expectation that the gym was going to be a tough and judgemental environment, saturated with young physically fit individuals. However, once they had completed their first session this opinion was changed. Many participants found the gym a comfortable environment which was less intense than expectations, “it was relaxed enough to not get you worked up” (Male C, 60). Likewise, participants were thankful it was not like gyms they classed as ‘normal’ with a younger target audience, “not like going to a gym where everyone tries to get a six-pack” (Female C, 66). Similarly, the gym facilitated a safe environment where participants were not comparing themselves to others which could have hindered their self-esteem, “it’s never a competition” (Male C, 74) and “no competition at a normal gym, oh look at her what are you wearing” (Female C, 72).

Importantly, most participants commented on the positive relationship they had with the instructor. For example, one patient stated, “I am delighted to have found you” (Female C, 83) whilst another patient appreciated the knowledge instructor contributed by stating, “friendly welcoming instructors that know what they are doing” (Female C, 72) and “I think you and

[instructor] are absolutely wonderful" (Male C, 68). Similarly, it was highlighted that a personable, friendly approach was vital to keep participants attending and enjoying the SEP, "It isn't the same when I have done the class with other people, the energy levels are not the same, we don't have as much of a laugh" (Male C, 51). Likewise, one patient stated, "I think a barrier would be if the instructor was iffy and pressured and not friendly and welcoming" (Female C, 72). Finally, one patient was grateful for the energetic atmosphere created by expressing, "they get the older generation fired up in a good way, but it's only made like that because of the instructors" (Male C, 67).

7.4.4.2 Sub theme 1b. - Knowledge sharing and co-learning

In addition to socialisation, many participants highlighted how they enjoyed being in the company and sharing knowledge with people who had been diagnosed with the same disease. Intermittent claudication (IC) is not a well-known condition; therefore, participants expressed their appreciation for being able to socialise with like-minded individuals who had been diagnosed with IC and therefore dealt with similar symptoms. One patient stated, "being here with people in the same boat as you who understood what you were going through" (Female C, 66). Agreeing with this another patient described, "I think it's good we are all in the same boat with the same problem and we can talk about it together" (Female C, 74) and "being part of a group of people doing the same thing with the same problem" (Female C, 66). Despite not completing the programme, (Male NC, 60) expressed his gratitude for being with relatable people "you are with like-minded people... you know hobbling about but it is doing us good." In addition, one patient highlighted how meeting others with IC allowed everyone to see the vast variation of symptoms from mild to severe. This led to participants revaluating the severity of symptoms and appreciating that they were not as severe as they thought "some people made you think you were not as bad and other people made you think yeah it does hurt" (Female C,

66). Consequently, participants had an increased positive mindset towards improving their symptoms.

In addition, several participants highlighted they took part in the SEP to help the research team and they took pride knowing they were increasing the knowledge for future diagnosis and exercise guidelines. For example, one patient simply stated, “if it helps improve someone else as well then why not” (Female C, 66). Other comments included “I am always putting my body forward for research” (Female C, 83). Equally, two participants stated they were taking part for the benefit of their own health and the research “to hopefully improve my fitness and to help with the programme and the research” (Male C, 77) and “I believe in anything that improves myself and other peoples so if I can help it’s a good cause” (Male NC, 60). Likewise, a few participants mentioned the SEP was useful to increase their knowledge of the disease “I learnt a lot about my condition which I didn’t understand” (Female C, 66) and “I used as much information as I could to see if I could improve it” (Male C, 82).

7.4.5 Theme 2: Contributors to Physical and Mental Wellbeing

During the interviews, the participants described how the SEP was a positive contributor to their physical and mental wellbeing. Particularly, their improvement in symptoms of IC and changes to their daily life habits were seen as important. Some participants were initially reluctant to take part, however this reluctance was replaced with dedication once participants saw the benefits of the SEP. Furthermore, participants were able to increase their confidence and overcome mental health barriers related to exercise.

7.4.5.1 Sub theme 2a. Reluctance and Dedication

Although participants enjoyed the social and learning experience of the SEP, it was clear several participants were originally reluctant to take part and simply joined due to the signposting from medical professionals. One patient stated, “to be honest with you I felt like I had very little choice, I felt like if I didn’t do anything the NHS would say right forget it you know” (Male C, 68). Similarly, a patient mentioned, “I thought it would help and it was strongly recommended by the vascular nurses” (Male C, 62).

Additionally, one patient mentioned they took part in the SEP because they didn’t want to miss the opportunity of potentially having future surgery “I felt if I didn’t do anything then they would say well if you can’t help yourself then they won’t operate or anything” (Male C, 68). Lastly, one patient shared his disinclination to take part in the SEP and only chose to participate due fear of amputation, “I was told by the vascular surgeon that if I didn’t walk half an hour a day then I would have to have my leg off. So, he did frighten me” (Male NC, 60).

Conversely, several participants expressed their willingness towards participating in the SEP. One patient described the opportunity as a god send, “I wanted help and thought this was a god send when I got the phone call” (Female C, 66). Likewise, several participants explained their dedication towards the SEP, “you are enrolled and feel like you have an element of responsibility to turn up. Yeah, it’s the commitment and also a commitment to ourselves and then yourselves” (Male NC, 60).

Even though two participants were unable to complete the programme, both highlighted they were sad to have to withdraw because they were committed to the programme. One patient said, “I didn’t want to not take part Sally, I would have loved to keep going” (Male NC, 60). Additionally, the second patient mentioned it was an unfortunate cascade of additional illness

which stopped her from completing the SEP, “well three things... costochondritis, surgery and covid. It was one thing after another” (Female NC, 81). This emphasises that participants were willing to take part in the SEP however some factors were out of their control.

7.4.5.2 Subtheme 2b. Improvement in Symptoms and Daily Life

Most participants described a definite improvement of their symptomatic symptoms of IC. One patient stated, “It has definitely erm stretched out the length of time before my legs starts cramping you know my calves start cramping” (Male C, 67) and another stated “Ohhh obviously the improvement in my claudication was quite incredible. Really. I there was no doubt about it, it helped a lot” (Male C, 77).

Equally, one patient explained how the symptoms were not as severe as they used to be and the recovery was quicker “The symptoms don’t come on as soon anywhere near as soon and when they do, they aren’t as severe and the recovery is far quicker” (Male C, 77). Another patient stated “I definitely saw an improvement. It’s improved my distance without erm getting severe pain” (Male C, 60).

During the programme, participants were able to identify and monitor their improvement during the programme, this gave them an incentive to continue “I have seen in the gym that I can do more, like you say I altered the speed of 3.2 I could only do one minute but now I can do nearly 2 minutes. So, I can see it must be doing something for me to be able to do more in the gym” (Male C, 58). Similarly, a patient shared “I found I could do more on the treadmill I used to like going on the treadmill and like I had gone from 5 to 10 minutes” (Male NC, 74). That said, a few participants perceived no improvement in their IC symptoms, however they were consciously able to identify the level of pain in their calves and know how to manage it

better. One patient stated, “I’ll be honest not a huge impact because it has not gone away erm, but it has made me conscious of the level of pain when it starts and so on and making me accept that I can just stop and rest but then I’ll be alright, and I can get going again in a couple of minutes” (Female C, 72).

In addition to improvement of symptoms, participants also described an increase in their habitual activity around their home and throughout their daily lives. One patient commented on how an improvement in her symptoms allowed her to now go on a walking holiday which she had been scared to do previously, “I was frightened in case I couldn’t keep up with people who wouldn’t understand but now I go out again and go on a walking holiday which I didn’t go on last year” (Female C, 66). Similarly, many participants explained how they could walk further when going to the supermarket and keep up with family members, “My wife can take me around the shopping” (Male C, 77) and “I can measure this quite easily because before I started the programme I used to park my car in the carpark in Chorley and cut through some buildings to get to M&S and by the time I got there my legs were killing me. Whereas now I walk straight past M&S and I can go round the market and do all sorts of shopping” (Female C, 83). Finally, one patient was proud to share his improvement walking to the local shop, “I couldn’t get to the end of the street without getting cramp, you know it took me three goes just to get to the local shop which is a quarter of a mile away if that! Now I can get to and from the shop! So, for me that is a massive thing!” (Male C, 51). This incentive to measure their increase habitual activity was probably driven by their increase confidence and knowledge of their IC.

That said, two participants perceived no improvement in their daily activities, “I must admit walking on pavements is not as easy as walking on the treadmill” (Male C, 68). Another one told, “The only long part of exercise I get beside coming here is putting the bins out and I am

still by the time I take the bin out and walk back I am in agony so that bit hasn't changed" (Male C, 58). Interestingly, both participants did say they saw an improvement in their symptomatic symptoms in a gym environment.

7.4.5.3 Subtheme 2c. Overcoming Mental Barriers

Overcoming personal mental health barriers were mentioned by five participants. One patient described an improvement in their mental health as being more important than their physical improvement, "if I have to be totally honest with you it has done my mental health more good than my physical health" (Female C, 66). Supporting this, one patient explained that the SEP had provided them with a sense of purpose "when you retire there is not a lot of purpose and I need purpose. So, to come twice a week whilst it was difficult, I knew I had to be there and from my mind point of view that was a good thing" (Male C, 67). Finally, a lady was grateful for the knowledge and advice provided during the class "A general understanding has made me feel better mental wise" (Female C, 66).

An increase in confidence was also highlighted by participants on many occasions. One patient stated, "yeah you lose that fear of walking" (Male C, 74). Whilst another patient shared, "I got more into it and more confident, as I am not a confident person" (Male C, 51). As such, some participants described that their confidence grew due to being surrounded by participants with the same condition, as mentioned earlier, "erm it gave me a little bit more confidence in the fact that I realised that I wasn't the only person in this position with PAD" (Female C, 66). Likewise, one male observed that his confidence grew based on the supervision in the room which allowed him to push his claudication pain further than he usually would "I certainly wouldn't have the confidence knowing I have trained CPR Instructors in the room because that

is where half my confidence came from! You know I knew I could push myself and if you fall over someone will sort you out!" (Male C, 51).

