# Extracorporeal shockwave therapy as a novel treatment for Intermittent Claudication

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## Abstract

**Background –** Intermittent claudication is a prevalent manifestation of peripheral arterial disease and affects about 3% of the UK population. Its conservative management includes best medical therapy, smoking cessation and supervised exercise, however exercise uptake among patients is poor. Pilot data has demonstrated that extracorporeal shockwave therapy is effective for improving walking distance in patients with intermittent claudication. The work of this thesis aims to consider its effectiveness for improving quality of life.

**Methods –** In a double-blind, sham-controlled, randomised trial, patients with intermittent claudication were randomised in a 1:1 ratio to extracorporeal shockwave therapy or sham treatment. The primary endpoint was change in physical functioning at 12-week follow-up, as measured by the SF-36. Secondary endpoints included changes in walking distances, and changes in ankle brachial pressure index pre and post exercise, amongst others.

**Results –** 138 patients were recruited and randomised. The intervention group had a significantly higher physical functioning score at 12 weeks (Mdn 41 vs 34, p=0.033), though not significant at secondary analysis. They also had significantly longer claudication distance (Mdn 125 vs 88, p=0.004) and maximum walking distances (Mdn 179 vs 129, p=0.013). No significant difference in ABPI between the two groups was evident.

**Conclusion –** This study demonstrates that extracorporeal shockwave Therapy is clinically effective for improving walking distances and may have a positive effect in quality of life in patients with intermittent claudication. It should be considered as an adjunct to conservative management, especially in patients not willing or unable to participate in supervised exercise programs.

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## Author's declarations

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.

## Author's contributions to this work

I have led this trial from June 2018 until the present. This includes the coordination and personal completion of recruitment, treatment and follow up of 50 out of 138 participants in this trial. I have also led on the completion of follow up of an additional 53 participants in this trial.

I have written a substantial amendment to the protocol/trial and submitted via the Integrated Research Application System (IRAS) to the National Research Ethics Service (NRES).

I have reviewed the trial screening log, all participants CRFs and transcribed all data into a database of my own design.

I have reviewed and corrected the treadmill calculation formulae and adjusted all data pertaining to walking distances and walking times as they were incorrectly calculated and reported by my predecessors.

I have analyzed all the data presented in this Thesis as well as any data presented in external meetings (Appendix 2).

I have written the Thesis presented below in its entirety.

# Chapter 1 – Introduction

## Section 1.1 – Pathophysiology of intermittent claudication

### 1.1.2 – Anatomy of arteries

The function of the arterial circulation within the human body is primarily the delivery of oxygen to all tissues for their individual metabolic needs, along with glucose, vital nutrients, and hormones. It comprises of elastic arteries, muscular arteries and arterioles (Barbara Young, 2006). Elastic arteries form the major vessels within the arterial tree such as the aorta, the common carotids and the subclavian arteries (Barbara Young, 2006). The muscular arteries form the main distributing branches within the arterial tree such as the femoral, brachial and cerebral arteries (Barbara Young, 2006). Finally, the arterioles are the terminal branches within the arterial tree and supply the capillaries. All arteries have three histologically distinct layers; the inner most tunica intima, the tunica media and the outer most tunica adventitia. The tunica intima is a layer of endothelial cells supported by connective tissue made of elastin and smooth muscle cells known as myointimal cells (Barbara Young, 2006). The tunica media consists of elastin, collagen and smooth muscle cells. Lastly, the tunica adventitia is a collagenous layer that also contains the vasa vasorum, which are essential in supplying blood the tunica adventitia and media in large arteries (Barbara Young, 2006).

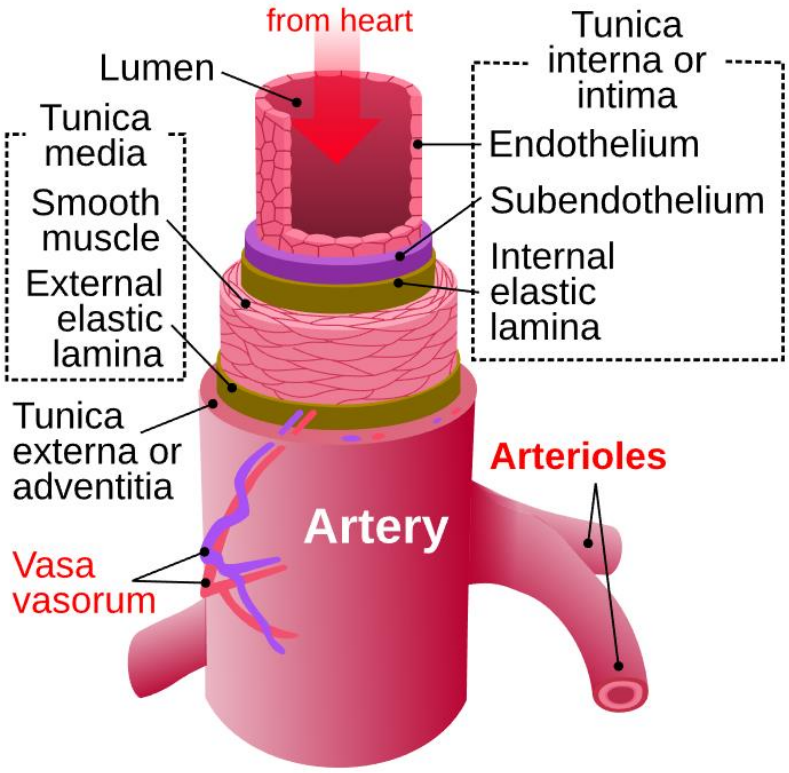



Figure 1 – The histological structure of the artery (Wikipedia, 2013b).

Macroscopic size is not the only separating characteristic between elastic arteries, muscular arteries and arterioles. Histological differences in the tunica media and adventitia are the defining characteristics. In contrast to elastic arteries, where the elastin and collagen is found mostly in the media (Barbara Young, 2006), the elastin in muscular arteries is concentrated in two sheets between the three layers, known as the internal and external elastic lamina (Barbara Young, 2006). The transition from muscular arteries to arterioles is not clearly demarcated but it is a gradual loss of the elastic lamina and smooth muscle layers (Barbara Young, 2006).

### 1.1.3 – Anatomy of arterial tree and supply to the lower limbs

The arterial circulation is traditionally thought to start from the ascending aorta at the base of the left ventricle and supplying the heart itself via the coronary arteries. As it travels through

to the superior mediastinum it forms the arch of the aorta which supplies the upper limbs and the head. The descending or thoracic aorta supplies the thoracic viscera and exits the thorax at the aortic hiatus of the diaphragm at the level of the twelfth thoracic vertebrae (Drake, Vogl, Wayne and Mitchell, 2009). The abdominal aorta supplies the abdominal viscera via five main branches; the coeliac trunk, the superior and inferior mesenteric arteries, and the right and left renal arteries. At the level of the fourth lumbar vertebrae the abdominal aorta bifurcates to the right and left common iliac arteries which bifurcate again at the level of the intervertebral disc between the fifth lumbar and the first sacral vertebrae to give the internal and external iliac arteries (Drake, Vogl, Wayne and Mitchell, 2009). The internal iliac arteries supply the pelvic viscera and the external iliac arteries courses through the pelvis inferiorly to supply the lower limbs.

The external iliac artery becomes the femoral artery as it crosses the inguinal ligament to enter the femoral triangle. One of the largest branches of the femoral artery is the profunda femoris artery or deep femoral artery, and it supplies the muscles of the thigh. Distal to the site of the deep femoral artery branch, the femoral artery is sometimes referred to as the superficial femoral artery, and it descends through the thigh in the adductor canal. As it passes out of the adductor canal through the adductor hiatus it becomes the popliteal artery, which bifurcates at the level of the inferior boarder of the popliteus muscle to give the anterior and posterior tibial arteries which supply the muscles of the leg (Drake, Vogl, Wayne and Mitchell, 2009). The posterior tibial artery descends through the leg in the deep posterior compartment and it passes inferior-posteriorly to the medial malleolus to enter the foot and supply its plantar aspect via two branches; the medial and lateral plantar arteries (Drake, Vogl, Wayne and Mitchell, 2009). The lateral plantar artery forms the deep plantar arch. The anterior tibial artery descends through the leg in the anterior compartment and as it crosses the ankle joint it becomes the

dorsalis pedis artery and it supplies the dorsal aspect of the foot. The arterial circulation in the dorsal and plantar aspect of the foot connect via perforating branches as well as the connection between the deep plantar arch and the deep plantar artery, the terminal branch of the dorsalis pedis artery (Drake, Vogl, Wayne and Mitchell, 2009).

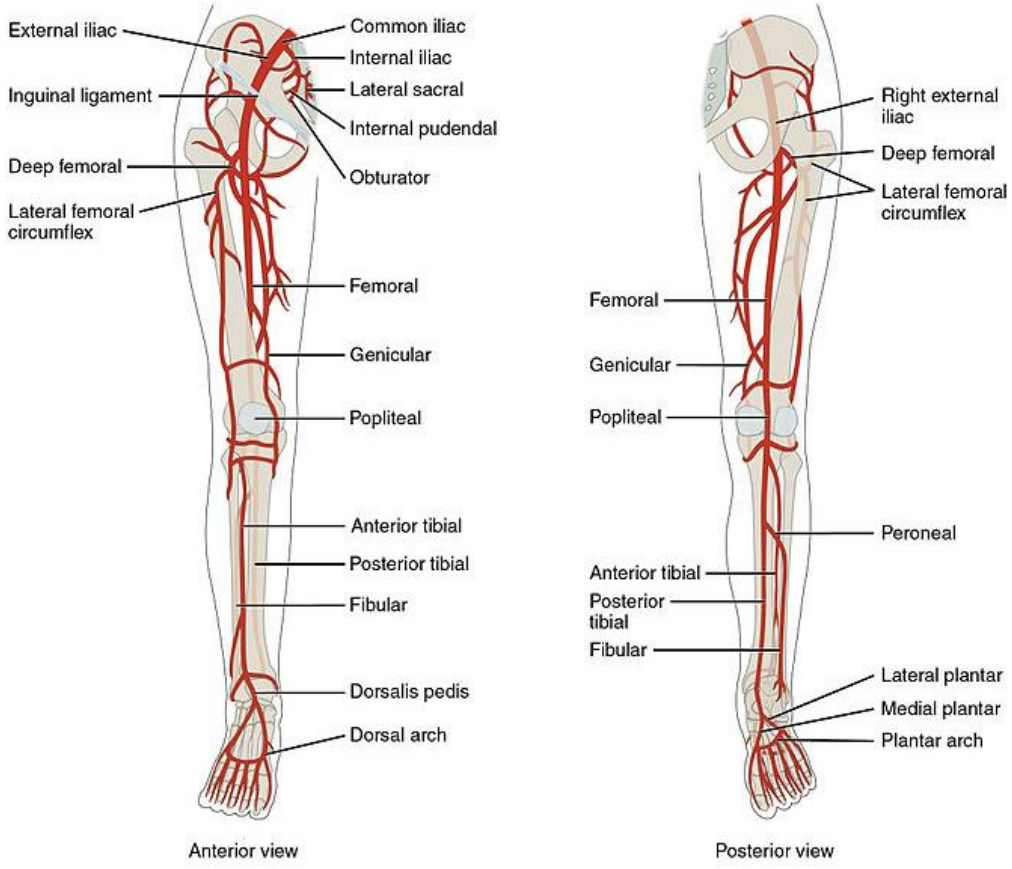



Figure 2 – The lower limb arterial tree (Wikipedia, 2013a)

A disruption of blood flow at any part of this arterial tree can affect the viscera and musculature distal to it, ranging from inadequate arterial supply during increased metabolic demand such as that seen in intermittent claudication to complete lack of arterial supply and tissue death such as that seen in limb ischaemia.

### 1.1.4 – Atherosclerosis

Atherosclerosis comes from two Greek root words “αθήρη”, which means coarsely ground wheat or grain, referring to the macroscopic appearance of atherosclerotic plaques and “σκλήρωση” which means hardening, referring to the arterial wall hardening in the process of atherosclerosis formation. The pathogenesis of atherosclerosis is best understood by explaining the physiological and then pathological response of arterial endothelium to injurious stimuli.

Arterial endothelium as part of the tunica intima plays a major role in arterial wall homeostasis. Endothelium is crucial in maintaining the permeability barrier between the arterial lumen and the supplied tissues, modulation of blood flow (Kumar *et al.*, 2009), maintaining anti-thrombotic but also pro-thrombotic regulators and the oxidation of LDL (Kumar *et al.*, 2009). Healthy arterial endothelium responds to external stimuli such as cytokines, bacterial products, viruses, lipids and glycosylation products by expressing vasoactive mediators, growth factors, and adhesion molecules as part of a process called endothelial activation (Kumar *et al.*, 2009; Pober, Min and Bradley, 2009). However constant pathologic stimulation of the arterial endothelium by excessive endothelial activation from factors such as hypertension, lipids and advanced glycation end-products, hypoxia and by-products of cigarette smoke (Kumar *et al.*, 2009; Pober, Min and Bradley, 2009) will result in endothelial dysfunction. Endothelial dysfunction is a state of altered arterial endothelium phenotype (Kumar *et al.*, 2009) creating a pro-thrombotic, abnormally adhesive and vasoactively impaired endothelium (Kumar *et al.*, 2009; Pober, Min and Bradley, 2009). Therefore, the first step in atherosclerosis formation is

a “chronic inflammatory and healing response of the arterial wall to endothelial injury” (Ross, 1999).

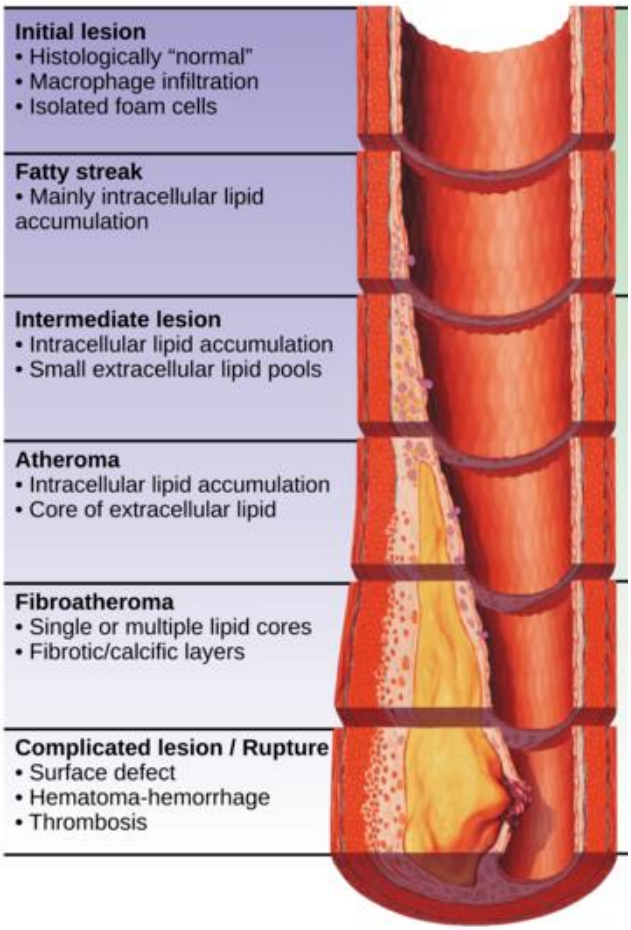



Figure 3 – Progression of atherosclerosis (Wikipedia, 2006)

The healing process is initiated as a response to injury to the endothelium and endothelial dysfunction. Endothelial and smooth muscle cells migrate into the tunica intima from the underlying media and from circulating vascular progenitors (Sata, 2006; Kumar *et al.*, 2009) causing intimal thickening with the formation of neointima. Smooth muscle cells within the neointima not only proliferate but also synthesize elastin and collagen further adding to the intimal thickening (Sata, 2006; Kumar *et al.*, 2009). With removal of the injurious stimulus the smooth muscle proliferation within the neointima can eventually halt however the intimal thickening as a result of the healing process is permanent (Kumar *et al.*, 2009).

Chronic dyslipidaemia contributes further injury to the arterial endothelium accentuating the formation of dysfunctional endothelium, as a result of increased local oxygen free radicals within the endothelium (Ross, 1999; Gau and Wright, 2006; Kumar *et al.*, 2009). Dysfunctional arterial endothelium becomes more permeable to substances like cholesterol (Ross, 1999; Pober, Min and Bradley, 2009), in particular low density lipoproteins. Low density lipoproteins are oxidized in the neointima by oxygen free radicals produced by macrophages or the endothelial cells themselves (Ross, 1999; Gau and Wright, 2006; Kumar *et al.*, 2009), stimulating the recruitment of more monocytes and macrophages to the site of injury. The recruited macrophages continue to oxidize low density lipoproteins but also engulf low density lipoproteins to form lipid-laden macrophages also known as foam cells (Ross, 1999; Gau and Wright, 2006; Kumar *et al.*, 2009). Despite the fact that the initial recruitment of macrophages to the site of the dysfunctional endothelium is a protective response in order to remove harmful lipids (Kumar *et al.*, 2009), this creates a loop of continued low density lipoproteins oxidation, further injury to endothelium via oxygen free radicals, further recruitment of monocytes and macrophages and perpetuation of a chronic inflammatory state, especially with the recruitment of T lymphocytes to the neointima (Ross, 1999; Gau and Wright, 2006; Kumar *et al.*, 2009). Endothelial dysfunction also promotes monocyte adhesion to the arterial endothelium reinforcing the recruitment of monocytes/macrophages to the site (Ross, 1999; Gau and Wright, 2006; Kumar *et al.*, 2009).

The accumulation of foam cells creates the earliest form of an atherosclerotic plaque, the fatty streak (Ross, 1999; Kumar *et al.*, 2009). As more and more lipid accumulates within the intima, along with smooth muscle proliferation and elastin and collagen deposition, a fatty streak evolves to an atherosclerotic plaque (Ross, 1999; Gau and Wright, 2006; Kumar *et al.*, 2009). Atheroma build up within the arterial wall is of major clinical significance not only due to the

gradual reduction of the lumen diameter by atherosclerotic stenosis. Disruption or obstruction of arterial blood flow distal to the lesion can also occur from rupture or ulceration of the atherosclerotic plaque, exposing the highly thrombogenic fibrofatty atheroma to blood, causing acute thrombosis (Ross, 1999; Kumar *et al.*, 2009). Plaque rupture or ulceration can also release atherosclerotic particles that travel distal to the lesion and can occlude arteries of smaller caliber (Kumar *et al.*, 2009).

### 1.1.5 – Clinical presentation of intermittent claudication

Claudication comes from the Latin word "claudicare" which means to limp. Intermittent claudication refers to a cramping pain in a group of tissues with increased metabolic demands, and rapid easing of this pain on return of metabolic demands to baseline or rest. Intermittent claudication is the initial manifestation of peripheral arterial disease, where disruption or gradual chronic occlusion of part of the arterial tree, reduces the amount of blood flow distal to it and hence unable to deliver adequate oxygen and other vital substances to meet increased metabolic demands.

Lower limb intermittent claudication classically manifests in one or both calf muscles on walking a relatively constant distance, and it is reproducible once the pain has subsided with rest (Garden *et al.*, 2012). Depending on the location of arterial compromise, lower limb intermittent claudication can affect the thigh and/or the buttocks. Other symptoms may include a cold or pale foot, especially upon exertion (Garden *et al.*, 2012). Patients will most commonly report risk factors for arterial damage and formation of atherosclerosis in their peripheral circulation, with a smoking history, hypertension, dyslipidaemia, diabetes, and a history of other cardiovascular disease, such as coronary artery disease and/or cerebrovascular disease.

Confirmation of peripheral arterial disease and intermittent claudication diagnosis is largely clinical, with radiological investigations recommended only if an invasive intervention is planned (NICE, 2018). The above clinical history combined with clinical examination can be definitive enough for diagnosis. Bed side tests can aid in the diagnosis such as ankle brachial pressure index, which is the ratio of the systolic blood pressure measured at the brachial artery versus the systolic blood pressure measure at either the dorsalis pedis or posterior tibial artery. An ankle brachial pressure index of less than 0.9 strongly indicates to the presence of peripheral arterial disease and it is associated with increased risk of major cardiovascular events and all cause mortality (Fowkes *et al.*, 2008; Criqui *et al.*, 2010). A normal ankle brachial pressure index at rest however should not be reassuring of the absence of peripheral arterial disease. Given that the manifestation of intermittent claudication symptoms is upon exertion of the affected musculature of the lower limb, post exercise measurement of ankle brachial pressure index can reveal the presence of the disease. This can be achieved with a standardized treadmill test in an outpatient setting, where a decrease of more than 20% in ankle brachial pressure index is diagnostic of peripheral arterial disease (Aboyans *et al.*, 2018).

