Alternative Exercise Programmes for the Treatment of Intermittent Claudication – From Unsupervised Home-Based Walking to Supervised High-Intensity Interval Cycling

Volume 1

By

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Being a thesis submitted for the degree of Doctor of Philosophy

The University of Hull and the University of York

Hull York Medical School

January 2021

Presentations

Pymer, S., Palmer, J., Harwood, A.E., Ingle, L., Smith, G.E., and Chetter, I.C. High-Intensity Interval Training as an Exercise Intervention for Intermittent Claudication. *In* the Allam Lecture, Hull, UK, 29th March 2019.

Pymer, S., Nichols, S., Prosser, J., Birkett, S., Carroll, S., and Ingle, L. Does exercise prescription based on estimated heart rate training zones exceed the ventilatory anaerobic threshold in patients with coronary heart disease?: A United Kingdom perspective. *In* the BACPR exercise professionals group study day, Birmingham, UK, 17th May 2019.

Pymer, S., Palmer, J., Ibeggazene, S., Cai, P., Harwood, A.E., Ingle, L., Wallace, T., Smith, G.E., and Chetter, I.C. Low-volume, short-duration high intensity interval training as a treatment option for intermittent claudication: Early experience from a single UK centre. *In* The Vascular Society Annual Scientific Meeting, Manchester, November 2019.

Pymer, S. Supervised Exercise Programmes for the Treatment of Intermittent Claudication. *In* BACPAR annual Conference, Wolverhampton, UK, November 2019.

Pymer, S., Palmer, J., Ibeggazene, S., Cai, P., Harwood, A.E., Ingle, L., Carroll, S., Wallace, T., Smith, G.E., and Chetter, I.C. Low-volume, short-duration high intensity interval training as a treatment option for intermittent claudication. *In* 29th World Conference of the International Union of Angiology. Rome, Italy (conducted online), April 2020.

Pymer, S. Alternative Exercise Programmes for the Treatment of Intermittent Claudication – From Home to High-Intensity. Coventry University Seminar Series, Coventry, January 2021.

Published contributions from this thesis

Pymer, S., Tew, G.A., Palmer, J., Ingle, L., Smith, G.E., Chetter, I.C., and Harwood, A.E (2018). Home-based exercise programmes for individuals with intermittent claudication: A protocol for an updated systematic review and meta-analysis. *SAGE Open Medicine.* 6: 1-5.

Pymer, S., Palmer, J., Harwood, A.E., Ingle, L., Smith, G.E., and Chetter, I.C. (2019). A systematic review of high-intensity interval training as an exercise intervention for intermittent claudication. *Journal of Vascular Surgery.* 70(6): 2076-2087.

Pymer, S., Ibeggazene, S., Palmer, J., Smith, G.E., Harwood, A.E., Carroll, S., Ingle, L., and Chetter, I.C (2020). Considering the feasibility, tolerability and safety of high-intensity interval training as a novel treatment for patients with intermittent claudication. *Journal of Cardiopulmonary Rehabilitation and Prevention.* Online ahead of print.

Pymer, S., Harwood, A.E., Ibeggazene, S., McGregor, G., Huang, C., Twiddy, M., Nicholls, A.R., Ingle, L., Carroll, S., Long, J., Rooms, M., and Chetter I.C. (2020) High INtensity Interval Training In pATiEnts with intermittent claudication (INITIATE): protocol for a multicentre, proof-of-concept, prospective interventional study. *BMJ Open*, 10(7), 38825.

Full list of Publications

Pymer, S., Tew, G.A., Palmer, J., Ingle, L., Smith, G.E., Chetter, I.C., and Harwood, A.E. (2018) Home-based exercise programmes for individuals with intermittent claudication: A protocol for an updated systematic review and meta-analysis. *SAGE Open Medicine.* 6: 1-5.

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Pymer, S., Harwood, A.E., Ibeggazene, S., McGregor, G., Huang, C., Twiddy, M., Nicholls, A.R., Ingle, L., Carroll, S., Long, J., Rooms, M., and Chetter I.C. (2020) High INtensity Interval Training In pATiEnts with intermittent claudication (INITIATE): protocol for a multicentre, proof-of-concept, prospective interventional study. *BMJ Open*, 10(7), 38825.

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Palmer, J., **Pymer, S.,** Smith, G.E., Harwood, A.E., Ingle, L., Huang, C., Chetter, I.C. (2020). Presurgery exercise-based conditioning interventions (prehabilitation) in adults undergoing lower limb surgery for peripheral arterial disease. *Cochrane Database of Systematic Reviews.*

Harwood, A.E., **Pymer, S.,** Ingle, L., Doherty, P., Chetter, I.C., Parmenter, B., Askew, C.D., and Tew, G.A. (2020). Exercise Training for Intermittent Claudication: A Narrative Review and Summary of Guidelines for Practitioners. *BMJOpen Sport and Exercise Medicine. 0: e000897*.

Abstract

Supervised exercise programmes (SEP) for intermittent claudication (IC) suffer from low provision and uptake rates. As such, alternative interventions should be explored, such as home-based exercise programmes (HEP) and high-intensity interval training (HIIT). This thesis aimed to synthesise the current evidence for HEPs and provide evidence-based recommendations for practitioners. A second systematic review was performed to synthesise the evidence for HIIT, designed to inform a cohort study considering the safety, tolerability, feasibility, efficacy and acceptability of HIIT for patients with IC

Evidence from this thesis suggests that HEPs are potentially efficacious as long as they are sufficiently structured and include appropriate; frequency (≥3x week), intensity (moderate-maximal claudication), time (20 increasing to 60 minutes) and type (walking) principles. They also need to be supported by including education, feedback, goal setting, action planning and monitoring. However, this HEP structure is currently untested, meaning further adequately powered research is required.

Evidence for HIIT was limited but suggested that low-volume, short-duration protocols were efficacious. This informed the first cohort study which identified that a large proportion of patients were unable to achieve a maximal effort cardiopulmonary exercise test, likely due to deconditioning. This meant that *conventional* HIIT was not feasible for these patients and as such, they were excluded, leading to a low completion rate. However, these deconditioned patients may accrue the most benefit. As such, the exclusion criteria were altered, and these patients were included and provided with a personalised, submaximal HIIT programme. A second cohort study was performed to consider the feasibility of this slightly altered programme. The findings suggest that the exclusion criteria are now appropriate and that the HIIT protocol is feasible, tolerable and acceptable, whilst also being potentially safe and efficacious. These findings should be confirmed before larger randomised trials of HIIT versus SEPs are performed.

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Acknowledgements

I would like to express my profound gratitude to my supervisors; Professor Ian Chetter, Professor Lee Ingle, Mr George Smith and Dr Amy Harwood who have dedicated their time and efforts to supporting me through this thesis and no doubt beyond. I was also like to thank them for initially giving me the opportunity to undertake this research in 2017. By doing so they provided me an initial opportunity to work in the world of clinical research and for that I will always be grateful. I also wish to thank Mr Brian Johnson and Dr Vivek Shrivastava for their support as members of my Thesis Advisory Panel.

I would also like to thank Professors Lee Ingle and Sean Carroll for initially igniting my interest in clinical exercise physiology, an interest that remains strong as ever thanks to their ongoing expertise, debate and support in the area.

I would also like to thank all those that have provided direct support in the vascular lab to help with this thesis and my professional development (as well as providing laughs to keep me sane!!) including; Jonathon Prosser, Jack Altoft, Paris Cai, Saïd Ibeggazene, Joanne Palmer, Louise Hitchman, Joshua Totty, Hayley Crane, Gemma Boam, Amber Stafford, Abduraheem Mohamed, Josie Hatfield, Tracey Roe, Anna Firth, Claire Acey, Caroline Jennison, Lynne Andrews, Judith Long, Carole Tennison, Claire Worrell, Rachael McDonald and Debbie McDonald. I am also grateful to all the vascular consultants and their registrars for their support of this project.

I would also like to thank all the undergraduate and postgraduate students who gave their time to support me both within and outside of this project.

Most importantly, I would like to thank family for their support before during and after this PhD, without which I would not be where I am today. I will always be eternally grateful. To Rachael Pymer, Toni-Ann Pymer and Philip Cross, this one is for you!

Finally, to Lydia Woolley (soon to be Pymer!). You have been the one to experience first-hand the highs and lows that have come every day throughout my PhD and always stood strong and provided me the support, guidance and words of inspiration I needed. I will be eternally grateful for your support, love and patience, for which I know you have needed plenty. Here's to the next chapter!

Dedicated to Wilhelmina Ada Chapman.

Author's Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources'. 'I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Chapter 1: Introduction

1.1 Peripheral Arterial Disease

Peripheral arterial disease (PAD) is caused by atherosclerotic stenosis or occlusion of the arteries that supply the lower limbs resulting in a reduction in arterial blood flow (1, 2). PAD can be either symptomatic or asymptomatic with three to four asymptomatic patients for every symptomatic one (3). The clinical disease spectrum is therefore wide, ranging from asymptomatic disease, to limb- and life-threatening symptomatic disease. Symptomatic PAD most commonly presents as an ambulatory induced muscular leg pain, which is quickly relieved by rest, known as intermittent claudication (IC) (2, 4-6). The most severe manifestation of symptomatic PAD is critical limb threatening ischaemia (CLTI), which causes rest pain, ulceration and / or gangrene and can ultimately lead to amputation (3, 6). Symptomatic disease has a detrimental effect on ambulation, which in turn affects functional capacity and quality of life (QoL) (7, 8), whilst asymptomatic disease carries an increased risk of future ambulation restriction, lower extremity ulcers, or the need for vascular intervention (7). In addition, PAD is a strong independent predictor of cardiovascular morbidity and mortality as well as all-cause mortality (7). As such, those with PAD have an increased mortality risk compared to those without PAD, often of cardiovascular origin (9).

1.1.1 Epidemiology and Prevalence

Although PAD can be asymptomatic meaning that the true incidence and prevalence is unknown, it is a common disease estimated in 2010 to affect more than 202 million people worldwide (10-12). In 2015, this estimate had increased to 237 million (13). In addition, previous population studies have shown that the prevalence of PAD increases from approximately 3% in people aged less than 60 to approximately 15-20% in people aged 70 or older (11, 12, 14).

A systematic review published in 2019 estimated the global distribution of PAD, comparing the prevalence between populations living in high-income countries (HIC) and low or middle-income countries (LMIC) (13). In HIC's the prevalence of PAD increased with age for both men and women, though there was some disparity in the prevalence rate between sexes. The prevalence rate was lower in men than in women up to the age of 75, where it became greater in men than in

women (3.9% vs. 5.1% at 45-49 compared to 27.4% vs. 24.5% at 85-89 years). In LMIC's, the opposite was evident. Again, the prevalence rate increased with advancing age, but was slightly lower in women than in men up to the age of 55, where it became greater in women than in men (4.8% vs. 5.0% at 45-49 compared with 14.3% vs. 12.6% at 85-89 years).
Interestingly, due to world population ageing it was estimated that between 2010 and 2015 the prevalence of PAD increased by 17% worldwide, with a much greater increase in LMIC's (23%) compared to HIC's (4%) (13).

Despite these increases in prevalence, evidence has shown that there is a general trend for a decrease in incidence. A recent study across EU15+ countries between 1990 and 2017 demonstrated that in all but one country there was a decrease in the incidence of PAD across both males and females, with the second largest relative decreases noted in the UK (males -23%, females -25%) (15). However, the same study has also noted increasing mortality rates attributed to PAD, despite these reducing incidence rates. The PAD mortality rates increased for females across all countries and in all but three countries for males. In contrast to the falling PAD incidence, the UK had the largest relative increase in PAD related mortality between 1990-2017 (+140% males and +158% females) (15). Consequently, in the context of an increasing mortality rate and decreasing incidence rate, the UK had the largest increase in the mortality incidence index (mortality divided by incidence, +216% males and +242% females). The authors attribute these findings to a lack of compliance with secondary prevention measures and highlight goal directed medical therapy as a priority to reduce PAD mortality (15).

1.1.2 Risk Factors

PAD development is multifactorial and involves both non-modifiable (such as age and ethnicity) and modifiable (such as smoking and hypertension) risk factors which are similar to those for other atherosclerotic diseases, such as coronary artery disease (CAD) and cerebrovascular disease (7, 16). The UK National Institute for Health and Care Excellence (NICE) guidelines for PAD treatment recommend

secondary prevention of cardiovascular disease via risk factor modification such as smoking cessation and appropriate pharmacological therapy (17).

1.1.2.(a) Smoking

Smoking is considered the most important modifiable risk factor for developing PAD (16), and this relationship was first established in 1911 when Erb reported that IC was three times more common in smokers than non-smokers (18). In addition, the severity of PAD tends to increase with the number of cigarettes smoked (18) and the Edinburgh artery study showed that the age and sex adjusted increased risk of PAD was approximately two-fold for moderate smokers (≤25 pack-years) and four-fold for heavy smokers (>25 pack-years) (19). It has also been suggested that the diagnosis of PAD is made a decade earlier in smokers compared to non-smokers and the association between smoking and PAD is greater than the association between smoking and CAD (18). Consequently, there has been a long-standing advocation for interventions to decrease or eliminate smoking in patients with PAD (18). This is important, as the Edinburgh artery study showed that ex-smokers, who stopped in the last 5 years, had reduced odds ratios for PAD compared with current smokers across the whole PAD spectrum (20). It is therefore unsurprising that smoking cessation constitutes a large component of best medical therapy (BMT) for PAD (17).

1.1.2.(b) Ethnicity

Research has identified that the risk for PAD is increased in certain ethnic groups, with black ethnicity being a strong independent risk factor that is not explained by higher levels of other risk factors, such as diabetes or hypertension (14, 21). In addition, one study that pooled data from seven community-based studies identified that for American Indian and African American women, there was an exponential increase in PAD prevalence that occurred a decade earlier than in all other ethnic groups (22). For African American men, there was an exponential increase as soon as the disease became prevalent in this population, at around 50-59 years of age (22).

One of the individual studies within this analysis noted that Hispanics and Asians had lower rates of PAD than whites, but this did not reach statistical significance

(21). However, this may have been a paradoxical finding for the South Asian population given that they have a worse risk factor profile and a greater premature CAD death rate compared to the general population (23, 24). Therefore, as PAD increases with age, South Asians may not live long enough to develop PAD symptoms, thus explaining the lower rates identified (23).

1.1.2.(c) Gender

It is reported that there is a slightly greater prevalence of PAD in men than women, especially in younger age groups (18). One population study noted a prevalence of 16.8% in women and 19.8% in men, but the general practice setting in which this was conducted may have resulted in higher disease detection (25). A second study noted a rate of 3.6% in women and 6.1% in men, with gender being a significant predictor of PAD (21). However, when the prevalence estimates were adjusted for age in the first study, the gender differences were much lower at 1% and when other risk factors such as diabetes and hypertension were added to the model in the second study, gender was no longer significant. These studies, along with others that demonstrate a more equal distribution of PAD across genders (14, 26), therefore provide conflicting evidence and suggest that gender may not be a risk factor.

In 2010, it was highlighted that gender differences may be influenced by country. In HIC's it was estimated that the prevalence was largely similar between men and women, increasing with advancing age from 2.7-2.8% at 25-29 years to 11.8-12.1% at 70-74 years (6, 10). However in LMIC's, age-specific rates appeared lower in men than in women, with differences being more pronounced at younger ages (1.2% vs. 4.0% at 25-29 years and 12.3% vs. 13.7% at 80-84 years) (6, 10).

When this was reconsidered in 2015, the findings were somewhat different (13). In HIC's, disparities were noted between men and women, with the prevalence rate being lower in men up to the age of 75, where it became greater than in women (3.9% vs. 5.1% at 45-49 compared to 27.4% vs. 24.5% at 85-89 years). In LMIC's, the previous disparities were not apparent at younger ages but did appear with increasing age and the prevalence became greater in women than in men (4.8% vs. 5.0% at 45-49 compared with 14.3% vs. 12.6% at 85-89 years).

This overall and somewhat conflicting evidence therefore suggests that further epidemiological work is required to understand the role of gender in PAD.

1.1.2.(d) Age

Advancing age is considered a significant factor for the development of cardiovascular diseases and this has been demonstrated in those with PAD, with age being significantly associated with the disease worldwide (10). In addition, those aged 75 years or older have an approximately 8-fold increased risk of PAD compared to those aged <60 years (12). Two worldwide systematic reviews also estimated the prevalence of PAD across both men and women and LMIC's and HIC's, (10). Regardless of gender or income status, the prevalence of PAD increased with advancing age (6, 10).

1.1.2.(e) Diabetes Mellitus

Diabetes is associated with the development of PAD and it is one of the two strongest risk factors alongside smoking (18, 27). Compared to non-diabetic PAD patients, those with diabetes develop PAD at a younger age and have more comorbidities such as CAD, congestive heart failure, and a higher body mass index (BMI) (28-30). Those with diabetes also have worse lower extremity function (30) and a greater severity of arterial disease in the distal segments (i.e. below the knee). They also present later, with more advanced and complex disease, requiring multi-vessel intervention (28, 29). Consequently, those with PAD and diabetes are at much higher risk of further complications. In those with PAD presenting for angiography or revascularisation, diabetics have a five-fold increased risk of amputation and an approximately two to four-and-a-half-fold increased risk of mortality (28, 29, 31). It has also been demonstrated that PAD patients with diabetes die significantly younger, on average 6.5 years earlier, than those without diabetes (31).

However, diabetics may have an element of peripheral diabetic neuropathy, the process of nerve damage caused by hyperglycaemia which can affect the feet, legs, hands and arms (32). Consequently, these patients may not have a classic history of symptomatic PAD due to impaired sensory feedback which may mask the pain

(27, 30, 31). These patients are more likely to have leg pain with exertion and rest or more subtle symptoms, such as a slow walking velocity, that may be attributed to ageing rather than PAD, thus causing them to present later with more advanced disease, resulting in these worse outcomes (31, 33).

1.1.2.(f) Hypertension

Hypertension is associated with PAD, but the risk of developing PAD secondary to hypertension is lower compared to other risk factors such as diabetes and smoking (18). Both prevalence and incidence studies have identified that the odds ratio for PAD in patients with hypertension is between 1.5-1.7 (10, 34), with one study also reporting an odds ratio of 1.8 after adjusting for concomitant risk factors (14).

For patients with PAD, NICE recommends the prevention, diagnosis and management of high blood pressure (17). In addition, the treatment of hypertension in the PAD patient should be a principal objective for a primary care provider (34). This is important as intensive blood pressure treatment in diabetic PAD patients reduces the number of cardiovascular events (35). In addition, the inverse relationship between ankle-brachial pressure index (ABPI) and cardiovascular events is abolished with aggressive blood pressure management (35).

1.1.2.(g) Dyslipidaemia

A total fasting cholesterol level of >7 mmol/L has been associated with a two-fold increase in the incidence of IC, though the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol has been identified as the best predictor of PAD (18). The reason for this is likely to be that patients with PAD have lower levels of HDL than controls, even in the context of a normal total cholesterol (36, 37). As such, total cholesterol levels may be normal, but the total cholesterol/HDL ratio may be abnormal in the presence of PAD. It is therefore important to assess both total cholesterol and HDL levels in patients with PAD.

In addition, further dyslipidaemia may be present with one study demonstrating increased serum triglycerides, intermediate- and very low-density lipoprotein (VLDL) cholesterol, and VLDL triglycerides/HDL cholesterol ratio in patients with

PAD (36). This study also noted that there were no significant differences for lipid or lipoprotein concentrations between ex-smoking and non-smoking patients. For current smokers however, there was a significant increase in serum triglycerides, VLDL triglycerides, and in the VLDL triglycerides/HDL cholesterol ratio along with a significant reduction in HDL when compared to ex- and non-smokers (36). This further highlights the importance of smoking cessation for reducing cardiovascular risk.

This evidence suggests that dyslipidaemia acts as a major risk factor for PAD with a particular focus on HDL/total cholesterol ratio, serum triglycerides, and intermediate- and very low-density lipoproteins.

1.1.2.(h) Other

There is also limited evidence for other risk factors that may contribute to the development of PAD, though they have not been extensively explored. These factors include raised C-reactive protein, hyperviscosity, hypercoagulability, hyperhomocysteinemia and chronic renal insufficiency (18).

1.1.3 Pathophysiology

PAD is characterised by reduced blood flow secondary to atherosclerosis, and as such, the pathophysiology is best considered via the study of this atherosclerotic process in general (38, 39). This process occurs in three stages, preceded by endothelial dysfunction which is characterised by inadequate vascular function and endothelial damage (2, 38). Impaired vascular function is often identified by flow-mediated dilatation, whilst increased levels of von Willebrand Factor may indicate endothelial damage (40). This endothelial damage causes increased permeability and allows the recruitment of leucocytes to the intimal layer of the vessel wall, dependant on two groups of adhesion molecules; selectins, responsible for acute molecule adhesion and immunoglobins, responsible for sustained molecule adhesion (38, 41). The migration of these cells into the intima is mediated by chemoattractant chemokines and oxidised LDL, via a process called diapedesis. Once these cells have migrated into the intima, they take on a foam-like appearance due to the accumulation of lipids, referred to as macrophages. These, in conjunction with T lymphocytes form what are known as fatty streaks, the first and earliest recognisable stage of atherosclerosis, which is reversible (38, 41).

However, the accumulation of more foam cells within the intima converts this into an advanced, irreversible plaque that has a lipid rich core, separated from the blood stream by a fibrous cap (2). This is the second stage of the atherosclerotic process. This plaque is considered stable and uncomplicated at this point, until the final stage occurs whereby the fibrous cap is dislodged, making it unstable, and the subintimal lipid rich contents are exposed to the circulating blood stream (2, 38, 42). The most important components of this core are the proaggregatory thrombogenic substances, which when exposed to the blood stream, initiate the coagulation cascade, with tissue factor and platelets being the most influential (38). Via glycoprotein Ia/IIa/Ib receptors, a monolayer of platelets adhere to collagen fibrils and von Willebrand factors (38). This is followed by a release reaction whereby a number of antagonists, including thrombin, are secreted by the platelets. These platelets also undergo structural changes and activate additional glycoprotein IIb/IIIa receptors on their surface. Platelets are bridged together by fibrinogen, creating a matrix of cells known as a platelet plug. This plug can become firmly attached to the vessel wall and continue to grow until it occludes the lumen, or can become detached and flow into the peripheral vessels (2, 38). Both stable and unstable plaques can be flow limiting, though the amount of vessel diameter reduction required for the flow limitation to become significant, and potentially cause symptoms, is not easily definable and depends on the degree of stenosis and flow velocities. At rest, femoral artery flow velocities of 20 cm/s have been recorded, meaning that for a stenosis to become haemodynamically significant at such velocities, it would need to be >90% (2). However, the metabolic requirements of distal tissues are higher in the exercising individual and as such, a velocity increase up to 150 cm/s may be required, meaning that at such velocities, a ≥50% stenosis may be haemodynamically significant (2). As such, the level of stenosis required to be haemodynamically significant will be patient specific and dependant on physical activity status. A patient who is sedentary is unlikely to have a stenosis that is haemodynamically significant and symptom inducing until it nears 90%, whereas a patient who is active, may experience symptoms closer to 50%.

It is however important to note that the cause of limb symptoms in PAD is more complex than flow-limiting lesions, given that atherosclerotic disease occurs in the context of multiple disease processes, which likely contribute in isolation and in combination, to the clinical status of the PAD patient (39). These processes include vascular dysfunction, impaired microcirculatory flow, inflammation, and alterations in skeletal muscle, all of which contribute, in combination with fixed atherosclerotic lesions, to lower limb symptoms (Figure 1). Although endothelial dysfunction is a precursor to atherosclerosis, the continuing dynamic dysfunction may also contribute to limb symptoms due to a reduction in nitric oxide bioavailability, which limits vasodilation and impedes the increase of blood flow with exercise. In addition, this is compounded by skeletal muscle ischaemia which causes local inflammation, further reducing nitric oxide bioavailability and vasodilation (39).

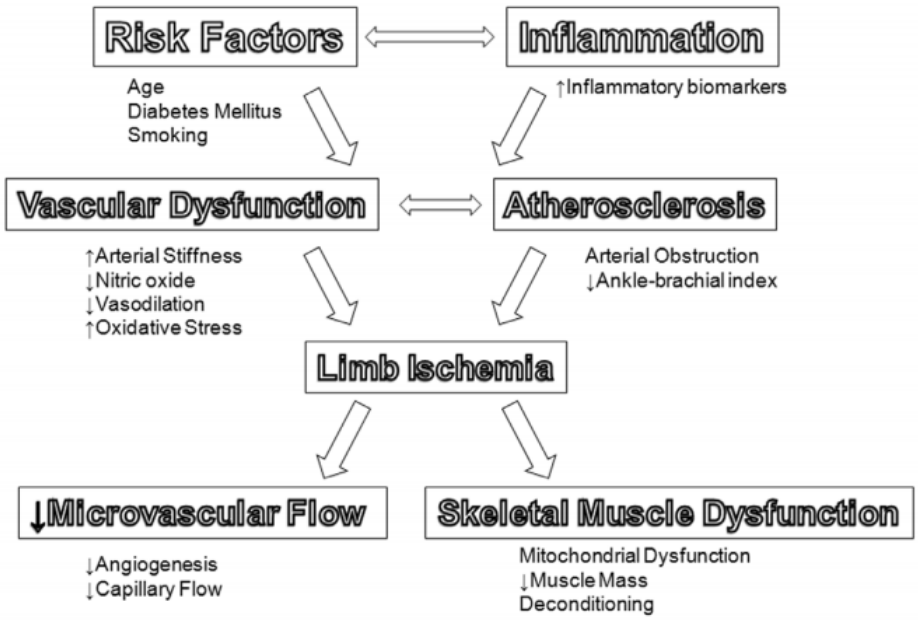


Figure 1 - Mechanisms of limb symptoms in PAD

Microvascular flow may also be inadequate in those with PAD, which can affect limb function. Indeed, one study has demonstrated that reduced capillary density, an approximation of the microcirculatory system, is not only present in patients

with PAD, but is also associated with a reduction in all three of the functional measures of peak oxygen consumption, intermittent claudication time and maximum walking time (43).

Finally, repeated ischaemic episodes have detrimental effects on skeletal muscle structure, with PAD patients having reduced calf skeletal muscle content and increased calf skeletal muscle fat content, with further reductions in ABPI amplifying these effects (44). In addition to its structure, the metabolic status of the skeletal muscle also becomes altered and impaired, with mitochondrial dysfunction contributing to this process (39, 45). This metabolic dysfunction further contributes to the exercise intolerance and functional impairment of those with PAD (45).

Overall, the pathophysiological process behind PAD is atherosclerotic and the atherosclerotic cascade is the driver of this condition. However, individual disease processes within this cascade act in isolation as well as in combination, to contribute to the functional impairment and limb symptoms experienced by patients with PAD.

1.1.4 Clinical Presentation

In all patients with PAD, the pathophysiological process outlined above is the common cause. However, patients do not always present homogenously as the disease spectrum ranges from asymptomatic, whereby the patient may be unaware that they have PAD, to severely symptomatic, whereby the patient's limb and life may be at immediate threat.

1.1.4.(a) Asymptomatic Disease

The progression of PAD does not appear to be affected by whether or not the patient has symptoms of the leg, with no evidence to suggest that the risk of deterioration and ultimate progression to CLTI is dependent on symptoms (18). The initial symptomatic manifestation may be influenced by comorbid factors that limit functional capacity such as arthritis, angina or chronic obstructive pulmonary disease (COPD), meaning that some patients may initially present with CLTI without any prior IC as they may be too sedentary to induce claudication (18, 46). Indeed, one study has found that those with asymptomatic PAD have significantly smaller

calf muscle area, higher calf muscle percent fat and poorer lower extremity functional performance compared to those with IC (47). In addition, another study noted that inactive, apparently asymptomatic patients had a slower walking velocity compared to IC patients and more than 50% developed leg pain during the 6-minute walk test (6-MWT) (48). Therefore, 'asymptomatic' patients may in fact slow their usual walking speed or walk shorter distances to avoid experiencing any symptoms (47).

In addition to reducing lower extremity function, asymptomatic disease increases the risk of acquiring ulcers and / or requiring vascular intervention whilst also increasing the risk of coronary and cerebrovascular events and mortality (7), meaning that clinicians should not treat asymptomatic disease as a benign form of PAD.

1.1.4.(b) Intermittent Claudication

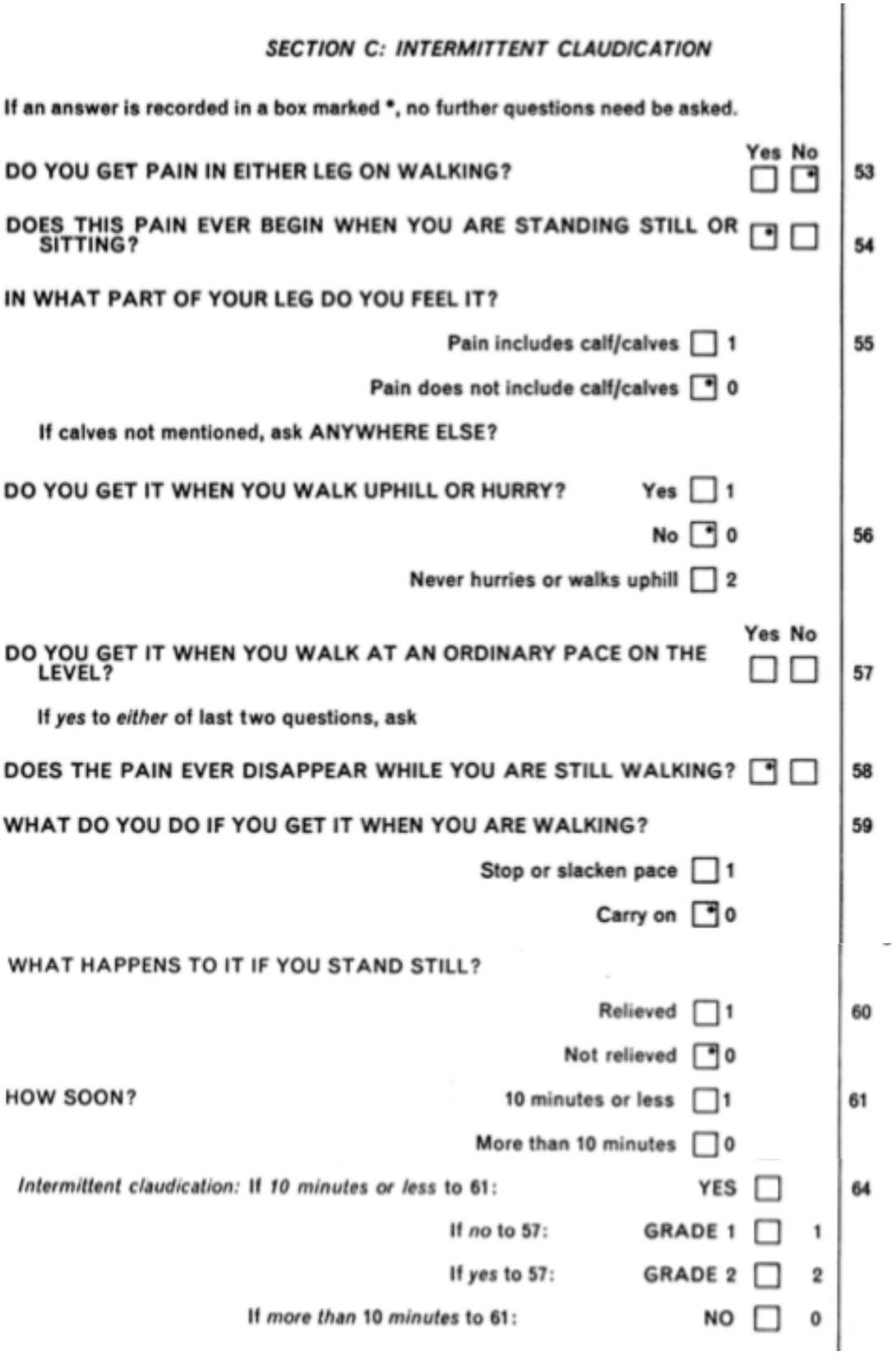
The most common symptomatic manifestation of PAD is IC, which affects 10-35% of the PAD population. IC is characterised by a reproducible ischaemic aching pain in the muscles of the leg, precipitated by exertion and relieved with rest (4, 16, 18). IC pain is caused by exercise-induced ischaemia, leading to an oxygen supply and demand imbalance (49). During exercise, the increased oxygen demand of the working muscles cannot be met due to atherosclerotic arteries, leading them to work anaerobically (2). Consequently, a build-up of lactic acid and other metabolites occurs causing a pain or cramping sensation in the affected lower limb (2). This pain is resolved within minutes of rest, but the cycle of lactic acid and metabolite accumulation, resulting in lower limb pain, reoccurs with further exercise.

Early work by G.A. Rose in 1962 aimed to determine the precise characteristics of the pain experienced by hospital patients with IC and which of these characteristics could effectively distinguish it from other types of leg pain (50). From this, a definition was derived and a simple questionnaire created and validated (50). The following definition of IC was set out:

> "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 a majority of occasions in 10 minutes or less from the time when the subject stands still.
(6) It must never disappear while walking continues." (50; p.649)

From this, the WHO/Rose questionnaire was developed (Figure 2). This questionnaire states that if an answer is recorded in a box marked with an asterisk, no further questions need to be asked and the patient is considered to not have IC. Importantly, if the patient indicates that the pain does not include the calf or calves, they are deemed to not have IC (50). This is important as it has been noted that the muscles affected by claudication are determined by the site of disease and patients with IC may not always have pain in the calf (Figure 3) (51). Likely compounded by this, the WHO/Rose questionnaire demonstrated only moderate sensitivity (60-68%) despite excellent specificity (90-100%) (52).



SECTION C: INTERMITTENT CLAUDICATION

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

DO YOU GET PAIN IN EITHER LEG ON WALKING? Yes ☐ No ☐ 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? Yes ☐ No ☐ 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

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

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 - WHO / Rose questionnaire

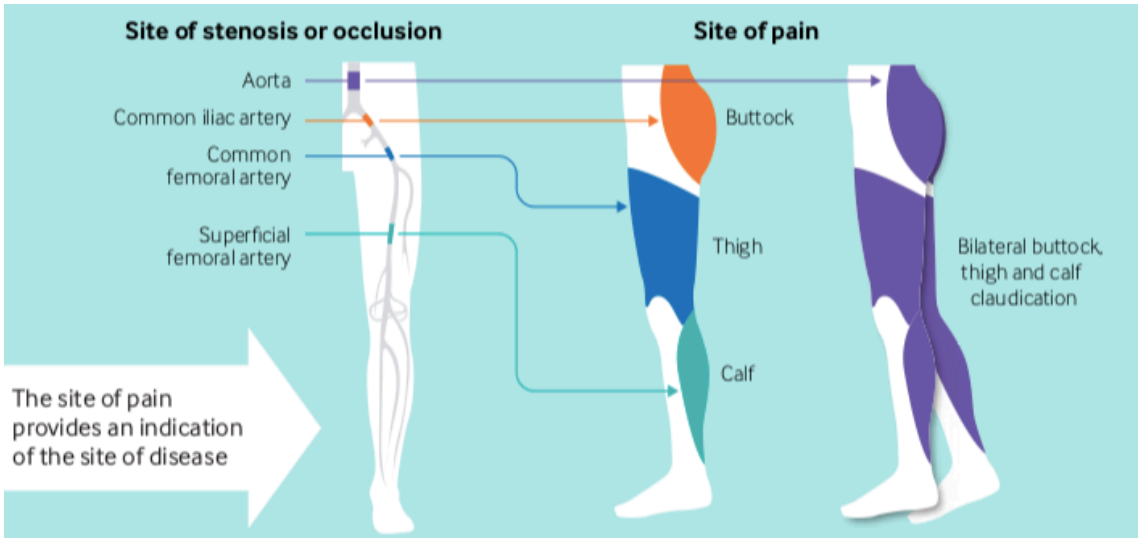


Figure 3 - Location of symptoms based on site of disease

As such, the Edinburgh claudication questionnaire (ECQ) was developed to try and improve this sensitivity and specificity (Figure 4) (52). The ECQ shares a number of similarities to the WHO / Rose questionnaire, though there are some subtle differences. The question that asks if the pain disappears whilst the patient is still walking has been removed. This is because patients may walk slower to alleviate the pain, but they have still reacted to it. More importantly however, patients no longer have to indicate pain in the calf to be considered to have IC. Instead, a diagram is used to indicate where pain is present, and the terms *definite* and *atypical* claudication are used depending upon the location of symptoms. A *definite* claudicant is one who provides a positive response to the ECQ and indicates pain in the calf, regardless of whether pain is marked in other sites. An *atypical* claudicant also provides a positive response to the ECQ but indicates pain in the thigh or buttock in the absence of calf pain. The modifications to the WHO/Rose questionnaire, which generated the ECQ, had the desired effect as the specificity remained excellent at 99% and the sensitivity increased to 91% (52).

THE EDINBURGH CLAUDICATION QUESTIONNAIRE[1]

(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.

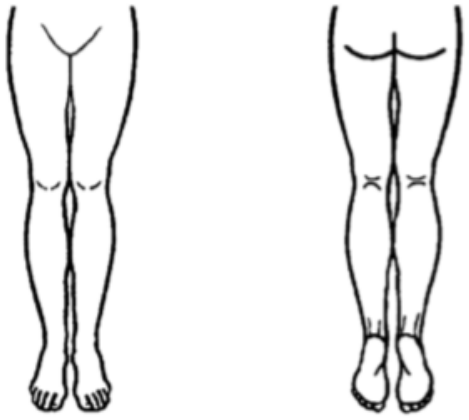
(2) Does this pain ever begin when you are standing still or sitting?
Yes
No

(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 "x" 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 4 - Edinburgh claudication questionnaire

Despite PAD being pathologically progressive, clinically it remains stable in most cases. However, those with IC will continue to be affected by global balance abnormalities and impairment, reduced functional capacity and restricted ambulation that affects their ability to perform daily activities and in turn, QoL (2, 7, 8, 18, 53, 54). Potentially aided by the development of collateral vessels, adaptation of the ischaemic muscles, an alteration in gait pattern or a combination thereof, it is widely accepted that ≈75% of patients with IC will not significantly deteriorate, suggesting that initial conservative management as recommended by UK guidance is appropriate (17, 18). This conservative management trajectory recommends secondary prevention of cardiovascular disease including smoking cessation, diet, weight management and exercise, statin and antiplatelet therapy and the prevention, diagnosis and management of diabetes and hypertension (17).

For the ≈25% of patients who do deteriorate, the rate of deterioration is much steeper in the first year after onset (7.5-8.3%), compared to subsequent years (2.2-3.0%) (18, 55, 56). The majority of these patients experience only a worsening of their claudication, whilst a minority experience CLTI (18). In addition, it is widely accepted that progression to CLTI requiring amputation is a rare outcome for those with IC, with approximately 1-3% of patients requiring major amputation (18). This has been confirmed in a recent study that demonstrated an overall amputation rate of 3.5%, with a major amputation rate of 1.6% (57). Interestingly, it appears that those who undergo early revascularisation rather than initial conservative management are at an increased risk of further revascularisation and amputation, strengthening the argument for the NICE recommended conservative management trajectory (58). However, amputation is still a major fear for PAD patients, meaning that they should be reassured that it is a rare and unlikely outcome, with the exception of the diabetic subgroup who are at a four-fold increased risk of CLTI and therefore amputation (18). It may also be beneficial for patients to be informed that the risk of amputation is potentially increased with early revascularisation, which may encourage compliance with initial conservative management (58).

As only a quarter of patients significantly deteriorate, it is difficult to predict the risk in a newly presenting claudicant, though the various aforementioned risk factors undoubtedly contribute to the progression (18). However, ABPI is the best predictor with an index <0.5 or an ankle systolic pressure <70mmHg being significantly associated with disease progression. Indeed, those with the lowest ankle pressure (40-60 mmHg), infer an 8.5% annual risk of progression to severe ischaemia or limb loss, with one study noting than no patients with an ankle pressure >70mmHg required an amputation during the observational period (18, 55). Another factor that is important to consider is walking distance. One meta-analysis has shown that a shorter walking distance is associated with an increased risk of cardiovascular and all-cause mortality for those with PAD (59). It was demonstrated that those in the lowest quintile for walking endurance had more than twice the risk compared to those in the highest quintile (59). A number of other easily measurable yet novel factors are associated with increased mortality risk including a slower 4-metre walking velocity, a lower walking impairment questionnaire (WIQ) stair-climbing score and poor hip extension, knee flexion and plantar flexion strength (59).

1.1.4.(c) Critical Limb Threatening Ischaemia

Based on indirect evidence from studies of IC progression, population surveys and assumptions from major amputation rates it is estimated that there will be between 500-1000 new CLTI cases every year per million in the European and North American population (18). Of those with documented PAD, approximately 5-10% will develop CLTI over a 5 year period (18). However, due to population ageing and a rise in the incidence of diabetes and chronic kidney disease, the prevalence of CLTI is likely to increase (46). CLTI, which emerged late in the history of PAD, manifests as a result of arterial insufficiency that reduces distal perfusion pressure, severely disturbing the microcirculation and nutrient blood flow resulting in chronic inadequate tissue perfusion at rest (60, 61). In order to emphasise the chronicity of the ischemia, it is also termed chronic CLTI in order to differentiate it from acute limb ischaemia (ALI), which is a sudden onset of severe limb hypoperfusion (61). Therefore, the term CLTI should only be used for those with

chronic ischaemic disease, which is defined as the presence of symptoms for more than 2 weeks (18).

Unlike those with IC, who experience exercise-induced ischaemia, those with CLTI have ischaemia at rest meaning there is inadequate perfusion to sustain the viability of distal tissues (49). CLTI is therefore characterised by pain at rest, trophic skin changes, gangrene of the foot and non-healing ulcers, and may present as one or a combination of these signs or symptoms (18, 46, 60, 61). A patient may initially present with a nonhealing ulcer following minor trauma to the foot, without any significant history of claudication due to the aforementioned comorbidities that limit ambulation or the presence of diabetic neuropathy that could have masked the claudication pain (46). Conversely, rest pain, which is described as intractable, can occur in the absence of skin changes and tissue loss (46, 49, 60, 61). The pain often worsens when the patient is in a supine position (e.g., in bed) and may lessen with dependency (49, 61). Given that this pain can disturb sleep or render the patient unable to walk, analgesia is often provided (49).
Although CLTI is a clinical diagnosis on the basis of the above signs and symptoms, it is important that it is confirmed objectively (46, 62). Objective criteria for diagnosing CLTI include an ABPI of ≤0.4, an ankle pressure of <50mmHg or a toe or transcutaneous tissue oxygen pressure of <30mmHg (46). These criteria are also suggested by the TASC II guidelines, though for patients with ulceration or gangrene, a diagnosis of CLTI is based on an ankle pressure <70mmHg or a toe pressure <50mmHg due to the additional perfusion requirements needed for healing, above those that are required to support intact skin and tissues (18).

Although CLTI is not a surgical emergency, it does require urgent aggressive treatment given the characteristically high risk of limb loss and mortality associated with it (3). All patients with CLTI must immediately receive BMT, risk factor modification, pain control, effective wound care and treatment of any concomitant infection (63). However, as there is no effective medical treatment therapy, the primary treatment option for CLTI is revascularisation to improve limb perfusion with the aim of augmenting distal flow to relieve ischaemic pain, aid wound

healing, preserve a functional limb and ambulatory status whilst preventing amputation and prolonging survival (3, 61, 62). The main techniques for revascularisation are surgical (lower extremity bypass and endarterectomy), endovascular (angioplasty, stenting and atherectomy) or hybrid procedures (a combination of surgical and endovascular techniques) (61, 64). However, uncertainty remains about the role of surgical versus endovascular therapy (64).

The BASIL multicentre randomised controlled trial (RCT) randomised 452 patients with CLTI due to infrainguinal disease to either a surgery first or angioplasty first strategy (65). Medium term results showed that the outcomes of amputation-free survival, all-cause mortality and QoL were broadly similar for both strategies, suggesting that these patients can be reasonably treated by either method in the first instance (65). However, the immediate failure and 12-month reintervention rate was higher for angioplasty, though an initial clinically failed angioplasty did not impact upon the results of any subsequently necessary surgical intervention (65). For the surgery first strategy, early morbidity was significantly higher and the hospital costs in the first 12 months after randomisation were about a third higher than for angioplasty (65). In the long-term, there was tentative data to suggest that after 2 years, surgery appeared to be associated with a significant risk reduction of future amputation, death or both (65). It was therefore recommended that if patients have significant comorbidities and are expected to live less than 1-2 years, they should where possible, be offered angioplasty first as this is cheaper in the short-term and should not preclude future surgery if appropriate (65). Conversely, if a patient is relatively fit and expected to live more than 2 years post-intervention, the potential long-term durability and reduced reintervention rate of surgery could outweigh the initially increased morbidity and cost (65).
Further data is also being generated for those with infra-popliteal disease via the ongoing BASIL-2 trial (66). As such, an evidence-based revascularisation approach will soon be available for a large proportion of those with CLTI.

However, a number of patients who present with CLTI will be poor candidates for both surgical and endovascular revascularisation due to the complexity of their

PAD and / or medical comorbidities (46, 62). These patients, constituting approximately a quarter of the CLTI cohort, therefore receive conservative management initially (18). This entails risk factor modification (smoking cessation, glycaemic and blood pressure control and dyslipidaemia management especially with statin therapy) and pain and wound management. Primary amputation may also be offered to patients with CLTI to improve QoL and perhaps increase event-free survival (46).

Generally, for patients presenting with CLTI, the primary treatment is revascularisation for 50%, primary amputation for 25% or conservative management alone for the remaining 25% (18). Regardless of the primary treatment, only a quarter of patients will have their CLTI successful resolved, whilst also avoiding amputation, at 1 year (18). Of the remaining 75%, 25% will die, 30% will be alive with an amputation and 20% will have continuing CLTI (18).

1.1.4.(d) Acute Limb Ischaemia

Acute limb ischaemia (ALI) is defined as a sudden decrease in, or worsening of, limb perfusion that has been present for less than 14 days, causing a threat to lower extremity mobility and / or viability (18, 67). This sudden decrease in limb perfusion is also likely to be associated with new or worsening signs and symptoms and is a medical emergency (18, 68). ALI is considered a sequel to PAD as in situ thrombosis or distal embolization secondary to underlying atherosclerotic disease are the two most common aetiologies (68). However, it is often difficult to differentiate between these two causes, with thrombosis being more common in lower extremity bypass grafts (67, 68). Other causes of lower limb ALI include emboli of cardiac origin, arterial dissection, thrombosis secondary to a hypercoagulable state or aneurysmal disease, trauma or vasculitis (67, 68). In recent years, the number of ALI cases caused by emboli has reduced, possibly secondary to less cardiac valvular disease and better anticoagulation management of atrial fibrillation (18). Despite this, a recent population-based study noted that the prevalent underlying cause for ALI was an embolism, which accounted for 46% of cases (69).

There is limited information on the incidence of ALI, but the TASC II guidelines suggest that based on national registries and regional surveys it is around 14 per 100,000 per year (18). A more recent population-based study however reported an incidence of 10 per 100,000 per year (69). Importantly, routine hospital episode and death coding has a sensitivity and specificity of 48.5% and 47.9% for acute vascular events, whereas the methods used in the latter study have 100% sensitivity and specificity, suggesting that this is the most accurate incidence rate to date (69).

There are a number of treatment options for ALI that range from urgent revascularisation (by surgical, endovascular or hybrid methods) to amputation (68, 70). However, correct categorisation of the patient on the basis of a number of signs and symptoms is vital to ensure that the correct surgical decision is taken. One such categorisation method is that proposed by Rutherford that ranges from viable (category I) to irreversible (category III) ALI (71). A patient in category I will have no continuing ischaemic pain or nerve deficit accompanied by clearly audible doppler arterial flow signals in a pedal artery, meaning that the limb is not immediately threatened, and revascularisation can be performed within hours, rather than immediately (63, 71). Category II, which encompasses reversible ischaemia, means that the limb is salvageable if the arterial obstruction is quickly relieved. It includes two subcategories based on the level of threat to the limb, which can be marginal (IIa) or immediate (IIb) (71). Pedal arterial doppler signals are inaudible for both subcategories, but those in IIa do not experience continuous pain but rather a numbness with minimal or transient sensory deficit, limited to the toes, meaning the limb is salvageable if treated promptly (71). Those in IIb however experience ischaemic rest pain that is persistent, alongside a detectable sensation loss above the toes or a continuous lack of all sensation in the toes. For these patients, the limb is only salvageable with immediate revascularisation. Finally, those in category III have irreversible ischaemia which without amputation will lead to major tissue loss with permanent nerve damage. These patients will have profound sensory loss with muscle paralysis that extends above the foot with absent capillary skin flow distally. They may also demonstrate skin marbling

changes and neither arterial or venous doppler signals will be audible in the foot (71).

For those in category II, where prompt action is required, it is important that the appropriate revascularisation technique is used, whether that is surgical, endovascular or hybrid. A recent study that considered these techniques for patients in category II demonstrated that endovascular revascularisation resulted in a significantly shorter length of stay as well as a reduction in morbidity (postoperative transfusion and major amputation) at 30 days, when compared to surgical or hybrid techniques (70). However, there was no difference between the three techniques for 30-day need for reintervention, myocardial infarction, stroke or mortality (70).

With regards to longer term outcomes for patients with ALI as a whole (all Rutherford categories), there is a significant risk of future limb loss at 1 (6.6%) and 5 (16.9%) years (69). Interestingly, amputation free survival appears to be initially lower for ALI patients compared to CLTI patients at 3 months (59.1% vs. 75.7%) but this becomes higher at 5 years (36.7% vs. 27.1%). Finally, there is also a significant mortality risk for patients with ALI, which is approximately 25% at 30 days, increasing to 44% at 5 years (69).

1.1.4.(e) PAD Classification

Clearly, the PAD spectrum is vast and as outlined above ranges from asymptomatic disease to CLTI, with patients within each stratum having varying levels of disease and symptoms. As such, two widely used classification systems have been adopted, namely the Rutherford and Fontaine classifications. The Fontaine classification is based solely on symptomatic manifestation and categorises patients into one of four stages. Stage I is asymptomatic, stage II is IC with IIA being claudication at a distance of >200m and IIB <200m, stage III is rest pain and stage IV is necrosis and / or gangrene (72). The Rutherford classification is an adaption of this and considers both symptoms and objective findings. This classification ranges from 0-6 with 0 being asymptomatic, 1, 2 and 3 being mild, moderate and severe claudication respectively and 4, 5 and 6 being rest pain, minor and major tissue loss respectively (71). Table 1 outlines the full symptomatic and objective criteria of the Rutherford

classification. The treadmill test refers to a standard 5-minute test performed at 2.0 mp/h and 12% incline.

Table 1 - Rutherford classification

Grade	Category	Clinical Description	Objective criteria
0	0	Asymptomatic – no haemodynamically significant occlusive disease	Normal treadmill or reactive hyperaemia test
	1	Mild claudication	Completes treadmill exercise; ankle pressure after exercise >50 mmHg but at least 20 mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise and ankle pressure after exercise <50 mmHg
II	4	Ischaemic rest pain	Resting ankle pressure <40 mmHg, flat or barely pulsatile ankle or metatarsal pulse volume recording, toe pressure <30 mmHg
III	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischaemia	Resting ankle pressure <60 mmHg, ankle or metatarsal pulse volume recording flat or barely pulsatile, toe pressure <40 mmHg
	6	Major tissue loss – extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5.

Although other elements of the PAD spectrum will be considered where relevant, IC will be the main focus for the remainder of this thesis.

1.1.5 Clinical Examinations

Clinical examinations are vital for the diagnosis of PAD. Any patient with suspected IC secondary to PAD should undergo a complete examination which initially involves a detailed history and questioning about the standard cardiovascular risk factors. This should then be followed by a full drug and medical history which should document previous vascular interventions along with any comorbidities such as CAD and cancer. A full history of the current vascular specific problem should then be obtained followed by a thorough general examination and a specific peripheral vascular examination (16, 18, 73).

1.1.5.(a) Clinical History

The consultation should begin with a thorough personal and familial clinical history. Family history of CAD, cerebrovascular disease, PAD and abdominal aortic aneurysmal disease should be identified whilst also establishing if there is a history of premature cardiovascular disease (CVD). Personal clinical history should then be established including the evaluation of global cardiovascular risk factors including hypertension, diabetes, dyslipidaemia, prior CVD, kidney disease, lifestyle and dietary habits, psycho-social factors and smoking, which should also include current and past smoking habits and estimated lifetime pack years (63, 73). Before moving onto the physical examination a review of symptoms related to different vascular territories should also be conducted (63).

1.1.5.(b) General Physical Examination

The general physical examination should include the measurement of blood pressure in both arms, evaluation of heart rate (HR), rhythm and pulse volume via palpation of the radial and brachial arteries, auscultation of the heart for evidence of valvular pathology (i.e. murmurs) or congestive failure (i.e. gallops), focussed neurological assessment to identify signs of previous ischaemic stroke, a systemic evaluation to identify pathological signs outside of the vasculature (i.e. COPD) and an abdominal examination to assess for an abdominal aortic aneurysm (AAA) (18, 73).

1.1.5.(c) Peripheral Vascular Examinations

Following this general examination, focus should move to the limbs. Initially, a skin examination should be performed, noting any colour and temperature changes, or

differences, in the feet. Atrophied muscles should also be noted, as should decreased hair growth and dry, brittle skin and nails. It is also important to identify scars from previous vascular surgery and any limb or digit amputations (18, 73, 74). Capillary refill time should also be assessed, though this may be unreliable as it can be affected by external temperature and asymmetric rather than absolute findings should be considered (73). Importantly, the feet should be examined closely for signs of tissue loss such as ulceration or gangrene (16). Ischaemic ulcers usually occur on the lateral malleolus, the tips of the toes, the metatarsal heads or the hallux and are often dry and painful, making them distinguishable from venous ulcers which are more often on the medial malleolus and painless (74). If ulceration is noted, the size and distribution should be recorded, as well as the health of the surrounding skin (73). Accurate mapping of the ulcer may also be of benefit as this can aid the objective assessment of changes. The ulcer base should also be assessed for signs of healing (granulation tissue) or signs of an infection process (slough) (73).

A positive Buerger's test may also provide a more subtle indication of lower limb ischaemia and may be considered during the initial examination. However, as it is unlikely to alter patient management, it is not always used (73). For this test, the patient is in the supine position and their legs are raised to 45 degrees. A clear reduction in perfusion with concomitant venous guttering is considered a positive test. The legs are held in this position for 2 minutes and then swung over the side of the couch to a dependant position. Should reactive hyperaemia occur, the foot will turn to a sunset red, which also indicates a positive test (73). This hyperaemic reaction is the result of a loss of capillary autoregulation in the ischaemic limb (16).

After this initial assessment process, the peripheral pulses should be examined, as per NICE guidance (17). The upper (radial, ulnar, brachial and carotid) and lower limb (femoral, popliteal, dorsalis pedis and posterior tibial) arterial pulses should be assessed and graded zero (absent), one (diminished) or two (normal) for simplicity (18). However, an especially prominent femoral or popliteal pulse may indicate the presence of an aneurysm, which may warrant further investigation via

ultrasound imaging (18, 73). The location of diminished or absent pulses can also provide some information on the site of disease. A diminished or absent femoral pulse may indicate aorto-iliac disease reducing inflow to the limb, whereas a normal femoral but abnormal pedal pulses suggests preserved inflow but significant disease in the leg (18). Pulse assessment should be correlated to symptoms to determine the lateralisation of disease (18). One important consideration for the physical examination is that a small number of healthy adults may have an absent dorsalis pedis pulse due to anterior tibial artery branching. This situation may require the distal aspect of the anterior tibial artery to be detected and assessed at the ankle (18).

1.1.6 Diagnostic Approach

A diagnosis of IC can be suspected on the basis of the clinical examination, but should be confirmed via objective tests to aid in the management and follow-up of the patient (63). These objective tests are important because despite excellent specificity, pulse palpation has demonstrated poor sensitivity for the diagnosis of PAD (75).

1.1.6.(a) Laboratory Tests

Laboratory tests should begin with minimal biological assessments such as fasting plasma glucose and serum lipid profile, creatinine, creatinine clearance, blood count, uric acid and urine analysis (63). Based on the findings from these tests, the clinical history or the physical examination, additional tests may be required such as glycated haemoglobin (63).

1.1.6.(b) Ankle Brachial Pressure Index

The first diagnostic step after the clinical examination is the ABPI, which has demonstrated superior sensitivity and specificity compared to the pulse examination and is used routinely in vascular clinics (63, 76). For the measurement of ABPI, the patient should be in the supine position and allowed to rest for a period of 5-10 minutes before measurement begins (63). Following this, an appropriately sized blood pressure cuff is used to measure the systolic blood pressure (SBP) in the brachial artery of both arms and the dorsalis pedis and posterior tibial arteries of both feet. A doppler probe is placed on each artery to

detect audible pulsatile flow. The blood pressure cuff is then inflated until flow is no longer audible and the SBP is identified as the pressure at which audible flow returns following gradual cuff deflation (2, 18, 63). The ABPI is then calculated by dividing the highest systolic ankle pressure in each leg by the highest systolic arm pressure. A normal ABPI is considered to be between 1.0-1.4, whilst an index between 0.9-0.99 is borderline. A of value of <0.90 is abnormal and considered diagnostic for PAD, carrying with it a three-to-six-fold elevated risk of cardiovascular mortality (18). Typically, patients with IC will have an ABPI between 0.4-0.89, with an ABPI of <0.4 usually indicative of CLTI. However, some patients with IC may have a normal resting ABPI meaning a further ABPI measurement is needed following an exercise test to diagnose PAD (63). A value of >1.40 is considered falsely elevated due to medial arterial stiffening often caused by diabetes, renal insufficiency or other diseases that cause calcification (18, 63). In this case, the ABPI measurement is unreliable for the assessment of PAD due to incompressible vessels and other tests are required for an accurate diagnosis. One option is the measurement of toe pressures which provides an accurate measurement of distal limb systolic pressures in digital arteries that tend not to become calcified and incompressible (18). From this, the toe-brachial pressure index (TBPI) can be calculated. A small occlusive cuff is placed on the first or second toe, with a flow sensor. The cuff is inflated to occlude the vessel and the SBP is identified as the point at which flow returns on the sensor following gradual deflation. As the toe pressure is approximately 30mmHg lower than the ankle pressure, an abnormal TBPI is considered to be <0.7 (18). This test however also has limitations, as it may not be possible to measure the pressure at the first or second toe due to ulceration or tissue loss (18).

1.1.6.(c) Exercise Testing

As previously mentioned, measuring ABPI following an exercise test can be useful for detecting PAD in those with a normal resting ABPI. The exercise test generally takes place in the form of a constant load treadmill test (or a plantar-flexion test for those unable to tolerate a treadmill test) (63). Patients will walk on the treadmill and indicate when pain commences, and this is referred to as the intermittent claudication distance (ICD). The test is then stopped when the patient

is unable to continue walking due to claudication pain and this is termed the maximum walking distance (MWD). ICD and MWD are usually presented in meters, calculated by multiplying the walking time in seconds, by the treadmill speed, in meters per second. The post-exercise ABPI is then recorded immediately following cessation of the test and a systolic ankle pressure decrease of >20mmHg or a post-exercise ABPI decrease of >20% indicates the presence of PAD (63, 71).