7.4.6 Theme 3: Programme Facilitators and Barriers

Potential barriers were identified by all 17 participants interviewed. However, most participants interviewed completed the programme so were not affected by the barriers, but they were still able to identify the influence for other participants.

7.4.6.1 Subtheme 3a. Physical Barriers

Two key barriers were identified for participants attending the SEP, namely transport/location and time. The cost of the programme was mentioned however only minimally. With regards to transport and location, it was made clear that if the participants did not drive, they would struggle to attend the SEP as many people lived further afield than in the centre of Preston. Although these were not barriers for most personally, they appreciated it could present as a barrier for other people. A patient from Penwortham stated "if someone was living in Penwortham and didn't have a car it might be an issue because you are looking at two buses to the bus station and one up. It could cause an issue" (Male C, 51). Likewise, a patient in Leyland mentioned "where I come from it would be a case of two buses and two buses back. But it's not just that I would be panicking in case I wasn't back in time for picking the children up from school" (Female C, 66).

In addition, two patients highlighted travelling to Heartbeat NWCC from most surrounding areas relies on getting two buses as opposed to one. One patient stated, "people would probably think hang on a minute I have to catch two buses you can't really get one" (Male C, 58). That said, one patient who did have to get the bus to class didn't find this an issue at all "I don't

have to pay for my travel because I am over 75 and I have a bus pass" (Male C, 82). Conversely, several participants thought the location of the class was brilliant, "the location is excellent for me" (Female C, 83) and "No I am literally only a mile away" (Male C, 60). Furthermore, the participants commented on the free unlimited parking available at the site, "it's a good location here, plenty of parking" (Male C, 74) and "it's really accessible" (Male C, 62).

With regards to the time of the class, many participants mentioned they would have preferred it to be earlier in the day as opposed to being around lunch time (12:15pm/13:30pm) as it caused some inconvenience to their day. Participants stated, "I wouldn't have minded it a bit earlier in the morning, it ties your day up a bit" (Male C, 82) and "I think the middle of the day is an awkward time yeah but that's just me!" (Female C, 66). Equally, some participants liked the time of the classes as it suited their lifestyle, "Daytime 12-1 is ideal for me" (Male C, 60) and "No it was perfect for me" (Male C, 51).

That said, the participants who were content with the class time still respected that it wouldn't suit everybody "I suppose if you get a class earlier in a morning then people might work and if they do afternoon shifts then they couldn't come" (Male C, 58). Whilst another stated, "But you know you can't pick and choose!" (Female C, 72). Although time of the class presented as a barrier for some participants there was no dropouts based on this. Therefore, suggesting that the benefit of the SEP was more important than the slight inconvenience of the class time.

Most participants commented that the class was value for money and therefore financial cost did not cause a major barrier to taking part "No I think it is really inexpensive" (Male C, 62) and "I think it is very very cheap to come here and it's really good value, it's cheaper than going to any gym" (Female NC, 81). Nevertheless, some participants did mention that when

you factor in the cost of travel with the class fees then it would be cheaper to go to a gym closer to home, “I know the gym round the corner from me is £20 a month. So, I am a bit like you know the only difference is the travelling. If this is going to be £25 a month plus travelling and the gym nearer to me is only £20 a month” (Male C, 58).

As mentioned earlier the main barrier which contributed to the drop out of participants were other uncontrollable health issues. Both dropouts who accepted to be interviewed dropped out due to medical reasons “Bad back and I have a hernia and each side of my groin” (Male NC, 74) and “Costochondritis, surgery and covid” (Female NC, 81). Other barriers included wanting the SEP to be spread out more equally during the week, rather than having one day to rest in between. The patient summarised “The only thing I would like in a way is to spread out the Wednesday and Friday. So have Tuesday and Friday or Monday and Thursday” (Female C, 83).

Interestingly, one patient commented that the entrance to Heartbeat itself was uninviting and could be a potential barrier for future members “I do think the entrance into Heartbeat leaves you absolutely cold. I think the reception lets the place down. There’s nothing on the walls, there’s no nice anything, you could just lose yourself in a nice picture… it doesn’t look inviting does it” (Female C, 66).

7.4.6.2 Subtheme 3b. Exercise Programme Structure

Most participants enjoyed the class and initially didn’t identify specific details, “I found the programme as a whole good, it’s good for your fitness yeah” (Male C, 74) and “the classes and the exercises I couldn’t say anything bad about them at all” (Male C, 51). More specifically, when probed, participants highlighted they particularly enjoyed the structure of the class with

the warmup and cool downs. One patient mentioned “The warmup and cool downs were really helpful in the beginning” (Male C, 62) and “The warmup exercises, I appreciated them, those actually do help and get you going” (Male C, 68).

Most participants were happy with the six weight-bearing exercises designed to bring on their claudication pain. Although one patient mentioned that they would like to “go on a little bit more” (Male C, 82) once they had completed the research trial. Also, a patient did mention he would like to include some upper body exercises “the one thing I am concentrating on now… I am doing more upper body” (Male C, 77).

Next, it was evident some participants found it difficult working to a set level of claudication pain. As the level of claudication pain was very subjective, it seemed participants randomised to moderate pain were unsure when it was right to stop exercising “I still don’t get how you can say right I am now moderate because you have got nothing and then for me it’s like POW, it doesn’t do a build-up” (Female C, 66). Likewise, participants had been led to believe that maximal pain was the most beneficial and so struggled having to work at a lower level of claudication pain “I was moderate pain and sometimes you want to push yourself a little bit further because you are not quite sure what benefit you are getting from moderate… which isn’t really what I was led to believe” (Male C, 68). Similarly, one patient randomised to moderate claudication pain was apprehensive at first “this was a challenge because once you get used to a pain you just keep going because you are used to it” (Female C, 72). However later this patient recognised that after consistency and discipline it may not require maximal pain to have a positive benefit, “I was noticing a difference in the distance I could walk” (Female C, 72).

Whether the patient found the SEP easy or difficult mainly depended on the level of claudication pain they were randomised to. For example, a response from a patient randomised to pain-free claudication pain, “I found it easy because I only went to pain level 1” (Male C, 67) significantly differed from a patient randomised to maximal level of claudication pain “I found it hard! At first it was really hard because I didn’t know where my max pain level was because I hadn’t pushed to it” (Male C, 51). One patient stated the programme was hard and then got progressively easier once he had become familiar with the exercises “hard at first because I had never done anything like that for a while” (Female NC, 81). Whereas once patient said it was hard dependent on their level of physical activity undertake in the morning or the day before the SEP “dependent on erm how much I had done the day before or the morning before I came” (Female C, 66).

Additional comments on the structure of the SEP were how participants enjoyed the music which was added to the main body of the session “the music stimulates you. I think without the music you would think oh god. But with the music you can become jolly” (Female NC, 81). Moreover, a patient enjoyed the simplicity of the circuit “It’s not overdone, and I think if it was a lot more complicated that is off putting for people that are older” (Female C, 74). Lastly, participants reiterated how they appreciated the social interaction as mentioned in the above theme “I mean every week you come, and you are laughing at something or other because there are some funny characters in there and you get to know them!” (Female C, 66).

7.4.7 Theme 4: Awareness to Promote the SEP

For all the barriers above, many participants offered solutions and ways to help raise awareness to promote the exercise programme.

7.4.7.1 Subtheme 4a. Face to Face Interaction

It was suggested that visiting the research centre may be beneficial to promote the exercise intervention and allow participants to see the exercise session, where participants could observe others already taking part. One patient suggested this would be of benefit to reduce the fear of the unknown as participants are unsure what to expect when they attend the SEP, "We need an open day where we just get people down and say come and look at what we do in class and get all the good ones and good at doing things and say come on we have to show them. Just show people. Maybe they are going to be frightened of joining. We need to get people in to see what we do" (Female C, 66). Equally, one patient emphasised that new starters should just be introduced to Heartbeat "just shown them Heartbeat and show them what is happening. Show them the exercise programme" (Male C, 77).

An alternative but similar suggestion was to arrange a clinic for current class members to meet prospective participants who are thinking of taking part in the exercise programme "Even if it is possible to let you go to a clinic where people are meeting people like me and we can just chat to people" (Female C, 83). This would allow new participants to gain a better understanding of the exercise programme and give the opportunity to ask current participants of their experiences and benefits of taking part in the exercise programme. Furthermore, it may reduce the fear of apprehension when attending their first session if they recognise a familiar face they have met in the clinic. As mentioned above, many participants commented on the social side of the SEP, if this was discussed face-to-face with prospective participants more participants may uptake. As one patient mentioned "I would promote the social side of it as well I think it is really important" (Female C, 66). Similarly, one participant highlighted the importance of talking to others to allow for a greater promotion of the programme "It's like running a friendship centre it's like word of mouth" (Female C, 83).

7.4.7.2 Subtheme 4b. Patient Feedback & Increased Publicity

A vast number of suggestions were made to promote Heartbeat NWCC, the centre for the exercise programme. Although Heartbeat was originally just for cardiac participants, it has now developed and provides supervised exercise classes for many cardiovascular diseases including PAD. However, some participants indicated this is not clear nor well promoted "I just thought it was for hearts" (Male C, 82) and "Yeah to more offer PAD and I don't think many people know about that" (Male C, 60).

When asked how we could promote the exercise programme may participants stressed it needed to be advertised more "I suppose it's publicity" (Female C, 83) and "advertise it more" (Male C, 62). Whilst encouraged to suggest were we could advertise the programme; many participants suggested their local doctor's surgery. One participant suggested, "For one it should be in every GP Practice. Not just a piece of paper with a drawing pin to it, it should be coated in plastic stuck on there forever for everyone to see" (Male C, 67). Another participant stated, "get flyers up in doctor's surgeries and notice boards. Well, that knowledge needs to be out and about that people can get a form" (Female C, 72).