Where further investigation is required, the usual first choice would be that of a duplex ultrasound. It is a great tool for the initial assessment of the lower limb arterial tree with a 90% sensitivity and more than 95% specificity in detecting narrowing or blockage within the lower limb arterial tree (Collins *et al.*, 2007). It is a fast, safe, and cost effective imaging modality, but it is however operator dependent introducing some interobserver variability in results especially in the more challenging to assess areas of the lower limb arterial tree such as the iliac arteries above the inguinal ligament and the crural arteries below the knee (Collins *et al.*, 2007). If more detail imaging is required, especially when iliac or crural artery disease is suspected clinically, magnetic resonance angiography provides the highest diagnostic accuracy

among the available non-invasive imaging modalities with sensitivity and specificity of over 95% (Collins *et al.*, 2007). It is however not as readily accessible and available as duplex ultrasound, it poses contraindications to its use in patients with metallic implants, it requires intravenous contrast that can have a serious impact on kidney function especially in cases where that is already impaired (Ramalho *et al.*, 2016) and it can not assess areas where endovascular treatment in the form of steel stents has been used before (Aboyans *et al.*, 2018). It is however the more cost effective option when the imaging of the area of concern is not easily visualized by duplex ultrasound. The last of the available noninvasive imaging modalities is computed tomography angiography which also has over 95% sensitivity and specificity in the assessment of narrowing or blockage of any part of the arterial tree (Collins *et al.*, 2007) and has the advantage over magnetic resonance angiography for time to completion and imaging areas previously treated by steels stents (Aboyans *et al.*, 2018). It does however pose a significant risk with the use of iodinated contrast agents to kidney function as well as allergic reactions and ionized radiation (Aboyans *et al.*, 2018). It is also not as sensitive and specific as magnetic resonance angiography when imaging heavily calcified disease below the knee (Collins *et al.*, 2007) as seen in the distribution of disease in patients with diabetes mellitus (Jude *et al.*, 2001). Digital subtraction angiography is considered to be the gold standard investigation for lower limb peripheral arterial disease, however it is an invasive investigation and should only be undertaken when simultaneous intervention in the form of angioplasty is planned to take place (Aboyans *et al.*, 2018; NICE, 2018). It confers the same risks as computed tomography angiography with regards to intravenous contrast and radiation with the added risks of an invasive procedure such as haemorrhage, damage to blood vessels, acute limb ischaemia and limb loss (Axisa *et al.*, 2002) and therefore reserved for life-limiting intermittent claudication which has failed conservative management (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018).

## Section 1.2 – Epidemiology of intermittent claudication

### 1.2.1 – The Global burden of peripheral arterial disease

The leading cause of death worldwide is cardiovascular disease, costing the lives of almost 20 million people in 2019, with the majority of which being coronary and cerebrovascular disease (WHO, 2013; Roth *et al.*, 2020). This number is set to rise with the continuing aging population worldwide (Fowkes *et al.*, 2013). Major cardiovascular events and chronic cardiovascular disease do not only confer high mortality but also morbidity, disability and cost to the global healthcare system (Tarride *et al.*, 2009; Gheorghe *et al.*, 2018; Roth *et al.*, 2020). The vast majority of the cardiovascular disease burden can be prevented with risk factor modification (See Section 1.3.1), leading to the World Health Organization setting a global action plan for the prevention and control of noncommunicable diseases and an aim for a 25% relative risk reduction in overall mortality as a result of cardiovascular disease by 2025 (WHO, 2013).

More than 200 million people globally suffer from peripheral arterial disease, with 40.5 million of those in Europe (Fowkes *et al.*, 2013; Song *et al.*, 2019), a number which has doubled in the last 30 years (Roth *et al.*, 2020). In higher income countries there is no significant difference in the prevalence of peripheral arterial disease between men and women (Fowkes *et al.*, 2013) however, that is not the case in lower income countries with women having higher prevalence than men, a difference that diminishes with age (Fowkes *et al.*, 2013). The prevalence of peripheral arterial disease increases with age in both genders and among higher and lower income countries (Fowkes *et al.*, 2013) reaching a prevalence of nearly 20% in the population over the age of 80 years (Fowkes *et al.*, 2013; Aboyans *et al.*, 2018). Nearly 30 people per 100,000 population worldwide die yearly of peripheral arterial disease (Fowkes *et al.*, 2013; Sampson *et al.*, 2014) indicating a significant global burden of this disease.

Peripheral arterial disease encompasses a range of disease severity from asymptomatic disease to critical limb threatening ischaemia and limb loss. Surprisingly, up to 10% of people with peripheral arterial disease are completely asymptomatic, and that figure doubles for people over the age of 70 years (Norgren *et al.*, 2007). The progression from asymptomatic to symptomatic disease is reported to be low in the literature (Mizzi *et al.*, 2019). Intermittent claudication is the most common symptomatic manifestation of peripheral arterial disease (Harwood *et al.*, 2020) with a prevalence of around 6% in people over the age of 60 years (Norgren *et al.*, 2007) though some studies report this as high as 30% (Eldrup *et al.*, 2006; Fowkes *et al.*, 2016).

### 1.2.2 – Intermittent claudication in the UK

Peripheral arterial disease is estimated to affect around 20% of the UK population aged between 55 and 75 years (FOWKES *et al.*, 1991; NICE, 2011) with around 5% of them experiencing symptoms of intermittent claudication (FOWKES *et al.*, 1991).

## Section 1.3 – Management of intermittent claudication

The management of intermittent claudication is entirely reliant on the clinical presentation and impact of this on the patient's activities of daily living and quality of life. Non-life limiting intermittent claudication should be treated conservatively with risk factor modification, best medical therapy, and participation in supervised exercise programs (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018) all of which have been shown to improve symptoms of intermittent claudication (Quick and Cotton, 2005; Ritti Dias *et al.*, 2009; Gerhard-Herman *et al.*, 2017; Lane *et al.*, 2017a; Aboyans *et al.*, 2018; NICE, 2018). Invasive revascularization procedures such as percutaneous angioplasty and surgical bypass, should be reserved for patients that have failed conservative management and

continue to suffer from life limiting symptoms (Aboyans *et al.*, 2018; NICE, 2018). When successful, these invasive revascularization procedures confer an immediate improvement or even resolution of the patients' symptoms (Nordanstig, Taft, *et al.*, 2014; Malgor *et al.*, 2015; Regensteiner *et al.*, 2016), however the perioperative risks, the long term durability, and the lack of long term benefit in comparison to conservative management (Siracuse *et al.*, 2012a; Djerf *et al.*, 2020; Levin *et al.*, 2021) do not justify their use in non-life limiting intermittent claudication (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018).


Figure 4 – Infographic, Exercise for Intermittent Claudication (Tew *et al.*, 2020)

### 1.3.1 – Risk factor modification

Cigarette smoking is an independent risk factor for the development and progression of peripheral arterial disease, increasing the risk in comparison to nonsmokers as high as fourfold (Joosten *et al.*, 2012; Criqui and Aboyans, 2015a). Previous history of smoking as well as second hand smoking is also associated with the development of peripheral arterial disease (Joosten *et al.*, 2012; Criqui and Aboyans, 2015a; Lu, Mackay and Pell, 2018) and that effect

is noted to return to baseline or nonsmoking risk only after more than 10 years of smoking cessation (Joosten *et al.*, 2012). Smoking cessation is integral to the management of intermittent claudication (Gerhard-Herman *et al.*, 2017; Ratchford, 2017; Aboyans *et al.*, 2018; NICE, 2018), and it has been shown to improve patients' symptoms (Quick and Cotton, 2005) and overall survival (Faulkner, House and Castleden, 1983) as well as the well established, wider health benefits (Samet, 1991, 1992; Lightwood and Glantz, 1997).

Hypertension or raised systolic blood pressure is also an independent risk factor for the development and progression of peripheral arterial disease (Joosten *et al.*, 2012; Criqui and Aboyans, 2015a; Aboyans *et al.*, 2018). Hypertension in patients with intermittent claudication should be treated according to the latest guidance (Mancia *et al.*, 2013; NICE, 2019) and aiming for less than 140mmHg in systolic and 90mmHg in diastolic blood pressure.

Dyslipidaemia or hypercholesterolaemia is an additional independent risk factor for the development and progression of peripheral arterial disease (Joosten *et al.*, 2012; Criqui and Aboyans, 2015a; Aboyans *et al.*, 2018). Though the rationale of lipid lowering treatment in peripheral arterial disease is the reduction of major cardiovascular events (Aung *et al.*, 2007; Heart Protection Study Collaborative Group, 2007; Kumbhani *et al.*, 2014), simvastatin in particular has been shown to improve walking times and distances in patients with intermittent claudication (Momsen *et al.*, 2009). Dyslipidaemia in patients with intermittent claudication should be treated according to the latest guidance (NICE, 2014; Mach *et al.*, 2020) with an aim to reduce serum low-density lipoprotein cholesterol to less than 1.8mmol/L (Piepoli *et al.*, 2016).

Diabetes mellitus has a more complex relationship with peripheral arterial disease and intermittent claudication in comparison to the above risk factors. Though generally strongly associated with an increased risk of developing peripheral arterial disease (Criqui and Aboyans, 2015b; Aboyans *et al.*, 2018), the lower prevalence of diabetes mellitus in the general population in comparison to smoking, dyslipidaemia or hypertension, means its population attributable fraction for the incidence of peripheral arterial disease is much lower than the other modifiable risk factors (Joosten *et al.*, 2012). In addition to that, impaired glucose tolerance or even newly diagnosed diabetes mellitus is not associated with peripheral arterial disease as long standing or known diabetes mellitus are (Beks *et al.*, 1995). As expected, duration of diabetes mellitus, severity and control of the disease (measured by HbA1c levels) and use of insulin therapy, are all recognized risk factors for the development and progression of peripheral arterial disease (Jude *et al.*, 2001; Joosten *et al.*, 2012; Althouse *et al.*, 2014; Criqui and Aboyans, 2015b). Diabetes mellitus in patients with intermittent claudication should be treated according to the latest guidance (NICE, 2015; Cosentino *et al.*, 2020) with an aim to reduce serum HbA1c to less than 53mmol/mol.

Raised body mass index or obesity remains a puzzling risk factor for peripheral arterial disease. Multiple, large epidemiological studies have not been able to identify a significant association between raised body mass index and peripheral arterial disease (Ingolfsson *et al.*, 1994; Meijer *et al.*, 2000; Ness, Aronow and Ahn, 2000; Hooi *et al.*, 2001; Murabito *et al.*, 2002; Allison *et al.*, 2006; Criqui and Aboyans, 2015b), some of which have even found obesity to be a "protective" or inversely related factor to peripheral arterial disease and intermittent claudication (Newman *et al.*, 1993; Beks *et al.*, 1995). An argument can be made however on the design and analysis of such epidemiological studies and their approach to risk factors. Raised body mass index has well known associations to hypertension, dyslipidaemia and

diabetes mellitus (Criqui and Aboyans, 2015a) all of which are strongly associated with the development and progression of peripheral arterial disease as mentioned above. Therefore, in an epidemiological analysis where obesity is scrutinized individually while correcting or matching for the above known risk factors, may not provide a "real world" impact of obesity to the development and progression of peripheral arterial disease. As expected, two studies that had not found an association between raised body mass index and peripheral arterial disease, showed a significant association in unadjusted models or models adjusted only for age and gender (Gerald *et al.*, 1992; Ness, Aronow and Ahn, 2000; Murabito *et al.*, 2002). Lastly, cigarette smoking has been associated with lower body mass index (Criqui and Aboyans, 2015a), therefore a lower body mass index may falsely show association with peripheral arterial disease, if a major risk factor such as smoking is not accounted for. Consequently, when people who have never smoked are investigated, a direct association between raised body mass index and development of peripheral arterial disease is found (Ix *et al.*, 2011). Patients with intermittent claudication and raised body mass index should therefore be encouraged to lose weight to reduce their risk of all cause morbidity and mortality (Gonzalez *et al.*, 2010) and improve their pain free walking distance (Ritti Dias *et al.*, 2009).

### 1.3.2 – Best medical therapy

In general, best medical therapy for the management of intermittent claudication broadly refers to antiplatelet and lipid lowering therapy. This however, should not take away from the medical therapy required for risk factor modification such as anti-hypertensive and diabetic medical therapy and optimal management of those should not be neglected (See section 1.3.1).

Lipid lowering therapy is a must in the management of peripheral arterial disease and intermittent claudication (See Section 1.3.1). It is recommended that patients with intermittent

claudication receive high intensity statin therapy regardless of what their lipid profile is (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018; Mach *et al.*, 2020) as it significantly reduces the risk of major cardiovascular events (Heart Protection Study Collaborative Group, 2007) and well as the previously mentioned improvements seen in walking distances (Momsen *et al.*, 2009).

Antiplatelet therapy is also a must in the management of peripheral arterial disease as it has been shown to reduce both lower limb and other major cardiovascular events, as well as all cause mortality in patients with symptomatic peripheral arterial disease (Gent, 1996; Baigent *et al.*, 2002; Cacoub *et al.*, 2009; Wong *et al.*, 2011; Schmit *et al.*, 2014; Aboyans *et al.*, 2018), as no benefit of antiplatelet therapy has been found in asymptomatic disease (Schmit *et al.*, 2014). In addition to the above, antiplatelet therapy in patients with intermittent claudication has been shown to significantly improve the pain free walking distance (Momsen *et al.*, 2009; Wong *et al.*, 2011).

With the publication of the Voyager PAD and COMPASS trials (Eikelboom *et al.*, 2017; Bonaca *et al.*, 2020), there is an increased clinical use of low dose anticoagulation therapy in combination with antiplatelet therapy especially in more severe peripheral arterial disease, though this is not yet formally recommended by official guidance (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018). The use of low dose anticoagulation therapy in combination with antiplatelet therapy in patients with peripheral arterial disease has shown a reduction in both lower limb and major cardiovascular events (Steffel *et al.*, 2020; Kaplovitch *et al.*, 2021), though this benefit was only observed in more severe peripheral arterial disease rather than intermittent claudication (Kaplovitch *et al.*, 2021). Currently there is no evidence

for the use of this therapy combination in intermittent claudication though studies are underway (Ramacciotti *et al.*, 2022).

### 1.3.3 – Exercise therapy

There is an abundance of evidence to support the participation in supervised exercise programs in patients with intermittent claudication (Gerhard-Herman *et al.*, 2017; Lane *et al.*, 2017a; Aboyans *et al.*, 2018; Hageman *et al.*, 2018; NICE, 2018). Overall, when compared to no exercise, supervised exercise programs increase pain free and maximum walking distances in patients with intermittent claudication by a median of 82 and 120 meters respectively (Lane *et al.*, 2017a). However when shorter term outcomes are assessed at three months follow up, supervised exercise only conferred an improvement in pain free walking distance and not maximum walking distance (Lane *et al.*, 2017a). With regards to quality of life, when supervised exercise is compared to no exercise, there is a significant improvement in several domains of the SF-36 quality of life questionnaire, including physical functioning and physical summary score (Lane *et al.*, 2017a). There was no difference in ankle brachial pressure indexes or all cause mortality (Lane *et al.*, 2017a).

Despite the clear evidence for the benefit of supervised exercise and the strong recommendation for its inclusion in standard care by the latest guidance, only a small proportion of patients with intermittent claudication have access locally to a supervised exercise program in the UK (Harwood *et al.*, 2022). Even in areas where supervised exercise programs are provided for patients with intermittent claudication, participation and then subsequent completion of these programs is very low (Harwood *et al.*, 2016a) with patients showing preference to home base or solo exercising, with a duration of less than 1 hour per session (Harwood, Hitchman, *et al.*, 2018).

Given the above, the majority of patients with intermittent claudication, would only receive walking advice by their treating clinician as the standard of care. Supervised exercise is superior to walking advice in significantly improving both pain free and maximum walking distances (Hageman *et al.*, 2018), however, there was no significant benefit of supervised exercise over walking advice in the short term assessment of quality of life (Hageman *et al.*, 2018). A significant improvement in physical functioning and physical summary score as measured by SF-36 quality of life questionnaire is only seen after nine months of follow up when supervised exercise is compared against walking advice (Hageman *et al.*, 2018). There was no difference in ankle brachial pressure indexes or all cause mortality (Hageman *et al.*, 2018).

### 1.3.4 – Invasive interventions

As previously discussed, invasive interventions in the form of percutaneous angioplasty and/or open surgical bypass should be restricted to patients with life limiting intermittent claudication and who have showed no improvement with adherence to risk factor modification, best medical therapy and participation in supervised exercise programs (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018).

Lower limb percutaneous angioplasty generally involves the introduction of angiography catheters, wires, and other equipment into a lower limb artery through the skin under local anaesthetic. Iodinated contrast agents are delivered directly into the artery and X-ray radiation is used to assess the lower limb arterial tree. Once the area of narrowing or blockage is found, intravascular balloons are introduced to this area and expanded in an attempt to return the arterial lumen to a more haemodynamically favorable diameter.

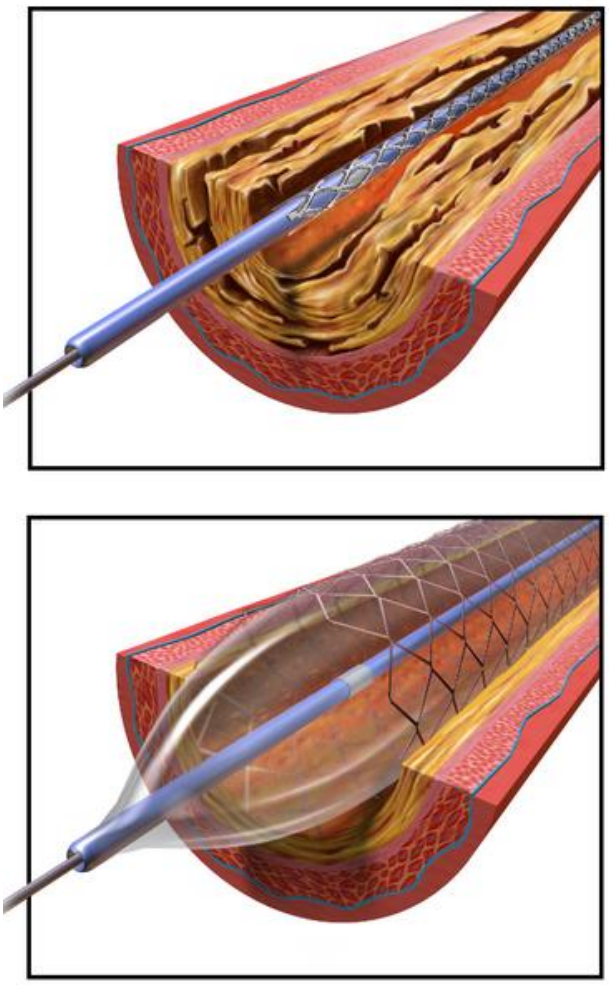


Figure 5 – Arterial balloon angioplasty and stent

However, isolated balloon angioplasty carries the risk of arterial recoil and residual or future restenosis and therefore intravascular stents are most often deployed to prevent the above and maintain a haemodynamically favorable intraluminal diameter (Aboyans *et al.*, 2018). There are a variety of stents available in the market, with the most recent advancement being drug eluding stents, in an effort to minimize future in stent restenosis via neointimal hyperplasia mechanisms and improve future outcomes (Bangalore *et al.*, 2012; Aboyans *et al.*, 2018).

Open surgical bypass generally involves the use of an autologous conduit, for example the great saphenous vein, or a prosthetic conduit, such as a PTFE graft, to bypass an area of

narrowing or blockage within the lower limb arterial tree. The conduit is usually planted in a segment above the diseased area where blood flow is not compromised to a segment below that area where the artery is healthy and relatively disease free so that adequate blood can reach the distal lower limb.

Depending on the location, extend and pattern of atherosclerotic disease, percutaneous angioplasty or open surgical bypass could be used in isolation or in combination in a hybrid procedure.

In comparison to the minimally invasive nature of percutaneous angioplasty, open surgical bypass is a major undertaking with longer hospital stay, higher risk of infection and other post operative complications (Siracuse *et al.*, 2012b; El Yamany, Mohamed and Kamel, 2020). However it shows a better improvement of intermittent claudication symptoms and has higher patency rates when compared to percutaneous angioplasty (Siracuse *et al.*, 2012b; Aboyans *et al.*, 2018; El Yamany, Mohamed and Kamel, 2020).

The decision making involved in choosing the appropriate invasive, revascularization technique is multifactorial and broadly based:

1) The anatomical location and extend of atherosclerotic disease
2) Patient fitness and likely tolerability of each treatment
3) Treating centre expertise and capabilities
4) Patient preference

Whichever invasive, revascularization technique is employed, risk factor modification, best medical therapy and exercise should continue to be an important part of the management and treatment plan of these patients.

## Section 1.4 – Quality of life in intermittent claudication

The World Health Organization defines quality of life "as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." (WHO, no date). The National Institute for Health and Care Excellence builds on this by defining it as "a combination of a person's physical, mental and social well-being; not merely the absence of disease" (*Glossary | NICE*, no date).

The impact of intermittent claudication on quality of life is well-documented and affects all aspects including functional/physical, social and mental health (Pell, 1995; Khaira, Hanger and Shearman, 1996; Hallberg, Risberg and Thomsen, 1999). Therefore quality of life forms an essential part of patient outcomes in intermittent claudication research, though there is no consensus on which quality of life questionnaire is the most suitable for use in this cohort of patients (Harwood *et al.*, 2017). Moreover, clinicians have been shown to rate patients' quality of life poorly with little correlation to patient reported quality of life (Hicken, Lossing and Ameli, 2000). It is therefore imperative that quality of life is measured by well validated, reliable, and reproducible quality of life questionnaires. There is an abundance of generic or disease specific health related quality of life questionnaires.