1.1.6.(d) Imaging Modalities

There are a number of imaging modalities available to further explore the extent and site(s) of PAD including duplex ultrasound and angiography.

Duplex ultrasound refers to a scanning procedure whereby both gray scale and doppler information are recorded (77). The aim of the duplex ultrasound is to identify the location and severity of stenoses (77). Stenoses are graded based on the peak systolic velocity (PSV) ratio of the target or stenosed vessels and adjacent non-stenosed vessels. A PSV ratio of >2:1 indicates >50% stenosis, with a ratio >4:1 suggesting >75% stenosis and >7:1 suggesting >90% stenosis (77). In addition to identifying the site and severity of a stenosis, duplex ultrasound is also recommended for the surveillance of peripheral arterial bypass grafts, as it can preserve graft patency (77). One drawback of the duplex ultrasound is that it does not provide a roadmap of the vasculature to aid treatment or surgical planning, unlike other imagine techniques (78). However, it can provide a similar role and suggest whether a patient is a better candidate for angioplasty or surgical reconstruction, whilst having the added benefit of avoiding the possible complications associated with other imaging techniques such as angiography (78).

When a detailed roadmap is required, angiography is considered the gold-standard imaging test and provides a detailed image of the full arterial tree (18). There are a number of angiographic techniques including magnetic resonance angiography, computed tomography angiography, and digital subtraction angiography, with the choice of imaging dependant on both the patient and the site of disease.

Although these imaging techniques are available, they are not required for the majority of PAD patients, as UK guidelines only recommend further imaging when revascularisation is being considered (17).

1.1.7 Management

1.1.7.(a) Best Medical Therapy (BMT)

As previously mentioned, those with PAD are at an increased risk of mortality, usually of cardiovascular origin (7). As such, BMT aims to reduce this risk by optimising cardiovascular risk factors via smoking cessation, healthy diet and weight loss, exercise therapy, antiplatelet and lipid-lowering therapy, and the diagnosis and treatment of hypertension and diabetes (18, 63, 79).

1.1.7.(b) Smoking Cessation

Smoking cessation is pivotal for reducing disease progression in those with established PAD. One study found that patients with PAD who quit smoking ≤1 year after undergoing angiography had significantly lower rates of all-cause mortality and amputation (80). This benefit was maintained even after adjustment for other risk factors such as age, CAD, diabetes and pharmacotherapy, suggesting that smoking cessation was independently associated with this benefit (80). Another study also found that in patients undergoing a lower extremity bypass, those who continued to smoke had a three-fold increased risk of graft failure, with a clear dose-response identified, suggesting that patency was further decreased in heavy versus moderate smokers (81). However, it has been noted that there is a greater risk of graft failure in smokers who are identified via biochemical markers rather than self-report. Therefore, the ability of some smokers to deceive their physician about their smoking status may mean that the risk of graft failure in smokers is even greater (81). Interestingly, for patients who stopped smoking at the time of the procedure, during the hospital stay, graft patency was comparable to never smokers (81).

The TASC II guidelines recommend that for the best cessation rates, physicians should advise patients to quit smoking at every visit, in combination with nicotine replacement therapy, the antidepressant bupropion and behaviour modification

(18). One such behaviour modification programme has been studied in patients with PAD, and demonstrated significantly greater cessation rates in those randomised to receive a tailored PAD-specific counselling intervention (21.3%) compared to those receiving minimal intervention (6.8%) (82). Despite such evidence and recommendations, a large study has demonstrated that two-thirds of active smokers who attend a vascular clinic for PAD continue to smoke 12 months later, with one in 10 relapsing after quitting at some point over the previous 12 months (83). For the active smokers at baseline, the probability of smoking 12 months later was 72%, with the greatest likelihood of quitting being at 3 months (21%), compared to 6 (11%) and 12 months (12%). For those who stopped smoking, the likelihood of relapse was 18% between 3 and 6 months and 25% between 6 and 12 months. One key finding of this study was that the most effective cessation support measures were dramatically underutilised. Most patients received some form of intervention (75%), but the vast majority received only physician advice to quit. Only 16% were referred to a counselling programme and just 11% received pharmacologic treatment or nicotine replacement therapy (83). This led the authors to conclude that future research should focus on identifying optimal strategies for implementing consistent cessation support.

One such strategy has been provided by the American College of Cardiology (Figure 5) (84), that could be implemented across vascular clinics to maximise patient and clinician engagement in appropriate smoking cessation methods and as such, maximise smoking cessation and improve outcomes in those with PAD.

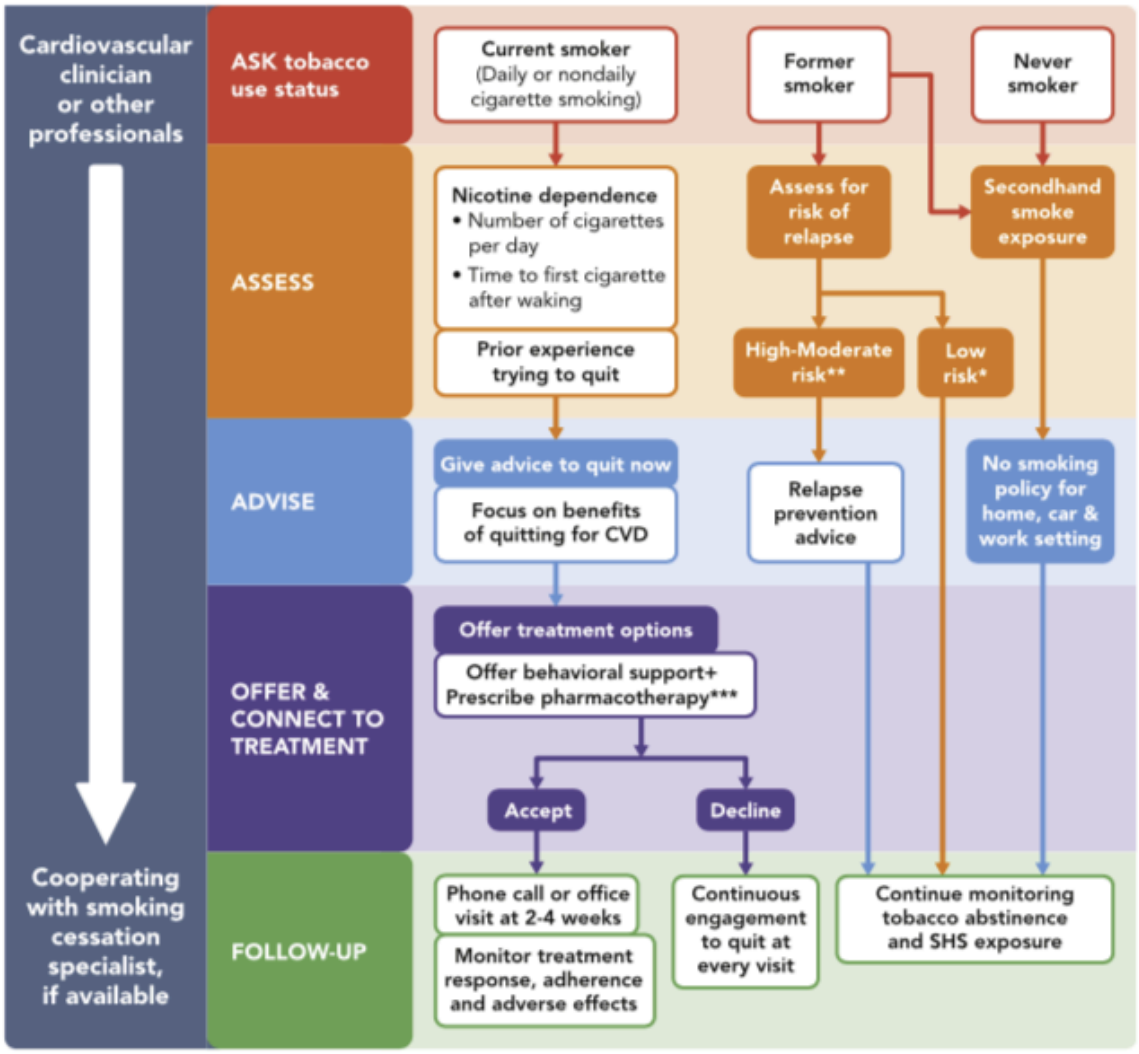


Figure 5 - American College of Cardiology pathway for smoking cessation (84)

1.1.7.(c) Weight Reduction and Lifestyle Modification

Information and guidance regarding weight reduction and modification is limited. The European Society of Cardiology recommend a healthy diet, weight loss and regular physical exercise, without providing specific information on how to achieve a healthy diet and weight loss (63). Specific guidance is given for exercise therapy, which will be explored later in this thesis. The TASC II guidelines do provide more specific advice for diet and weight loss, suggesting that patients who are overweight or obese (BMI ≥25 kg/m^2) should be counselled for weight reduction by following a diet that reduces caloric intake, thus creating a negative caloric balance, by restricting carbohydrates and increasing exercise (18).

There is, however, a need for more comprehensive guidance with regards to weight reduction and diet and lifestyle modification for those with PAD.

1.1.7.(d) Lipid Lowering Therapy

An early Cochrane review considering the evidence for lipid lowering therapy in PAD found that such therapy had no effect on all-cause mortality or total cardiovascular events (85). However, this review included statins and a number of other agents, including those not recognised in the British National Formulary as lipid-lowering agents. In the subgroup analyses that included only studies using statins, there were significant reductions in total cardiovascular events, total coronary events, strokes and revascularisations for those randomised to receive statins (85). This led the authors to conclude that the only class of drug with consistent and statistically significant evidence of a beneficial effect across the spectrum of possible events was statins (85). This was primarily driven by the results from the Heart Protection Study (HPS) which was a large RCT that included 6,748 patients with PAD who had a non-fasting blood total cholesterol of ≥3.5 mmol/L (86). This study found that treatment with statins was associated with a highly significant proportional reduction (22%) in major vascular events, representing an absolute reduction of 63 events per 1000 patients (86). This reduction was independent of the pre-treatment lipid low-density lipoprotein cholesterol (LDL-C) concentrations, with similar reductions seen in those with a baseline LDL of >3.0 mmol/L vs. <3.0 mmol/L. Importantly, this reduction was also independent of the nature of pre-existing PAD, with reductions being similar amongst those with prior revascularisation or amputation and those with medically managed PAD.

The HPS also demonstrated significant reductions in further vascular events (i.e. occurring after the first event) and individual vascular events (i.e. coronary events, strokes and revascularisations) for those treated with statins (86). However, the study failed to demonstrate a beneficial effect of statins on the incidence of amputation, though the number of such events was low. More recently, data from the REACH study demonstrated that treatment with statin therapy provided an approximately 18% reduction in adverse limb outcomes including; worsening claudication or new CLTI, new lower-extremity revascularisation and new

ischaemic amputation (87). The study also confirmed the findings that statins reduce major vascular events whilst providing new evidence to suggest that statin therapy reduces all-cause and cardiovascular mortality (87). Therefore, the current evidence suggests that statin therapy reduces major cardiovascular events, cardiovascular mortality, all-cause mortality, revascularisations and adverse limb outcomes.

Based on these benefits, international guidelines provide a class IA recommendation that for all patients with PAD, treatment with a statin is indicated (88). This is in spite of the aforementioned Cochrane review, which states that statin therapy is only indicated for those with a total cholesterol of ≥3.5 mmol/L, based on the HPS (85). However, given that the HPS demonstrated a benefit regardless of LDL-C concentration, that the vast majority of patients will present with a total cholesterol of ≥3.5 mmol/L, and that the authors themselves recommend routine statin therapy for PAD, the recommendation to provide statin therapy to all with PAD appears justified.

The therapeutic target for statin treatment is based on LDL-C, which should be reduced to <1.8 mmol/L or decreased by ≥50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (63). However, despite the evidence and recommendations, a recent UK-based study suggested that the number of patient's prescribed statin therapy between 2012-2014 was sub-optimal (66%) (89). As such, further work is needed to identify barriers to patient and physician compliance with statin use across the PAD spectrum to maximise benefit (87).

1.1.7.(e) Antiplatelet Therapy

Antiplatelet therapy now has a longstanding role in the treatment of cardiovascular diseases including PAD. One of the largest studies to date from the antiplatelet trialists' collaboration (ATC) noted that in 135,000 high-risk patients (including those with PAD), antiplatelet treatment reduced the occurrence of serious vascular events by approximately 25%, including; non-fatal myocardial infarction, non-fatal stroke and vascular mortality (90, 91). In the subgroup of >9,000 PAD patients, there was also a reduction of 23% in major vascular events, and this reduction was similar for those who had IC and those who underwent angioplasty or bypass

procedures (91). This led the group to conclude that antiplatelet therapy, with a particular focus on Aspirin, should be considered routinely for all patients at high risk of occlusive vascular events. Consequently, Aspirin was often the antiplatelet regimen of choice for the treatment of PAD until more recently. When considering the subset of PAD patients included in this ATC study, almost two-thirds were treated with a regimen other than Aspirin, suggesting that these beneficial effects may have been driven by an alternative therapeutic regimen (92, 93). Indeed, the CAPRIE trial, the largest trial to consider Clopidogrel vs. Aspirin in patients with symptomatic PAD showed that there was a 23.8% relative risk reduction in event rate for those assigned to the Clopidogrel arm (92). It is therefore suggested that the benefit of Clopidogrel over Aspirin is truly much greater for patients with PAD. Therefore, for patients with symptomatic PAD without clinically manifest coronary or cerebrovascular disease, Clopidogrel monotherapy is recommended as the first choice for antiplatelet therapy (17, 63, 94). More recently, it has been suggested that Rivaroxaban, an anticoagulant, in conjunction with Aspirin should be considered for patients with PAD. This is based on the COMPASS and VOYAGER trials whereby patients with PAD who were randomised to receive Rivaroxaban plus Aspirin had better outcomes than those randomised to Aspirin alone (95, 96). However, the lack of a Clopidogrel arm in these trials meant that there was no comparison to guideline recommended treatment. As such, unless a trial of Rivaroxaban vs. Clopidogrel is performed, antiplatelet therapy via Clopidogrel is likely to remain as the recommended treatment for those with PAD.

Despite this evidence for the benefit of antiplatelet therapy, the proportion of patients with PAD who received it between 2012-2014 was 56%, with only 11% of these receiving clopidogrel (89). Therefore, as with statin therapy, further work is required to increase antiplatelet use to maximise patient benefit.

1.1.7.(f) Hypertension Control

Hypertension control is also a vital element of secondary prevention of cardiovascular disease amongst those with PAD and NICE recommends that hypertension should be identified (SBP ≥140mmHg and / or diastolic blood pressure ≥90mmHg) and appropriately managed in these patients (17, 97). The

European Society of Cardiology and European Society of Hypertension task force recommend that when antihypertensives are used, the initial target is a blood pressure of <140/90mmHg for all patients (97). If well tolerated, this should be targeted to 130/80mmHg or lower. Interestingly however, for patients with PAD there appears to be a J shaped relationship, whereby an excessive reduction in blood pressure, appears to increase the risk of death and cardiovascular events (98). As such, the European Society of Cardiology guidelines recommend that in all patients with PAD and hypertension, blood pressure should be controlled at <140/90 mmHg (63). However, the same guidelines also recommend exercising caution to ensure that the SBP does not reduce to <120 mmHg, based on the aforementioned J-shaped relationship.

A number of antihypertensive regimens are identified by the European Society of Cardiology including; diuretics, ß-Blockers, calcium channel blockers, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor-blockers based on a number of studies (63). One study considered calcium channel blockers with or without angiotensin-converting-enzyme inhibitors and ß-Blockers with or without diuretics and noted no difference between regimens in terms of a reduction in cardiovascular mortality (98). Two other studies considered angiotensin-converting-enzyme inhibitors and angiotensin-receptor-blockers and noted a 22% relative risk reduction in death and cardiovascular events compared to placebo in those with PAD, with both appearing comparable (99, 100). One of these studies however, also randomised patients to a combined regimen of these treatments and found that it was associated with more adverse events with no increase in benefit (99). Based on this evidence, the recommended treatment for patients with PAD and hypertension is an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor-blocker.

1.1.7.(g) Diabetes Control

Diabetes control constitutes a vital element of BMT and for patients with PAD and diabetes, strict glycaemic control is recommended (63). However, not all patients will have known diabetes and NICE recommends the prevention and diagnosis of diabetes as well as the management of it (17). Therefore, all patients with PAD

should be screened for diabetes and prevention advice given to those without diabetes and appropriate action taken for those identified as diabetic. The American Diabetes Association note that a diagnosis of diabetes should be made on the basis of fasting plasma glucose (≥7.0 mmol/L), the 2 hour plasma glucose during an oral glucose tolerance test (≥11.1 mmol/L) or glycated haemoglobin (HbA1c; ≥6.5%) (101). Furthermore, in the absence of unequivocal hyperglycaemia, two abnormal test results from the same sample or two separate samples are required.

As type 2 diabetes accounts for 90-95% of all diabetes, this is the most likely type in those with PAD (101). Glycaemic treatment targets for those with diabetes should be individualised, though a target HbA1c level of <7%, ideally <6.5%, is generally recommended to reduce microvascular complications, and has been specifically recommended for those with PAD (27, 102). For elderly patients with long-standing diabetes, limited life-expectancy, frailty and multiple co-morbidities, less stringent targets of ≤8-9% may be adequate (102).

The integral component for appropriate glycaemic control is lifestyle change, such as diet, weight loss and exercise, which is recommended as the first line treatment. The European Society of Cardiology recommend reduced caloric intake to lower excessive body weight, a Mediterranean diet and ≥150 minutes of moderate-vigorous physical activity per week (102). A weight loss target of at least 5% bodyweight appears to be required in order to provide beneficial effects on HbA1c, lipids and blood pressure for those with diabetes who are overweight (103). However, a target greater than this may be more beneficial. The Look AHEAD trial noted that over a median follow-up of 13.5 years, a weight loss of 6% was associated with reductions in HbA1c and other cardiovascular risk factors (104). Interestingly, the benefits appeared greatest at 1-year follow-up, which was also when weight loss was at its greatest (8.6%), suggesting that a target of at least 8.6% can maximise health benefits in those with diabetes. In addition, weight loss also appears important for those with pre-diabetes or diabetes risk factors, as each additional kilogram of weight loss in these individuals, has been associated with a

43% lower risk of diabetes (105). As such, lifestyle changes, started as early as possible (including those with pre-diabetes) are vital.

If lifestyle changes are inadequate and HbA1c remains high, which NICE defines as ≥6.5% (or above individualised threshold), then initial drug therapy via metformin should be offered (106). If HbA1c control is inadequate with metformin, drug intensification with dual therapy should be considered, followed by triple therapy or insulin, should control still remain suboptimal (106).
However, more recent guidelines suggest that for patients with atherosclerotic CVD, and therefore those with PAD, initial drug therapy should be initiated with a sodium-glucose co-transporter 2 inhibitor (such as canagliflozin) or a glucagon-like peptide-1 receptor agonist (such as exenatide) to reduce cardiovascular events (102).

1.1.7.(h) Vascular Specific Pharmacotherapy

The pharmacological treatment of cardiovascular risk factors aims to reduce the risk of cardiovascular events rather than provide any symptomatic reduction or relief, though some treatments do achieve this, notably statins (18). A meta-analysis considered the robust evidence base to evaluate drugs for the treatment of IC symptoms and included; antiplatelets, lipid-lowering agents, phosphodiesterase inhibitors, prostaglandins and vasodilators (107). The results demonstrated that lipid-lowering agents were the most effective, follow by antiplatelets, prostaglandins vasodilators and phosphodiesterase inhibitors respectively (107).

However, lipid-lowering agents and antiplatelets are not considered vascular specific treatment drugs and any beneficial effect on symptoms is a by-product of their primary function. Therefore, other vascular specific drugs are often prescribed in an attempt to provide additional symptomatic relief. These drugs include cilostazol, naftidrofuryl, and pentoxifylline, though they are not as effective as exercise therapy or successful revascularisation (18). One review has considered these three drugs and noted that they were all associated with an increase in walking distance, though not significantly so for pentoxifylline, as the confidence

intervals crossed the line of no effect (108). Naftidrofuryl was the most effective providing a 60% improvement followed by cilostazol which provided a 25% improvement. However, when considering the 95% confidence intervals, these improvements could have been as low as 20% and 11% respectively, which is clinically negligible. In addition, the authors provided an estimate of the treatment effect of these drugs in a new study and identified that naftidrofuryl would still be most effective, followed by cilostazol, though the lower bound of the confidence interval for the former was lower at 9%, and crossed the line of no effect for the latter (108). As such, the efficacy of these treatments, especially pentoxifylline and cilostazol, remains doubtful.

Consequently, NICE recommends that treatment with such drugs, is via naftidrofuryl and it should only be considered when exercise therapy has not provided a satisfactory improvement and the patient does not want to be considered for a revascularisation procedure (17). In addition, progress should be reviewed after 3-6 months and naftidrofuryl treatment discontinued if there has been no symptomatic benefit.

1.2 Outcome Measures in Intermittent Claudication

Treatment of IC must address the lower-extremity disability (i.e. reduced exercise performance) and the overall impact of the disease. As such, treatment should result in improved vascular status of the lower-limbs and a reduction in the patients risk of cardiovascular events, often achieved via the above strategies (18). The primary treatment goal however, especially from a patient perspective is to relieve symptoms during walking and improve exercise performance (18). As such, the clinical success of treatment in individual patients is assessed via objective measures of walking performance on a treadmill, and patient-based measures such as the use of validated, disease specific or generic health status questionnaires (18).

1.2.1 Objective Outcome Measures – Intermittent Claudication Distance and Maximum Walking Distance

Treadmill testing is the tool often used before and after treatment to identify any symptomatic improvements, evidenced via changes in ICD and MWD. Choosing an appropriate test protocol, either graded or constant load, is important. Graded

tests have an increasing workload until MWD is reached whereas constant load tests by definition remain at the same workload throughout. Constant load tests are easy to perform, but have limited reproducibility, with coefficients of variation of between 30% and 40% (109). Previous research demonstrated that when PAD patients were tested twice per month for 4 months, there was a significant increase in walking distances for the group tested on a constant load protocol between month 0 to month 1 and month 1 to month 2, which was not apparent in the group tested using a graded protocol (110). Furthermore, ICD and MWD measures were more reliable during graded tests, with other measures such as ABPI being reliable for both tests (110). Importantly, there is a suggestion of a habituation effect with constant load tests that is not apparent with graded tests, meaning that three constant load tests are required to obtain reliable measures, whereas just one graded test is needed (110). Therefore, for diagnosing PAD via a treadmill test, a constant load protocol can be used as it is easier to perform, but for outcome measurement, a graded protocol is recommended (111).

More recently, it has been suggested that the 6-MWT should be used for clinical trial outcome measurement rather than treadmill tests, as it is more representative of walking in daily life (112). However, in contrast to graded treadmill tests, the performance characteristics of the 6-MWT are based on single-centre studies, meaning its applicability to international, multi-centre RCT's is not established (113). In addition, the correlation between the 6-MWT and other clinical parameters is based on cross-sectional data and lacks robustness. Therefore, current evidence supports the continued use of the graded treadmill test as an outcome measure for clinical trials.

1.2.2 Quality of Life Outcome Measures

QoL measures provide important patient-level outcomes, used in conjunction with clinical outcomes, following an intervention (114). Several QoL tools are available to use and are usually generic or disease-specific in nature.

1.2.2.(a) Short-Form 36 Questionnaire

The Medical Outcomes Study Short Form 36 (SF-36) is a widely used tool for measuring generic QoL. The SF-36 fulfils strict reliability and validity criteria whilst

also being practical, acceptable, brief and easy to use, which is important for researchers who wish to add a general health measurement to their disease specific QoL outcomes (115). Indeed, the SF-36 is recommended as the most appropriate generic tool for those with lower-limb ischaemia (116). The SF-36 contains 36 questions, providing scores across eight different domains including; physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (117). Each scale is scored from 0-100%, with 0% indicating worst possible health and 100% best possible health. A physical and mental summary score can also be obtained with physical functioning, role-physical, bodily pain and general health contributing to the physical component summary and vitality, social functioning, role-emotional and mental health contributing to the mental component summary (117). Although the SF-36 is the most appropriate generic tool for patients with PAD, there is a paucity of information about minimally clinically important differences (MCID) across each domain, in this population. However, recent work has suggested small, moderate and large MCID's for the physical functioning domain following a 3-month exercise intervention of 3, 9 and 14% respectively (118). Therefore, trialists adopting the SF-36 should present any changes in physical functioning in the context of both statistical significance and its MCID.

1.2.2.(b) Vascular Quality of Life Questionnaire

The Kings College London Vascular Quality of Life (VascuQoL) questionnaire was designed specifically for use in those with lower-limb ischaemia (114). It is valid, reliable, responsive to within-patient change and applicable across the whole disease spectrum, ranging from IC to CLTI (114). This therefore means that patients can be followed up using the same scale whether their condition improves or deteriorates. The VascuQoL consists of 25 questions which are subdivided into five domains: pain, symptoms, activities, social and emotional. Each domain is scored out of seven, with seven indicating the best score and one the worst. A total score is then also calculated by dividing the total score by 25.

1.2.2.(c) Walking Impairment Questionnaire

The Walking Impairment Questionnaire was developed and validated to assess treatment effects in patients with IC (111). It provides an estimate of a patients walking endurance, speed and stair climbing ability in the community by producing a distance, speed and stair climbing domain score (119). The speed and distance scores have been shown to correlate with ICD, MWD, the 6-MWT and the timed 4-minute walk test and are responsive to interventions such as exercise therapy and revascularisation (119-123). For each domain score, the participant rates their ability to perform specific tasks (e.g. walking 1500 feet) on a 0-4 Likert scale, with a score of 0 indicating an inability to perform the task and a score of 4 indicating no difficulty. The score indicated for each task is then multiplied by a pre-specified weight for that task and the products are summed and then divided by the maximum score possible to obtain a percent score, with 0% indicating an inability to perform any of the tasks and 100% indicating no difficulty with any of the tasks (124).

1.2.2.(d) Intermittent Claudication Questionnaire

The intermittent claudication questionnaire is a patient-assessed, condition-specific tool that measures health-related QoL in patients with IC (125). It is a self-administered tool that is easy to understand, quick to complete and score, reliable, valid, and responsive to change (125). It is also significantly correlated with MWD, the walking impairment questionnaire and all eight domains of the SF-36 (125). The questionnaire has 16 items, which use a five- or six-point scale. The score for each equally weighted item is then summed and transformed to a scale ranging from 0 (best possible health state) to 100 (worst possible health state) (125).

1.3 Exercise Physiology Outcomes

In addition to walking performance and QoL measures, the success of treatment interventions, especially those that are exercise based, can also be established by considering changes in the physiological response to exercise. A number of physiological variables can be established via cardiopulmonary exercise testing (CPET) that give an indication about the efficiency of the cardiovascular system.

1.3.1 Cardiorespiratory Fitness and Cardiopulmonary Exercise Testing

Historically, the exercise tolerance test (ETT) was used as a diagnostic and prognostic tool for assessing patients with known or suspected CAD (126). ETT's require a patient to complete a treadmill test whilst their HR, electrocardiogram (ECG) and blood pressure are monitored for any signs of myocardial ischaemia during exercise (126). However, this method has poor sensitivity and specificity to detect CAD, meaning it is usually reserved for those at an 'intermediate' risk (126, 127). CPET systems add to existing ETT measures by also providing a breath-by-breath measurement of oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) (128). Such systems have demonstrated good to excellent test-retest repeatability with interclass correlation coefficients ranging from 0.84-0.96 and within-subject coefficients of variation often being <0.12 (129). This means that the CPET is a powerful non-invasive physiological investigation that provides the clinician with in-depth, reliable information surpassing that obtainable from standard ETT's (130). Not only does the addition of gas analysis improve the sensitivity and specificity of detecting myocardial ischaemia, it provides a more comprehensive insight into exercise tolerance by providing a holistic assessment of the interconnected cardiovascular, metabolic and ventilatory responses to exercise, allowing a rigorous appraisal of the integrity of the cardiorespiratory system (127, 128, 130, 131). In fact, *Guazzi et al. 2012* note that CPET is the 'gold-standard' measure of cardiorespiratory fitness (CRF) and is '…a superior method to:

1. Accurately quantify CRF
2. Delineate the physiologic system(s) underlying exercise responses, which can be applied as a means to identify the exercise-limiting pathophysiology mechanisms(s) and / or performance differences, and
3. Formulate function-based prognostic stratification.' (132; p.2262)

The wealth of information provided means that CPET has become more widely used in a clinical setting and is not reserved solely for cardiac physiology investigations. As such, CPET is now indicated in a number of instances including to

identify differential diagnoses for exercise intolerance, to assess perioperative risk in those undergoing major abdominal vascular surgery, to determine prognosis and eligibility for cardiac transplantation in heart failure patients and for effective exercise prescription (128, 133-137). It is also effective for assessing the therapeutic benefit of an exercise rehabilitation intervention (133).

CPET protocols include an initial period of warm-up, followed by an incremental exercise phase with increasing workloads and a post-maximal effort recovery period (138). Regardless of the testing modality used, the incremental phase can either be step or ramp in nature. However, the response of key variables such as $\dot{V}O_2$ and $\dot{V}CO_2$ lag behind changes in work rate, meaning that protocols employing small to modest increments in work rate per stage are preferred (130). In addition, exercise test protocols with large stage-to-stage increments may cause premature patient termination, whilst also having a weaker relationship between $\dot{V}O_2$ and work rate (128). Individual ramp protocols are therefore recommended for clinical testing as they involve modest increments in work rate per stage, typically 5-20W increments at intervals of <10 to 60 seconds, thus preserving the relationship between $\dot{V}O_2$ and work rate (128, 130). The exercise workload selection should be individualised to a patients perceived exercise capacity with the aim of eliciting volitional exhaustion within 8-12 minutes (130). Test protocols that use modest increases in work rate may still provide results indicating a non-linear relationship between $\dot{V}O_2$ and work rate when the test duration is <6 minutes whereas tests lasting >12 minutes may cause subjects to terminate due to localised muscle fatigue rather than cardiopulmonary endpoints (128).

Testing can be performed using a cycle ergometer or treadmill, with a number of different protocols available on each modality. The selection of an appropriate modality and protocol is vital when performing tests with patient populations. In those who are untrained, it is widely accepted that $\dot{V}O_2$ at peak exercise will be 10-20% lower on a cycle compared to a treadmill due to localised leg fatigue (128, 138). However, cycle ergometry is usually preferred in those with gait or balance instability which is often the case for patient populations. In addition, treadmill

protocols also have large stage-to-stage increments which may cause premature lactate accumulation and therefore premature cessation of exercise (139). Furthermore, it is also important to note that for those with IC, treadmill testing may induce calf claudication pain, causing a premature cessation of exercise, that may not occur on a cycle. Indeed, it has been demonstrated that for those with IC, the limiting symptom during treadmill testing is predominantly in the calf, whereas for cycle testing, the limiting symptoms are more varied and include thigh pain (141). One possible explanation for this symptomatic difference between the cycle and the treadmill could be due to differences in the acute physiological response between the two modalities. When walking, pain is often felt in the muscles that are most distal to the vascular obstruction, which may be due to the fact that the metabolic strain, muscle activation and blood flow demands are similar between the calf and thigh muscles, though the calf muscles are a smaller group (142, 143). During cycling, the metabolic strain, muscle activation and blood flow demands are significantly higher in the thigh muscles, meaning that symptoms may be felt more proximally (142, 143). Given that the thigh muscles are a larger group than the calf muscles, it may therefore be easier to withstand these symptoms for longer when cycling, resulting in higher intensities being reached (141). As such it is not surprising that for patients with IC, treadmill and cycle CPET responses are highly correlated and the 10-20% difference in $\dot{V}O_2$ may not be apparent (140). In addition, cardiometabolic responses including peak HR and respiratory exchange ratio (RER) are higher on a cycle compared to a treadmill, suggesting that patients are indeed able to reach a higher intensity on this modality (140). Consequently, a cycle CPET may be more appropriate for those with IC when the aim is to stress the cardiopulmonary system, rather than the peripheral musculature, such as testing before and after a treatment programme to determine its efficacy (140).

1.3.2 Cardiorespiratory Fitness Parameters

As previously mentioned, CPET provides a holistic assessment of the interconnected cardiovascular, metabolic and ventilatory responses to exercise, and allows for a rigorous appraisal of the integrity of the cardiorespiratory system. As such, CPET provides a wealth of variables, with the most pertinent ones outlined below.

1.3.2.(a) Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_{2Max}$) is considered to be the variable that defines the limits of the cardiorespiratory system during CPET and is the measure that quantifies CRF. It is defined by the Fick equation:

$$\dot{V}O_{2Max} = (HR \times SV) \times [C(a - v)O_2]$$

Where HR is heart rate, SV is stroke volume and $[C(a - v)O_2]$ is arteriovenous difference (128). $\dot{V}O_{2Max}$ is measured in litres of oxygen per minute but is usually expressed relative to the individual in $mL \cdot kg^{-1} \cdot min^{-1}$ to normalise for bodyweight and allow inter-subject comparison. This is important as an individual with a larger body weight will have a higher absolute $\dot{V}O_2$, based simply on their larger mass (128).

However, one important caveat of $\dot{V}O_{2Max}$ is that it implies that an individual has reached their physiological limit, historically defined by a plateau in $\dot{V}O_2$ with an increasing workload, requiring maximal effort to be achieved and sustained for a specific period (128, 130). This plateau is rarely observed in a patient population, despite maximal effort being put forth. As such, the term peak oxygen uptake ($\dot{V}O_{2Peak}$) may be more appropriate to describe objectively measured CRF in clinical populations, as the physiological limit is rarely reached (128, 130).

1.3.2.(b) Peak Oxygen Uptake

$\dot{V}O_{2Peak}$ is the highest $\dot{V}O_2$ obtained during exercise which should be calculated by appropriately averaging the breath-by-breath data over a period of 10-60 seconds (132). The averaging period is dependent on the protocol used, with shorter averaging intervals recommended for protocols with shorter stages and longer intervals for protocols with longer stages (132). Verification of a peak or maximal effort is vital for accurate test and $\dot{V}O_{2Peak}$ interpretation, especially when $\dot{V}O_{2Peak}$ is reduced and no clear physiological limitation is elicited during exercise. A maximal effort can be confirmed when two or more of the criteria in table 2 are achieved (130).

Table 2 - Criteria for maximal effort during cardiopulmonary exercise testing

Criteria:
A plateau in $\dot{V}O_2$ (or failure in increase $\dot{V}O_2$ by 150 mL · min^{-1}) with increased workload.
Failure of HR to increase with further increases in exercise intensity (achieving >85% of age predicted HRMax is a well recognised indicator of patient effort).
RPE at peak exercise >17 on the 6-20 scale or >7 on the 0-10 scale.
A peak RER ≥1.10. Peak RER is perhaps the most accurate and objective non-invasive indicator of subject effort during CPET.
A post exercise venous lactate concentration >8.0 mmol · L^{-1}
HR = heart rate; HRMax = maximum heart rate; RER = respiratory exchange ratio; RPE = rating of perceived exertion; $\dot{V}O_2$ = oxygen uptake.

However, some patients may also be unable to achieve these criteria, despite putting forward a perceived maximal effort, due to marked deconditioning. For example in a study by *Ingle et al. 2008,* 42% of patients with chronic heart failure were unable to achieve an RER of >1.0 (144).

As with $\dot{V}O_{2Max}$, $\dot{V}O_{2Peak}$ is expressed relative to bodyweight in mL·kg^{-1}·min^{-1}. However, $\dot{V}O_{2Peak}$ is subject to normal age-related decline due to a decrease in central and peripheral performance, and normal sex-related differences influenced by differences in maximal cardiac output. It is therefore recommended that $\dot{V}O_{2Peak}$ is also reported as a percentage of the patients predicted value to account for age and sex differences, with a value of 75% being the lower limit of normal (132, 145). There are a number of predictive equations available to use with minimal variability for individuals of average height who are not obese (145). However, when subjects become more diverse, (i.e. are shorter, taller or obese), which is often the case with patient populations, the difference in the values given between equations increases (145). Selecting an appropriate equation is of great importance for ascertaining whether the patient's $\dot{V}O_{2Peak}$ and related variables are within normal limits or reduced. The Study of Health In Pomerania (SHIP) (146) and Hansen/Wasserman (145) equations are the most similar across a broad age, height and weight range with the former being derived from a well-selected, very-

large German population, including meticulously measured and well-analysed data (145). Therefore, either of these two equations are recommended for predicting $\dot{V}O_{2Peak}$ in Western societies. However, the SHIP equations are still relatively contemporary, meaning that they are yet to be adopted in most exercise physiology laboratories in the UK, which continue to use the Hansen/Wasserman equations.

No previous work has considered the prognostic value of directly measured CRF ($\dot{V}O_{2Peak}$) on the risk of mortality in patients with PAD. One study has however considered the prognostic value of estimated CRF, in metabolic equivalents (METs; $\dot{V}O_{2Peak}$ in $mL \cdot kg^{-1} \cdot min^{-1}/3.5$) (147), from peak treadmill speed and grade (148). Compared with non-survivors at follow-up, survivors had a greater estimated exercise capacity, equating to 1.5 METs or 5.25 $mL \cdot kg^{-1} \cdot min^{-1}$. In addition, exercise capacity was the strongest predictor of both all-cause and cardiovascular mortality, with survival amongst those with an exercise capacity of ≥5 METs being significantly greater than those with a capacity of <5 METs (148). The authors also noted that each additional MET achieved on the treadmill, translated to a 20% age-adjusted reduction in mortality, whilst moving from the lowest quartile (<4 METs) into the next quartile (4-6 METs) was associated with a 20-30% reduction in mortality (148). Finally, exercise capacity predicted mortality independent of other traditional risk factors, leading the authors to conclude that it should be given as much consideration as a risk factor (148).

However, it is yet to be determined in PAD patients if this prognostic value translates to directly measured, rather than estimated, CRF.
In those with heart failure directly measured CRF is an independent predictor of mortality, which is also the case for those with CAD (144, 149). Work by *Keteyian et al. 2008* showed that $\dot{V}O_{2Peak}$ was a strong predictor of all-cause mortality across both men and women with CAD, which importantly was also the case for the subgroup of patients who were following evidence-based care (149). Interestingly, every 1 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_{2Peak}$ was associated with an approximately 15% decrease in the risk of death. For men, a $\dot{V}O_{2Peak}$ of <15 $mL \cdot kg^{-1} \cdot min^{-1}$ or >19 $mL \cdot kg^{-}$

^{1}·min^{-1} was associated with the highest and lowest risk for annual all-cause mortality respectively, whereas for women, these values were <12 mL·kg^{-1}·min^{-1} and >16.5 mL·kg^{-1}·min^{-1} respectively (149).

However, $\dot{V}O_{2Peak}$ may not be applicable to all, as some patients may be unable to put forth the required peak or maximal effort, often due to motivation or functional limitation. Therefore, submaximal markers of CRF, which are not affected by motivation, such as the ventilatory anaerobic threshold (VAT), may hold greater utility in this scenario (150).

1.3.2.(c) The Ventilatory Anaerobic Threshold

During incremental exercise, $\dot{V}O_2$ and $\dot{V}CO_2$ increase linearly until a point at which, oxidative metabolism can no longer sustain the required workload, as the oxygen supply to the working muscles cannot meet the oxygen requirements (139). This initial supply-demand imbalance is termed the anaerobic threshold (AT) (128). This imbalance results in an increased dependence on anaerobic glycolysis to maintain higher work rates, which produces lactate as the final by-product (i.e. the lactate threshold; LT) (128). When lactic acid dissociates to create this lactate, it also generates H+ ions which are buffered by bicarbonate (151). This buffering causes an excess production of CO_2 compared to what would be expected from aerobic metabolism (139). This excess CO_2 is then ventilated causing a characteristic breakpoint in the $\dot{V}O_2$ and $\dot{V}CO_2$ relationship, detected via ventilatory gas analysis, termed the VAT, which is a reflection of the AT and the LT (128, 139). Consequently, the terms AT, LT and VAT are often used interchangeably, when they are in fact related but different events (128).

As the VAT is determined non-invasively, it is the preferred and most widely used method to consider the transition from aerobic to anaerobic metabolism and as such, it will be explored further in this thesis.

There are a number of methods that can utilise gas exchange data to determine the VAT, with the V-slope method being the most widely adopted (152). This method involves plotting $\dot{V}CO_2$ as a function of $\dot{V}O_2$ during an incremental test. After approximately the first minute of exercise, the points progress linearly in a slope of approximately 1.0, up to the point of the VAT, where this linear slope

breaks and $\dot{V}CO_2$ accelerates faster than $\dot{V}O_2$, resulting in a slope above 1.0 (145). A line of best fit is drawn from the initiation of exercise to the break point and a second line drawn from the end of exercise to the same point. The data point closest to where the lines dissect marks the VAT (Figure 6).

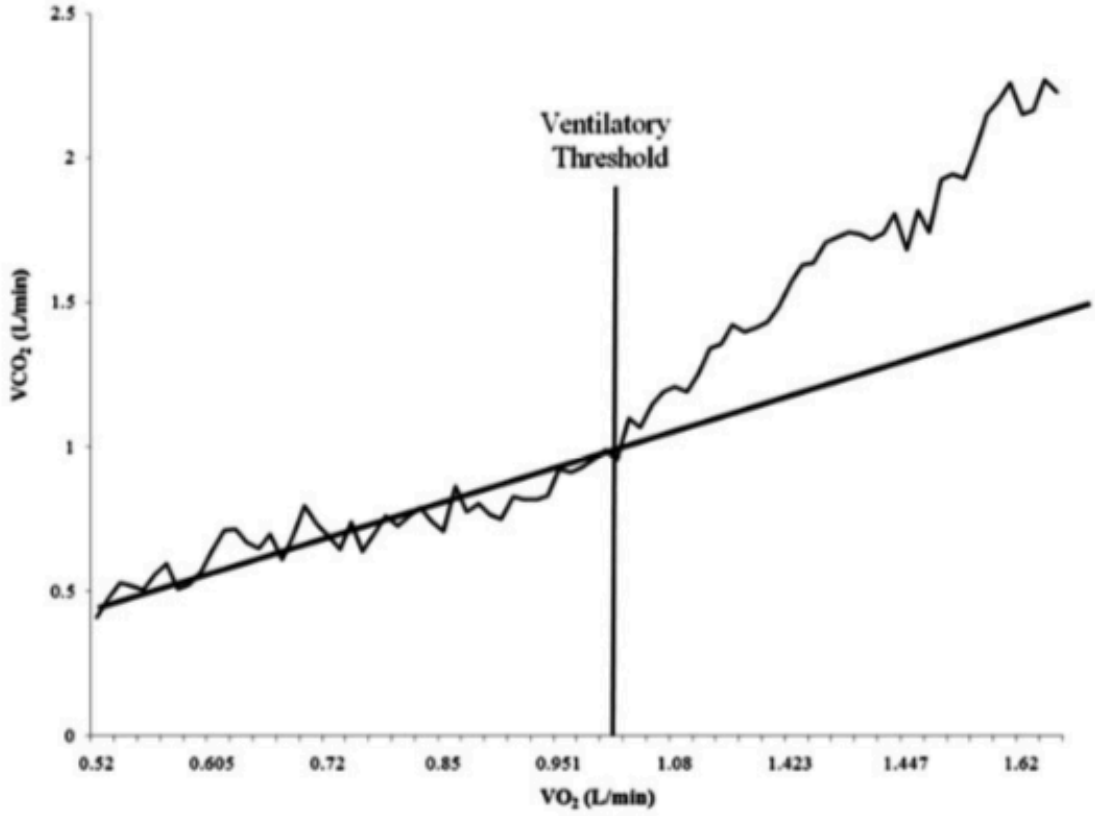


Figure 6 – The ventilatory anaerobic threshold identified using the V-slope method

In addition, the increase in $\dot{V}CO_2$ increases respiratory drive, which maintains the relationship between $\dot{V}E$ and $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$; ventilatory equivalents for CO_2) (151). However, above the VAT, the relationship between $\dot{V}E$ and $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$; ventilatory equivalents for O_2) inverts, leading to an increase in $\dot{V}E/\dot{V}O_2$ despite a constant $\dot{V}E/\dot{V}CO_2$ (151). The ventilatory equivalents method involves plotting $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ against time and the VAT is determined as the nadir of the of the $\dot{V}E/\dot{V}O_2$ relationship (Figure 7) (151). A further, less used method is the excess CO_2 method, which determines the VAT as the point at which $\dot{V}CO_2$ changes from steady state to excessive, calculated by (($\dot{V}CO_2$/ $\dot{V}O_2$) - $\dot{V}CO_2$) (153).

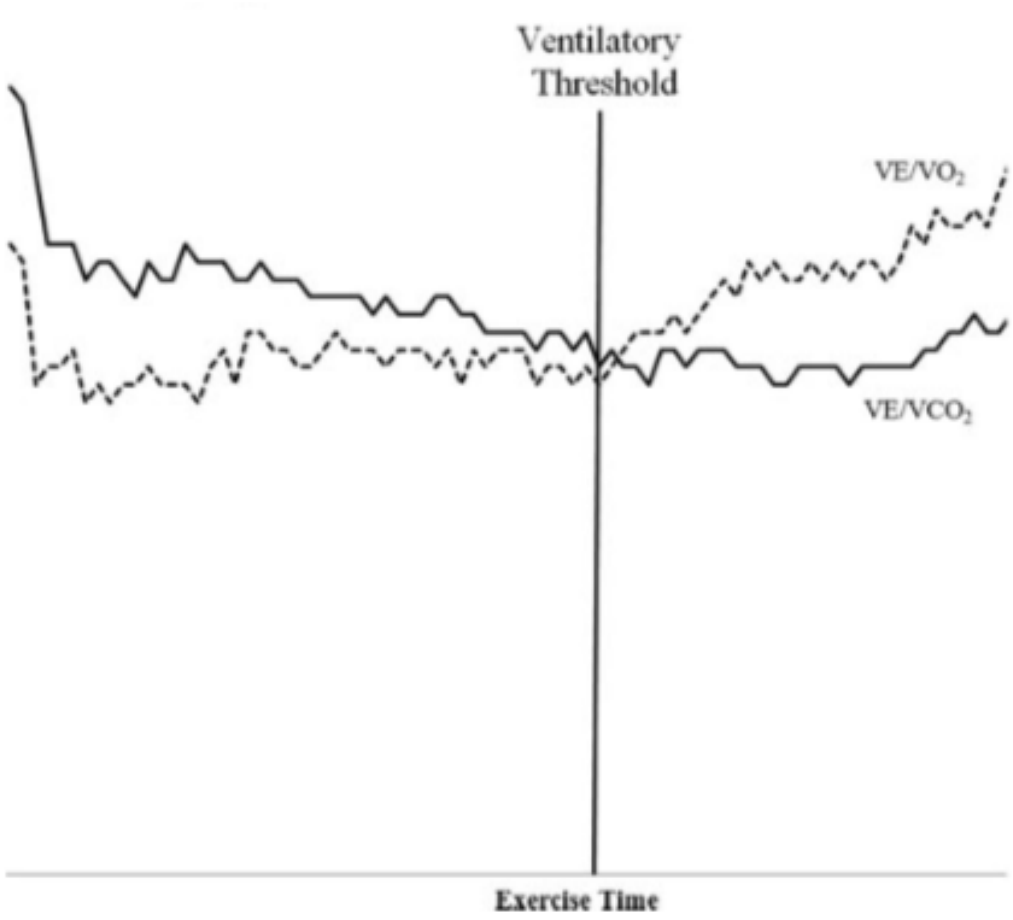


Figure 7 – The ventilatory anaerobic threshold identified using the ventilatory equivalents method

Although these methods can be used independently to determine the VAT, they should be used in combination, given that determination is subjective and may vary between observers (154). One large study considered the inter-observer and inter-site agreement of the VAT in heart failure patients and identified somewhat wide limits of agreement (≈200mL·min^{-1}) with coefficients of variance ranging between 5-10% (154). Using a combination of the above methods may reduce these differences whilst also reducing the number of tests that have an indeterminate VAT (153). Often, the V-slope method is the primary method, which is verified using the ventilatory equivalents method. For this, the time point of the nadir of the $\dot{V}E/\dot{V}O_2$ relationship is compared to the point at which the two lines of best fit dissect. If they are at the same or a similar point, then the VAT has been accurately determined. A further way to improve the accuracy of VAT determination would be to ensure it is determined by two independent reviewers. If the difference between the two is >10%, a third blinded reviewer should

determine the VAT and an average of the two most similar should be used, if they are within 10% of each other. If none of the three determinations are within 10% of each other, the VAT should be deemed indeterminate (154).

Once the VAT has been determined, it should be expressed relative to bodyweight ($mL \cdot kg^{-1} \cdot min^{-1}$) and as a percentage of $\dot{V}O_{2Peak}$. It is widely accepted that the VAT occurs at approximately 45-65% of $\dot{V}O_{2Peak}$ in healthy untrained individuals, but is higher, reaching 80% in endurance-trained athletes (128). The VAT can also be expressed as a percentage of predicted $\dot{V}O_{2Peak}$, with a value <40% indicating abnormality (150). However reported, the VAT is an important measure that can be used to aid exercise prescription for both healthy and diseased populations (151). However, the VAT has also demonstrated a mode dependency, meaning that for effective exercise prescription, the same modality should be used for both testing and training (128, 137).

The VAT is also an important component of CRF which has been shown to improve following a successful exercise programme in both healthy and diseased populations (155, 156). An increase in the VAT allows for a greater exercise intensity to be sustained in the absence of increasing blood lactate (155). Despite this, changes in the VAT following an exercise programme are seldom reported in the PAD literature, as they are unlikely to be considered as important as changes in walking distances. However, the VAT is likely to improve following an exercise programme as patients are encouraged to walk to the point of pain, which often exceeds VAT (157). This means that during their training regimen, patients are frequently exercising above the VAT, which provides a strong metabolic stimulus, and is likely to result in an improved VAT over time, suggesting it should be reported (157).

The VAT has also demonstrated predictive value with regards to improvements in walking distance following a supervised exercise programme (SEP) in those with IC (158). Specifically, those with a higher baseline VAT, demonstrated the smallest improvement, and those with a lower baseline VAT, demonstrated the greatest

improvement (158). However, as previously mentioned, the onset of leg pain occurs above VAT (157). As such, it is likely that those who had a higher baseline VAT could also walk further at baseline, given the higher absolute workload required to induce the VAT and therefore leg pain. Consequently, this suggests that the potential margin for improvement in those with a higher VAT was smaller, which may have contributed to these findings.

Despite demonstrating this predictive value, the prognostic value of the VAT has not been explored in those with PAD. It has however, been explored in other vascular and non-vascular populations. In those undergoing AAA repair, a VAT of <10.2 $mL \cdot kg^{-1} \cdot min^{-1}$ is associated with a >6-fold increased risk of 30-day mortality (159). Similarly, for those with heart failure, a VAT of <11 $mL \cdot kg^{-1} \cdot min^{-1}$ is associated with an approximately 4-fold increased risk of mortality within 2 years, and the VAT also predicts shorter-term (within 6 months) mortality (160).
However, the VAT may be indeterminate due to exercise oscillatory ventilation and / or a short test time, which may also hold prognostic significance (150). One study in patients with heart failure found that those with an indeterminate VAT had a poorer prognosis than those who achieved a VAT ≤8.5$mL \cdot kg^{-1} \cdot min^{-1}$, a value which in itself already carries an increased risk (160, 161).

Given the evidence in other clinical populations, the VAT and $\dot{V}O_{2Peak}$ are likely to hold prognostic value in those with PAD and this warrants further investigation.

1.3.2.(d) Respiratory Exchange Ratio

Peak RER is defined as the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ at peak exercise, and it should be expressed over the same averaging period as $\dot{V}O_{2Peak}$ (132). During a CPET, achievement of at least 85% of age-predicted maximum HR is considered to indicate sufficient patient effort (table 2) (128). However, in the general population, there is wide variability in the HR response to exercise (± 12bpm), meaning that the ability to gauge subject effort by HR response alone is impacted (128). In addition, the widespread use of ß-blockers further complicates the use of HR response to gauge subject effort. The use of these agents significantly blunts the maximal HR response, which is not considered within predictive maximal HR

equations (128). The RER obviates the need to assess patient effort via HR response. As exercise begins to progress to higher intensities, the RER increases as $\dot{V}CO_2$ outpaces $\dot{V}O_2$ due to an increase in anaerobic glycolysis. This physiological response occurs in all subjects, making it a much more accurate, reliable and widely adopted gauge of patient effort, with a value ≥1.10 indicating excellent or maximal effort (128, 132, 151). In addition to providing an indication of effort, RER has been shown to be an independent predictor of mortality in patients with heart failure, with those achieving an RER of <1.0 being at an increased risk compared to than those achieving an RER >1.0 (162).

1.3.2.(e) Minute Ventilation / Carbon Dioxide Production Slope

The minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) slope provides an indication of ventilatory efficiency during exercise and demonstrates the respiratory rate required to eliminate 1 litre of CO_2 (151). As $\dot{V}E$ is modulated by the metabolic and anaerobic production of $\dot{V}CO_2$, the relationship between these two variables is tightly coupled (128). This relationship can be expressed as the ratio of $\dot{V}E$ to $\dot{V}CO_2$ or as is more often the case, the slope value, calculated by linear regression (128, 163). As with other CPET variables, there is no research considering the value of the $\dot{V}E/\dot{V}CO_2$ ratio in patients with PAD, despite the evidence for its ability to predict outcomes for vascular patients undergoing AAA surgery (136, 164).

The same is true for the $\dot{V}E/\dot{V}CO_2$ slope, despite its overwhelming prognostic value in the heart failure population, with some suggesting that it is superior to $\dot{V}O_{2Peak}$ (165-167). A number of studies have considered a prognostic cut-off for the slope gradient in those with heart failure, with a general consensus of 34 being suggested (166). However, this is often considered as a dichotomous cut-off despite a large range of values being observed (166). Therefore, a multilevel classification system has been proposed for the heart failure population, to identify the increasing risk with increasing values (166). An algorithm based on this outlines the 2-year risk of adverse events (ranging from <5% to ≈50%) for each classification (166). Specific recommendations are also made for each classification that include repeat testing, a review of medical management and the initiation of an exercise programme.

Although its main consideration is in those with heart failure, and there is a paucity of evidence for its value in PAD, the $\dot{V}E/\dot{V}CO_2$ slope may still hold clinical value in this population, especially considering that it has been shown to significantly improve following a SEP (158).

1.3.2.(f) Oxygen Pulse and Oxygen Uptake versus Work Rate Slope

As previously mentioned, the Fick equation defines $\dot{V}O_{2Max}$ as the product of maximum cardiac output and arteriovenous oxygen difference (138). Therefore, by modifying this equation and dividing $\dot{V}O_{2Max}$ by maximum HR we are able to obtain an estimation of stroke volume, termed oxygen pulse (O_2/HR). Peak O_2/HR is therefore equal to peak stroke volume multiplied by peak arteriovenous oxygen difference (138). However, the arteriovenous oxygen difference reaches a physiological limit and has little variability across a wide spectrum. As such, most of the variation identified in peak O_2/HR is due to variation in peak stroke volume (138). O_2/HR is usually plotted over time and it can be identified at any point during a test, by simply dividing $\dot{V}O_2$ by HR.

O_2/HR can be useful in the detection of subtle changes in stroke volume that accompany ischaemia-induced left ventricular dysfunction, therefore aiding in the diagnosis of exercise-induced myocardial ischaemia (128, 168). In normal subjects, there will be a continuously increasing O_2/HR until peak values are reached. When myocardial ischaemia develops during exercise, this can lead to a reduction in myocardial contractility which reduces stroke volume thus manifesting as a flattening or inflection of the O_2/HR response, despite an increase in workload (128, 151). CAD becomes functionally important when myocardial oxygen demand exceeds extractable oxygen flow (168). When oxygen demand exceeds oxygen supply to an area of the myocardium, that area must stop contracting. During exercise, a point may be reached whereby the diastolic time is reduced due to an increase in HR. This means that coronary artery filling is also reduced, whilst myocardial work is increasing, meaning that demand will outweigh supply in an ischaemic region of the myocardium (168). This region of the myocardium will therefore not be able to contract during exercise. At this point, stroke volume will decrease whilst HR will subsequently increase to sustain cardiac output, thus

causing O_2/HR to become flat or decrease (168). This reduction in stroke volume is also likely to cause the oxygen flow to the exercising muscles to decrease, causing a subsequent decrease in the slope of $\dot{V}O_2$ relative to work rate ($\Delta\dot{V}O_2/\Delta WR$) (168). It is therefore possible to detect myocardial ischaemia in those with and without documented CAD by combining these two parameters (127, 168). In healthy individuals, a normal increase of 10 ± 1 mL·min^{-1}·watt is apparent until peak exercise (145). In the context of myocardial ischaemia, an initial slope of 10 ± 1 mL·min^{-1}·watt is maintained up to the point of the ischaemic threshold (slope 1). At the ischaemic threshold, there is an abrupt decrease in $\dot{V}O_2$ which manifests as a break point in the $\Delta\dot{V}O_2/\Delta WR$ slope, creating a second slope (slope 2) which has a cut-off value of 3.9 mL·min^{-1}·watt (168). This is referred to as a double slope sign (168). The double slope sign should be accompanied by a simultaneous flattening in O_2/HR which must have the same duration as slope 2 of the $\Delta\dot{V}O_2/\Delta WR$ slope to be positive for myocardial ischaemia (Figure 8) (127).

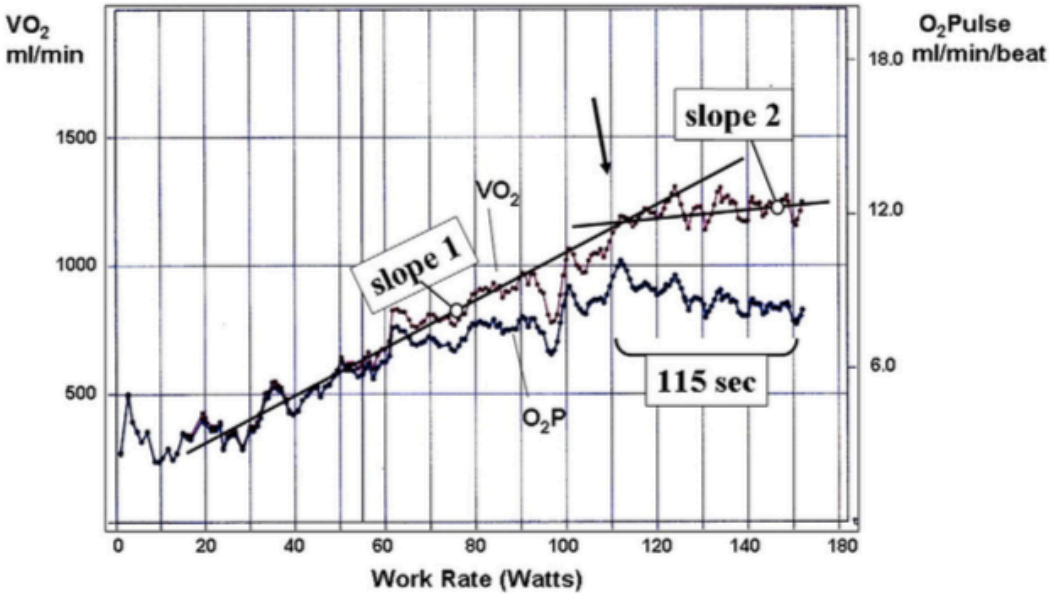


Figure 8 - Example of myocardial ischaemia identified via CPET. Note the two slopes in $\Delta\dot{V}O_2/\Delta WR$ slope and the simultaneous flattening in O_2/HR, with the same duration as slope 2 of the $\Delta\dot{V}O_2/\Delta WR$ slope.