Likewise, one patient mentioned "It would be good if people's doctors recommended it" (Male C, 51). Agreeing with this, one patient mentioned it would be useful if the doctor could refer you straight to Heartbeat without having to go through the vascular team at the hospital "Perhaps having more GPs able to refer you to it. I mean it was only through the hospital service that I even know about it" (Female C, 72). Furthermore, one patient highlighted how it would be better publicised in a GP surgery than at hospital due to the current waiting times "I

don’t think people really read things in hospital as much as GPs because you are waiting. In our doctors there’s a new building and TV on the wall” (Female C, 74).

Other suggestions to promote the programme included distributing leaflets so people can read about the SEP in their own time “Pick up a leaflet and look at it in their own time and then make a decision” (Male C, 51). One patient suggested advertising the programme on public transport where there is a big audience “on bus stops, on buses… where people stop!” (Female C, 66).

When asked how we could promote the programme, many participants were cautious that Heartbeat was a charity and therefore had limited funds. One patient stated, “Whilst I realise it’s a charity, the only way to get more people into the classes is to let people know about it through advertising which I know costs money” (Male C, 67). Similarly, another patient mentioned, “To go on TV would take all your funds and resources. Yeah, especially when it’s a charity” (Male NC, 74). Lastly, when talking about advertising, one patient added “there are quite a few cheap ways around” (Male C, 67), showing his awareness of Heartbeat’s financial budget.

7.5 Discussion

The aim of this study was to explore patient experiences of a novel exercise programme where participants were randomised to one of three levels of claudication pain. Further aims were to understand if participants found the exercise programme easy/difficult, their enjoyment, potential ways of improving the service and reasons for non-completion through semi-structured interviews.

Overall, all participants stated they enjoyed the programme and would recommend it to prospective participants. Most participants were grateful for the social interaction and rapport built with like-minded individuals who endured similar symptoms of IC. Furthermore, the majority of participants believed they noticed a symptomatic improvement in their symptoms of IC. This suggests it is acceptable and effective. Although some barriers towards the programme where highlighted, participants stated they were due to personal preference and understood they could not suit everyone.

7.5.1 The Importance of Social Interaction and Support

Overall, many participants stated they enjoyed taking part in the class as it allowed them to make friendships and meet like-minded individuals who had the same condition. Furthermore, some participants mentioned they would have felt uncomfortable and embarrassed it if was a one-to-one. This is important as a previous study has shown that information and encouragement from significant social referents has been associated with physical activity levels in older adults (Clark, 1999). Recent research has found that social support and companionship is valuable to facilitate walking activity as participants with IC are sensitive to the social attention which comes with symptomatic conditions and having to rest due to leg pain (Martin et al., 2000). Therefore, this study supports previous research whereby participants have described the value of being with likeminded individuals who understand their condition and are aware they may need rest breaks after a period of walking (Galea et al., 2008).

Indeed, participants in this study enjoyed being in a comfortable environment with participants who had common goals and did not feel like they were in competition. This is of importance because it has been found that rest breaks accompanied by fellow participants talking about

similar interests can be helpful in alleviating anxieties about appearing conspicuous. Furthermore, it helps pass time whilst the pain subsides without the patient feeling guilty or in the spotlight (Galea et al., 2008). Given that PAD is an overarching construct ranging from the mildest to severe IC, the results of this study reinforce the importance of social interaction between participants which allows them to discuss their symptoms and treatment.

Additionally, the SEP took place after a national pandemic and two-year lockdown due to COVID-19. This could have drawn attention to the importance of social interaction and made participants appreciative of the group environment. High risk participants and those who lived on their own during the pandemic would have had limited interaction during this time and therefore may have found it a relief to finally be able have conversations and socialise with others.

Most participants mentioned the encouraging relationship they had built with the instructor. This was valuable as participants stated that the energy, support and information shared by the instructor was one reason why the participants attended the SEP. A previous study highlighted the importance of person-centred care with specific, consistent and clear information provided (Gorely et al., 2015). Future ways to improve social interaction and support could be to harness the support from spouses, close friends and family members. Earlier research has found corroborating evidence for the importance of companionship in supporting physical activity levels amongst older adults. Therefore, by providing educational talks for family and friends this may increase the support and awareness of the condition and therefore more participants may adhere to the SEP (Dubbert et al., 2002).

An honourable relationship with the instructor and fellow class members provides strong evidence of SEP adherence and promotion. According to the theory of planned behaviour, individuals use information around them to make informed decisions about whether to perform a behaviour (Ajzen, 1985). A previous study suggested participants with IC rely on attitudinal, behavioural control and social normative cues to develop physical activity intentions (Galea and Bray, 2006). Therefore, this study supports that when surrounded by like-minded people with the same believes and attitudes, participants are more likely to uptake in the SEP.

Several participants stated they wanted to take part in the research trial to help with the research and enable outcomes to help others, this is known as altruism. A previous systematic review looking into why participants took part in research found altruism to be one of three dominant facilitators for research (Sheridan et al., 2020). However, if participants do have a sense of pride to take part because it is a research trial, it is questionable whether they would still uptake once the research trial comes to an end and it just becomes standard care.

7.5.2 Contributors to Physical and Mental Well-being

Acknowledgement of the barriers leading to reluctance in participants with PAD is crucial in augmenting exercise programmes to suit the population with IC. Of the participants in this study, the minority expressed reluctance to take part and only did so because of the fear associated with amputation or vascular nurses' advice. It was evident the SEP had not been explained thoroughly and the participants were unaware what they were signing up to. This finding is similar to a previous study whereby patients reported a lack of empathy from medical professionals, feelings of dismissal and a lack of awareness of them as a person (Gorely et al., 2015). Like previous studies (Gorely et al., 2015, Galea et al., 2008), the patients were left confused by medical professionals as the benefits of a SEP had not been clearly explained. An

explanation for this could be related to the results of a recent survey where the importance of SEPs were only deemed slightly important and not important at all to commissioning bodies (Harwood et al., 2017c). As they are responsible for deciding if the service needs implementing in a clinical setting, the lack of value given to SEPs may lead to a reduce promotion of external programmes.

This and prior studies (Gorely et al., 2015, Galea et al., 2008), highlight the need for an educational intervention explaining what to do when experiencing claudication pain and how the SEP leads to changes that benefit the participant. Likewise, earlier studies have highlighted a lack of understanding of IC which has become a mental barrier for taking part in the SEP (Treat-Jacobson et al., 2002, Harwood et al., 2017a). An educational intervention will be crucial to the success of any programme. It is evident the participants need to believe in the outcomes associated with pain which will consequently reduce the feeling of reluctance, as perceived in this study. A previous pilot study concluded educational programmes were feasible, acceptable and potentially useful for improving walking capacity (Tew et al., 2015). Although, a fully powered randomised control trial and an added educational programme is yet to be undertaken.

Following the exercise programme, it was evident most participants found an improvement in their symptoms of IC. This was an anticipated finding due to the significant body of research supporting the benefits of SEPs (Lane et al., 2017a, Lauret et al., 2014). Furthermore, participants were able to monitor and identify their improvement during the programme. Participants noticed they could walk further and improve the speed and incline of the treadmill. This is important as once the patient begins to see an improvement in their walking performance, they become more motivated (Harwood et al., 2017a). Previous studies have

found low motivation as one of the main reasons for poor adherence (Lin et al., 2019a). Therefore, the higher the motivation of the patient, the higher the sense of achievement and incentive, consequently increasing adherence to the programme.

In addition, several participants reported they had improvement in their habitual activities and could take part in family events such as walking and shopping. However, one patient mentioned he saw no change in habitual activity even though he had an improvement in his maximal walking distance following the 24-week intervention. Therefore, although the intervention had been successful, he saw it as a failure. This could have been due to the environmental factors which are controlled in a gym environment. The patient mentioned that he lived in a hilly area. Interestingly, a previous study found the presence of obstacles such as hills and stairs are one of the most prevalent environmental barriers to physical activity (Barbosa et al., 2015a). This finding could explain why the patient saw no change in his symptoms outside of the gym environment as it is not representative of environmental obstacles (i.e., uneven pavements and hilly landscapes).

Finally, the SEP increased the confidence and motivation for many participants. Perhaps participants were more confident and motivated in a gym environment and therefore pushed themselves to achieve more than at home, this may explain the discrepancy in improvement dependent on the setting. Furthermore, participants became confident in their ability to manage the symptoms associated with IC, including the unpleasant pain and discomfort when walking. A previous study recognised various coping strategies for tolerating and overcoming their symptoms (Galea et al., 2008). One of these techniques include distraction and diverting attention away from the pain, which is evident in this study. As participants socialised, had fun and emphasised enjoyed in aspects of the session such as the music, it could be suggested all

these were successful distraction techniques. Furthermore, the use of pain-coping strategies is linked to confidence in a participants ability to function physically and to manage pain symptom (Galea et al., 2008). In the future, a complimentary health psychology intervention could be implemented to help participants develop coping strategies for the pain. Previous research has found health psychology interventions beneficial for increasing walking distance (Cunningham et al., 2011).

7.5.3 Programme Facilitators and Barriers

Two key physical barriers were identified which were transport/location and time. Transport and location has been identified in previous research as a barrier to a SEP (Harwood et al., 2017b). Similar to these findings, it has been found that participants who have to rely on public transport and catching multiple buses to attend their class are less likely to attend (Harwood et al., 2017a). However, previous research suggests that the cost of the bus has also been a limitation to attending the SEP (Barbosa et al., 2015b), yet in this study many participants mentioned the benefits of having a free bus pass due to being aged 65 or over.

Also, it was mentioned that the time of the class and the day at which it was scheduled needed to fit in with a patient's day to day lives. Likewise, one of the most cited barriers for non-attendance in a previous study was the inconvenience of the SEP time and the time to travel (Harwood et al., 2017a, Harwood et al., 2018). Although some participants did not mind the SEP being at lunch time due to most of the participants being of retired age, many did suggest that mid-morning would be most favourable.

It is essential to address the issues of location and time of the SEP. A possible solution would be to open more centres, so there are extra locations available, and participants do not have to

travel as far. For example, in this study, participants living in Leyland and Penwortham currently must travel to Preston to take part in the SEP. Figure 7.1 shows the distance and times to travel to Preston from surrounding areas. However, this may be hard to implement due to the current access, funding and support of commissioning bodies to fund the SEPs (Harwood et al., 2022, Harwood et al., 2017c).