A generic quality of life questionnaire needs to be applicable to any disease, any disease severity and validated across multiple patient groups and across national borders (Beattie *et al.*, 1997; Scott and Kester, 1998). The EuroQol 5D (EQ-5D) and Medical Outcome Study 36-item Short-Form Health Status Survey (SF-36) have been widely used and extensively validated generic quality of life

questionnaires in peripheral arterial disease and intermittent claudication (De Vries *et al.*, 2005; Mehta *et al.*, 2006; Gulati *et al.*, 2009; Conijn *et al.*, 2016; Harwood *et al.*, 2017; Vaidya *et al.*, 2018) and have been shown to detect improvements in quality of life following treatment (Chetter *et al.*, 1999, 2003). Recent reviews on the variety of quality of life questionnaires used in intermittent claudication research has shown that the SF-36 is most common questionnaire used (Harwood *et al.*, 2017; Lane *et al.*, 2017b). The physical functioning domain of the SF-36 is the most impaired by intermittent claudication (Izquierdo-Porrera *et al.*, 2005), but as previously demonstrated by Tsai et al (Tsai *et al.*, 2002), it is the most likely to respond to the successful treatment of intermittent claudication, when compared to other measures of quality of life. It is also the only domain that is consistently improved with exercise trials in intermittent claudication (Lane *et al.*, 2017a; Hageman *et al.*, 2018) and therefore a point of reference within the current recommendations for treatment (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018). EQ-5D has the added advantage of forming part of the NICE reference case for cost per quality adjusted life years analysis, providing data for cost effectiveness analysis.

A disease specific quality of life questionnaire extensively used for peripheral arterial disease and validated to detect quality of life changes across the entire spectrum of peripheral arterial disease is the King's College Hospital's Vascular Quality of Life Questionnaire (VascuQoL) (Morgan *et al.*, 2001; Mehta *et al.*, 2006; Mays *et al.*, 2011; Conijn *et al.*, 2016) and has been reported to be the most responsive of disease specific questionnaires in peripheral arterial disease (De Vries *et al.*, 2005; Mehta *et al.*, 2006). It is important to note however, that despite its disease specific nature, the VascuQol questionnaire attempts to encompass all peripheral arterial disease with questions pertaining to rest pain and ulceration, describing more advanced disease stages of peripheral arterial disease, which are not relevant to intermittent claudication and may limit its responsiveness to successful treatment of it (A. P. Conijn *et al.*, 2015).

Given that intermittent claudication has a well-documented impact on quality of life in terms of functional/physical, social and mental health (Pell, 1995) and that treatments and interventions for intermittent claudication are guided by the impact of symptoms in quality of life (Aboyans *et al.*, 2018; O'Banion *et al.*, 2023), any novel intervention introduced for the management of intermittent claudication needs to show an effect on quality of life (I. C. Chetter *et al.*, 1997; Gulati *et al.*, 2009; O'Banion *et al.*, 2023). Despite the above there is still no standardization or consistency within the published literature for quality of life questionnaires in patients with peripheral arterial disease and intermittent claudication (Harwood *et al.*, 2017) despite recommendations for such standardization (C. Chetter *et al.*, 1997; Gulati *et al.*, 2009).More importantly, the vast majority of research in intermittent claudication focuses on "objective" outcome measures such as walking distances, ankle brachial pressure index and other forms of perfusion assessment which may not necessarily correlate with generic quality of life measures (Barletta *et al.*, 1996; Mazari *et al.*, 2010; Chetter *et al.*, 2016). Even when correlation with quality of life of life measures and walking distances is established (Mehta *et al.*, 2006; Nordanstig, Broeren, *et al.*, 2014; Golledge *et al.*, 2020), this does not necessarily represent causation (Ibeggazene and Klonizakis, 2023) and we might not be able to solely rely on walking distances as a measure of success or failure of an intervention for intermittent claudication.

## Section 1.5 – Minimum Clinically Important Difference

As stated above (Section 1.4) patient reported outcomes play a significant role in intermittent claudication research. Change in quantitative/objective measure may be statistically significant from a numerical point of view but that does not necessarily translate to a tangible, "real world" change in quality of life. This also applies to numerical significant changes to quality of life measures. Clinically Important Difference refers to the "change that would be considered meaningful and worthwhile by the patient" (Copay *et al.*, 2007; McGlothlin and Lewis, 2014) and was introduced in an effort to

provide more “real world” and tangible measures of change beyond the purely mathematical “statistical significance” (Copay *et al.*, 2007). Minimum Clinically Important Difference is the smallest change required to be considered meaningful and worthwhile by the patient (Copay *et al.*, 2007; McGlothlin and Lewis, 2014; Anne P. Conijn *et al.*, 2015) and as an outcome measure re-aligns the focus of research to a more patient-centered approach. As such efforts by Conijn and colleagues to establish the MCID in quality of life measures such as the VascuQol and Walking Impairment Questionnaire in patients with intermittent claudication (Anne P. Conijn *et al.*, 2015; Conijn *et al.*, 2016) can provide insights to the true/”real world” impact of treatment modalities for intermittent claudication and whether those truly match with “objective” outcome measures such as walking distances and ankle brachial pressure index.

Minimum Clinically Important Difference is usually calculated via two methods, Anchor-based and distribution based methods (Copay *et al.*, 2007; McGlothlin and Lewis, 2014; Anne P. Conijn *et al.*, 2015). Anchor-based methods use a separate measure to compare with the patient reported outcome such as quality of life. For example Conjin and colleagues compared the changes in VascuQol and Walking Impairment Questionnaire following treatment for intermittent claudication against a simple scale of condition 1) improved 2) unchanged 3) deteriorated (Anne P. Conijn *et al.*, 2015). An obvious limitation to this, is that determining which separate measure to use and the scale of measure (Copay *et al.*, 2007; McGlothlin and Lewis, 2014). The use of patient reported outcomes such as quality of life was introduced in order to replace “objective”/quantitative measures that may not necessarily reflect what’s an important outcome for the patients, and that is now re-introduced to identify the minimum clinically important difference is definitely contradictory and a major limitation to anchor-based methods (Copay *et al.*, 2007; McGlothlin and Lewis, 2014). Distribution-based methods use either the standard error of measurement, effect size, or standard deviation to compare any change in patient reported outcomes (Copay *et al.*, 2007; McGlothlin and Lewis, 2014). The inherent

mathematical robustness of distribution-based methods is its biggest limitation as it consequently ignores a change that is clinically significant to the patient and focuses on the statistical significance. Moreover, MICD calculated using distribution-based methods can only be applied to the cohort of patients on which it is based and does not have wider applicability (Copay *et al.*, 2007; McGlothlin and Lewis, 2014).

## Section 1.6 – Extracorporeal shockwave therapy

### 1.6.1 – The history of extracorporeal shockwave therapy

A shockwave is said to be a "transient, short-term acoustic pulse with high peak pressure and a very short rise to peak pressure time on the order of magnitude of nanoseconds" (Mittermayr *et al.*, 2012a). In simpler terms shockwave is a form of sound wave, comprised of compression and expansion of the medium it travels in (air, water, solids), but with a more sudden change in stress, density and temperature than ordinary sound waves (Britannica, no date). The more recognised causes for the generation of shockwaves are explosions, lightning and military airplanes traveling faster than the speed of sound. Shockwaves have a higher capacity to transmit energy, than ordinary acoustic waves, which can be used to destroy materials (Thiel, 2001). A classic example of that is an explosion shattering windows much further away than its immediate surroundings. This capacity to transmit energy however, is not only for destructive purposes as it can also be used in deep sea investigations, as they can travel further than ordinary acoustic waves (Thiel, 2001).

The first documented effect of sho"kwav's on humans was the assessment of soldiers at sea in World War II (Krause, 1997). These soldiers were exposed to underwater explosions and exhibited internal lung injuries without any obvious external trauma (Krause, 1997), and as we

now know caused by primary blast injury (Wightman and Gladish, 2001). The rapid changes in pressure caused by the propagating shockwave in fractions of a second, transfer large amounts of energy and force to the tissues, especially air filled organs such as bowel and lungs (Wightman and Gladish, 2001). It wasn't until the 1950s that more interest was focused on shockwaves and their controlled use for destructive purposes, with the emergence of the first patent for an electrohydraulic shockwave generator (Krause, 1997). It took a further 10 years before the effects of shockwaves on biological tissue was investigated in Germany (Krause, 1997). The transmission of shockwaves through the body revealed that shockwaves did not create significant side effects when traveling through denser tissue such as muscle, adipose and connective tissue, and even less through bone (Thiel, 2001). However, it did reveal the dangers of transmission through tissues like lung, bowel and brain (Thiel, 2001). These investigations sparked the concept of renal lithotripsy using shockwaves.

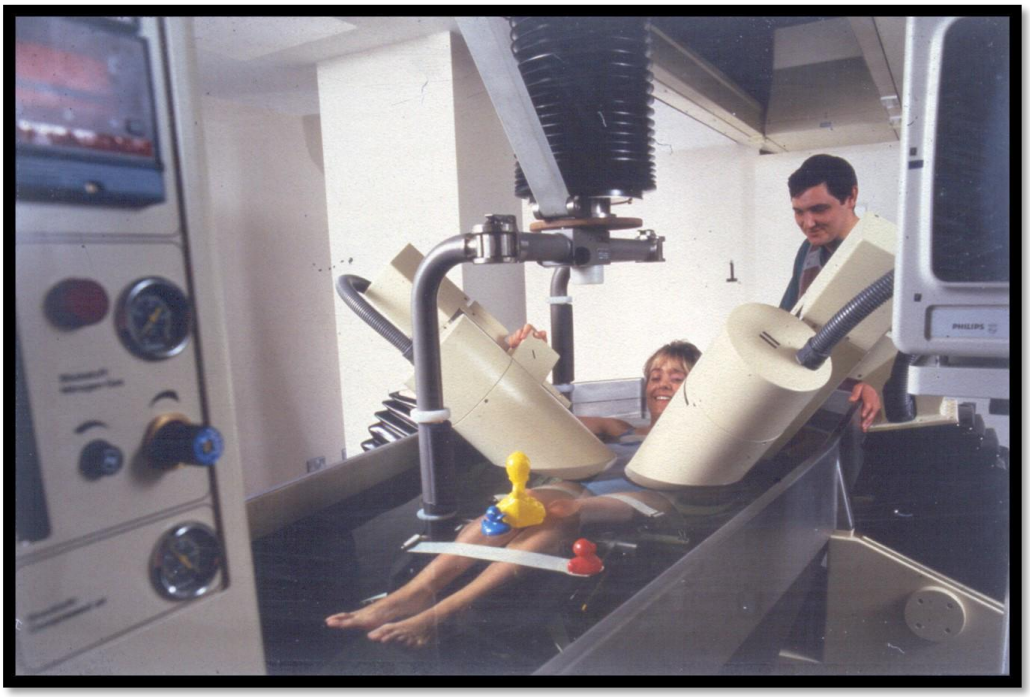


Figure 6 – The Dornie HM3 in use in Guy's and St Thomas' Hospital (Dornier HM3, no date)

The first in vitro renal lithotripsy was conducted in 1971 (Häusler and Kiefer, 1971), and 9 years later the first patient underwent the same procedure (Krause, 1997). By 1983, the first commercially available equipment for renal lithotripsy was in use in Germany, called the Dornier HM3 (Krause, 1997; Elmansy and Lingeman, 2016). The technology for renal lithotripsy has since advanced, negating the use of water baths for patient immersion and introduction of fluoroscopy or ultrasound systems for the localization of renal stones (Thiel, 2001; Elmansy and Lingeman, 2016).

With a concern for the effects of shockwave on the surrounding structures, and in particular the ilium in the pelvis for more distal ureteric stones, further experiments were conducted (Thiel, 2001). They showed that the bone was actually not adversely affected , but instead showed an increased bone mineral density (Chamberlain and Colborne, 2016). This osteogenic reaction was found to stimulate healing of fractures, (Haupt, 1997; Thiel, 2001) leading to the first successful treatment of a non-union fracture using shockwave in 1988 in Germany (Haupt, 1997). From there the use of extracorporeal shockwave expanded in orthopaedic practice with applications beyond bone healing to tendon and other soft tissue conditions (Wang, 2012).

### 1.6.2 – The use of extracorporeal shockwave therapy beyond renal lithotripsy

The exact mechanism by which extracorporeal shockwave therapy induces this osteogenic reaction within bone tissue is still largely unknown, however the most prevailing explanation for this effect is via the cellular mechanism of mechanotransduction (Chamberlain and Colborne, 2016). Mechanotransduction is the cellular ability to convert mechanical stimuli into biochemical signals, which then in turn drive intracellular changes (Dobner, Amadi and Lee,

2012). Similar to a mechanical load on the musculoskeletal system (such as lifting weights), extracorporeal shockwave releases energy and pressure on their targeted area exerting a mechanical force to the underlying tissue (Chamberlain and Colborne, 2016). Such forces generate fluid flow within cortical bone, stimulating osteocytes and in turn osteoblasts via a cascade of growth factor release, giving rise to the aforementioned osteogenic response to extracorporeal shockwave (Figure 2).

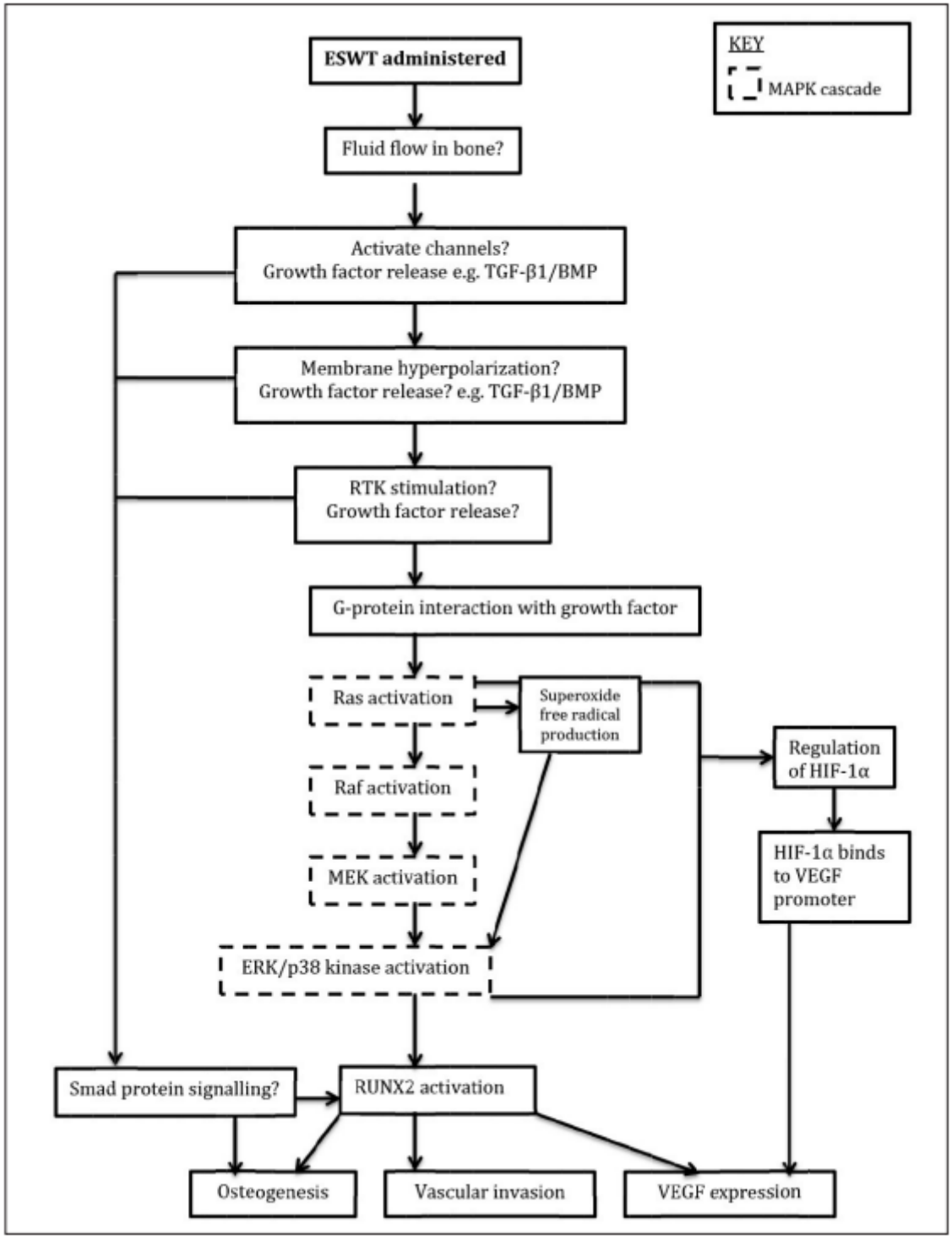



Figure 7 – Proposed mechanism of action of extracorporeal shockwave therapy (Chamberlain and Colborne, 2016)

The use of extracorporeal shockwave therapy rapidly expanded from osteogenesis in animal models to a vast variety of orthopaedic disorders including but not limited to plantar fasciitis,

lateral epicondylitis of the elbow (tennis elbow), calcific tendinitis of the shoulder and Achilles tendonitis (Wang, 2012). It has thus been shown to be safe and effective in treating these disorders, often negating the need for invasive interventions and surgery, and showing low, almost negligible complications (Wang, 2012).

As seen in Figure 2, osteogenesis is not the only mechanotransduction effect of extracorporeal shockwave therapy. The upregulation of VEGF expression via extracorporeal shockwave (Chamberlain and Colborne, 2016) promotes angiogenesis, an integral part of healing (Kumar *et al.*, 2009; Carmignano and Carmignano, 2019). Along with growth factor release stimulation, activation of the immune system via the TLR3 pathway, suppression of pro-inflammatory cytokines and enhanced expression of wound healing genes (Carmignano and Carmignano, 2019), extracorporeal shockwave has been shown to have a positive effect on wound healing (Mittermayr *et al.*, 2012b; Carmignano and Carmignano, 2019). Though studies investigating the effects of extracorporeal shockwave in wound healing largely focus on chronic or difficult to heal wounds (Mittermayr *et al.*, 2012b; Carmignano and Carmignano, 2019) such as lower limb venous ulcers (Schaden *et al.*, 2007; Saggini *et al.*, 2008) and diabetic foot ulcers (Hitchman *et al.*, 2019), it continues to show promising results in improved healing as well as safety with no adverse event or wound deterioration (Mittermayr *et al.*, 2012a).

### 1.6.3 – The use of extracorporeal shockwave therapy in peripheral arterial disease

The angiogenic effects of extracorporeal shockwave therapy and their role in cardiovascular disease would not have been ignored. Confirmation of upregulation of VEGF by extracorporeal shockwave therapy in vitro studies (Gutersohn, Caspari and Erbel, 2000; Nishida *et al.*, 2004),

lead to in vivo assessment of its effects. Nishida and colleagues demonstrated improved myocardial perfusion and function via angiographically evident coronary collaterals in a porcine model of chronic myocardial ischaemia (Nishida *et al.*, 2004). These results were then replicated in human studies. Patients with severe angina and no other options for coronary revascularization, underwent extracorporeal shockwave therapy to the area of ischaemia and subsequently showed improved anginal symptoms and improved myocardial perfusion in the treatment area (Fukumoto *et al.*, 2006). To provide even more robust evidence, Kikuchi and colleagues randomized patients with severe angina and no other options for coronary revascularization, to extracorporeal shockwave therapy or placebo (Kikuchi *et al.*, 2010). They too found significant improvement in patient reported symptoms, and exercise tolerance, as well as in objectives measures of improved myocardial perfusion via significantly higher left ventricular stroke volume and ejection fraction in the treated group (Kikuchi *et al.*, 2010).

These promising results in angiogenesis and amelioration of ischaemia provided the grounds for the expansion of research into the effects of extracorporeal shockwave therapy in the management and treatment of peripheral arterial disease. Ciccone and colleagues randomized patients with peripheral arterial disease to receive extracorporeal shockwave therapy targeted at the site of atherosclerosis in the lower limb arterial tree guided by ultrasound or placebo (Ciccone *et al.*, 2012). They found improved symptoms and pain, as well as a significant improvement in pain free walking distance for the actively treated group, though no difference in ankle brachial pressure index. Three further prospective studies assessed the effects of extracorporeal shockwave therapy in the management of patients with peripheral arterial disease by directing the shockwave therapy at the calf muscle bulk (Serizawa *et al.*, 2012; Tara *et al.*, 2014). In keeping with the above trials, Serizawa and colleagues found that extracorporeal shockwave therapy improved maximum walking distance and symptoms

(Serizawa *et al.*, 2012) while Tara and colleagues investigated transcutaneous oxygen tension and found a significant improvement in both the calf and the foot after treatment (Tara *et al.*, 2014). All studies reported no adverse events or side effects from the treatment (Ciccone *et al.*, 2012; Serizawa *et al.*, 2012; Tara *et al.*, 2014).