Importantly, it is suggested that exercise induced abnormalities in left ventricular function begin before ST-segment changes and symptoms, meaning that abnormal changes in $\dot{V}O_2$ reflective of exercise induced ischaemia may be detectible prior to ECG changes and clinical signs. Indeed, *Belardinelli et al. 2003* found that in those

with suspected CAD who developed ST depression and had a positive nuclear imaging scan, $\dot{V}O_2$ flattening started almost 4 minutes before ECG changes (127). This phenomenon is yet to be considered in patients with PAD. However, given the high prevalence of coexisting CAD, the role of $\dot{V}O_2$ flattening as a diagnostic criterion for these patients should be identified. This is especially pertinent given that these patients also have a reduced functional capacity, meaning that the CPET may not be of sufficient duration to elicit ECG changes (18).

1.4 Exercise Therapy

All of the above variables are measured during incremental exercise and provide an insight into the cardiovascular response to increasing metabolic demand. Often, the aim of appropriate exercise prescription in both clinical and healthy populations is to improve these physiological parameters whilst also providing symptomatic / cardiovascular risk benefit where appropriate. This is also the case for patients with IC. In addition to providing symptomatic benefit, exercise therapy for patients with IC should aim to improve parameters of CRF, such as the VAT and $\dot{V}O_{2Peak}$, as this is likely to provide a prognostic benefit, as outlined previously. Across all populations appropriate exercise prescription includes consideration of the frequency, intensity, time (duration) and type of exercise (FITT principle) which is applicable to aerobic, resistance and flexibility training (169). However, aerobic exercise, especially for those with IC, is the integral component.

1.4.1 Exercise in Intermittent Claudication

Exercise prescription for clinical populations is often tailored to the specific condition. For IC, exercise therapy is an important component of treatment, which can take the form of unsupervised exercise, supervised exercise and home-based exercise. Each approach has a differing level of exercise prescription and as such efficacy.

1.4.1.(a) Unsupervised Exercise

Unsupervised exercise originally consisted of basic advice to “go home and walk” (170), which for a number of centres without access to any formal exercise regime (171), may still be the case. However, such an approach is not effective (172). When basic advice such as this was compared to SEPs, SEPs provided a greater

mean improvement of 210m in MWD, which constitutes a large MCID (118, 173). Therefore, this form of basic exercise advice, should not be given routinely, and ideally all patients should be offered a SEP.

1.4.1.(b) Supervised Exercise Programmes

SEPs are first-line recommended treatment for patients with IC in national and international guidelines (17, 63, 88). These are class IA recommendations, meaning that they are strong, supported by high quality evidence and that the benefits far outweigh the risks (63, 88). Indeed, SEPs are considered safe, with one review including 2,876 patients reporting an all-cause event rate of one per 10,340 patient hours. In addition, the number of events in the 32% of patient hours that included cardiac screening was the same as for the 68% without cardiac screening, leading to the conclusion that cardiac screening prior to a SEP is not useful (174). However, some studies included in this review excluded those with cardiovascular or respiratory co-morbidities, meaning that generalising the results to those with major co-morbidities is hazardous (174). As such, patients should at least undergo basic medical screening and an interview to detect any absolute contraindications to exercise, as recommended for those undergoing cardiovascular rehabilitation (CR; 175). Those with evident contraindications to exercise should be referred back to the appropriate specialty for management prior to commencing a SEP.

The evidence for the benefit of SEPs is irrefutable, and demonstrates that compared to basic exercise advice, they are superior for improving both ICD and MWD (173). In addition, one study demonstrated that the symptomatic benefit following a 6-month SEP was superior to both optimal medical care and primary stenting for patients with aortoiliac disease (176). At 6-month follow-up, the SEP group had a significantly greater improvement in maximum walking time compared to the medical care and stenting groups (176). At 18 months (i.e., 12 months after SEP completion), this significant difference was maintained compared to the medical care group, but not the stenting group (177). Another study also demonstrated that invasive treatment (endovascular or surgical procedure) plus a SEP provided superior improvements compared to a SEP alone for QoL and ICD, but not MWD at 12-month follow-up (178). However, at 5-years, this superiority was

no longer evident and there were no significant differences between groups for any QoL or functional outcomes (179). This evidence therefore suggests that possibly in the short-term, and certainly the long-term, SEPs are equal to invasive alternatives for symptomatic improvement.

However, it has been suggested that a SEP can be upgraded from a symptomatic intervention, to a prognostically preventative strategy (180). Indeed, it has been demonstrated that completion of a SEP, as opposed to non-completion, is an independent predictor of cardiovascular death and as such, successful completion can reduce cardiovascular mortality and morbidity by 52% and 30% respectively (180). Importantly, these benefits are still maintained 10 years after completion of the programme. The estimated cardiovascular death free rates for SEP completers compared with non-completers were 98% vs 92% at 3 years, 96% vs 83% at 5 years and 80% vs 58% at 10 years (180).

Despite proven safety and efficacy, and international guidance (17, 18, 88), which although slightly variable, is largely similar, there is no consensus on the most appropriate SEP design, with regards to the FITT principle. There is also a lack of sufficient detail when describing SEPs in clinical trials, which hinders and impacts upon future studies and clinical practice (181). Despite this, the majority of SEP provision in research studies is based on intermittent walking at an intensity that is sufficient to induce claudication pain (172). However, benefits are also obtainable with other modalities, including upper and lower limb cycling and resistance training with no clear evidence of a difference between walking and these alternative exercise methods (182-184).

In an attempt to improve standardisation, recent detailed guidance has been provided (172), which recommends that SEPs should be provided on-site by exercise professionals and overseen by a clinical lead. Such programmes should consist of intermittent treadmill walking whereby patients walk at a speed and gradient that induces claudication pain within 3-5 minutes, though they should continue walking until the pain reaches near-maximal levels. The patient should

then rest until the pain has abated before walking again to the same near-maximal level. This cycle should be repeated for at least 30 minutes a day, at least 3 days per week for a period of at least 3 months (172). The guidance also provides information on appropriate assessment tools and exercise and monitoring equipment. Therefore, international guidelines should adopt these evidence-based recommendations for SEPs and provide identical guidance to reduce variability.

1.4.1.(c) Uptake, Adherence and Barriers to SEPs

Despite its proven effectiveness and minimal risk, patient engagement is a major problem for SEPs. It has recently been shown that less than a quarter of patients who are screened for a SEP are subsequently recruited to it, with over 40% of screen failures being due to a lack of interest or patient refusal (185). Other key reasons for SEP refusal are comorbidities that affect the ability to exercise and a lack of knowledge about its benefits (185). Indeed, one review noted that comorbid health concerns were the most frequently reported barriers to walking among participants (186). This was also compounded by a lack of knowledge, with the review reporting that patients had a limited understanding of the pathology of IC, its risk factors and the benefits of walking upon both of these (186). As such, the poor engagement in exercise for IC is related to a plethora of factors that act as barriers. Furthermore, of those that do attend a SEP, approximately 25% do not complete it, with more than half of those who withdraw, choosing to do so due to a lack of motivation or symptomatic improvement (185). Therefore, only around one in five patients with IC receive and complete a SEP, the recommended first line treatment.

Although patients often choose not to take part in a programme, it is also worth noting that not all patients will have access to one. A UK based survey considered SEP provision and identified that just 42% of vascular units have one available (171). Key barriers to provision include a lack of funding, staffing and facilities. The centres with a SEP reported that they are usually provided at a hub centre, meaning local provision for those at spoke sites is poor. It is therefore unsurprising that 12% of patients reported being unable to attend a SEP due to distance (171, 185).

Alternative exercise programmes that are more acceptable and accessible for patients and providers may improve these provision, uptake and completion rates. One study surveyed patients about exercise programmes in order to identify potential alternatives. The majority of patients indicated that they would prefer to exercise at home, with an element of ongoing support, whilst over a third still indicated a preference for a hospital-based programme (187). Interestingly, 50% of patients also indicated a preference for short duration, high-intensity exercise. This would suggest that there is a need to develop a variety of effective exercise programmes, rather than just a traditional SEP, for patients with IC. Two possible examples are home-based exercise programmes (HEP) and high-intensity interval training (HIIT).

1.4.1.(d) Home-Based Exercise Programmes

HEPs are structured interventions that promote self-managed walking in the community and provide specific recommendations with regards to the duration, frequency and / or intensity of exercise that should be performed, rather than basic "go home and walk" advice (188). In addition, patients can be monitored, often via pedometers, accelerometers, physical activity monitors or simple exercise logbooks.

A recent Cochrane review considered the evidence base for HEPs and compared them to both SEPs and basic walking advice. This demonstrated that for improving MWD, HEPs were inferior to SEPs and no better than walking advice (173). However, the mean difference in MWD between SEPs and walking advice was 210m, but lower at 120m between SEPs and HEPs, suggesting there is a potential benefit of HEPs over walking advice (173). In addition, there were drawbacks with the analysis of this review, as it only combined studies that reported outcomes at the same time point (i.e., 3months), rather than combining all of the studies using their planned primary assessment time point (i.e., at completion of the intervention). The latter method would be more appropriate given that the interventions were designed to have the greatest effect at their designated primary timepoint (189).

A more recent review therefore summated the results at the planned primary assessment endpoint of each trial and noted that structured HEPs significantly improved MWD, ICD, 6MWT and physical activity in relation to controls not receiving an exercise programme (189). However, this review also suffered limitations that affect applicability. Firstly, it included those with asymptomatic PAD, for whom currently, structured exercise programmes are not recommended meaning it may not be generalisable to those with IC. Secondly, a number of the included studies were reasonably outdated, oversimplified and not reflective of available resources in modern healthcare. Finally, and most importantly, there was marked heterogeneity between the included studies with regards to the FITT principle (189).

As such, the current evidence base is certainly conflicting. Therefore, as with SEPs, there is no consensus on the most appropriate HEP design, and international guidance is vague, suggesting that the FITT principle should follow that of a SEP (88).

When looking at individual studies within the aforementioned reviews, it is possible to elucidate the effective components to inform an appropriate prescription. Four studies have reported structured HEPs that were roughly similar in their FITT design, consisting of walking performed ≥3 days per week for 6-12 weeks prescribed based on time or steps per day (190-193). All four studies also actively monitored patients via activity trackers or pedometers and reported significant improvements in walking distance in comparison to controls, with one being comparable to a SEP (190-193).

Consequently, despite the conflicting level 1a evidence for the benefit of HEPs (173, 189), it appears that studies adopting similar designs and an element of monitoring can be efficacious. Therefore, further studies of structured HEPs that adopt an appropriate and similar FITT principle, and an element of monitoring, via the use of modern technology, appear warranted. This will allow for a homogenous evidence base to be built, to inform future guideline recommendations.

1.4.1.(e) High-Intensity Interval Training (HIIT)

HIIT requires individuals to undertake repeated intervals of high-intensity exercise that are interspersed with either rest or lower-intensity recovery periods (194). It has been studied across healthy and a number of clinical populations and has demonstrated similar or superior physical benefits when compared to lower intensity programmes (195-200). For example, a number of meta-analyses have demonstrated that HIIT is superior to moderate intensity continuous training (MICT) for improving CRF in those with CAD (195-197). There is also evidence that HIIT can improve some cardiometabolic risk factors in the obese population (199), and that it is superior to MICT for improving CRF in those with lifestyle-induced cardiometabolic diseases (198). Recent evidence also supports the safety of HIIT in those with CAD and heart failure, with the major cardiovascular event rate being one in every 11,333 HIIT hours (194).

However, in contrast to the aforementioned evidence, one large, recent, RCT in those with CAD failed to demonstrate that HIIT was superior to MICT, though this may have been due to the HIIT protocol chosen, which was 4 minutes of work interspersed with 3 minutes of rest (201). The authors stated that the training intensity often had to be decreased in the HIIT group to avoid extreme hyperventilation or premature termination of pedalling (201). Furthermore, the average achieved intensity was 88% of peak HR, which was lower than the prescribed HIIT target zone of 90-95%. This led the authors to suggest that HIIT at 90-95% of peak HR is not feasible, at least not for 4-minute intervals (201).

In another study, with AAA patients, 2-minute HIIT intervals were used and the achieved intensity was again, lower than intended (202). This data would suggest that HIIT intervals shorter than 2 minutes may be more appropriate in certain clinical populations (e.g. patients with PAD).

The evidence for HIIT in patients with IC is much more limited than for other clinical populations. It would however, be reasonable to assume, given the substantial evidence supporting HIIT in those with CAD, a similar disease aetiology, that benefits could be provided for those with IC. Yet, no systematic review evidence has been published to date.

There are however, some small studies considering HIIT in those with IC, that include treadmill walking (203, 204), upper- and lower-limb cycling (183), and resistance training (182). These studies suggest that HIIT can provide significant improvements in walking distance, both in relation to baseline and in relation to no-exercise controls. One of the two treadmill based studies included both high- and low-intensity walking for 6 months and found that both groups had a similar improvement in walking distance (204). However, the 6-month duration of this programme suggests that longer low-intensity programmes are required to elicit comparable benefits to higher intensity programmes, which can provide improvements in just 6 weeks (203).

Although limited, this evidence does appear promising and suggests that HIIT, across a variety of modalities, may provide a benefit for those with IC. However, a thorough, systematic review of the published evidence is required. When such a review is conducted, the reported methods of potentially eligible studies must be carefully considered. For example, the upper- and lower-limb cycling study noted above did not specifically mention the term HIIT, despite performing such a regimen, whilst another study claimed to perform HIIT but this was not reflected in the methods (205).

Once this systematic review has been conducted, an appropriate evidence-based intervention should be designed, refined and evaluated to establish the potential of HIIT in those with IC.

1.4.2 Aims of this Thesis

The above literature review identified a need to develop suitable exercise alternatives to traditional SEPs, with HEPs and HIIT showing potential.
As such, this thesis aimed to consider both of these alternative exercise interventions.

With regards to HEPs, there is already a substantial body of published evidence utilising a number of different interventions. Therefore, the aim was to synthesise this evidence via a systematic review and meta-analysis to identify the effective HEP components and make appropriately informed recommendations for practitioners.

With regards to HIIT, there is limited evidence considering its use for the treatment of IC, meaning an appropriate intervention is yet to be developed. In such circumstances, the medical research council note that a systematic review should be conducted to inform the intervention (206). This evidence-based intervention should then be tested for its feasibility.
Therefore, this thesis also aimed to synthesise the evidence for HIIT in those with IC, via a systematic review. This review was then used to develop an appropriate, evidence based HIIT intervention which was tested for its feasibility, tolerability, safety, potential efficacy and acceptability.

Chapter 2: Study One: Home-based Exercise Programmes for Individuals with Intermittent Claudication: A Systematic Review and Meta-Analysis

2.1 Declaration

This study has been accepted for publication in the Journal of Vascular Surgery. The protocol is also published in SAGE Open Medicine (188). For both of these publications, Sean Pymer (SP) is first and corresponding author. SP contributed to the conception and design, analysis and interpretation, data collection, writing the articles, critical revision of the articles, final approval of the articles, and has overall responsibility.

2.2 Introduction

Previous work has identified that SEPs, although first-line recommended treatment for IC, are under-utilised at both provision and patient level (171, 185). As such, there is a need to develop alternative exercise programmes that are more acceptable and accessible for patients and providers. HEPs are one such alternative that can be performed in the patient's own time, at a location of their choosing. However, as noted in chapter one, the evidence base for HEPs is largely heterogeneous and it is not known which HEP components, if any, are efficacious.

2.3 Aim

The aim of this review was to consider the effectiveness of HEPs in relation to three comparator groups: SEPs, basic exercise advice or no exercise controls. A secondary aim was to identify the most effective HEP components and provide recommendations for a structured, evidence-based, effective HEP for patients with IC.

2.4 Methods

This systematic review was conducted in accordance with the previously published protocol and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (188, 207). It was also prospectively registered on PROSPERO (CRD42018091248).

2.4.1 Search Strategy and Inclusion Criteria

Prospective non-randomised and randomised controlled trials (RCT's) that considered the effect of a HEP versus a comparator arm (a SEP, basic exercise

advice or no exercise control) on walking distance, QoL and/or physical activity for patients with IC were included. Only patients with IC were included and authors of studies that included other PAD sub-groups (i.e., asymptomatic or atypical leg pain) were contacted to obtain the data for the IC sub-group. Other PAD sub-groups were not included as exercise therapy is only currently recommended for the treatment of IC (17).

HEPs were defined as those that included structured advice to increase physical activity by guiding patients in terms of frequency, intensity and/or duration rather than basic advice to "go home and walk". Occasionally, the HEP group were referred to as a control group but were included if the exercise information given was sufficiently structured. We also included HEPs that utilised monitoring via pedometers, accelerometers, physical activity monitors, or any combination thereof. Those with regular interactions with study staff were also included, but were limited to a maximum of two interactions per week (208). Interactions included communication with study staff either in person or via remote means.

For comparator arms, SEPs included any actively supervised exercise regime for the treatment of IC regardless of the frequency, duration or intensity. The basic exercise advice group included those who were encouraged to walk more at home, without any specific or structured recommendations. The no exercise control group consisted of those who either received no exercise-specific advice or were told to maintain their usual physical activity levels.

The search was conducted across five databases (CINAHL, PEDro, Medline, EMBASE and Cochrane CENTRAL) using search terms related to IC, PAD and HEPs (full search given in appendix 2). In addition, authors of trials identified in the grey literature as potentially eligible, via searches of registries and the web of science conference proceedings, were contacted to obtain study outcome reports where possible. Only studies published in the English language were included and no date restrictions were applied. Searches were performed from database inception and completed in March 2020.

2.4.2 Data Management, Selection and Collection Process

Titles and abstracts were interrogated for eligibility by two independent reviewers (SP and JP). Full texts of any potentially eligible articles were then independently screened against the inclusion criteria. Reference lists of any screened full texts were also hand searched for other relevant studies. Any disagreement between the two reviewers was resolved by consensus with a third (SI).

Data extraction was independently performed by two reviewers (SP and SI) using a standardised form. Extracted data was then inputted onto a Microsoft Excel database (Microsoft, 2010, Redmond, WA, USA). Data extraction included study characteristics, sample size and description, a description of the intervention and comparator conditions, outcome measures, length of follow-up and relevant main findings.

2.4.3 Outcome Measures

The primary outcome was treadmill measured MWD. Secondary outcomes included ICD, 6-minute walk distance (6-MWD), health-related QoL, and physical activity, either objectively measured or self-reported. If ICD and MWD were reported in minutes as intermittent claudication time and maximum walking time, this was translated into metres based on treadmill speed during testing.

2.4.4 Risk of Bias and Rating the Quality of Evidence

The risk of bias in individual studies was assessed by two independent reviewers (SP and SI) using the Cochrane collaboration tool v.1, which includes six domains (209). Information was extracted from each study and a judgement made for each domain that was rated as either, 'high risk', 'low risk' or 'unclear risk' if sufficient detail was not provided. Any disagreements were resolved via discussion.

The quality of meta-analysed evidence was assessed by two independent reviewers (SP and SI) using the GRADE approach (210). An initial assessment was made based on the design of the studies included within the meta-analyses (i.e. RCT's or non-RCT's). This assessment was then revised based on the following criteria; risk of bias, inconsistency, indirectness, imprecision and publication bias. Quality level was then finally categorised based on this revision as; high (very confident that the true effect lies close to the estimate of effect), moderate (the true effect is likely to be

close to the estimate of effect, but may be substantially different), low (the true effect may be substantially different from the estimate of effect), or very low (the true effect is likely to be substantially different from the estimate of effect).

2.4.5 Data Analysis and Synthesis

Both RCT's and non-RCT's were included and a summary of findings table was produced for each comparison. Where possible, a meta-analysis of RCT's was performed. Where data was not provided to allow entry into a meta-analysis, study authors were contacted, and relevant data requested, though in all but two cases, this was not provided. Meta-analysis was performed using Review Manager 5 (RevMan 2014), to produce forest plots with an overall effect estimate of mean difference and associated 95% confidence intervals. As the interventions and outcomes differed between trials, random effects models were used for all meta-analyses as this method considers heterogeneity within the effect estimate (211). For meta-analyses, post-intervention mean and standard deviation was used unless only change scores were given. We have summated the results at the planned primary assessment point of each trial, rather than at designated time-points (e.g. 6 weeks) as this is the point at which the intervention is designed to have the greatest effect (189).

A head-to-head analysis considering the effectiveness of HEPs versus each comparator arm was conducted and the results are presented as HEPs versus SEPs, HEPs versus basic exercise advice and HEPs versus no exercise controls. As specified in the protocol, sub-group analysis was performed based on the presence or absence of monitoring. Monitoring included either self-monitoring, using devices such as pedometers, or remote monitoring, using activity monitors. Other pre-specified sub-group analyses were not performed due to insufficient data. Furthermore, the robustness of the analyses was determined via sensitivity analysis. For this, we removed RCT's with a higher risk of bias assessment and repeated the analysis (212). Further sensitivity analyses were also performed using change scores from baseline (where reported) instead of final measurement scores as has been recommended (213). When certain studies reported only final

measurement scores, these were used in conjunction with the change scores that were reported for the purpose of sensitivity analyses.

We also considered the individual components of effective HEPs, such as the frequency, intensity, time and type of exercise and the use of monitoring, dietary and lifestyle advice or psychological components. Effective HEPs were identified as those that induced a significantly greater change ($p<0.05$) for at least one outcome, when compared with the basic exercise advice or no exercise control comparator groups. For trials only comparing a HEP to a SEP, the HEP was considered effective if it induced a significant positive change from baseline ($p<0.05$). The effective individual components were then identified as those that were evident (and similar) within the majority of these HEPs.

2.5 Results

2.5.1 Search Results

The search yielded a total of 4,411 results. Twenty-six articles (122, 182, 190-193, 214-233), reporting 23 studies, were ultimately included in this review, with 18 contributing to meta-analyses (Figure 9). Nine articles included in the previous review were excluded and 17 additional articles were identified. For the nine articles that were previously included, reasons for exclusion in the current review were; lack of an appropriate comparator arm and the inclusion of patients with atypical leg pain. The way that HEPs were defined was heterogeneous with a number of studies referring to their HEP as 'walking advice' or 'unsupervised exercise' when it was in fact structured and included a specific prescription.

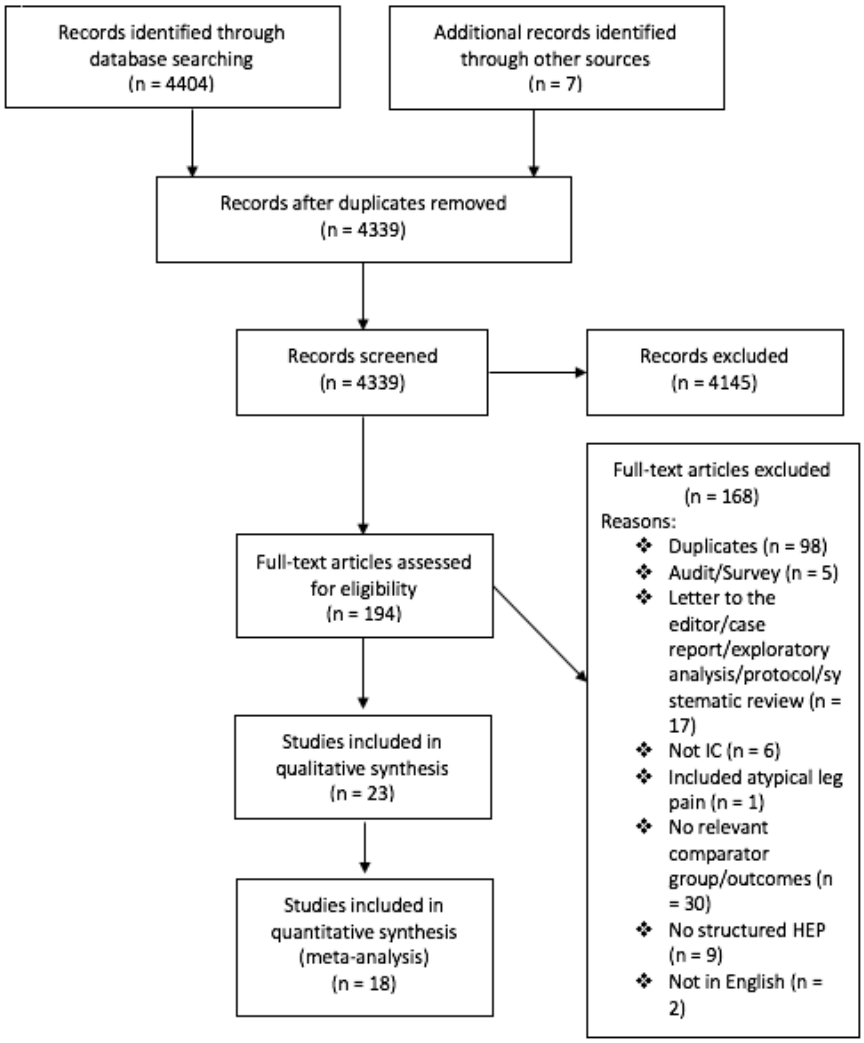


Figure 9 - PRISMA flow diagram

2.5.2 Included Trials

Of the included trials, three were non-randomised and compared HEPs to SEPs (219-221). The remaining trials were RCT's, and nine compared HEPs to SEPs (122, 182, 192, 214, 216, 223, 227, 228, 231), three compared HEPs to basic exercise advice (190, 217, 218), two compared HEPs to both these groups (193, 230) and six compared HEPs to no exercise controls (191, 215, 224, 226, 232, 233). A graphical summary of the results is presented in figure 10.

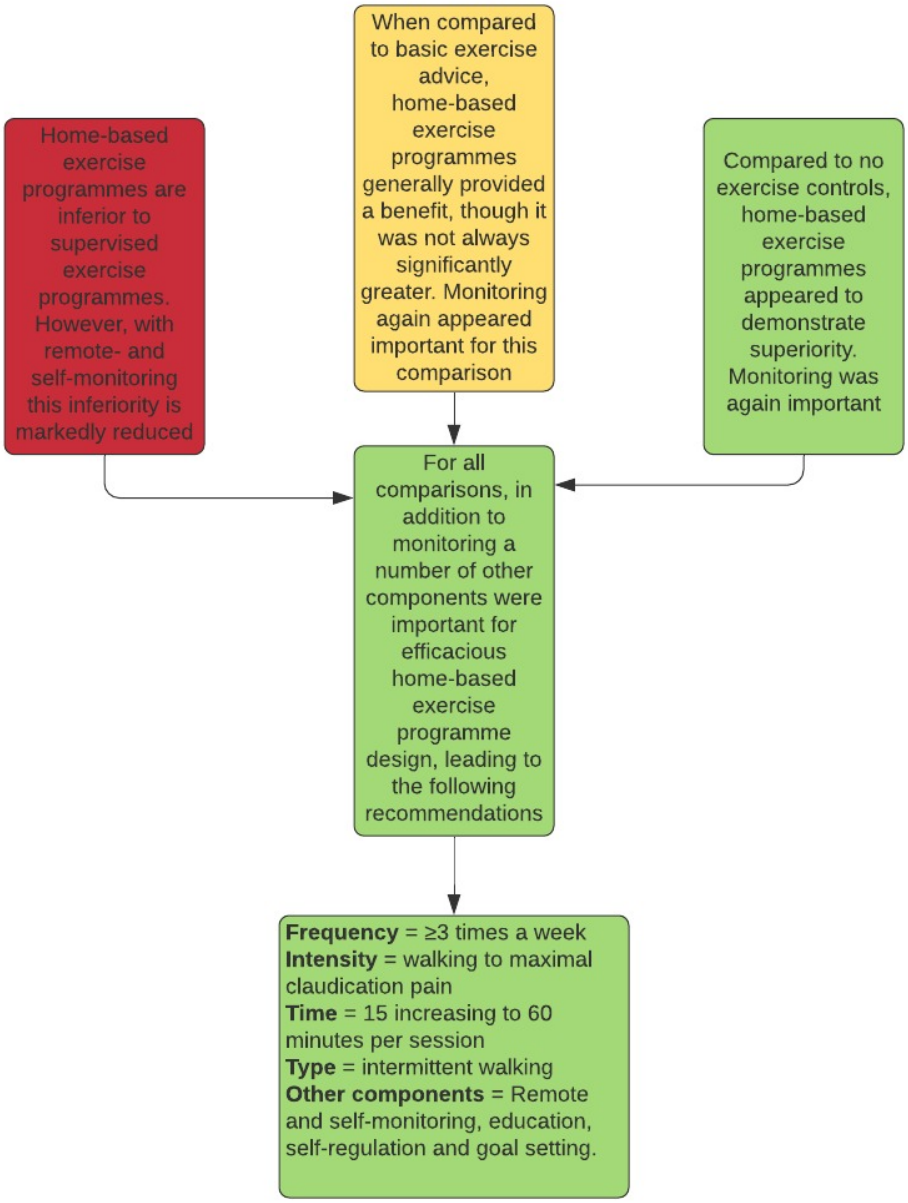


Figure 10 - Graphical summary of the results

The total number of recruited patients was 1,907. All studies used walking as the mode of exercise for the HEP. The frequency of training was more varied, with 3 times per week being the minimum prescription and 3 times per day, the maximum. The duration of exercise was either prescribed as minutes per session or number of steps per day. Exercise intensity was not always specified but was often based on reaching a mild or near-maximal level of claudication pain. Programme duration and length of follow-up ranged from 6 weeks to 12 months.
All but one study (218) reported treadmill MWD and / or 6-MWD, whilst seven did not report ICD (215, 216, 218, 224, 226, 230, 233). There was a lack of consistency between studies with regards to how walking distances were reported; either in minutes or metres, and how they were measured; with 15 using a graded treadmill test, five a constant load treadmill test and two the 6-MWT. Three studies also reported both treadmill and 6-MWT MWD. One study, from 1966, was included, but not used in meta-analyses which is contrary to other reviews (189, 232), because the treadmill test was not standardised between patients. Generic and disease specific QoL was measured in 14 studies via the WIQ, the SF-36, SF-20, or SF-12, the Intermittent Claudication Questionnaire (ICQ), the World Health Organisation quality of life questionnaire, the Vascular Quality of Life Questionnaire or the Euroqol-5D.

2.5.3 Quality Assessment and Risk of Bias

All outcomes were rated via GRADE as very low, low or moderate quality (tables 3-5). The most common reason for rating down was due to imprecision based on wide confidence intervals and/or small sample sizes. Some outcomes were also rated down for inconsistency due to heterogeneity, and indirectness related to differences between interventions.

The risk of bias summary is shown in Figure 11. All studies were rated as high risk for performance bias as due to the nature of the interventions, it is not possible for participants to be blinded. Across the other domains, there was little evidence of a high risk of bias (other than for selective outcome reporting). However, there was often inadequate information to imply a low risk of bias, resulting in a number of domains being rated as ‘unclear’.

Table 3 – GRADE for HEPs vs SEPs outcomes

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Intermittent claudication distance							
7	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Maximum walking distance							
8	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: 6-Minute walk distance							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Daily steps							
2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	No important indirectness (0)	Serious risk of imprecision (-1)		3
Outcome: Walking impairment questionnaire Distance							

3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Walking impairment questionnaire speed							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Walking impairment questionnaire climbing							
2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	important indirectness (-1)	Serious risk of imprecision (-1)		2
Outcome: Physical functioning							
5	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Role physical							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Bodily pain							

3	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2
Outcome: General health							
3	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2
Outcome: Vitality							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Social functioning							
4	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2
Outcome: Role emotional							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Mental health							

3	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2
Outcome: Intermittent claudication distance - active monitoring							
2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	No important indirectness (0)	Serious risk of imprecision (-1)		3
Outcome: Maximum walking distance - active monitoring							
2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	No important indirectness (0)	Serious risk of imprecision (-1)		3
Outcome: Intermittent claudication distance – no active monitoring							
5	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Maximum walking distance – no active monitoring							
6	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Physical component summary							

3	Randomised trials (4)	No serious risk of bias (0)	No Important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2
Outcome: Mental component summary							
3	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2

Table 4 - GRADE for HEPs vs basic exercise advice outcomes

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Intermittent claudication distance							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Maximum walking distance							
4	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Daily steps							

3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Walking impairment questionnaire Distance							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Walking impairment questionnaire speed							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Walking impairment questionnaire climbing							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Maximum walking distance active monitoring							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Maximum walking distance no active monitoring							

2	Randomised trials (4)	Serious risk of bias (-1)	Important inconsistency (-1)	No important indirectness (0)	Serious risk of imprecision (-1)		1
Outcome: Intermittent claudication questionnaire							
2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	Important indirectness (-1)	Serious risk of imprecision (-1)		2

Table 5 - GRADE for HEPs vs no exercise control outcomes

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Maximum walking distance							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: 6-Minute walk distance							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Daily steps							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Walking impairment questionnaire Distance							

2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	No important indirectness (0)	Serious risk of imprecision (-1)		3
Outcome: Walking impairment questionnaire speed							
2	Randomised trials (4)	No serious risk of bias (0)	No important inconsistency (0)	No important indirectness (0)	Serious risk of imprecision (-1)		3
Outcome: Walking impairment questionnaire climbing							
2	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		3
Outcome: Mental component summary							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1
Outcome: Physical component summary							
3	Randomised trials (4)	No serious risk of bias (0)	Important inconsistency (-1)	Important indirectness (-1)	Serious risk of imprecision (-1)		1

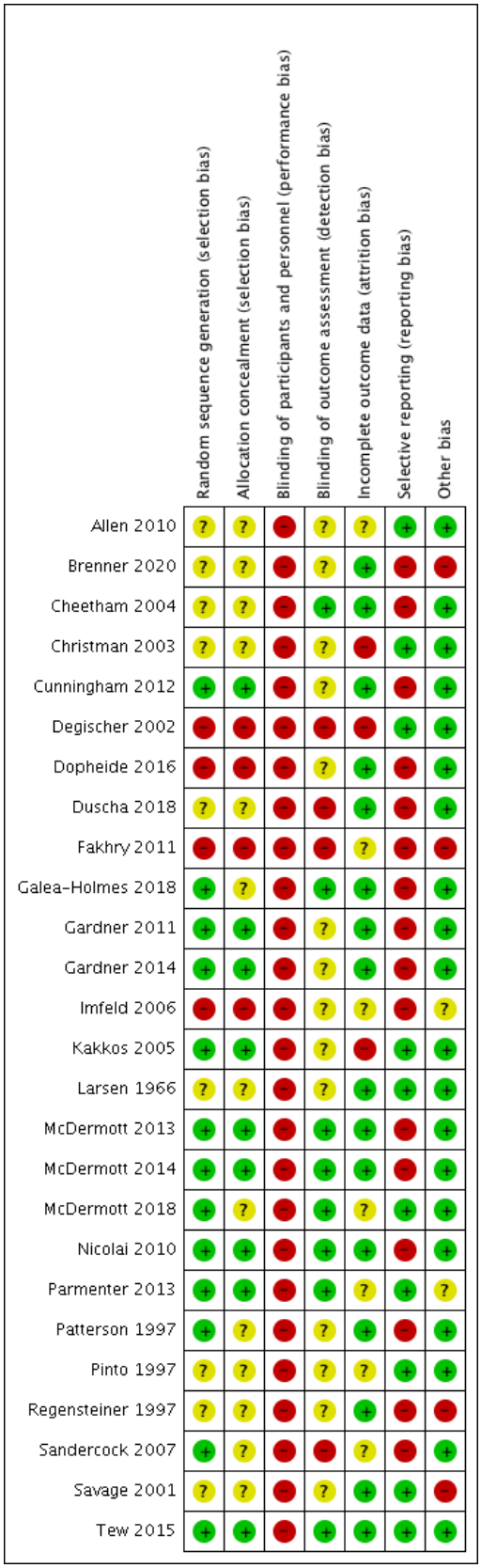


Figure 11 - Risk of bias summary

2.5.4 HEPs vs. SEPs

Table 6 outlines the narrative findings of all studies that compared HEPs with SEPs (122, 182, 192, 193, 214, 216, 219-221, 223, 227, 228, 230, 231). Overall, for MWD there were statistically significant improvements in half of the HEP groups, and in all of the SEP groups. For between-group analyses, there were significantly greater improvements following the SEP in nine of the 14 studies. For ICD, there were statistically significant improvements in half of the HEP groups and in 11 of the 14 SEP groups, with four of the SEP groups demonstrating significantly greater improvements than the HEP groups. For the three studies that adopted monitoring for the HEP groups, there were no significant differences compared to the SEP groups for improvements in ICD (192, 193, 220). For MWD, one study reported no significant difference between groups (192), another reported a significantly greater improvement in the SEP group (193) and the final study noted a significant improvement in the SEP group but not the HEP group (p = .06) (220). The latter study also reported that individual increases were 'much higher' in the SEP group, though the difference in improvements between groups was 5% and it was not compared statistically.

For QoL outcomes, there were significant improvements in the WIQ and the physical functioning domain and physical component summary score of the SF-36 with improvements largely similar between groups.

Table 6 - Studies comparing home-based exercise programmes with supervised exercise programmes (n = 14)

Study (country, design)	**Sample**	**Description of Interventions**	**Outcome Measure, follow-up**	**Main findings**
Allen, 2010 (214), (USA) RCT.	Total *n* = 74. Stable IC (>3 months), with a resting ABPI <0.9. Patients with CLTI, revascularisation procedure in the last 3 months or severe co-morbidities were excluded.	**HEP:** 3 months of walking 3 times per week for 30 minutes. Intensity was not specified. **Monitoring:** Subjects were asked to keep careful notes regarding their activity and were called every 3 weeks to ask exercise related questions. **SEP:** Intermittent treadmill walking until moderate to severe pain for 30-40 minutes per session, 3 times per week for 3 months. **Monitoring:** None.	ICD and MWD determined by graded treadmill test – 3 months.	Significant improvements in ICD and MWD for the SEP group but not the HEP group. No between group comparison made.
Cheetham, 2004 (216) (UK), RCT.	Total *n* = 59. Stable IC (>6 months). Positive ABPI with PAD confirmed by Duplex, positive Edinburgh claudication questionnaire, able	**HEP:** 6 months of walking to near maximal pain, 3 times per week for at least 30 minutes a session. **Monitoring:** None. **SEP:** A 45-minute exercise and motivation class – with circuit-based exercise performed for 30 minutes, once weekly, for 6 months. Circuit	MWD determined by constant load treadmill test – 3, 6, 9 and 12 months.	Significant improvements in MWD in both the HEP and SEP groups at each time point, with significantly greater improvements in the SEP group.

	to walk >300m on the flat in 6 minutes. Patients with CLTI, revascularisation within last 2 years, or significant co-morbidities were excluded.	involved 2 minutes of walking interspersed with 2 minutes of an alternate exercise. Intensity was not specified. **Monitoring: None.**		
Degischer, 2002 (219) (Switzerland), non-RCT.	Total *n* = 69. Stable IC (>3 months) confirmed with ABPI <0.95, with a subjective walking distance 50-500m. Those unable to walk on a treadmill, who had revascularisation within 3 months, or significant co-morbidities were excluded.	**HEP:** 3 months of intermittent walking to 60% of maximum claudication pain, for at least 60 minutes daily for 3 months. **Monitoring:** weekly phone calls to offer advice for any exercise problems, patients also kept an exercise logbook. **SEP:** 3 months of intermittent walking to 60% of maximum claudication pain for 60 minutes, 3 times per week. **Monitoring: None.**	ICD and MWD determined from graded treadmill test - 3 and 6 months.	Significant improvements in ICD in both groups at all time points, with a greater improvement in the SEP group. Significant improvement in MWD at all time-points in the SEP group with no improvement in the HEP group. The improvement was significantly greater in the SEP group at 6 months.
Dopheide, 2016 (220)	Total *n* = 60. Patients aged >18 years with IC	**HEP:** At least 30 mins, up to 60 mins, walking per day on at least 3-5 days per week. Walking with an intensity	ICD and MWD from a constant load	Significant increases in ICD for both the HEP and SEP groups with

(Germany), non-RCT.	(Rutherford 1-3 or Fontaine II A/B). Those with significant co-morbidities were excluded.	to nearly reach their typical claudication sensation then rest and repeat the distance at a lower intensity. **Monitoring:** Patients controlled their weekly walking with a pedometer. **SEP:** SEP patients received the same HEP prescription and also performed supervised training once per week on top of this, though the SEP was not described. **Monitoring:** Patients controlled their weekly walking with a pedometer.	test – 6 months.	individual increases reported as similar between groups. For MWD, there was a significant increase in the SEP group, but not the HEP group (p = .06). Individual increases were reported as 'much higher' in the SEP group, though the difference in percentage improvement between groups was 5% and it was not compared statistically.
Fakhry, 2011 (221) (Netherlands), non-RCT.	Total n = 217. Patients with IC confirmed via ABPI and a MWD of <350m during treadmill test. Patients eligible for a concurrent RCT or with significant co-morbidities were excluded.	**HEP:** At least 1 session daily for 6 months, with regular walks also encouraged in the daily routine. Each exercise session consisted of 30 minutes walking at a speed to elicit near-maximal claudication pain, interspersed with 1-minute of walking at a very slow pace. **Monitoring:** Monitoring visits at weeks 2, 8, 16 and 24 to assess progress (ICD and MWD) and discuss exercise sessions performed. New	ICD and MWD from a constant load treadmill test and QoL – 6 and 12 months.	Significant improvement in, MWD, VascuQoL score and physical functioning in the HEP group at 6 and 12 months. ICD was significantly improved in the HEP group at 12 months but not 6 months. There was a significantly greater change in ICD

		targets were set and education about IC was given. Patients were strongly encouraged to adhere to the recommended programme. **SEP:** 2 sessions weekly for 6 months consisting of 30 minutes intermittent treadmill walking, whereby patients walked to near maximal pain, then decreased the workload and continued exercising at this reduced workload until pain subsided then workload was increased again. **Monitoring:** None.		and MWD in the SEP group compared to the HEP group at 6 and 12 months. There were no significant differences between groups for QoL measures other than the SF-36 general health domain and the overall rating scale score which was significantly greater in the SEP group at 6 months, but not maintained at 12 months.
Gardner, 2011 (192) (USA), RCT.	Total *n* = 119. IC secondary to PAD with ambulation during a treadmill test limited by leg pain consistent with IC and a positive ABPI. Patients with asymptomatic PAD,	**HEP:** 3 months of intermittent walking to near maximal claudication pain 3 times per week. Duration progressively increased by 5 minutes biweekly from 20 to 45 minutes. **Monitoring:** Patients were monitored by a step activity monitor and logbook which were returned to staff at weeks 1, 2, 4, 6, 8, 10 and 12. During these 15-minute meetings, data were downloaded, results	ICD and MWD from a graded treadmill test, QoL and physical activity – 3 months.	Significant improvement across both groups for ICD, MWD, WIQ scores, and physical functioning, with no significant differences between groups. There was also a significant improvement across a number of physical activity measures in the HEP

	exercise tolerance limited by other factors or significant comorbidities were excluded.	reviewed, and feedback provided for the upcoming month of training. **SEP:** Intermittent treadmill walking to near maximal claudication pain, performed 3 times per week for 3 months. Walking duration began at 15 minutes and increased by 5 minutes biweekly up to 40 minutes. **Monitoring:** During exercise sessions, patients wore a step activity monitor.		group, not evident in the SEP group including: maximum 20-, 30- and 60-minute cadence and average cadence in strides/min.
Gardner, 2014 (193), (USA), RCT.	Total *n* = 180. Symptomatic PAD confirmed with ambulatory leg pain during treadmill test and ABPI. Patients with asymptomatic PAD, exercise tolerance limited by other factors or significant comorbidities were excluded.	**HEP:** 3 months of intermittent walking to mild-moderate claudication pain 3 times per week. Duration progressively increased by 5 minutes biweekly from 20 to 45 minutes. **Monitoring:** Patients were monitored by a step activity monitor and logbook which were returned to staff at weeks 1, 4, 8, and 12. During these 15-minute meetings, data were downloaded, results reviewed, and feedback provided for the upcoming month of training.	ICD and MWD from a graded treadmill test, 6-MWD, QoL and physical activity – 3 months.	There was a significant improvement across both groups for ICD, MWD, WIQ scores, and physical functioning, with no significant differences between groups, except for MWD which was significantly greater in the SEP group. There was a significantly greater improvement in 6-MWD for the HEP group, compared to the SEP group.

		SEP: Intermittent treadmill walking to mild to moderate claudication pain, performed 3 times per week for 3 months. Walking duration began at 15 minutes and increased biweekly up to 40 minutes. **Monitoring:** None.		There was also a significant improvement across a number of physical activity measures in the HEP group, not evident in the SEP group including: maximum 20-, 30- and 60-minute cadence and average cadence in strides/min.
Kakkos, 2005 (223) (UK), RCT.	Total *n* = 34. Stable IC (>6 months, assessed using the San Diego claudication questionnaire), due to SFA occlusion >6cm on Duplex. Patients who had undergone Revascularisation <6 months ago, had CLTI, where unable to manage treadmill walking and/or training, had severe	**HEP:** Daily exercise by walking as much as possible to near maximal pain, for a period of at least 45 minutes for 6 months. **Monitoring:** None. **SEP:** Daily exercise by walking as much as possible to near maximal pain in conjunction with a SEP consisting of intermittent treadmill walking to moderate pain for 50 minutes, 3 times per week for 6 months. **Monitoring:** Compliance was assessed with logbooks.	ICD and MWD from a constant speed treadmill test and QoL – 6 weeks, 6 months and 12 months.	ICD and MWD were significantly improved at each time point in the SEP group, but not the HEP group, with changes in MWD being significantly greater in the SEP group at 6 and 12 months. There were no changes in any QoL measures other than bodily pain at 6 weeks in the SEP group, which was not maintained.

	co-morbidities or could walk <50m or >300m were excluded.			
Nicolai, 2010 (227) (Netherlands), RCT.	Total *n* = 304. Fontaine stage II PAD, with an ABPI <0.9 and a MWD <500m. Patients who had previously completed a SEP or had revascularisation or significant co-morbidities were excluded.	**HEP:** 3 walking sessions per day, during which maximum pain should be reached 3 times, i.e. walking to maximum pain 9 times per day, spread over 3 sessions, for 12 months. **Monitoring:** None. **SEP:** Patients were given the same instructions as the HEP group but also performed a SEP which included 2-3 sessions per week of interval walking to submaximal pain for 30 minutes. This was tailored to the individual need of the patient during the treatment year. **Monitoring:** Half of the SEP patients were randomised to a SEP with 'feedback' group, whereby they received a personal activity monitor, that assessed physical activity during normal life. Patients were instructed to wear this during the day for 1 year and to record the scores, which	ICD and MWD from a graded treadmill test and QoL – 12 months.	Significant improvements in ICD and MWD for both groups, which was significantly greater in the SEP group. Significant QoL improvements across both groups for WIQ distance, speed, stairs and total score, with the improvements being significantly greater in the SEP group except for the stair climbing score. Both groups had significant improvements in the physical functioning and physical and mental summary scores, with the SEP group also having significant improvements in the

		were used to give feedback to patients about their walking outside of the SEP.		additional domains of role physical, pain and social function. The SEP group also had significantly greater improvements than the HEP group for the physical functioning, pain, and physical summary score.
Parmenter, 2013 (182) (Aus), RCT.	Total *n* = 22. Aged >50 years with IC secondary to PAD confirmed by a vascular surgeon. Those with asymptomatic PAD, CLTI, or significant co-morbidities were excluded, as were those currently undertaking regular moderate-high intensity exercise.	**HEP:** Intermittent walking at usual pace to maximum pain for a period of 30 minutes, 3 times per week for 6 months. **Monitoring:** Participants recorded each walk in a diary handed in at the end of the programme. **SEP:** 6 months of high or low intensity progressive resistance training performed 3 times per week. **Monitoring:** None.	ICD and MWD from 6-MWT – 6 months.	No significant changes in ICD and MWD were observed in the HEP and low intensity SEP groups, whereas the high-intensity SEP group had a significant improvement in MWD, which was significantly greater than the HEP group.

Patterson, 1997 (228) (USA), RCT Psychological outcomes reported by Pinto, 1997 (229).	Total *n* = 55. Patients aged 50-75 with IC (>3 months), confirmed via ABPI. Patients with CLTI or those with exercise-related ischaemia making exercise unsafe were excluded.	**HEP:** Walking to 'tolerance' for a period of 20-40 minutes, 3 times per week for 3 months. **Monitoring:** Weekly exercise logs, reviewed by nurses at weekly lectures. Individual exercise counselling was also provided at these sessions. **SEP:** 3 60-minute sessions per week for 3 months including arm and leg cycle ergometry and treadmill walking. Intermittent treadmill walking involved walking to 75% of MWD before resting until ABPI returned to 75% of the resting value before exercising again. **Monitoring:** Both groups attended weekly lectures on addressing risk factors, nutrition, exercise and potential complications.	ICD and MWD from a graded treadmill test and QoL – 3 and 6 months. Psychological outcomes included POMS, pain perception, exercise-related constructs (self-efficacy) and knowledge of risk factors for atherosclerosis.	Significant improvements in ICD and MWD in both groups at 3 and 6 months, with a greater improvement demonstrated in the SEP group. Both groups also had significant improvements in physical functioning, pain and the physical component summary at 3 and 6 months, with no differences between groups. There were significant reductions in both groups for POMS scales of tension, depression and confusion as well as an improvement in the general activity score (a composite of scales assessing participation in chores, outdoor work, activities away from

				home and social activities). There were no changes in either group for self-reported pain severity, interference or affective distress related to pain, self-efficacy and knowledge of risk factors for atherosclerosis were also unchanged.
Regensteiner 1997 (122) (USA), RCT.	Total *n* = 20. Stable IC (>3 months) confirmed via ABPI with claudication being the limiting symptom during community-based activity and treadmill walking. Patients who had CLTI, were unable to walk at 2 mp/h, had undergone	**HEP:** Intermittent walking at a pace as rapid as possible up to moderate pain for a period of 35 minutes, increasing weekly up to 50 minutes, 3 times per week for 3 months. **Monitoring:** The supervising nurse called patients weekly for support and to record number of sessions and walking time per session. **SEP:** Intermittent treadmill walking to mild-moderate pain for a period of 35 minutes, increasing each session up to 50 minutes, 3 times per week for 3 months.	ICD, MWD from graded treadmill test and QoL – 3 months.	No significant increases in ICD or MWD for the HEP group, with significant increases seen in the SEP group, with the increase in MWD being significantly greater than the HEP group. The SEP group also had a significant increase in the SF-36 physical functioning score and WIQ distance, speed and claudication severity

	revascularisation <12 months ago, had diabetes or significant co-morbidities were excluded.	**Monitoring:** None.		scores, whereas the HEP group had only an improvement in the WIQ distance score. There were, however, no differences between groups for improvements in QoL measures.
Sandercock 2007 (230) (UK), RCT.	Total *n* = 52. All patients were confirmed as having symptomatic IC during walking using the leg pain scale, confirmed via ABPI. Those unable to complete a familiarisation test or had significant co-morbidities were excluded.	**HEP:** 3 months of walking at an intensity of 12-14 on the RPE scale for 30 minutes, 3 times per week. **Monitoring:** HEP patients were given an exercise diary to complete and were contacted once weekly via telephone to give encouragement. **SEP:** 3 months of treadmill walking at a work rate of 70-75% $\dot{V}O_{2Peak}$ for 30 minutes, twice per week. SEP patients were instructed to complete 1 additional 30-minute walking session per week. **Monitoring:** SEP patients were also given an exercise diary to compete.	MWD from a graded treadmill test – 6 weeks and 3 months.	A significant improvement in MWD for the SEP group, thought it was not significantly greater than the HEP group, who showed no significant improvement.
Savage 2001 (231) (USA), RCT.	Total *n* = 21.	**HEP:** Intermittent walking to the point of intense pain at least 3 times per week for a total walking duration	ICD and MWD from a graded treadmill test	There were no significant improvements in ICD in

	Aged >50 years with a clinical diagnosis of IC. Patients who had severe co-morbidities, were smokers or had a functioning lower extremity bypass were excluded.	of 15 minutes, gradually increasing to 40 minutes for 6 months. **Monitoring:** Brief contact monthly from a registered nurse who discussed the programme. **SEP:** 3 sessions per week of intermittent treadmill walking to the point of intense pain for a period of 15 minutes, increasing by 5 minutes biweekly up to 40 minutes, for 3 months. After 3 months, patients in the SEP group then completed 3 months of the HEP. **Monitoring:** None.	and QoL – 3 and 6 months.	both groups at 3 months, though the SEP group did have a significant improvement at 6 months. However, ICD was significantly greater for the SEP group compared to the HEP group at 3 months, though this difference was not apparent at 6 months. Both groups had significant improvements in MWD at 3 and 6 months and the changes were similar between groups. There were no significant changes in any QoL measures at 3 or 6 months in both groups.

6-MWD = six-minute walk distance, 6-MWT = six-minute walk test, ABPI = ankle/brachial pressure index, CLTI = critical limb threatening ischaemia, HEP = home-based exercise programme, IC = intermittent claudication, ICD = intermittent claudication distance, MWD = maximum walking distance, PAD = peripheral arterial disease, POMS = profile of mood states, QoL = quality of life, RCT = Randomised Controlled Trial, RPE = rating of perceived exertion., SEP = supervised exercise programme, SFA = superficial femoral artery, $\dot{V}O_{2Peak}$ = peak oxygen consumption,
VascuQoL = vascular quality of life tool, WIQ = walking impairment questionnaire

2.5.5 HEPs vs. SEPs - Meta-analysis

The meta-analysis for MWD including eight studies and 334 participants showed an overall improvement favouring SEPs (MD 139m, 95% CI 45 to 232m, *p* = .004, very-low-quality evidence; Figure 12). ICD also favoured SEPs including seven studies and 306 participants (MD 84m, 95% CI 25 to 143m, *p* = .005, very-low-quality evidence; Figure 13). However, these differences were no longer significant in the sub-group analyses of trials which included monitoring (moderate-quality evidence; Figures 12 and 13). 6-MWD was not significantly different between groups (very-low-quality evidence).

The SF-36 measures of pain (MD 7.8, 95% CI 2.6 to 13.0, *p* = .006, low-quality evidence) and social functioning (MD 5.6, 95% CI 1.2 to 10.0 *p* = .04, low-quality evidence) significantly favoured SEPs. The WIQ domain of distance also significantly favoured SEPs (MD 8.9, 95% CI 2.1 to 15.7 *p* = .01, very-low-quality evidence). The remaining QoL measures showed no significant mean difference between groups, which was also the case for daily steps (very-low to moderate-quality evidence).

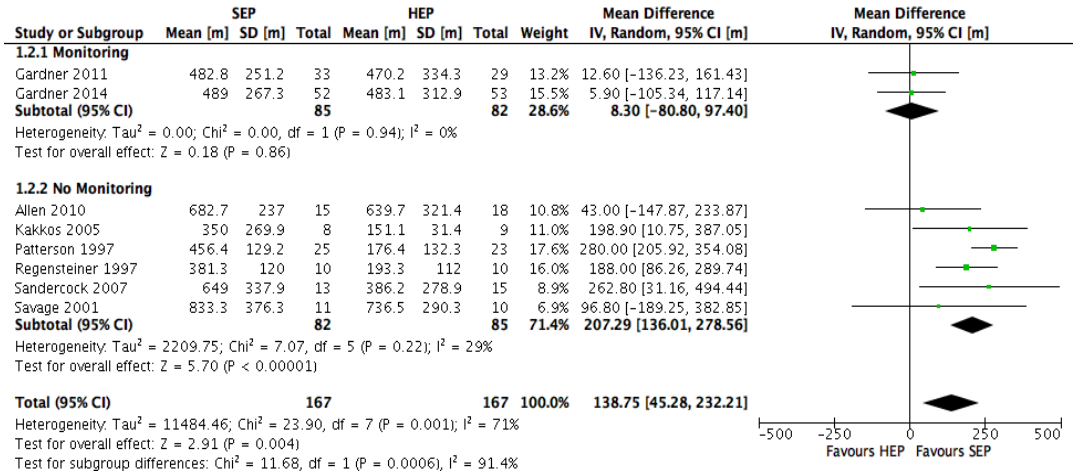


Figure 12 - Comparison 1 - HEPs vs. SEPs (including sub-group analysis) for maximum walking distance

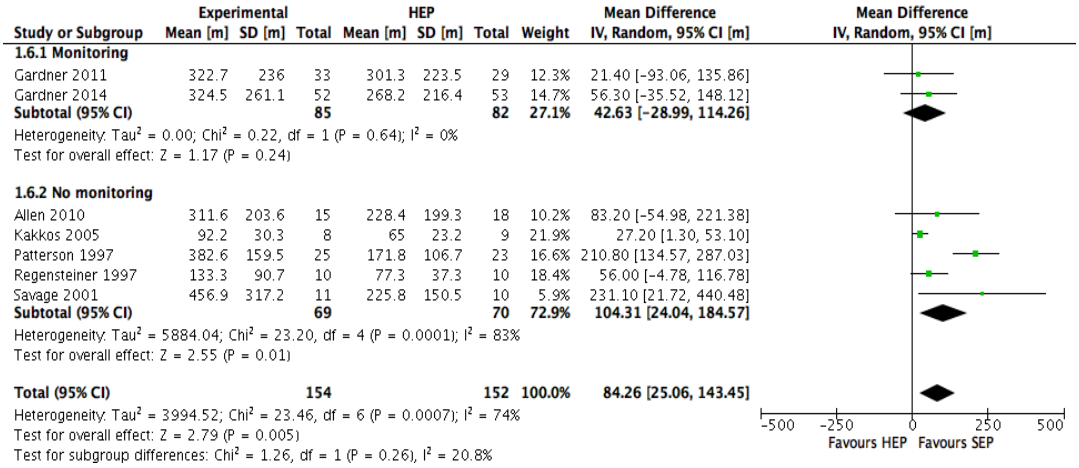


Figure 13 - Comparison 1 - HEPs vs. SEPs (including sub-group analysis) for intermittent claudication distance

2.5.6 Sensitivity Analysis

When using change scores, some outcomes were altered. The monitoring sub-groups for MWD and ICD now significantly favoured SEPs, albeit with a much smaller magnitude of effect, approximately half, of the overall effect (Figures 14 and 15). In addition, 6-MWD now significantly favoured HEPs (Figure 16) whilst the physical component summary of the SF-36 now significantly favoured SEPs (MD = 2.7; 95%CI; 0.2 – 5.1; *p* = .03).