Another possible solution would be to integrate PAD patients into the current cardiac rehabilitation (CR) classes which are widespread and readily available. This has been highlighted in the latest British Association of Cardiac Rehabilitation and Prevention Standards and Core Components (2023) where PAD patients have been listed as eligible to take part in cardiac rehabilitation. These standards advocate an investment in cardiovascular prevention and rehabilitation services and therefore benefit suggest PAD patients would hugely benefit. This would also provide a solution for the limiting factor of class time for PAD patients. At Heartbeat CR classes run from 7am until 7pm in the evening, therefore providing an opportunity for participants to choose from morning or evening classes, consequently allowing the classes to become more accessible.

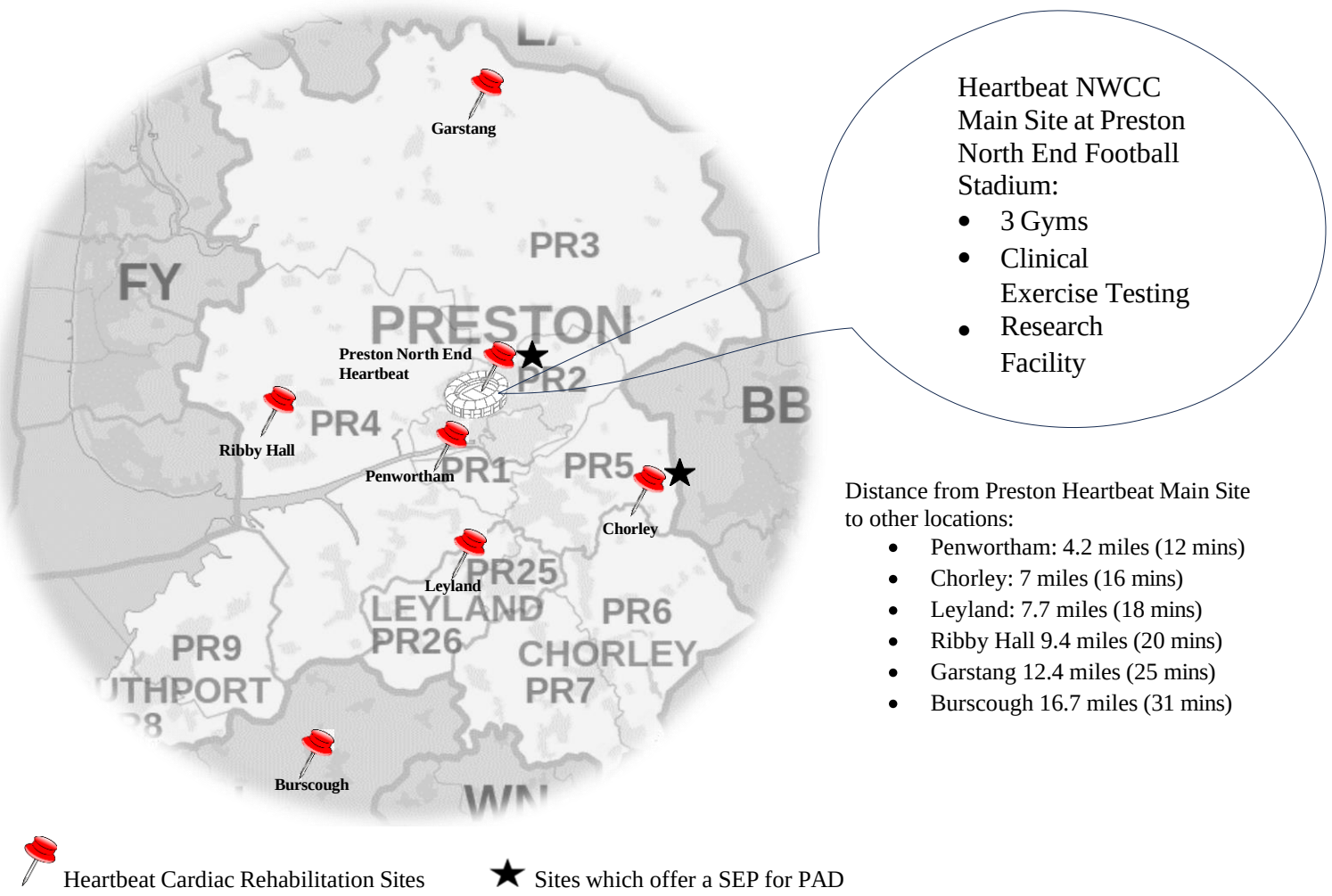


Figure 7.1. Heartbeat Class Locations and PAD SEP availability

According to the National Audit of Cardiac Rehabilitation Quality and Outcomes Report 2022, there are 233 CR programmes across the United Kingdom (NACR Report 2022). Moreover, Heartbeat has over 100 CR classes which run at various times and locations. As such, allowing PAD participants to join these classes will allow a variety of choice for class time and location, removing aforesaid barrier above. Combining CR and IC patients is a topic already being

explored (Caldow et al., 2019b), however providers will need to ensure familiarity of specific outcomes (i.e. maximal and pain-free walking distance) and exercises (i.e. calf raises that provoke pain) for vascular patients. That said, this could be hard to implement as CR is not universally delivered and centres have different standards. Additionally, findings from this study have highlighted how participants with IC like being surrounded by people with the same condition as themselves. Therefore, this needs to be considered and could be a limitation if they are integrated into a CR class which does not have any other IC patients in.

Next, several participants suggested they would have liked more variety in the exercises and had the opportunity to incorporate upper body exercises. Previous research suggests the use of alternative exercise such as resistance and non-weight bearing aerobic exercise has demonstrated a higher motivation amongst participants leading to a greater compliance of the programme (Parmenter et al., 2011). An online survey was designed to address the key points regarding access to SEPs for patients with IC (Harwood et al., 2017c). Of the 89 responses received, 37 reported they had access to the SEP. Of the 37 units only 5 had reported a >90% completion rate. Indeed, of these, 4 out of the 5 used a combination of aerobic and resistance exercise in their SEP. This supports the above study and suggests a mix method approach may increase the commitment to exercise. Likewise, as mentioned in chapter 2, alternative modes of exercise such as cycling, upper arm ergometry and strength training have shown similar effects on walking distance (Lauret et al., 2014).

With regards to the length of each session, no patient specified that it was too long or too short. Therefore, suggesting that the one-hour session, including a 10-minute warm-up and 10-minute cool down, was acceptable and well tolerated. Two participants appreciated the warm-up as it prepared them for the exercise session. The structure of the class corresponds to the

recommendations from NICE guidelines and as no patient brought this up, it suggests it is a suitable length of time (NICE, 2012).

The duration of the programme was two sessions a week for 24 weeks. Surprisingly, no participant indicated this was a burden, even though the minimum recommended length of a SEP for patients with IC is only 12 weeks (NICE, 2012). Previous research demonstrated improvements in pain-free and maximum walking distance were largely achieved in the first two months of a SEP (Gardner et al., 2012). Alternatively, earlier research saw the benefits of a SEP following 3-months in the intervention (Bulmer and Coombes, 2004, Gommans et al., 2014, Fokkenrood et al., 2013b). Therefore, it may have been more realistic to reduce the duration to 12 weeks, which may have increased the uptake to a SEP.

Finally, a common barrier was working to a set level of claudication pain. Participants, especially working at moderate claudication pain, expressed a level of uncertainty into what benefits this was going to achieve after always being told to work to maximal pain which is the current recommend guidelines (NICE, 2012). Perhaps moderate pain may be more subjective compared to working until pain-free or maximal pain which may be easier to determine. Similarly, a previous study explained patients expressed a lack of clarity about whether they should stop at the onset of pain or attempt to walk through to maximal pain and what level of claudication pain was actually required to achieve benefits in symptoms (Gorely et al., 2015). In this study, several participants working to maximal claudication pain stated they found it hard to reach that level of pain as they had never done anything like this before. Previous studies support our findings and suggest that working until maximal claudication pain or the fear of pain may discourage patients from exercising (Gorely et al., 2015, Harwood et al., 2017a, Harwood et al., 2018, Lin et al., 2019a, Sharath et al., 2017). The need to rest because of leg

pain has been associated with lower levels of physical activity and adherence to SEPs, therefore exercising patients to maximal pain continues to serve as a barrier to continued activity in patients with IC (Lin et al., 2019a).

To overcome this, various systematic reviews (and chapter 3) have highlighted how patients are still able to see an improvement in their walking distance when working at a lower work rate which does not induce claudication pain (Parmenter et al., 2011, Al-Jundi et al., 2013) Furthermore, working at a lower rate may increase participate and adherence as the pain barrier, seen in this and many other studies. Likewise, previous studies have found the use of other exercises, such as arm ergometer, to produce superior results in cardiorespiratory fitness and could also improve pain-free and maximal walking distance (Parmenter et al., 2015, Treat-Jacobson et al., 2009). As this exercise does not stimulate claudication pain this could be included in SEPs to try and promote uptake.

7.5.4 Awareness to Promote the SEP

Finally, many participants stated they were unaware of the opportunity to take part in this SEP until they were referred by the vascular nurses. As such, it was evident participants thought it should be better publicised for this clinical population e.g., create better links with GP surgeries. A reason for this, as explained above, could be due to commissioning bodies not warranting SEPs as important and so funding remains largely unavailable (Harwood et al., 2021). Likewise, Heartbeat NWCC, the site for the randomised control trial, is a charity and is not commissioned. Therefore, they rely largely on government funds and the Heartbeat lottery. As such, any form of external advertising will come as a financial burden. Feedback from these interviews led to the creation of participant feedback posters to promote the SEP in the vascular clinic at Lancashire Teaching Hospitals (figures 7.2 – 7.5).