All the above, lead to the design and execution of a pilot study within the Academic Vascular Surgery Unit in Hull York Medical School and Hull Royal Infirmary which informed the basis of the trial discussed in this thesis (Cayton *et al.*, 2017). Patients with stable intermittent claudication, established on best medical therapy, were recruited and randomized to receive extracorporeal shockwave therapy directed at the calf of the symptomatic lower limb or placebo (Harwood, Green, *et al.*, 2018). After 3 weeks of treatment delivered 3 times a week, patients were followed up until 1 year (Green *et al.*, 2018). This pilot study found a significant improvement in both pain free and maximum walking distance in the actively treated group up to 3 months of follow up (Harwood, Green, *et al.*, 2018) but unfortunately this was not statistically significant after 1 year (Green *et al.*, 2018). There was also an improvement in various domains of quality of life (Harwood, Green, *et al.*, 2018). Again, no adverse events or side effects from the treatment were reported.

### 1.6.4 – The proposed mechanism of action of extracorporeal shockwave therapy in its use in peripheral arterial disease

In vitro and in vivo studies have been conducted to ascertain the mechanism of action of extracorprproreal shockwave therapy in the setting of peripheral arterial disease. In keeping with the examination of effects of extracorporeal shockwave therapy and VEGF, four animal model studies simulating ischaemia in a hind leg, showed an increase in VEGF levels after treatment

(Aicher *et al.*, 2006; Oi *et al.*, 2008; Tepeköylü *et al.*, 2013; Holfeld *et al.*, 2014) with one study recording a fivefold increase within 60 minutes of treatment (Holfeld *et al.*, 2014).

Placental growth factor upregulates VEGF and promotes arteriogenesis (Luttun, Tjwa and Carmeliet, 2002). The genes responsible for the expression of placental growth factor as well as its receptor were found to significantly increase after shockwave treatment in comparison to a control, in murine model of acute hind limb ischaemia (Holfeld *et al.*, 2014). In addition, human endothelial progenitor cells are involved in vasculogenesis at sites of acute ischaemia via VEGF and SDF-1 receptors (Yoder, 2012). Extracorporeal shockwave therapy has been shown to increase the levels of VEGF and SDF-1 in animal models of chronic limb ischaemia, reaching a level comparable to that of acute limb ischeamia and thus improving the recruitment of human endothelial progenitor cells at sites of ischaemia and promoting vasculogenesis (Aicher *et al.*, 2006).

This biochemical enhancement of angiogenesis was recorded at a micro and a macrovascular level. At a microvascular level improvements were detected using laser doppler flowmetry in two animal studies (Tepeköylü *et al.*, 2013; Holfeld *et al.*, 2014) as well as the previously mentioned study conducted by Tara and colleagues found improved transcutaneous oxygen tension (Tara *et al.*, 2014). At a macrovascular level, another animal ischaemic hind limb study showed significantly increased collaterals, detected at angiography in animals that received extracorporeal shockwave treatment (Oi *et al.*, 2008). This positive result however was not replicated in human studies were computed tomography angiography did not reveal any appreciable collaterals (Serizawa *et al.*, 2012).

Given the above, it is safe to hypothesize that the trials investigating the effects of extracorporeal shockwave therapy in peripheral arterial disease, have shown improvements due to neovascularization within the targeted area and as a consequence improved perfusion and therefore symptoms.

## Section 1.7 – Trial rational and hypothesis

The above literature review reveals the need for an alternative, non-invasive treatment for the conservative management of patients with stable intermittent claudication and a gap in the current body of evidence for the use of extracorporeal shockwave therapy as an adjunct to that management.

The pilot data has shown extracorporeal shockwave therapy for this use to be safe, well tolerated by participants and strongly suggested an improvement in pain free and maximum walking distances as well as generic and disease specific quality of life (Harwood, Green, *et al.*, 2018).

Given the above, a fully powered, randomized controlled trial, would formulate the appropriate next step to complete the gap in the current evidence base.

The hypothesis for this trial is that the use of extracorporeal shockwave therapy in addition to standard conservative treatment of patients with stable intermittent claudication will improve quality of life.

# Chapter 2 – Methodology for the extracorporeal shockwave therapy in lower limb intermittent claudication trial.

## Section 2.1 – Study design

A single center, double-blind, placebo-controlled, randomized study. Participants were randomized to receive either extracorporeal shockwave treatment or a placebo treatment to the index lower limb on a 1:1 ratio.

## Section 2.2 – Sample size calculation

Ware and his colleagues (Ware *et al.*, 1993) published estimates of the sample size necessary to reliably detect any statistically significant differences in SF-36 quality of life questionnaire scores between two experimental groups. In order to demonstrate 10-point difference or more in Physical Functioning as measured by the SF-36 questionnaire at 80% power and 5% significance, 55 participants in each treatment group were required (Ware *et al.*, 1993). Evaluating the adherence and completion rates of our own supervised exercise program for patients with lower limb intermittent claudication managed conservatively as well as the published literature (Harwood *et al.*, 2016a), we decided to allow for a 20% attrition rate for this study and therefore an additional 14 participants per group would be needed, giving a total of 138 participants required.

## Section 2.3 – Trial approvals

The Research and Development Department of Hull and East Yorkshire NHS Trust acted as the sponsor in this study. Funding was provided by the Academic Department of Vascular Surgery at Hull York Medical School.

The protocols, patient information leaflets, consent forms, and all other documents pertaining to this research study were submitted via the Integrated Research Application System (IRAS) to the National

Research Ethics Service (NRES) and approved by the National Research Ethics Committee East of England, Cambridge East.

The study registration and approval numbers are as follows:

1. National Research Ethics Committee East of England, Cambridge East Project Number: 14/EE/1257
2. IRAS Project ID: 166137
3. NCT registration number: 02652078

## Section 2.4 – Study outcome measures

### Primary outcome

Effect of extracorporeal shockwave therapy in comparison to placebo treatment on quality of life as measured by the physical functioning domain of the SF-36 quality of life questionnaire in patients with lower limb intermittent claudication.

### Secondary outcomes

Effect of extracorporeal shockwave therapy in comparison to placebo treatment in patients with lower limb intermittent claudication on:

1. Claudication distance, defined as the time of onset of claudication pain while walking.
2. Maximum walking distance, defined as the maximum distance of walking tolerated.
3. Before and after exercise/walking ankle brachial pressure index.
4. Patient self-reported maximum walking distance.
5. Quality of life as measured by EQ-5D-3L, VascuQoL and the remaining seven domains of SF-36 quality of life questionnaire.

6. Microcirculatory flow as measured by laser doppler flowmetry.
7. Patient acceptability and tolerability of extracorporeal shockwave treatment.

## Section 2.5 – Subject screening and recruitment

Participants were identified in the vascular surgery outpatient setting. Consultant vascular surgeons took verbal consent to contact from patients with lower limb intermittent claudication, that were to be managed conservatively and who had refused to participate in the supervised exercise program. A referral letter was then sent to the Academic Vascular Surgery Unit with the relevant patient information and the patients were pre-screened against the inclusion and exclusion criteria for this trial using data obtained from clinical notes. If the patient met all criteria, then a letter explaining their referral to this study and a patient information leaflet for this study was posted to the patient's address (Appendix 4). The potential participants were then contacted via telephone to confirm their interest in participating and to arrange a baseline visit.

Inclusion criteria included the following:

1. Patients with lower limb intermittent claudication (unilateral or bilateral with an index leg symptomatically worse than the other) with unchanged walking distance and/or reported pain for at least 3 months prior to participation.
2. Patients over the age of 18 years.
3. Patients able to provide written, informed consent for trial participation.
4. Patients able to adhere to the study protocol and attend all follow up visits.
5. Patients already established on "best medical therapy" for the management of peripheral arterial disease with an antiplatelet and/or statin medication.

Exclusion criteria included the following:

1. Active malignancy.
2. Pregnancy (pregnancy test to be performed at baseline visit if necessary).
3. Patients on anticoagulation medication.
4. Patients with known coagulopathies.

At the baseline visit, all inclusion and exclusion criteria were re-checked, and once any questions regarding the trial were answered to the satisfaction of the patients, an assessment of capacity to consent was undertaken. If capable of giving consent and agreeable to participation, the patient signed the consent form with the clinical research fellow coordinating the study witnessing (Appendix 5). Baseline assessment was then started with recording of demographic data, cardiovascular risk history, all past medical and surgical history, and drug and allergies history. Baseline assessment continued with a laser doppler flowmetry assessment of the medial aspect of the calf and the dorsum of the foot for both lower limbs, an ankle brachial pressure index at rest for both lower limbs, a treadmill exercise test to assess claudication and maximum walking distance and then a repeat of the laser doppler and ankle brachial pressure index post exercise. Baseline assessment was then concluded with the completion of 3 quality of life questionnaires to establish the baseline/pre-treatment state. Questionnaires used included the EQ-5D-3L, SF-36 and VascuQol (Appendix 6, 7 and 8).

Claudication and maximum walking distances were measured on a treadmill set to a speed of up to 1.6 miles per hour (or as fast as tolerated by participants with very limited mobility), at 10% incline for as long as the participant could tolerate or for a maximum of 10 minutes. Using the speed, time of claudication onset and overall time on the treadmill, the claudication and maximum walk distance was calculated.

Ankle brachial pressure index was measured using a handheld doppler, recording the pressure of both dorsalis pedis and posterior tibial doppler signals in both lower limbs. The highest for each foot was used for the calculation.

Laser doppler flowmetry assessment was done using the moorVMS-LDF2 laser doppler monitor with moorVMS Vascular Monitoring System for Windows. MoorVMS-LDF2 skin probes were attached to the dorsum of both feet and the medial aspect of both calves of each participant. The average pre and post exercise flux from 5 minutes of continuous monitoring was recorded in perfusion units (PU). Instructions for use by the manufacturer do not specify environmental conditions for optimum measurement, but simply refer to "a room maintained at a constant temperature and humidity" (Moor Instruments, no date). Room temperature was controlled with an air-conditioning system at 24 degrees Celsius. Humidity was not controlled during measurements. In addition, "spot lamps and sunshine" can affect laser doppler flowmetry as per manufacturer's instructions for use (Moor Instruments, no date), however the clinical room where these measurements were taken did not have any windows (no sunlight interference) and only had overhead fluorescent light (no spot lamps).

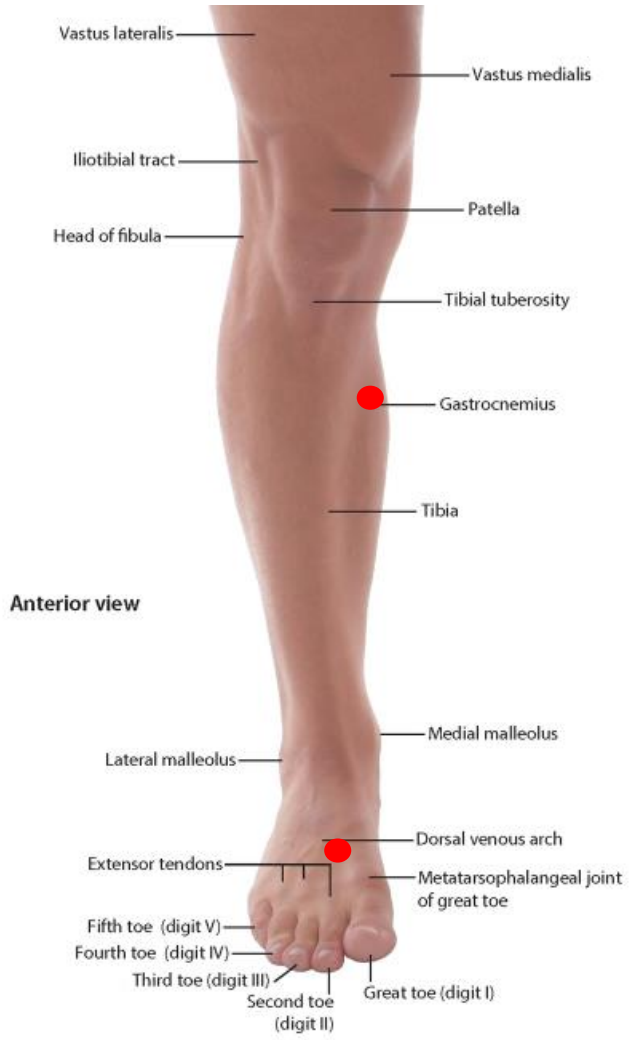



Figure 8 – Diagram of Laser Doppler probe placement (Drake, Vogl, Wayne and Mitchell, 2009)

Simple, non-stratified randomization on a 1:1 ratio was completed at the end of the baseline visit via an online randomization service, Sealed Envelope LTD, London, UK. Participants were allocated to either the extracorporeal shockwave treatment (intervention) group (A) or placebo treatment (control) group (B).

Once the baseline visit was completed with successful recruitment and randomization letters were posted to the participants GP and referring consultant vascular surgeon to inform them of their patient's participation in this trial (Appendix 9 and 10).

## Section 2.6 – Treatment protocol

Participants received a total of 9 treatments over a 3-week period. At the end of each session participants' tolerance of the treatment was assessed. All participants were asked to complete a 10cm visual analogue score for pain, whereby the furthest most left end of the scale indicated no pain, and the furthest most right end of the scale indicated the worst pain imaginable.

All participants were asked to lie prone during the treatment sessions, so as to expose the index leg calf for treatment. Participants randomized to the active treatment group, received extracorporeal shockwaves using the PiezoWave 2 shockwave system (Richard Wolf GmBH, Germany) in accordance with the manufacturer's instructions and unchanged from its current clinical use at 100 impulses 0.1mJ/mm per $cm^2$ and provided by trained staff. An area of 6cm by 5cm on each head of the gastrocnemius muscle on the index leg was treated, receiving 100 impulses per $cm^2$, calculating as 6000 impulses/5Hz/0.1mJ/$mm^2$ in total. The above was replicated with the generator set to off and a recording of the generator sound played via an MP3 speaker mounted on the equipment for the participants randomized to the placebo group.

Figure 9 – PiezoWave 2 Richard Wolf GmBH

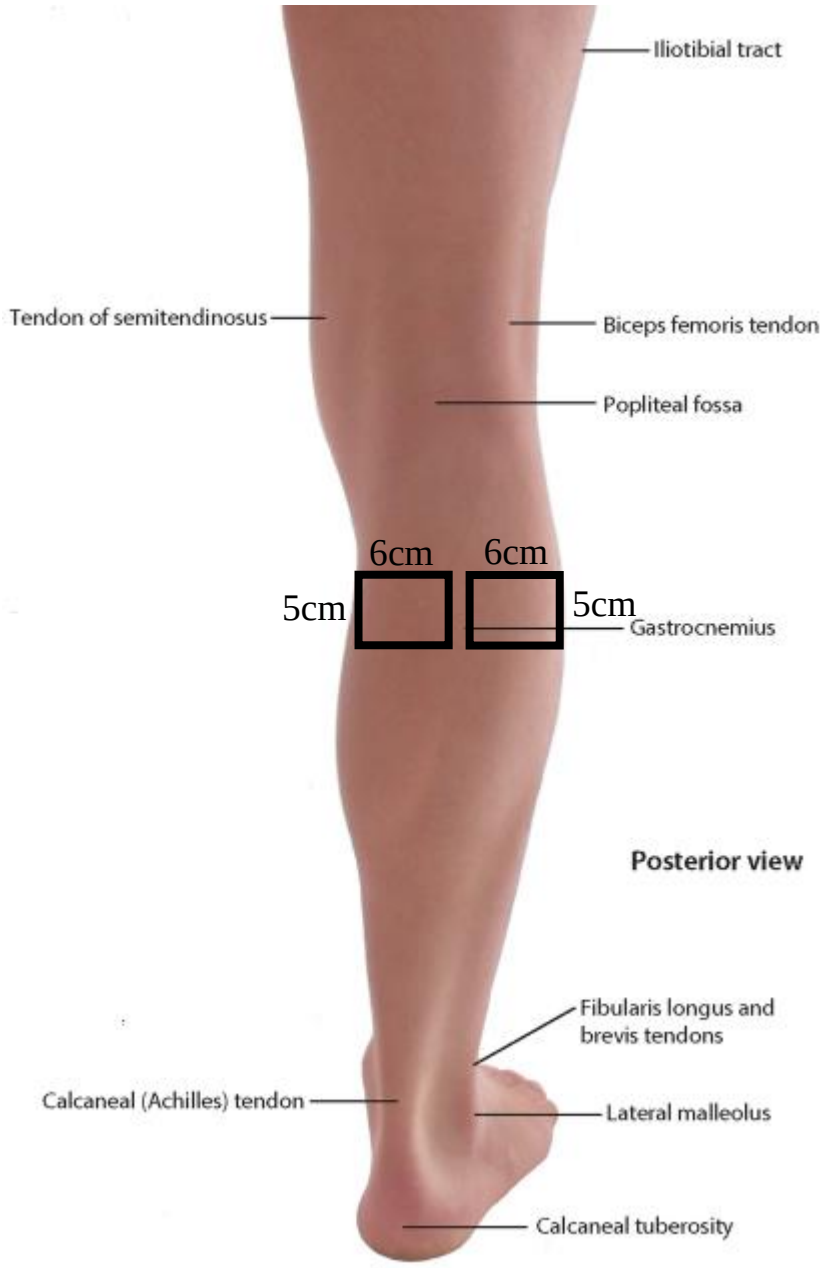



Figure 10 – Diagram of extracorporeal shockwave treatment area (Drake, Vogl, Wayne and Mitchell, 2009)

The treatments were all delivered in an outpatient clinic room with an adjustable examination couch where patients could lie prone. This treatment set up could be easily replicated at any outpatient or community clinical environment. The use of the PiezoWabe 2 machine is very straightforward and any clinical member of staff could deliver it (no specialized knowledge required).

## Section 2.7 – Follow up protocol

Participants were followed up at the end of the 3-week treatment (week 4), 4 weeks after that (week 8), and finally 4 weeks after that (week 12). Follow up assessment started with recording of health or medication changes and any adverse events during or after the treatment.

Follow up assessment continued with a laser doppler flowmetry assessment of the medial aspect of the calf and the dorsum of the foot for both lower limbs, an ankle brachial pressure index for both lower limbs, a treadmill exercise test to assess claudication and maximum walking distance and then a repeat of the laser doppler and ankle brachial pressure index post exercise as described above in the baseline visit protocol (Section 2.1.4). Follow up assessment concluded with the completion of the 3 quality of life questionnaires. Questionnaires used included the EQ-5D-3L, SF-36 and VascuQol (Appendix 7, 8 and 9).

All follow up assessments and outcome measures were completed by assessors blinded to the group allocation of each participant. Follow up assessors included vascular research nurses and research fellows within the Academic Vascular Surgery Unit. Tracy Roe (vascular research nurse) and Sean Pymer (PhD candidate) completed the majority of follow ups assessments though due to availability other assessors were involved as well.

## Section 2.8 – Statistical analysis plan

Data was analyzed using SPSS (IBM, Version 28, New York, USA). A *p*-value of $<0.05$ was considered statistically significant. Analysis was performed upon intention to treat, according to randomization group for all outcomes in this trial.

Baseline characteristics and outcome measures are presented as means and standard deviations for parametric data, medians and interquartile range (IQR) for non-parametric data. The Shapiro-Wilk test was used to determine the normality of distribution. Mann-Whitney U and Kruskal-Wallis tests were used to estimate the difference in outcomes between groups. Secondary analysis by one-way analysis of co-variance (ANCOVA) using rank transformation of non-parametric data was carried out to compare outcomes when controlling for baseline characteristics.

# Chapter 3 – Results for the extracorporeal shockwave therapy in lower limb intermittent claudication trial.

## Section 3.1 – Participant screening and randomization

Figure 1 shows the progression of recruited participants from the point of screening and selection through the randomized controlled trial protocol for treatment and follow up (CONSORT Diagram).

During the recruitment phase, 522 patients were assessed for eligibility for possible participation in this trial. 389 out of 522 patients assessed were eligible. Of these eligible patients, 79 declined to participate without a reason and 76 reported being unable to participate for various reasons including but not limited to time commitment, work related scheduling and transportation to the research site. 96 patients were excluded for various other reasons including but not limited to, opting to have a planned intervention for their intermittent claudication, worsening symptoms of intermittent claudication and patients screened and contacted for participation but did not reply prior to the completion of the recruitment phase.

138 patients were recruited and randomized in this trial. 68 participants were allocated to the intervention group. 61 received their allocated intervention as per the protocol, with 6 participants withdrawing from the study prior or during the treatment phase and 1 participant withdrawing from the study due to another medical condition. 70 participants were allocated to the control group. 61 received their allocated intervention as per the protocol, with 6 participants withdrawing from the study prior or during the treatment phase and 3 participants withdrawing from the study due to another medical condition.

Of the 61 participants in the intervention group who received their allocated treatment as per the protocol, 3 were lost to follow up and 3 formally withdrew from the study after the treatment phase. Of the 61 participants in the control group who received their allocated treatment as per the protocol, 5 were lost to follow up and 1 formally withdrew from the study after the treatment phase.

Throughout the study period there were no side effects or serious adverse events recorded that were related to extracorporeal shockwave therapy. One patient in the intervention group withdrew during the treatment period because they were unable to tolerate lying flat and prone due to dyspnoea.