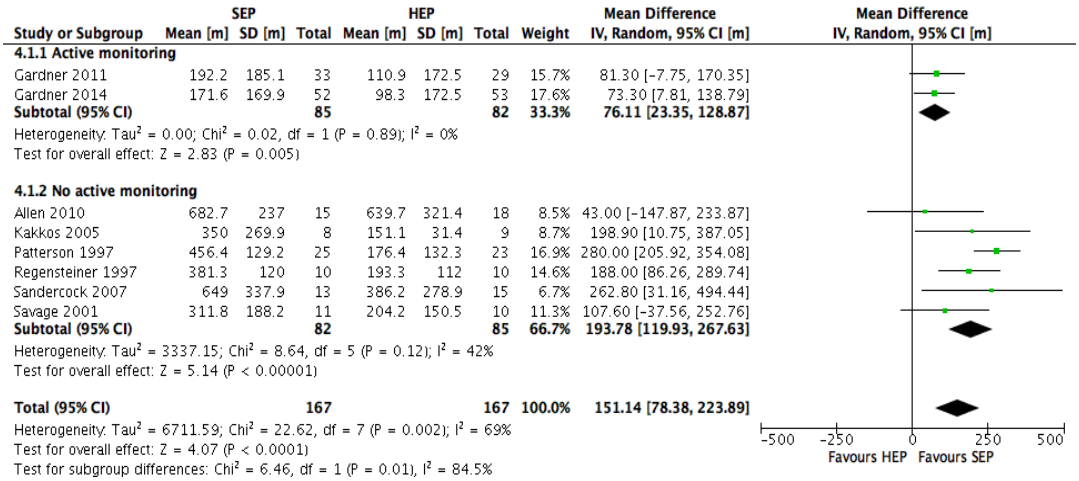


Figure 14 - Comparison 1 - HEPs vs. SEPs sensitivity analysis for maximum walking distance using change scores

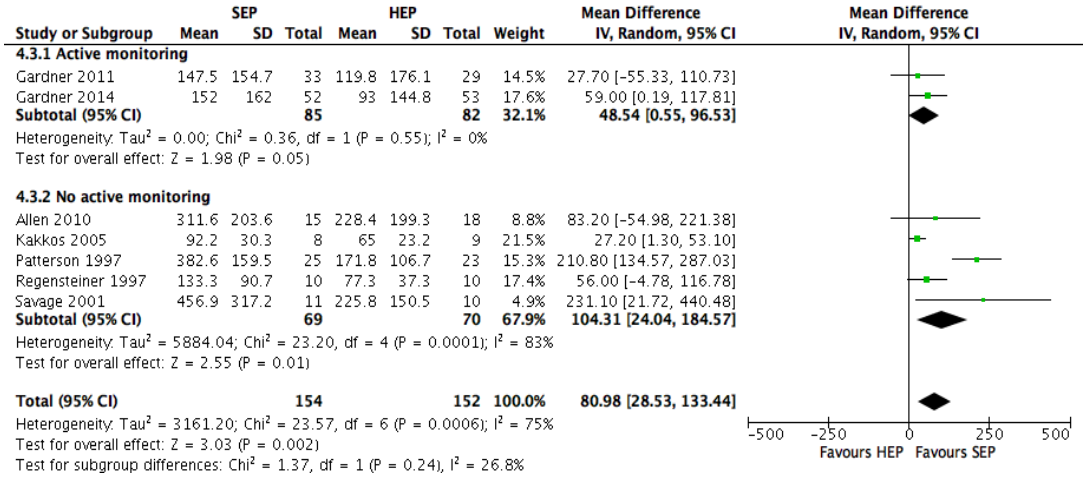


Figure 15 - Comparison 1 - HEPs vs. SEPs sensitivity analysis for intermittent claudication distance using change scores.

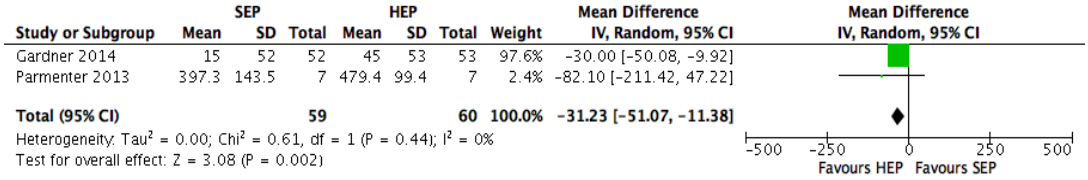


Figure 16 - Comparison 1 - HEPs vs. SEPs sensitivity analysis for six-minute walk distance using change scores

When sensitivity analyses were performed based on the risk of bias, for MWD the overall effect no longer significantly favoured SEPs when the two highest risk studies were simultaneously removed (Figure 17). The physical component summary of the SF-36 significantly favoured SEPs when one of the highest risk studies was removed, but not when the other two were individually removed. Similarly, the SF-36 domain of pain was no longer significant when one of the highest risk studies was removed, but when the other three studies were individually removed, it remained significant. Finally, the physical functioning domain of the SF-36 significantly favoured SEPs when the highest risk study was removed, whilst the WIQ distance score no longer significantly favoured SEPs when the highest risk study was removed.

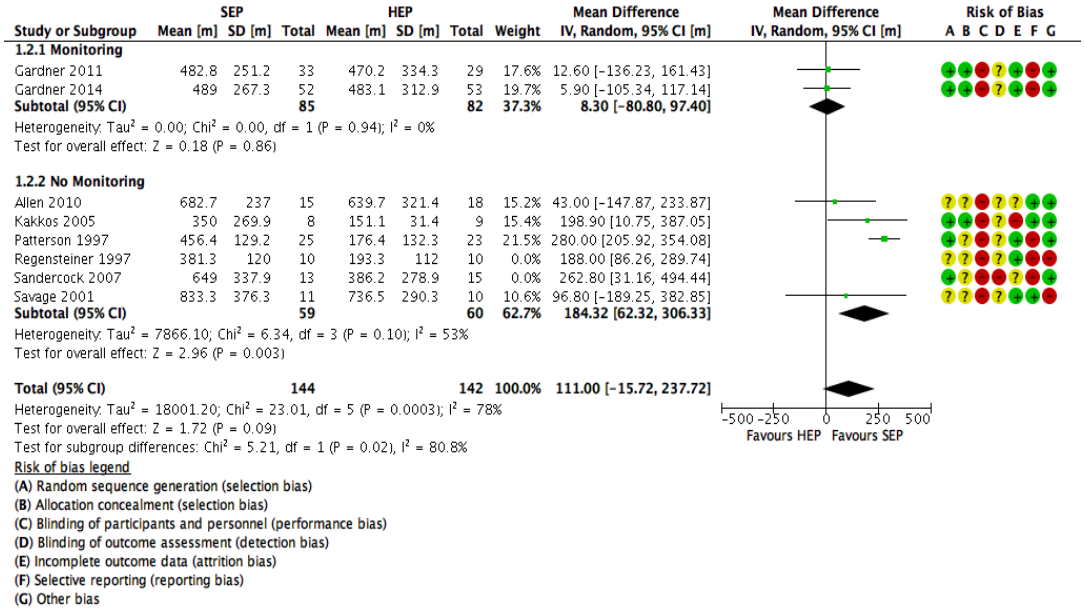


Figure 17 - Comparison 1 - HEPs vs SEPs sensitivity analysis for maximum walking distance based on risk of bias

2.5.7 HEPs vs. Basic Exercise Advice

Table 7 outlines the narrative findings of the five studies that compared HEPs with basic exercise advice (190, 192, 217, 218, 230). Three studies reported change from baseline with two noting significant improvements in MWD and ICD for the HEP group. Two studies, which included monitoring, also demonstrated significantly greater improvements in MWD for the HEP group compared to the basic exercise advice group.

For QoL outcomes, there were statistically significant improvements in the WIQ and the physical functioning domain of the SF-36, with the improvements in the WIQ being significantly greater than the basic exercise advice group in one study. For two studies that reported physical activity measures, there were significantly greater improvements in daily steps and cadence for the HEP groups compared to the basic exercise advice groups (192, 218).

Table 7 - Studies comparing home-based exercise programmes with basic exercise advice (n = 5).

Study (country, design)	Sample	Description of Interventions	Outcome Measure, follow-up	Main findings
Christman 2003 (217), (USA), RCT.	Total *n* = 38. Aged 40-75 with IC symptoms confirmed via ABPI. Those with CLTI, severe co-morbidities or those in the action or maintenance phase of the transtheoretical model were excluded.	**HEP:** Individualised programme with initial frequency and intensity based on physical ability, exercise history and access to an exercise location. However, prescription was based on walking towards a frequency/duration of 3 times per week for 30 minutes a session walking to near maximal pain for 3 months. **Monitoring:** Patients kept an exercise diary that was reviewed each week with the nurse investigator. **Basic exercise advice:** Admonition by their vascular physician to begin exercising and quit smoking with no additional follow- up. **Monitoring:** None.	ICD and MWD from a graded treadmill test – 3 and 6 months.	Significant improvements in ICD and MWD at 3 months in the HEP group that were not evident in the basic exercise advice group, though the difference between groups was not statistically significant. The improvement in ICD was maintained at 6 months but not for MWD (p = .07).
Cunningham., 2011 (218) (UK), RCT.	Total *n* = 58.	**HEP:** Individualised training plan based on the recommendation to walk for at least 30 minutes, 3 times	QoL via ICQ and WHOQOL, steps per day	There was a significantly greater improvement in the

	Newly diagnosed IC confirmed via symptoms and ABPI or imaging. Patients unable to give informed consent or with severe co-morbidities were excluded.	per week to near maximal pain for 4 months. **Monitoring:** Phone call at 6 and 12 weeks to discuss progress against the action plan, general QoL and perceived ICD. **Basic exercise advice:** Behaviour change advice, including advice to increase walking and an information sheet about PAD. **Monitoring:** phone call at 6 and 12 weeks to discuss general QoL and perceived ICD.	and perceived ICD – 4 months.	HEP vs. basic exercise advice group for steps per day, perceived ICD, and WHOQOL but not the ICQ.
Gardner, 2011 (192) (USA), RCT.	Total *n* = 119. IC secondary to PAD with ambulation during a treadmill test limited by leg pain consistent with IC and a positive ABPI. Patients with asymptomatic PAD, exercise tolerance limited by other factors	**HEP:** 3 months of intermittent walking to near maximal claudication pain 3 times per week. Duration progressively increased by 5 minutes biweekly from 20 to 45 minutes. **Monitoring:** Patients were monitored by a step activity monitor and logbook which were returned to staff at weeks 1, 2, 4, 6, 8, 10 and 12. During these 15-minute meetings, data were downloaded, results reviewed, and feedback provided for the upcoming month of training.	ICD and MWD from a graded treadmill test, QoL via WIQ and physical functioning of the SF-36 and physical activity – 3 months.	Significant improvement in ICD and MWD for the HEP group that were significantly greater than the basic exercise advice group. There were also significant improvements in all QoL measures in the HEP group, though these were not superior

	or significant comorbidities were excluded.	**Basic exercise advice:** Patients randomized to this group were encouraged to walk more on their own, but they did not receive specific recommendations about an exercise program during the study. **Monitoring:** None.		to basic exercise advice. There was also a significantly superior improvement in the HEP group for maximum 20-, 30- and 60-minute cadence and average cadence in strides/min.
Sandercock, 2007 (230) (UK), RCT.	Total *n* = 52. All patients were confirmed as having symptomatic IC during walking using the leg pain scale, confirmed via ABPI. Those unable to complete a familiarisation test or had significant co-morbidities were excluded.	**HEP:** 3 months of walking at an intensity of 12-14 on the RPE scale for 30 minutes, 3 times per week. **Monitoring:** HEP patients were given an exercise diary to complete and were contacted once weekly via telephone to give encouragement. **Basic exercise advice:** The basic exercise advice group were given verbal information regarding the safety and efficacy of walking exercise but no specific instructions regarding exercise duration, intensity or frequency. **Monitoring:** None.	MWD from a graded treadmill test – 6 weeks and 3 months.	No significant improvement in MWD at 6 weeks and 3 months in the HEP group in comparison to baseline or the basic exercise advice group.
Tew, 2015 (190) (UK), RCT.	Total *n* = 23. Aged >18 years with stable IC (>3 months).	**HEP:** Patients initially attended a workshop which involved a number of components including plotting	ICD and MWD from graded treadmill test,	A significantly greater improvement in MWD and 6-MWD for the HEP

	Patients with CLTI, previous or planned lower limb revascularisation or severe co-morbidities were excluded.	their steps/day scores (from baseline) and receiving a pedometer and walking diary. Patients then set their first action plan, based on a goal of daily step counts and were encouraged to gradually build up their total daily steps to >7500 and to perform at least 2500 of them as 'exercise steps' which is approximately 30 minutes of walking. During these steps patients should walk at a speed that evokes a strong claudication pain and persevere as long as tolerable. **Monitoring:** Participants were involved in setting their own short- and long-term walking goals based on their daily step count at baseline. Participants were encouraged to wear their pedometer on a daily basis and self-monitor their activity and intensity of claudication using the specifically designed exercise diary. 2 weeks after the initial workshop, patients were contacted via phone to review progress, discuss goal setting and barriers, with the aim of	6-MWD, daily steps and QoL via WIQ and ICQ score – 6 weeks.	group. There were also significantly greater improvements in the HEP group for WIQ domains of speed, distance and climbing, but not for ICD, daily steps and ICQ score.

		supporting maintenance of behaviour change. **Basic exercise advice:** Usual care included provision of a brief information leaflet on PAD which the authors confirmed included a section on the promotion of walking. **Monitoring:** None.		
6-MWD = six-minute walk distance, ABPI = ankle/brachial pressure index, HEP = home-based exercise programme, ICD = intermittent claudication distance, ICQ = intermittent claudication questionnaire, MWD = maximum walking distance, PAD = peripheral arterial disease, QoL = quality of life, RCT = Randomised Controlled Trial, RPE = rating of perceived exertion., SF-36 = Short-form 36 IC = intermittent claudication, TBPI = toe/brachial pressure index CLTI = critical limb threaning ischaemia, WHOQOL = world health organisation quality of life, WIQ = walking impairment questionnaire			

2.5.8 HEPs vs. Basic Exercise Advice - Meta-analysis

The meta-analysis for MWD including four studies and 137 participants showed no significant difference between groups (MD 39.0m, 95% CI -123.1 to 201.1m, *p* = .64, very-low-quality evidence; Figure 18). For the sub-group analysis, findings were not altered by studies adopting monitoring. However, monitoring appeared important as there was a trend (*p* = .05) for HEPs without it to be inferior to basic exercise advice (very-low-quality evidence, Figure 18). For ICD, including three studies and 109 participants, there was a significant between group difference, favouring HEPs (MD 64.5m, 95% CI 14.1 to 114.8m, *p* = .01, very-low-quality evidence; Figure 19). Two of the three studies in this analysis adopted monitoring, precluding sub-group analysis. There was also a significant between group difference for the ICQ, favouring HEPs (MD -16.2, 95% CI -24.5 to -7.9, *p* = <.01, low-quality-evidence). There was no significant mean difference for daily steps or the WIQ (very-low-quality evidence).

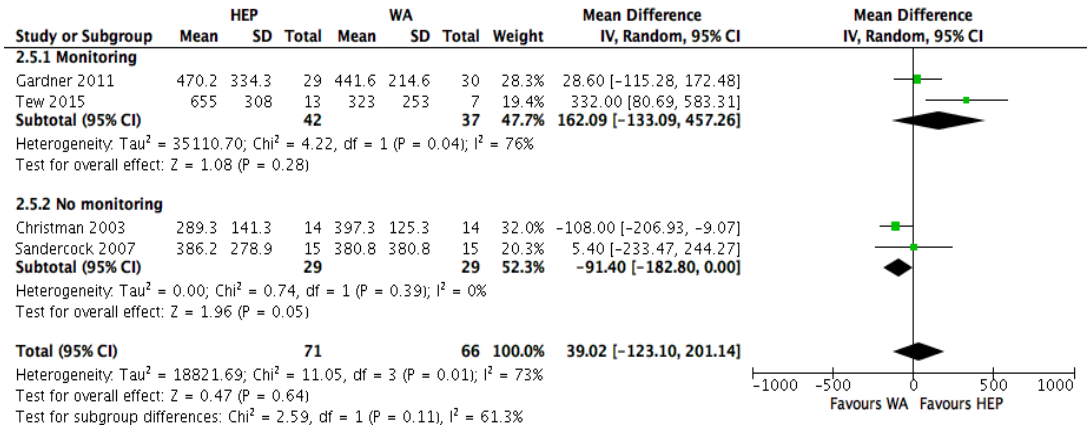


Figure 18 - Comparison 2 - HEPs vs. basic exercise advice (including sub-group analysis) for maximum walking distance

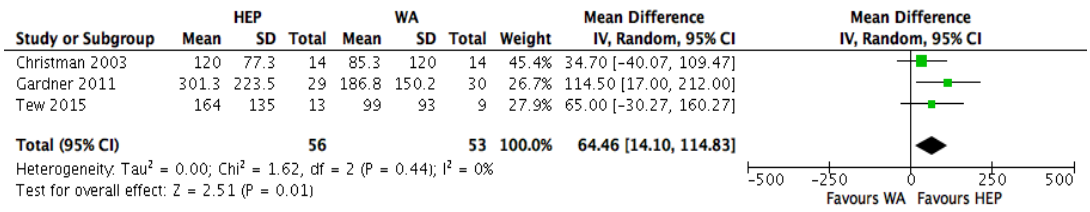


Figure 19 - Comparison 2 - HEPs vs. basic exercise advice for intermittent claudication distance

2.5.9 Sensitivity Analysis

When using change scores, no outcomes were altered other than MWD. The overall effect remained insignificant, but the active monitoring sub-group now significantly favoured HEPs (MD 126.0m, 95% CI 50.1 to 201.9m, *p* = .001; Figure 20).

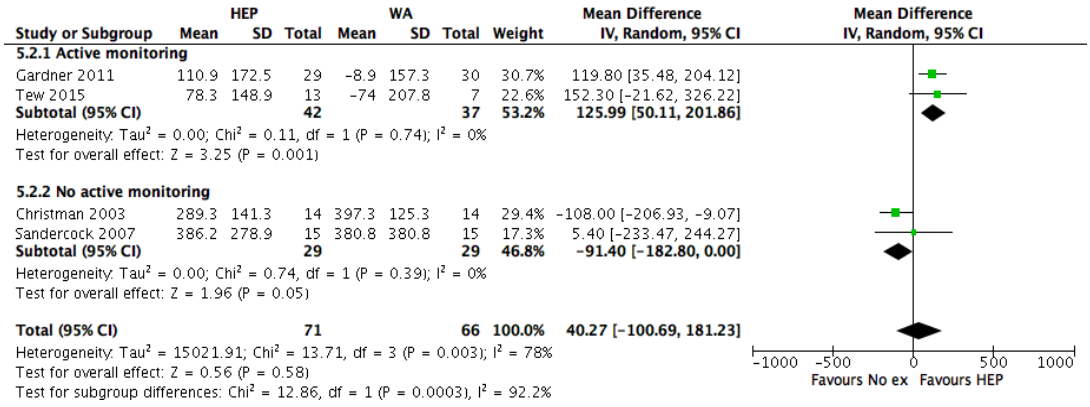


Figure 20 - Comparison 2 - HEPs vs basic exercise advice sensitivity analysis for maximum walking distance using change scores

When sensitivity analyses were performed based on the risk of bias, ICD remained significant when one of the two highest risk studies was removed but became insignificant when the other study was removed. Similarly, daily steps significantly favoured HEPs when one of the two highest risk studies was removed, but not when the other study was removed.

2.5.10 HEPs vs. No Exercise Controls

Table 8 outlines the narrative findings of all six studies that compared HEPs with no exercise controls (191, 215, 224, 226, 232, 233). Three studies provided statistical comparison and there were significant improvements in MWD and ICD for the HEP groups, which were generally, significantly greater than the control groups. Two studies provided statistical comparison for the 6-MWD with one demonstrating a significant improvement in the HEP group and the other showing no significant difference compared to baseline or control.

For QoL outcomes, there were improvements in the WIQ domains though these were not analysed statistically. The SF-12 and SF-36 outcomes were variable between studies.

Table 8 - Studies comparing home-based exercise programmes with no exercise control (n = 6)

Study (country, design)	Sample	Description of Interventions	Outcome Measure, follow-up	Main findings
Brenner, 2020 (215) (Canada), RCT.	Total *n* = 48. Stable PAD with symptoms of IC, confirmed via ABPI. Patients already in an exercise programme or with severe co-morbidities were excluded.	**HEP:** 3 months of walking 5 days per week, starting with 0.4 km per day, reaching 3.2 km by the final week. Walking was performed at a low intensity (≤40% heart rate reserve and an RPE of 11-13) up to the point of minimal claudication pain (2/10) i.e. a low-intensity, pain-free walking programme. **Monitoring:** Patients recorded heart rate, RPE, and pain score in their activity log. **Control:** Told to continue with their normal lifestyle. **Monitoring:** Patients recorded the amount, type and duration of activity in an activity log, along with heart rate.	MWD from a graded treadmill test – 3 months.	Significant increase in MWD for the HEP group, which was significantly greater than the control group.
Duscha, 2018 (191) (USA), RCT.	Total *n* = 20. All patients limited by IC confirmed via ABPI.	**HEP:** A 3-month personalised walking programme based on steps/day at baseline. During weeks 1-4 patients were told to increase their walking by 2500 steps/day over their baseline	ICD and MWD from a graded treadmill test and a number of physical	Significant increase in ICD and MWD for the HEP group, with a significantly greater increase in ICD but not

	Patients with CLTI, revascularisation <3 months ago or severe co-morbidities were excluded.	activity, by 3750 steps/day during weeks 5-8 and by 5000 steps/day during weeks 9-12. No mention of intensity. **Monitoring:** Patients wore a Fitbit activity tracker and data was downloaded weekly. If patients failed to sync their data, it looked suspicious or their step count fell below the prescription for 2 consecutive weeks, a phone call was initiated for resolution. In addition, if the prescribed step count was not attained at the end of any month, the subject was told not to increase their steps until the step goal was attained. If any patients reached 10000 steps per day, they were told to maintain this amount without further increase. Patients also received an electronic copy of a PAD book and weekly emails containing a PAD tip of the week coinciding with a chapter of the book. Patients were also given feedback and an opportunity to ask questions at monthly phone calls.	activity measures– 3 months.	MWD (p = .06) when compared to the control group. No significant improvements in any physical activity measures in either group.

		Control: No specific lifestyle info and encouraged to follow guidance given by their physician. **Monitoring:** None.		
Galea-Holmes 2018 (233) (UK), RCT.	Total *n* = 24. IC established by a vascular surgeon, confirmed via the San Diego Claudication Questionnaire. Patients who had CLTI or asymptomatic PAD, were scheduled for surgery within 4 months, were limited by other comorbidities or had contraindications to walking were excluded.	**HEP:** A personalised walking programme, adopting behaviour change techniques, based on the recommendations of 30 minutes of walking, ≥3 times per week, at a "brisk pace" to elicit pain within 3-5 minutes for 3 months. **Monitoring:** Patients received 2 individual 60-minute face-to-face sessions at weeks 1 and 2 and 2 20-minute booster phone calls at weeks 6 and 12. N.B – after 3 months, the aim was for patients to continue a programme of self-directed activity without 'supervision' (assumed to mean monitoring). **Control:** Targeted dietary behaviour based on the British Heart Foundation recommendations. **Monitoring:** Mirrored the treatment intervention but targeted dietary behaviour rather than walking.	6-MWD, daily steps and QoL via the SF-12 – 4 months.	Slight reduction in 6-MWD in the HEP group (-8.5m) versus a slight increase in the control group (+10m). There was an improvement in the mental component summary, and a decrease in the physical component summary of the SF-12 for the HEP group, whilst the opposite occurred in the control group. There was also an increase in daily steps in the HEP group, with a slight reduction in the control group. N.B – no statistical comparisons were made against baseline

				or between groups for any outcome.
Larsen 1966 (232) (Denmark), RCT.	Total *n* = 14 . Stable IC (≥6 months). Patients unwilling to exercise 1 hour per day or who had significant co-morbidities precluding normal physical activity were excluded.	**HEP:** 6 months of daily intermittent walking for 60 minutes whereby patients walked for as long as they could stand the claudication pain before resting. **Monitoring:** Via a pedometer and re-assessment every month. **Control:** Placebo tablets. **Monitoring:** None.	ICD and MWD from a constant load treadmill test that had an individualised gradient to induce IC within 2-3 minutes – 6 months.	Significant improvements for the HEP group in both ICD and MWD, and a slight reduction in both for the control group, though the between-group changes were not compared statistically.
McDermott, 2013 (224) (USA), RCT – 12 month follow-up reported in McDermott 2014 (225).	Total *n* = 194. All patients with PAD were included with a positive ABPI or report from a vascular laboratory demonstrating PAD. N.B – Authors provided data for those with IC only. Patients with CLTI, and those who had undergone	**HEP:** For the first 6 months, the HEP group met once weekly for a 90-minute session with other participants, during which 45 minutes involved a facilitator led discussion and 45 minutes walking around an indoor track. Participants were also told to engage in up to 50 minutes of intermittent walking, to severe pain, at least 5 days per week. After 6 months, the programme was exclusively home-based for a further 6 months.	MWD from graded treadmill test, 6-MWD, and QoL via WIQ and SF-12 physical and mental component summary – 6 and 12 months.	Greater improvements in MWD, 6-MWD and WIQ distance and speed score for the HEP group at 6 months. Similar improvements in the SF-12 physical summary scores between groups. Slightly greater improvements in the control group for the WIQ climbing score

	revascularisation <3 months ago or were expected to have revascularisation within the next 12 months, or those with severe co-morbidities were excluded.	**Monitoring:** For the first 6 months, patients visited the research centre weekly for the 90-minute session outlined above. Patients also completed a questionnaire listing walking goals for the week. They recorded the actual time spent walking each day during the week and this was reviewed by the facilitator who provided brief individualised feedback. After 6 months, participants were assisted with continued adherence to their HEP by telephone contact, which was weekly for the first 3 months, then monthly for the final 3 months. **Control:** Health education control condition. **Monitoring:** For the first 6 months the control group attended sessions with other PAD participants and lectures were provided on topics including managing hypertension, cancer screening, and vaccinations. For the final 6 months, telephone calls were provided at the same frequency as those in the HEP group. Education materials were mailed to participants		and the SF-12 mental component summary. N.B – no statistical comparisons were made against baseline or between groups for any outcome other than 6-MWD which showed a significant improvement vs. baseline for the HEP group but not compared to the control group (p = .06). At 12 months, there were greater improvements in 6-MWD, the WIQ speed and stair climbing score and the SF-12 physical component summary for the HEP group, but greater improvements for the control in the WIQ distance score, though

		and reviewed during these phone calls.		again these were not compared statistically.
McDermott, 2018 (226) (USA), RCT.	Total *n* = 200. All patients with PAD were included with a positive ABPI or report from a vascular laboratory demonstrating PAD. N.B – Authors provided data for those with IC only. Patients with CLTI, and those who had undergone revascularisation <3 months ago or were expected to have revascularisation within the next 9 months, or those with severe co-morbidities were excluded.	**HEP:** During the first month of the intervention, participants were asked to attend 4 weekly sessions with the coach (weeks 1 and 2) or with other participants and the coach (weeks 3 and 4). During these sessions, participants walked for exercise and were assisted in setting goals for walking exercise and shown how to enter their walking exercise activity on the study website. After this, patients were given an individualised programme that typically involved intermittent walking, to severe pain, 5 days per week, starting at 10-15 minutes progressing to 50 minutes a session for 9 months. **Monitoring:** Patients wore a Fitbit monitor and data was uploaded to the study website and was visible to the coach. After the first month of onsite sessions, the coach called patients weekly during months 1 and 2, biweekly from months 3-5 and monthly from months 5-9. Telephone	6-MWT, QoL via WIQ and physical and mental component summary from SF-36 – 9 months.	A small improvement in the 6-MWD for the HEP group at 9 months, with a greater improvement in the control group. There were greater improvements in the WIQ distance, speed, and climbing scores for the HEP group. There were similar improvements in the physical component summary between groups, with a reduction in mental component summary in the HEP group. N.B – no statistical comparisons were made against baseline or between groups for any outcome other than 6-MWD which

		calls were structured and included discussion of progress towards exercise goals, review of the wearable activity monitor data, challenges encountered, strategies to overcome challenges, setting of new walking exercise goals, and a summary of the telephone call content. Twice per month, group telephone calls for intervention participants were led by the coach and included a topic of the month such as managing pain during exercise and exercising in cold weather. Participants were encouraged to share their successes and challenges with other participants. **Control:** No study intervention. **Monitoring:** Monthly phone calls to obtain information on adverse events, and exercise information was collected every 3 months.		was not significantly different from baseline or between groups.
6-MWD = six-minute walk distance, ABPI = ankle/brachial pressure index, CLTI = critical limb threatening ischaemia, HEP = home-based exercise programme, ICD = intermittent claudication distance, MWD = maximum walking distance, PAD = peripheral arterial disease, QoL = quality of life, RCT = Randomised Controlled Trial, RPE = rating of perceived exertion, SF-12/36 = Short-form 12/36 IC = intermittent claudication, WIQ = walking impairment questionnaire				

Of the two studies that reported physical activity measures, only one provided statistical comparison and demonstrated no significant improvement in either group (190, 191). Of the three studies that adopted monitoring via an activity monitor or pedometer, two reported significant improvements in MWD for the HEP group and one of these also reported a greater improvement compared to the control group (191).

2.5.11 HEPs vs. No Exercise Controls - Meta-analysis

The meta-analysis for MWD including three studies and 100 participants, revealed a mean difference of 136m, favouring HEPs, though it was not significant (95% CI -2 to 273m, *p* = .05, very-low-quality evidence; Figure 21). There were insufficient studies to perform a meta-analysis of ICD or a sub-group analysis of MWD. There was no significant mean difference for daily steps, 6-MWD, the WIQ or the physical and mental component summaries of the SF-12/36 (moderate to very-low-quality evidence).

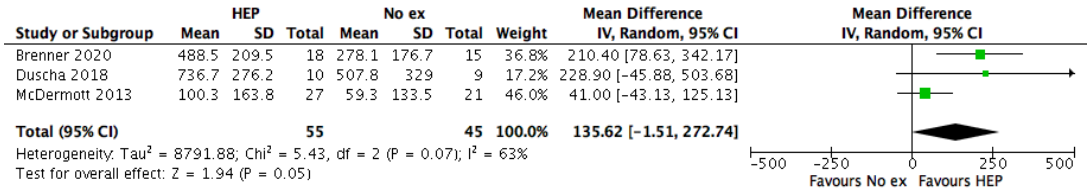


Figure 21 - Comparison 3 - HEPs vs. no exercise for maximum walking distance

2.5.12 Sensitivity Analysis

When using change scores, MWD now significantly favoured HEPs (Figure 22). When sensitivity analyses were performed based on the risk of bias, MWD remained insignificant when removing the two highest risk studies individually.

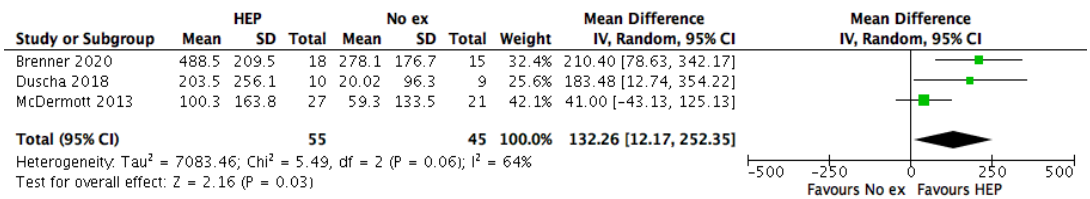


Figure 22 - Comparison 3 - HEPs vs no exercise sensitivity analysis for maximum walking distance using change scores

2.5.13 HEP Adherence

HEP adherence was poorly reported, stated in only seven studies (191-193, 215, 216, 218, 219) and it was assessed via self-reported methods in four of these (215, 216, 218, 219). Three studies were able to receive quantified adherence information via their remote monitoring methods (191-193).

Four studies reported an adherence of >80% (192, 193, 215, 218), and the lowest reported was 67%. One HEP, prescribed on the basis of step count, reported poor adherence to the prescribed steps, but did not report adherence to the prescribed frequency of exercise (191).

2.6 Discussion

The aim of this systematic review and meta-analysis was to provide an up-to-date comprehensive overview of the evidence base for HEPs versus SEPs, basic exercise advice and no exercise controls for patients with IC. Comparable to a recent review (208), the overall findings indicate that HEPs are inferior to SEPs for improvements in ICD and MWD. However, HEPs may be more effective than basic exercise advice, and certainly more so than no exercise at all, as noted in a previous review (170). One novel finding is that for all comparisons, monitoring appeared to be an important contributing factor to an effective HEP.

The apparent superiority of SEPs compared to HEPs, could be due to differences in the exercise dose between the two programme types, secondary to the heterogeneity evident within HEPs. SEPs are, within reason, clearly defined as structured exercise programmes with recommended FITT principles (17, 88, 169, 172). Whilst some heterogeneity remains within SEPs, they are increasingly similar (234). HEPs are much less established and suffer greater heterogeneity, meaning there is more variety in how they are utilised, especially with regards to the FITT principle. The resulting difference in exercise dose between the two regimens is particularly apparent when looking at individual studies included in this review. Three studies included SEPs that had (up to 40-minute) longer individual sessions than the HEP (214, 223, 228), whilst two SEP groups were also told to complete the HEP in conjunction with the SEP (220, 223), meaning they received at least one extra exercise session per week, compared to the HEP only group. Conversely,

three HEPs prescribed daily walking (219, 223, 227), up to a maximum of 3 times per day, versus a frequency of 2-3 times per week for the SEP group. This HEP prescription may be too intense and discourage engagement, especially given the reduced functional capacity evident in these patients (1). As such, heterogeneity may be greater for HEPs than it is for SEPs, especially with regards to dose, which contributes to their inferiority.

In addition, the terminology used to describe HEPs may also be contributing to their inferiority. HEP descriptions included 'exercise advice' or 'unsupervised exercise', which for patients can either be too vague, or even perceived as optional (in the case of exercise advice). This problem is compounded by recent guidelines which identify that home-based walking is a useful alternative to SEPs, but refer only to simple 'unsupervised' or 'non-supervised' exercise, without providing any specific recommendations (63). It is therefore important that patients are made aware that exercise therapy, including HEPs when appropriate, constitutes part of their treatment regime and should be adhered to. In addition, this exercise therapy should be provided in a way that is structured and multifaceted, rather than via simple advice.

However, our sub-group analyses provide novel findings and suggest that HEPs may not always be inferior to SEPs. Specifically, HEPs adopting remote or self-monitoring, via pedometers and / or activity monitors were equivalent to SEPs, or at least reduced their superiority by half for improvements in walking distance. Furthermore, the results also suggest that HEPs without monitoring may be inferior to basic exercise advice. One possible explanation for the apparent benefit of monitoring is that it can provide a form of remote supervision, with four of the seven monitoring studies having the facility to regularly feedback data to the study team (191-193, 226). For SEPs, it has been demonstrated that the intensity of supervision is associated with the level of improvement in walking distance (208). It would therefore be reasonable to assume that this remote supervision will be more effective than little or no supervision (or monitoring) at all. However, based on the findings of three studies in this review (192, 193, 226), for remote

monitoring to be most effective, and to add specificity to feedback, the device should only be worn during exercise sessions, rather than at all times during the day.

In addition to remote monitoring, self-monitoring, with the use of pedometers and exercise diaries, also appeared effective. This is not surprising given that pedometer use is associated with a reactive effect, with the greatest reactivity seen in those who are asked to record their daily step count in an activity diary (235). This process of recording daily step count may increase awareness of activity levels, leading to effective goal-setting and greater confidence for walking. Monitoring via exercise diaries without step-monitors or via telephone calls is ineffective. Clearly, given the variety of monitoring methods available, standardisation is required. However, we recommend a pedometer in conjunction with an exercise diary as the minimum.

In addition to monitoring, a number of other HEP components were identified in studies, which in isolation, appeared to provide similar benefits compared to SEPs (192, 193, 220, 231), or superior benefits compared to basic exercise advice or no exercise controls (190-192, 215). As such, we have created an example supported home-based exercise programme (SHEP), outlined in table 9. Our programme is structured and includes a detailed prescription based on the FITT principle, and incorporates support including regular feedback (ideally in real-time), goal setting and patient education with appropriate theoretical underpinning. These elements have demonstrated good patient adherence, have recently been highlighted as important from a PAD patient perspective (236) and provide a holistic, patient-centred approach.

Table 9 - Recommended supported home-based exercise programme components

Frequency:	At least ≥3 times per week, and ideally ≥5 times per week.
Intensity:	Walking to maximal claudication pain, or at least mild to moderate pain.
Time:	The overall exercise time should be gradual and personalised based on baseline capacity, starting at 15 minutes per session, increasing up to 60 minutes per session. Exercise can also be prescribed on the basis of daily step count, based on the baseline number of steps per day, with an eventual target of >7,500 steps per day, with 2,500 of these performed as exercise steps to maximal claudication pain. However, adherence to this type of prescription may be lower. The programme duration is of less importance as patients would ideally continue the programme indefinitely, but a duration of 6 weeks is recommended as the absolute minimum. Patients should however be evaluated every 3-6 months to ensure improvement is occurring.
Type:	Intermittent walking
Monitoring and other considerations	Remote and self-monitoring should take place via the use of pedometers, step activity monitors or technology that includes these components (i.e. smart phones). This monitoring is considered vital for an effective HEP. Other vital elements include; education about PAD, self-regulation and goal setting. Patients should be encouraged to make short- and long-term goals and create action plans to complete them. This process should be repeated for each subsequent goal and underpinned by a theoretical framework.

Only one study has combined these components into a deliverable structured HEP (190), though it was not an adequately powered RCT. As such, future, larger, longer-term studies that adopt this SHEP and provide it in a way that is accessible and pragmatic, such as via telehealth (alongside other monitoring), which has shown promise in other clinical populations (237, 238), are required. Such studies should report the intervention in full to aid replication in clinical practice (181). In addition, they should also report the clinical and cost-effectiveness along with the patient eligibility, recruitment, adherence and completion rates. This important information is required to build an appropriate evidence base for the effectiveness of a standardised, structured SHEP for patients with IC. It will also allow us to identify if such a SHEP is indeed an acceptable alternative to SEPs.

However, in the absence of such an evidence base, HEPs should currently only be considered when SEPs are unavailable or impractical. HEPs should also be considered in exceptional circumstances, such as during the COVID-19 pandemic, which has suspended SEP availability and practicality. Under these normal and exceptional circumstances, we recommend that a structured SHEP, based on the components outlined in table 9, is likely most effective, and should be provided to engage more patients in appropriate lifestyle and exercise behaviour change. Such a programme could also be used to aid continued engagement for those who do complete a SEP, as currently, there is limited provision of long-term exercise recommendations.

2.7 Limitations

This review and its findings are not without limitations. Firstly, a number of studies provided inadequate data to allow for entry into a meta-analysis, meaning the meta-analyses provided herein do not encompass the full evidence base. In addition, a number of outcomes that were suitable for meta-analysis were restricted by moderate to very-low-quality evidence, small sample sizes and a lack of robustness to sensitivity analyses, meaning their interpretation is limited. With regards to the risk of bias assessment, the widely adopted Cochrane tool was used. However, such a tool may not be directly applicable to lifestyle and exercise interventions, as it is not possible to blind participants and personnel delivering the

intervention to the treatment groups, as would be possible with drug trials for example. Other tools, such as the Physiotherapy Evidence Database (PEDro) scale, have been developed for rating the quality of trials including physical therapist interventions, but still include criteria for blinding of participants or personnel. As such, a tool specifically designed for interventions where blinding of participants and personnel is not possible is required. Finally, due to the limited number of studies included in each meta-analysis, publication bias could not be excluded via funnel plot.

2.8 Conclusion

Overall, HEPs still appear inferior to SEPs. However, with remote- and self-monitoring this inferiority is markedly reduced. Compared to basic exercise advice, HEPs generally provided a benefit, though this was not always significantly greater. However, HEPs did appear to demonstrate superiority compared to no exercise controls for improvements in MWD, though with very-low-quality evidence. As such, evidence for HEPs suggests they should only be recommended when SEPs are unavailable or impractical. When HEPs are appropriate, they should be structured and personalised, taking into account the specific FITT (and other) principles outlined in the recommendations above. Larger, longer-term studies combining all of these elements into one accessible, pragmatic SHEP, potentially via telehealth, should provide the future direction of HEP-based research for patients with IC.

Chapter 3: Study Two: High-Intensity Interval Training as an Exercise Intervention for Intermittent Claudication: A Systematic Review

3.1 Declaration

This study has been published in the Journal of Vascular Surgery (239), with Sean Pymer (SP) as first and corresponding author. SP contributed to the conception and design, analysis and interpretation, data collection, writing the article, critical revision of the article, final approval of the article, and has overall responsibility.

3.2 Introduction

A key participant barrier to SEPs is lack of time (187). HIIT is a more time-efficient alternative that has the potential to overcome this barrier and may even be preferred by patients (187). In addition, this time-efficiency may make it easier to implement for providers. As such, HIIT should be explored as an alternative to SEPs for patients with IC.

As noted in chapter one, a number of HIIT studies have been conducted in those with IC, but a comprehensive overview of the evidence is yet to be provided.

3.3 Aim

The aim of this study was to perform a systematic review to identify and synthesise the available evidence considering HIIT as an exercise intervention for patients with IC. This review aims to inform the design of future studies as well as those outlined in chapters four and five of this thesis.

3.4 Methods

A systematic review was performed in accordance with the PRISMA guidelines (240).

3.4.1 Search Strategy

The MEDLINE, Embase and CENTRAL databases were searched for full text articles published in the English language relating to adults (>18 years old). Searches were performed from database inception and were completed by February 2018. Titles and abstracts were independently screened for inclusion by two investigators (SP and Miss Joanne Palmer, JP), and any disagreement resolved by discussion with a third (Amy Elizabeth Harwood, AEH). Full texts of any potentially eligible articles were then independently screened against the inclusion criteria with reference lists

of these studies also hand searched for other relevant papers. Search terms included “Intermittent claudication” [OR] “Peripheral Arterial Disease” [AND] “High intensity interval training” [OR] “HIIT” [OR] “High intensity exercise”. When appropriate, all trees were exploded (full search given in appendix 3).

3.4.2 Inclusion Criteria

Both randomised and prospective non-randomised studies that investigated HIIT in patients diagnosed with IC (Fontaine II/Rutherford 1-3) were included. Studies that included patients with asymptomatic PAD were excluded. Similar to a recent systematic review in patients with CAD, HIIT was defined as an interval approach conducted at ≥85% peak HR or another surrogate measure (i.e. ≥80% maximal exercise capacity / $\dot{V}O_{2Peak}$ or a rating of perceived exertion ≥15) (194). There were no exclusion criteria based on programme duration, frequency, protocol (i.e. ratio between length of exercise and rest periods) or the use of a comparator arm.

3.4.3 Data Extraction

Data extraction was performed using a standardised form and inputted into Microsoft Excel (Microsoft, 2010, Redmond, WA, USA). The data extraction included information on study characteristics (to assess quality), sample size, inclusion/exclusion criteria, intervention components, outcome measures and main findings. The primary outcome measure was maximum walking distance or time (MWD/T), and secondary measures included intermittent claudication distance or time (ICD/T), QoL, $\dot{V}O_{2Peak}$ and recruitment and adherence rates. For key outcome measures, such as walking distance and $\dot{V}O_{2Peak}$ (where reported appropriately), mean difference (MD) and between group effect sizes (ES) were calculated and adjusted for small sample-sizes using Hedges bias-correction (241). These effect sizes were interpreted as small (≥0.20 - <0.50), moderate (≥0.50 - <0.80) and large (≥0.80) (242). Where necessary, study authors were contacted for more information to allow computation of ES.

3.4.4 Risk of Bias

Studies were independently assessed for risk of bias by two investigators (SP and JP) and disagreement was resolved by discussion with a third (AEH). We adopted the Cochrane Collaboration tool which consists of six domains, namely; selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias

(209). Each domain was rated as either high, unclear or low risk of bias. Study authors were contacted for more information when the risk of bias was deemed unclear.

3.4.5 Quality Assessment

Quality assessment was conducted using a modified version of the PEDro scale. The PEDro scale awards a score out of 10 based on different criteria such as allocation concealment and blinding (243). As supervision is considered a vital element of exercise programmes for IC (173), this was added as an extra quality criterion as with a previous review, leading to a total possible score of 11 (244).

3.5 Results

3.5.1 Search Results

The search yielded a total of 2,027 results after duplicates were removed. Nine articles (182, 183, 203, 204, 245-249), reporting eight studies, were ultimately included in this review as shown in Figure 23.

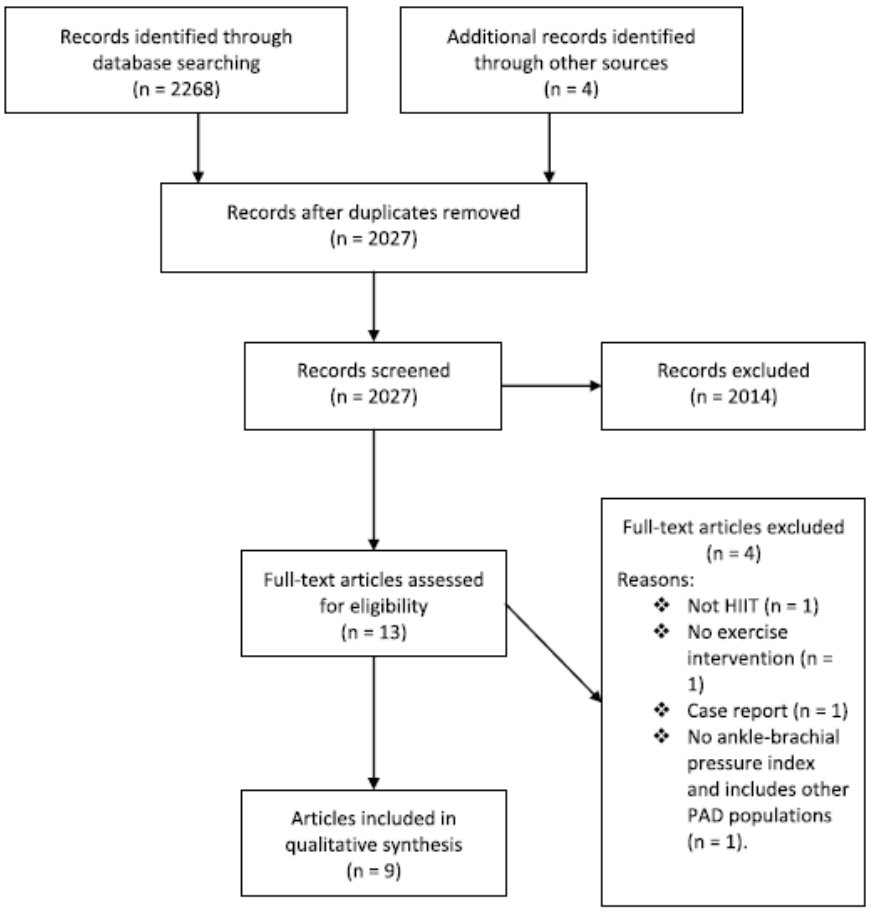


Figure 23 - PRISMA flow diagram

3.5.2 Included Trials

Included trials compared outcomes between HIIT and a low-intensity SEP or between HIIT and an “unsupervised” control group who were medically managed and given exercise advice without any supervised exercise intervention.

Two studies compared HIIT with low-intensity exercise (204, 247) and two included three arms and investigated two HIIT groups versus an unsupervised control group (183, 245, 246). Of the remaining studies, one included high-intensity resistance training versus low-intensity resistance training versus an unsupervised control group (182), and the other three compared HIIT to an unsupervised control group (203, 248, 249). Follow-up ranged from 6 to 72 weeks and an intention-to-treat analysis was used in only one study (183, 246). Studies are summarised in table 10 and a graphical summary of the results is presented in Figure 24)

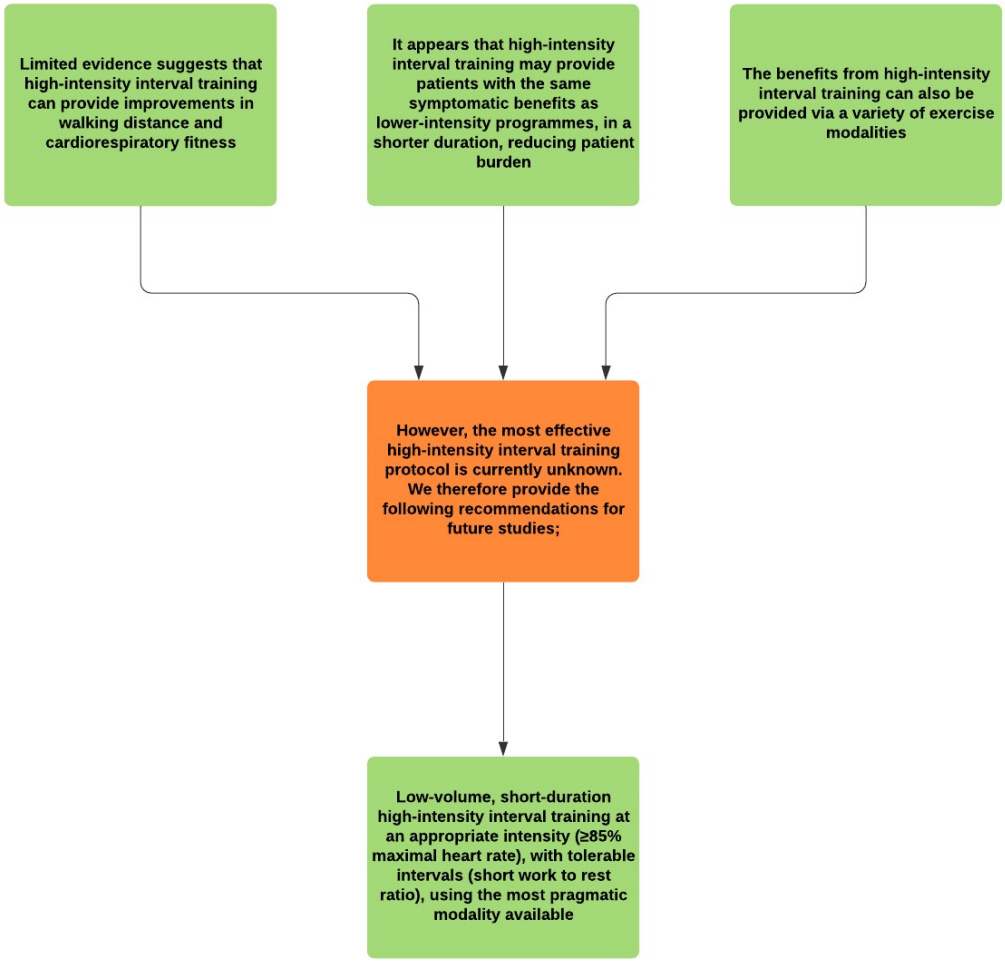


Figure 24 - Graphical summary of results

The total number of recruited patients within the studies was 350. HIIT programmes varied widely between studies and included treadmill walking (203, 204, 247, 248) upper limb or lower limb cycling (183, 245) plantar flexion (249) or resistance training (182). The frequencyand duration of the programmes also varied, and they were generally completed 2-3 times per week for 12 to 40 minutes per session, for a period of 6 weeks to 6 months. HIIT intensity also ranged from 80% to 100% of maximal workload achieved at baseline.

All but one study included walking distance as an outcome measure. However, reporting was not consistent with walking capacity reported in either meters or seconds. Walking capacity was also measured via various testing methods including a graded treadmill protocol (203, 204, 248, 249) the incremental shuttle walk test (183, 245) and the 6-MWT (182). The study that did not include walking measurements reported time-to-exhaustion from a treadmill test (247). However, the authors did not state whether exhaustion constituted maximal claudication pain, therefore this study was not included in the analysis of walking distances. $\dot{V}O_{2Peak}$ was included in six studies and was measured using a treadmill (203, 204, 247-249) or cycle ergometer (183, 245). Generic and disease-specific QoL was reported in three studies (204, 245, 246), using a combination of the SF-36 and the WIQ.

Table 10 - Summary of the included HIIT studies

Study (country, design, quality)	Sample	Description of Interventions	Outcome Measure, follow-up	Main findings
Zwierska, 2005 (183) (UK), Randomised trial, quality = 7/11. QoL and longer term follow-up reported by Saxton 2011 (246). Quality = 8/11. N.B. Difference in quality scores	Total *n* = 104. Stable IC (>12 months), with a clinical diagnosis of PAD confirmed by ABPI. Patients with CLTI, a revascularisation procedure in the last 12 months or severe co-morbidities were excluded.	**HIIT:** 24 weeks of prescribed upper or lower limb exercise performed twice per week for 40 minutes. Intervals were performed using a 2:2-minute work/rest ratio with the work intervals completed at 85-90% limb specific $\dot{V}O_{2Peak}$. Outcome measures were assessed at weeks 6, 12, 18 and 24 to allow for adjustments in exercise intensity – re-testing replaced the exercise sessions in that week.	ICD and MWD determined by ISWT, $\dot{V}O_{2Peak}$, SF-36 and WIQ - 24 weeks and 72 weeks.	24 weeks of upper and lower limb HIIT significantly improved ICD, MWD and $\dot{V}O_{2Peak}$ (all p= <0.01 vs. baseline and controls), whilst also significantly improving a number of QoL domains. Walking improvements were maintained at 72 weeks.

based on the methods reported in each article. HIIT vs. Control.		**Control:** Lifestyle advice including encouragement to undertake regular exercise.		
Walker, 2000 (245), (UK), Randomised trial, quality = 5/11. HIIT vs. Control.	Total *n* = 67. Stable IC (>12 months). Patients were excluded if they had undergone revascularisation in the last 12 months or had limiting angina, dyspnoea or arthritis.	**HIIT:** 6 weeks of prescribed upper or lower limb exercise performed twice per week for 40 minutes. Intervals were performed using a 2:2-minute work/rest ratio. Work intervals were completed at the penultimate load achieved at baseline (authors describe this as 'near to cardiac capacity') for the first 3 weeks and at maximal arm/leg power achieved at baseline for the final 3 weeks (i.e. 100% of aerobic capacity).	ICD and MWD determined by ISWT. QoL measured using the SF-36 – 6 weeks.	6 weeks of upper and lower limb HIIT significantly improved ICD MWD, and the physical functioning and role limitation-physical domains of the SF-36 (all *p* = <0.05 vs. baseline), with no changes seen in controls. N.B. the control group may not be comparable as patients were recruited 'ad-hoc' and not randomised. Therefore, it may comprise patients

		Control: An additional untrained group recruited on an ad-hoc basis in parallel to the main trial who were given lifestyle advice including encouragement to undertake regular exercise.		less motivated to undertake exercise.
Wood, 2006 (203), (Aus), Randomised trial, quality = 5/11. HIIT vs. Control.	Total *n* = 13. Stable PAD and IC (> 6months), Fontaine Stage II and an ABPI <0.9 or a maximum reduction in ankle systolic pressure exceeding 20mmHg after exercise. Patients who had uncontrolled co-morbidities, had undergone vascular surgery in the last 6 months, had a stroke or coronary event in the last 12 months or lived more than an hour	**HIIT:** 6 weeks of prescribed treadmill walking, performed 3 times per week for 40 minutes. Intervals were performed using a 2:2-minute work/rest ratio, with work completed at 80% $\dot{V}O_{2Peak}$ for the first 3 weeks and at 100% $\dot{V}O_{2Peak}$ for the final 3 weeks. **Control:** Sedentary control asked to continue their normal daily activities.	ICT, MWT and $\dot{V}O_{2Peak}$ measured by incremental treadmill test – 6 weeks.	6 weeks of treadmill HIIT significantly increased MWT (p = 0.009 vs. baseline), but the change was not significantly greater than the control group (MD = 220s, p = 0.059; BG-ES; 0.31). There were also non-significant trends for an increase in ICT (p = 0.066) and $\dot{V}O_{2Peak}$ (p = 0.069; MD = 150s, BG-ES = 0.60). No changes occurred in the control group.

	from the lab by car were excluded.			
Wang, 2008 (249), (Norway), Randomised trial, quality = 6/11. HIIT vs. Control.	Total *n* = 27. Unilateral or bilateral ABPI ≤0.90 and functional limitations from IC. None of the patients had undergone revascularisation in the last 6 months and were excluded if pain was not of vascular origin, if exercise tolerance was limited by other factors or if they were unable to perform treadmill test procedures.	**HIIT:** 8 weeks of prescribed plantar flexion exercise performed 3 times per week for 40 minutes. Work intervals were completed for 4 minutes on each leg at 80% maximum work rate and increased by increments of 1 Watt to maintain intensity (no time scale for these increments was mentioned). **Control:** Exercise advice in accordance with American Heart Association guidelines.	Plantar flexion power output, treadmill $\dot{V}O_{2Peak}$ and MWT – 8 weeks.	8 weeks of plantar flexion HIIT significantly improved plantar flexion power output (p = 0.003 vs. baseline, p = <0.05 vs. control, MD = 2.3W, BG-ES = 1.18), MWT (p = 0.009 vs. baseline, p = <0.05 vs. controls, MD = 173s, BG-ES = 0.53), and treadmill $\dot{V}O_{2Peak}$ (p = 0.002 vs. baseline, p = <0.05 vs. control, MD = 0.19L, BG-ES = 0.35).
Helgerud, 2009 (248), (Norway), non-randomised	Total *n* = 18. The training group were volunteer patients taken from a sample previously randomised to the training	**HIIT:** 8 weeks of prescribed plantar flexion exercise followed by 8 weeks of treadmill walking. The post-test score from the	Treadmill $\dot{V}O_{2Peak}$ and MWT – 8 weeks (i.e. 16 weeks total).	8 weeks of treadmill HIIT significantly improved treadmill $\dot{V}O_{2Peak}$ (MD = 0.22L, BG-ES = 0.43) and MWT in relation to a

trial, quality = 4/11. HIIT vs. Control.	group in the Wang (2008) study. Fontaine stage II PAD, a history of IC together with functional limitations from IC and a resting ABPI of ≤0.90; patients were excluded if they were aged >75 years, had undergone revascularisation in the last 6m, they could not perform treadmill/plantar flexion exercise or test procedures, exercise pain was not of vascular origin or their physical capacity was limited by factors other than IC.	plantar flexion programme acted as the baseline for the treadmill programme, which is reported here. 8 weeks of prescribed treadmill walking performed 3 times per week for 40 minutes. Intervals were performed 4 times and consisted of 4 minutes of walking at 90-95% HR_{Peak} interspersed with 3 minutes of walking at 60% HR_{Peak}. The target workload was achieved by adjusting treadmill grade. Training intensity was increased as patients 'became more fit'. **Control:** Exercise advice in accordance with American Heart Association guidelines. The control group was only followed		control group (MD = 200s, BG-ES = 0.60; both p = <0.05 vs. baseline and controls).

		for the initial 8 weeks, for the duration of the Wang (2008) study, and not for the duration of this study.		
Parmenter, 2013 (182), (Aus), Randomised trial, quality = 7/11. HIIT vs. low-intensity vs. control.	Total *n* = 22. Aged ≥50 with IC from PAD, as confirmed by a vascular surgeon. Exclusion criteria were; asymptomatic PAD, tissue necrosis or gangrene, significant cognitive impairment, inability to comply with study requirements, and / or current participation in regular moderate- to high-intensity exercise. Those with specific contraindications to progressive resistance training or who were awaiting vascular surgical intervention were also excluded.	**HIIT:** 24 weeks of prescribed resistance training, performed 3 times per week. The training consisted of 3 sets of 8 repetitions of weightlifting exercises for seven major muscle groups. Initial intensity was set at 50% 1RM and increased over 4 sessions to 80% 1RM. 1RM was retested biweekly and intensity was adjusted according to an RPE of 15-18 for each set. **LI:** Same as for the HIIT group but intensity was set at 20% 1RM and increased by 2% 1RM each session up to 30% 1RM. Once 30%	ICD and MWD from 6MWT – 24 weeks.	24 weeks of HIIT resistance training significantly improved MWD, and this was superior to the usual-care control (p = 0.009, MD = 69.8m, BG-ES = 0.74) and low-intensity groups (p = 0.002, MD = 68.7m, BG-ES = 0.53). There was a non-significant improvement in ICD (76.7%) in the HIIT group. The change was also not significantly different from the control or LI groups, despite large (MD = 121.9m, BG-ES = 1.32) and moderate (MD

		1RM was reached, this was maintained for the remainder of the trial. **Control:** Lifestyle advice with instructions to walk intermittently outside unsupervised for up to 30 minutes, 3 times per week. Exercise sessions were recorded in an exercise diary.		= 80.2m, BG-ES = 0.58) effect sizes respectively.
Slordahl, 2005 (247), (Norway), Randomised trial, quality = 4/11. HIIT vs. low-intensity.	Total *n* = 19. ABPI of ≤0.90, with IC limiting exercise capacity. Patients were excluded if they were unable to walk on a treadmill at 4 km/h or their walking capacity was limited by factors other than IC.	**HIIT:** 8 weeks of prescribed treadmill walking, performed 3 times per week for 40 minutes. Intervals were performed 8 times and consisted of 2 minutes of walking at 80% $\dot{V}O_{2Peak}$ (corresponding to 90%HR_{Peak}) interspersed with 3-minute rest periods. **LI:** 8 weeks of prescribed treadmill walking,	$\dot{V}O_{2Peak}$ and work economy – 8 weeks.	8 weeks of treadmill HIIT was more effective than LI treadmill exercise to improve $\dot{V}O_{2Peak}$ in IC patients (p = <0.05). Work economy improved by 14% in both groups.

		performed 3 times per week for 30 minutes. Walking was performed at 60% $\dot{V}O_{2Peak}$ (corresponding to 70%HR_{Peak}) and was done either continuously or intermittently with 5-minute breaks if walking was impeded by severe pain. Testing was repeated at weeks 2 and 4 for both groups and workload was adjusted as required.		
Gardner, 2005 (204), (USA), randomised trial, quality = 5/11. HIIT vs. low-intensity.	Total *n* = 77. Fontaine stage II PAD - History of IC, exercise tolerance limited by IC during the screening treadmill test, an ABPI <0.90 at rest and ability to live independently at home. Patients were excluded for absence of PAD, exercise	**HIIT:** 24 weeks of intermittent treadmill walking to near maximal claudication pain, performed 3 times per week starting at 12 minutes and progressing monthly to 17, 21, 26, 30 and 35 minutes to match the caloric expenditure of the LI group. Intensity was	ICD, MWD and $\dot{V}O_{2Peak}$ from graded treadmill test. Walking economy, 6MWT, WIQ, and SF-36 – 24 weeks.	24 weeks of high or low-intensity treadmill walking significantly improved ICD (BG-ES = 0.18 favours HIIT), MWD (BG-ES = 0.06 favours HIIT), 6MWT performance, walking economy, (all *p* = <0.01 vs. baseline), $\dot{V}O_{2Peak}$ (BG-ES = 0.05, favours LI), WIQ distance score, physical

	tolerance limited by factors other than IC (e.g., angina), active cancer, renal or liver disease, and current use of pentoxifylline or cilostazol for the treatment of IC.	set at 80% of the treadmill grade achieved during the baseline maximal effort treadmill test. **LI:** Same as for the HIIT group but the intensity was set at 40% and the duration started at 15 minutes and progressed by 5 minutes monthly up to 40 minutes. For both groups, there was no set interval - patients walked at 2 mph until their claudication pain reached a score of three out of four, after which they rested. This walk/rest pattern was continued until the prescribed number of minutes was completed.		functioning and bodily pain (all p=<0.05 vs. baseline). All changes were similar between groups (p = > 0.05).
1RM = 1 repetition maximum, 6MWT = 6-minute walk test, ABPI = ankle/brachial pressure index, BG-ES = between-group effect size, CLTI = critical limb threatening ischaemia, HIIT = high-intensity interval training, HRPeak = peak heart rate, IC = intermittent claudication, ICD = initial claudication distance, ICT = initial claudication time, ISWT = incremental shuttle walk test, LI = low-intensity, MWD = maximum				

walking distance, MWT = maximum walking time, PAD = peripheral arterial disease, QoL = quality of life, RPE = rating of perceived exertion, SF-36 = short-form 36, $\dot{V}O_{2Peak}$ = peak oxygen consumption, WIQ = walking impairment questionnaire

3.5.3 Quality Assessment and Risk of Bias

The risk of bias summary is shown in Figure 25 and study quality in table 11. The mean score on the PEDro scale was 5.67 ± 1.41. In all studies there was a lack of allocation concealment, limited blinding of outcome assessors and patients and / or limited use of an intention-to-treat analysis. Future studies would benefit from adopting bias reduction methods such as using a central allocation system and ensuring that outcome assessors are blinded to the allocated treatment groups. In addition, when these methods are adopted, it is imperative that they are appropriately reported. Due to the limited number of studies, no publication bias assessment was made.