It was also suggested that prospective members should be given the opportunity to attend Heartbeat on an open day whilst one of the classes are taking place, so they can observe what happens within the hour. This would allow new members to see how the classes are run and reduce the fear of the known. It would allow for participants see the variety in disease severity and hopefully reduce the feeling of embarrassment or failure. A similar suggestion was to set up a clinic with current class members and prospective members, where participants just chat amongst themselves and discuss experiences. This would give new members the chance to ask any questions and concerns they may have. This may be of benefit to prospective participants as it could remove the fear and apprehension attending their first session knowing there will be a familiar face. As mentioned above, social support has been found as a facilitator for physical activity in patients with IC (Galea and Bray, 2006). Finally, possibly a self-referral pathway could be developed whereby patients with suspected IC could complete a form which is assessed by Heartbeat and allow them entry onto the programme.

7.6 Strengths and Limitations

There was a sufficient sample size included in the completer interviews (n = 15), which is key to gaining depth and insight when analysing qualitative data. Additionally, a broad and representative age range for participants with IC (51-83 years) was achieved. Of the interviewees, only 35% were female, though this was to be expected, as explained in chapter 2, the prevalence of PAD is higher in men than women. However, only two participants who withdrew from the SEP agreed to attend an interview, which meant this group was not fully represented. Furthermore, the interviews took place from two centres in the North-West which meant the data may lack geographic diversity. Also, there was limited time to share the

transcripts with participants before they were analysed which would have enabled further clarification.

7.7 Reflective Statement

I am a British Association of Cardiac Rehabilitation and Prevention Exercise Professional at Heartbeat. I am a healthy and fit individual with no known health conditions; therefore, I could not relate with patient experiences and their symptoms of IC. As my professional background is an exercise instructor, I have a positive outlook on exercise and support the evidence regarding SEPs and their positive impact on IC. Conscious that I had this pre-existing knowledge, I made a deliberate effort through the interviews to divert from leading questions which always favoured the positive comments. As I became a more confident interviewer, I addressed the negative comments in detail, making sure the interviewee was happy confiding in me, even though I was a member of the research team. To lessen this, at the start of the interview I asked participants to be as open and honest as possible, explaining that nothing would be taken personally, and everything would remain completely anonymous. That said, I understand some participants may have still withheld information to please me. As I was responsible for conducting all the interviews, this may have explained why only two of the non-completers agreed to have an interview, possibly they were embarrassed to give honest answers as to why they didn't want to take part in the programme. As such, in the future it would be useful to have an independent researcher conducting the interviews. Therefore, the risk of unwanted social desirability bias would be eliminated. To try and overcome this, any negative comments were fully reported and included in the study.

7.8 Conclusions

The aim of this study was to explore patient experiences of the SEP, whereby participants were randomised to one of three levels of claudication pain. Overall, it was evident that most patient enjoyed the SEP and noticed substantial improvements in their symptoms of IC regardless of the level of claudication pain they were randomised to. That said, apprehension still existed around which level of pain was optimal for patient benefit. Participants randomised to moderate pain were notably uncertain after normally being told to work through the pain by clinicians. Besides this, participants highlighted how they liked being in a group environment where they could meet like-minded individuals who had similar symptoms. Overall, it seems that regardless of the level of claudication pain participants all accepted the SEP and would take part again.