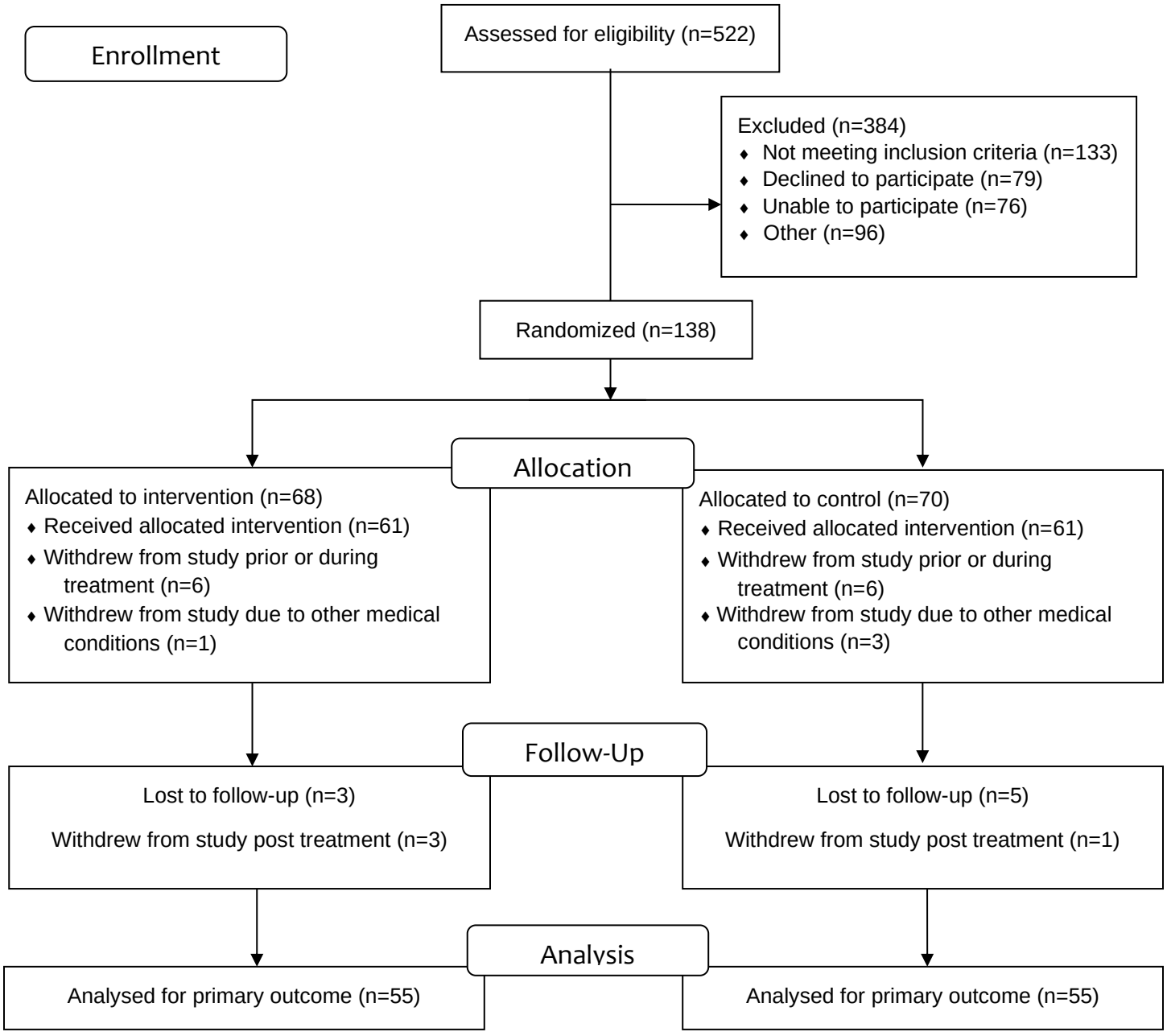



Figure 11 – CONSORT Diagram

Participants baseline characteristics and risk factors for developing peripheral arterial disease and intermittent claudication, such as age, gender, cigarette smoking history as well as other medical co-morbidities are comparted in Table 1. No significant differences were observed between the two groups at baseline assessment except for age, where the intervention group participants were statistically younger with a mean age of 66 years when compared to the control group participants with a mean age of 67 years (p=0.031).

| Baseline Demographics | Intervention Group | Control Group |
|---|---|---|
| Male gender (%) | 44 (64.7) | 48 (68.6) |
| Age Mean ± SD (years) | 66 ± 10.7 | 67 ± 8.5 |
| BMI Median (IQR) ($kg/m^2$) | 27.9 (24.3-30.9) | 27.8 (24.1-29.9) |
| Smoking status (%) | | |
| • Current smoker | 31 (45.6) | 25 (35.7) |
| • Ex-smoker | 33 (48.5) | 38 (54.3) |
| • Never smoker | 4 (5.9) | 7 (5.6) |
| Diabetes (%) | 16 (23.5) | 25 (35.7) |
| HTN (%) | 40 (58.8) | 43 (61.4) |
| History of CAD/IHD (%) | 22 (32.3) | 31 (44.3) |
| History of CVA (%) | 7 (10.3) | 6 (8.6) |
| Site of claudication | | |
| • Calf (%) | 62 (91.2) | 66 (94.3) |
| • Calf and thigh (%) | 6 (8.8) | 4 (5.7) |
| Bilateral claudication (%) | 7 (10.3) | 8 (11.4) |

Table 1 – Baseline Characteristics.

Key: BMI – Body Mass Index, HTN – Hypertension, CAD – Coronary Artery Disease,

IHD – Ischaemic Heart Disease, CVA – Cerebrovascular Accident

## Section 3.2 – Primary outcome – SF36 physical functionality domain

Normalized medians of the physical functioning domain of the SF-36 quality of life questionnaire at 12-week follow up were statistically significant between the two groups. The intervention group recorded a median physical functioning domain score of 41.3 (IQR 31.2 – 46.1) and the control group recorded a median physical functioning domain score of 34.6 (IQR 28.8 – 42.7) ($p$=0.033). There was no statistically significant intragroup difference from baseline to 12-week follow up, with the physical functioning domain score of the intervention group at 36.5 (IQR 30.8 – 44.2) at baseline ($p$=0.107) and the control group at 33.0 (IQR 26.9 – 38.9) at baseline ($p$=0.117).

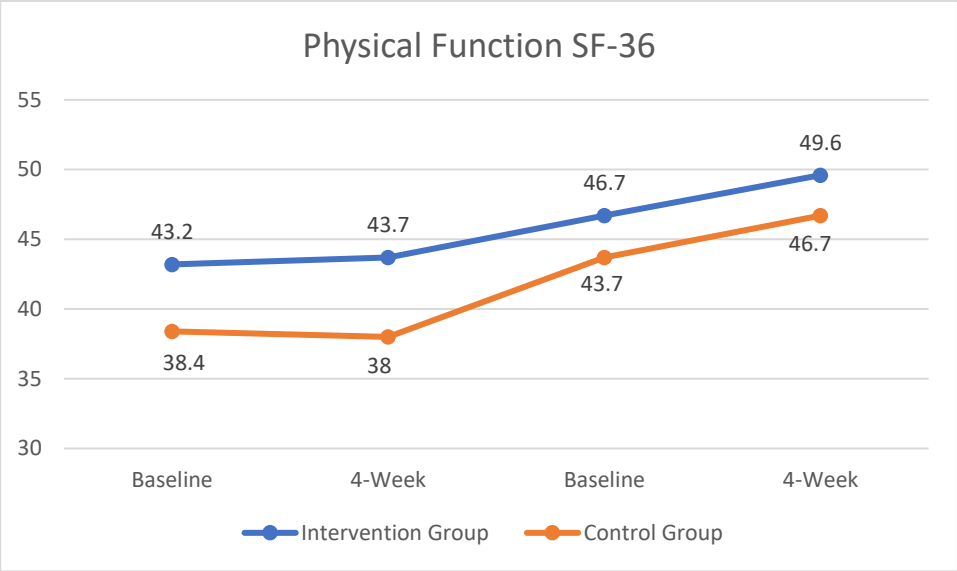



Figure 12 – Physical Function SF-36 across follow up time points.

## Section 3.3 – Secondary outcomes

### 3.3.1 – Pain free walking distance

Pain-free walking distance between the groups was similar at baseline. The median pain free walking distance in the intervention group was 49 meters (IQR 32.7 – 82.4) and 40 meters (IQR 22.7 – 72.1) in the control group (p=0.099). At 12-week follow up the intervention group had a significantly higher median pain free walking distance, compared to the control group. Median pain free walking distance was 106 meters (IQR 67.5 – 157.6) in the intervention group

versus 70 meters (IQR 43.5 – 106) in the control group ($p$=0.004) at 12-week follow up. This increase of pain-free walking distance from baseline to 12-week follow up was statistically significant within each group, in intra-group analysis ($p$<0.001 respectively).

Pain-free walking distance was also significantly higher in the intervention group when compared to the control group at 4-week and 8-week follow up (See Table 2).

| **Pain-free walking distance Meters (IQR)** | **Intervention Group** | **Control Group** | **p value** |
|---|---|---|---|
| Baseline | 49 (32.7 – 82.4) | 40 (22.7 – 72.1) | 0.099 |
| 4-weeks | 87 (58.2 – 127.8) | 58 (30.5 – 110.9) | 0.027 |
| 8-weeks | 98 (56.1 – 147.1) | 60 (37.1 – 91.2) | 0.006 |
| 12-weeks | 106 (67.5 – 157.6) | 70 (43.5 – 106) | 0.004 |

Table 2 – Median pain-free walking distance.

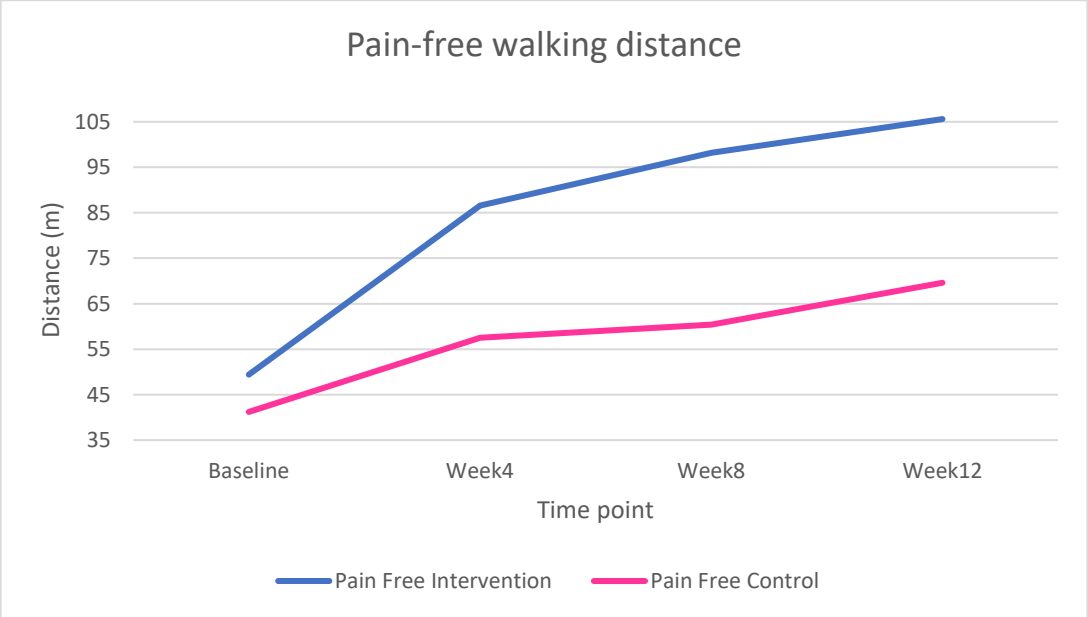



Figure 13 – Continuing improvement in pain free walking distance after cessation of treatment.

### 3.3.2 – Maximum walking distance

Maximum walking distance between the groups was similar at baseline. The median maximum walking distance in the intervention group was 85 meters (IQR 55.4 – 132.5) and 93 meters (IQR 47.5 – 141.1) in the control group at baseline (p=0.928). At 12-week follow up the intervention group had a significantly higher median maximum walking distance, compared to the control group. Median maximum walking distance was 172 meters (IQR 118.6 – 239.3) in the intervention group versus 114 meters (IQR 68.7 – 200.9) in the control group ($p$=0.013). This increase of maximum walking distance from baseline to 12-week follow up was statistically significant within each group, in intra-group analysis (Intervention group $p$<0.001 and control group $p$=0.046).

Maximum walking distance was also significantly higher in the intervention group when compared to the control group at 8-week follow up (Table 3).

| **Maximum walking distance Meters (IQR)** | **Intervention Group** | **Control Group** | **p value** |
|---|---|---|---|
| Baseline | 85 (55.4 – 132.5) | 93 (47.5 – 141.1) | 0.928 |
| 4-weeks | 142 (90.3 – 176.1) | 103 (54.1 – 195.1) | 0.123 |
| 8-weeks | 158 (107.5 – 256.8) | 110 (62.4 – 200.6) | 0.041 |
| 12-weeks | 172 (118.6 – 239.3) | 114 (68.7 – 200.9) | 0.013 |

Table 3 – Median maximum walking distance.

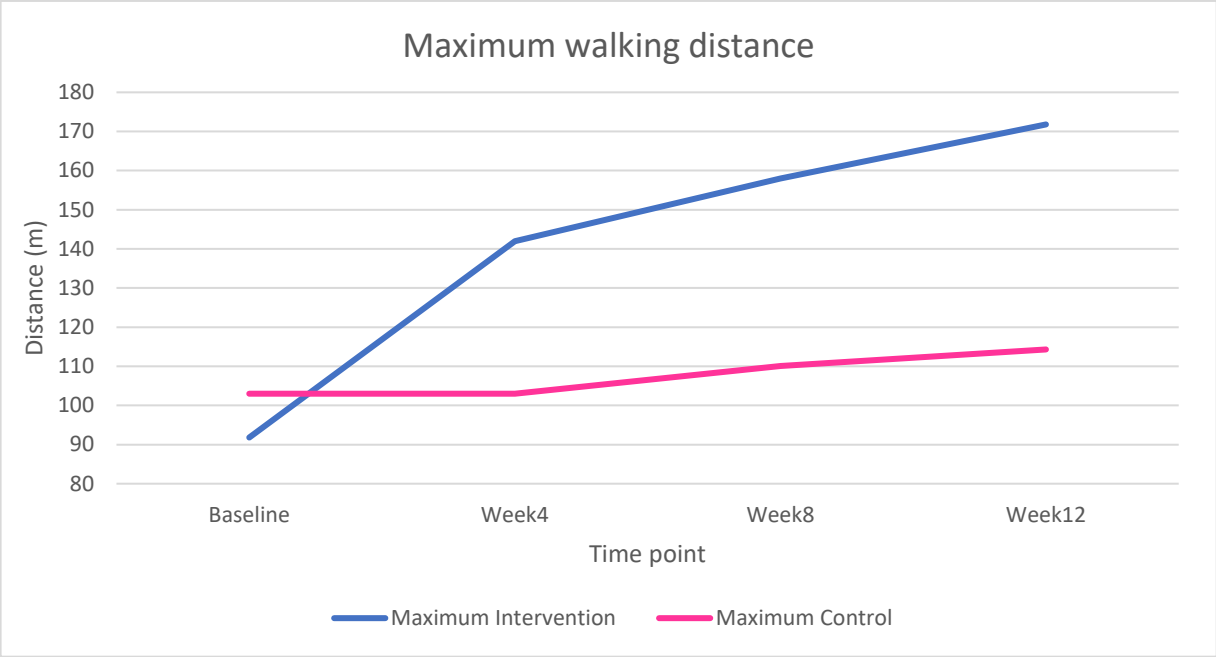



Figure 14 – Continuing improvement in maximum walking distance after cessation of treatment.

### 3.3.3 – Participant self-reported maximum walking distance

Participants self-reported maximum walking distance at baseline was comparable between the two groups with a median of 183 meters (IQR 100.0 – 275.0) for the intervention group and a median of 136 meters (IQR 50.0 – 200.0) for the control group ($p$=0.116). There was also no significant difference at 12-week follow up with a median of 287 meters (IQR 200.0 – 887.0) for the intervention group and a median of 274 meters (IQR 182.9 – 804.7) for the control group ($p$=0.566). When comparing the change in self-reported maximum walking distance within each group from baseline to week 12 follow up, both groups had a statistically significant increase ($p$=<0.001). There was no statistically significant difference between the groups at week 4 and week 8 follow up (See Table 4).

| **Self-reported maximum walking distance Meters (IQR)** | **Intervention Group** | **Control Group** | **p value** |
|---|---|---|---|
| Baseline | 183 (100-275) | 136 (50 – 200) | 0.116 |
| 4-weeks | 262 (183 – 512.2) | 200 (100 – 393.2) | 0.101 |
| 8-weeks | 214.3 (140.4 – 763.5) | 239.5 (182.9 – 804.7) | 0.592 |
| 12-weeks | 287 (200 – 887) | 274 (182.9 – 804.7) | 0.566 |

Table 4 – Median self-reported maximum walking distance.

### 3.3.4 – Ankle Brachial Pressure Index

Ankle brachial pressure index at baseline was comparable between the two groups with a median pre-exercise value of 0.62 (IQR 0.51 – 0.75) for the intervention group and 0.68 (IQR 0.53 – 0.88) for the control group ($p$=0.119) and a median post-exercise value of 0.29 (IQR 0.15 – 0.45) for the intervention group and 0.36 (IQR 0.18 – 0.63) for the control group ($p$=0.059). There were no significant differences in ankle brachial pressure index at any of the follow up time points (See Table 5).

| ABPI | Intervention Group | Control Group | p value |
|---|---|---|---|
| Baseline Pre-Exercise | 0.62 (0.51 – 0.75) | 0.68 (0.53 – 0.88) | 0.119 |
| Baseline Post-Exercise | 0.29 (0.15 – 0.45) | 0.36 (0.18 – 0.63) | 0.059 |
| 4-weeks Pre-Exercise | 0.64 (0.51 – 0.79) | 0.70 (0.53 – 0.91) | 0.274 |
| 4-weeks Post-Exercise | 0.33 (0.16 – 0.68) | 0.34 (0.17 – 0.59) | 0.820 |
| 8-weeks Pre-Exercise | 0.68 (0.50 – 0.79) | 0.70 (0.56 – 0.89) | 0.323 |
| 8-weeks Post-Exercise | 0.31 (0.17 – 0.52) | 0.38 (0.27 – 0.59) | 0.165 |
| 12-weeks Pre-Exercise | 0.62 (0.51 – 0.80) | 0.70 (0.57 – 0.93) | 0.091 |
| 12-weeks Post-Exercise | 0.33 (0.17 – 0.48) | 0.40 (0.20 – 0.60) | 0.300 |

Table 5 – Median ankle brachial pressure index pre and post exercise.

### 3.3.5 – Laser doppler flowmetry

Laser doppler flowmetry at baseline was comparable between the two groups with a calf median pre-exercise value of 13 (IQR 9.3 – 21.2) for the intervention group and 12 (IQR 10.0 – 15.9) for the control group ($p$=0.418) and a calf median post-exercise value of 12 (IQR 8.1 – 19.7) for the intervention group and 13 (IQR 10.3 – 19.9) for the control group ($p$=0.534). There were no significant differences in laser doppler flowmetry at any of the follow up time points in either the foot or the calf (See Table 6 and Table 7).

| Laser Doppler Flux (PU) | Intervention Group | Control Group | p value |
|---|---|---|---|
| Baseline Pre-Exercise Calf | 13 (9.3 – 21.2) | 12 (10.0 – 15.9) | 0.418 |
| Baseline Post-Exercise Calf | 12 (8.1 – 19.7) | 13 (10.3 – 19.9) | 0.534 |
| 4-weeks Pre-Exercise Calf | 16 (11.5 – 21.9) | 17 (13.8 – 23.2) | 0.284 |
| 4-weeks Post-Exercise Calf | 15 (11.6 – 19.0) | 16 (12.3 – 22.4) | 0.620 |
| 8-weeks Pre-Exercise Calf | 21 (11.6 – 28.5) | 18 (11.5 – 21.0) | 0.322 |
| 8-weeks Post-Exercise Calf | 13 (9.2 – 20.8) | 13 (10.3 – 26.0) | 0.658 |
| 12-weeks Pre-Exercise Calf | 15 (9.4 – 24.4) | 17 (10.9 – 23.7) | 0.581 |
| 12-weeks Post-Exercise Calf | 18 (12.4 – 38.2) | 17 (10.6 – 26.8) | 0.510 |

Table 6 – Median PU in laser doppler flowmetry at the calf.

| Laser Doppler Flux (PU) | Intervention Group | Control Group | p value |
|---|---|---|---|
| Baseline Pre-Exercise Foot | 13 (8.1 – 19.5) | 17 (11.2 – 30.4) | 0.166 |
| Baseline Post-Exercise Foot | 11 (9.0 – 13.4) | 14.7 (10.0 – 20.2) | 0.080 |
| 4-weeks Pre-Exercise Foot | 15 (11.0 – 25.3) | 18 (11.3 – 23.9) | 0.775 |
| 4-weeks Post-Exercise Foot | 13 (11.4 – 16.1) | 15 (8.1 – 17.1) | 1.00 |
| 8-weeks Pre-Exercise Foot | 17 (11.2 – 34.5) | 20 (12.4 – 29.3) | 0.734 |
| 8-weeks Post-Exercise Foot | 13 (9.1 – 21.4) | 12 (9.3 – 18.1) | 0.865 |
| 12-weeks Pre-Exercise Foot | 12 (9.2 – 25.6) | 27 (12.0 – 34.4) | 0.087 |
| 12-weeks Post-Exercise Foot | 12 (7.7 – 20.7) | 14 (10.6 – 28.7) | 0.309 |

Table 7 – Median PU in laser doppler flowmetry at the foot.