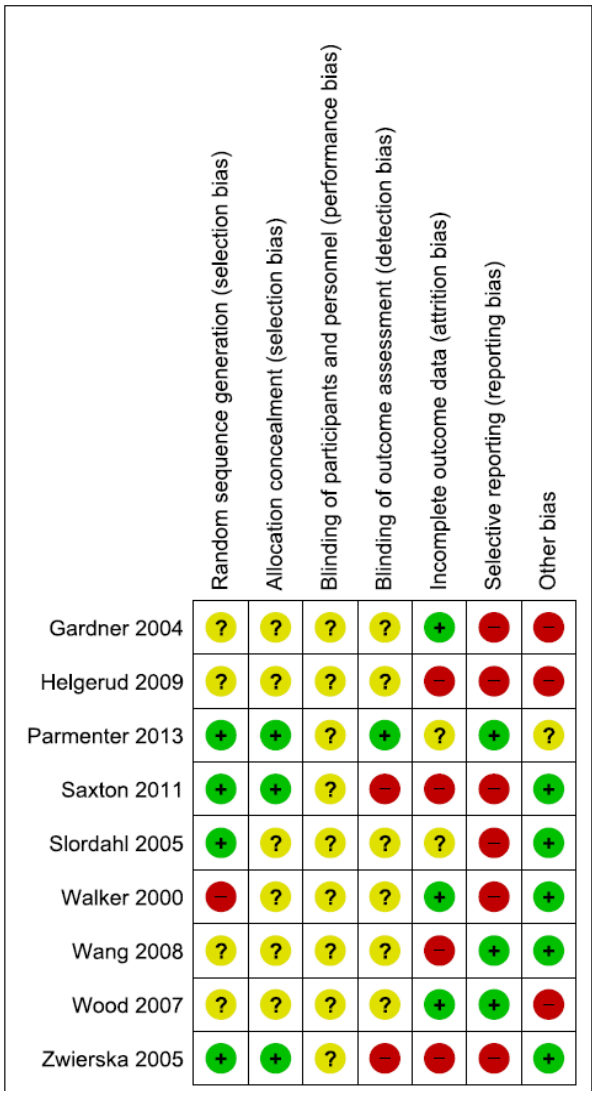


Figure 25 - Risk of bias summary

Table 11 - Quality assessment of included trials according to a modified PEDro scale

Trial	Author, Year[Ref]	Eligibility criteria specified	Random allocation	Concealed allocation	Baseline similarity	Blinding of all subjects	Blinding of therapists	Blinding of assessors	Measures of key outcomes >85% of initial subjects	Intention –to-treat analysis	Between group statistics	Point measures & measures of variability	Supervised all sessions	Final score [a] (/11)
1	Parmenter, 2013 (n=22) (182)	1	1	1	0	0	0	1	1	0	1	1	1	7
2	Helgerud, 2009 (n=21) (248)	1	0	0	0	0	0	0	1	0	1	1	1	4
3	Wood, 2006 (n=13) (203)	1	1	0	0	0	0	0	1	0	1	1	1	5
4	Gardner, 2005 (n=77) (204)	1	1	0	1	0	0	0	0	0	1	1	1	5
5	Wang, 2008 (n=27) (249)	1	1	0	1	0	0	0	1	0	1	1	1	6
6	Zwierska, 2005 (n=104) (183)	1	1	0	1	0	0	0	1	1	1	1	1	7
6	Saxton, 2011 (n=104) (246)	1	1	1	1	0	0	0	1	1	1	1	1	8
7	Walker, 2000 (n=67) (245)	1	1	0	1	0	0	0	1	0	0	1	1	5

8	Slørdahl, 2005 (n=19) (247)	1	1	0	0	0	0	0	0	0	1	1	1	4

Ref=Reference; 0=no; 1=yes

3.5.4 Clinical Outcomes

3.5.4.(a) Effect on Walking Distances

Three trials reported MWD in meters (182, 183, 245) and three trials reported MWT in seconds (203, 248, 249). The results showed that all modes of exercise significantly improved MWD/T. Two trials considering the effect of upper and lower limb HIIT on MWD reported significant improvements from baseline (both p = <0.05) (183, 245), with one of these studies reporting that the changes were significantly greater than controls (183). Two trials considering treadmill HIIT reported significant improvements in MWT (p = <0.05). The improvement reported by *Helgerud et al 2009* was significantly greater than the unsupervised control group, with a moderate ES (p = <0.05, MD = 200s, ES = 0.60) (248). *Wood et al 2006* reported a 45% improvement in MWT, but this did not reach statistical significance versus the unsupervised control group (p = 0.059, MD = 220s, ES = 0.31) (203). *Wang et al 2008* considered the effect of plantar flexion HIIT on MWT and reported a significant improvement versus baseline (p = 0.009), which was also significantly greater than controls (p = <0.05, MD = 173s, ES = 0.53) (249). Finally, *Parmenter et al 2013* considered the effect of a resistance-based HIIT programme on MWD and reported a significant improvement versus baseline (p = 0.05), which was also significantly greater than the control group (p = 0.009, MD = 69.8m, ES = 0.74) (182). Full detail in table 10.

Gardner et al 2005 considered the effect of a 6-month high or low-intensity treadmill programme on MWD and reported that both groups had significant improvements (p = <0.01), and that the change was similar between groups (p = >0.05; MD = 14m, ES = 0.06, favours high intensity; table 10) (204). *Parmenter et al 2013* also considered the effect of a high or low-intensity resistance-based programme on MWD (182), with the HIIT group demonstrating a significant improvement (p = 0.05). The lower intensity group however, had a reduction of -12%

(between group MD = 68.7m, ES = 0.53, difference in change between groups *p* = 0.002) (182).

Three trials reported ICD in meters (182, 183, 245), and one trial reported ICT in seconds (203). The results from two trials showed that both upper and lower limb HIIT significantly improved ICD (both *p* = <0.01) (183, 245), with one reporting that the change was significantly greater than an unsupervised control group. The remaining study reporting ICD demonstrated a non-significant increase following resistance-based HIIT (182). For the study reporting ICT following treadmill based HIIT, there was a non-significant improvement (203). The two non-significant findings may have been affected by their small samples, as the effect sizes compared to the control group were large (MD = 121.9m, ES = 1.32) and moderate (MD = 150s, ES = 0.60) respectively.

Two trials also reported ICD for HIIT versus a low-intensity group (table 10) (182, 204). A 6-month resistance-based programme elicited a 77% improvement in the HIIT group and a 2% reduction in the low-intensity group. The improvement in the HIIT group was not significant, nor was it significantly greater than the low-intensity group. However, this may have been affected by the small sample as there was a moderate effect size (0.58, MD = 80.2) (182). Finally, a 6-month treadmill programme elicited significant improvements in both the HIIT and low-intensity groups (*p* = <0.01), with the magnitude of change being similar between groups (*p* = >0.05, MD = 24m, ES = 0.18, favouring high-intensity).

3.5.4.(b) Effect on Peak Oxygen Consumption

Four studies reported the effect of a HIIT programme on $\dot{V}O_{2Peak}$ versus a control group (table 10) (183, 203, 248, 249). A 6-month upper or lower limb cycling HIIT programme improved $\dot{V}O_{2Peak}$ compared to unsupervised controls (both *p* = <0.01), (183). An 8-week plantar flexion

HIIT programme resulted in a 12% increase in $\dot{V}O_{2Peak}$ (p = 0.002 versus baseline and <0.05 versus control, MD = 2.4 ml·kg^{-1}·min^{-1} ;ES = 0.54) in the training group (249). Two studies utilised a treadmill HIIT protocol with equivocal results. Six weeks of treadmill HIIT did not significantly improve $\dot{V}O_{2Peak}$ (p = 0.069, MD = 1 ml·kg^{-1}·min^{-1}, 0.18) (203), whereas 8 weeks of treadmill HIIT did (p = <0.05 versus baseline and controls, MD = 2.8 ml·kg^{-1}·min^{-1}, ES = 0.59) (248).

Two studies also reported the effect of HIIT or low-intensity exercise on $\dot{V}O_{2Peak}$ (table 10) (204, 247). An 8-week treadmill HIIT programme resulted in a significantly greater improvement in $\dot{V}O_{2Peak}$ compared to the low-intensity group (16% versus 9%, p = <0.05). In contrast, a 6-month programme induced significant changes in $\dot{V}O_{2Peak}$ for both groups (p = <0.05), and the between-group change was similar (p = >0.05, MD = 0.2 ml·kg^{-1}·min^{-1} ES = 0.05 favouring low-intensity).

3.5.4.(c) Effect on Quality of Life

Two studies of upper and lower limb cycling HIIT used the SF-36 questionnaire to assess QoL versus a control group (183, 245, 246). Following a 6-week programme, there were significant improvements in the physical functioning and role limitation physical domains (p = <0.05) for both exercise groups, with no changes occurring in the other six domains. There were also no changes in any domain for the control group (245). Following 24 weeks of training, there were significant mean differences between the upper limb cycling group and the control group for the vitality, general health, physical functioning, bodily pain and mental health domains (p = <0.05), with no differences in the other three domains (183, 246). Conversely, the lower limb cycling group only demonstrated a significant mean difference in relation to controls for the vitality and general health domains, with no differences in the other six domains. These significant mean differences were maintained at 72-week follow-up except for vitality in the lower limb group.

Zwierska et al 2005 also used the WIQ; with both exercise groups demonstrating significant improvements compared to the control group after 24 weeks in the domains of calf pain, walking speed and stair climbing. The upper limb group also demonstrated a significant improvement compared to controls in the domain of walking distance, which was not apparent in the lower limb group (183, 246). These improvements were not maintained at 72-week follow-up in the lower limb group, but were maintained for the stair climbing and walking distance domains in the upper limb group (246). Full detail in table 10.

3.5.5 Recruitment and Adherence

One study reported the number of patients screened to allow for calculation of the recruitment rate, which was approximately 20% (246). Completion rates were mostly in the region of 80-90%, with one study reporting a slightly lower rate of 70% and two reporting 100%. Adherence rates were also reported in the majority of studies and were generally >90%. One study reported rates that were slightly lower at 74-80% (204), whilst another study reported that the participants in the exercise group completed all planned training sessions (249).

3.5.6 Effect of Programme Duration and Modality

The HIIT programmes varied in duration between trials and provided differing levels of improvement.

Two 6-week programmes elicited improvements of between 61-122% and 32-50% in ICD/T and MWD/T respectively (203, 245). Two 8-week programmes reported improvements of ~15% in MWT but did not report ICT (248, 249). The remaining trials adopted 6-month programmes and elicited improvements of between 51-109% and 19-63% in ICD/T and MWD/T respectively (182, 183, 204).

Benefits were also obtainable from a number of modalities with improvements in ICD/T and MWD/T ranging from 57-93% and 31-50% following lower limb cycling respectively; from 51-122% and 29-47% following upper limb cycling respectively and from 61-109% and 15-63% following treadmill walking, respectively. Resistance training also

provided a 77% improvement in ICD and a 19% improvement in MWD. Finally, plantar flexion HIIT provided a 16% improvement in MWT.

3.6 Discussion

Recent evidence supports the effectiveness of HIIT in a number of clinical populations (196-199). This review aimed to appraise the evidence base for HIIT as a treatment option for patients with IC and provide standards for future HIIT studies in this population. Although the evidence base was limited, these results show that HIIT can improve a number of important outcomes for patients with IC including walking distance, $\dot{V}O_{2Peak}$ and QoL.

3.6.1 Improvements in Walking Distances

All studies that compared HIIT to a control group demonstrated significant improvements in MWD/T (182, 183, 203, 245, 248, 249), with changes occurring in as little as 6 weeks (203, 245). In addition, the majority of studies demonstrated significantly greater improvements than the control group, with moderate between-group effect sizes (182, 248, 249). Only two studies considered HIIT versus a low-intensity exercise group, however, one adopted a resistance-based programme, which is not routinely used for SEPs in the IC population (182). The other study compared a 6 month high versus low-intensity walking programme, similar to that adopted in most SEPs, with both groups demonstrating similar improvements in walking distances (204).

These results perhaps demonstrate that although low-intensity programmes do elicit comparable changes in walking distance, the 6-month duration of the programme suggests this may be gradual and takes longer than a high-intensity course of exercise, which elicited improvements in just 6 weeks (203, 204). However, no trial has compared a shorter term HIIT programme to a shorter term low-intensity programme.

A key benefit of HIIT, as these results demonstrate, is that it may be more time efficient, thus benefitting both patients (reducing the

burden of attending sessions) and providers (cost reduction). The findings of this review suggest that HIIT can provide the same symptomatic benefit in half the amount of time currently recommended for SEPs (203).

3.6.2 Peak Oxygen Uptake

$\dot{V}O_{2Peak}$ is considered to be the gold standard measure of CRF (250), and is a strong independent predictor of all-cause mortality (251, 252). The results suggest that a HIIT programme can elicit significant improvements in $\dot{V}O_{2Peak}$ that are also superior in comparison to controls (183, 248, 249). One study however, did not reach statistical significance for the improvement in $\dot{V}O_{2Peak}$ with a mean difference of 1 $ml \cdot kg^{-1} \cdot min^{-1}$ (203). Although this mean difference appears small, it may still be clinically meaningful. In a cohort study of cardiac patients undergoing CR, each 1 $ml \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_{2Peak}$ was associated with a ~15% decrease in all-cause mortality (149). As such, this relatively modest mean difference in $\dot{V}O_{2Peak}$ improvement may still provide a protective mortality effect for the HIIT group.

The studies that considered changes in $\dot{V}O_{2Peak}$ for HIIT versus low-intensity groups provided conflicting results (204, 247). A short-term 8-week HIIT programme resulted in significantly greater improvements in $\dot{V}O_{2Peak}$ compared to a low-intensity programme (247). Conversely, a longer, 6-month programme, led to significant but similar benefits in both the HIIT and low-intensity groups (204). As previously mentioned, the similar benefits obtained across both groups may have been obscured by the longer duration of the exercise programme. This leads us to believe that improvements in the HIIT group may have occurred much sooner, but these were masked by the longer programme duration. In addition, the lower intensity group were also required to complete a longer duration of 3-5 minutes per session, translating to an extra 9-15 minutes per week and 4.6 hours over the course of the

programme. This added exercise time in the low-intensity group may have also contributed to these similar increases in $\dot{V}O_{2Peak}$.

A recent meta-analysis in patients with CAD demonstrated that HIIT significantly improved $\dot{V}O_{2Peak}$, with benefits being obtained in as little as 4 weeks (196). Furthermore, a recent study considered an 8-week intervention of two low-volume HIIT protocols (<30 minutes per week) versus a MICT protocol (76 minutes per week) for previously sedentary individuals (200). The results showed that although all three groups demonstrated improvements in $\dot{V}O_{2Peak}$, the HIIT protocols induced a 4-11% greater improvement, required 60% less time commitment and had a substantially lower drop-out rate compared to the MICT group (200). Similarly, in the study of *Slørdahl et al 2005*, included in this review, the HIIT group demonstrated a significant improvement in $\dot{V}O_{2Peak}$ with an exercise time of just 16 minutes per 40-minute session, and a programme duration of just 8 weeks (247). These studies suggest that low-volume, short-duration HIIT protocols may be beneficial to induce improvements in $\dot{V}O_{2Peak}$. This needs to be evidenced in patients with PAD using randomised trials that consider low-volume, short-duration HIIT programmes versus usual-care exercise programmes.

3.6.3 Quality of Life

There was limited consideration of QoL amongst the included studies and it was reported in just three. A 6-week upper or lower limb HIIT programme elicited significant improvements in two domains of the SF-36 (245), whereas a longer, 24-week programme elicited a greater improvement in relation to controls in most of the SF-36 and WIQ domains (183, 246). Although this may suggest that longer HIIT programmes are more beneficial for improvements in QoL, a 6-month treadmill programme elicited more modest improvements, with significant changes only occurring in two SF-36 domains and one WIQ domain (204). These equivocal results suggest that more research into the effects of HIIT on QoL would be beneficial for determining the true

benefits of this exercise method. QoL should be included as an outcome measure in all future studies considering both HIIT and usual-care SEPs for the treatment of IC, as a recent Cochrane review of exercise for IC noted that QoL was only reported in two of the 32 included studies (234).

3.6.4 Recruitment and Adherence

Only one study reported their recruitment rate, which was slightly lower than previously reported for SEPs (185, 246). However, this may have been affected by the programme length of 6 months, which is twice the length recommended in UK guidelines (17).

It is important that future trials report the number of patients that were screened, to allow for calculation of recruitment rates. Such reporting is also recommended as part of the CONSORT flow diagram (253).

Completion rates were generally higher than those previously reported for SEPs (185), with two studies reporting 100% completion in their exercise groups. In addition, adherence to exercise sessions was reported in all but one study and was generally >90%. Only one study, which compared HIIT with low-intensity exercise, reported adherence rates lower than this (204). However, adherence was not significantly different between the two exercise groups (204).

It is also worth noting that the mean age of the patients initially recruited and subsequently randomised to the HIIT or comparator groups was similar to that previously reported for SEPs (234). It is therefore unlikely that HIIT recruitment and adherence is influenced by age, nor is it preferred by a younger patient group.

Therefore, considering these completion and adherence rates, that are at least comparable to SEPs, it appears that HIIT is well tolerated and acceptable in this population.

3.6.5 Future Directions

Although the results suggest that HIIT may provide improvements in walking distances, $\dot{V}O_{2Peak}$ and QoL, five of the eight included studies compared HIIT with either unsupervised exercise advice or a sedentary control group, whilst all of the HIIT groups were supervised. Given that SEPs are recommended as first-line treatment in the UK and that the intensity of supervision is related to improvements in walking distance, these groups may not provide a valid comparator (17, 208). Considering the overwhelming evidence for SEPs it may be unsurprising that supervised HIIT was more beneficial than these comparator groups, suggesting that any supervised exercise is better than none at all.

There was also a lack of standardisation with regards to the HIIT protocols, with varying modalities, intervals and intensities used, though this is also the case for usual SEPs despite the substantial evidence base (171, 181). The results suggest that benefits between different HIIT modalities are comparable, which is congruent with SEPs (184). The results also suggest that low-volume, short-duration HIIT can provide comparable benefits to longer-term protocols, but the most effective protocol is currently unknown. We therefore recommend that future studies use the most pragmatic modality available and adopt low-volume, short-duration HIIT at an appropriate intensity (i.e., ≥85% peak HR) with tolerable intervals (i.e., short work-to-rest ratio). Initially, feasibility studies are required to identify if low-volume, short-duration protocols such as this, are indeed suitable for patients with IC. If feasible, HIIT should then be compared to an appropriate control group (i.e., usual SEPs), to identify whether it can accrue similar or superior benefits and is indeed more time efficient. Although this future evidence may show that low-volume, short-duration HIIT is more time-efficient, it is important to recognise that it will still require a significant time commitment for patients. However, it is much less burdensome than current SEPs and is therefore likely to be more attractive to patients, healthcare professionals, employers and insurance providers.

Within the literature, there is also a lack of long-term follow-up data for patients with IC undergoing any form of exercise. We therefore recommend that future exercise trials in the IC population include a longer-term follow-up (i.e., 1 and 5 years).

3.7 Limitations

This review has a number of limitations which limit the conclusions that can be drawn from it. Firstly, most studies had an unclear risk of bias for a number of domains and also included small sample sizes, with one study recruiting only 13 patients. There was also considerable heterogeneity between studies, with outcome measures differing, especially with regards to walking distance, which was recorded using both over ground and treadmill walking tests and reported using both MWD and MWT. There is a need within the literature for a standardised protocol for testing and reporting walking distance in patients with IC to allow for more comparable results. In addition, the intervention protocols differed vastly between studies, in terms of the frequency, intensity, duration and type of exercise that was undertaken, making it difficult to implement a HIIT exercise programme in a real-world setting based upon findings from the current literature. Finally, as noted in the previous study, the PEDro and Cochrane tools, when applied to the types of interventions included in this review, have drawbacks. However, in the absence of more appropriate tools, their application here is justified.

3.8 Conclusion

On the basis of the evidence in this review, HIIT cannot yet be incorporated into exercise management protocols for IC and it is recommended that where possible, usual SEPs continue to be provided. However, this review provides initial evidence to suggest that HIIT can elicit improvements in walking distances and $\dot{V}O_{2Peak}$ whilst also potentially improving QoL in patients with IC. In addition, the completion and adherence rates suggest that HIIT is tolerable and

acceptable in this population. HIIT may also provide the same symptomatic benefit to patients in a shorter duration, limiting the burden for both the patient and the provider. The results also suggest that these benefits are obtainable across a variety of different exercise modalities.

Currently, however, there is insufficient evidence available to draw robust conclusions on the role of HIIT for patients with IC due to the heterogeneity of the interventions and small sample sizes of the included studies. Furthermore, this heterogeneity, in conjunction with the lack of screening and eligibility information, also makes it difficult to establish if any of these interventions are appropriate (i.e. feasible) for these patients. Therefore, initial feasibility work is required to identify if HIIT, designed based on our aforementioned recommendations (i.e. low volume, short duration), is suitable for patients with IC. If so, pilot RCTs comparing HIIT to usual SEPs, including physical and QoL outcome measures, with longer-term follow-up are required. This will then allow for full scale RCT's to be appropriately designed and adequately powered to further explore the potential benefits of HIIT in the IC population.

Chapter 4: Study Three: A Prospective Observational Cohort Study Considering the Feasibility, Tolerability and Safety of High Intensity Interval Training as a Novel Treatment Therapy for Patients with Intermittent Claudication.

4.1 Declaration

The following two chapters outline two cohort studies performed as part of this thesis. Following study three, a small change in the exclusion criteria was made and additional feasibility work performed (outlined in study four).

After recruiting the first 10 patients to study four, we were successful in obtaining a National Institute for Health Research grant to perform this as a larger, multi-centre, proof-of-concept study – INITIATE (254). As such, each participant enrolled after this, was recruited as part of the INITIATE study, which is ongoing. Therefore, the 20 patients recruited in study three, and the first 10 patients recruited in study four were amalgamated and written up as a single paper, published in the Journal of Cardiopulmonary Rehabilitation and Prevention (255). The next 10 patients referred to in study four, are the first 10 recruits of the INITIATE study (254).

For the Journal of Cardiopulmonary Rehabilitation and Prevention publication SP contributed to the conception and design, analysis and interpretation, data collection, writing the article, critical revision of the article, final approval of the article, and has overall responsibility.

For the INITIATE study SP was a co-applicant on the grant application and contributed to the conception and design and is currently leading on data collection. He also wrote the published protocol (254).

4.2 Introduction

Study Two (a systematic review of HIIT for the management of IC) identified that the evidence for HIIT in those with IC is limited. It did however suggest that low-volume, short-duration HIIT has the potential

to provide symptomatic improvements and warrants further investigation, initially via feasibility studies.

4.3 Aim

Therefore, the aim of this study was to consider the feasibility, tolerability, safety and potential efficacy of a novel low-volume, short-duration HIIT programme for patients with IC.

4.4 Methods and Study Design

4.4.1 Design

This prospective, interventional, before-after cohort study was conducted at a single tertiary vascular centre in the UK. Approval was obtained via a local NHS research ethics committee (Bradford Leeds – 18/YH/0112) and all patients provided written informed consent prior to participation.

4.4.2 Participants

Patients who were deemed eligible for our usual-care SEP were referred to the study by their vascular consultant. These patients had a confirmed clinical diagnosis of IC which was confirmed via ABPI and / or radiological imaging. Those who appeared to meet the inclusion / exclusion criteria were sent an invite letter and a patient information sheet (PIS) outlining the details of the study. Patients were then contacted at least a week later by telephone so that they could ask any questions and decide whether or not to take part. Those who decided to take part were then asked to attend a baseline assessment at the vascular laboratory. During this baseline visit, the study was explained in full, outstanding questions were answered, eligibility for participation was confirmed and informed consent was obtained. The baseline assessment also included a CPET and any patient who demonstrated exercise induced myocardial ischaemia, manifesting as significant ECG changes, an abnormal blood pressure response and / or anginal symptoms, was excluded. In addition, as a maximal effort CPET is required for accurate and effective *conventional* HIIT prescription,

patients were also excluded if they were unable to achieve maximal effort test criteria (see table 12) (139, 256). As CPET is not performed as part of routine care, patients meeting the other inclusion / exclusion criteria were consented prior to undertaking the test, then excluded if the above occurred.

As noted previously, the use of ß-Blockers significantly blunts the maximal heart rate response, which is not considered within predictive equations, meaning that for patients taking such therapy, achievement of 85% of age-predicted maximum heart rate may not be possible (128). In this case, greater emphasis was placed on other criteria, namely RER, which is the most reliable, non-invasive indicator of patient effort (128).

4.4.2.(a) Inclusion Criteria:

- Community dwelling adults aged 18 or over
- ABPI of <0.9 at rest or a drop of more than 20mmHg after exercise testing
- Ability to walk unaided
- English speaking and able to comply with exercise instructions

4.4.2.(b) Exclusion Criteria:

- Patients unable to provide informed consent
- Critical limb ischaemia / rest pain
- Active cancer treatment
- Unstable angina and / or heart failure and / or diabetes mellitus
- New or Uncontrolled arrhythmias
- Resting / uncontrolled tachycardia (>100bpm) and / or resting / uncontrolled hypertension (systolic blood pressure >180mmHg or diastolic blood pressure >100mmHg)
- Symptomatic hypotension

- Significant comorbidities that preclude safe participation in exercise testing and/or training according to the American College of Sports Medicine (ACSM) guidelines (257).

4.4.2.(c) Additional Exclusion Criteria

Following analysis of the CPET results, patients were prevented from continuing their involvement in the study if there was an indication of:

- Exercise-induced myocardial ischaemia or significant haemodynamic compromise (manifesting as significant ECG changes and / or an abnormal blood pressure response and / or anginal symptoms)
- An inability to perform a maximal effort CPET

Table 12 - Adopted maximal effort criteria

A Plateau in $\dot{V}O_2$ (or failure to increase by 150 ml/min) with an increasing workload (NB. this is rarely observed in a patient population)
Achievement of >85% of age-predicted maximal heart rate
An RER ($\dot{V}O_2/\dot{V}CO_2$) at peak exercise ≥1.10
An RPE of >17 on the 6-20 Borg scale
RER = respiratory exchange ratio, RPE = rating of perceived exertion, $\dot{V}CO_2$ = carbon dioxide production, $\dot{V}O_2$ = oxygen uptake. N.B. Maximal effort was confirmed if at least two of these criteria were achieved.

4.4.3 Outcomes

The primary outcomes of this study were feasibility, tolerability and safety. These primary outcomes were selected as the feasibility stage is vital when developing and testing an intervention, to identify problems with acceptability, compliance, delivery, recruitment and retention that can be addressed prior to larger-scale evaluation (206).
The secondary outcome was potential efficacy.

4.4.3.(a) Feasibility Measurement

Feasibility was measured by considering the eligibility (eligible / screened), recruitment (recruited / eligible) and completion (completed

/ recruited) rates. Therefore, a screening log was maintained detailing all patients who were referred to the study, whether they were eligible and invited to participate, and whether they accepted or declined (with reasons where freely given). This log also included details of patients who completed, withdrew or were excluded after signing informed consent.

4.4.3.(b) Tolerability Measurement

Tolerability considered reasons for patient withdrawal and whether they were related to the intervention. It also involved identifying if patients were able to reach and maintain the required intensity (as outlined below), for the duration of each session.

4.4.3.(c) Safety Measurement

Safety measurement involved considering adverse (AE) and serious adverse events (SAE) that were related to the intervention or study procedures. In accordance with the good clinical practice decision tree for AE reporting, an event was initially classified based on severity (i.e., either an AE or SAE). Next, it was ascertained whether the event was related to the study. If not, it was simply classified as an AE or SAE. If the event was directly or possibly related to the study, it was classified as a related or serious related event. For serious related events, it was identified whether the event was expected for the study. If so, it was finally classified as a serious related event. If it was not consistent with what was expected, it was classified as an unexpected serious related event. All AE's that were related to the study and unexpected were reported to the sponsor and ethics committee as appropriate.

4.4.3.(d) Efficacy Measurement

Potential indicators of clinical efficacy included ICD, MWD, ABPI, QoL and CRF measures, which are described below.

4.4.4 Baseline and Follow-up Visits

Baseline visits were scheduled for a mutually agreed date and follow-up visits were completed immediately, 4 weeks and 12 weeks after completion of the intervention.

Prior to each assessment visit, patients were asked to refrain from eating or smoking in the preceding 3 hours and to avoid unusual physical activity efforts in the preceding 12 hours (138). Patients were not requested to withhold any medications as testing was not performed for diagnostic reasons. Prior to each assessment, patients' medical notes were reviewed, and they were interviewed regarding their past and current medical history including previous diagnoses, current symptoms and medications. This information, in conjunction with a measurement of resting pulse and blood pressure was used to determine if any contraindications to exercise testing or training were present (169), and to ensure that the patient did not exhibit any of the exclusion criteria. Following this, several measurements were taken.

4.4.4.(a) Demographics

Baseline demographics were recorded including height measured using a stadiometer (Lorrimar, Hull, UK), and weight measured using calibrated scales (Marsden, Rotherham, UK). This allowed for the calculation of BMI, by dividing the weight by the height in meters squared (kg/m^2). Waist and hip circumferences were also measured, and waist-to-hip ratio calculated. Resting HR and blood pressure was also recorded at each visit.

4.4.4.(b) ABPI

ABPI was determined at rest and following the treadmill test using standardised procedures. The SBP was measured bilaterally in the brachial, dorsalis pedis and posterial tibial arteries using an appropriately sized sphygmomanometer, placed on the arms and above the ankles (63). A hand-held doppler was used to determine an optimal flow signal before the cuff was inflated until the signal was no

longer audible. The SBP was recorded as the highest pressure at which the flow signal returned during gradual cuff deflation. The ABPI was then calculated for each leg by dividing the highest SBP of the two ankle pressure sites (i.e., dorsalis pedis or posterior tibial), by the highest arm pressure.

4.4.4.(c) Initial Claudication and Maximum Walking Distance

As previously mentioned, graded treadmill tests are more appropriate for outcome measurement as they are more reliable for determining ICD and MWD and a familiarisation test is not required. Therefore, ICD and MWD were assessed using the Gardner/Skinner treadmill test which starts at 3.2 km/h with a 0% gradient (110). During the test, the speed remains constant whilst the gradient increases by 2% every 2 minutes, for a maximum of 15 minutes (110). For patients unable to walk at 3.2 km/h, the speed was reduced by the operator, but remained consistent at all follow-up visits to ensure standardisation. A stopwatch was started when the patient began walking and they indicated when they first began to feel IC pain, which was recorded as ICD. The patient continued to walk until the pain became too severe and they needed to stop, which was recorded as MWD. Patients able to walk ≥15 minutes at baseline were excluded.

4.4.4.(d) Quality of Life

As noted in chapter one, the SF-36 fulfils strict reliability and validity criteria and is the most appropriate generic questionnaire for those with lower limb ischaemia (115, 116). It can also be used in conjunction with disease specific questionnaires, such as the VascuQoL, which was specifically designed for those with lower ischaemia and is valid, reliable and responsive to within-patient change (114). As such, QoL was measured at all time points using the SF-36 and VascuQoL questionnaires.

4.4.4.(e) CPET

The CPET is a powerful non-invasive tool which provides a holistic assessment of the interconnected cardiovascular, metabolic and ventilatory responses to exercise and is the gold standard measure of CRF (130, 131). It also allows for the identification of potential myocardial ischaemia, informs accurate exercise prescription and assesses the effect of an exercise intervention. A symptom-limited, incremental ramp cycle (Lode Corival Serial, Groningen, Netherlands) CPET was performed at baseline and follow-up visits to aid exercise prescription and quantify CRF. A ramp cycle protocol was chosen due to the reasons outlined previously including the stronger oxygen uptake and work rate relationship and the fact that cycle testing is more appropriate for patients with IC.

Prior to each test, patients observed a 3-minute rest period whilst sitting on the cycle ergometer to obtain resting measurements. After this, patients completed a 3-minute reference or warm-up period of unloaded cycling. This was followed by progressive graded exercise with an adequately increasing workload, using an individualised ramp protocol of 10-20 Watts per minute, designed to elicit volitional exhaustion within 8-12 minutes, concluding with a recovery period (138). The target of reaching volitional exhaustion within 8-12 minutes is vital as the relationship between oxygen uptake and work rate may be non-linear for test durations of <6 minutes and other limiting factors such as local muscle fatigue may present in tests >12 minutes (128). Patients were instructed to maintain 65-70rpm throughout the test and in the absence of clinical indications for termination, were encouraged to exercise to volitional exhaustion. In addition, the requirement to give a maximal effort was thoroughly explained prior to the test and strong verbal encouragement was given throughout.

Patients were continuously monitored throughout the test via 12-lead electrocardiogram (ECG; (Mortara X-scribe, Mortara, Milwaukee, USA) which was applied after adequate skin preparation. Brachial blood pressure and oxygen saturation (Tango M2 system, SunTech Medical, Morrisville, USA) were also monitored and subjective effort was quantified using the 6-20 rating of perceived exertion (RPE) scale (128, 258). Patients were also observed for any adverse signs and / or symptoms and were asked to confirm that they were asymptomatic throughout. All tests were conducted by a member of the research team trained in immediate life support, with a second member trained in basic life support also present (259). Upon completion of the test, monitoring continued for at least 6 minutes and until ECG, HR and blood pressure changes returned to near resting values. Breath-by-breath gas exchange data was also collected using a metabolic cart (Ultima2, Medgraphics, St Paul, Minnesota, USA), calibrated to manufacturer's instructions prior to each test.

$\dot{V}O_{2Peak}$ was defined as the highest $\dot{V}O_2$ value achieved during exercise or early in recovery when data was averaged over 30 second intervals (132). This was recorded relative to bodyweight ($mL \cdot kg^{-1} \cdot min^{-1}$) and as a percentage of the predicted value, calculated using the Hansen/Wasserman equations, appropriate for each sex, as outlined below (145):

Females:

1. **Ideal weight (kg) = 0.65 x height (cm) – 42.8**
2. **Predicted $\dot{V}O_{2Peak}$ = 0.001 x height x (14.783 – 0.11 x age) + 0.006 x weight (actual – ideal)**

Males:

1. **Ideal weight (kg) = 0.79 x height (cm) – 60.7**
2. **If actual weight is ≥ ideal weight:**
   Predicted $\dot{V}O_{2Peak}$ = 0.0337 x height – 0.000165 x age x height – 1.963 + 0.006 x weight (actual – ideal).

If actual weight is < ideal weight:

Predicted $\dot{V}O_{2Peak}$ = 0.0337 x height – 0.000165 x age x height – 1.963 + 0.014 x weight (actual – ideal).

The VAT was estimated via the V-slope and ventilatory equivalents methods and recorded relative to bodyweight ($mL \cdot kg^{-1} \cdot min^{-1}$) and as a percentage of measured $\dot{V}O_{2Peak}$ (151, 152). For the estimation of the VAT, data was averaged over 5 second intervals.

Peak HR was recorded as the highest absolute value achieved during exercise or early in recovery, and as a percentage of the age-predicted value, calculated using the widely adopted 220 – age formula (138). The $\dot{V}E/\dot{V}CO_2$ slope was calculated by plotting $\dot{V}E$ on the *y*-axis and $\dot{V}CO_2$ on the *x*-axis, both in $L \cdot min^{-1}$, using all of the incremental test data. The slope was then identified using the linear equation of the relationship between these two variables (Figure 26).

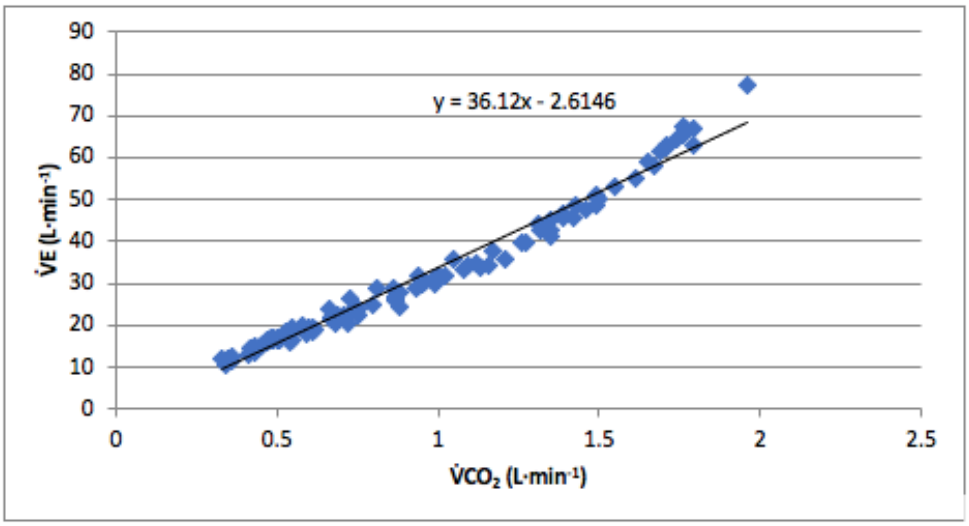


Figure 26 - $\dot{V}E/\dot{V}CO2$ slope

Peak RER was defined by dividing $\dot{V}CO_2$ by $\dot{V}O_2$, using data averaged over 30-second intervals. For this, only data collected during the incremental phase was used, as in recovery, $\dot{V}CO_2$ increases exponentially, which may give a falsely elevated RER value.

Peak O_2/HR was calculated by dividing $\dot{V}O_2$ by HR at peak exercise, using 30 second averaged data. Peak power output (PPO) was recorded as the highest value achieved, in watts, prior to the cessation of exercise. Finally, the $\Delta\dot{V}O_2/\Delta WR$ slope was calculated. When an incremental test is initiated, there is an initial delay before $\dot{V}O_2$ begins to increase in a linear fashion, which must be accounted for in the calculation of the $\Delta\dot{V}O_2/\Delta WR$ slope (145). As such, the following formula, which accounts for this, was used to calculate the $\Delta\dot{V}O_2/\Delta WR$ slope (145):

$\Delta\dot{V}O_2/\Delta WR$ slope = ($\dot{V}O_{2Peak}$ – unloaded $\dot{V}O_2$) / [(T – 0.75) x S]

where $\dot{V}O_2$ is measured in $mL \cdot min^{-1}$, T is the time of incremental exercise and S is the slope of the ramp of work rate increments in watts per minute.

4.4.4.(f) Spirometry

Spirometry is a useful adjunct to CPET, as it gives an insight into general respiratory health and can help to establish whether exercise intolerance or limitation is caused or contributed to by a ventilatory limitation. As such, unforced (vital capacity; VC and inspiratory capacity) and forced (forced expiratory volume in 1 second; FEV_1 and forced vital capacity; FVC) spirometry manoeuvres were performed in line with the American Thoracic Society guidelines, to substantiate the extent of any respiratory limitation (130, 260). VC is the change in volume, measured at the mouth, from a position of full inspiration to complete expiration. The VC manoeuvre also allows for the simultaneous measurement of inspiratory capacity, which is the volume change recorded at the mouth when taking a full inspiration from the point of passive expiration (260).

For the measurement of VC and inspiratory capacity, patients were in a seated position and a nose clip and mouthpiece was attached, ensuring no air leaks. Patients were then instructed to breathe as normally as possible, until end expiratory lung volume was stable, usually requiring four tidal breaths. Following this, patients were asked to take a deep

breath to total lung capacity (to record inspiratory capacity), then to exhale to residual volume (to record expiratory VC). The largest value from at least two acceptable measures was recorded.
Next, forced manoeuvres were conducted. FVC is defined as the maximal volume of air exhaled with maximally forced effort following maximal inspiration. FEV_1 is defined as the maximal volume of air exhaled in the first second of the maximally forced expiration, meaning that FEV_1 and FVC are derived from the same forced manoeuvre (260). As such there are three phases of this manoeuvre; an initial sharp maximal inhalation, an initial blast of exhalation and continued complete exhalation. The correct technique was demonstrated and enthusiastic coaching with appropriate body language and phrases was used. First, the patient was asked to assume the correct posture, which was maintained throughout, and the nose clip and mouthpiece were reattached. The patient was then instructed to inhale completely and rapidly, with a pause of <1second at total lung capacity before exhaling with an initial blast, continuing until no more air could be expelled and at least 6 seconds had elapsed. This process was repeated until at least three acceptable manoeuvres were performed. Acceptable manoeuvres are those that meet the within-manoeuvre criteria; (are free from artefacts, have good starts and show satisfactory exhalation) and between manoeuvre criteria; (the two largest FVC and FEV_1 values are within 150 mL^{-1} of each other) (260). The largest FVC and FEV_1 values were recorded from all of the usable curves and may not have come from the same curve.

However, these measures alone cannot sufficiently predict the extent to which respiratory disease limits exercise capacity (130). Other measures such as maximum voluntary ventilation (MVV) and subsequent breathing reserve derived from CPET are more appropriate to identify this limitation. MVV denotes the maximum volume of air ventilated in 60 seconds and can be directly determined from breathing

deeply and rapidly for 12 or 15 seconds (145). However, this is a difficult manoeuvre that is reliant upon subject co-operation, effort and technique. As such, MVV is often estimated from FEV_1. FEV_1 x 40 provides the best estimate of MVV and was used in this study (261). Breathing reserve was then calculated for all patients by using the maximal exercise $\dot{V}E$, recorded during CPET, and the estimated MVV, via the formula (1 – [peak $\dot{V}E$ / MVV]) (128).

A normal breathing reserve value is considered to be >20%, as in healthy subjects' respiratory capacity usually exceeds the demand of peak exercise (128, 130). Those limited by respiratory disease however, will have a breathing reserve close to zero, as cardiovascular efficiency exceeds respiratory efficiency (130).

4.4.5 Intervention

As noted in chapter one, studies in clinical populations have identified that HIIT cannot be performed at the required intensity for ≥2-minute intervals (201, 202). In addition, the systematic review performed in chapter three, which informed the intervention (206), recommended that future studies adopt a low-volume, short-duration HIIT programme for patients with IC (239). Therefore, this study adopted a pragmatic low-volume, short-duration HIIT protocol similar to one being considered in those with CAD (256). This HIIT programme was performed 3 times per week for 6 weeks, totalling 18 sessions. If participants missed any sessions, the intervention period was extended for up to 2 additional weeks to allow these sessions to be completed. Those who did not complete 18 sessions over the extended 8-week period were deemed to have satisfactorily completed the intervention if they had undertaken >80% of the HIIT sessions (i.e., ≥15 out of 18 sessions). All patients who completed the allotted 6-8 weeks for the intervention (regardless of whether they had completed ≥15 or <15 sessions) were followed up. Those selecting to discontinue the intervention prematurely were withdrawn. The number of sessions

completed, and the time taken to complete the programme was recorded for each patient. The HIIT intervention was performed using a cycle ergometer (Wattbike Trainer, Wattbike, Nottingham, UK), with exercise prescription based on the PPO achieved during the cycle CPET at baseline. The programme was delivered in a one-to-one fashion, with one instructor working with each patient individually.

The work to rest ratio was 1:1, with 1-minute of high-intensity exercise interspersed with 1-minute of low intensity exercise and 10 intervals were completed for an overall session time of 20 minutes (Figure 27). If required, a personalised, titrated introduction to the HIIT programme was used whereby less than 10 HIIT intervals were completed during the initial exercise sessions, with a target of completing 10 as quickly as possible and at least by the end of the second week. However, patients were not withdrawn if they were unable to achieve 10 intervals by the end of the second week and the number of sessions required to reach 10 intervals was recorded.

High-intensity intervals were set at 85-90% PPO from the baseline CPET, aiming to achieve ≥85-100% peak HR by the second interval. Low-intensity intervals were set at 20-25% PPO. Alteration between high- and low-intensity intervals was achieved by altering the cycling cadence. Some patients exceeded their peak HR from CPET during HIIT sessions and we adopted a pragmatic approach to this by allowing it to occur but monitored it on a case-by-case basis and reduced the intensity when it was deemed appropriate. These instances were also recorded. In addition, intensity was also increased on an individual basis. If ≥85% peak HR was not achieved by the second interval, the resistance/intensity was increased if it was likely to be tolerated, based on the RPE response. As such, increases in intensity were based on a combination of HR and RPE response.

Patients were continuously monitored via a Polar HR monitor (FT2, Polar electro, Kempele, Finland) and RPE, with both recorded at the end of each high-intensity interval. Real-time session data including HR,

cadence, speed, power output and distance was also recorded from the Wattbike using a USB stick.

All sessions were preceded by a 10-minute warm-up and followed by a 10-minute cool-down as is standard practice for exercise rehabilitation for older adults with chronic disease (175). Patients were also monitored for up to 10 minutes following the cool-down, to ensure HR was returning to near resting values and / or any symptoms had subsided.

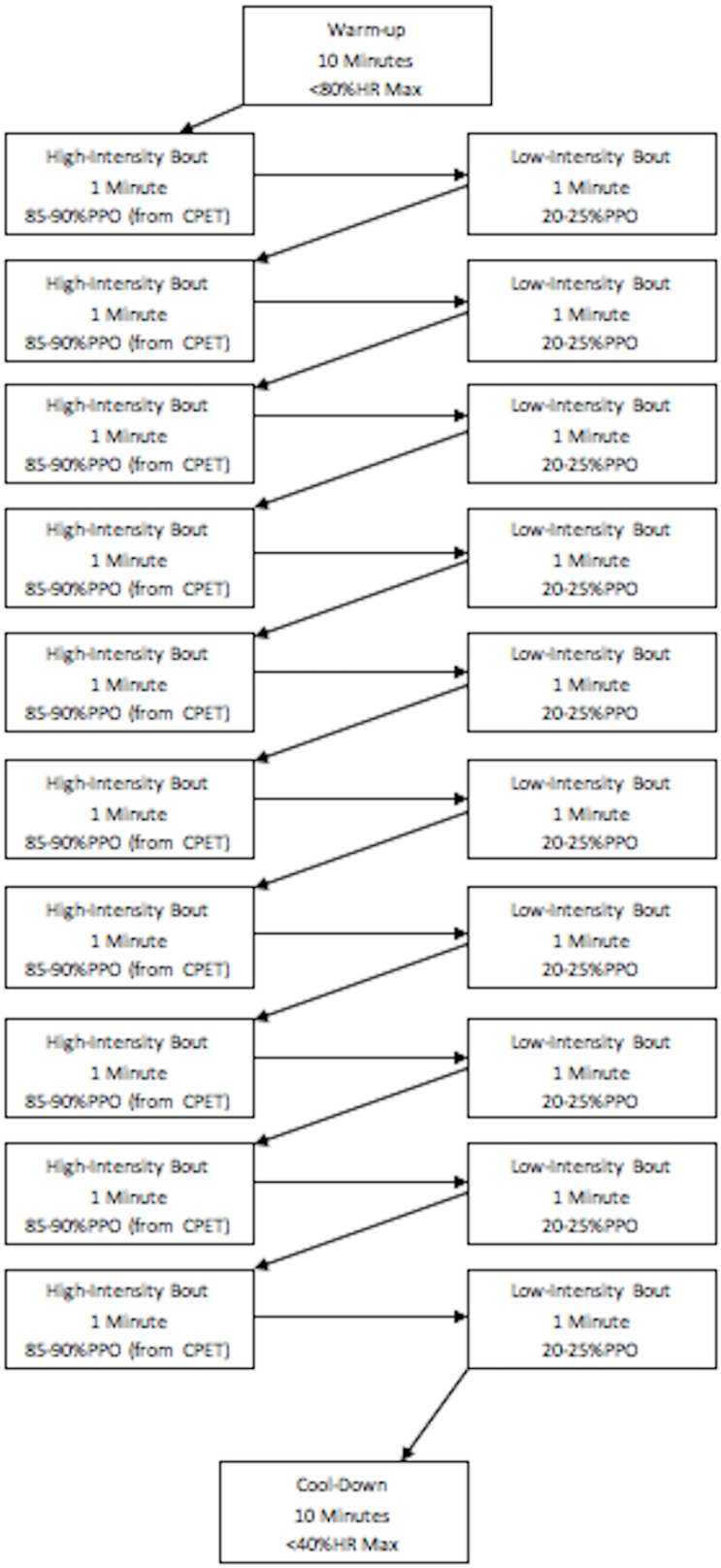


Figure 27 - High-intensity interval training intervention

4.4.6 Sample Size

As this was a feasibility study, no formal sample size calculation was required. We aimed to recruit 20 patients to generate sufficient feasibility, tolerability and safety information.

4.4.7 Statistical Analysis

Data normality was assessed by visual inspection of the histograms, in conjunction with the Shapiro-Wilk statistical test.

Normally distributed continuous data is presented as mean ± standard deviation (SD), and non-normally distributed data is presented as median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. For feasibility outcomes, eligibility, recruitment and completion rates are reported, as is the number of AE's for safety outcomes. Tolerability outcomes are reported as the number of sessions completed in full (all 10 intervals completed), the number of sessions where ≥85% of peak HR was achieved by the second interval, the mean number of sessions completed over the course of the programme and the mean time to completion, in weeks.

For efficacy outcomes, mean differences (± SD) in relation to baseline are reported where applicable. In addition, although not formally powered, statistical analyses were undertaken to provide an indication of potential efficacy. Paired samples t-tests or Wilcoxon Signed rank tests were used as appropriate, depending on distribution, with a *p*-value of <0.05 indicating statistical significance.

4.5 Results

4.5.1 Patient Characteristics

Baseline characteristics of all recruited patients (*n* = 20) are shown in table 13. Mean age was 69 ± 9 years, BMI was 28 ± 4 kg/m^2 and 80% were male. The mean ABPI of the worst leg was 0.65 ± 0.21. The majority (90%) of patients were on BMT, comprising of a statin and antiplatelet. However, blood pressure was generally poorly controlled at 148 ± 18 / 81 ± 7 mmHg, despite 60% of patients taking

antihypertensive medication. Forty percent of patients had diagnosed concomitant cardiac, cerebrovascular and / or respiratory disease. Baseline characteristics were similar between completers and non-completers.

Table 13 - Baseline characteristics

Variable	Overall cohort (*n*=20)	Completers (*n*=8)	Non-completers (*n*=12)
Age (years)	69 ± 9	72 ± 9	67 ± 9
Height (cm)	168.7 ± 10.7	171.1 ± 12.4	167.2.1 ±9.7
Weight (kg)	80.2 ± 16.7	85.1 ± 13.8	76.9 ± 18.2
BMI (kg/m^2)	27.9 ± 3.9	29 ± 2.9	27.2 ± 4.4
Waist-to-hip ratio	0.96 ± 0.07	0.98 ± 0.05	0.95 ± 0.07
Systolic blood pressure (mmHg)	148 ± 18	149 ± 19	148 ± 18
Diastolic blood pressure (mmHg)	81 ± 7	82 ± 7	80 ± 8
Resting heart rate (bpm)	69 ± 19	72 ± 11	67 ± 23
ABPI (worst leg)	0.65 ± 0.21	0.75 ± 0.22	0.58 ± 0.19
ICD (metres)	125.2 ± 119.5	123.3 ± 52	126.4 ± 151.4
MWD (metres)	293.1 ± 211.4	260 ± 96.3	315.2 ± 264.5
Gender			
• Male	16 (80%)	7 (88%)	9 (75%)
• Female	4 (20%)	3 (20%)	3 (25%)
Smoking Status:			
• Non-smoker	2 (10%)	2 (25%)	0 (0%)
• Ex-smoker	10 (50%)	3 (38%)	7 (58%)
• Current smoker	8 (40%)	3 (38%)	5 (42%)
Respiratory disease	3 (15%)	1 (13%)	2 (17%)
Coronary artery disease	4 (20%)	3 (38%)	1 (8%)
Cerebrovascular disease	1 (5%)	0 (0%)	1 (8%)
Diabetes	4 (20%)	2 (25%)	2 (17%)
Statin	19 (95%)	8 (100%)	11 (92%)
Antiplatelet	19 (95%)	7 (88%)	12 (100%)
Best medical therapy	19 (90%)	7 (88%)	11 (92%)
Antihypertensive	12 (60%)	4 (50%)	8 (67%)
Vasoactive treatment	10 (50%)	5 (63%)	5 (42%)
ß -blockade	6 (30%)	4 (50%)	2 (17%)

Values are given as count and percentage or mean ± SD. ABPI = Ankle-brachial pressure index, BMI = Body mass index, bpm = beats per minute, cm = centimetres, ICD = intermittent claudication distance, kg = kilogram, kg/m2 = kilograms per metre squared, mmHg = millimetres of mercury, MWD = maximum walking distance.

4.5.2 Feasibility

Between April 2018 and January 2019, 91 patients with IC were referred to the SEP and screened for this study. Of these, 54 (60%) were eligible and 20 (37%) consented to participate (Figure 28). The main reason for exclusion was severe or unstable cardiometabolic disease, whilst the main reason for declining the study was distance from the patients' home to the hospital.

Of these 20 patients, seven were excluded from further participation following baseline assessment. Two patients had abnormal ECG changes and were referred to cardiology, whilst five patients could not meet maximal effort CPET criteria. The peak RER and percentage of age-predicted maximum HR values for those excluded and those meeting maximal exercise test criteria were 0.9 and 1.1 and 72% and 83% respectively (table 14). Of these five patients unable to achieve a maximal test, one was taking ß-Blocker therapy and achieved an RER of 0.81 and reported an RPE of 20, confirming an inability to achieve a maximal test, in the context of ß-Blockers.

Table 14 - Baseline cardiopulmonary exercise testing variables for patients who were included or excluded on the basis of the ability to achieve maximal test criteria.