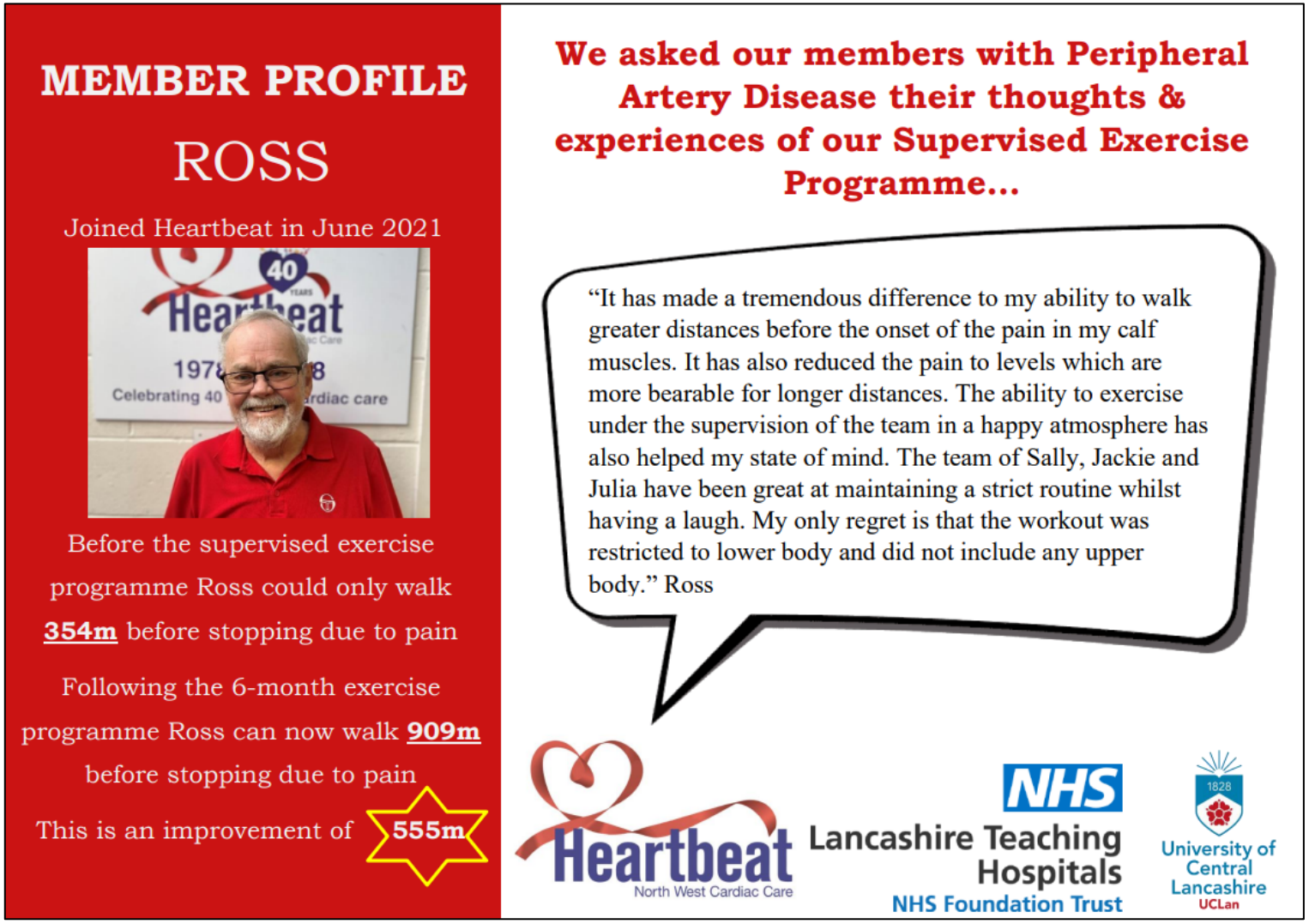


Figure 7.3. Patient Feedback Poster

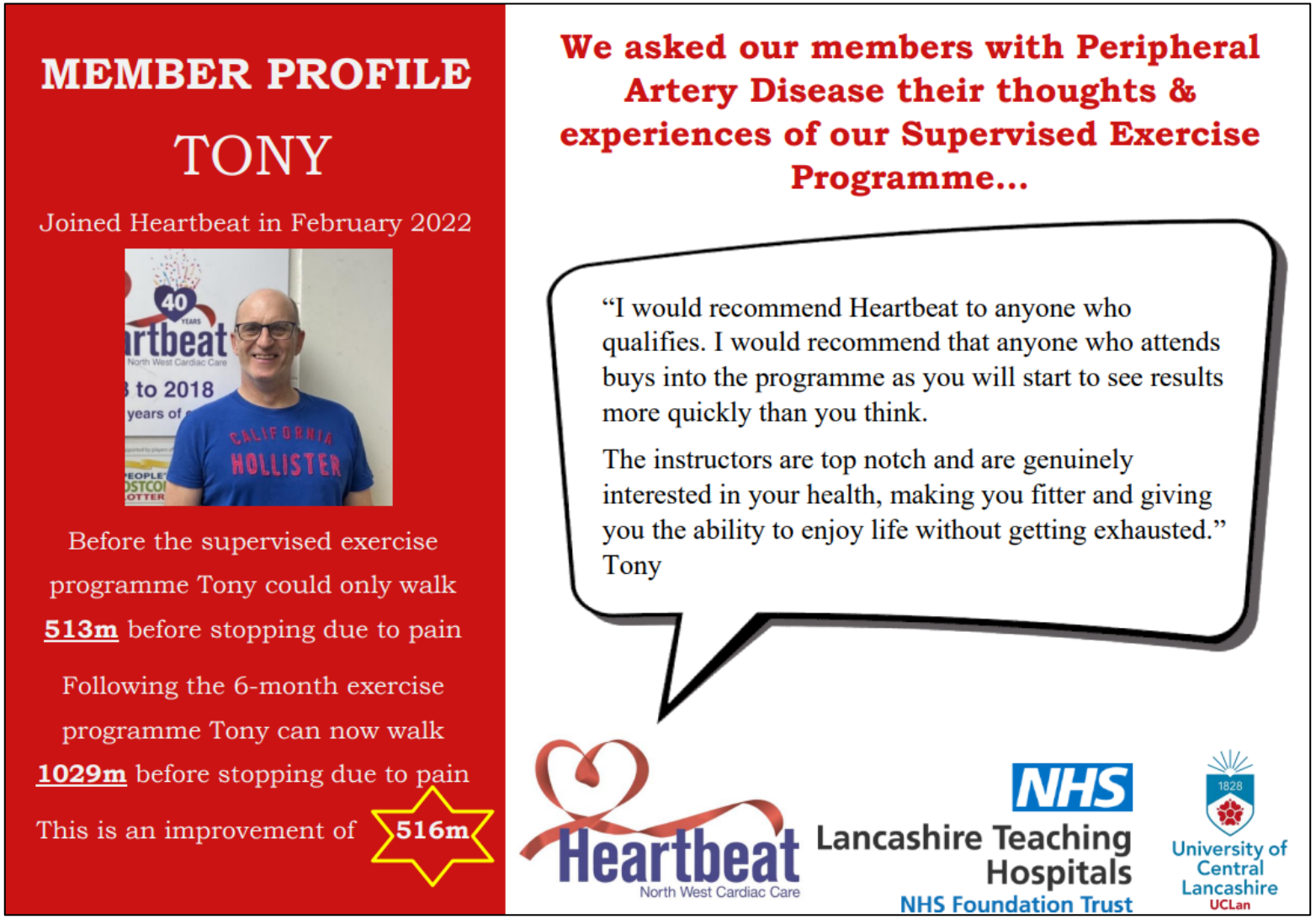


Figure 7.3. Patient Feedback Poster

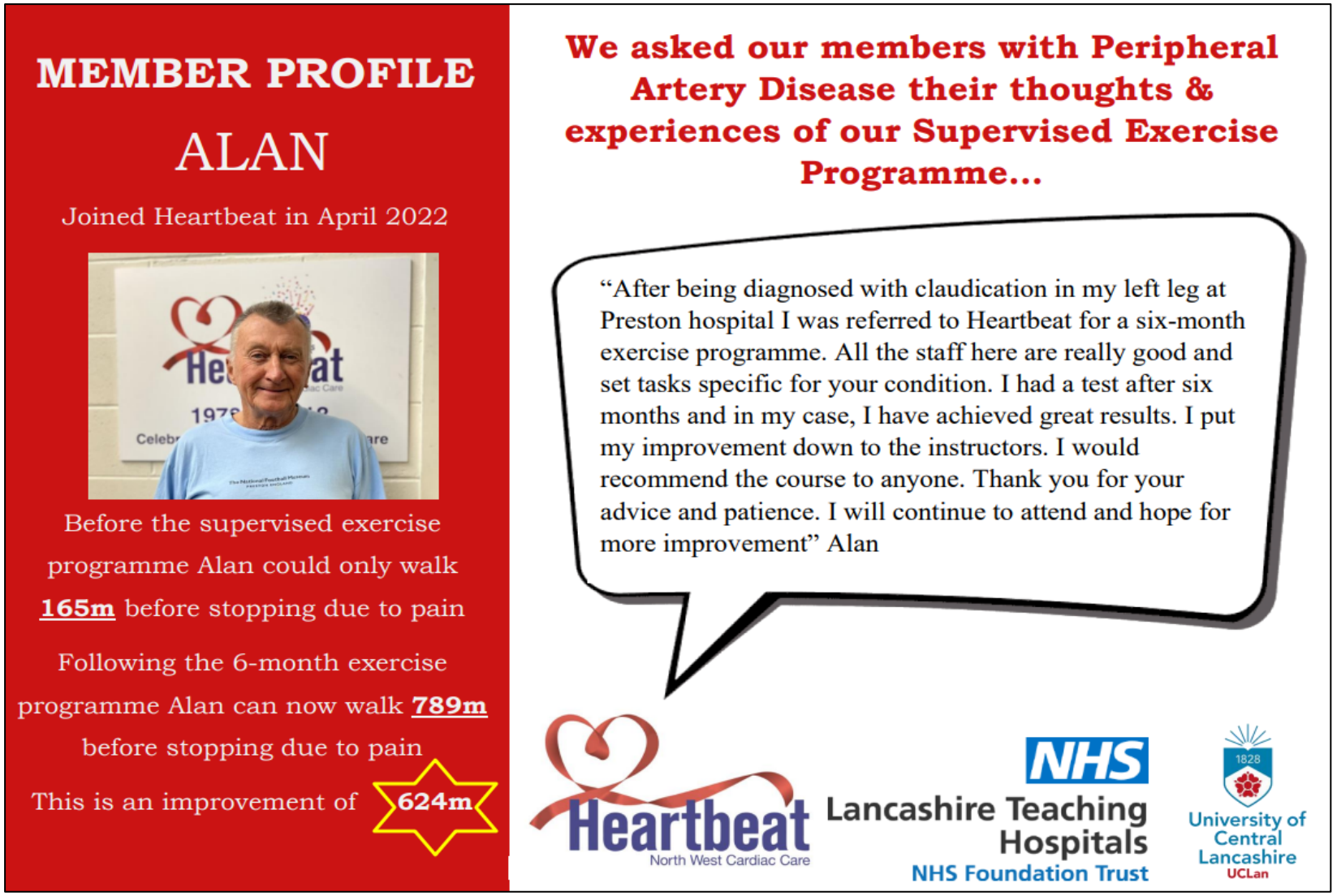


Figure 7.4. Patient Feedback Poster

Figure 7.5. Patient Feedback Poster

Chapter 8. Discussions and Conclusions

8.1 General Discussion

This thesis has presented a body of research that aimed to consider the optimal level of claudication pain for patients with IC by directly comparing pain free, moderate pain and maximal claudication pain using a randomised control design. Furthermore, the thesis reviewed previous research which had compared at least two different levels of pain. Finally, the thesis investigated patient experiences of a SEP, potential barriers and ways of improving the service. The NICE guidelines and a recent scientific statement by the American Heart Association, suggested that although maximal pain is the current recommended guidelines, other levels of claudication pain may be as effective (Treat-Jacobson et al., 2019, NICE, 2012). Therefore, this was the first randomised control trial to assess three levels of claudication pain on functional outcomes for patients with IC.

Chapter one and two aimed to provide a comprehensive overview of the current literature regarding the evidence for SEPs and IC. Chapter three identified that no RCT had compared maximal claudication against both pain-free and moderate pain (Seed et al., 2021). The findings of this systematic review supported the statement by the American Heart Association as both studies identified in the review found no statistically significant difference between moderate pain and pain-free on functional outcomes such as maximal and pain free walking distance. In the review both studies saw an increase in maximal walking distance for pain-free interventions (77% and 98%) and the moderate pain SEPs (128% and 100%) (Mika et al., 2013, Novakovic et al., 2019).

Chapter five of this thesis was a randomised control trial were patients were randomised to either pain free, moderate pain or the standard programme of maximal claudication pain (NICE, 2012). The results from this study did not demonstrate a statistically significant difference when comparing the different levels of claudication pain on functional outcomes. Although, it is likely that statistical significance was not achieved due to the under recruitment of patients and therefore was not fully powered to detect change. Despite this, the study found a larger MCID favouring maximal claudication pain. Therefore, suggesting that patients may need to exercise to maximal claudication pain to attain a benefit in maximal walking distance. This supports a previous study which found strong evidence in support of structured high pain and some evidence in support of structured low pain (Perks et al., 2022). However, if the results stay as they are when the trial is fully powered, this could dispute previous research which advocates pain-free or moderate claudication pain (Parmenter et al., 2015, Mika et al., 2013). Despite this new evidence being generated, the trial is still not fully powered to detect change. Once the trial is completed and the evidence evaluated, we can then draw conclusions on the most beneficial level of claudication pain.

Chapter six considered all of the guidelines and provided an overview of the inconsistencies regarding the optimal level of claudication pain. Utilising all this above knowledge, chapter five developed a brand-new SEP for patients with IC in the North-West of England designed with specific weight-bearing exercises to facilitate claudication pain.

Finally, chapter seven considered the acceptability and enjoyment of SEPs randomised at different levels of claudication pain by obtaining patient feedback via semi-structured interviews. Most participants stated they enjoyed the programme and would take part again.

Furthermore, many participants suggested ways to promote the programme to get more people with IC aware of the SEP and taking part. This suggests the SEP was acceptable.

In addition, most participants highlighted how they enjoyed the social interaction and group environment of the SEP. This supports the guidelines which suggests that exercise interventions should be supervised (NICE, 2012). As the SEP was initiated post a national pandemic, this could have influenced the importance of social interaction amongst class members. Restrictions existed during the national pandemic which limited interaction amongst friends and family, this could have impacted on participants mental wellbeing. However, attending Heartbeat and joining an environment where people have the same condition could have magnified the value of social interaction and support.

The interviews highlighted some physical barriers to the SEP including time of the class and transport. With regards to transport to the class, it was noted that some participants lived longer than 15 minutes away and therefore saw this as a burden to attending the classes. Furthermore, some patients who did not drive had to catch two buses to attend the classes. As such, it was suggested that more classes should be offered in several areas e.g., Penwortham to facilitate this. However, given that Heartbeat is a charity and rely on class donations this is not financially feasible. That said, Heartbeat do run CR classes in many external locations (figure 7.1, page 207) therefore PAD classes could integrate into these classes. This has recently been suggested in British Association of Cardiac Rehabilitation and Prevention Standards and Core Components (2023). Heartbeat has a wide range of CR classes running from Monday to Friday 7am-7pm therefore, integrating PAD patients with CR would also solve the barrier of PAD patients having to come at one set time twice a week. However, it is worth noting that the CR

recommendations are twice a week for 12-weeks yet this study asked participants to attend twice a week for 24-weeks (NICE, 2012). Previous research supports the national recommendation of 12-weeks for the greatest improvement in MWD and PFWD (Fakhry et al., 2012b, Bulmer and Coombes, 2004, Fokkenrood et al., 2013a).

8.2 Original Contribution to Knowledge

This thesis is a significant addition to the accumulated knowledge for patients with peripheral artery disease (PAD), as no research trial has directly measured maximal, pain-free and moderate claudication pain on functional outcomes and quality of life. The research can be used to implement a universal set of guidelines for SEPs which will optimise patient outcomes and encourage adherence.

8.3 Limitations

This thesis is not without limitations. In chapter two, the evidence was limited with only two studies used in the review. Both studies had small sample sizes, with only one adequately powered to detect change in MWD and neither study compared maximal claudication pain. This limited the conclusions that could be drawn from the data. Chapter six, the main RCT, was underpowered and did not recruit or retain a sufficient number of patients in relation to the power calculation. Therefore, an exploratory analysis of the intervention-based data was performed and should be interpreted cautiously. However, it is important to note that commencement of data collection was delayed due to COVID-19 pandemic and a national lockdown, therefore out of the researcher's control. In addition, the RCT was single centred which draws implications regarding external validity. Also, the single investigator (SS) performed all of the pre and post testing, therefore investigator blinding was not possible which

could have possibly created selection and participation bias. In chapter seven, those who withdrew from the programme were underrepresented, with just two patients interviewed. This is important as these participants would have most likely given negative views of the SEP. Future research needs to prioritise these participants to identify their thoughts and feelings.