### 3.3.6 – Quality of Life

The intervention group showed a statistically significant increase in quality of life as measured by the EQ-5D-3L quality of life questionnaire at 4-week follow up when compared to the control. Median EQ-5D-3L score for the intervention group at 4-week follow up was 0.66 (IQR 0.60 – 0.69) and 0.66 (0.36 – 0.69) for the control group (*p=0.034*). (See Appendix 3)

The intervention group also showed a statistically significant increase in quality of life as measured by the General Health, Vitality and Physical Component Summary domains of the SF-36 quality of life questionnaire at week 4 follow up when compared to the control (See Appendix 3).

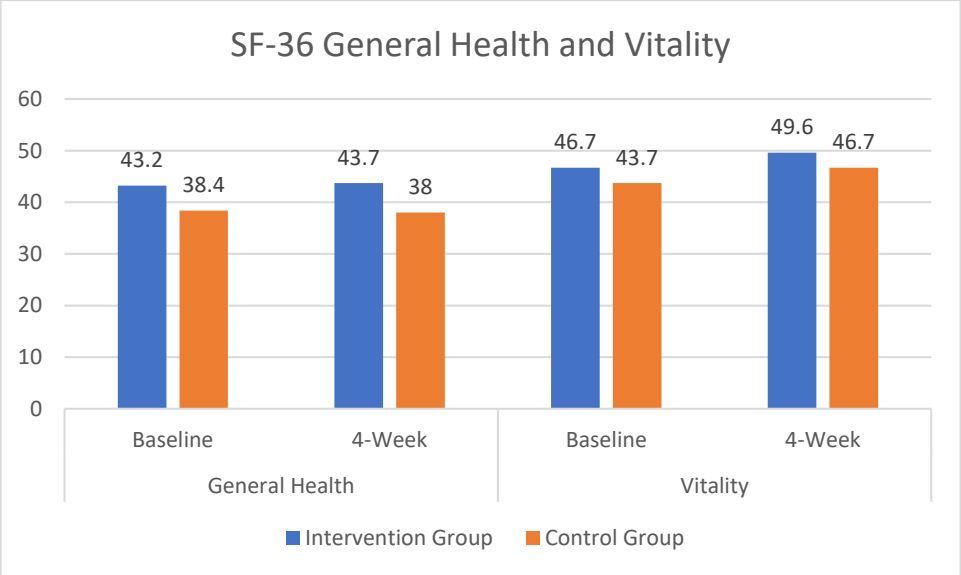



Figure 15 – SF-36 General Health and Vitality from baseline to 4-Week follow up.

The intervention group showed statistically significant improvement in multiple domains of SF-36 in intragroup analysis between baseline and follow up time points. The score for Physical Component Summary was significantly higher between baseline all follow up time points (4-week (p=0.02), 8-week (p=0.01), 12-week (p=0.05)). The score for Bodily Pain was significantly better between baseline and 4-week follow up (p=0.007) and baseline and 8-week

(p=0,02). The score for Vitality was also significantly better between baseline and 4-week follow up (p=0.009).

The control group had a statistically significant intragroup improvement in only one domain of SF-36 (Bodily pain between baseline and 4-week (p=0.02)).

There were no statistically significant differences in any of other measures of quality of life throughout the follow up period (See Appendix 3).

### 3.3.7 – Participant reported treatment pain

The participant reported treatment pain represented on a 10cm visual analog for pain was then transcribed to a number from 0 to 10, with 0 representing the far left side of the scale and indicating no pain, and 10 representing the far right side of the scale and indicating the worse pain imaginable.

The median pain score out of 10 for each treatment in the intervention group is presented in Table 9 below.

| Treatment Session | Median reported pain (IQR) |
|---|---|
| 1 | 3 (1 – 5) |
| 2 | 2 (1 – 5) |
| 3 | 2 (0 – 5) |
| 4 | 2 (0 – 4) |
| 5 | 1 (0 – 2) |
| 6 | 1 (0 – 2) |
| 7 | 1 (0 – 2) |
| 8 | 1 (0 – 2) |
| 9 | 0 (0 – 1) |

Table 8 – Median pain reported by intervention group participants per treatment session.

There is a statistically significant reduction in the pain reported during the last treatment session when compared to the first treatment ($p < 0.001$).

The median pain reported by the participants in the control group was consistently zero throughout every treatment session. No comparison was made for the participant reported treatment pain between the two groups given that the control group did not receive any treatment.

## Section 3.4 – Secondary Analysis

### Section 3.4.1 – Primary outcome

After adjustment for baseline variances (as outlined in Table 1, Section 3.1), there was no statistically significant difference in the physical functioning domain of the SF-36 quality of life questionnaire as 12-week follow up ($F(1, 94)=3.394$, $p=0.07$). Patients' history of coronary artery disease appears to have a significant effect on the physical functioning domain of the SF-36 questionnaire.

### Section 3.4.2 – Pain free walking distance

After adjustment for baseline variances (as outlined in Table 1, Section 3.1), pain free walking distances continue to be significantly higher in the intervention group when compared to the control group at all follow up time points.

4-Week follow up $F(1, 99)=5.562$, $p=0.02$.

8-Week follow up $F(1, 81)=9.774$, $p=0.002$.

12-Week follow up $F(1, 78)=10.779$, $p=0.002$.

### Section 3.4.3 – Maximum walking distance

After adjustment for baseline variances (as outlined in Table 1, Section 3.1), maximum walking distances continue to be significantly higher in the intervention group when compared to the control group at 12-Week follow up ($F(1, 92)=9.456$, $p=0.005$).

**Section 3.4.4 – Other secondary outcomes**

After adjustment for baseline variances (as outlined in Table 1, Section 3.1), SF-36 domains General Health and Vitality continue to be significantly higher in the intervention group when compared to the control group at 4-week follow up.

General Health $F(1, 97)=6.321$, $p=0.014$.

Vitality $F(1, 97)=6.231$, $p=0.014$.

No other outcomes that showed a statistically significant difference at primary analysis maintained a significant difference on secondary analysis with adjustment for baseline variance as above.

# Chapter 4 – Discussion for the extracorporeal shockwave therapy in lower limb intermittent claudication trial.

## Section 4.1 – Participant screening and randomization

The trial successfully recruited to full power as per the study protocol (See Chapter 2, Section 2.2). Although recruitment to this trial from referred, eligible patients was relatively low at 35%, this is higher than the reported recruitment to supervised exercise programs in the UK (Harwood *et al.*, 2016a). In addition, the proportion of patients recruited into the trial would have otherwise not participated in a supervised exercise program, but did engage with the non-invasive, outpatient setting treatment of extracorporeal shockwave therapy.

In a recently published survey (Harwood *et al.*, 2022), less than half of vascular units in the UK provide a supervised exercise program for patients with peripheral arterial disease. Taking into account the previously mentioned poor recruitment rates in the available supervised exercise programs (Harwood *et al.*, 2016a) and the fact that 25% of those recruited do not complete the program and 30% do not adhere to the program completely (Harwood *et al.*, 2016a), this paints a bleak picture for the full implementation of conservative management for patients with intermittent claudication as per all available clinical guidance (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018).

All the above demonstrate the need for an alternative adjunct to supervised exercise for the conservative management of patients with intermittent claudication. Given that the time commitment required is cited as a common barrier to a supervised exercise program (Harwood *et al.*, 2016a; Harwood, Hitchman, *et al.*, 2018), the protocol for extracorporeal shockwave therapy allows for a shorter time commitment when compared to supervised exercise and may have positively influenced

the patients' decision to participate when they had refused participation in a supervised exercise program. The time commitment benefit seen with extracorporeal shockwave therapy is across the total number of visits (9 vs 36), length of program (3 weeks vs 12 weeks) and time per session (30 mins vs 60 mins).

Consideration can be given to the exclusion criteria for this trial. The instructions for use by the manufacturer Richard Wolf GmBH, advise against the use of extracorporeal shockwave therapy in an area of cancer/tumour. However, given that this is a novel treatment in the field of vascular surgery and peripheral arterial disease, and previously not tested at this scale for this use, the exclusion criteria for the trial prohibited anyone with active cancer from participating. However, extracorporeal shockwave therapy is deemed safe for use in the orthopaedic setting as long as cancer is not present in the affect area and its use is safe and encouraged in the supportive care of cancer patients (Crevenna, Mickel and Keilani, 2019).

The transfer of energy within tissues in extracorporeal shockwave therapy carries a risk of tissue injury that could result in bleeding and formation of haematomas, with the International Society for Medical Shockwave Treatment declaring the use of anticoagulation therapy and/or a known coagulopathy to be contraindications to the use of extracorporeal shockwave therapy (ISMST, 2019). However, in the most widely studied application of extracorporeal shockwave therapy, symptomatic perirenal haematomas were only present in less than 1% of cases (Newman and Saltzman, 1991; Kostakopoulos *et al.*, 1995). There is no high-quality evidence with regards to the bleeding risk with the use of antiplatelets in extracorporeal shockwave therapy (Schnabel *et al.*, 2014), and in particular clopidogrel which would be prescribed for the majority of patients with peripheral arterial disease and intermittent claudication (Gent, 1996). This study did not record any adverse events or side effects, with all the study participants being on antiplatelet therapy. There is no evidence available comparing oral

anticoagulation therapy and the risk of bleeding with extracorporeal shockwave therapy, given that as an absolute contraindication, oral anticoagulation is suspended prior to extracorporeal shockwave therapy (Alsaikhan and Andonian, 2011; Schnabel *et al.*, 2014).

Strict exclusion criteria can limit the numbers recruited. This would be of importance when designing the next trial for extracorporeal shockwave therapy in intermittent claudication or its implementation in clinical practice and consider the inclusion of patients with cancer not involving the calf area. This study also provides reassurance on the safe use of extracorporeal shockwave therapy in patients on antiplatelet medication, and the lack of evidence for the use of VOYAGER/COMPASS regime in stable intermittent claudication should maximize the numbers of eligible patients.

## Section 4.2 – Primary outcome – SF36 physical functionality domain

The results have shown a potential positive effect on physical functioning as measured by SF-36. Though primary analysis revealed a significant improvement in the intervention group when compared to the control group at 12-week follow up, secondary (post-hoc) analysis showed that history of coronary artery disease had a significant impact on physical functioning and the difference between the two groups was no longer significant. However, the median scores for the intervention group were consistently higher than the control group at all follow up time points suggesting a trend for improvement. At 12-weeks follow up,this improvement in physical functioning was similar to that provided by the 12-week supervised exercise programs (Lane *et al.*, 2017a) and it represents a small to moderate minimal clinically important difference following such a program (Gardner, Montgomery and Wang, 2018).

The physical functioning domain of the SF-36 is the most impaired by intermittent claudication (Izquierdo-Porrera *et al.*, 2005), but as previously demonstrated by Tsai et al (Tsai *et al.*, 2002), it is

the most likely to respond to the successful treatment of intermittent claudication, when compared to other measures of quality of life. This means that the decision to power for changes in this domain was well justified. It is also the only domain that is consistently improved with exercise trials in intermittent claudication (Lane *et al.*, 2017a; Hageman *et al.*, 2018) and therefore a point of reference within the current recommendations for treatment (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018). It is important to note, however, that claudication symptoms were not entirely eradicated, but rather managed to enable patients to mobilize further, so there will be a continuing impact of intermittent claudication on quality of life. This will especially apply to the patients with bilateral claudication, as this trial only treated the index leg.

These findings suggest that extracorporeal shockwave therapy may have a positive impact on physical functioning as measured by SF-36, and may be able to elicit this at a much shorter time frame when compared to exercise.

## Section 4.3 – Secondary outcomes

### Section 4.3.1 – Pain free walking distance

Pain free walking distances were improved at each follow up time point, peaking at week 12 follow-up for both the intervention and the control group, with the biggest increase in median pain free walking distance between baseline and week 4 follow up (See Table 2). The improvements in the intervention group were comparable to those provided by supervised exercise therapy and represented a small to moderate minimal clinically important difference (Lane *et al.*, 2017b; Gardner, Montgomery and Wang, 2018). The pain free walking distance in the intervention group was statistically higher at every follow up time point (See Table 2),

which can be confidently attributed to the effects of extracorporeal shockwave therapy. These effects are evident even after the cessation of treatment as illustrated by Figure .

Secondary analysis further strengthens the positive effect of extracorporeal shockwave therapy on pain free walking distances.

## Section 4.3.2 – Maximum walking distance

Maximum walking distances were improved at each follow up time point, peaking at week 12 follow up for both the intervention and the control group, with the biggest increase in median maximum walking distance between baseline and week 4 follow up (See Table 3). The improvements in the intervention group were comparable to those provided by supervised exercise therapy and represented a small to moderate minimal clinically important difference (Lane *et al.*, 2017b; Gardner, Montgomery and Wang, 2018). However they were observed to be significant at a much sooner follow up time point than supervised exercise (Lane *et al.*, 2017b). The maximum walking distance in the intervention group was statistically higher at week 8 and week 12 follow up time point (See Table 3), which can be confidently attributed to the effects of extracorporeal shockwave therapy. These effects are evident even after the cessation of treatment as illustrated by Figure.

Secondary analysis further strengthens the positive effect of extracorporeal shockwave therapy on maximum walking distances.

## Section 4.3.3 – Participant self-reported maximum walking distance

The objective increase in the pain free and maximum walking distance in both the intervention and control group was accompanied by an increase in participant self-reported maximum walking distance. Although no statistically significant difference in participant self-reported maximum walking distance was recorded between the intervention and control groups at any follow up time points, the increase in maximum walking distance was significant enough to be noted by all participants in their day to day life, with statistically significant difference between baseline and week 12 follow up within each group (See Chapter 3, Section 3.3.3). This reinforces the validity of our placebo protocol and confirms adequate blinding of participants (Discussed further in Section 4.3.7).

## Section 4.3.4 – Ankle Brachial Pressure Index

There were no inter or intragroup statistically significant differences in ankle brachial pressure index values pre or post exercise at baseline or any of the follow up time points. Given that the extracorporeal shockwave therapy protocol in this trial did not target the site of the lower limb arterial inflow disease which caused the participants intermittent claudication symptoms, it is expected that there would be no recordable differences at a macrovascular level with changes in ankle brachial pressure index values. In addition, the proposed mechanism of action of extracorporeal shockwave therapy for use in the context of peripheral arterial disease is that of micro-neovascularisation within the gastrocnemius muscle bed (See Chapter 1, Section 1.4.4) which again, would not yield changes at macrovascular level and therefore no significant changes in ankle brachial pressure index.

## Section 4.3.5 – Laser Doppler Flowmetry

The proposed mechanism of action of extracorporeal shockwave therapy for use in the context of peripheral arterial disease, is that of micro-neovascularisation within the gastrocnemius muscle bed (See Chapter 1, Section 1.4.4), and therefore a change in PU measured by laser doppler flowmetry was anticipated in this study. However, there were no inter or intragroup statistically significant differences in PU as measured by laser doppler flowmetry pre or post exercise, at the calf or foot placement, at baseline or any of the follow up time points.

This could be explained by the superficial nature of this measurement, limited only to the skin at a maximum depth of 1 mm (Rajan *et al.*, no date; Vongsavan and Matthews, 1993), and therefore may be unable to detect changes in microvascular blood flow deep within the gastrocnemius muscle bed. This could be compounded by the limitations of the laser doppler flowmetry probe placement. The choice of the medial aspect of the gastrocnemius muscle allowed for a prolonged assessment of the gastrocnemius (5 minutes pre and 5 minutes post exercise per leg, see Chapter 2, Sections 2.5 and 2.7) to be done comfortably with the participants supine. An alternative placement of the probe overlying to the bulk of the gastrocnemius muscle may have yielded different results. Moreover, the selection of a second site at the dorsum of the foot, was done in order to assess any potential changes to microvascular blood flow distal to the site of treatment, and an area of the lower limb most affected by peripheral arterial disease. However, this did not yield any significant results either.

Environmental conditions during laser doppler flowmetry may influence the results obtained as eluded by previous literature (Winsor *et al.*, 1989; Vongsavan and Matthews, 1993; Petrofsky *et al.*, 2012; Chuong *et al.*, 2017). Though the manufacturers do not specify an exact set of environmental conditions for optimum measurements (Moor Instruments, no date) (See

Section 2.5), they advise for constant room temperature and humidity throughout its use. Winsor and his colleagues found that an ambient temperature of 23 degrees Celsius and a laser doppler flowmetry probe temperature of 40 degrees Celsius provided for the most optimum conditions for measurements (Winsor *et al.,* 1989), while Petrofsky and his colleagues found that humidity influenced skin blood flow and also demonstrated that patients with diabetes had significantly less skin blood than healthy controls and had more significant changes in skin blood flow at lower humidities than healthy controls. Finally, laser doppler employs laser light at a particular wavelength (785nm) and depends on the detection of a doppler shift of reflected/scattered light to provide measurements (Micheels, Aisbjorn and Sorensen, 1984). It is therefore expected that other light sources of similar wavelength may interfere with said measurements.

For the purposes of our study, the room temperature was controlled at 24 degrees Celsius throughout all baseline and follow up measurements. However, the probes were not heated to achieve a temperature of 40 degrees Celsius prior to measurement and may have provided unreliable data of microcirculation to the skin. In addition, "baseline" laser doppler flowmetry measurements are inherently unreliable but rather cutaneous vasodilation response to locally applied heat should be employed instead (McGarr *et al.*, 2023) particularly when measurements are taken from the calf as with this study. The unreliable nature of "baseline" laser doppler flowmetry measurements could have provided a set of results that do not reflect the true skin blood flow not only within the two groups but between measurements of the same patient on the same day (McGarr *et al.*, 2023). Humidity was unfortunately not controlled during this study either, which may again have influenced the results provided. In addition, given the demonstrated differences in skin blood flow in patients with diabetes, it is possible

that the obtained results may not reflect the true effect of angiogenesis of shockwave due to impaired skin blood flow and limited depth of penetration of laser doppler.

Finally, the influence of external light can not be discounted. However, the method by which the laser doppler probes are attached to the skin provided for "isolation" from external sources of light (Vongsavan and Matthews, 1993) and therefore unlikely to have influenced the results. In addition, the fluorescence light used in the room does not emit light of the wavelength detected by laser doppler flowmetry (Chuong *et al.*, 2017), and given the lack of windows and natural sunlight in the room it is unlikely that light could have negatively impacted on the laser doppler flowmetry results.

The absence of significant findings in laser doppler flowmetry may therefore not be a true reflection of changes to microcirculation and angiogenesis elicited by the extracorporeal shockwave treatment but a combination of the above factors.

## Section 4.3.6 – Quality of life

Significant improvement in General Health, Vitality and Physical Component Summary as measured by SF-36 quality of life questionnaire as well as EQ-5D-3L was seen at week 4 follow up (See Chapter 3, Section 3.3.6). Following secondary analysis, this significance was maintained for General Health and Vitality domains of SF-36. This further demonstrates that extracorporeal shockwave therapy is likely to have a positive impact on quality of life.. This differences were seen at 4-week follow up most likely to be due to the largest increase in pain-free and maximum walking distance occurring at 4-week follow up, where the positive effects of the active treatment might be more evident to the participants, and therefore more likely to experience and report an improvement in quality of life.

The remaining domains of SF-36 and other measures of quality of life did not show statistically significant improvements, however the median scores in the intervention group were consistently recorded as higher than that in the control group (See Table 8). The lack of statistical significance may be due to the trial being powered to detect a significant change in the physical functioning domain as measured by SF-36, therefore lack the sample size to detect changes in other outcome measures. The lack of improvement in other quality of life measures may also be due to the concomitant cardiovascular risk factors and co-morbidities suffered by the participants of this trial and in general patients with peripheral arterial disease, that impact upon their quality of life (Naito, Honma and Sekizawa, 2002; Trikkalinou, Papazafiropoulou and Melidonis, 2017; Sajobi *et al.*, 2018). This was especially demonstrated in the secondary analysis where patient history of coronary artery disease significantly impacted the physical functioning score differences between the two groups. As mentioned above (Section 4.2), In addition, a significant proportion of questions within the VascuQol questionnaire are phrased to interpret the patient's perception of symptoms as a consequence of "poor circulation". In a blinded study such as this, where patients in both groups may consider that they are receiving active treatment to improve their circulation, any perceived effect of the intervention can affect the results by influencing the patient's perception of the state of their circulation. Moreover, the VascuQol questionnaire attempts to encompass all peripheral arterial disease with questions pertaining to rest pain and ulceration which are not relevant to this study cohort, which may limit its responsiveness in this study (A. P. Conijn *et al.*, 2015). It is also important to note that claudication symptoms were not entirely eradicated, but rather managed to enable patients to mobilize further, so there will be a continuing impact of intermittent claudication on quality of life, and especially apply to the patients with bilateral claudication, as this trial

only treated the index leg. This may mean a limit to the VascuQol responsiveness when intermittent claudication symptoms persist.