Variable	**Included (*n* =13)**	**Excluded (*n* = 5)**
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	15.9 ± 3	12.5 ± 2
Peak RER	1.1 ± 0.1	0.9 ± 0.1
Peak RPE	19.8 ± 0.4	18.3 ± 2.1
Maximum heart rate (bpm)	126.5 ± 19.2	106.4 ± 13.6
Percentage of age predicted maximum heart rate (%)	82.9 ± 11.3	71.8 ± 10.1
Peak power output (W)	95.5 ± 33.7	57.3 ± 30.5

Values are given as mean ± SD. bpm = beats per minute, $mL \cdot kg^{-1} \cdot min^{-1}$ = millilitres per kilogram per minute, RER = respiratory exchange ratio, RPE = rating of perceived exertion, $\dot{V}O_{2peak}$ = peak oxygen uptake, W = Watts.
N.B. Two patients excluded on the basis of ischaemic ECG changes were not included.

Of the remaining 13 patients eligible and able to commence the HIIT programme, one withdrew due to an inability to tolerate the intervention, two withdrew due to developing a concurrent illness (unrelated to the study) and one withdrew due to moving out of the area.

Additionally, one patient withdrew due to an AE that was probably related to the intervention. Details of this AE are provided in the 'safety' section (p. 187-188).

Following these withdrawals, eight patients (40%) completed the supervised HIIT programme.

Of these, all eight attended their end of programme follow-up, five attended the 4-week post intervention follow-up, with one unable to undergo CPET due to acute illness, and seven attended the 12-week post intervention follow-up, with one refusing to undergo CPET (Figure 28). In addition, the end of programme and 12-week follow-up CPET data was not useable for one patient. As such, CPET outcomes were available for seven, four and six patients at the end of programme, 4-week and 12-week follow-ups respectively.

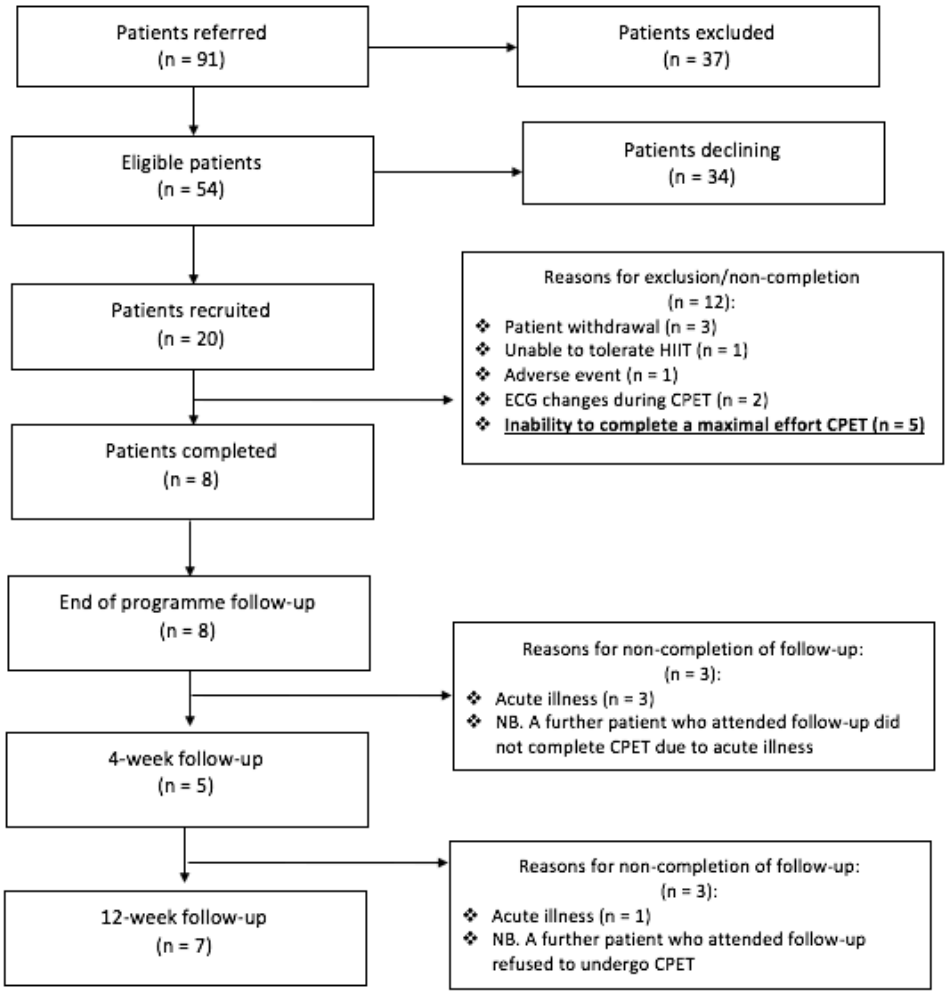


Figure 28 - Participant study flow

4.5.3 Tolerability

One patient in this cohort was unable to tolerate the intervention, due to a generally limited exercise tolerance, owing to a combination of comorbidities rather than just IC. For those that completed, all 18 sessions were attended for a 100% adherence rate, over an average of 6.5 ± 0.7 weeks. ≥85% peak HR was achieved by the second interval in 72% of sessions and all 10 intervals were completed in 92% of sessions, with all patients able to complete 10 intervals by week 2.

4.5.4 Safety

The aforementioned AE that led to withdrawal was an isolated episode of a 'dull chest ache' that occurred in the period between two exercise sessions. The patient was referred to cardiology where a diagnosis of *probable* angina was made but could not be confirmed as the patient

was needle phobic and as such, a diagnostic angiogram was refused. Although it is possible that this was related to the intervention, the symptomatic manifestation occurred in the period between two exercise sessions, meaning it could not be definitively attributed to it. In addition, one patient complained of some dizziness following two HIIT sessions. This was definitely related to the intervention, though it was only mild and resolved within minutes. No SAEs occurred during or immediately following any HIIT exercise sessions or study visits and as such, no changes were made to the intervention or study procedures.

4.5.5 Efficacy

Table 15 shows the clinical and QoL outcomes at each timepoint. Both ICD and MWD improved following the intervention, remaining above baseline at 4-week and 12-week follow-up (Figure 29). The improvements in MWD were also statistically significant at all time points (p = <0.05).

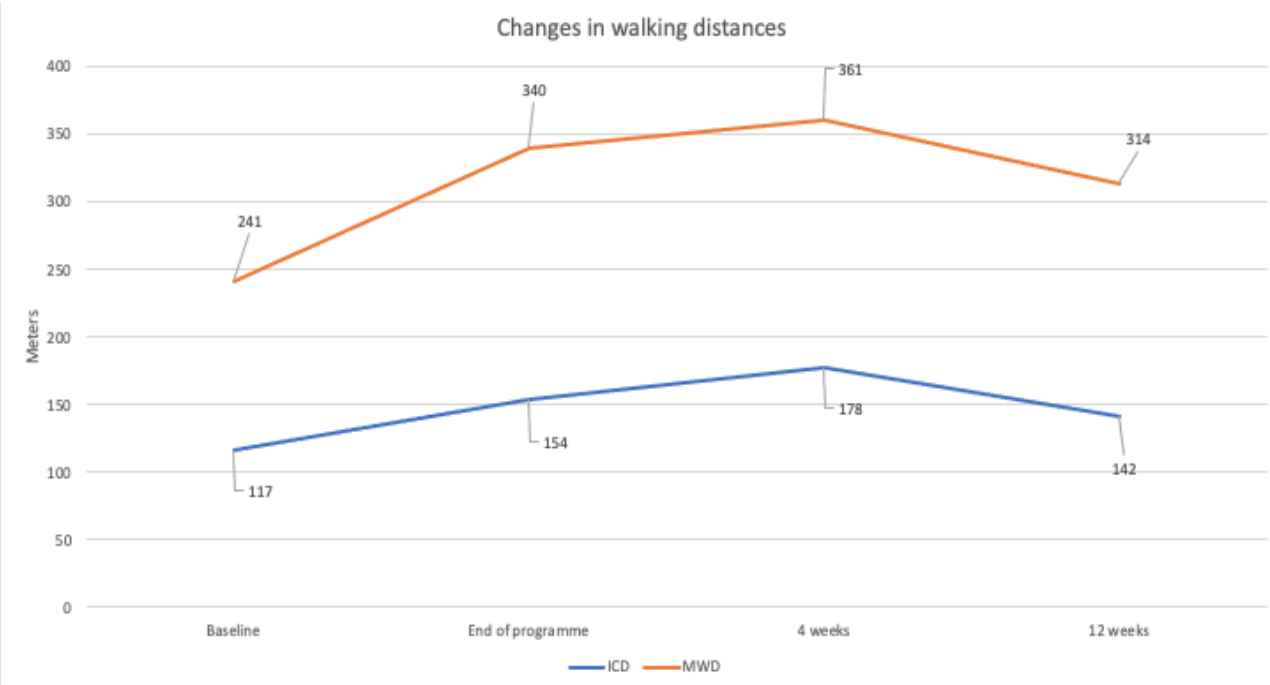


Figure 29 - Changes in walking distances

There were also improvements across all of the VascuQoL domains, which were maintained at each follow-up, though they were not significant. For the SF-36, all domains improved immediately following the programme with the improvements in vitality, mental health and the mental component summary being statistically significant (p = <0.05). These improvements largely remained at each time point with the exception of mental and general health, which were both reduced at 4- and 12-week follow-up. Vitality was the only domain to remain statistically significant at 12 weeks, though physical functioning also became significant at this time point.

Table 16 shows the CPET outcomes at each timepoint with mean changes in CRF shown in figure 30, and changes in PPO shown in figure 31. There was a small improvement in $\dot{V}O_{2Peak}$, that was reduced slightly at 12-week follow-up though it was still above baseline. The VAT remained the same immediately following the programme and increased slightly at 4-week follow-up, though this was not maintained at 12-week follow-up. The $\dot{V}E/\dot{V}CO_2$ slope was increased in relation to baseline at all timepoints, though this was marginal. The largest increases were seen in PPO and O_2-/HR, at around 10%. The increase in PPO was also statistically significant at the end of programme and 4-week follow-ups (p = <0.05), though this was not maintained at 12 weeks.
Other variables such as peak HR, RER and the $\Delta\dot{V}O_2/\Delta WR$ slope were largely unchanged.

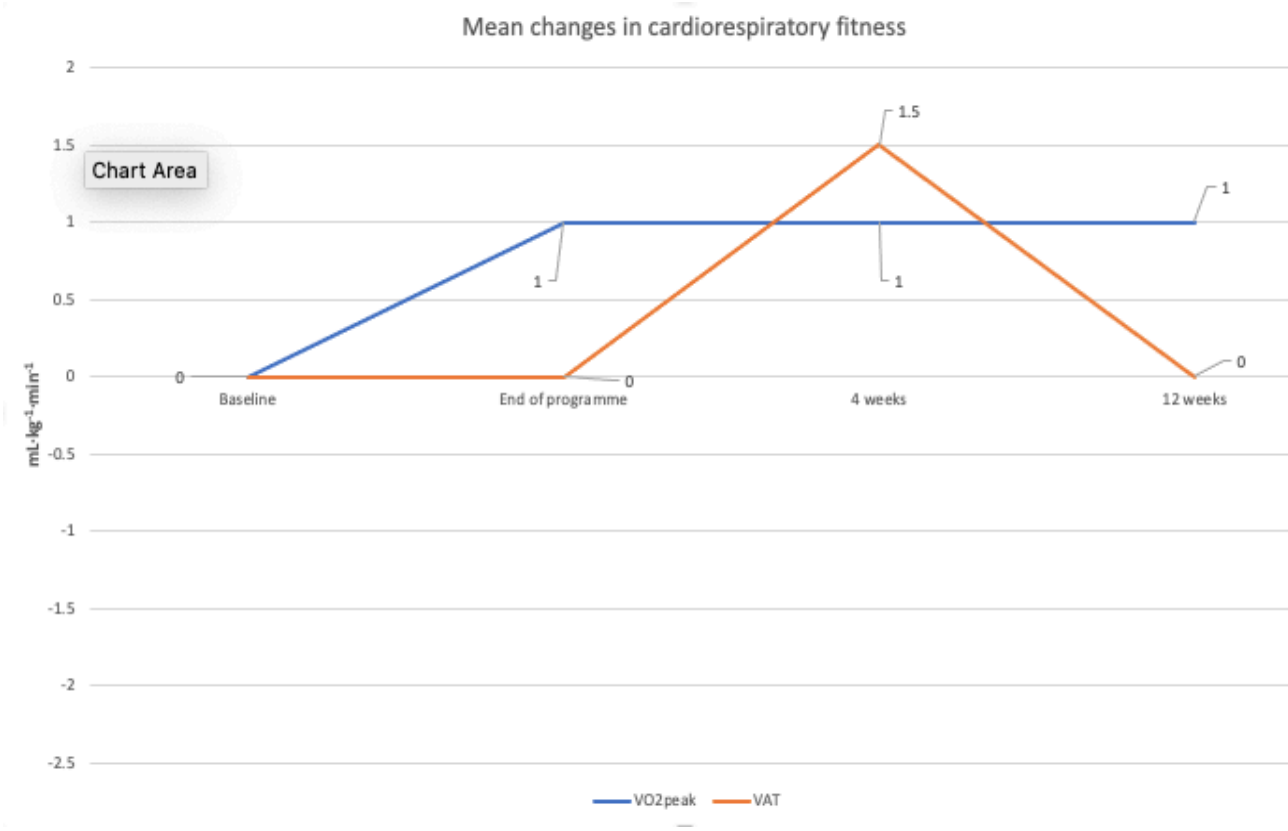


Figure 30 - Mean changes in cardiorespiratory fitness

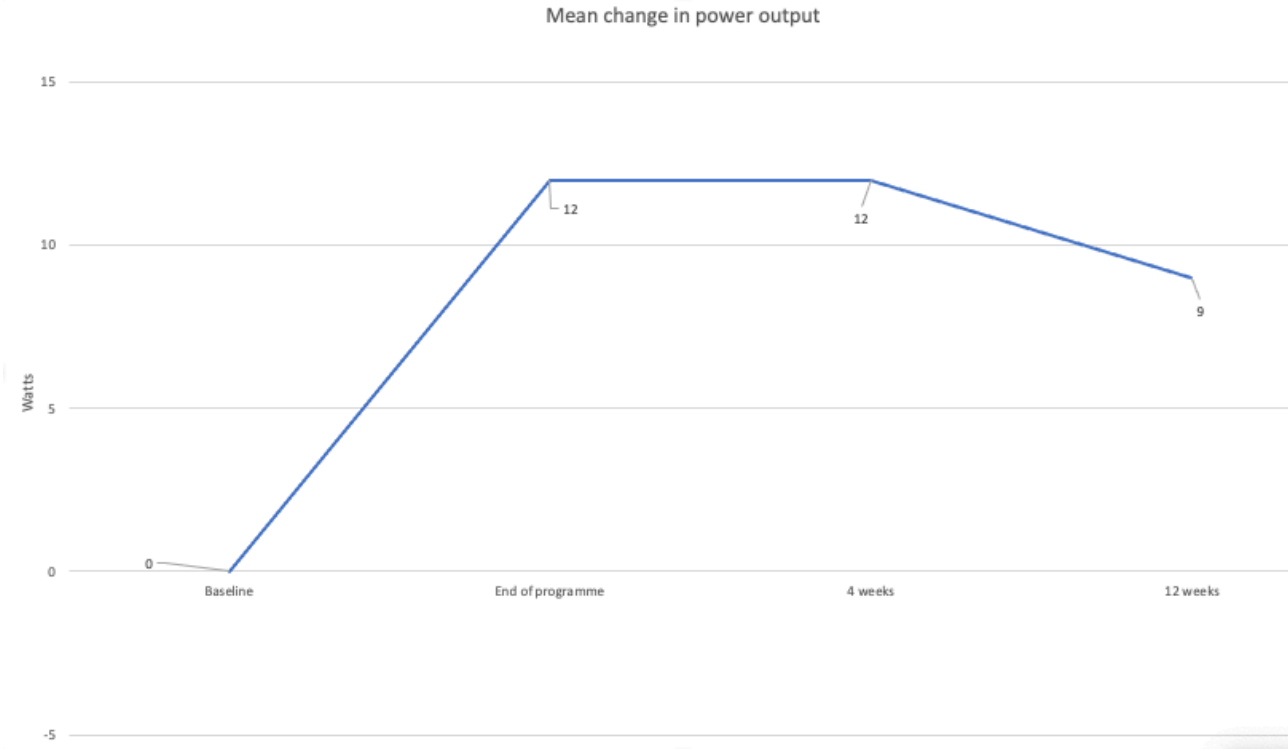


Figure 31 - Mean changes in peak power output

Table 15 - Clinical and quality of life outcome

Variable	Pre (*n*=8)	End of programme (*n*=8)	Mean change (*n*=8)	4-week follow-up (*n*=5)	Mean change (*n*=5)	12-week follow-up (*n*=7)	Mean change (*n*=7)
ICD (m)^	116.6 (107.5)	154.0 (75.8)		178.0 (156.2)		142.4 (260.8)	
MWD (m)^	241.2 (150.0)	340.9 (291.2)*		360.5 (389.8)*		314.2 (345.0)*	
Resting ABPI (mean both legs)	0.83 ± 0.18	0.82 ± 0.16	-0.01 ± 0.12	0.78 ± 0.2	0.03 ± 0.1	0.86 ± 0.19	0.03 ± 0.1
VascuQoL pain score	4.3 ± 1.4	4.6 ± 1.7	0.3 ± 0.7	5.0 ± 1.9	0.4 ± 1.7	4.9 ± 1.7	0.6 ± 1.1
VascuQoL social score	5.9 ± 1.5	6.1 ± 1.1	0.2 ± 0.6	6.7 ± 0.4	0.8 ± 1.5	6.6 ± 0.6	0.6 ± 1.4
VascuQoL activities score	4.6 ± 1.0	4.9 ± 1.1	0.3 ± 0.5	5.2 ± 1.1	0.5 ± 1.0	5.4 ± 0.8	0.7 ± 0.9
VascuQoL symptom score	5.4 ± 0.6	5.7 ± 0.6	0.3 ± 0.8	5.9 ± 0.8	0.5 ± 0.8	5.8 ± 0.7	0.3 ± 0.9
VascuQoL emotional score	5.7 ± 1.2	5.9 ± 0.9	0.1 ± 0.6	6.3 ± 0.6	0.4 ± 1.0	6.4 ± 0.4	0.5 ± 1.1
VascuQoL total score	5.1 ± 0.8	5.3 ± 0.9	0.2 ± 0.5	5.7 ± 0.8	0.5 ± 1.0	5.8 ± 0.7	0.5 ± 0.9
SF-36 physical functioning	54.4 ± 15.9	60.4 ± 19.6	6.0 ± 12.1	69.0 ± 22.5	9.0 ± 16.7	71.4 ± 17.0*	14.3 ± 15.1*

SF-36 role physical	55.5 ± 26.2	64.8 ± 21.9	9.4 ± 22.2	66.3 ± 28.5	16.3 ± 18.0	73.2 ± 27.2	16.1 ± 22.2
SF-36 pain^	51.0 (21.0)	51.5 (22.8)		51.0 (32.0)		61.0 (20.0)	
SF-36 general health	52.5 ± 19.3	59.9 ± 20.5	7.4 ± 17.6	55 ± 16.8	-6.0 ± 16.4	56.0 ± 17.6	-0.4 ± 9.6
SF-36 vitality	42.9 ± 15.9	59.4 ± 20.3*	16.5 ± 8.2*	62.5 ± 16.9	12.5 ± 8.8	57.3 ± 8.3*	10.4 ± 8.5*
SF-36 social functioning	75 ± 27	82.1 ± 24.9	7.1 ± 18.9	81.3 ± 16.1	12.5 ± 39.5	95.0 ± 11.2	7.5 ± 19.0
SF-36 role emotional^	87.5 (62.5)	95.8 (37.5)		100.0 (25.0)		100.0 (8.3)	
SF-36 mental health	67.1 ± 22.5	82.1 ± 18*	15 ± 8.7*	72.5 ± 10.4	-7.5 ± 11.9	71.7 ± 13.3	-2.5 ± 13.3
SF-36 physical component summary	40.7 ± 7.2	42.6 ± 6.8	1.8 ± 6.0	45.9 ± 11	4.2 ± 6.2	38.1 ± 20.6	4.5 ± 4.5
SF-36 mental component summary	48.3 ± 11.8	54.9 ± 10.4*	6.6 ± 3.1*	52.1 ± 5.8	1.1 ± 6.4	46.0 ± 22.7	1.0 ± 5.5

Data are presented as mean ± SD or as median and IQR (denoted by ^). * = p <0.05. ABPI = Ankle-brachial pressure index, ICD = intermittent claudication distance, M = meters, MWD = maximum walking distance, SF-36 = Short-Form 36, VascuQoL = vascular quality of life questionnaire.

Table 16 - Cardiopulmonary exercise testing outcomes

Variable	Pre (*n*=7)	End of programme (*n*=7)	Mean change (*n*=7)	4-week follow-up (*n*=4)	Mean change (*n*=4)	12-week follow-up (*n*=5)	Mean change (*n*=5)
$\dot{V}O_{2Peak}$ (L·min^{-1})	1.32 ± 0.18	1.39 ± 0.19	0.07 ± 0.21	1.40 ± 0.23	0.11 ± 0.11	1.41 ± 0.21	0.07 ± 0.11
$\dot{V}O_{2Peak}$ (mL·kg^{-1}·min^{-1})	16.0 ± 1.6	16.9 ± 1.6	0.9 ± 2.3	16.7 ± 0.9	1.1 ± 1.2	16.9 ± 1.5	0.7 ± 1.2
$\dot{V}O_{2Peak}$ (% predicted)	77.0 ± 14.0	81.4 ± 13.1	4.4 ± 10.9	85.2 ± 10.9	6.4 ± 4.2	83.7 ± 13.4	4.5 ± 5.0
VAT (mL·kg^{-1}·min^{-1})	10.2 ± 2.0	10.2 ± 2.0	0.0 ± 0.4	10.6 ± 0.7	1.5 ± 1.8	10.0 ± 1.0	0.4 ± 1.4
VAT (% of $\dot{V}O_{2Peak}$)	63.9 ± 10.3	60.6 ± 10.8	-3.3 ± 10.5	63.7 ± 6.5	4.6 ± 13.1	59.1 ± 5.7	-0.2 ± 8.4
Peak HR (bpm)	126 ± 20	123 ± 20	-3.6 ± 6.5	120 ± 15	4.3 ± 6.1	121 ± 20	-1.4 ± 2.9
Peak HR (% predicted)	85.1 ± 11.1	82.8 ± 11.9	-2.3 ± 4.3	84.6 ± 7.7	3.2 ± 4.7	84.0 ± 9.3	-1.1 ± 2.6
$\dot{V}E/\dot{V}CO2$ slope^	34.6 ± 5.3	35.4 ± 2.8	0.8 ± 3.5	35.5 ± 7.3	2.5 ± 2.3	34.5 ± 5.5	0.9 ± 2.7
O_2/HR (mL·beat)	10.8 ± 2.3	12.2 ± 3.0	1.4 ± 2.0	12.2 ± 2.8	0.8 ± 1.3	12.0 ± 2.1	0.9 ± 0.8
Δ$\dot{V}O2$/ΔWR slope (mL·min^{-1}·watt)	9.3 ± 1.7	9.5 ± 1.2	0.2 ± 1.2	9.7 ± 1.3	-0.2 ± 1.4	9.5 ± 0.9	-0.2 ± .86

RER	1.16 ± 0.14	1.13 ± 0.10	-0.03 ± 0.13	1.17 ± 0.13	-0.04 ± 0.10	1.17 ± 0.09	-0.03 ± 0.12
PPO (w)	100 ± 22	111 ± 27*	12 ± 10*	106 ± 19*	12 ± 6*	110 ± 21	9 ± 8

Data are presented as mean ± SD or as median and IQR (denoted by ^). * = p <0.05. bpm = beats per minute, HR = heart rate, mL·beat = millilitres per beat, mL·kg-1·min-1 = millilitres per kilogram per minute, mL·min-1·watt = millilitres per minute per watt, O2/HR = oxygen pulse, PPO = peak power output, RER = respiratory exchange ratio, VAT = Ventilatory Anaerobic Threshold, $\dot{V}E/\dot{V}CO2$ slope = minute ventilation to carbon dioxide production relationship, $\dot{V}O_{2Peak}$ = peak oxygen consumption, W = watts $\Delta\dot{V}O2/\Delta WR$ slope = oxygen uptake to work rate relationship.

4.6 Discussion

The aim of this study was to consider the feasibility, tolerability, safety and potential efficacy of a novel HIIT programme for patients with IC. The eligibility (60%), recruitment (37%) and patient withdrawal (20%) rates were similar to those recently reported for usual-care SEPs (185). However, completion rates were much lower (40%), owing to greater post-recruitment exclusions, mainly due to an inability to complete a maximal effort CPET, which accounted for five of the seven exclusions. When considering the tolerability data, only one patient withdrew due to an inability to tolerate the intervention and for completers, the majority of sessions were completed in full and at the required intensity over a duration of just over 6 weeks. As such, despite the low completion rate, it appears that this *conventional* HIIT programme may be feasible and tolerable for a subgroup of patients with IC, who are able to achieve the required intensity to undertake it.

It is important in feasibility cohort studies to consider whether the exclusion criteria are appropriate for the population under investigation. In this study, the post recruitment CPET exclusion criteria deserve specific discussion. Two of the 20 recruited patients were excluded due to positive ECG changes during CPET, indicative of myocardial ischaemia, though this is not surprising given the high prevalence of co-existing CAD in those with IC, which is often undiagnosed (63). This is a patient safety criterion which cannot, and should not, be altered. More saliently however, five patients were excluded due to an inability to achieve a maximal effort CPET, meaning that for these patients, *conventional* HIIT was not feasible and could not be prescribed. This inability to achieve a maximal effort CPET is likely due to severe deconditioning, or a reduction in CRF, as a result of IC, given that it causes a cycle of pain and physical activity avoidance. As pain increases with walking, patients walk less or for shorter distances, meaning that walking ability and muscle strength further

diminish causing further reductions in walking distance, all of which negatively impacts upon CRF (4). This is evidenced by the mean baseline $\dot{V}O_{2Peak}$ value in this study, which was approximately 15 $mL \cdot kg^{-1} \cdot min^{-1}$. A number of other studies have also demonstrated similar or even lower baseline $\dot{V}O_{2Peak}$ values in patients with IC (158, 204, 262). In contrast, a recent study considering HIIT in those with CAD reported a baseline value of approximately 23 $mL \cdot kg^{-1} \cdot min^{-1}$ whilst another study in more than 250 heart failure patients reported a baseline value of 17 $mL \cdot kg^{-1} \cdot min^{-1}$ (201, 263). This suggests that patients with IC are markedly more deconditioned than those with CAD and even those with heart failure which may explain why a number of patients were unable to achieve a maximal effort CPET, despite subjectively feeling as though they had performed to their limit. Indeed, the patients unable to achieve a maximal effort test in this cohort reported a mean RPE score of >18/20.

However, those with the lowest CRF may also be the ones that accrue the most benefit. Previous research has demonstrated that the VAT, a submaximal marker of CRF, is a significant predictor of improvements in MWD following a SEP. Specifically, those with the lowest VAT (i.e. the least fit patients), had the greatest improvement (158).
Therefore, alteration of the exclusion criteria and conduction of further feasibility work considering a 'submaximal' version of this short-term HIIT programme appears warranted. These altered criteria will not exclude patients if they are unable to achieve a maximal effort CPET but will instead include them and provide the same personalised, time-efficient interval training programme based on their individual CRF. The further feasibility work will then consider if the 'submaximal' HIIT programme and the altered inclusion / exclusion criteria are safe, feasible and tolerable for those with IC.
The rationale for this alteration and further feasibility work is three-fold. Firstly, if the patients who were excluded from this study due to

being unable to complete a maximal effort CPET, instead completed the intervention, the completion rate would be equivalent to that reported in SEP studies (185), and greater than that reported for the usual-care SEP in our centre (158), at 65%. Secondly, with a 50% reduction in the intervention time compared to usual SEPs, this personalised 'submaximal' HIIT programme, if applicable to a greater number of patients, has the potential to reduce patient burden, provide cost-savings and may be easier to implement.
Finally, the exercise prescription for SEPs is often focused on a *'one size fits all'* approach, based on the subjective measure of pain. This HIIT programme instead adopts an objective, personalised exercise prescription based on a CPET, potentially maximising the individual patient benefit. Such a CPET based approach has also been recommended in CR programmes both in the UK and internationally (137, 264).

With regards to safety, there were no SAEs that occurred during or immediately following any HIIT sessions or study visits, providing early support for the safety of HIIT in patients with IC, though further evidence is needed from a larger cohort of patients.

Finally, it is worth noting that those who completed the HIIT programme did accrue a statistically significant benefit in terms of MWD which is promising, especially given that the improvement was comparable to SEPs and represents a moderate to large MCID (118, 234).

4.7 Conclusion

This study has demonstrated that 40% of patients with IC were able to complete a *conventional* HIIT programme. They also derived a statistically significant clinical benefit from participating. However, a significant proportion of patients were unable to complete a maximal effort CPET, likely due to deconditioning. This precluded these patients

from undertaking the *conventional* HIIT programme and led to a low completion rate. These patients are, however, likely to accrue the most benefit from such a programme. Therefore, the clinical utility of HIIT may be expanded by including these patients and providing them with a personalised, 'submaximal' HIIT programme. This warrants further investigation.

Chapter 5: Study Four: A Prospective Observational Cohort Study Considering the Feasibility, Tolerability and Safety of a Submaximal, Personalised, High Intensity Interval Training Programme for Patients with Intermittent Claudication.

5.1 Introduction

Study three identified that a *conventional* HIIT programme may not be feasible for a significant proportion of patients with IC. This is because 5/20 patients were excluded due to being unable to achieve a maximal effort CPET. It is likely that these patients were unable to achieve a maximal effort test due to marked deconditioning. However, these least fit patients may also be the ones that accrue the most benefit (158). As such, study three recommended that these patients are included rather than excluded and provided with the same personalised, submaximal HIIT programme. It also recommended further feasibility to work to consider this.

5.2 Aim

This aim of this study was to consider the feasibility, tolerability, safety and potential efficacy of a personalised, submaximal HIIT programme for patients with IC.

It is important to note that repeat feasibility testing such as this is not uncommon and the medical research council state that depending on the results, a series of studies may be required to progressively refine the study design, prior to a full-scale evaluation (206).

5.3 Methods and Study Design

This study is similar to that outlined in chapter four. Therefore, a truncated version of the methodology will be provided in this chapter.

5.3.1 Design

This was a prospective, interventional, before-after cohort study that was informed by the previous study and conducted in the same UK tertiary vascular centre. A protocol amendment was submitted to the original research ethics committee (Bradford Leeds – 18/YH/0112) to

alter the exclusion criteria and increase the sample size, to allow this second cohort study to be conducted. This amendment was approved, and all patients signed informed consent prior to participation.

5.3.2 Participants

Patients were invited to the study following the same referral pathway outlined in the previous chapter, with referral made by a vascular consultant following a diagnosis of IC. These patients were invited via letter and PIS and contacted a week later so that they could ask any questions and decide whether or not to take part. Those who decided to take part were asked to attend a baseline assessment at the vascular laboratory which followed the same process outlined in the previous chapter. During this baseline assessment, patients were confirmed as eligible against the inclusion and exclusion criteria which mirrored the previous study, though the requirement to achieve a maximal effort CPET was removed:

5.3.2.(a) Inclusion Criteria:

- Community dwelling adults aged 18 or over.
- ABPI of <0.9 at rest or a drop of more than 20mmHg after exercise testing
- Ability to walk unaided
- English speaking and able to comply with exercise instructions

5.3.2.(b) Exclusion Criteria:

- Patients unable to provide informed consent
- Critical limb ischaemia / rest pain
- Active cancer treatment
- Unstable angina and / or heart failure and / or diabetes mellitus
- New or uncontrolled arrhythmias
- Resting / uncontrolled tachycardia (>100bpm) and / or resting / uncontrolled hypertension (systolic blood pressure >180mmHg or diastolic blood pressure >100mmHg)

- Symptomatic hypotension
- Significant comorbidities that preclude safe participation in exercise testing and/or training according to the ACSM guidelines (257).

5.3.2.(c) Additional Exclusion Criteria

Following analysis of the CPET results, patients were prevented from continuing their involvement in the study if there was an indication of:

- Exercise-induced ischaemia or significant haemodynamic compromise (manifesting as significant ECG changes and / or an abnormal blood pressure response and / or anginal symptoms).

5.3.3 Outcomes

As with the previous study, the primary outcomes were feasibility, tolerability and safety. The secondary outcome was potential efficacy. These outcomes were assessed using the same measures and methods outlined in the previous chapter.

5.3.4 Baseline and Follow-up Visits

Baseline visits were scheduled for a mutually agreed date and follow-up visits were completed immediately following completion of the programme and 4 and 12 weeks later. Instructions given to patients with regards to eating and smoking were the same as the previous chapter (p. 172), as were the processes for ensuring no contraindications to exercise or exclusion criteria were present (p. 172-173). Demographics, ABPI, ICD, MWD and QoL were measured, and spirometry and CPET performed, following the same processes outlined previously (p. 173-182). However, patients were no longer excluded due to an inability to achieve a maximal effort CPET.

5.3.5 Intervention

The intervention was unchanged from the previous study (p.179-182) and was performed 3 times per week for 6 weeks, totalling 18 sessions. The exercise prescription was based on the PPO achieved during the cycle CPET at baseline, personalised to each patient. Those who were unable to achieve a maximal effort CPET, were provided with the same,

submaximal, personalised programme as those who were able to achieve a maximal effort test.

The work to rest ratio was 1:1, with high-intensity intervals set at 85-90% PPO, aiming to achieve ≥85-100% peak HR by the second interval. Low-intensity intervals were set at 20-25% PPO. Ten intervals were completed for a 20-minute exercise session, preceded and followed by a 10-minute warm-up and cool-down (Figure 27). The number of intervals was titrated If required, with some patients completing less than 10 initially, with a target of achieving 10 as quickly as possible. The time taken to achieve 10 intervals was recorded.

Patients were continuously monitored via a Polar HR monitor (FT2, Polar electro, Kempele, Finland) and RPE, with both recorded at the end of each high-intensity interval. Real-time session data including HR, cadence, speed, power output and distance was also recorded from the Wattbike, using a USB stick.

5.3.6 Sample Size

As with the previous study, no formal sample size calculation was required. We aimed to recruit 20 patients, as this should provide sufficient feasibility, tolerability and safety information.

5.3.7 Statistical Analysis

The statistical analysis followed the same methods as those outlined in chapter four (p. 183).

5.4 Results

5.4.1 Patient Characteristics

Baseline characteristics of all recruited patients (*n* = 20) are shown in table 17. Mean age was 70 ± 7 years, BMI was 29 ± 4 kg/m^2 and 70% were male. The mean ABPI of the worst leg was 0.65 ± 0.18. The majority (95%) of patients were on BMT, comprising a statin and antiplatelet. One patient was intolerant to statins, so BMT consisted of antiplatelet therapy alone, whilst another patient was taking an anticoagulant, rather than an antiplatelet. As with the previous cohort, blood pressure was generally poorly controlled at 148 ± 22 / 77 ± 9

mmHg, despite 60% taking antihypertensive medication. Forty percent of patients had diagnosed concomitant cardiac, cerebrovascular and / or respiratory disease. Baseline characteristics were largely similar between completers and non-completers, though completers were slightly younger, had a slightly lower ABPI and could walk slightly further than non-completers.

Table 17 - Baseline characteristics

Variable	Overall cohort (*n*=20)	Completers (*n*=13)	Non-completers (*n*=7)
Age (years)	70 ± 7	68 ± 8	73 ± 4
Height (cm)	166.8 ± 8.4	166.9 ± 8.8	166.7 ± 8.3
Weight (kg)	79.0 ± 14.8	79.2 ± 15.8	78.6 ± 13.9
BMI (kg/m^2)	28.6 ± 3.9	28.8 ± 4.3	28.1 ± 3.4
Waist-to-hip ratio	0.95 ± 0.09	0.94 ±.0.10	0.96 ± 0.05
Systolic blood pressure (mmHg)	148 ± 22	149 ± 19	147 ± 28
Diastolic blood pressure (mmHg)	77 ± 9	78 ± 8	76 ± 12
Resting heart rate (bpm)	74 ± 13	74 ± 15	73 ± 10
ABPI (mean worst leg)	0.65 ± 0.18	0.60 ± 0.19	0.75 ± 0.12
ICD (metres)	116.3 ± 85.7	125.3 ± 94.5	99.5 ± 70.1
MWD (metres)	295.1 ± 169.1	317.8 ± 164.7	253.0 ± 181.8
Gender			
• Male	14 (70%)	9 (69%)	5 (71%)
• Female	6 (30%)	4 (31%)	2 (29%)
Smoking Status:			
• Non-smoker	0 (0%)	0 (0%)	0 (0%)
• Ex-smoker	14 (70%)	9 (69%)	5 (71%)
• Current smoker	6 (30%)	4 (31%)	2 (29%)
Respiratory disease	5 (25%)	3 (23%)	2 (29%)
Coronary artery disease	5 (25%)	2 (15%)	3 (43%)
Cerebrovascular disease	2 (10%)	2 (15%)	0 (0%)
Diabetes	6 (30%)	5 (39%)	1 (14%)
Statin	19 (95%)	13 (100%)	6 (86%)
Antiplatelet	18 (90%)	11 (85%)	7 (100%)
Best medical therapy	19 (95%)	12 (92%)	7 (100%)
Antihypertensive	12 (60%)	8 (62%)	4 (57%)

Vasoactive treatment	5 (25%)	8 (62%)	5 (71%)
Beta-blockade	13 (65%)	4 (31%)	1 (14%)
Values are given as count and percentage or mean ± SD. ABPI = Ankle-brachial pressure index, BMI = Body mass index, bpm = beats per minute, cm = centimetres, ICD = intermittent claudication distance, kg = kilogram, kg/m^2 = kilograms per metre squared, mmHg = millimetres of mercury, MWD = maximum walking distance.			

5.4.2 Feasibility

Between February 2019 and December 2019, 98 patients with IC were referred to the SEP and screened for this study. Of these, 72 (73%) were eligible and 20 (28%) consented to participate. The main reasons for ineligibility were severe or unstable cardiometabolic disorders, active cancer treatment or an inability to walk unaided. The main reasons for declining the study were a lack of time, distance to the hospital and feeling unable to exercise.

Of the 20 patients recruited, two were excluded from further participation following baseline assessment due to significant ECG changes.

Of the remaining 18 patients eligible and able to commence the HIIT programme, one withdrew due to an inability to tolerate the intervention, two withdrew following CPET, as they were unable to tolerate it and one patient withdrew 3 weeks after commencing the programme due to reported time constraints. One further withdrawal was due to a SAE that was possibly related to the intervention. This event was a popliteal aneurysm thrombosis that occurred in the period between two exercise sessions. The patient was admitted for surgery and underwent a lower limb bypass procedure, and as such was withdrawn. Whilst it is possible that this was related to the intervention, the first symptomatic manifestation (ALI) occurred 2 days after the last exercise session, meaning that it was not definitively related to it. As such, no changes were made to the intervention or study procedures.

Following these withdrawals, 13 patients (65%) completed the supervised HIIT programme (Figure 32).

Of these, all 13 attended their end of programme follow-up and 11 attended the 4-week post intervention follow-up, with the other two unable to attend due to the coronavirus disease 2019 (COVID-19) pandemic. Eight patients attended the 12-week post intervention follow-up, with three unable to attend due to the COVID-19 pandemic, one unable to attend due to acute illness and a further patient had died (Figure 32). CPET was not performed at the end of programme and 4-week follow-up for one patient as they had developed new resting ECG changes. A second patient also developed new, exercise-induced left bundle branch block at 12-week follow-up and did not undergo CPET. A final patient did not have useable CPET data at 4-week or 12-week follow-up due to technical issues. As such, CPET outcomes were available for 12, nine and six patients at the end of programme, 4-week and 12-week follow-ups respectively.

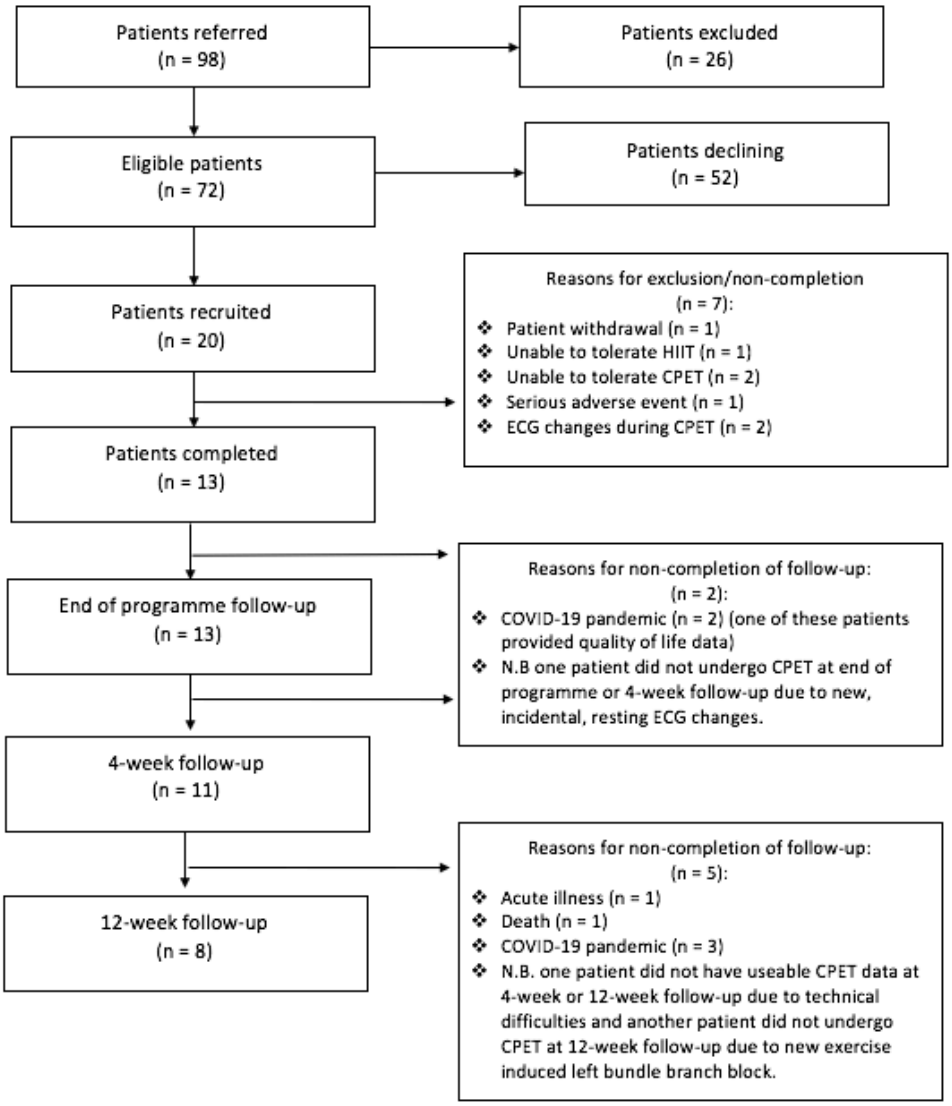


Figure 32 – Participant study flow

5.4.3 Tolerability

One patient in this cohort was unable to tolerate the intervention, due to breathlessness secondary to COPD. A further two patients withdrew following CPET, as they were not able to tolerate it. One of these patients could not tolerate it due to femur pain secondary to a previous fracture, whilst the other described feeling too fatigued after the test. None of these patients cited IC as the reason for being unable to tolerate the intervention or CPET.

For those that completed, all 18 sessions were attended, except for one patient who attended 17, as they did not want to rearrange a missed session. Mean time to completion of the intervention was 6.3 ± 0.7 weeks. ≥85% peak HR was achieved by the second interval in 73% of sessions and all 10 intervals were completed in 80% of sessions, with 12/13 patients able to complete all 10 intervals by the beginning of week 3. The remaining patient could still not complete all 10 intervals by the end of the programme due to generalised fatigue. Six of the 20 recruited patients were unable to achieve a maximal effort CPET, with three of these completing the programme.

5.4.4 Safety

The aforementioned SAE was the only one to be recorded and no AEs occurred during or immediately following any HIIT exercise sessions or study visits. The patient who developed new resting ECG changes had inverted T waves across the precordial leads that were not evident at baseline. They were referred to cardiology and were seen between the 4-week and 12-week follow-up assessment, by which time, these changes had resolved and were likely non-specific or related to lead placement. The final patient who developed a new, exercise-induced left bundle branch block had a known history of CAD, meaning this ECG pattern is not unexpected. It also occurred 12 weeks after completion of the intervention, meaning it is unlikely to be related. However, in the interest of patient safety the test was not performed.

5.4.5 Efficacy

Table 18 shows the clinical and QoL outcomes at each timepoint. Both ICD and MWD improved following the intervention (Figure 33). ICD continued to improve at each time point, with the largest improvement demonstrated at 12-week follow-up. MWD showed the greatest improvement immediately following the programme and declined slightly at the 4-week and 12-week follow-ups, though it still remained above the baseline value. There may also have been a slight ceiling effect for MWD as one patient completed the 15-minute treadmill test at all follow-up visits, meaning this did not represent their true MWD. The changes in ICD and MWD were also statistically significant at each time point (p = <0.05), with the exception of MWD at 12 weeks.

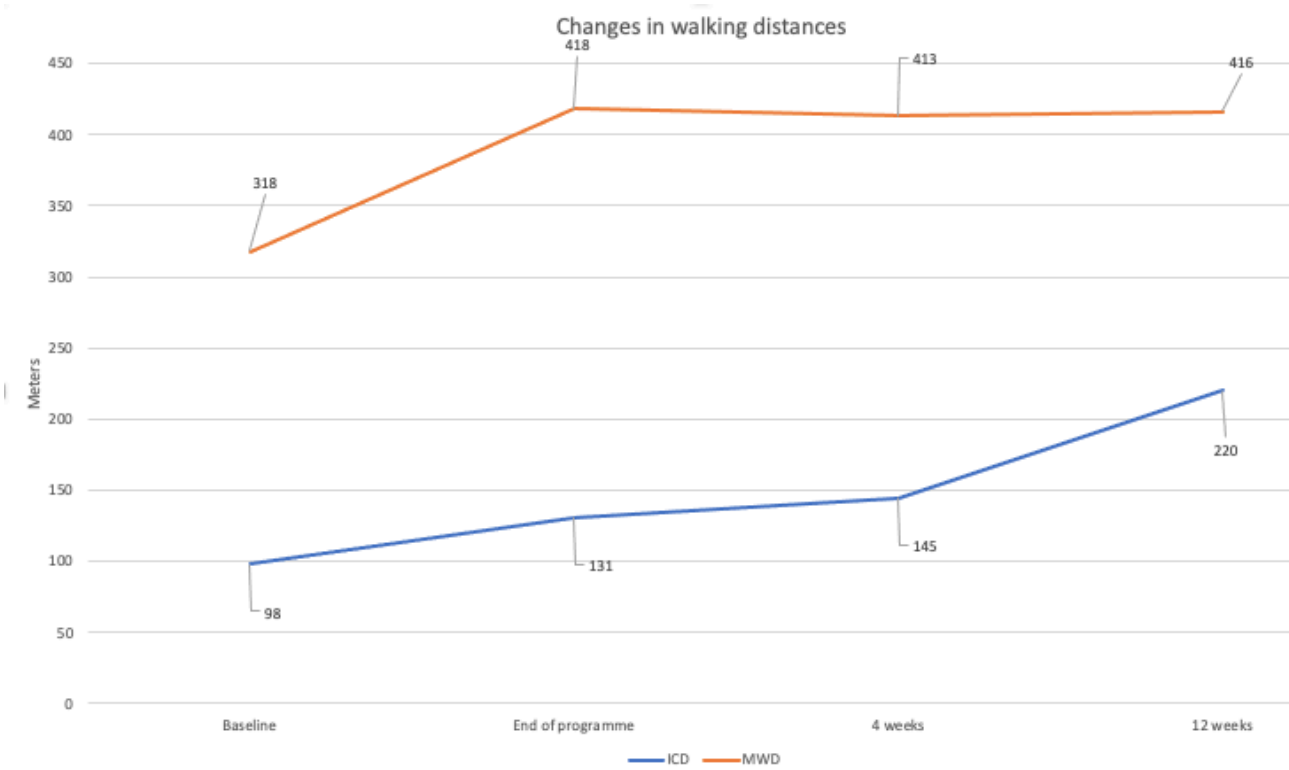


Figure 33 - Changes in walking distances

There were also improvements across all of the VascuQoL domains, with the pain, symptom and activities domains and the total score being statistically significant (p = <0.05). These improvements were also maintained at each follow-up, though no domain was statistically significant at 12 weeks.

For the SF-36, all domains improved immediately following the programme, with the largest improvement occurring in the domain of bodily pain, which was statistically significant, as was the physical component summary (p = <0.05). Each domain remained above baseline at 4-week follow-up with the exception of mental health and the mental component summary. Both bodily pain and the physical component summary were still statistically significant at 4 weeks, as was the physical functioning domain. At 12-week follow-up, most domains had either returned to baseline or were marginally lower. The physical component summary however, remained significantly improved compared to baseline.

Table 19 shows the CPET outcomes at each timepoint, with the changes in CRF shown in Figure 34 and the changes in PPO shown in Figure 35. There was a marginal improvement in $\dot{V}O_{2Peak}$ at the end of programme follow-up, that was maintained at 4-week follow-up. At 12 weeks, there was a slight reduction in $\dot{V}O_{2Peak}$, though this was again marginal. The VAT increased slightly immediately following the programme, though it was marginally reduced at 4-week and 12-week follow-up. The $\dot{V}E/\dot{V}CO_2$ slope was slightly increased in relation to baseline at all timepoints.

There was a statistically significant increase in PPO immediately following the programme (p = <0.05), but not at 4-week or 12-week follow-up. Peak HR was unchanged immediately following the programme but was slightly lower at 4-week and 12-week follow-up. Other variables such as O_2/HR, RER and the $\Delta\dot{V}O2/\Delta WR$ slope were largely unchanged.

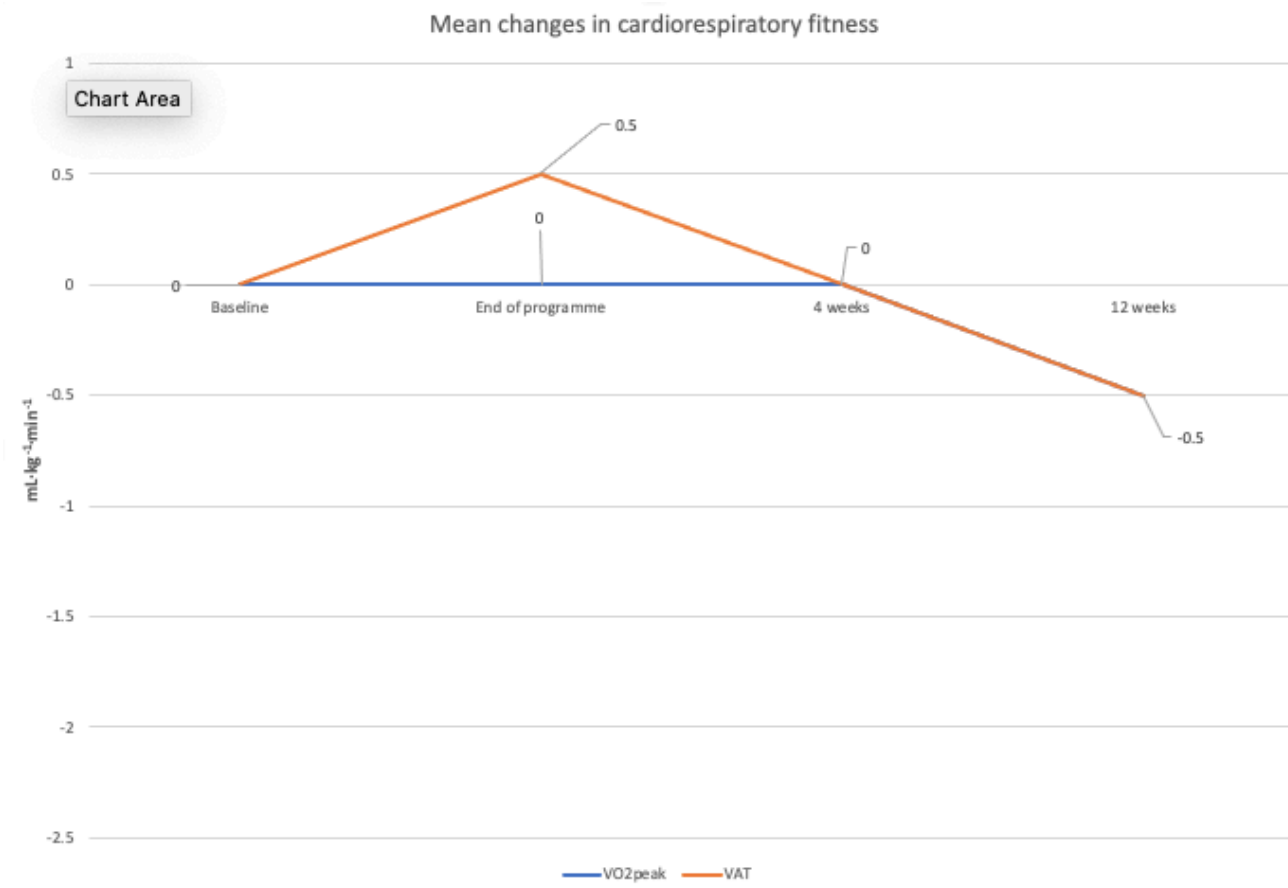


Figure 34 - Mean changes in cardiorespiratory fitness

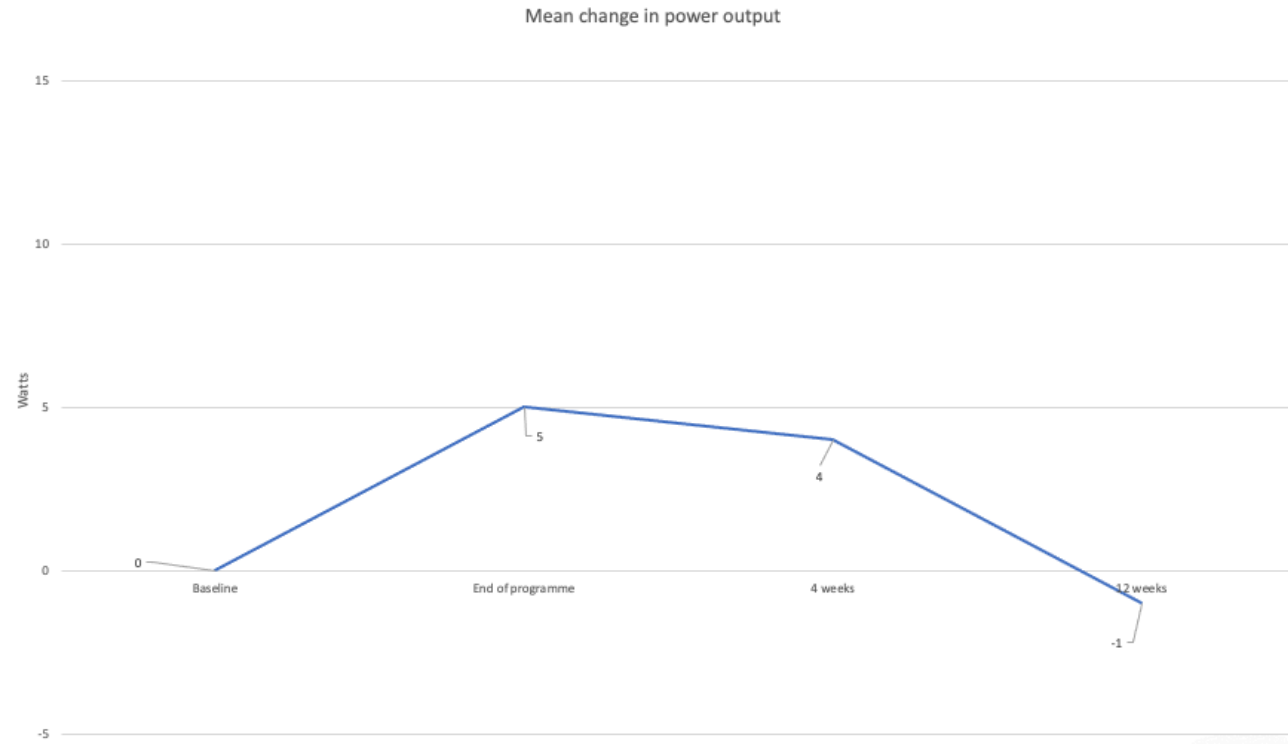


Figure 35 - Mean changes in peak power output

Table 18 - Clinical and quality of life outcomes

Variable	Pre (*n*=13)	End of programme (*n*=13)	Mean change (*n*=13)	4-week follow-up (*n*=11)	Mean change (*n*=11)	12-week follow-up (*n*=8)	Mean change (*n*=8)
ICD (m)^	97.9 (103.5)	130.8 (159.5)*		145.1 (274.8)*		220.3 (404.7)*	
MWD (m)	317.8 ± 164.7	417.5 ± 156.4*	99.7 ± 58.7*	412.5 ± 189.6*	88.9 ± 110.8*	416.4 ± 249.1	76.1 ± 141.8
Resting ABPI (mean both legs)	0.69 ± 0.19	0.73 ± 0.17*	0.05 ± 0.07*	0.71 ± 0.18	0.03 ± 0.12	0.77 ± 0.22	0.06 ± 0.14
VascuQoL pain score	4.1 ± 1.2	4.7 ± 1.3*	0.6 ± 0.9*	5.0 ± 1.3*	0.8 ± 1.1*	5.0 ± 1.3	0.7 ± 1.3
VascuQoL social score	5.3 ± 1.5	5.6 ± 1.5	0.3 ± 0.7	6.0 ± 1.6	0.6 ± 1.5	5.6 ± 1.5	0.3 ± 1.5
VascuQoL activities score	4.4 ± 1.2	4.9 ± 1.0*	0.5 ± 0.7*	5.3 ± 1.0*	0.8 ± 0.8*	4.7 ± 1.2	0.2 ± 1.2
VascuQoL symptom score^	5.5 (0.9)	6.0 (0.6)*		6.0 (0.7)		5.8 (1.5)	
VascuQoL emotional score	5.4 ± 1.7	5.6 ± 1.5	0.2 ± 0.9	5.8 ± 1.4	0.3 ± 1.6	6.0 ± 0.9	0.5 ± 1.2
VascuQoL total score	4.8 ± 1.1	5.3 ± 1.0*	0.4 ± 0.6*	5.6 ± 1.0*	0.7 ± 0.9*	5.4 ± 0.9	0.4 ± 1.1
SF-36 physical functioning^	55.0 (27.5)	60.0 (25.0)		62.5 (20.0)*		55.0 (20.0)	

SF-36 role physical	51.0 ± 22.7	55.8 ± 29.6	4.8 ± 17.7	61.5 ± 28.3	4.2 ± 17.5	58.0 ± 24.5	6.8 ± 17.6
SF-36 pain^	51.0 (30.5)	62.0 (44.0)*		61.5 (33.0)*		51.0 (43.0)	
SF-36 general health	48.4 ± 19.1	56.5 ± 22.5	8.1 ± 13.9	49.5 ± 15.3	1.0 ± 12.7	53.4 ± 21.2	3.2 ± 12.5
SF-36 vitality	48.1 ± 16.2	55.1 ± 19.8	7.0 ± 15.8	52.6 ± 19.1	4.2 ± 17.1	56.8 ± 15.2	8.5 ± 15.9
SF-36 social functioning^	87.5 (43.8)	100 (43.8)		100.0 (34.4)		75.0 (50.0)	
SF-36 role emotional^	66.7 (50.0)	91.7 (45.8)		100.0 (45.8)		66.7 (58.3)	
SF-36 mental health^	75.0 (20.0)	75.0 (25.0)		72.5 (27.5)		70.0 (35.0)	
SF-36 physical component summary	36.8 ± 6.0*	40.2 ± 7.7*	3.3 ± 4.8*	41.5 ± 6.2*	4.7 ± 4.9*	42.0 ± 8.4*	4.7 ± 6.9*
SF-36 mental component summary	51.4 ± 8.4	52.9 ± 8.2	1.5 ± 7.4	52.0 ± 9.8	0.0 ± 7.4	49.5 ± 10.3	-1.9 ± 7.5

Data are presented as mean ± SD or as median and IQR (denoted by ^). * = p <0.05. ABPI = Ankle-brachial pressure index, ICD = intermittent claudication distance, M = meters, MWD = maximum walking distance, SF-36 = Short-Form 36, VascuQoL = vascular quality of life questionnaire.