8.4 Future Research

The findings from this thesis have highlighted how uptake to SEPs remains low for patients with IC, with time and location of the class presenting as a barrier to exercise. To overcome this, future research should consider offering PAD patients a menu of options for rehabilitation as opposed to just a SEP. For example, previous research has highlighted the feasibility of HBEPs for patients with IC (Waddell et al., 2022). Therefore, patients could be given the option of other exercise interventions, similar to what is currently being offered in CR, such as HBEPs or an individualised hybrid exercise intervention. This could potentially reduce the barriers related to uptake. Future RCTs would be required to compare routine care SEPs to HBEPs and hybrid interventions.

8.5 Conclusions

SEPs play an important role in the treatment and management of patients with PAD, though there is discrepancy between guidelines as to what is the optimal level of claudication pain. This was the first study to assess three levels of claudication pain on functional outcomes in patients with IC. This study supports the current NICE guidelines which suggests maximal claudication pain seems to elicit a larger benefit in functional outcomes compared to pain-free and moderate claudication pain. Although these results are not statistically significant yet and

the trial is not fully powered, if the results stay as they the MCID suggest patients should be going to maximal claudication to attain a benefit in MWD.

Furthermore, this thesis demonstrated only 33% of patients were willing to undertake a SEP. Common barriers to exercise included travel, location and time of the classes. Therefore, future SEPs need to engage with their patient population to understand the barriers and try to develop a more effective exercise rehabilitation programme. As not all vascular units in the UK offer a SEP, a possible solution could be to integrate PAD patients into the current CR classes as highlighted in the British Association of Cardiac Rehabilitation and Prevention Standards and Core Components (2023).

8.6 Key Recommendations

To summarise there are a number of key recommendations to report from this thesis which include:

1. A training intervention whereby patients work to maximal claudication pain training seems to elicit a larger benefit in treadmill related MWD compared to pain-free and moderate claudication pain.

2. A supervised exercise programme for patients with PAD is important for patient confidence and adherence. Patients benefit from being in the company of likeminded individuals and under the supervision of an exercise professional.

3. Common barriers to exercise include time of the class, location and travel. Exercise interventions should facilitate flexibility of class times and locations to provide a greater accessibility for all patients.

4. There needs to be efficient communication between exercise professionals and medical professionals to allow for an effective referral pathway. This will limit the delay in waiting times from being seen at the hospital to starting the SEP.

5. Education may be required to explain and promote an exercise intervention to clinicians and medical professionals. They are the first point of contact for patients, so it is important they understand and promote the benefit of a SEP.

6. The personal barrier of pain with exertion remains with patients with IC following a 24-week SEP. Incorporating a psychological intervention alongside a SEP could encourage participants to change their beliefs and perceptions around claudication pain.

7. An opportunity should be provided for prospective new members to converse with current members to discuss their experiences of the exercise programme. This may increase uptake and adherence to the programmes.

8. Further RCTs are required which compare routine care SEPs to HBEPs and hybrid interventions. This could increase adherence to exercise interventions.

Personal Reflection

Beginning a PhD during a global pandemic felt like a daunting experience. I became grounded for what seemed like the foreseeable future, questioning when it would be possible to reach study participants due to the government restrictions. However, with the fantastic support of my supervisory team, I put this thought aside and looked at ways I could continue my research remotely. This allowed me to conduct and publish a systematic review of the current literature looking at the optimal level of claudication pain for patients with peripheral artery disease. Of, 1,543 studies only two met the inclusion criteria, highlighting the gap for research in this area. Alongside this, I published a commentary highlighting the limitations of current practise to clinicians and researchers.

Setting up a brand-new North-West referral pathway for PAD patients faced many challenges. There was a significant amount of time spent with the vascular consultant, nurses and CEO of Heartbeat Northwest Cardiac Care conducting meetings (virtual/face-to-face) and phone calls to make sure the referral pathway and transition from the national health service to Heartbeat ran as smoothly as possible. A lot of time was spent with the British Association of Cardiac Prevention and Rehabilitation (BACPR) Exercise Professionals informing them of the trial methodology, rationale and mostly importantly the justification of why we were exercising patients to different levels of claudication pain. Understandably, this was met with a lot of apprehension. Whilst setting up the referral pathway and supervised exercise programme I also took a 3-month course to be a Level 4 BACPR Exercise Professional which gave me the opportunity to deliver some of the classes at Heartbeat and ensure the protocol was delivered appropriately.

This experience has shown me that if exercising to levels of maximal claudication pain is most successful in providing optimal benefits in maximal and pain-free walking distance, a lot of support will be required to patients who perceive pain as a barrier to exercise. Changing the adherence and uptake of UK peripheral artery disease supervised exercise programmes is a challenge faced by many researchers. However, with anticipation of more people presenting with the disease, because of an ageing population, I think this belief needs to change and evolve. I feel addressing barriers such as perceived level of pain and accessibility of classes (time/location) is essential and can be achieved through teamwork with the main driving force being a focus on patient care.

There were many setbacks throughout my PhD journey, but just as many achievements. As a novice researcher I have been extremely grateful for the guidance of my supervisor. From the beginning of this journey, Stefan taught me to celebrate small successes along the way (i.e., paper publications and successful lectures teaching) as well as pick me up when I faced challenges. As a result, my self-belief and competence of a researcher has significantly developed. I look forward to implementing the skills I have developed to future academic/research roles.

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Declarations

Chapter 3 - This study has been accepted by the Annals of Vascular Surgery. For this publication Sally Seed (SS) is the first author. SS contributed to the concept and design, interpretation and analysis, writing the article, critical revision of the article and the final approval. She has overall responsibility.

Chapter 5 - This thesis chapter forms part of a UK multicentred randomised control trial (trial number: NCT04370327). The protocol has been published in Therapeutic Advances in Cardiovascular Disease (Birkett et al., 2022a). For this publication, SS contributed to the methodology, writing, reviewing and editing of this article and is a named author on the published paper.

Chapter 6 - This commentary has been published in Vascular Journal (Seed et al., 2023), with SS as the first and corresponding author. SS contributed to the concept and design, writing the article, critical revisions of the article and final approval of the article. She has overall responsibility.

Appendices

Appendix A - Ethical Approval Form

Health Research Authority

North West - Preston Research Ethics Committee

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

10 December 2020

Mr Anselm Egun
Royal Preston Hospital, Sharoe Green Lane
Sharoe Green Lane, Fulwood,
PR2 9HT

Dear Mr Egun

Study title:	**The Effects of Exercise Prescribed at Different Levels of Intermittent Claudication Pain on Functional Outcomes in Patients with Intermittent Claudication**
REC reference:	**20/NW/0401**
IRAS project ID:	**283436**

Thank you for your response of 18 November 2020, 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 Chair.

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.

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

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

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

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

Registration of Clinical Trials

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

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

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

You should notify the REC of the registration details. We will audit these as part of the annual progress reporting process.

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

After ethical review: Reporting requirements

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

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

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

Approved documents

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

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP letter]	1.0	28 April 2020

IRAS Application Form [IRAS_Form_25092020]		25 September 2020
Other [Amy Harwood CV]		
Other [Jonathan Sinclair CV]		
Other [Focus group topic guide]		
Other [Barrier to exercise Q]		
Other [Interview topic guide]	V1.0	02 November 2020
Other [Responses]		02 November 2020
Participant consent form [Consent]	V2.0	30 October 2020
Participant information sheet (PIS) [PIS]	V2.0	30 October 2020
Research protocol or project proposal [Protocol]	V2.0	02 November 2020
Summary CV for Chief Investigator (CI) [CI CV]		
Summary CV for student [Sally Seed CV]		21 July 2020
Summary CV for supervisor (student research) [Stefan Birkett CV]		21 July 2020
Validated questionnaire [SF-36 questionnaire]		
Validated questionnaire [Walking Impairment questionnaire]		
Validated questionnaire [VascQual questionnaire]		
Validated questionnaire [EQ-5D-5L questionnaire]		

Statement of compliance

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

User Feedback

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

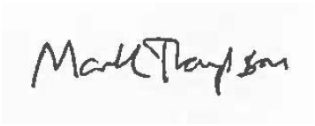
HRA Learning

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

IRAS project ID: 283436 Please quote this number on all correspondence

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

Yours sincerely



On behalf of Professor Karen Wright Chair

Email:preston.rec@hra.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: Dr Kina Bennett, Lancashire Teaching Hospitals NHS Foundation Trust

Appendix B - Participant Information Sheet

PARTICIPANT INFORMATION SHEET

Study Title: The Effects of Exercise Prescribed at Different Levels of Intermittent Claudication Pain on Functional Outcomes in Patients with Intermittent Claudication

Chief investigator Mr Anselm Egun (Consultant Vascular Surgeon)

Researchers: Dr Stefan Birkett (Lecturer in Exercise Science), Professor Lee Ingle (Professor of Exercise Science for Health & Rehabilitation) Dr Jonathan Sinclair (Reader in Sport, Exercise & Nutritional Sciences), Sean Pymer (PhD student), Edward Caldow (Lecturer in Exercise Nutrition & Health) & Sally Seed (PhD student), Amy Harwood (Research Fellow).

Dear Participant,

You are invited to take part in a research study. Before you decide, it is important for you to understand why the study is being done and what it will involve for you. Please take time to read the following information carefully. Discuss it with friends, relatives or your GP if you wish. It is up to you to decide whether or not to take part in this study. Whatever you decide, the standard of care you receive will not be affected. If there is anything that is unclear, or you would like more information, please do not hesitate to ask.

What is the purpose of the study?