## Section 4.3.7 – Influence of best medical therapy in outcome measures

The most recent guidance on the conservative management of intermittent claudication (Gerhard-Herman *et al.*, 2017; Aboyans *et al.*, 2018; NICE, 2018) (See Chapter 1, Section 1.3) advocates for risk factor modification, anti-platelet and lipid lowering therapy (best medical therapy) as well as supervised exercise program participation. The participants in this trial had already refused participation in supervised exercise programs and had already received smoking cessation advice, risk factor modification, best medical therapy and exercise advise from the referring clinician. Smoking cessation and best medical therapy have been shown to improve maximum walking distances in patients with intermittent claudication (Momsen *et al.*, 2009; Aboyans *et al.*, 2018). Despite the well documented benefits of best medical therapy in peripheral arterial disease, recent studies by Wawruch et al. (Wawruch *et al.*, 2019, 2021) have shown that after 5 years of follow up, up to 33% of patients with peripheral arterial disease were non-adherent to their antiplatelet therapy and up to 35% of patients were non-adherent to their statin therapy, with the biggest proportion of non-adherence in the first year, at 14% and 18% respectively.

In this trial, participants were encouraged at every treatment and follow up visit to continue with smoking cessation where applicable and regular exercise/walking as well as ensuring they continued to adhere to the prescribed best medical therapy.

Though the intragroup increase in the physical functioning domain score as measured by the SF-36 quality of life questionnaire from baseline to week 12 follow up for both the intervention

and control group was not statistically significant, there is still a positive, upward trend in this score throughout the follow up period (See Chapter 3, Section 3.2, See Table 8). In addition, both the intragroup pain free and maximum walking distance were statistically higher from baseline to week 12 follow up for the intervention and the control group (See Chapter 3, Section 3.3.1 and 3.3.2). This objective improvement was also accompanied by a significant increase in intragroup subjective walking performance between baseline and week 12 follow-up for both the intervention and control groups (See Chapter 3, Section 3.3.3).

This can be attributed to the positive effects of strict adherence to conservative management, as well as the more frequent encouragement and advice for participant-directed exercise/walking, which the participants would have only had once at their outpatient consultation with the referring clinician. More importantly, this further suggests adequate participant blinding and validates our placebo protocol in the use of extracorporeal shockwave therapy.

## Section 4.3.8 – Participant reported treatment pain

Participants in the intervention group reported very low pain or discomfort during the treatment, confirming that this treatment is well tolerated by all participants. The highest median pain was recorded the first time they underwent the treatment and the lowest during the last. This can be attributed to an initial surprise due to unexpected and previously not experienced sensation of extracorporeal shockwave therapy within a muscle bulk and the later accommodation or habituation to the treatment itself.

# Chapter 5 – Conclusions

## Section 5.1 – Trial appraisal

This trial has successfully recruited to full power, though no convincing statistical significance in the primary outcome was found to confidently reject the null hypothesis.

Randomization was via a recognized, online program to minimize the risk of allocation bias.

The improvement shown in outcome measures in the control group, confirms the validity of the protocol with regards to the delivery of the placebo treatment and successful blinding of the participants. Therefore, any difference in outcome measures between the intervention and the control group can be confidently attributed to the positive effects of extracorporeal shockwave therapy. The blinding of the outcome assessors also reduced the risk of reporting bias, especially given that outcome measures such as ankle brachial pressure index are assessor dependent.

The measured outcomes conform with the latest guidance of reporting outcomes for trials regarding peripheral arterial disease and intermittent claudication (Stoner *et al.*, 2016; Arndt *et al.*, 2022) covering both quality of life measures as well as walking distances assessed by a standardized protocol and ankle brachial pressure index. This makes the critical evaluation of the outcomes of this trial and comparison with the current published outcomes of other accepted and experimental interventions more robust. It also reduces the risk of reporting bias.

Thankfully the last patient underwent their 12-week follow up just before the COVID-19 pandemic lockdown in the UK started (March 2020). The one year follow up for this trial was however interrupted by the COVID-19 pandemic and is therefore incomplete and not presented as part of this thesis. Following the restart of research activity, we consulted a health economist and statistician with

regards to performing delayed 1 year follow ups. We were advised against this, as this would see a stark difference of time to follow up, and the data this would provide would not be reliable or dependable. Longer term follow up data could have informed on the durability of this treatment with regards to patient outcomes but also inform on protocol design and delivery of treatment for future research (See Section 5.2).

The trial was based within a hospital outpatient setting and therefore, not easily accessible by all potential/eligible patients. This may have unintentionally selected for the more mobile, less impaired by intermittent claudication and less infirm patients and more likely to show improvement upon successful treatment.

To maximize recruitment potential, patients with both unilateral and bilateral intermittent claudication were eligible to participate in this trial, however in bilateral claudication only the index leg was treated. This meant that if even the index leg was successfully treated as part of this trial, patients would continue to be symptomatic of intermittent claudication and limited in their mobility and quality of life.

This trial collected information on quality of life from three different quality of life questionnaires as shown in Appendix 7, 8 and 9. This resulted in a 15 page long "bundle" of questionnaires with 68 individual questions. Questionnaire fatigue is well documented in the literature resulting in participants providing inconsistent responses that may not necessarily be truthful or accurate in an attempt to reduce the time and effort of completing the required questionnaires (Egleston, Miller and Meropol, 2011). The order in which questions are presented also affects the responses collected (Krosnick and Alwin, 1987; Holbrook *et al.*, 2007). In this trial the SF-36 questionnaire was presented first, as physical functioning as measured by SF-36 was the primary outcome, followed by EQ-5D-3L

and the VascuQol. This may have unintentionally affected the responses received and observed outcomes in those domains. In addition, participants of health related questionnaires are more likely to respond favorably to questions, again in an effort to reduce the burden of questionnaire fatigue (Mathiowetz and Lair, 1994; Hill and Pylypchuk, 2006) further affecting the results. Given the above, some of the questionnaires were partially completed. This was also in combination with data collection done by previous research fellows leading on the trial (prior to myself starting in June 2018) who may not have been as vigilant of questionnaire completion as expected. The calculators for all three quality of life questionnaires would still provide a score for each domain despite the partial data input and that score was used in the final analysis. This may have inadvertently influenced the results, by providing scores that may not have necessarily reflected the true state of quality of life of the participants at the time of reporting, had the entirety of the questionnaire was completed.

The study is also limited by the use of a constant load treadmill test, for assessing walking distances. Though a reliable test, especially when assessing maximum walking distance in patients with intermittent claudication (Nicolaï *et al.*, 2009), it has disadvantages in terms of test, re-test reliability when compared to a graded treadmill test and may not be as closely related to every day walking as the 6-minute walking test (McDermott *et al.*, 2014).

Healthcare resource utilization data was not collected in this trial and along with the lack of complete one year follow up data, precludes from the undertaking of a robust and reliable cost effectiveness analysis, as using only the EQ-5D-3L data at week 12 follow up will result in unreliable and largely speculative cost effectiveness analysis.

## Section 5.2 – Future directions

### Section 5.2.1 – Long term follow up

As previously mentioned, the one year follow up was interrupted by the COVID-19 pandemic and was not completed. Participants in this study have been consented for more long term follow up to five years after initial recruitment. This follow up would demonstrate the long term durability of extracorporeal shockwave therapy and offer insights to the progression of the disease and whether the participants required invasive treatment for their symptomatic intermittent claudication in the mean time. It would also allow data to be collected on adherence to risk factor modification and best medical therapy and correlation of that to disease progression. Lastly, with more complete long term EQ-5D-3L data, there might be a scope for a cost effectiveness analysis, though that might again not be representative of the effects of the treatment, especially in the case of invasive interventions in the mean time and change in symptomatology.

### Section 5.2.2 – Patient and Public involvement

Patient and public involvement focus groups offer unique insights to the design, planning and execution of clinical trials. With regards to this trial, it would be crucial to obtain this unique insight on blinding, treatment satisfaction and acceptability of outcome measures and therefore inform the design of future trials.

Involvement of patients who have participated and completed a supervised exercise program would also be crucial in offering their invaluable insight especially the effects of group treatment (in contrast to the individual treatment in this trial), accessibility to supervised exercise and the addition of extracorporeal shockwave treatment to the standard of care.

Bringing the two groups of patients together would also allow for a discussion on the most participant acceptable design of a trial to compare supervised exercise against extracorporeal shockwave therapy.

## Section 5.2.3 – Comparative trials with supervised exercise

Multiple options appear to be viable in the design of a trial to compare extracorporeal shockwave therapy with supervised exercise.

A non-inferiority randomized trial directly comparing supervised exercise and extracorporeal shockwave therapy appears to be the most attractive option. It would allow head to head comparison of an experimental treatment with the established and recommended current treatment.

Alternatively, extracorporeal shockwave therapy could be assessed for its added benefit to the current recommended management strategy, with a trial comparing supervised exercise and extracorporeal shockwave therapy against supervised exercise alone. Building on this premise a three arm trial comparing supervised exercise and extracorporeal shockwave therapy against supervised exercise alone and extracorporeal shockwave therapy alone may also be a viable option.

Successful execution of trials in supervised exercise for intermittent claudication however does pose center eligibility and recruitment problems due to the scant provision and availability of supervised exercise programs across the UK (Harwood *et al.*, 2022). In addition, given reported patient adherence and recruitment to supervised exercise (Harwood *et al.*, 2016b) and

recruitment rates within this trial (See Chapter 3, Section 3.1), this would further hamper recruitment.

## Section 5.2.4 – Dosing trials

Within the published literature there is no consensus on the ideal dosing of extracorporeal shockwave therapy in peripheral arterial disease. Variations occur at the site of treatment, frequency and number of treatment sessions and time between treatments, energy flux density, and frequency and total shockwaves delivered per session (Raza *et al.*, 2017).

Given previous clinical studies supporting the delivery of extracorporeal shockwave therapy in the muscle bulk of the calf (Serizawa *et al.*, 2012; Tara *et al.*, 2014; Harwood, Green, *et al.*, 2018) and the proposed mechanism of action (See Chapter 1, Section 1.5), we would advocate for continuing treatment in that area.

Potential dosing trials could assess the frequency and number of treatment sessions, as an increase in frequency and number of sessions has previously shown improved and long-lasting results (Serizawa *et al.*, 2012). Investigating the time between treatments could also provide valuable insight in the longevity of extracorporeal shockwave therapy effects, with potential trials adding a "top up" treatment either 6 months or 1 year to potentially maximize the longevity and durability of treatment.

Potential dosing trials assessing a varying energy flux density, and frequency and total shockwaves delivered per session could achieve that by following the protocol of this trial (See Chapter 2) and separating investigation groups according to treatment. The short term follow up period in this trial (3 months) could initially reveal dosing regimes that confer for significant

improvement in outcomes, with more long term follow up informing on durability and longevity.

## Section 5.2.5 – Mechanism of action trials

Chapter 1, Section 1.5 presents the most accepted hypothesis on the mechanism of action of extracorporeal shockwave therapy in peripheral arterial disease and intermittent claudication. Any of the aforementioned, future trials must include provisions for the confirmation of the above hypothesis.

Given that VEGF appears to have the most critical role in the angiogenic pathway stimulated by shockwave therapy, as assessment of serum VEGF before and after treatment would provide that additional insight in its role in the mechanism of action. Correlation of VEGF levels with improvements in clinical outcomes such as walking distances and quality of life can further confirm that relationship. Collecting serum sample for VEGF immediately before and immediately after treatment can further demonstrate VEGF's acuity of response to shockwave treatment. Considerations can be taken for the site of sample retrieval, where a choice of lower limb vessel, especially if acuity of response to treatment is being investigated, might be a better choice, than the usual arm site, where systemic cofounders can affect results. Along with VEGF serum can be analyzed for placental growth factor and human endothelial progenitor cells.

As mentioned before, the gold standard for imaging the lower limb arterial tree is angiography. This could be employed to assess macrovascular changes within the muscle bed following extracorporeal shockwave therapy. However, consideration must be given to the invasive nature of this imaging nodality and perhaps an alternative, non-invasive modality could be

chosen such as magnetic resonance angiography. Computed tomography angiography has already been used and has not been able to demonstrate positive results, in addition to the risks of ionizing radiation and use of intravenous contrast.

Assessment of microcirculation should not be neglected, especially given the aforementioned mechanism of action. As discussed in Chapter 4, Section 4.3.5, the laser doppler position could be adjusted to overly the gastrocnemius muscle bulk and could potentially detected differences in PU not detected in this study. In addition, important environmental conditions that could influence laser doppler flowmetry should be controlled to maximize the reliability of those measurements. Consideration also should be given to other non-invasive techniques such as near-infrared spectroscopy and TcPO2 measurements which have already been extensively used in vascular surgery and lower limb peripheral arterial disease (Watanabe *et al.*, 2004; Catella, Long and Mazzolai, 2021).

## Section 5.3 – Final conclusions

This is the first adequately powered, double-blind, placebo-controlled, randomized trial to consider extracorporeal shockwave therapy for the management of lower limb intermittent claudication. It has shown recruitment and adherence to protocol rates similar to that of the supervised exercise program in the UK (Harwood *et al.*, 2016a), while targeting a subgroup of patients with intermittent claudication that had already declined or completed the supervised exercise program and would have otherwise not received any other intervention apart from smoking cessation advice, risk factor modification, best medical therapy and exercise advice. It has successfully demonstrated efficacy for improving walking distancesl comparable to those reported for supervised exercise (Lane *et al.*, 2017a), and has shown a potential positive effect on quality of life, within a cohort of patients with stable intermittent claudication. This trial has also demonstrated that extracorporeal shockwave therapy is

safe, acceptable, and tolerable for patients with intermittent claudication, with no recorded side effects or adverse events related to its use, and that can be delivered successfully at an outpatient or even community setting. In conclusion, given the promising results presented herein, further research considering the role of extracorporeal shockwave therapy in the management of intermittent claudication is warranted, to reinforce the above trial in support of its integration in clinical guidance and practice as an adjunct to the conservative management of intermittent claudication.

## References

Aboyans, V. *et al.* (2018) 'Editor's Choice – 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)', *European Journal of Vascular and Endovascular Surgery*, 55(3), pp. 305–368. doi: 10.1016/j.ejvs.2017.07.018.

Aicher, A. *et al.* (2006) 'Low-Energy Shock Wave for Enhancing Recruitment of Endothelial Progenitor Cells', *Circulation*, 114(25), pp. 2823–2830. doi: 10.1161/CIRCULATIONAHA.106.628623.

Allison, M. A. *et al.* (2006) 'The Effect of Novel Cardiovascular Risk Factors on the Ethnic-Specific Odds for Peripheral Arterial Disease in the Multi-Ethnic Study of Atherosclerosis (MESA)', *Journal of the American College of Cardiology*, 48(6), pp. 1190–1197. doi: 10.1016/J.JACC.2006.05.049.

Alsaikhan, B. and Andonian, S. (2011) 'Shock wave lithotripsy in patients requiring anticoagulation or antiplatelet agents', *Canadian Urological Association Journal*, 5(1), p. 53. doi: 10.5489/CUAJ.09140.

Althouse, A. D. *et al.* (2014) 'Risk Factors for Incident Peripheral Arterial Disease in Type 2 Diabetes: Results From the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) Trial', *Diabetes Care*, 37(5), pp. 1346–1352. doi: 10.2337/DC13-2303.

Arndt, H. *et al.* (2022) 'A Delphi Consensus on Patient-reported Outcomes for Registries and Trials including Patients with Intermittent Claudication: Recommendations and Reporting Standard', *European Journal of Vascular and Endovascular Surgery*. doi: 10.1016/J.EJVS.2022.08.011.

Aung, P. P. *et al.* (2007) 'Lipid-lowering for peripheral arterial disease of the lower limb', *Cochrane Database of Systematic Reviews*, (4). doi: 10.1002/14651858.CD000123.PUB2/MEDIA/CDSR/CD000123/IMAGE_N/NCD000123-CMP-001-14.PNG.

Axisa, B. *et al.* (2002) 'Complications following peripheral angioplasty.', *Annals of The Royal College of Surgeons of England*, 84(1), p. 39. Available at: /pmc/articles/PMC2503753/?report=abstract (Accessed: 23 October 2022).

Baigent, C. *et al.* (2002) 'Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients', *BMJ : British Medical Journal*, 324(7329), p. 71. doi: 10.1136/BMJ.324.7329.71.

Bangalore, S. *et al.* (2012) 'Short-and long-term outcomes with drug-eluting and bare-metal coronary stents: A mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials', *Circulation*, 125(23), pp. 2873–2891. doi: 10.1161/CIRCULATIONAHA.112.097014/-/DC1.

Barbara Young, G. O. & P. W. (2006) *Wheater's Functional Histology: A Text and Colour Atlas*, *Churchill Livingstone*. Elsevier Inc. doi: 10.7861/clinmedicine.14-4-453.

Barletta, G. *et al.* (1996) 'Quality of life in patients with intermittent claudication: Relationship with laboratory exercise performance', *Vascular Medicine*, 1(1), pp. 3–7. doi: 10.1177/1358863X9600100102.

Beattie, D. K. *et al.* (1997) 'Quality of life assessment in vascular disease: Towards a consensus', *European Journal of Vascular and Endovascular Surgery*, 13(1), pp. 9–13. doi: 10.1016/S1078-5884(97)80044-5.

Beks, P. J. *et al.* (1995) 'Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn Study', *Diabetologia 1995 38:1*, 38(1), pp. 86–96. doi: 10.1007/BF02369357.

Bonaca, M. P. *et al.* (2020) 'Rivaroxaban in Peripheral Artery Disease after Revascularization', *New England Journal of Medicine*, 382(21), pp. 1994–2004. doi: 10.1056/NEJMOA2000052/SUPPL_FILE/NEJMOA2000052_DATA-SHARING.PDF.

Britannica (no date) *shock wave | Definition & Facts |*. Available at: https://www.britannica.com/science/shock-wave (Accessed: 23 October 2022).

Cacoub, P. P. *et al.* (2009) 'Patients with peripheral arterial disease in the CHARISMA trial', *European Heart Journal*, 30(2), pp. 192–201. doi: 10.1093/EURHEARTJ/EHN534.

Carmignano, S. M. and Carmignano, S. M. (2019) 'Extracorporeal Shock Wave Therapy in Chronic Wound Care', *Physical Therapy Effectiveness*. doi: 10.5772/INTECHOPEN.89592.

Catella, J., Long, A. and Mazzolai, L. (2021) 'What Is Currently the Role of TcPO2 in the Choice of the Amputation Level of Lower Limbs? A Comprehensive Review', *Journal of Clinical Medicine*, 10(7), p. 1413. doi: 10.3390/JCM10071413.

Cayton, T. *et al.* (2017) 'Extracorporeal shockwave therapy for the treatment of lower limb intermittent claudication: study protocol for a randomised controlled trial (the SHOCKWAVE 1 trial)', *Trials*, 18(1), p. 104. doi: 10.1186/s13063-017-1844-4.

Chamberlain, G. A. and Colborne, G. R. (2016) 'A review of the cellular and molecular effects of extracorporeal shockwave therapy', *Veterinary and Comparative Orthopaedics and Traumatology*, 29(2), pp. 99–107. doi: 10.3415/VCOT-15-04-0057/ID/JR0057-53.

Chetter, C. *et al.* (1997) 'ESVS PRIZE WINNER 1996 Quality of Life Analysis in Patients with Lower Limb Ischaemia: Suggestions for European Standardisation', *Eur J Vasc Endovasc Surg*, 13, pp. 597–604.

Chetter, I. C. *et al.* (1997) 'Quality of life analysis in patients with lower limb ischaemia: Suggestions for European standardisation', *European Journal of Vascular and Endovascular Surgery*, 13(6), pp. 597–604. doi: 10.1016/S1078-5884(97)80070-6.

Chetter, I. C. *et al.* (1999) 'Does angioplasty improve the quality of life for claudicants?: A prospective study', *Annals of Vascular Surgery*, 13(1), pp. 93–103. doi: 10.1007/s100169900226.

Chetter, I. C. *et al.* (2003) 'Prospective analysis of quality of life in patients following infrainguinal reconstruction for chronic critical ischaemia', *British Journal of Surgery*, 85(7), pp. 951–955. doi: 10.1046/J.1365-2168.1998.00752.X.

Chetter, I. C. *et al.* (2016) 'Correlating Clinical Indicators of Lower-Limb Ischaemia with Quality of Life', *http://dx.doi.org/10.1177/096721099700500404*, 5(4), pp. 361–366. doi: 10.1177/096721099700500404.

Chuong, A. *et al.* (2017) 'The effect of ambient lighting on Laser Doppler Imaging of a standardized cutaneous injury model', *International Journal of Burns and Trauma*, 7(7), p. 147. Available at: /pmc/articles/PMC5768931/ (Accessed: 20 December 2023).

Ciccone, M. M. *et al.* (2012) 'Shockwave Therapy in Patients with Peripheral Artery Disease', *Advances in Therapy 2012 29:8*, 29(8), pp. 698–707. doi: 10.1007/S12325-012-0038-4.

Collins, R. *et al.* (2007) 'A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease', *Health Technology Assessment*, 11(20). doi: 10.3310/HTA11200.