Table 19 - Cardiopulmonary exercise testing outcomes

Variable	Pre (*n*=12)	End of programme (*n*=12)	Mean change (*n*=12)	4-week follow-up (*n*=9)	Mean change (*n*=9)	12-week follow-up (*n*=6)	Mean change (*n*=6)
$\dot{V}O_{2Peak}$ (L·min^{-1})	1.17 (0.47)	1.24 (0.51)		1.05 (0.41)		0.96 (0.40)	
$\dot{V}O_{2Peak}$ (mL·kg^{-1}·min^{-1})	15.9 ± 3.7	16.0 ± 3.3	0.1 ± 1.6	15.3 ± 4.5	0.2 ± 1.8	14.3 ± 4.4	-0.5 ± 1.0
$\dot{V}O_{2Peak}$ (% predicted)	74.5 ± 16.6	75.1 ± 16.1	0.5 ± 6.6	72.8 ± 21.3	0.8 ± 6.8	70.6 ± 18.9	-1.7 ± 4.4
VAT (mL·kg^{-1}·min^{-1})	9.4 ± 1.3	9.9 ± 1.4	0.5 ± 1.0	9.2 ± 1.1	-0.1 ± 1.4	8.9 ± 1.4	-0.5 ± 0.5
VAT (% of $\dot{V}O_{2Peak}$)	60.7 ± 11.2	63.0 ± 9.3	2.3 ± 5.4	62.3 ± 10.2	-0.9 ± 5.8	64.2 ± 8.6	-1.5 ± 5.0
Peak HR (bpm)^	126 (21)	131 (21)		117 (33)		122 (33)	
Peak HR (% predicted)^	84.3 (9.6)	84.5 (17.8)		79.9 (18.4)		80.7 (26.8)	
$\dot{V}E/\dot{V}CO2$ slope	35.8 ± 4.1	37.1 ± 5.8	1.3 ± 5.0	39.1 ± 7.6	3.6 ± 10.5	40.3 ± 7.9	4.4 ± 7.4
O_2/HR (mL·beat)^	10.2 (3.3)	10.3 (2.0)		9.5 (3.2)		8.9 (1.3)	
$\Delta\dot{V}O2/\Delta WR$ slope (mL·min^{-1}·watt)	9.2 ± 1.4	8.6 ± 1.2	-0.5 ± 1.3	8.4 ± 1.7	-0.2 ± 1.5	8.9 ± 1.0	0.9 ± 1.5
RER	1.17 ± 0.15	1.17 ± 0.08	0.00 ± 0.13	1.12 ± 0.05	-0.08 ± 0.15	1.12 ± 0.07	-0.12 ± 0.17

PPO (w)	93 ± 34	98 ± 34*	5 ± 7*	88.1 ± 26.9	4 ± 8	83 ± 31	-1 ± 9

Data are presented as mean ± SD or as median and IQR (denoted by ^). * = *p* <0.05. bpm = beats per minute, HR = heart rate, mL·beat = millilitres per beat, mL·kg-1·min-1 = millilitres per kilogram per minute, mL·min-1·watt = millilitres per minute per watt, O2/HR = oxygen pulse, PPO = peak power output, RER = respiratory exchange ratio, VAT = Ventilatory Anaerobic Threshold, V̇E/V̇CO2 slope = minute ventilation to carbon dioxide production relationship, V̇O2Peak = peak oxygen consumption, W = watts, ΔV̇O2/ΔWR slope = oxygen uptake to work rate relationship.

5.5 Discussion

Study three identified that a *conventional* HIIT programme may not be feasible for a significant proportion of patients with IC. Therefore, the aim of this study was to consider the feasibility, tolerability and safety of a submaximal, novel HIIT programme for patients with IC, using newly defined exclusion criteria. The eligibility and recruitment rates were comparable to study three. Importantly however, completion rates were higher, and similar to those reported within a systematic review of exercise training trials for patients with IC (185). In addition, the eligibility and completion rates were higher than those recently reported for the usual-care care SEP in our centre (158), suggesting that HIIT may be a feasible alternative. This increase in completion rate was likely aided by the exclusion criteria alteration, which allowed more patients to progress to the intervention. Of the six patients in this cohort unable to complete a maximal effort CPET, three completed the programme, increasing the theoretical completion rate from 50% to 65%. The patient withdrawal rate in this study (20%), was similar to that in study three, but slightly higher than HIIT programmes in other clinical populations, which report figures closer to 10% (201, 263). However, the present withdrawal rate may be inflated by the small sample size and is similar to SEPs (185), suggesting that HIIT is no less tolerable than current practice, further supporting the feasibility of this intervention.

When considering tolerability, only one of the aforementioned patient withdrawals was due to an inability to tolerate the intervention. However, this patient had severe COPD, which was the main contributing factor, as they were limited more by breathlessness than symptoms of PAD. In hindsight, this patient should not have been recruited to the study.

A further two patients also withdrew due to an inability to tolerate the CPET, rather than the intervention. One patient had a previous femur

fracture and complained that femur pain was the limiting factor during the test, rather than symptoms of PAD whilst the other stated that they felt excessively fatigued following the test. Consequently, the three patients unable to tolerate the intervention or study procedures were limited by other factors or co-morbidities rather than IC. This is not surprising given that patients with IC often suffer from multi-morbidity, though those that completed the programme, also had other co-morbidities. This suggests that some co-morbidities may impact upon tolerability more than others. It is therefore important that this is considered in future studies to identify if any specific co-morbidities are likely to preclude participation in a HIIT programme.

For those who completed the programme, the majority of sessions were completed in full in just over 6 weeks. In addition, only one patient was unable to complete all 10 intervals by the beginning of week 3. This patient did not complete all 10 intervals in any session over the 6-week period, due to generalised fatigue. For clarity, this patient had a 147m (207%) increase in MWD. Therefore, despite an inherently lower exercise dose, this suggests that patients who cannot complete the intervention in full, may still obtain a benefit. This should inform future studies and patients should not be withdrawn if they are unable to complete 10 intervals within a certain timeframe, rather the titration should be individualised to each patient's ability.

The required intensity was also reached in the majority of sessions. If ≥85% peak HR was not achieved by the second interval within an individual session, it was achieved by the fifth interval in the majority of cases. One patient did not achieve ≥85% peak HR by the second interval in any session, possibly due to an exaggerated HR response to CPET. At baseline, the patient achieved 125% of their age-predicted maximum HR, which may not have been reachable during short-bursts of HIIT, but rather required a sustained effort. Indeed, they did not

achieve the required HR during HIIT, despite reaching the required power output in 94% of the completed intervals. In addition, they also achieved 124%, 118% and 123% of their age-predicted maximum HR at each respective follow-up appointment, suggesting it was not an isolated event and strengthening the possibility of an exaggerated CPET response. When this patient was excluded from the tolerability analysis, ≥85% peak HR was achieved by the second interval in 80% of sessions. Not only does this suggest that the intensity is tolerable, it also shows that for the majority of patients, the intervention was delivered as intended. This will be important for future studies as intervention fidelity can give researchers the confidence to attribute outcomes to their intervention, rather than to other, unknown elements (265, 266).

Overall, these feasibility and tolerability results suggest that this intervention is appropriate for patients with IC. In addition, the lower post-recruitment exclusion rate and the consequently increased completion rate compared to study three, also suggests that the inclusion and exclusion criteria are now appropriate for this population.

With regards to safety, across the two cohort studies there were three AEs that were possibly related, one of which was serious. However, no SAEs occurred during or immediately following any HIIT sessions or study visits. In addition, the only AE definitely related to the intervention was mild (dizziness), and not unexpected for this type of exercise, given that dizziness is often reported during sprint interval training (267), and has been reported in patients with heart failure undergoing HIIT (194). Accordingly, studies three and four provide an early indication that HIIT may be safe for patients with IC, though further evidence is required.

These early safety findings may be influenced by the use of CPET at baseline, which may help to screen out those at an increased risk of a

cardiac event during exercise. Current evidence suggests that CPET prior to a SEP is not necessary, as the number of patients screened out due to an abnormal CPET is low (3.5%) (174).

However, across these two cohort studies, almost three times as many patients (10%) were excluded following a positive baseline CPET. One possible reason for this discrepancy could be the use of a cycle ergometer rather than a treadmill. Often, CPET performed before a SEP is done in conjunction with the assessment of MWD, using a treadmill. This means that the test may be prematurely terminated due to the onset of IC. CPET on a cycle ergometer is terminated due to a variety of symptoms, not just IC (141). In addition, cycle-based testing can induce a greater metabolic response (140), and therefore myocardial workload. As such, this testing method may be more likely to unearth ischaemic changes, which are not unexpected, given the high proportion of PAD patients with coexisting, possibly undiagnosed, CAD (18).

Of the patients excluded following a positive baseline CPET, one had confirmed significant single vessel disease and was medically managed, another had confirmed triple vessel disease and underwent quadruple coronary artery bypass grafting, and another required permanent pacemaker insertion, thus ruling out false positives.

Furthermore, although SEPs are currently considered safe without the need for CPET, due to a low all-cause event rate, it would be reasonable to assume that the relative intensity for SEPs is lower than that for HIIT. Therefore, SEPs may be less likely to elicit an adverse cardiac response, compared to HIIT. Clearly, the potential cardiac risks presented by HIIT in patients with IC remain largely undefined and further evidence is needed from larger cohorts of patients. Certainly, any exercise programme adopting HIIT should undertake CPET (with exercise ECG screening) prior to prescribing and performing exercise to ensure accurate prescription and patient safety.

As with study three, those who completed the programme demonstrated a statistically significant improvement in both ICD and MWD, which was maintained or increased at each follow-up. However, this study was not designed or powered to detect a significant improvement and these changes are suggestive rather than definitive in nature.

Despite this, although the improvements in MWD were slightly smaller than the previous study and those reported for SEPs, they still represent a small to moderate MCID and may have been comparable to SEPs had it not been for the ceiling effect for one patient (118, 234). The improvements in ICD also represent a small to moderate MCID, and became greater than SEPs at 12-week follow-up (118, 234).

As such, based on the results of these two studies, HIIT programmes for patients with IC appear to have the potential to provide clinical and symptomatic improvements and warrant further investigation. As the intervention period is reduced from 12 to 6 weeks, with potentially comparable outcomes, HIIT can reduce patient attendance burden and may be easier to deliver. This may therefore provide a cost reduction at both patient and service delivery level. Finally, this HIIT programme moves away from a *one size fits all* approach and instead adopts a personalised exercise prescription based on a CPET, with the ability to maximise patient benefit.

The feasibility, tolerability, safety and potential efficacy findings presented here should be confirmed by the ongoing, multi-centre, proof-of-concept study (254), before RCT's considering HIIT versus usual-care SEPs are performed.

5.6 Limitations

Both of the previous studies and their findings are not without limitations. One key limitation is that patients were recruited following referral to a usual-care SEP. It is therefore not possible to identify if

patients who chose to take part are simply those who would have also chosen to take part in the SEP.

In addition, the single-centre design and the lack of a comparison group are also limitations. However, this initial feasibility work is vital to identify whether the intervention and inclusion / exclusion criteria are appropriate, or whether they need to be altered, as has been demonstrated.

5.7 Conclusion

This study has provided novel, but preliminary findings to suggest that a modified, submaximal HIIT programme is feasible, tolerable and potentially efficacious for patients with IC. It has also provided an early indication that, with relevant pre-screening, HIIT may be safe for these patients. Therefore, following a small change in the exclusion criteria, this study suggests that the intervention and inclusion / exclusion criteria are now appropriate for this population. These findings should be confirmed in a larger, multi-centre study, before randomised efficacy trials are performed.

Chapter 6: Study Five: Patient Acceptability of High-Intensity Interval Training for Intermittent Claudication: A Qualitative Study

6.1 Introduction

The preceding chapters have focussed on alternative exercise programmes to improve uptake and adherence to exercise therapy for patients with IC, with the main consideration being the feasibility of HIIT. However, the preceding chapters have also been quantitatively focused and the medical research council note that for feasibility studies, a mixture of quantitative and qualitative methods is likely to be needed, to understand patient level experiences, and therefore acceptability (206).

As such, it is important to consider this HIIT programme from the patient perspective. Semi-structured interviews are effective for this purpose as they allow researchers to explore patient perspectives and how they interpret their experiences (268).

6.2 Aim and Objective

This study aimed to consider the acceptability of HIIT from the perspective of the patient. This was achieved via semi-structured interviews conducted with a subset of patients who were involved in the previous two studies (chapters four and five). The main objective of these interviews was to explore patients experiences of the programme, why they took part, why they dropped out or why they refused to take part.

6.3 Methods and Study Design

6.3.1 Participants

Patients who were screened and invited to participate in studies three or four (chapters four and five) were eligible to participate in this study. Semi-structured interviews were conducted with patients sampled from three distinct groups:

Group one: Patients who completed the HIIT programme (completers). These interviews considered the patients experience of the

programme, how easy or hard they found it and whether they would be willing to undertake it again.

Group two: Those who agreed to participate in the HIIT programme but discontinued after ≥1 session (withdrawers). These interviews explored why patients dropped out of the programme and what could have prevented them from doing so.

Group three: Patients who were eligible for the HIIT programme but declined to participate (decliners). These interviews explored why patients chose not to participate in the programme and whether the study material could have been amended to be more appealing.

6.3.2 Interview

The interview was outlined in the PIS and an optional clause was provided on the consent form for groups one and two, whereby they could identify whether they were willing to participate in an interview. For group three, patients were signposted to the interview section of the PIS that they had received and those agreeing to be interviewed signed an interview specific consent form. For those interviewed via telephone, the consent form was read to the patient and verbal consent obtained.

An interview guide (appendix 4) with a pre-determined set of open questions was used but the interviews were flexible to allow the interviewer to ask further probing questions based on patient responses. All interviews were conducted face-to-face in a private room or over the telephone. They were also recorded using a Dictaphone, transcribed verbatim and anonymised. All interviews were conducted by SP who had attended a National Centre for Social Research (NatCen) training course. SP was also supervised by an expert mixed methodologist.

Patients were informed that they did not have to answer any questions that they felt uncomfortable with and that all responses were confidential.

Often, telephone interviews are considered less attractive than face-to-face interviews as the lack of visual cues can inhibit contextual and nonverbal data, rapport, probing and interpretation (269). However, there is a lack of evidence to suggest that they produce lower quality data (269). In addition, telephone interviews may allow participants to feel more relaxed about disclosing sensitive information (269). As such, providing the option of a telephone interview was appropriate and the medium used was based on patient preference and / or the COVID-19 pandemic.

6.3.3 Sample Size

A specific, pre-specified sample size is not possible for interview data as the aim is to collect data until saturation is reached (270). Saturation is the point at which no new categories or relevant themes are emerging from the data (270). However, research suggests that between six and 12 interviews is sufficient (271). As such, a target of 10 interviews per group was set as the minimum to achieve saturation, though it was difficult to recruit patients to groups two and three.

6.3.4 Data Analysis

Data was analysed via inductive thematic analysis, whereby themes were identified from within the data (272). This involved reading and re-reading the transcripts to identify patterns of responses that were related to the research question and could be grouped together under a theme heading. An inductive approach meant that the themes emerged from within the data and were not based on a pre-existing coding frame (272).

For this analysis, initial codes were identified based on the patterns of responses. These initial codes were then merged into final codes which were grouped together under a theme heading as appropriate (table 20). A sample of coding is presented in appendix 5. To ensure that the analysis was robust, the coding frame and raw data was reviewed by a member of the supervisory team who is an expert in mixed methods research. Feedback was then provided before the final coding frame

was created. Finally, data was managed using a qualitative computer software package (NVivo).

Table 20 - Coding table

Initial Code	Merged code	Theme
Difficulty	Overall thoughts of the programme	Patient feedback
Acute effect		
Positives		
Negatives		
Willingness to do again and encourage others		
Programme structure	Exercise programme components	
Group based vs. 1 to 1		
Type of exercise		
Possible Changes		
Took part to help us and others - altruism	Facilitators	Programme facilitators and barriers (and how to reduce them)
Took part for own health or symptoms – personal benefit		
Cost	Physical barriers	
Health or lifestyle		
Location / transport		
Time		
Motivation to exercise	Mental barriers	
Lack of understanding		
Apprehension		
Reimbursement	Reduce physical barriers	
Addressing time barriers		
More local centres		
Peer encouragement or feedback	Reduce mental barriers	
Visiting the facility / taster session		
Emphasise benefits		
Personable approach		
Improvement in symptoms / walking	Improvement in symptoms, walking and health	Symptom / health changes
Improvement in health		
Making and monitoring own progress		
Lack of symptomatic improvement	Lack of improvement in symptoms, walking and health	

6.4 Results

6.4.1 Recruitment

Sixteen of the 21 patients who completed the exercise programme participated in an interview. Of eight patients who withdrew from the programme, four were invited to interview, with two agreeing to participate. Out of the 86 patients who declined the exercise programme, 12 were interviewed. It was felt at this point that saturation had been reached, though it is possible that new information would have been provided by withdrawers, had more agreed to interview.

The mean interview length was 14 minutes and 12 seconds (range; 6 minutes and 12 seconds to 27 minutes and 23 seconds).

6.4.2 Patients

Of the 30 interviewees, 20 (67%) were male and the mean age was 70 ± 8 years, ranging from 51 to 89 years. For completers, the mean age was 72 ± 7 years and 81% were male, for withdrawers, the mean age was 68 ± 2 years and 50% were male and for decliners, the mean age was 70 ± 9 years, and 50% were male. Seventeen patients were interviewed at the hospital and 13 were interviewed via telephone. All patients consented to interview via written or verbal consent.

6.4.3 Thematic Analysis

Data analysis resulted in three major themes emerging, with several sub-themes identified within these. An outline of these themes and sub-themes is presented in table 21.

Table 21 - Themes and sub-themes identified

Theme	Sub-theme
1. Patient feedback	• Overall thoughts of the programme • Exercise programme components
2. Programme facilitators and barriers	• Facilitators • Physical Barriers • Mental barriers • Possible solutions to barriers
3. Symptomatic / health changes	• Improvement in symptoms, walking and health • Lack of improvement in symptoms, walking and health

6.4.4 Theme 1: Patient Feedback

6.4.4.(a) Subtheme 1a: Overall Thoughts of the Programme

Of the patients who took part in the programme, the majority stated that they thought it was good and that they enjoyed taking part in it, with general comments made such as *"I thought it was really good"*, and *"yeah I must say I enjoyed it".* One patient who withdrew due to a concurrent health issue also noted that they enjoyed the programme and that they had no intentions of withdrawing *"because I knew, well, I never knew, I thought, I'll complete this course [the programme], I knew in my head, oh definitely, I had no intentions of stopping"* (withdrawer, male, 69).

A number of patients found the programme useful or enjoyable, but disliked certain aspects of it, though this did not hinder their overall experience. For example, one patient noted that they *"found it [the programme] very useful"* but also stated *"… I mean the physical, nobody likes the physical exertion, but erm, you know you've got to go through it, or it won't help you"* (completer, male, 74). Another patient

stated that "*it's worth it*" and that they "*enjoyed it*" despite describing it as "*tough*" (completer, male, 66).

Some patients however, mainly females, stated that they did not mind doing the programme, or said they experienced satisfaction from it, but did not necessarily enjoy it as such. For example, *"I don't think enjoys the right word for me, but I do feel good after I've done it, I'm pleased that I've done it and I've done it okay, so it's more about the satisfaction of completing it, rather than enjoying doing it"* (completer, female, 66).

Finally, one patient stated that they did not enjoy the programme and actually dreaded coming but nevertheless completed it… *"oh no, I didn't, there was nothing I enjoyed about it, no, no", "I did dread it, every time, I did dread it…"* (completer, female 71).

Clearly, individual patient experiences and thoughts of the programme varied greatly, ranging from enjoyment to dread, though the latter was reported by just one patient. Most patients either enjoyed the programme or at least did not mind doing it and there were more positive than negative comments, suggesting that it was acceptable for the majority who took part.

Despite the majority of comments being positive, only two patients commented that they found the programme easy, with one stating *"well it was on the side of easy, rather than on the side of difficult"* (completer, male, 84). The other patient noted that they expected the programme to be more difficult than it was… *"it was probably a little easier than I anticipated"* (completer, male, 76).

Consequently, most patients described the programme as difficult, though the description again differed between patients. Some described it as "hard", whilst others described it as "not easy". One patient also described it as "gruelling".

Patients also described different experiences of how the difficulty changed over the course of the programme. Firstly, two patients noted that the programme got harder as it progressed and attributed this to an increase in intensity… *"…easy to start off with then you up the grade a bit, and it's a bit harder and then very hard at the end"* (completer, male, 78). Despite 13 patients having an increase in intensity over the course of the programme, this concurrent increase in difficulty was only cited by two.

The majority of patients actually stated that the programme got easier as it progressed. For example, one patient stated… *"erm, I found it hard at first, but it did get a lot easier as the weeks went on"* (completer, male, 68). One possible reason for this may be that initially, patients do not know what to expect of the programme, or how it will make them feel. For example, it was noted that *"it gets easier, because after the first two sessions, you know what to expect, you know what you're gonna feel like…"* (withdrawer, male, 69). It also appears that the first session may be the most difficult, with one patient stating

"it was [difficult] at first, yeah, it was at first, yeah, I don't know how I got off that bloody seat to be honest with you, first time I went on it, but I did…" (completer, male, 71).

This therefore suggests that once patients complete the first week or so, the programme may begin to feel easier, as they know what to expect.

Another possible explanation is that patients may begin to feel fitter over the course of the programme, making it seem easier. This means that if the programme remains stable (i.e. no need to increase the intensity), patients may perceive that it becomes easier as they feel fitter, or if the intensity is increased, patients may feel better equipped to cope with it, due to their perception of increased fitness. For example, one patient when asked noted

"[interviewer: and do you think because at points we were having to increase the resistance to try and get you to the heart rate level that we

wanted to get you at. Do you think that you were comfortable with that?]
Patient: oh yes, I appreciate why you did it, erm, and erm, obviously it shows that I was getting a bit fitter" (completer, male, 68).

However, despite the majority stating it got easier, none of the patients stated that the programme became easy… *"I think, once I got over that initial maybe the first two or three, then I do think I found it a little bit easier, I don't think I ever found it easy…"* (completer, female 66).
Some patients actually noted that the programme got easier initially, but then became more difficult again… *"very difficult to start with, then it sort of gets a bit easier in the middle, but then I found it got really hard towards the end"* (completer, male, 69). Finally, two patients also commented that the programme was difficult, but did not comment on whether this changed, meaning it is likely that the difficulty remained the same for them throughout.

It is also important to understand why patients chose to continue the programme, despite finding it difficult. Some patients highlighted that they felt the programme needed to be difficult to make it worthwhile, with one patient stating, *"I mean it's not gonna be easy, is it, there'd be no point doing it if it was easy"* (completer, female, 66). Similarly, a number of patients noted that although the programme was difficult, it was not out of their capabilities to complete it, with one patient stating *"oh the bike was hard, yes it was hard, but err, it's not impossible"* (completer, male, 72) and another stating *"because you can do it at your own pace and not, you're not getting pushed and pushed and pushed, you're all set out to do what you can do in your capabilities"* (completer, male, 51).
However, the majority of patients stated that the reason they continued despite finding the programme difficult, and sometimes painful, was because of their personal mental attitude, and having the

"push", "desire" and "determination" to go "through it" and to not let the programme "beat" them. For example, one patient stated *"…but I think it's about determination and sometimes you've just got to go that bit further haven't you and just push yourself a bit more to get a result"* (completer, female, 66), whilst another stated *"…but if you've got the push, like I have, then it doesn't become too hard, if you haven't got any push at all, it's going to be very painful for them people you know what I mean?"* (completer, male, 66). Other patients simply stated that the reason they continued was because once they start something, they want to complete it, which was the case for the patient who dreaded the programme… *"Because I do that, I do, I start, even if I dread something, if I say I'm gonna do it, I do it"* (completer, female, 71). Similarly, another patient stated, *"but then I stuck with it, because usually when I start something, I've got to finish it, yeah"* (completer, female, 76). A similar statement was also made by a patient who declined the programme; *"for me, if you're going to start on that sort of routine, erm, you've got to keep it up if you possibly can, otherwise it's not gonna be any good to you"* (decliner, female, 84).

In addition to describing their general thoughts and how difficult they found the programme, a number of patients also described various acute effects of it.

A small number of patients reported leg pain or burning whilst cycling, mainly in the quadriceps region rather than in the calves. This is likely to be because the quadriceps are the predominant working muscles during cycling. For example, one patient noted *"no, I didn't, to be honest, I didn't get any cramps in my calves, it was in these muscles here *rubs top of legs*"* (completer, male, 68). However, some patients reported a more general feeling of pain, rather than stating where it was felt *"…sometimes on the bike I would be alright for the first one or two, three sessions maybe, and then it just got right painful for the next three or four or five then it sort of eased off again…"* (completer, male,

72). One other acute physical effect was reported by one patient, who noted that they felt fatigued for the rest of the day following each session, which contributed to their withdrawal from the programme… *"erm, but when I got home then it were rest of the day, shattered…"* (withdrawer, female, 66).

Some patients that completed the programme also reported acute mental effects that were positive, describing a sense of satisfaction or achievement after completing each session… *"well I think it makes you, I think it's got this ability to make you feel good for completing it, when, each session I am talking about…"* (completer, female, 66). Finally, one patient noted feeling a bit of a "buzz" after each session… *"aaaah, fantastic, I feel like doing marathon straight after… I feel fantastic like I can walk straight down corridor, straight down steps, across the road and home… I feel as though I've got special soles in my shoes*" (completer, male, 72).

One final element that is important to consider is whether those who took part in the programme would be willing to do so again, and recommend it to others. Two female patients either stated that they did not know whether they would do the programme again, *"I don't know, I don't know that, erm, no I don't know. I'd have to think about that one"* (completer, female, 76), or said that they would, when it was more apparent that they would not *"yeah I think I would, yeah, yeah, but I'm not gonna, no"* (completer, female, 71).

The majority of patients however, stated that they would be willing to do the programme again either immediately *"oh yeah, without even blinking, I'd do it, straight away"* (completer, male, 51) or in the future *"I probably would complete it again, but maybe in a couple of months, you know"* (completer, male, 66).

A number of patients also stated that they would recommend the programme to others *"I would certainly recommend anybody to do it, if there was anybody in the same circumstances"* (completer, male, 74),

which was also the case for the patient who suggested that they would not do the programme again *"but I wouldn't say to anybody; 'oh don't go', no I'd say you're alright, if you've got the time"* (completer, female, 71).

6.4.4.(b) Subtheme 1b: Exercise Programme Components

It is also important to get an understanding of what patients think about the structure of the programme. Firstly, most of the patients who completed the programme simply stated that "everything was fine". More specifically, with regards to the frequency (3 times per week) and duration (6 weeks) of the programme, a number of patients stated that this was fine or that they were happy to do it, with some stating that it was better than the 12-week duration proposed for the usual-care SEP. A similar number of patients however, mainly those that declined the programme, stated that this time commitment was still too burdensome. These time-based factors will be considered in more detail in the 'barriers' section of this chapter (p. 323-241).

Most patients were happy with the length of each session, including the warm-up and cool-down, with one stating that it should not be shortened… *"No, not from my perspective, if it was sort of 20 minutes or half an hour, then I would probably think twice about doing it, but although it's only an extra 15 minutes, you can get everything in in that 45 minutes, so, so yeah, was good"* (completer, male, 69). Two patients, however, did not see the value in the warm-up and cool-down and stated that 10 minutes for each was too long *"yeah, yeah, yeah I think 5 minutes, I think from my point of view, 5 minutes would have been enough…"* (completer, male, 73).

With regards to the 20-minute HIIT intervention itself, despite most patients stating that "everything was fine", some did state that, as expected, this was the hardest part of the programme…

"the erm, the 10 minutes flat out on the bike I didn't enjoy, [interviewer: The HIIT intervals, the hard bit you didn't really enjoy, but the] I enjoyed the overall, yeah, that was just a big part [interviewer: the bit that you disliked the most or liked the least…] was the flat out bits" (completer, male, 66).

However, as mentioned previously, this difficulty did not stop patients from completing the programme and only two patients were unable to tolerate the intervention.

With regards to the type of exercise used in the programme, cycling, there was mixed feedback. Some patients preferred cycling as opposed to treadmill walking

"…I think erm with the cycling it's the least sort of physical type of exercise if that, that sounds a bit funny [interviewer: you're taking the weight off your legs?] I was gonna say I think it's easier than a treadmill, for instance, erm, which I think is more of a problem" (completer, male, 74),

though there were issues with the seat

"Not keen on the saddle but I think that's the same with most bikes" (completer, female, 66).

Conversely, two patients stated that they would prefer treadmill exercise to cycling, though one of these was unable to cycle due to previous orthopaedic surgery. A number of patients also suggested that a variety of exercises may be better

"I think where your legs are concerned, it's better to use the cycle and possibly the treadmill, but erm, can you, you use a rowing machine? you know for you, you are using your legs on there aren't you as well…" (completer, male, 81). Finally, some patients felt that the type of exercise did not matter, *"I would have done it whether it was cycling or on the treadmill"* (completer, male, 76).

Another important element to consider, is the possibility of the programme being group-based rather than one-to-one to aid scalability. The majority of patients stated that they preferred a one-to-one approach *"oh no I think one-to-one is a better thing"* (completer, male, 78), though most would still attend a group-based programme *"erm, but it [a group programme] wouldn't stop me doing it"* (completer, male, 76) and appreciated that some patients may prefer it *"some other people might prefer doing it in a group"* (completer, male, 69). One patient stated that they would prefer a group-based programme, whilst another was unsure and stated that a group programme may work, if all the participants were of a similar age. A number of other patients stated that it did not matter to them whether it was group-based or one-to-one… *"I mean I can work a one-to-one or I can work in a group, doesn't bother me"* (completer, male, 66). However, several comments were made regarding the potential knock-on effects of a group-based programme, that were both positive and negative. It was highlighted that a group programme may cause some to feel embarrassed or judged *"cause you're judging if you're in a group and I'd sooner do what you can do yourself then it's just down to you"* (completer, male, 66), whilst others stated that it would add an element of competition that may or may not provide added motivation *"well, I think, no I don't think so, I think it would make it a bit more comp… well if you're a competitive person it will make you competitive, but if you're not a competitive person, you'd feel a bit shy and back away and that"* (completer, male, 68). Finally, the patient who noted that they would prefer a group-based programme stated, *"I think you get a bit more confidence if you're like in a group"* (completer, male, 81).

One important consideration is that a group-based programme would add an element of social interaction between patients. This was highlighted by one patient who was unable to participate in the HIIT

programme but undertook a usual-care SEP and appreciated the social element of it…

"I can't speak for everybody else but looking at it and I look at it as a social event as well as the exercise. Because I think some people miss that" (decliner, male, 71).

However, this may have an undesired effect on patients exercise performance…*" I think if you get a group of people you gab, then they stop pedalling don't they like I did that time. I don't know"* (completer, female, 76).

In addition to direct feedback about the programme, a small number of potential changes were suggested. The main suggestion was to include a variety of exercises, rather than just cycling. Some patients also suggested that the programme could be reduced to 1-2 sessions per week, which will be considered in the next theme of this chapter, 'facilitators and barriers' (p.231). Other suggestions included reducing the length of the warm-up and cool-down, offering weekend sessions and increasing the programme duration to 12 weeks whilst reducing the frequency to twice per week, though each of these suggestions were made by just one patient. Two patients also specifically stated that they had no changes to suggest.

6.4.5 Theme 2: Programme Facilitators and Barriers

A number of potential facilitators and barriers were identified by all patients. Interestingly, patients that completed the programme who were therefore less affected by barriers, were still able to identify those that may be impactful to others.

6.4.5.(a) Subtheme 2a: Facilitators

Two main facilitators, or reasons for participation, were highlighted – altruism and personal benefit.

A number of patients highlighted that they took part in the programme because they wanted to help the research team, and other patients, by contributing to the advancement of healthcare. For example, one

patient simply stated, *"I just hope that it's helped you [by taking part]* (completer, male, 84)*"* whilst another noted *"and hopefully if things progress and you people see progression, things will advance, hopefully people will be better off for it"* (completer, male, 78).

Similarly, some patients highlighted that they took part in the programme because it offered an opportunity to help the national health service…

"because they've done well for me have the hospitals as you know what they've done for me the hospitals and I'll never say no to anything and I'll always help the hospital if I can and I'll do anything they want me to" (withdrawer, male, 69).

Some patients also noted that they took part in the programme to try and improve their symptoms, health or both. Some were quite broad, simply stating that they took part in the programme to "help" themselves…

"I just thought, if something can help me, I'll go for it, no matter what it is, I'll go for it" (completer, male, 66), whilst others were more specific, stating that they took part in the programme to try and improve their symptoms and health… *"erm, because I wanted to improve my walking actually in the obviously erm, and perhaps improve my health as well"* (completer, male, 68).

One patient noted that they took part more to prevent a deterioration, rather than to obtain a benefit…

"yeah, I think, erm, obviously you're conscious of a prospect of a deterioration I think, erm, and you hope that the programme and what you follow up with will help that or, slow it down at least, yeah" (completer, male, 74).

They were, however, aware that an improvement may be possible and suggested that taking part was somewhat of a no-lose situation, as there were no other immediate treatment options available …

"well, you felt you had to try in the hope it would do you some good, because at the end of the day, you'd already lost some time if you didn't do anything, but there was always the prospect of an improvement, yeah".

Other patients noted something similar, stating that the programme was worth "trying".

Finally, it is worth noting that these two reasons for participation were often cited in conjunction with each other, meaning that patients took part in the programme to help us and others, but also to help themselves… *"the two things, a. that it helps you and b. that it helps me. If you can achieve either one of those, that would be worthwhile doing. If you can achieve both well that's fine"* (completer, male, 84).

6.4.5.(b) Subtheme 2b: Physical Barriers

In addition to facilitators, a number of barriers were also apparent. Firstly, three key physical barriers were identified, namely cost, location / transport and time. These barriers either affected patients in isolation or in combination with each other. With regards to time, it was identified that the programme frequency of 3 times per week may be too burdensome… *"I mean like I say, I'd have been willing, it was just the fact it was too many days for me"* (decliner, female, 64).

In addition, the 6-week duration may also have been a barrier *"[interviewer: so do you think in general 6 weeks is too long?] interviewee: I'd say so, in my personal opinion I'd say so, yes"* (decliner, male, 59).

However, for some patients, especially those that took part, this was not the case

"when that was offered to me, I thought, 6 weeks, pfft, I could do 6 weeks, don't have a problem with that" (completer, male, 66).

Importantly, it was identified that for some, the 6-week HIIT duration was more attractive than the 12-week usual-care SEP duration…

"I think really it was about our lifestyle, I felt 6 weeks would fit in much better because we go to London a lot like you know, we had to postpone when we started because we were going, we were going away, so we do because we've got family in different places, so we do go here and there and I thought if its 12 weeks, for me that is a long time to go without seeing my grandchildren. So that's probably my main reason for choosing the 6 weeks, I'd rather have done it in a concentrated time rather than spread it out" (completer, female, 66).

Another issue with regards to time was based on the programme scheduling and whether it would fit in with patients' daily lives. One patient stated

"…you put the dates on the Monday, Wednesday and Friday and I thought, well I can do that, but if you'd have put Tuesday, Thursday and summat, I wouldn't have done it" (completer, female, 71).

It was also stated that the time of day was important…

"if you've got it over and done with by 10 O'clock, you've still got the rest of the day whereas if you're out and about doing things and you're thinking, oh I better get myself home and ready to, you know what I mean?" (completer, female, 66).

One patient did state that an evening slot would be more suitable due to work, but the majority stated that morning times were better.

Two patients also highlighted that the delay between seeing the consultant and being invited to the programme may be a barrier

"I was waiting quite a long time and I'd quite forgotten about it when I got the letter… because I mean, you have other, you have other plans don't you, you know if you say you're going on trials you might forget about it and have something arranged, especially when it's 3 times a week, I mean how do you know you've got 3 times a week free at that time?" (completer, female, 66).

This delay is mainly caused by administrative procedures, as following the consultation, a letter needs to be dictated, checked, typed and then finally sent to the research team.

For location / transport, the main barrier was the distance from the patient's home to the hospital in conjunction with a limited access to transport

"erm, I didn't have the transport to get through. Erm, it was too awkward I'd have to catch two buses and erm it was just, with my leg not being so good, it was too far to get through so I couldn't do it" (decliner, male, 69).

However, location / transport was mainly mentioned as a barrier in combination with time, usually because of the additional travel time required to attend the programme…

"yeah, 3 times a week for 6 weeks becomes a bit of a bite by the end of it, but I suppose that's only because I've got an hours travelling to get here and an hour to get back so it takes our whole morning, although I'm only here for an hour with you" (completer, male, 76).

Travel time and location were also highlighted as barriers by a number of other patients, especially if they did not drive

*"err, just because of the timings because I work at *** and I don't have a car so it would mean going on buses to Hull Royal and it just meant taking such a big chunk out of each day, it's just not feasible really"* (decliner, female, 62).

One patient who did drive, used the park and ride facility but noted that travel time contributed to their withdrawal from the programme…

"yeah, that was because of where I live sort of travel time, and it yeah, I were leaving home at 10:00 and I were lucky to get in at 1:00 [interviewer: so, it was a significant time?] it was really, 3 days a week, it was quite significant" (withdrawer, female, 66).

The cost of transport was also highlighted as a barrier…
"like I say it more than anything it's the fact that it was travelling backwards and forwards to Hull and we don't drive so it's, even then it's still gonna cost you isn't it, but yes it was just the bus fares" (decliner, female, 63).
This barrier was also highlighted by one patient that completed the programme who stated that for the limited time that they did it, cost did not matter, but it may have become an issue if they were to attend for a longer term…
"yes, I mean the costs, doing it for a limited time doesn't matter, but if you were doing it consistently, it may become a factor. Petrol, I mean what's petrol now, £6 a gallon? And I'm using more than a gallon a day, on coming" (completer, male, 84).
Parking costs were also highlighted as an issue, with one patient opting to use the park and ride as an alternative… *"I must admit, before park and ride popped into my head, I thought I aren't paying all that out in parking fees 3 days a week"* (withdrawer, female, 66).

Conversely, a number of patients, when directly asked, stated that they did not perceive time, location / transport or cost as barriers
"not really, no, because erm, I'm retired now, so don't have to take time off work" (completer, male, 68) and
"I only live 40-minute ride [away] for me and her [patient's wife], which is no problem" (withdrawer, male, 69) and
"no, well I do have to get a couple of buses, but the cost wasn't the issue because I've got a bus pass anyway" (decliner, female, 69).

Other patients however, stated that although these were not necessarily barriers for them personally, they could appreciate that they were barriers for others…

"I mean for me I'm probably fortunate to have the income to do it whereas somebody might just have their old age pension or whatever and probably couldn't afford to do it" (completer, male, 69), and *"I think really, I mean I'm okay, I'm a pensioner so I get a free bus pass but if I was younger and doing it, I'd wanna be able to claim bus fares, definitely…"* (completer, female, 71).

Finally, some patients did recognise these as barriers, but the potential benefit of taking part was a greater facilitator…
*"not to me, I mean I actually work 3 days a week [in Hull], but erm, only one of the days was a workday so the other two I was coming in, from **** and going back to **** but you feel it's worthwhile to make the effort if it's going to do you some good"* (completer, male, 74).

Other physical barriers included severe co-morbidities or other health issues…
"well, I can't get out the house, I can't walk far, I've got COPD and I've got pleural plaque and pleural thickening you know what I mean? And I just, I'm out of breath most of the time" (decliner, male, 77),
family commitments… *"…because I've got erm my son who's got disabilities and I'm going through a lot of problems with him at the moment yeah. I can't leave him with anybody you see"* (decliner, female, 59)
and lifestyle choices… *"erm, this is maybe irrelevant, I'm a smoker and it did say no smoking for 3 hours beforehand and then you'll be there all that however long it took, [interviewer: so, you'd be desperate for a fag by the time you've got out?] I don't know as if I'll be desperate, but it was a factor, I thought oh for god sake you know, 3 hours before I actually get there and then and as much as yeah giving up smoking is one thing, but it's not as easy as what people seem to think it is"* (decliner, female, 63).

6.4.5.(c) Subtheme 2c: Mental Barriers

In addition to physical barriers, a number of mental barriers were also identified. Firstly, some patients felt that a lack of motivation to exercise may be a barrier for others and attributed non-engagement to an element of laziness. For example, one patient noted…

"well a lot of people, probably because they're lazy, you know what I mean? It's as simple as that. They get overweight, they don't wanna do anything, just sit on their arses and do nothing" (completer, male, 66).

Another patient also stated, *"I don't understand why they won't do it because, but people are strange, and you've got to want to help yourself"* (completer, female, 66). Similarly, a number of patients stated that "if they want to do it, they will do it", suggesting that they believe motivation is a key determinant for engagement…

"I think if people wanna take part, they will do, no matter how, how the letter of introduction is and if they don't wanna take part, they won't take part will they?" (completer, male, 78).

A personal lack of motivation to exercise was also highlighted by some patients *"…because it's as I told you before, exercise is not something that's at the top of my list, never has been"* (completer, female, 66).

As well as being a barrier for the HIIT programme specifically, a lack of motivation was also apparent for exercise in general. A number of patients were sceptical about whether they, or others, would perform an exercise programme in their own time at home… *"yeah, for myself it wouldn't work because I'm lazy, I wouldn't do it… so no, I wouldn't do anything myself at home"* (decliner, female, 62).

As such, some patients actually stated that they were more likely to be motivated to exercise at a centre-based programme than in their own time…

"I'm better if I've got something I've got to do, where I've got people I'm meeting and I'm doing something with somebody than if I'm just

going to the gym when I feel like it because I can always think of something else I could be doing…" (completer, female, 66).
This therefore suggests that motivation is context specific and some patients may have greater motivation to exercise in a structured, supervised facility. Having access to such a facility may therefore be a facilitator for those with limited motivation to exercise in their own time.

Some patients, however, may not necessarily lack the motivation to exercise but rather the understanding of their condition, exercise and the benefits of it. For example, one patient, who was a smoker, was unsure of why they had IC, because they felt that they had been active all of their life…
"…my legs have been in use sort of all my life to retirement. [interviewer: and that is something people find quite difficult to understand when we say well exercise is the treatment. A lot of people say well I've exercised all my life…] I wouldn't say I've exercised but I've been on my legs, I've used my legs, I've danced, I've done recreational things which means you're on your legs or your feet and you think, well why is this the case?" (withdrawer, female, 66).
This suggests that patients may be unaware of other factors, such as smoking, that may be detrimental to their health and contribute to their IC.
Another patient did not know how exercise could help their IC, due to a limited understanding of its pathophysiology and the potential mechanism of action
"…but at the end of the day I am just trying to think how could exercises do anything do anything to your artery, if it is furred up how does exercise clear it?" (decliner, male, 78).

One patient also stated, *"it doesn't appear to me that there are particularly any results from this programme, it's results for you doing*

the research, but I don't know if the people are getting any sort of results to say at the end of it, that has done you good and you're better than when you started…" (withdrawer, female, 66). Although this comment is specific to the HIIT programme, which as of yet, has not demonstrated efficacy, it does highlight a lack of understanding of the general benefits of exercise for IC.

In addition to a lack of understanding with regards to the benefits of exercise, there was also a limited understanding of exercise in general and who could perform it. Patients often had a misconception that they were unable to exercise, often due to a fear of making their condition or health worse. For example, one patient noted that they were unsure about whether exercise would worsen their IC…

"I told you I joined this gym, I only joined this gym because it was a half price special with a family member, and I haven't been because of these pains in my legs and I didn't know whether it was gonna exaggerate it" (completer, male, 75).

Another patient noted a fear of exacerbating other co-morbidities as a barrier. Although severe co-morbidities can preclude exercise, as noted above, this patient cited mild co-morbidities as a barrier, when exercise would still be appropriate…

"I've got heart problems as well, well I've had a heart attack and I've got AF [atrial fibrillation] and I wouldn't want to start them off again, because they seem to be coping at the moment so anything that would put pressure on it, erm, knock it out of kilter again, erm I'd just be a bit frightened" (decliner, female, 84).

This misconception remained for one patient, despite completing the HIIT programme, suggesting that direct experience may still not reduce this barrier…

"and I can't exactly do exercises now, I can't like you would do at one time, go on the trampoline and skip and what have you, all that's gone,

I can't do nothing like that, I'd die wouldn't I, I'd have a heart attack wouldn't I, I'd be dead" (completer, female, 71).

Other patients noted that they were simply unsure of what exercise to do and how often to do it… *"yes, I would not have had a clue what exercise to go into if I had have gone straight into a gym as opposed to coming here"* (completer, male, 74). This again suggests a limited understanding of exercise and the general principles.

Some patients however, demonstrated an understanding of some elements, but not others. For example, some patients understood the benefits of exercise, but were not sure of what to do or how to do it. Others stated that they knew the importance of exercise but not for their specific condition.

Finally, some patients demonstrated an understanding of exercise, but felt that they already did enough in their own time…

"for me personally, if I wasn't working or anything then yes, I would have gone along with it because obviously I'd have been sitting more, but because I am working and I am moving about on it, I just don't think there's gonna be any more benefits from what I am actually doing" (decliner, female, 64).

A lack of understanding was also apparent for some patients who took part in the programme, suggesting that having some knowledge of the condition or exercise may be sufficient to prevent this barrier from precluding engagement.

The next mental barrier was apprehension or a lack of confidence, whereby some patients were apprehensive or unsure about their ability to do the programme.

"…I was a bit worried thinking you know, I've never been on a bike for 40 years, you know, I mean seriously, it's erm, so some people will be

thinking you know, am I gonna make a fool of myself here you know…?" (completer, male, 71), and

"erm, when you told me what it was I was going to be doing, I had my doubts as to whether I'd be able to do that… when I knew it was sort of that HIIT stuff, I was a bit concerned" (completer, female, 66).

Some patients described this apprehension more as a "fear of failure" or a "fear of the unknown". Other patients were more subtle about this apprehension, stating that they were "surprised" that they were able to do the programme… *"well, I, I was pleasantly surprised that I was able to do it, relatively straightforward"* (completer, male, 84).

Although this lack of confidence or apprehension was mentioned by some patients that declined the programme, it was mostly cited by patients that completed it. This suggests that although it acted as a barrier, it was often not sufficient to prevent participation.

In addition, by taking part in the programme, these patients were able to increase their confidence and understanding of exercise, reducing these barriers further and giving them an incentive to continue…

Patient: "And it give me a lot more confidence as well.

[interviewer: And then in terms of sort of you said you feel more confident, just is it in terms of you feel more comfortable about exercising in general, do you feel like you know your condition a bit better or?]

Patient: well, a mixture of them all of them all yeah. Erm, because I know I can do these things now and erm, it's proved to me that I can do them so I make an effort to do more now, yeah" (completer, male, 68).

Another patient also stated… *"Like you know, I've never been one for exercising really, a lot erm, but you reach a stage and you think, should I be doing that or, whereas now, I know I've got much more insight into what it is, what exercise is you know things like heart rate, blood*

pressure, what it does, what it means sort of thing, so yeah I find it very helpful that, yeah" (completer, male, 71).

6.4.5.(d) Subtheme 2d: Possible Solutions to Barriers

For all of the aforementioned barriers, the extent to which they affect each individual will determine whether they are strong enough to prevent participation. This was demonstrated by several patients who still took part in the programme, despite citing these barriers. However, for some patients, for whom these barriers do preclude participation, solutions to help overcome them are required.

A number of patients offered one simple solution to reducing cost as a barrier, suggesting that funds could be made available to reimburse patients, whether this be for travel or parking costs…

"if you wanted to sort of entice people, erm, that might be an issue that you sort of say look, if you've got a problem with costs, with travelling or you know, parking, we'll, we'll you know reimburse you, for your outside costs" (completer, male, 71).

For the barrier of time, there were some different elements to address. Firstly, it was highlighted that the length of time between the patient being referred and starting the programme, resulting from the administrative process, may be a barrier. It was suggested that it would be beneficial for a member of the research team to be available to discuss the study with potentially eligible patients immediately following their consultation. This would provide an opportunity to thoroughly explain the study, and provide the PIS, at the time of referral, significantly reducing this barrier.

Secondly, it was highlighted that the programme scheduling needed to fit in with patients' daily lives. As such, offering flexibility to suit each patient, as opposed to set days and times, was suggested to make the programme more accessible *"or even if they were weekend sessions, that you know. That would make it easier"* (decliner, female, 62).

Finally, some patients highlighted that the programme frequency of 3 times per week was too burdensome. As such, it was suggested that reducing this to once or twice per week may be better *"I think it's, if I had to go somewhere it's too much… yeah, I could do two [times a week], yeah"* (decliner, female, 59).

In addition, it was highlighted that the 6-week duration may be too long, though some stated that if it was less than this, it would be too short… *"no I think if it's shorter [than 6 weeks], it's a waste of time really, doesn't give you enough time does it"* (decliner, female, 59). Furthermore, it was also stated that the 6-week duration was more attractive than the 12-week option. Interestingly, some felt that 6 weeks would still be enough time if the frequency was reduced from 3 times per week, though one patient did state that the programme length could be increased if the frequency was reduced.

The final physical barrier was location / transport, which also interlinked with the other barriers of cost and time. As such, reducing this barrier could potentially reduce all three. Patients identified that this barrier could be reduced by delivering the programme in other centres that were more local *"yes, yes, that would have been a lot better, something a bit closer, it seems just a trek you know, from home and that"* (decliner, female, 69).

It was suggested that these centres could be provided via local hospital facilities or leisure centres, though two patients did highlight concerns with using local leisure facilities.

The first patient stated, *"erm, well there's only across the road at the sports centre there, which is right on my doorstep but erm, I mean, I don't class the people in there as experienced as the hospital, you know erm, I know they've done courses and things, but they're not nurses and they're not, you know, they're not medical"* (decliner, female, 84).

The second patient said, *"…I think erm, people are bit more reticent of going to a like community centre, because they might know people there whereas in hospital, it's like anonymous isn't it? People don't know what you're doing here and things"* (completer, male, 68). Therefore, if the programme were to be delivered using leisure facilities, patients should be reassured that appropriately trained staff would be supervising them at all times, and that the sessions would take place in a private room, rather than a public gymnasium.

A number of suggestions were also made that could potentially reduce mental barriers. However, in contrast to the physical barriers, these suggestions would address a number of the mental barriers concurrently, rather than in isolation. The first suggestion was to include a section in the PIS providing feedback from patients who have taken part in the programme. This would allow prospective patients to get an understanding of the programme and how it feels from their peers, who suffer with the same health condition. For these patients, having this information may increase their motivation and confidence to exercise, and reduce their apprehension. This is because it would help them to understand that other patients in a similar position have been able to successfully participate in the programme…
"Erm, yes it [including patient feedback] probably would [encourage more people to take part] because if you can hear from people who have done it then you think, oh yes, that, you know, that sounds good" (decliner, female, 62).
Including such a section in the PIS also provides an opportunity to emphasise the benefits of the programme, potentially addressing any lack of understanding with regards to the benefits of exercise for IC…
"if you can give examples of when people have progressed, to prospective you know patients erm, I think you know, they'd maybe look at it and think well that could happen for me. I could get better like they are" (completer, male, 68) and

"I think erm, maybe one thing would be publicity, that you send out, you could almost say well erm, we have noted improvements in a number of people that have been on the programme which again would be a bit of additional encouragement" (completer, male, 74).

Including such examples of patient improvement, in conjunction with patient feedback, therefore has the potential to address all three of the aforementioned mental barriers.

It was also suggested that visiting the research facility may be beneficial for reducing mental barriers… *"I came on the first day and you said, here's all the tests you know, but wouldn't it be nice if you had a little visit, perhaps […] and you sort of say well look you're gonna be on there, and you're gonna be on there"* (completer, female, 71), especially if this was during an exercise session, where patients could observe others already taking part…

"yeah then of course if it's during a session, they would get to see other people on the course then I think that would certainly put them at ease I think" (decliner, male, 71).

This may reduce any "fear of the unknown", as patients will have seen the facilities and know what to expect. It may also reduce any "fear of failure", as patients can observe others with the same condition, successfully participating in the programme. It would also allow prospective patients to ask those taking part in the programme about any benefits they may have attained from attending.

Furthermore, patients would be able to see how we would monitor them during a HIIT session, which may reduce their apprehension further… "*no I think it's actually a bit reassuring that you know you are being monitored and you're not gonna flake out, halfway through*" (completer, male, 74).

An alternative, but similar suggestion was to run the programme with group-based sessions as this would allow newly starting patients to observe others, thus increasing their own confidence and motivation *"I don't think it really matters, but erm, one-to-one is good, but maybe you should have two or three, because then it gives them confidence as well, I think you get a bit more confidence if you're like in a group"* (completer, male, 81).

It was however, also noted, that a group scenario may increase the likelihood of embarrassment or apprehension *"personally, I prefer the one-to-one, because then you get rid of any embarrassment or nervousness or whatever…"*(completer, male, 69).

As such, one patient suggested starting with an initial one-to-one session, before moving into the group-based programme *"…but maybe say after the first session, you went into a bigger group or something like that"* (completer, male, 74).

Another similar recommendation was to allow patients to have a 'taster session' before they decide whether or not to participate *"…they just wanna do it, try it, just come for a session, a session, and just see if you like it"* (completer, male, 51).

Other patients also made comments such as "*I suppose we could have a go*" (decliner, female, 84) and "*but you don't know until you do it*" (decliner, male, 78), suggesting a taster session may be beneficial for helping patients realise what they can achieve.

Finally, and arguably most importantly, it was highlighted that having a personable, friendly approach is vital to reducing patient apprehension…

"I think the fact that you talk to people is important because I think people, some people in particular when they come into places like this, feel apprehensive, and I think that the people that I have come across… are friendly and talk to you is good because I think people need to feel

comfortable before they can do things like that. So, I think that's important" (completer, female, 66)

6.4.6 Theme 3: Symptomatic / Health Changes

In conjunction with the quantitative measures of walking performance, it is important to identify whether patients feel that they have had a subjective improvement following participation in the programme. Arguably, if a patient recognises a symptomatic benefit, this is more important than any change in the quantitative measures of walking performance.

6.4.6.(a) Subtheme 3a: Improvement in Symptoms, Walking and Health

The majority of patients described a definite subjective symptomatic improvement

"oh yes, yeah, before I used to have regular stops to where I was going erm, but now I can walk further and when I do have to stop erm, I don't have to stop for as long to recuperate" (completer, male 68), and *"yeah, it's, I do feel that I can walk much further now, erm, as far as pain's concerned, I don't think I feel as much pain in my leg as I did before we started"* (completer, male, 76).

However, some patients did describe an improvement, but were not as definitive about it…

"Erm, yeah there's times where I go out and I think yeah that's a lot better and then there will be times where I go out and it kicks in and I think, oh it's not, but I think it's better than when I first started, you know because I wasn't really doing anything of any distance, but now I, you know I'll attempt them" (completer, male, 66).

Another patient reported… *"yeah, yeah, it's made it sometimes, as I say, sometimes it's easier and sometimes it's just not, sometimes I can go 100 yards and I'm in agony, but then again, recently, it seems to be I can do a lot further now errr, most of the times, where before it were like well you couldn't really tell"* (completer, male, 72).

Interestingly, the first quote was from a patient who did not demonstrate an objective improvement, despite suggesting that they had subjectively improved.

Similarly, one patient had a marginal objective improvement in their walking distance but noted that they were now no longer limited by calf pain, but rather their hip osteoarthritis…

"they [calves] have improved yeah, because I noticed a lot of that when I was coming here this morning, oh I don't feel anything in my calf muscles and it's usually, they hurt you know… but I felt my hips on that, on that treadmill and that was painful… but my calves, didn't feel a great deal" (completer, male, 66).

These examples highlight the value of using a mixed methods approach.

In addition to an improvement in their symptoms, patients also described feeling an improvement in their fitness and overall wellbeing…

"I think it's made me feel better generally, as well as my legs, so I think it's been really good" (completer, female, 66) and *"in 6 weeks, it's done me a hell of a lot of good, I've lost 3 kilos, I'm fitter than I've ever been in my life and I can do a lot more"* (completer, male, 51).

Some patients were also able to identify and monitor an improvement during the programme, and this gave them an incentive to continue…

"but erm, I could see myself, I enjoyed myself, could see myself getting fitter and going longer and doing more. [interviewer: so, you could, it felt like you were progressing, so it was giving you the motivation…] oh yes, to carry on, yes" (completer, male, 68).

This incentive to continue was likely driven by an increase in the patients understanding of the benefits of exercise for IC, given that they have experienced them first-hand.

6.4.6.(b) Subtheme 3b: Lack of Improvement in Symptoms, Walking and Health

Only three patients subjectively reported a lack of symptomatic improvement, though none of them stated that their symptoms had worsened. The first patient stated, *"at the moment, there doesn't feel to be any improvement in my walking…"* (completer, male, 84), whilst another stated *"yeah, I would say about the same"* (completer, female, 76). Neither of these patients demonstrated an improvement in their treadmill MWD, meaning these comments were accurate.

However, the last patient to report no improvement in their walking, actually had an objective improvement of 100meters…

"erm, no, things are very similar, the distance I walk, I always go by, when I leave me flat to where the bus stop is and by time I get to it erm it's kicked in and even at the end of the programme, if I go now, by the time I get to the bus stop, it's kicked in, you know what I mean?" (completer, male, 78).