Exercise training helps recovery following a diagnosis of intermittent claudication (leg pain). We would like to understand more about the benefits of different intensities of exercise such as pain free, moderate pain or maximal pain leg pain. The results of this study will help us to understand what the best approach is for people who have intermittent claudication. We hope it will help us to design better exercise programmes for patients in the future.

Why have I been invited?

You are being asked to take part in this study because you are attending a supervised exercise programme specially designed for people with intermittent claudication. Approximately 51 patients will be enrolled.

Do I have to take part?
It is up to you to decide whether or not to take part. We will go through this information sheet with you, which we will then give you to keep. If you do agree to take part, you will be asked to sign a consent form. You are free to withdraw at any time up to the analysis of the anonymised data. After that time the researchers will not be able to identify individuals data. If you decide not to take part, or to withdraw at any time, the standard of care you receive will not be affected and you can attend the exercise programme as normal.

What will happen to me if I take part?
You will undergo several tests at the start, middle and end of your 24-week rehabilitation programme. You will need to bring any necessary prescribed medications to the classes such as a GTN spray or inhalers. Tests will include:

1. ***Clinical Examination:*** A member of the Heartbeat team will measure blood pressure, resting heart rate, measure height, ankle pressure, weight, waist and hip

2. ***Treadmill walking test:*** Set at a constant speed of 3.2km/h and incremental gradient beginning at 0% increasing 2% every two minutes, for a maximum of 15 minutes, conducted by a trained technician. This is designed to provoke maximal claudication pain.

3. ***Questionnaires:*** You will be asked to complete 8 questionnaires that will assess quality of life, barriers to physical activity and dietary intake

4. ***Semi-structured interview (optional):*** To evaluate your experience we will conduct an interview at the end of your 24-week programme. This is an informal conversation. The proposed themes of the interview will be experiences of the exercise sessions, factors that influences attendance and possible barriers. Members of the research (Stefan Birkett and Sally Seed) will conduct the interview.

What are the benefits of taking part?
This research project may not offer you any direct benefit at this time. If any of our measurements discover anything abnormal with your health, which we envisage the likelihood of this to be very low, you will receive prompt and appropriate medical care and attention.

What are the risks of taking part?

Exercise testing carries a very small risk of complications, such as injury or dizziness. Otherwise, the study mainly involves information gathering and non-invasive measurements. We do not anticipate any serious risk to you. This study will not involve you taking extra medication and it will not affect your treatment in any way. If you have concerns about any aspect of this study, please speak to the study staff who will be able to answer your questions. Their contact details are found at the end of this information sheet. In the very unlikely event of you being harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism is available to you. Please contact:

Dr Stefan Birkett
Lecturer in Exercise Science
University of Central Lancashire
Preston
PR1 2HE
Email: Sbirkett4@uclan.ac.uk
Tel: 01772 893335

How will we use information about you?

We will need to use information from you and your medical records for this research project.

This information will include your name, contact details, past medical history, NHS number and current diagnosis. This will be held at Heartbeat North West. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team

WHAT IF I CHANGE MY MIND ABOUT TAKING PART?

You can choose to withdraw at any time, without giving a reason. Your standard of care will not be affected if you change your mind.

Will my taking part in this study be kept confidential?

If you consent to take part in the study, all information which is collected about you during the course of the research will be kept strictly confidential. Your name and address will be removed from all study data (anonymised) and a study identification number assigned. Your GP would be contacted in the event of abnormal findings arising from the study

What will happen to the results of the research study?

The results of this study will be published after all the information has been analysed. You will not be identified in any publication or report. If you would like a final report, please contact Dr Stefan Birkett (address below).

Video recording and photography (OPTIONAL)

With your consent, we may take photographs or record short video clips of you undergoing the exercise training. This will be used for conference presentations and to publicise the research project on social media. This is completely optional; you do not have to agree to this.

Who has reviewed the research study protocol?

This protocol will be reviewed by North West – Preston Research Ethics Committee.

WHO SHOULD I CONTACT IF I AM UNHAPPY WITH MY TREATMENTMENT AND WISH TO MAKE A COMPLAINT.

If you have a specific concern or query about the research you can contact the study team on the details below. For a more independent contact, you can contact the Research Governance lead within the Centre for Health Research and Innovation at Lancashire Teaching Hospitals by contacting 01772 522031. You may also wish to talk to the hospitals Patient Advice and Liaison Service (PALS) which provides support to patients, families and visitors. Hopefully, in most cases they will be able to sort out your concerns very quickly. However if you are not satisfied with the response that you receive you can make a complaint in writing. Please contact the Trust's Customer Care department on 01772 522521 or email customer.care@lthtr.nhs.uk who can they will assist you with your complaint.

Contact for further information:

If you require further information or have any questions, please contact:-

Chief Investigator: Mr Anselm Egun
Consultant Vascular Surgeon
Lancashire Teaching Hospitals NHS Foundation Trust
Email: Ansy.Egun@lthtr.nhs.uk

Principle Investigator: Dr Stefan Birkett
Lecturer in Exercise Science
University of Central Lancashire
Preston
PR1 2HE
Email: Sbirkett4@uclan.ac.uk
Tel: 01772 893335

Thank you for considering taking part in this research study.

Appendix C - Consent Form

CONSENT FORM

Title: The Effects of Exercise Prescribed at Different Levels of Intermittent Claudication Pain on Functional Outcomes in Patients with Intermittent Claudication

Research team: Mr Anselm Egun (Consultant Vascular Surgeon), Dr Stefan Birkett (Lecturer in Exercise Science), Professor Lee Ingle (Professor of Exercise Science for Health & Rehabilitation) Dr Jonathan Sinclair (Reader in Sport, Exercise & Nutritional Sciences), Sean Pymer (PhD student), Edward Caldow (Lecturer in Exercise Nutrition & Health) & Sally Seed (PhD student), Amy Harwood (Research Fellow).

Please read the following statements and initial the boxes to indicate your agreement

	Please initial box
I confirm that I have read and understand the information sheet, _ _ / _ _/_ _ for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary, and that I am free to withdraw up until the point when data collection is finished, without giving a reason. In the event of withdrawal from the study I also understand that my data will be deleted.	☐
I agree that my data gathered in this study may be stored (after it has been fully anonymised) on a password protected and using Microsoft Onedrive. This will be for a maximum of 5 years.	☐
I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from [*company name*], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I agree to my GP being informed of in the event of abnormal findings arising from this study.	☐
I understand that it will not be possible to withdraw my data from the study after final analysis has been undertaken.	☐
I agree to take part in the above study.	☐
I agree to take part in an interview after the 24 weeks (optional)	☐
I agree for photographs or recording to be taken of me undergoing the exercise training	☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Appendix D - Case Report Form

Pain Free vs Moderate Pain vs Maximal Claudication Pain Data Collection Form

Participant Study ID:_____Week No:_____

Randomised to:

PF ☐ MOD-P ☐ MAX-P ☐ DOB: _ _/_ _/_ _ _ _

Age _____ Gender: Male ☐ Female ☐ Date of visit _ _/ _ _/ _ _ _ _

Inclusion Criteria	**YES**	**NO**
• Patient has read and understood the PIS	☐	☐
• Patient is aged >18 years old	☐	☐
• Has a resting ankle brachial pressure index <0.9	☐	☐
• Patient is English speaking and able to follow exercise instructions	☐	☐
• Patient is able to walk unaided	☐	☐
• Patient is able to and has given informed consent	☐	☐
• Able to comply with guidelines for participation in exercise testing and prescription	☐	☐

Exclusion Criteria	**YES**	**NO**
• Patient has critical limb threatening ischemia (rest pain and/or tissue loss)	☐	☐
• The patient is undergoing cancer treatment	☐	☐
• The patient has significant comorbidities or contraindications to exercise training or testing in accordance with the American College of Sports Medicine	☐	☐
• Unstable/uncontrolled coronary heart disease	☐	☐

Referral Diagnosis:

Date of diagnosis _ _ / _ _ /_____ Referred from: _____

Past Medical History/ Risk Factors

Previous Cardiovascular Event(s) and Date (s): _____

Any previous Surgery and Date (s): _____

Risk Factors:	**Yes**	**No**	**Former**
Smoker	☐	☐	☐
Hypertension	☐	☐	
Diabetes	Type I ☐	Type II ☐	None ☐
Hyperlipidaemia	☐	☐	
Coronary Heart Disease	☐	☐	
Family history of PAD	☐	☐	

Orthopaedic Limitations: _____

Symptoms:

Painful ache in the legs: No ☐ At Rest ☐ On Exertion ☐

↓

(If yes) Is the pain: Mild ☐ Severe ☐ AND Relieved at Rest ☐

	Yes	No
Numbness or weakness of the legs	☐	☐
Hair loss on the legs/feet	☐	☐
Slow growing toenails	☐	☐

Medications:

Warfarin	☐	Antiplatelets	☐	Diuretics	☐
ACE Inhibitors	☐	Statins	☐	Calcium Channel Blockers	☐
Naftidrofuryl Oxalate	☐	Beta Blockers	☐	Post-Menopausal medication	☐

Other (s):

_____

_____

Physical Examination

Weight: _ _. _ _ kg Height (shoes off): _ _ _._ cm BMI: _ _._ _ kg/m^2 Resting HR _ _._ bpm

Waist Circumference: _ _ _._ cm Hip Circumference: _ _ _._cm Hip to Waist Ratio: _._ _

Systolic Blood Pressure: _ _ _ mmHg Diastolic Blood Pressure _ _ _ mmHg ABPI _._ _

Questionnaires and Activity Monitor

The Kings College Vascular Quality of Life ☐ Barriers to PA Questionnaire ☐

Walking Impairment Questionnaire ☐ __Nutrition Questionnaires ☐

date given (_ _ /_ _ /_____)

Gardner Skinner Treadmill Protocol – Constant 3.2km/h, gradient 0% increase by 2% every 2 mins

Pain Free Walking Distance: _ _ _._ _ m Maximal Walking Distance: _____ m

Treadmill gradient at the end of test: _ _ % Overall time of test: _ _ mins

---

Completed by:

Name: _____ Signature: _____ Date: _____/ _____/ _____