6.5 Discussion

The aim of this study was to get an understanding of the acceptability of a novel HIIT programme for patients with IC, by collecting detailed feedback via semi-structured interviews. Firstly, it is important to note that there was some divergence in views between patients, though this is not unexpected (273).

Nevertheless, the majority of patients stated that despite finding it difficult, they enjoyed the programme or at least did not mind doing it and would complete it again. This suggests that it was acceptable. In addition to this, a number of facilitators and barriers were also discussed, and potential solutions to these barriers identified, which can inform future studies. Finally, the majority of patients reported a symptomatic benefit following participation, suggesting it was worthwhile.

6.5.1 Patient Feedback

Feedback from patients mainly suggested that during the HIIT sessions, they found it difficult, and sometimes unenjoyable, but upon completion they felt a sense of satisfaction and even a buzz. In addition, when reflecting on the programme overall, most patients reported having enjoyed it.

Although considered qualitatively in this study, enjoyment of HIIT has recently been considered quantitatively in a number of populations including adolescents, recreationally active adults, overweight and obese adults and patients with CAD (274-278). The most widely used enjoyment measure within these studies was affective valence (affect), which considers feelings of pleasure and displeasure, and whether we perceive a stimulus as being good or bad (279). It is measured via the 11-point feeling scale (FS), ranging from -5 (very bad) to +5 (very good), with 0 indicating neutrality. Often the FS is used in combination with the exercise enjoyment scale (EES; single item, seven-point scale ranging from not at all to extremely enjoyable) and the physical activity enjoyment scale (PACES; 18 bipolar statements on a seven-point scale ranging from I enjoy it to I hate it, which are summed to provide a total score). These scales can be applied before (FS and EES), during (FS and EES) and after (FS, EES and PACES) exercise.

This recent interest in HIIT enjoyment is based on the dual-mode theory (DMT), which states that with increasing exercise intensity, affect is reduced. More specifically, this theory suggests that exercise intensities below the VAT do not negatively impact upon in-task affect, whilst intensities exceeding this threshold cause a decline in affect (280). With further increases in intensity, further declines in affect are reported and when maximal capacity is reached, affect becomes significantly less positive and crosses neutrality, becoming negative (280). However, this theory was generated based on continuous

exercise and recent studies have considered if it translates to interval exercise, including HIIT.

A systematic review published in 2018 demonstrated that compared to MICT, HIIT produced similar affective responses and significantly greater EES and PACES responses (281). This suggests that the DMT may not directly translate to HIIT. However, when considering the individual studies within this review, there were various HIIT protocols employed which were not directly comparable, and the MICT programmes included both moderate and vigorous intensities (i.e., intensities above and below the VAT). In addition, a number of studies were excluded from this review, meaning it did not encapsulate the whole evidence base and the methods were not entirely appropriate as a mean of the affect scores measured before, during and after exercise was entered into the meta-analysis.

A more recent and thoroughly conducted systematic review considered HIIT in comparison to both MICT and vigorous intensity continuous training (VICT). The findings demonstrated that for HIIT, affective responses were significantly lower than MICT and comparable to VICT, during, immediately following and 2 minutes after exercise (282). This therefore suggests that the DMT does translate to HIIT and that HIIT is considered less pleasant than MICT. Interestingly, post-exercise enjoyment measured via PACES still significantly favoured HIIT, compared to MICT, in this analysis (282). This is likely to be because the PACES score is not measured immediately following exercise, as is the case with affect, but it is measured around 5-20 minutes later, allowing time for a sense of achievement or satisfaction to be felt, and subsequently reported.

This notion that participants rate HIIT as less pleasant, or more difficult, during exercise, but more enjoyable post-exercise, is in keeping with our qualitative findings. Indeed, patients stated that they did not

necessarily enjoy performing HIIT, and certainly found it difficult, but did feel good after each session, and even reported feeling a “buzz”.

A number of reasons have been postulated as to why lower affect is reported during HIIT, but greater enjoyment is reported following HIIT. Firstly, the intermittent nature of HIIT means that the included recovery intervals provide participants with a break (278, 283). This is important because although both HIIT and VICT are performed above the VAT, the breaks provided by the recovery intervals during HIIT may provide a break from the less positive affect, something not possible with either MICT or VICT (275, 278). This may also cause a potential rebound effect, whereby affect is more positive during the recovery periods that follow the aversive stimulus generated by the work periods (275). Indeed, two studies that measured affect during the recovery intervals, demonstrated that it was higher than during the work intervals, and returned to levels that were similar to and sometimes greater than MICT (284, 285).
Therefore, due to the higher affect reported during recovery, the average affect over the course of a HIIT session may be higher than both MICT and VICT. This, in combination with a final rebound effect, may contribute to the higher post-exercise enjoyment reported. However, one of the two studies demonstrating this possibility also reported that affect was similar between HIIT and MICT during work intervals (285), which is contrary to the main body of evidence. As such, more data considering average affect, by measuring it during recovery intervals, is required.

Another possible reason for the greater post-exercise enjoyment reported following HIIT, is that participants are able to break down the HIIT session into short, known and manageable periods of exercise, interspersed with rest. This means that they are able to push harder for a known period of time, before getting a rest, allowing them to tackle

each work interval individually (283). Consequently, following each work interval participants are able to experience a sense of accomplishment, which serves to increase self-efficacy, something that is not possible with continuous exercise (283). These continuous, successive accomplishments are however interrupted by periods of less pleasant work intervals, meaning that the greatest sense of achievement may be realised following, rather than during the HIIT session, which contributes to the lower in-task affect but greater post-exercise enjoyment reported (278). Indeed, this was highlighted in our findings with a number of patients reporting that the work intervals were the least pleasant part, but that they enjoyed the programme overall, possibly due to experiencing this sense of achievement throughout.

Furthermore, evidence has also demonstrated that following HIIT, participants feel confident that they can perform it again, which is not the case for VICT, possibly due to this continuously increasing self-efficacy (283). This was again demonstrated in our findings, as it was stated that with each HIIT session, patients felt more confident in their ability to perform it, especially if they noted progress.

One final consideration is that by offering an ever-changing stimulus, HIIT provides more variety, and is less monotonous than MICT, contributing to the greater post-exercise enjoyment (274, 278). Indeed, this was also suggested by one patient in the present study and has been anecdotally reported in those with the metabolic syndrome and heart failure (286, 287). However, this ever-changing stimulus may still not maximise participant enjoyment as HIIT is often performed on a single modality (e.g., cycle or treadmill), when patient's may prefer a variety of modalities, as indicated in our findings. Providing such variety would involve employing a circuit-based approach, which would mean adopting a lower intensity and a longer session length, due to the time required to move between and set up apparatus. As such, this

approach may maximise enjoyment, but would be at the detriment of time-efficiency and time is a key barrier for those with IC (187). Furthermore, there is some evidence to suggest that in healthy populations, a lower-intensity circuit-based programme is less efficacious for providing physiological benefits than HIIT (288), and patients in the current study did appreciate that a higher intensity was required to be beneficial. Therefore, HIIT appears to strike the perfect balance between time-efficiency, physiological benefits and enjoyment.

However, as previously mentioned, there are a number of different HIIT protocols employed, all of which may induce varying levels of affect and enjoyment. *Niven et al 2020* noted that within the studies included in their systematic review, the number of intervals ranged from 4-10, the interval duration ranged from 6 seconds to 4 minutes and the intensity ranged from 75% maximum HR to all-out effort (282). It appears that for affective and enjoyment responses, HIIT intensity and duration are the most important factors. Firstly, one study considered a similar HIIT protocol to that used here (8 x 1 min intervals), with varying intensities of 70%, 85% and 100% PPO, in adolescents (275). The findings showed that for the majority of participants, affective responses remained positive during the final interval in the 70% and 85% conditions but became negative in the 100% condition, suggesting that a critical threshold is reached between 85-100% (275). However, the majority of participants in the 70% condition did not reach an intensity that is considered congruent with HIIT and presumed to facilitate sufficient health benefits (≥90% maximum HR), whilst most in the 85% condition did.

Another study considered HIIT duration, comparing 1:1 ratios of 30s, 60s and 120s intervals, with a 20-minute VICT arm (289). The findings showed that affect was more positive in the 30s and 60s HIIT protocols compared to the 120s and VICT protocols, though the actual intensity was slightly lower than what would be congruent with HIIT. A further

study also demonstrated that HIIT adopting 2-minute work periods interspersed with 1-minute rest periods resulted in significantly lower affect compared to VICT (290). This study also reported that >50% of the included participants were unable to complete the 2-minute work intervals (290), suggesting that greater recovery periods, or more likely, shorter work periods, are more appropriate. Therefore, these findings suggest that a HIIT protocol using a 1:1 work to rest ratio with 30 or 60s intervals performed at 85% PPO, is the most appropriate to provide more positive affect and the required intensity (275, 278, 289). Our HIIT protocol satisfies these criteria and should be adopted in future studies in patients with IC, as it appears to be acceptable, pleasant and enjoyable whilst also providing the appropriate HR stimulus. In addition, these future studies should also consider measuring affect over the course of the programme, both during the work intervals and during recovery, to add important data to this growing area.

Despite the advantages of the current HIIT programme noted above, a number of changes were either suggested by patients or are likely to occur in the future as a result of upscaling and these should be discussed.

With regards to the type of exercise, the majority of patients stated that they either did not mind cycling or preferred it to treadmill walking. However, it was suggested by some that having a variety of exercises to perform, via a circuit-based approach, would improve the programme. Whilst this may be possible, such an approach is likely to come at the detriment of intensity and time-efficiency. As such, keeping the single modality cycle-based approach appears most appropriate, as this was largely acceptable to patients and will allow them to reach the required intensity (140).

When considering the structure of the programme, currently it is one-to-one, with the instructor working with each patient individually. This

structure is provided due to the infancy of the programme and it is anticipated that future studies will be able to upscale and adopt a group-based programme. It should be noted that most patients preferred a one-to-one approach, though the majority would not be put off by a group-based scenario. Some patients highlighted that a group-based programme may lead to embarrassment, especially if patients are unsure about their ability to perform the exercise. However, it was also suggested that this group-based approach may give patients more confidence as they are able to see what others can achieve. It can also add an element of support and an opportunity for socialisation with peers. Clearly, a group-based approach will be needed to aid scalability and clinical exercise programmes, including SEPs, are often performed this way (175). Although there may be some initial concerns, it appears that a group-based approach would be acceptable for most, especially considering that the patients will be of a similar age range.

With regards to the frequency and duration of the programme, it appears that 3 times per week for 6 weeks is more acceptable than 12 weeks, suggesting that this HIIT programme may have somewhat reduced the time barrier that is cited for standard SEPs (187). However, some patients did still state that 3 times per week for 6 weeks was too burdensome, suggesting that this barrier has not been completely eradicated. Arguably, 6 weeks is the shortest realistic duration for an exercise intervention to provide a significant benefit (208, 234), and is half of that recommended as the minimum (291), meaning it is unlikely that this can be reduced further. As such, it may be more realistic to reduce the frequency of the programme from 3 times per week to once or twice, as suggested by some patients. However, 3 times per week is the optimal frequency for improving walking distance in patients with IC, and improvements are smaller with frequencies that are less than 3 times per week, though RCT evidence is lacking (291-293). As such, it

appears that currently, based on the available evidence, a frequency and duration of 3 times per week for 6 weeks is appropriate and is more acceptable than 12 weeks.

With regards to the length of each session, no patients specified that it needed to be longer or shorter, suggesting that it is currently acceptable. Despite this, two patients did state that 10 minutes for the warm-up and cool-down was too long, and that 5 minutes may have been more appropriate. However, for adults with chronic disease, a graduated warm-up of 5-10 minutes is recommended (257), and for those undergoing CR, guidelines recommend a 15-minute warm-up and a 10-minute cool-down (175). These recommendations, and the fact that this was highlighted by only two patients, who still completed the programme, suggests that 10 minutes is an appropriate length of time.

Considering the actual 20-minute HIIT intervention, it is unsurprising that this was considered to be the most difficult element. Despite this, only a small number of patients were unable to tolerate it and some stated that it needed to be difficult to make it worthwhile. Notably, a number of patients stated that the first week or two were the most difficult, and that the programme became easier as it progressed. This has also been noted for a usual-care SEP, suggesting that it may be a characteristic element of exercise in general for patients with IC, rather than something specific to HIIT (294).

However, for some, the programme may not get easier and for these patients it is important that it remains pragmatic and flexible to suit their needs. For example, one patient was unable to complete all 10 intervals by the second week, as prescribed. However, rather than discontinuing the intervention, they completed it by performing as many intervals as they felt able, which led to them more than tripling their MWD (from 71 meters to 218 meters). As such, it appears that the

HIIT intervention itself is acceptable for most patients, so long as it remains pragmatic.

One final element to consider, based on patient feedback, is the acute effect of the programme. Firstly, a number of patients reported feeling a sense of achievement or a "buzz" after each session. This is likely due to the pattern of affective responses and the final rebound effect as noted above.

With regards to physical effects, a number of patients reported leg pain during the programme, though this was general quadriceps pain rather than claudication symptoms. This is in keeping with previous research which demonstrated that the primary limiting symptom felt during treadmill testing was in the calf, whereas during cycling, it was in the quadriceps (141). Interestingly, the majority of patients continued with the programme despite this pain, often stating that they would not let it "beat" them or that they were determined to "push" through and finish it, suggesting an element of mental toughness. Mental toughness and coping strategies such as positive self-talk, have been previously highlighted as mechanisms used by patients to continue walking in spite of pain (186). Interestingly, behavioural coping strategies such as stopping to take breaks, have also been highlighted (186). As such, it can be postulated that patients use mental coping strategies, which in conjunction with the frequent breaks that are built into the HIIT programme, aid them to continue cycling, despite this feeling of pain.

6.5.2 Programme Facilitators and Barriers

Two key facilitators were identified: altruism and personal benefit. With regards to altruism, a number of patients stated that they took part in the programme because they wanted to help the research team to advance science, which would ultimately help other patients in the future. Often, patients stated that if they, or others, had taken from the national health service, a way to give back to it was via research participation, with one stating it should be dutiful. Altruism, including

benefits to science and helping others, has recently been highlighted as a key facilitator to research participation, meaning this finding is not unexpected (295). However, if this HIIT programme is incorporated into routine care and is no longer used solely for research, it is possible that the patients who gave altruistic reasons for participation, would choose not to participate. This is something that needs to be considered in future implementation work.

In addition to altruism, patients also expressed that they took part in the programme to help themselves, either via an improvement in their general health, symptoms or both. Again, this has been previously highlighted as a key facilitator across various research settings and designs (295), but also specifically for patients with IC (186, 296). Interestingly, some patients noted that either of these facilitators were sufficient for participation. As such, patients were willing to participate if either they benefitted from the programme or we as researchers benefitted from their participation. If both were achievable, it was considered more of a bonus.

In addition to facilitators, several barriers were also identified, that were both physical and mental. Firstly, the time commitment of attending the programme was noted as a barrier. A lack of time has been previously cited as a barrier to exercise in a number of studies (186, 294, 296, 297). This can be due to other commitments, such as caring for others (294),which was highlighted by one patient in this study. However, as addressed above, it appears that the current HIIT programme has reduced the time barrier as much as possible thus far.

Next, it was noted that the programme scheduling needed to fit in with patient's daily lives, which has also been previously highlighted (294). A group of patients who attended a usual-care SEP, that ran from 4 until 5pm, highlighted this time as a key restrictive barrier (294). As such, it is

clear that if this HIIT programme is to be scaled up, an important consideration would be the time of day that it is performed. Our findings suggest that mid-morning appears to be the most favourable time, likely due to the fact that a large proportion of patients with PAD are over retirement age (13).

Finally, it was highlighted that the delay between referral and actually starting the programme, often caused by administrative processes, could be a barrier to patients. Although this has not been considered previously, it has been identified that there can be a delay in receiving the diagnosis of PAD, even after seeking medical care, which is frustrating (299). As such, another delay in receiving treatment, in the form of exercise, is also likely to lead to frustration. One potential solution to this barrier would be to have research fellows available during clinic appointments to discuss the study with potentially eligible patients and provide them with the PIS, meaning they receive all the required information immediately upon referral. However, although not specifically mentioned by patients, a seemingly more feasible solution would be to use nurse led rather than consultant led IC assessment clinics. Such clinics have proven efficacious for improving wait times and would again allow patients to receive all of the required information, in detail, at the point of referral (300).

With regards to location/transport issues, these have also been highlighted previously as barriers to a standard SEP (294). Similar to the current study, it was identified that a reliance on public transport, and the time that this takes, often requiring multiple buses, was a key deterrent for patients (294). In addition, the current study also identified that the costs associated with such travel may be a barrier. This has again been highlighted previously and may be due to the relationship between low socioeconomic status and PAD (294, 297, 301). This cost barrier may also increase health inequalities amongst

patients with PAD as those unable to afford to pay for travel, may be unable to access their treatment, whilst the more affluent patients are able to access it.

It is therefore important to address these location/transport and associated cost issues. One possible solution would be to make more centres available so that patients could choose to attend the one closest to them. However, this may not be possible given the current funding, staffing and facility constraints that already preclude widespread SEP implementation (171), though HIIT may reduce these barriers, potentially increasing provision opportunities.

An alternative solution would be to allow patients with IC to be referred into established CR programmes, which are more readily available nationwide, with 230 centres currently open (302). In addition, HIIT using the same protocol, is currently being considered in UK CR services (256), suggesting that in future, HIIT could also be provided to patients with IC in this setting. This option of referring patients with IC to CR programmes is currently being explored in the UK (303), but it is not routine practice. It is however, important to note that uptake rates for CR programmes, despite their wider availability, are also poor at 50%, suggesting that addressing other barriers would still be required (302).

One final physical barrier was the presence of severe co-morbidities or other health conditions that preclude exercise, which has also been noted previously in patients with IC (186, 297, 298). However, it should be identified whether these co-morbidities are indeed severe enough to preclude exercise or whether they are milder in nature, meaning that exercise is not contraindicated (e.g., stable CAD). This can be established via a thorough conversation with the patient, which should be initiated if it appears that co-morbidities act the most salient barrier.

Interestingly however, our findings, along with others (294), indicate that for some, these aforementioned physical barriers, with the exception of severe co-morbidities, can be overcome if perceived personal benefit acts as a greater facilitator. As such, the extent to which these barriers and facilitators impact upon each individual will likely determine whether they influence engagement with the programme.

In addition to physical barriers, a number of mental barriers were also identified, as were some potential solutions. Firstly, a number of patients noted that a lack of motivation to exercise may be a barrier, which has been highlighted previously in patients with IC (186, 296, 298). However, it was also highlighted that some patients were aware of this, and they felt that having a centre-based programme to attend would give them more motivation than if they were to exercise on their own, in their own time. This is not surprising given that supervision and access to a structured SEP both act as facilitators to exercise (186, 298). As such, a lack of motivation does act as a barrier, but if patients are aware of it, it may also act as a facilitator.

The most common mental barrier was a lack of understanding of IC (including its pathophysiology and risk factors) and exercise (including who can perform it and how). Again, this has been highlighted previously (186, 294, 296, 298, 299), and there is a distinct need for a specific patient education programme to address this barrier, which would be well received by patients (296). One such education programme, which aimed to promote walking, has been piloted and included information about IC and exercise (190). The findings suggested that the programme was potentially efficacious, warrants further investigation and may be useful for filling this resource gap (190).

In addition to a limited understanding of exercise in general, a number of patients were unaware of the benefits of exercise, or lacked the confidence to exercise, which has been noted previously (186, 294, 296-298). Some suggestions were made that can address these barriers. First, it was suggested that feedback from participants who have previously taken part in the HIIT intervention could be added to the PIS. This would give prospective patients an understanding of the programme and how it feels from the perspective of their peers. It would also allow them to identify that patients with similar health conditions have been able to complete the programme, which may help them to realise their own ability to do it. Adding feedback to the PIS may be possible given that the Health Research Authority guidance states that one size does not fit all and that the PIS 'should be as long as it needs to be'.

It was also suggested that this could be furthered and the benefits that previous patients have had from participating in the programme should be highlighted in the PIS. This could increase patients understanding of the benefits of exercise for IC. This is an important consideration as participants need to believe that they will benefit from exercise to take part (186, 296), which has also been identified from our data, suggesting that adding such information would improve uptake. However, including this additional information may mean that the PIS becomes overly long and arduous to read, meaning such material may be missed by patients. Therefore, communicating this information in a concise and engaging manner, such as via an infographic or standalone leaflet, may be more appropriate (304).

The next suggestion was for patients to visit the facility, potentially during an exercise session, so that they can observe others taking part. This would reduce their fear of the unknown, as they could become familiar with the facilities, and also their fear of failure as they would be able to observe other patients successfully participating in the

programme. In addition, it would offer an opportunity to spend time with others experiencing the same disease. This may provide an element of social support which has previously been identified as a facilitator for walking and may act as such in this case (186, 298).
A similar suggestion was to utilise a group-based approach to allow newly starting patients to see that other, similar patients were able to do the programme. Again, this would also provide a supportive environment, though it would require the patient to overcome their initial fears to attend the first session. Both options of attending the facility prior to starting or adopting a group-based programme would be feasible. However, with these options, the fear of failure or lack of confidence and understanding may still be too great and preclude participation. For such patients, it was suggested that a 'taster' session could be adopted whereby they attend for one session to try the programme before deciding whether they want to take part. However, given that the intervention is currently only used for research purposes, this would be inappropriate and may artificially inflate the withdrawal rate. Consequently, undertaking an initial one-to-one session before moving into a group-based scenario may be most appropriate for those with the greatest fear of failure.

One final consideration with regards to a lack of understanding is that some patients were aware of the benefits of exercise, but felt that they already did enough, often due to being active at work. This highlights a limited understanding of the difference between physical activity and exercise and although both share common elements, there are distinct differences. Physical activity is performed by everyone to sustain life, and the amount and method by which it is performed varies between individuals (305). Exercise, however, is a subcategory of physical activity that is planned, structured, repetitive, and purposive, with the objective of improving components of physical fitness, such as walking capacity (305). As such, physical activity does not always constitute

exercise, and the latter is required to improve MWD.
Again, this is something that can be addressed in the PIS.

6.5.3 Symptomatic Change Over the Course of the Programme

Following the programme, the majority of patients reported an improvement in their symptoms. This is not an unexpected finding given the overwhelming evidence for the benefits of SEPs (234), possible in as little as 6 weeks (208), regardless of modality (184). In addition, a number of patients also reported that they had an improvement in their fitness, and that they were "able to do more". However, the quantitative changes in CRF were variable. The first cohort of patients demonstrated a 1 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_{2Peak}$ (chapter 4), similar to that reported in a 6-week treadmill HIIT programme (203), whilst the second cohort had a negligible improvement of 0.1 $mL \cdot kg^{-1} \cdot min^{-1}$ (chapter 5). These variable findings mean that we are unable to substantiate the subjective feelings of improved fitness. As such, a key consideration for future efficacy studies will be whether improvements in walking are accompanied by improvements in $\dot{V}O_{2Peak}$ or whether patients are simply attributing their improvement in walking to a perceived improvement in fitness.

Interestingly, patients were able to identify an improvement in their walking ability during the course of the programme, and this gave them an incentive to continue. This has also been noted during a usual-care SEP, whereby patients began to notice an improvement in their walking distance after approximately 2 weeks and this helped them to realise how beneficial exercise is, incentivising them to continue (294). This realisation of a benefit is important as although believing an improvement will occur acts as an initial facilitator to walking, actually experiencing it enables continued engagement (296).

However, it is important to note that not all patients who completed the programme reported an improvement. There were three

completers (two male) who reported no improvement in their walking, though they also reported no deterioration. Of these three patients, one actually demonstrated an objective improvement in their MWD. This suggests that patients use their own everyday markers for improvement, and although this patient had improved their treadmill MWD, meaning the intervention had achieved its goal, their personal symptomatic relief goals had not been achieved, meaning the intervention had in their eyes, failed.

The remaining two patients who reported no improvement also demonstrated no improvement on the treadmill test. However, this is not surprising given the notion of 'non-responders' to exercise which although controversial has been demonstrated in those with chronic conditions (306, 307). Although this has not been considered in patients with IC, non-responders to exercise are also likely to exist in this context.

6.6 Strengths and Limitations

The relatively large sample included in this qualitative analysis, is a key strength of this study. In addition, it is likely that this sample is largely representative of the population with IC, given that it included a broad age range (51-89 years) and an equal mix of unilateral and bilateral patients. However, as these patients were also from a single centre in one area of the UK, they are likely to be more similar to each other than to patients from other areas, meaning that the lack of geographic diversity may have impacted upon the data that was collected.

In addition, only two patients who withdrew from the programme agreed to be interviewed, meaning that this group is not fully represented. Next, due to the COVID-19 pandemic, several interviews had to be performed over the telephone, which may have impacted upon the data collected. It has been previously noted that interviews conducted over the telephone are, on average, shorter than those conducted face-to-face and this may be due to interviewees speaking for less time, rather than a proportional reduction in talk from both

parties (308). This suggests that interview data collected via telephone may not be as rich as that collected via face-to-face methods.

The use of telephone interviews also means that vital non-verbal communication may have been missed (269), leading to the misinterpretation of some information.

However, as noted previously, there is limited evidence to suggest that telephone interviews produce lower-quality data than face-to-face interviews. In addition, in this study, the telephone interviews were only 40 seconds shorter, on average, than those conducted face-to-face. As such, although it remains possible that the data could have been affected by the use of telephone interviewing, it seems unlikely in this case.

One final limitation is that the transcripts were not shared with patients prior to analysis for clarification, which may have again impacted upon interpretation.

6.7 Reflexivity Statement

In qualitative research, the researcher impacts upon the findings of the study and objectivity is not present (309). Reflexivity therefore relates to being aware of and sensitive to, how the researcher and research process can impact upon the setting and people being studied, questions being asked, data being collected and how it is interpreted (310, 311). The researcher therefore needs to consider and describe their personal characteristics that are relevant to the research, such as gender, race, age, sexual orientation, immigration status, personal experiences, beliefs, biases and assumptions (310, 311). They also need to describe whether they are an insider or an outsider and / or whether they have shared experiences with the participants (309). Providing such information increases the credibility of the findings and also deepens the readers understanding of the work (309).

I am a 28-year-old, apparently healthy male, with no known health conditions. I therefore do not have shared experiences with the

participants who suffer with IC. However, as a regular exerciser and someone who undertakes HIIT, I do have a shared experience of how they may feel during such an exercise programme, though my experience may be more positive than theirs.

My professional background is that of an exercise physiologist. This means that I have knowledge of the evidence supporting exercise, and HIIT, in clinical populations. This may have unconsciously biased the way in which questions were asked and the way the data was analysed, with a focus on positive aspects and aspects that are congruent with already published data. Being aware of this meant that leading questions were actively avoided, and negative comments were actively sought. In addition, when negative elements of the programme were highlighted, additional questions were asked in future interviews regarding that subject, to ensure that patients felt comfortable providing such information. Also, following the initial interviews, and as my confidence grew, I felt able to ask specific probing questions with regards to negative aspects, without feeling embarrassed or guarded. However, as I delivered the intervention and conducted the interviews, patients may still not have felt comfortable disclosing negative information and may have withheld it in an attempt to please the researcher. To minimise this, I ensured that at the start of each interview, I asked patients to be as honest as possible and informed them that whatever they said would not be taken personally. This fact may also have contributed to the limited number of withdrawals agreeing to be interviewed, as they may not have felt that it was possible to be honest with me about their feelings of the programme. Therefore, in future, it may be worthwhile asking an independent member of the research team to conduct these interviews.

Despite this, any negative comments have been reported fully and transparently, to minimise the impact of any bias.

The reflexive process was continuous throughout this study, and I employed a number of strategies to maintain it. First, I undertook regular self-reflection. When transcribing the interviews, I paid close attention to the way in which I asked questions to ensure that they were not leading to the patient. I also considered whether I had asked sufficient probing questions when discussing negative aspects. Next, peer review was also adopted, and I worked with an expert mixed methodologist to revise the topic guide. We also met at regular intervals to review and discuss the data and emerging codes and themes.

Finally, by using the Nvivo software, I was able to maintain an audit trail of the analysis process, from raw data, to initial codes, to merged codes, to final themes.

6.8 Validity and Reliability

There are a number of tools in qualitative inquiry that can be employed to increase validity and reliability (312). However, these tools often rely on multiple members of a research team, who are all involved in the research design, data collection and data analysis processes. As an individual researcher was solely responsible for undertaking these processes, (though with supervisory guidance) a number of these tools had to be adapted. Their application does, however, still increase the validity and reliability of this work.

First, triangulation was used whereby data was collected from multiple sources, through the use of three distinct groups, to reduce bias (312). It is recommended that the data from these different sources is compared and the degree of divergence or convergence documented. Although during the current analysis, the data from these different groups was not directly compared, data from each group was included in each theme and subtheme, suggesting convergence was present, substantially increasing validity (312). Next, it is recommended that the whole research team is involved in topic guide development to aid familiarisation (312). Although not applicable to the current study as

only one researcher needed to be familiar with the guide, two members of the supervisory team did review it and provide feedback. It was also reviewed by the research ethics committee. Similarly, it is important that the data collector knows the purpose behind each question to aid probing. As the researcher who performed the interviews designed the study, intervention and topic guide, they clearly had this knowledge.

With regards to data analysis, the use of intercoder agreement checks is recommended. These checks consider the extent to which two or more analysts code the same data in the same way (312). The aim is to have a high level of agreement, ideally of at least 80%. However, when only one researcher analyses the data, as with the current study, there are two other options. First, the same analyst can act as primary and secondary reviewer, whereby they undertake the first round of coding and return to review it after a period of absence from the data. This can reduce any temporary distorting effects caused by immersion in the data (312). The second option is to provide a colleague with the data and ask them to look over a random section of coded text to ensure that the connections between the raw data and the codes are intuitive and sensical. Feedback is then used to revise any codes or coding as necessary. Both of these options were adopted in the current study and although they are different from conducting intercoder agreement checks, they do still take a big step towards addressing any potential issues with validity and reliability (312).

Finally, direct quotes have been used to connect the researchers interpretations with what was actually said by the participants and negative cases have been highlighted, which increases validity and reliability (312).

6.9 Conclusion

The aim of this study was to consider the acceptability of a novel HIIT programme for patients with IC, designed to maximise patient benefit and reduce the barrier of time. Overall, the majority of patients stated that they enjoyed, or did not mind, performing the programme and despite finding it difficult would complete it again. In addition, the structure of 3 sessions per week for 6 weeks also appeared acceptable to most, and although it was still too much for some, it was more attractive than the usual-care SEP duration of 12 weeks. As such, it appears that patients largely found this HIIT programme acceptable, suggesting that further research, as noted in the previous chapters, is warranted.

One final consideration is that this chapter has also identified a number of barriers and how they can be addressed, which can maximise future study recruitment.

Chapter 7: Discussion and Conclusions

7.1 Discussion

This thesis has presented a body of research that aimed to consider the role of alternative exercise programmes for patients with IC, namely HEPs and HIIT. The need to explore these alternative programmes was borne out of previous work which showed that despite being first-line recommended treatment in both national and international guidelines (17, 63, 88), SEPs are rarely available and when they are, they are underutilised (171, 185, 313). Study one aimed to provide a comprehensive overview of the evidence for HEPs for patients with IC. This allowed for the identification of key HEP components that are likely to be effective, which informed our recommendations for practitioners. As the evidence base for HEPs was already well established, further intervention development was not required in the context of this PhD.

Study two considered the somewhat more limited evidence base for HIIT in patients with IC. The findings of this study were then used to develop a HIIT intervention, which was tested via a feasibility cohort study (study 3). The findings from this study prompted refinement of the inclusion and exclusion criteria for the HIIT programme. The intervention, with newly defined inclusion and exclusion criteria, was then re-tested for feasibility in study four. Finally, study five considered the patient acceptability of this HIIT programme, via semi-structured interview feedback.

7.1.1 Home-Based Exercise Programmes

Although SEPs are recommended as first-line treatment for IC, the provision, uptake and adherence rates in the UK and USA are poor (171, 185, 313). As such, guidelines now advocate HEPs as a useful alternative (63, 88). However, study one identified that HEPs are inferior to SEPs, and other evidence suggests that they may be no more effective than basic exercise advice (173). This is however, a somewhat narrow view given the heterogeneity between HEPs and the fact that

some were much more structured than others. As such, in study one, we also considered each intervention individually and identified certain features that were common in a number of HEPs that appeared to be beneficial. These elements included appropriate FITT recommendations, along with patient education, goal setting, action planning and monitoring, with the latter appearing to be vital. Recent guidelines have identified the importance of HEP structure with regards to exercise prescription, support from healthcare providers, behaviour change techniques and the use of monitoring (88). However, they fail to provide specific recommendations and highlight that additional research is required to identify the most effective HEP for improving functional status and QoL. It is likely that our evidence based SHEP (table 9) is most effective, though it remains untested. It is, however, similar to one used in a previous pilot RCT which demonstrated that the HEP was acceptable and potentially more effective than BMT with exercise advice (190). As such, further feasibility / pilot work is not required, though a fully powered RCT is needed to establish the efficacy of this SHEP for improving walking distance and QoL in patients with IC, something that was beyond the scope of this thesis.

Such an RCT is immediately pertinent given the COVID-19 pandemic, which has increased the need for HEP provision. Its relevance will however, remain in the longer-term, given the limited SEP availability (171). To aid this immediate and longer-term provision, it is vital that this SHEP is delivered in a way that is accessible and pragmatic. One possible way to achieve this could be via telehealth, which involves the use of information and communication technologies to aid delivery of the intervention (237). A systematic review of such interventions for patients undergoing CR included a number of technologies such as telephones, biosensors, websites, computers, smart phones and apps (237). The findings suggested that telehealth CR was at least as effective as supervised centre-based CR (237). However, it has been

highlighted that a number of the telehealth interventions included in this review (e.g. telephones, desktop computers and teleconferences), still by their nature, confined patients to fixed locations (238). As such, increasingly powerful mobile technologies may be more appropriate as they can provide delivery models that are flexible and interactive whilst allowing real-time monitoring and instantaneous feedback (238). This has been recently considered via an app-based remote CR programme which included 12 weeks of individualised exercise prescription, predominantly walking, performed 3 times per week for 30-60 minutes at an individually prescribed intensity (238). In addition, the app allowed real-time remote exercise monitoring of multiple participants, individualised audio coaching, feedback and social support. It also allowed patients to review their exercise performance data, set individual goals and review their automated goal achievements to aid self-monitoring. Finally, theoretically underpinned behaviour change education was also provided by direct messaging (238). The results demonstrated that this app was comparable to centre-based CR and was statistically non-inferior for improvements in CRF, whilst also being at least 70% cheaper to deliver. The authors therefore concluded that this remote-CR app is an effective, cost-efficient alternative that can complement existing CR whilst satisfying patient preference and improving accessibility (238).

This app clearly provides the combination of components outlined previously, with the theoretical underpinning required to effectively deliver this SHEP in an easily accessible format. It also appears to be efficacious. Therefore, development or refinement of this app, so that it is specific to those with IC, is required and would be the ideal way to deliver this SHEP in the aforementioned RCT. It appears that this would also be well received by patients with PAD, given that a recent study has highlighted patient interest in smartphone supported exercise (236). Elements such as information, feedback and choosing goals along

with access to physicians and therapists were identified as important and can be provided via this app (236).

There are two ongoing studies considering app based HEPs for patients with IC that include some structured elements such as frequency, intensity, duration, feedback and PAD education (314, 315). However, they still omit other vital elements such as goal setting and action planning. In addition, they are both in the pilot stage, which as previously mentioned may be superfluous. However, it could be argued that despite a similar SHEP being piloted previously, it has never been trialled using an app, suggesting that this piloting stage may be required.

Despite this new evidence being generated, it still does not consider the complete SHEP, with vital components missing. As such, there remains a need for a fully powered RCT to consider the efficacy of our evidence based SHEP, delivered via an app, that incorporates all of the outlined elements. As results from the aforementioned pilot RCT's are still pending, a cautious approach would be to include an internal pilot, though this may not be necessary.

7.1.2 High-Intensity Interval Training

HIIT also has the potential to be a useful alternative to usual-care SEPs, given that it is more time-efficient and has demonstrated efficacy in those with CAD (196, 197). However, the evidence for the role of HIIT in patients with IC is much less established, as demonstrated in study two. This study demonstrated that for patients with IC, HIIT does seem to improve walking distance in relation to controls, possibly in as little as 6 weeks, across a variety of modalities. In addition, it suggested that longer low-intensity programmes were required in order to obtain benefits similar to those from short-term HIIT. These findings support the notion of HIIT being a time-efficient alternative for patients with IC. However, the evidence was insufficient to allow robust conclusions to be drawn, given the small sample sizes and heterogeneous HIIT

interventions in the included studies. Despite this, the findings allowed us to provide recommendations for a HIIT protocol which appears most appropriate. We recommended adopting the most pragmatic modality available and using low-volume, short-duration HIIT at an appropriate intensity (≥85% peak HR) with tolerable intervals (i.e., short work to rest ratio). Such a protocol is also likely to produce the most pleasant affective responses and the required intensity, as noted previously (275, 278, 289). However, compared to the aforementioned SHEP, the evidence for this HIIT protocol was much more limited, meaning initial feasibility work was required.

As such, these recommendations informed the HIIT intervention for study three, which considered the feasibility of HIIT performed 3 times per week for a period of 6 weeks on a cycle, with a 1:1 work to rest ratio, performed at 85-90%PPO, aiming to achieve ≥85% peak HR. Initially, it appeared that this HIIT intervention may not be feasible for those with IC due to a low completion rate (40%). However, the low completion rate was not due to the intervention, it was due to a significant proportion of patients who were excluded following their baseline assessment. Specifically, 25% of patients were unable to perform a maximal effort CPET, precluding them from undertaking a *conventional* HIIT programme. This finding is in contrast to large HIIT studies in those with CAD and heart failure, which demonstrated that these patients were able to achieve maximal effort tests, with RER values of ≥1.10 at baseline (201, 263). For those with IC, this inability to achieve a maximal effort test is likely due to deconditioning, given that the $\dot{V}O_{2Peak}$ values in studies three and four were lower than the aforementioned CAD and heart failure cohorts (201, 263). However, it is possible that those who are more deconditioned have the most to gain. It has been demonstrated that CRF, expressed as the VAT, is a significant predictor of improvements in MWD (158). More specifically, patients with a lower VAT have a greater improvement in MWD than those with a higher VAT. As such, excluding the most deconditioned

patients based on an inability to achieve a maximal test may be inappropriate, given their scope for improvement. Therefore, the results from study three, informed study four. The findings from study three suggested that the intervention may be appropriate, but the inclusion / exclusion criteria were not. As such, the exclusion criteria were altered for study four and patients unable to achieve a maximal test were now included and provided with the same personalised, but submaximal, HIIT programme. The resulting increase in completion rate from 40% to 65%, which is higher than our usual-care SEP (158), and comparable to what is reported in the literature (185), suggests that including these patients was warranted and it is in fact a more pragmatic approach. In addition, the findings also suggest that those who are more deconditioned, are just as able to complete the programme as their more conditioned counterparts. Indeed, of the six patients in the second cohort unable to achieve a maximal test, only two were unable to tolerate HIIT or the CPET. As such, the findings from study four suggest that following a small change, the inclusion / exclusion criteria are now appropriate. The findings also suggest that the intervention is appropriate, whilst providing an indication that it is safe and potentially efficacious. This should be confirmed by a proof-of-concept study, which is ongoing (254).

If this is confirmed, a future pilot RCT, followed by a fully powered definitive RCT, of HIIT versus SEPs should be performed. This further work appears warranted given the findings of studies two, three and four, which suggest that HIIT can improve MWD to the same extent as SEPs, which represents a moderate to large MCID (118, 234). The initial pilot RCT of HIIT versus SEPs should be performed with MWD as the primary outcome to generate the information required to calculate the sample size for a definitive RCT. An important secondary outcome would be changes in CRF established via $\dot{V}O_{2Peak}$. This would be an interesting outcome given that studies three and four demonstrated

conflicting findings with regards to improvements in $\dot{V}O_{2Peak}$. Study three demonstrated a 1 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement following HIIT, whilst study four demonstrated no improvement. The latter finding is contrary to HIIT studies in other populations, which have demonstrated significant improvements in $\dot{V}O_{2Peak}$ (201, 263). It is however in keeping with SEP data, which suggests that significant changes in MWD are not accompanied by significant changes in CRF (158, 262). Therefore, including this as a secondary outcome in future studies is important as it will allow identification of whether HIIT, in contrast to SEPs, significantly improves CRF.

For a definitive RCT, the power calculation, with MWD as the primary outcome, should be based on non-inferiority, rather than superiority. This is because SEPs are an established treatment, meaning they would act as an active control (316). If the results demonstrate that HIIT is non-inferior to SEPs, this would be a positive outcome as it would suggest that HIIT is just as effective for improving MWD. One important caveat of a non-inferiority trial, which differentiates it from an equivalence trial, is that it would also identify if HIIT is superior to SEPs, which would again be a positive outcome (316). This non-inferiority RCT would therefore identify whether HIIT can be offered as an alternative, rather than a replacement, to SEPs. This is important as ideally centres would be able to offer both a usual-care SEP and a HIIT programme, giving patients and clinicians a choice about exercise therapy. However, there is a distinct lack of SEP centres, due to limited funding (171, 316). Provisional funding may be easier to obtain for a 6-week HIIT programme, given that it is half the length of a usual-care SEP. Therefore, if evidence can be generated to suggest that HIIT can be used instead of a SEP, this may improve exercise provision for patients with IC.

Another option, as noted previously, would be to integrate patients with IC into existing CR services, especially given that HIIT is currently

being considered within them (256). This would allow for the utilisation of existing resources to offer both a SEP and a HIIT programme. However, it is important to consider that there may be difficulties in upscaling this HIIT programme and providing it in routine practice as an alternative to SEPs. For example, a CPET is required for accurate exercise prescription and to ensure patient safety. However, CPET is not often undertaken as part of routine care and it is not considered necessary prior to a SEP (174). In addition, the number of patients who can be reasonably supervised during a HIIT session is yet to be established, and it is not known whether this is comparable to SEPs. As such, should a definitive RCT demonstrate that HIIT is a useful adjunct to SEPs, implementation studies may be required, specifically considering whether an alternative, more routinely used exercise test can be used, instead of a CPET.

7.1.3 Patient Feedback and Barriers

Study five considered the acceptability of HIIT by obtaining patient feedback via semi-structured interviews. The majority of patients stated that they enjoyed the programme, or at least did not mind doing it, would complete it again and recommend it to others, suggesting it is acceptable.

In addition, it was also highlighted that the 6-week HIIT duration is more acceptable than the 12-week SEP duration, suggesting that the time barrier has been reduced. It has not, however, been eradicated as some patients still stated that 3 times per week was too burdensome. It was suggested that 1-2 sessions per week may be better. However, the overall exercise dose has already been halved by the HIIT programme, being 6 rather than 12 weeks, which is the shortest reasonable programme duration expected to provide a benefit (208). By also reducing the frequency, the exercise dose may be excessively reduced, impacting upon outcomes. Evidence also suggests that the optimal frequency for improving walking distance in patients with PAD is 3

times per week (291-293). As such, it appears that the time barrier has been reduced as much as is reasonably possibly thus far. However, no RCT has been specifically designed to identify the optimal frequency of exercise for patients with IC (291). As such, should the aforementioned RCT identify that HIIT is a useful adjunctive exercise therapy, future work could consider the optimal frequency to identify the minimum HIIT dose that patients should perform to accrue a benefit. This would identify how much the time barrier can be reduced before impacting upon outcomes.

In addition to time, other physical barriers were identified including transport and cost, which have been highlighted previously (186, 294, 296, 297). With regards to transport, it was noted that the additional burden of travelling contributed to the time barrier. As such, it was suggested that more local centres could be made available, though given the provision barriers (171), it is unlikely that new centres can be provided. Therefore, integration of patients with IC into existing CR programmes could be more feasible, both for providing usual-care SEPs and HIIT. This is currently being considered (256, 303). It is also worth noting that should evidence be generated to support reducing the frequency of exercise to less than 3 times per week, as mentioned previously, this would also reduce the barrier of transport, given that patients would not be required to travel to the centre as frequently. With regards to cost, it was simply suggested that to reduce this barrier, patients should be reimbursed for any costs they incur during participation in the study. Indeed, this practice is recommended by the National Institute for Health Research. However, clinical studies do not always receive funding support from research bodies and are often departmental or university funded. Therefore, universities should consider making small funds available for this purpose, to reduce this barrier and increase voluntary research participation.

Finally, a number of mental barriers were identified including a lack of motivation, understanding and confidence, all of which have been identified previously (186, 294, 296, 298, 299). Some suggestions were made to reduce these mental barriers though almost all of them required patients to initially engage with the HIIT programme in some way. For some patients, these mental barriers may be too great and preclude this initial engagement, meaning there is no opportunity to reduce them. As such, these barriers may need to be identified and reduced at the initial point of contact with the consultant, prior to referral to the programme. However, this is unlikely to be feasible given the limited time available for a consultation with each patient. Indeed, it has been previously noted that the time needed to offer proper counselling in relation to lifestyle changes, as would be required to identify and address these barriers, is far greater than what can be provided by the surgical team (317). The time required to counsel these patients could however be provided via nurse led IC clinics, which could potentially replace consultant led IC clinics (300). Nurse led clinics allow sufficient time for patients to receive aggressive risk factor management as well as thorough education regarding exercise (including appropriate referrals), its benefits and who can perform it, which should also address any mental barriers (300). Previous work has identified that for patients with PAD, a nurse led assessment/management clinic resulted in improved prescription of, and compliance with, statin and antiplatelet therapy, as well as significant reductions in cholesterol levels and 10-year cardiovascular risk (317, 318). However, RCT evidence is lacking, though it is being generated (319). Furthermore, it is yet to be established whether clinics such as these impact upon uptake and adherence to exercise programmes. It does however seem reasonable that such clinics, by identifying and addressing mental barriers, could lead to an increase in the number of patients attending exercise programmes in general, as

well as future HIIT research programmes, and this warrants further investigation.

7.2 Limitations

This thesis and its findings are not without limitations. Firstly, with regards to study one, a number of the included trials did not report all of their measured outcomes or did not present the data sufficiently to allow for entry into a meta-analysis. As such, it is possible that the findings may have differed, had all of the data been available. For study two, the evidence was limited with small samples and clear heterogeneity. This therefore limited the conclusions that could be drawn from the data. However, the recommendations provided, along with the findings from studies three and four, should hopefully set the foundation for a more homogenous future evidence base. With regards to studies three and four, some follow-up appointments were missed. For study three, this was mainly due to patient illness, which prevented them from being able to attend the department. For study four, data collection was mainly limited by the COVID-19 pandemic and national lockdown. However, these factors were out of the researchers control and remote QoL follow-ups were performed where possible, to minimise impact. In addition, efficacy measures were secondary outcomes, meaning that missing data had a minimal impact upon the key aims and findings. Finally, in study five, those who withdrew from the programme were underrepresented, with just two patients interviewed, despite the efforts of the researcher. This is important considering that these patients are likely to have the most negative views of the programme. Future studies of HIIT in patients with IC, namely the proof-of-concept study, should prioritise these patients for interview, to identify if their feelings are different from those identified here.

7.3 Conclusion

SEPs are recommended as first-line treatment for patients with IC but suboptimal provision, uptake and completion rates limit their effectiveness, meaning alternative programmes are required. When considering the evidence, more recent investigations have identified that HEPs can be an effective alternative to SEPs for providing improvements in walking distance. From these investigations, several key HEP components were identified, and an example SHEP created, which is likely to be efficacious. However, it remains untested meaning that a fully powered RCT delivering this SHEP in a way that is accessible and pragmatic, potentially via telehealth, is required.

The evidence for HIIT in patients with IC is much more limited. However, it appears that low-volume, short-duration HIIT may be effective for improving CRF and MWD. This finding informed the remainder of this thesis which considered the feasibility of low-volume, short-duration HIIT for patients with IC. Initial findings demonstrated that for a number of patients, a *conventional* HIIT programme, prescribed based on a maximal effort CPET is not feasible, likely due to deconditioning. However, as these patients have the potential to accrue the most benefit, they should be included, rather than excluded, and prescribed the same personalised, submaximal HIIT programme, based on their individual CRF. Indeed, with the inclusion of these patients, this HIIT programme now appears feasible, tolerable and acceptable. The findings also provide an early indication that HIIT is safe and potentially efficacious for this population. These findings should be confirmed by the ongoing proof-of-concept study before efficacy-based trials are conducted to consider HIIT compared to usual-care SEPs. Only once this evidence has been provided, can the role of HIIT in routine practice be considered, with the aid of implementation studies.

7.4 Key Findings

In summary, there are a number of key findings to report from this thesis:

1. Study one identified that HEPs may be beneficial for patients with IC, as long as they are supported and include a number of key components. These components include appropriate FITT principles, used in conjunction with self and remote monitoring, education, goal setting, action planning, and appropriate theoretical underpinning.

2. Study two found that the evidence for HIIT in patients with IC is limited, though it did suggest that HIIT may be beneficial for improving MWD and CRF. Low-volume, short-duration HIIT was particularly pertinent as it appears that this provides improvements that are equivalent to longer term protocols but requires a lesser time commitment.

3. Study three considered a low-volume, short-duration HIIT programme and identified that a number of patients with IC were not able to achieve a maximal effort CPET due to deconditioning. This precluded them from undertaking a *conventional* HIIT programme and as such they were excluded. However, these patients may accrue the most benefit and should be included and provided with the same personalised, low-volume, short-duration, submaximal HIIT programme, prescribed based on their baseline CRF.

4. Study four evaluated this personalised, low-volume, short-duration, submaximal HIIT programme and found that it appears to be feasible and tolerable, whilst also being potentially safe and efficacious. Study five also suggests that it is acceptable to patients. This needs to be confirmed by the

ongoing proof-of-concept study (254) before a pilot RCT of HIIT vs. SEPs is undertaken.

5. Study five also suggests that this HIIT programme has reduced the widely cited time barrier, though further work will be needed to understand how much this barrier can be minimised before it impacts upon outcomes. This study also identified other physical and mental barriers as well as strategies to reduce them. For mental barriers specifically, there is a distinct need for appropriate patient education. This could be provided via specific education programmes or nurse led IC clinics.

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Appendix 1 - list of abbreviations

AAA	Abdominal Aortic Aneurysm
ABPI	Ankle-Brachial Pressure Index
AE	Adverse Event
ALI	Acute Limb Ischaemia
AT	Anaerobic Threshold
ATC	Antiplatelet Trialists' Collaboration
BMI	Body Mass Index
BMT	Best Medical Therapy
CAD	Coronary Artery Disease
CLTI	Critical Limb Threatening Ischaemia
COPD	Chronic Obstructive Lung Disease
COVID-19	Coronavirus Disease 2019
CPET	Cardiopulmonary Exercise Test
CR	Cardiovascular Rehabilitation
CRF	Cardiorespiratory Fitness
CVD	Cardiovascular Disease
DMT	Dual-Mode Theory
ECG	Electrocardiogram
ECQ	Edinburgh Claudication Questionnaire
EES	Exercise Enjoyment Scale
ES	Effect Size
ETT	Exercise Tolerance Test
FEV_1	Forced Expiratory Volume in 1 second
FITT	Frequency, Intensity, Time and Type
FS	Feeling Scale
FVC	Forced Vital Capacity
HDL	High Density Lipoprotein
HEP	Home-based exercise programme
HIC	High Income Country
HIIT	High-Intensity Interval Training
HPS	Heart Protection Study
HR	Heart Rate
IC	Intermittent Claudication

ICD	Intermittent Claudication Distance
Kg	Kilogram
Kg/m^2	Kilogram per meter squared
LDL-C	Low Density Lipoprotein Cholesterol
LMIC	Low-Middle Income Country
LT	Lactate Threshold
MCID	Minimally Clinically Important Difference
MD	Mean Difference
MET	Metabolic Equivalent
MICT	Moderate Intensity Continuous Training
Ml/kg/min	Millilitres per Kilogram per Minute
MVV	Maximum Voluntary Ventilation
MWD	Maximum Walking Distance
NICE	National Institute for Health and Care Excellence
O_2	Oxygen
PACES	Physical Activity Enjoyment Scale
PEDro	Physiotherapy Evidence Database
$P_{ET}CO_2$	End Tidal Carbon Dioxide Pressure
$P_{ET}O_2$	End Tidal Oxygen Pressure
PIS	Patient Information Sheet
PPO	Peak Power Output
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSV	Peak Systolic Velocity
QoL	Quality of Life
RCT	Randomised Controlled Trial
RER	Respiratory Exchange Ratio
RPE	Rating of Perceived Exertion
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEP	Supervised Exercise Programme
SF-36	Short-Form 36
SHIP	The Study of Health in Pomerania

TBPI	Toe-Brachial Pressure Index
VascuQoL	Kings College London Vascular Quality of Life Questionnaire
VAT	Ventilatory Anaerobic Threshold
VC	Vital Capacity
$\dot{V}CO_2$	Carbon Dioxide Production
$\dot{V}E$	Minute Ventilation
$\dot{V}E/\dot{V}CO_2$	Ventilatory Equivalents for Carbon Dioxide
$\dot{V}E/\dot{V}O_2$	Ventilatory Equivalents for Oxygen
VICT	Vigorous Intensity Continuous Training
VLDL	Very Low-Density Lipoprotein
$\dot{V}O_2$	Oxygen Uptake
$\dot{V}O_{2Max}$	Maximal Oxygen Uptake
$\dot{V}O_{2Peak}$	Peak Oxygen Uptake
WIQ	Walking Impairment Questionnaire

Appendix 2 - chapter 2 search terms

Search	Terms
1	Intermittent claudication
2	Arterial occlusive diseases
3	Peripheral arterial disease
4	Peripheral vascular diseases
5	Vascular diseases
6	PAD
7	PAD-IC
8	PVD
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10	Home training
11	Home based
12	Non-supervised exercise
13	Unsupervised exercise
14	Home based exercise
15	Home based walking
16	Home based exercise programme
17	Home based supported exercise
18	Home based exercise program
19	Community based
20	Community walking programme
21	Community walking program
22	16 OR 17 OR 18 OR 19 OR 20 OR 21
23	Exercise Therapy
24	Exercise
25	Rehabilitation
26	Walking therapy
27	23 OR 24 OR 25 OR 26 OR 27
28	9 AND 22 AND 27

Appendix 3 - chapter 3 search terms

Search	Terms
1	exp. Peripheral Arterial Disease/
2	peripheral artery disease.mp.
3	exp Peripheral Vascular Diseases/
4	exp Arterial Occlusive Diseases/
5	exp Vascular Diseases/
6	atherosclero*.mp.
7	arteriosclero*.mp.
8	isch?emia.mp.
9	exp Femoral Artery/
10	exp Iliac Artery/
11	exp Popliteal Artery/
12	PAD.mp.
13	PVD.mp.
14	PAD-IC.mp.
15	exp Intermittent Claudication/
16	exp Lower Extremity/
17	lower limbs.mp. or Lower Extremity/
18	steno*.mp.
19	lesions.mp.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp High-Intensity Interval Training/

22	HIT.mp.
23	HIIT.mp.
24	aerobic interval training.mp.
25	AIT.mp.
26	high-intensity training.mp.
27	high intensity training.mp.
28	high intensity interval training.mp.
29	high intensity exercise.mp.
30	sprint interval training.mp.
31	high-intensity intermittent training.mp.
32	high intensity intermittent training.mp.
33	interval training.mp.
34	interval exercise.mp.
35	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	moderate continuous training.mp.
37	MCT.mp.
38	moderate interval training.mp.
39	moderate intensity interval training.mp.
40	MIT.mp.
41	MIIT.mp.
42	moderate intensity exercise.mp.
43	aerobic training.mp.

44	aerobic exercise.mp. or Exercise/
45	continuous endurance training.mp.
46	continuous training.mp.
47	continuous exercise.mp.
48	continuous endurance exercise.mp.
49	moderate intensity steady state.mp.
50	MISS.mp.
51	moderate intensity steady.mp.
52	MIS.mp.
53	moderate intensity supervised exercise.mp.
54	supervised exercise programme.mp.
55	SUP.mp.
56	SEP.mp.
57	continuous exercise therapy.mp.
58	exp Exercise Therapy/
59	moderate intensity training.mp.
60	moderate intensity continuous training.mp.
61	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62	20 and 35 and 61

Appendix 4 - interview topic guide

"Exploring patient experiences to consider the acceptability of high-intensity interval training as a treatment option for intermittent claudication"

Research aims to explore:

1. **Patients experience of the High-Intensity Interval training programme**
2. **How easy or hard 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)**

1. **Introduction**
    - Introduce self
    - Explain: Nature & purpose of research
    - Who the research is for
    - Introduce audio recorder
    - Stress confidentiality
2. **Background**
    - Household composition
    - Employment status and details
    - Spare time activities / hobbies
3. **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?
- Move to Q5&6.

4. **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?
    - Move to Q5&6.

5. **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?

6. **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?

7. IF NEVER TAKEN PART:
    - Why did they choose to decline the exercise programme?
    - Could we have changed the information pack to make it more appealing?
    - If we had some patient feedback from someone who has completed the programme, who had the same condition, and other conditions like COPD and they explained that they could do the programme and they had improvements in walking distances and their health – would that encourage more people?
    - Why do you think other people do not take part in the programme?
    - Anything we can do, i.e. cost? Location? Etc.
    - Do you take part in regular exercise? What encourages / discourages you?
    - Home based programme?
8. **Potential ways of improving the service**
    - How could we encourage more people to take part?
    - Anything else they would like to add

NEXT STEPS:

- *Thank-you for taking part, do you have any outstanding questions about the research?*

- *Reassure the participant about confidentiality and anonymity*
- *Ask if they would like to be informed of the outcomes of the research (take e-mail address if that is their preferred way of being informed).*

Appendix 5 - coding example

Interviewer: so, the first questions sort of very general, overall, what did you think of the programme itself?

Patient: I thought it was really good, erm, when you told me what it was I was going to be doing, I had my doubts as to whether I'd be able to do that, because it's as I told you before exercise is not something that's at the top of my list, never has been so I was, when I knew it was that sort of HIIT stuff, I was a bit concerned, I think it's made me feel better generally, as well as my legs, so I think it's been really good.

Interviewer: good, so you were initially sort of a bit sceptical about whether you would be able to do it…

Patient: I wasn't sceptical, I was just concerned that it might be beyond my capabilities really.

Interviewer: okay, and in terms of how you found the programme would you say it was difficult, easy, somewhere in between?

Patient: I don't think it's easy, but I think if you really want to do it, because I think it's about d… I mean it's not gonna be easy is it there'd be no point in doing it if it was easy, but I think it's about determination, and sometimes you've just got to go that bit further haven't you and just push yourself a bit more to get a result, I mean it's not magic is it, it's not just gonna happen you've got to do something yourself and put some effort in so, I found it good.

Green – coded as patient feedback > overall thoughts of the programme (initial codes include positives and difficulty)

Yellow– coded as programme barriers and facilitators > mental barriers (initial codes include apprehension and motivation to exercise)

Red – coded as symptom / health changes > Improvement in symptoms, walking and health (initial codes include improvement in symptoms / walking and improvement in health)