Conijn, Anne P. *et al.* (2015) 'Introducing the Concept of the Minimally Important Difference to Determine a Clinically Relevant Change on Patient-Reported Outcome Measures in Patients with Intermittent Claudication', *CardioVascular and Interventional Radiology*, 38(5), pp. 1112–1118. doi: 10.1007/S00270-015-1060-0/TABLES/3.

Conijn, A. P. *et al.* (2015) 'Test-retest Reliability and Measurement Error Are Excellent for the Dutch Version of the VascuQol Questionnaire in Patients with Intermittent Claudication', *European Journal of Vascular and Endovascular Surgery*, 50(4), pp. 502–505. doi: 10.1016/j.ejvs.2015.07.007.

Conijn, A. P. *et al.* (2016) 'Determining the Minimally Important Difference for the VascuQol Sumscore and Its Domains in Patients with Intermittent Claudication', *European Journal of Vascular and Endovascular Surgery*, 51(4), pp. 550–556. doi: 10.1016/j.ejvs.2015.12.012.

Copay, A. G. *et al.* (2007) 'Understanding the minimum clinically important difference: a review of concepts and methods', *The spine journal : official journal of the North American Spine Society*, 7(5), pp. 541–546. doi: 10.1016/J.SPINEE.2007.01.008.

Cosentino, F. *et al.* (2020) '2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASDThe Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)', *European Heart Journal*, 41(2), pp. 255–323. doi: 10.1093/EURHEARTJ/EHZ486.

Crevenna, R., Mickel, M. and Keilani, M. (2019) 'Extracorporeal shock wave therapy in the supportive care and rehabilitation of cancer patients', *Supportive Care in Cancer*, 27(11), p. 4039. doi: 10.1007/S00520-019-05046-Y.

Criqui, M. H. *et al.* (2010) 'The Ankle-Brachial Index and Incident Cardiovascular Events in the Multi-Ethnic Study of Atherosclerosis (MESA)', *Journal of the American College of Cardiology*, 56(18), p. 1506. doi: 10.1016/J.JACC.2010.04.060.

Criqui, M. H. and Aboyans, V. (2015a) 'Epidemiology of Peripheral Artery Disease', *Circulation Research*, 116(9), pp. 1509–1526. doi: 10.1161/CIRCRESAHA.116.303849/FORMAT/EPUB.

Criqui, M. H. and Aboyans, V. (2015b) 'Epidemiology of Peripheral Artery Disease', *Circulation Research*, 116(9), pp. 1509–1526. doi: 10.1161/CIRCRESAHA.116.303849.

Djerf, H. *et al.* (2020) 'Absence of Long-Term Benefit of Revascularization in Patients with Intermittent Claudication: Five-Year Results from the IRONIC Randomized Controlled Trial', *Circulation: Cardiovascular Interventions*, 13(1). doi: 10.1161/CIRCINTERVENTIONS.119.008450.

Dobner, S., Amadi, O. C. and Lee, R. T. (2012) 'Cardiovascular Mechanotransduction', *Muscle: Fundamental Biology and Mechanisms of Disease*, 1–2, pp. 173–186. doi: 10.1016/B978-0-12-381510-1.00014-4.

Dornier HM3 (no date) *Matthew Bultitude on Twitter: 'Just found amazing old pic of Dornier HM3 lithotripter @GSTTnhs from early '80's - and those were my ducks in it!!! http://t.co/KRym1A4W6s' / Twitter*. Available at: https://twitter.com/mattbultitude/status/591343014271922176 (Accessed: 24 October 2022).

Drake, R. L., Vogl, Wayne, A. and Mitchell, A. W. M. (2009) *Gray's Anatomy for Students, 2nd Edition, Elsevier Health Sciences*. Elsevier Health Sciences. doi: 1437720552.

Egleston, B. L., Miller, S. M. and Meropol, N. J. (2011) 'The impact of misclassification due to survey response fatigue on estimation and identifiability of treatment effects', *Statistics in medicine*, 30(30), p. 3560. doi: 10.1002/SIM.4377.

Eikelboom, J. W. *et al.* (2017) 'Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease', *New England Journal of Medicine*, 377(14), pp. 1319–1330. doi: 10.1056/NEJMOA1709118/SUPPL_FILE/NEJMOA1709118_DISCLOSURES.PDF.

Eldrup, N. *et al.* (2006) 'Ankle brachial index, C-reactive protein, and central augmentation index to identify individuals with severe atherosclerosis', *European Heart Journal*, 27(3), pp. 316–322. doi: 10.1093/EURHEARTJ/EHI644.

Elmansy, H. E. and Lingeman, J. E. (2016) 'Recent advances in lithotripsy technology and treatment strategies: A systematic review update', *International Journal of Surgery*, 36(PD), pp. 676–680. doi: 10.1016/J.IJSU.2016.11.097.

Faulkner, K. W., House, A. K. and Castleden, W. M. (1983) 'The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease', *The Medical journal of Australia*, 1(5), pp. 217–219. doi: 10.5694/J.1326-5377.1983.TB99395.X.

Fowkes, F. G. R. *et al.* (2013) 'Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis', *The Lancet*, 382(9901), pp. 1329–1340. doi: 10.1016/S0140-6736(13)61249-0.

Fowkes, F. G. R. *et al.* (2016) 'Peripheral artery disease: epidemiology and global perspectives', *Nature Reviews Cardiology 2016 14:3*, 14(3), pp. 156–170. doi: 10.1038/nrcardio.2016.179.

FOWKES, F. G. R. *et al.* (1991) 'Edinburgh Artery Study: Prevalence of Asymptomatic and Symptomatic Peripheral Arterial Disease in the General Population', *International Journal of Epidemiology*, 20(2), pp. 384–392. doi: 10.1093/ije/20.2.384.

Fowkes, G. *et al.* (2008) 'Ankle Brachial Index Combined with Framingham Risk Score to Predict Cardiovascular Events and Mortality: A Meta-analysis', *JAMA : the journal of the American Medical Association*, 300(2), p. 197. doi: 10.1001/JAMA.300.2.197.

Fukumoto, Y. *et al.* (2006) 'Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease.', *Coronary Artery Disease*, 17(1), pp. 63–70. doi: 10.1097/00019501-200602000-00011.

Garden, O. J. *et al.* (2012) 'Principles and practice of surgery 6th edition', pp. 240–241. Available at: https://books.google.com.eg/books?id=T8BpQO8bOTcC&pg=PA237&dq=macroscopic+findings+of+ulcerative+colitis&hl=en&sa=X&ved=0ahUKEwiO5NyP3sHYAhUB16QKHZfnCwAQ6AEILzAB#v=onepage&q=macroscopic findings of ulcerative colitis&f=false (Accessed: 2 February 2020).

Gardner, A. W., Montgomery, P. S. and Wang, M. (2018) 'Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease', *Vascular Medicine (United Kingdom)*, 23(4), pp. 349–357. doi: 10.1177/1358863X18762599.

Gau, G. T. and Wright, R. S. (2006) 'Pathophysiology, Diagnosis, and Management of Dyslipidemia', *Current Problems in Cardiology*, 31(7), pp. 445–486. doi: 10.1016/j.cpcardiol.2006.03.001.

Gent, M. (1996) 'A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)', *Lancet*, 348(9038), pp. 1329–1339. doi: 10.1016/S0140-

6736(96)09457-3.

Gerald, F. *et al.* (1992) ‘Smoking, Lipids, Glucose Intolerance, and Blood Pressure as Risk Factors for Peripheral Atherosclerosis Compared with Ischemic Heart Disease in the Edinburgh Artery Study’, *American Journal of Epidemiology*, 135(4), pp. 331–340. doi: 10.1093/OXFORDJOURNALS.AJE.A116294.

Gerhard-Herman, M. D. *et al.* (2017) ‘2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines’, *Journal of the American College of Cardiology*, 69(11), pp. e71–e126. doi: 10.1016/J.JACC.2016.11.007.

Gheorghe, A. *et al.* (2018) ‘The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: A systematic review’, *BMC Public Health*, 18(1), pp. 1–11. doi: 10.1186/S12889-018-5806-X/TABLES/4.

*Glossary | NICE* (no date). Available at: https://www.nice.org.uk/Glossary?letter=H (Accessed: 23 October 2022).

Golledge, J. *et al.* (2020) ‘Relationship Between Disease Specific Quality of Life Measures, Physical Performance, and Activity in People with Intermittent Claudication Caused by Peripheral Artery Disease’, *European Journal of Vascular and Endovascular Surgery*, 59(6), pp. 957–964. doi: 10.1016/j.ejvs.2020.02.006.

Gonzalez, A. B. de *et al.* (2010) ‘Body-Mass Index and Mortality among 1.46 Million White Adults’, *The New England journal of medicine*, 363(23), p. 2211. doi: 10.1056/NEJMOA1000367.

Green, J. L. *et al.* (2018) ‘Extracorporeal shockwave therapy for intermittent claudication: Medium-term outcomes from a double-blind randomised placebo-controlled pilot trial’, *https://doi.org/10.1177/1708538118773618*, 26(5), pp. 531–539. doi: 10.1177/1708538118773618.

Gulati, S. *et al.* (2009) ‘Quality of life in patients with lower limb ischemia; revised suggestions for analysis’, *Journal of Vascular Surgery*, 49(1), pp. 122–126. doi: 10.1016/j.jvs.2008.08.011.

Gutersohn, A., Caspari, G. and Erbel, R. (2000) ‘Upregulation of Vascular endothelial growth factor m-RNA in Human umbilical vascular endothelial cells via shock waves’, *European Journal of Heart Failure*, 2, pp. 42–42. doi: 10.1016/S1388-9842(00)80143-9.

Hageman, D. *et al.* (2018) ‘Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication’, *Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.CD005263.pub4.

Hallberg, I. R., Risberg, B. and Thomsen, M. B. (1999) ‘Quality of life associated with varying degrees of chronic lower limb ischaemia: comparison with a healthy sample’, *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery*, 17(4), pp. 319–325. doi: 10.1053/EJVS.1998.0773.

Harwood, A. E. *et al.* (2016a) ‘A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication’, *Annals of Vascular Surgery*. Elsevier Inc., pp. 280–289. doi: 10.1016/j.avsg.2016.02.009.

Harwood, A. E. *et al.* (2016b) 'A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication', *Annals of Vascular Surgery*, 34, pp. 280–289. doi: 10.1016/j.avsg.2016.02.009.

Harwood, A. E. *et al.* (2017) 'Quality of life in patients with intermittent claudication', *Gefasschirurgie*, 22(3), p. 159. doi: 10.1007/S00772-017-0269-4.

Harwood, A. E., Green, J., *et al.* (2018) 'A feasibility double-blind randomized placebo-controlled trial of extracorporeal shockwave therapy as a novel treatment for intermittent claudication', *Journal of Vascular Surgery*, 67(2), pp. 514-521.e2. doi: 10.1016/j.jvs.2017.07.105.

Harwood, A. E., Hitchman, L. H., *et al.* (2018) 'Preferred exercise modalities in patients with intermittent claudication', *Journal of Vascular Nursing*, 36(2), pp. 81–84. doi: 10.1016/j.jvn.2017.12.002.

Harwood, A. E. *et al.* (2020) 'Exercise training for intermittent claudication: A narrative review and summary of guidelines for practitioners', *BMJ Open Sport and Exercise Medicine*. BMJ Publishing Group. doi: 10.1136/bmjsem-2020-000897.

Harwood, A. E. *et al.* (2022) 'Provision of exercise services in patients with peripheral artery disease in the United Kingdom', *Vascular*, 30(5), pp. 874–881. doi: 10.1177/17085381211035259/ASSET/IMAGES/LARGE/10.1177_17085381211035259-FIG2.JPEG.

Haupt, G. (1997) 'Use of Extracorporeal Shock Waves in the Treatment of Pseudarthrosis,

Tendinopathy and Other Orthopedic Diseases', *The Journal of Urology*, 158(1), pp. 4–11. doi: 10.1097/00005392-199707000-00003.

Häusler, E. and Kiefer, W. (1971) 'Anregung von stoßwellen in flüssigkeiten durch hochgeschwindigkeitswassertropfen', *Verhand Dtsch Physikal Gesellschaft*.

Heart Protection Study Collaborative Group (2007) 'Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions', *Journal of Vascular Surgery*, 45(4), pp. 645-654.e1. doi: 10.1016/J.JVS.2006.12.054.

Hicken, G. J., Lossing, A. G. and Ameli, F. M. (2000) 'Assessment of generic health-related quality of life in patients with intermittent claudication', *European Journal of Vascular and Endovascular Surgery*, 20(4), pp. 336–341. doi: 10.1053/ejvs.2000.1198.

Hill, S. C. and Pylypchuk, Y. (2006) 'Reports of fewer activity limitations: Recovery, survey fatigue, or switching respondent?', *Medical Care*, 44(5 SUPPL.). doi: 10.1097/01.MLR.0000208199.13219.8B.

Hitchman, L. H. *et al.* (2019) 'Extracorporeal Shockwave Therapy for Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis', *Annals of Vascular Surgery*, 56, pp. 330–339. doi: 10.1016/J.AVSG.2018.10.013.

Holbrook, A. L. *et al.* (2007) 'Response Order Effects in Dichotomous Categorical Questions Presented OrallyThe Impact of Question and Respondent Attributes', *Public Opinion Quarterly*,

71(3), pp. 325–348. doi: 10.1093/POQ/NFM024.

Holfeld, J. *et al.* (2014) 'Low Energy Shock Wave Therapy Induces Angiogenesis in Acute Hind-Limb Ischemia via VEGF Receptor 2 Phosphorylation', *PLOS ONE*, 9(8), p. e103982. doi: 10.1371/JOURNAL.PONE.0103982.

Hooi, J. D. *et al.* (2001) 'Incidence of and Risk Factors for Asymptomatic Peripheral Arterial Occlusive Disease: A Longitudinal Study', *American Journal of Epidemiology*, 153(7), pp. 666–672. doi: 10.1093/AJE/153.7.666.

Ibeggazene, S. and Klonizakis, M. (2023) 'Clinical outcomes in intermittent claudication – time for a change?', *https://doi.org/10.1024/0301-1526/a001087*, 52(5), pp. 349–350. doi: 10.1024/0301-1526/A001087.

Ingolfsson, I. Ö. *et al.* (1994) 'A marked decline in the prevalence and incidence of intermittent claudication in icelandic men 1968–1986: A strong relationship to smoking and serum cholesterol—The Reykjavik study', *Journal of Clinical Epidemiology*, 47(11), pp. 1237–1243. doi: 10.1016/0895-4356(94)90128-7.

ISMST (2019) 'ISMST Guidelines'.

Ix, J. H. *et al.* (2011) 'Association of Body Mass Index With Peripheral Arterial Disease in Older Adults: The Cardiovascular Health Study', *American Journal of Epidemiology*, 174(9), p. 1036. doi: 10.1093/AJE/KWR228.

Izquierdo-Porrera, A. M. *et al.* (2005) 'Relationship between objective measures of peripheral arterial disease severity to self-reported quality of life in older adults with intermittent claudication', *Journal of Vascular Surgery*, 41(4), pp. 625–630. doi: 10.1016/j.jvs.2005.01.012.

Joosten, M. M. *et al.* (2012) 'Associations Between Conventional Cardiovascular Risk Factors and Risk of Peripheral Artery Disease in Men', *JAMA*, 308(16), pp. 1660–1667. doi: 10.1001/JAMA.2012.13415.

Jude, E. B. *et al.* (2001) 'Peripheral Arterial Disease in Diabetic and Nondiabetic PatientsA comparison of severity and outcome', *Diabetes Care*, 24(8), pp. 1433–1437. doi: 10.2337/DIACARE.24.8.1433.

Kaplovitch, E. *et al.* (2021) 'Rivaroxaban and Aspirin in Patients With Symptomatic Lower Extremity Peripheral Artery Disease: A Subanalysis of the COMPASS Randomized Clinical Trial', *JAMA Cardiology*, 6(1), pp. 21–29. doi: 10.1001/JAMACARDIO.2020.4390.

Khaira, H. S., Hanger, R. and Shearman, C. P. (1996) 'Quality of life in patients with intermittent claudication', *European Journal of Vascular and Endovascular Surgery*, 11(1), pp. 65–69. doi: 10.1016/S1078-5884(96)80136-5.

Kikuchi, Y. *et al.* (2010) 'Double-Blind and Placebo-Controlled Study of the Effectiveness and Safety of Extracorporeal Cardiac Shock Wave Therapy for Severe Angina Pectoris', *Circulation Journal*, 74(3), pp. 589–591. doi: 10.1253/CIRCJ.CJ-09-1028.

Kostakopoulos, A. *et al.* (1995) ‘Subcapsular Hematoma due to ESWL: Risk Factors’, *Urologia Internationalis*, 55(1), pp. 21–24. doi: 10.1159/000282741.

Krause, H. (1997) ‘Physik und Technik Medizinischer Stoßwellensysteme’, *Extrakorporale Stoßwellentherapie.*, (Weinheim: Chapman & Hall GmbH), pp. 15–34.

Krosnick, J. A. and Alwin, D. F. (1987) ‘AN EVALUATION OF A COGNITIVE THEORY OF RESPONSE-ORDER EFFECTS IN SURVEY MEASUREMENT’, *Public Opinion Quarterly*, 51(2), pp. 201–219. doi: 10.1086/269029.

Kumar, V. *et al.* (2009) *Robbins and Coutran’s Pathologic Basis of Disease*. 8th edn, *Book*. 8th edn. Elsevier.

Kumbhani, D. J. *et al.* (2014) ‘Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry’, *European Heart Journal*, 35(41), p. 2864. doi: 10.1093/EURHEARTJ/EHU080.

Lane, R. *et al.* (2017a) ‘Exercise for intermittent claudication’, *Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.CD000990.pub4.

Lane, R. *et al.* (2017b) ‘Exercise for intermittent claudication’, *Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.CD000990.pub4.

Levin, S. R. *et al.* (2021) ‘Tibial bypass in patients with intermittent claudication is associated with poor outcomes’, *Journal of Vascular Surgery*, 73(2), pp. 564-571.e1. doi: 10.1016/j.jvs.2020.06.118.

Lightwood, J. M. and Glantz, S. A. (1997) 'Short-term Economic and Health Benefits of Smoking Cessation', *Circulation*, 96(4), pp. 1089–1096. doi: 10.1161/01.CIR.96.4.1089.

Lu, L., Mackay, D. F. and Pell, J. P. (2018) 'Secondhand smoke exposure and risk of incident peripheral arterial disease and mortality: a Scotland-wide retrospective cohort study of 4045 non-smokers with cotinine measurement', *BMC Public Health*, 18(1). doi: 10.1186/S12889-018-5227-X.

Luttun, A., Tjwa, M. and Carmeliet, P. (2002) 'Placental Growth Factor (PlGF) and Its Receptor Flt-1 (VEGFR-1)', *Annals of the New York Academy of Sciences*, 979(1), pp. 80–93. doi: 10.1111/J.1749-6632.2002.TB04870.X.

Mach, F. *et al.* (2020) '2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk', *European Heart Journal*, 41(1), pp. 111–188. doi: 10.1093/EURHEARTJ/EHZ455.

Malgor, R. D. *et al.* (2015) 'A systematic review of treatment of intermittent claudication in the lower extremities', *Journal of Vascular Surgery*, 61(3), pp. 54S-73S. doi: 10.1016/j.jvs.2014.12.007.

Mancia, G. *et al.* (2013) 'The task force for the management ofarterial hypertension of the european society ofhypertension (esh) and of the european society of cardiology (esc)', *Journal of Hypertension*, 31(7), pp. 1281–1357. doi: 10.1097/01.HJH.0000431740.32696.CC.

Mathiowetz, N. A. and Lair, T. J. (1994) 'Getting Better? Change or Error in the Measurement of Functional Limitations', *Journal of Economic and Social Measurement*, 20(3), pp. 237–262. doi:

10.3233/JEM-1994-20305.

Mays, R. J. *et al.* (2011) 'Assessment of functional status and quality of life in claudication'. doi: 10.1016/j.jvs.2010.11.092.

Mazari, F. A. K. *et al.* (2010) 'An analysis of relationship between quality of life indices and clinical improvement following intervention in patients with intermittent claudication due to femoropopliteal disease', *Journal of vascular surgery*, 52(1), pp. 77–84. doi: 10.1016/J.JVS.2010.01.085.

McDermott, M. M. *et al.* (2014) 'The Six-Minute Walk is a Better Outcome Measure than Treadmill Walking Tests in Therapeutic Trials of Patients with Peripheral Artery Disease', *Circulation*, 130(1), p. 61. doi: 10.1161/CIRCULATIONAHA.114.007002.

McGarr, G. W. *et al.* (2023) 'Reliability of laser-Doppler flowmetry derived measurements of forearm and calf cutaneous vasodilation during gradual local heating in young adults', *Microvascular Research*, 146, p. 104470. doi: 10.1016/J.MVR.2022.104470.

McGlothlin, A. E. and Lewis, R. J. (2014) 'Minimal Clinically Important Difference: Defining What Really Matters to Patients', *JAMA*, 312(13), pp. 1342–1343. doi: 10.1001/JAMA.2014.13128.

Mehta, T. *et al.* (2006) 'Assessing the validity and responsiveness of disease-specific quality of life instruments in intermittent claudication', *European Journal of Vascular and Endovascular Surgery*, 31(1), pp. 46–52. doi: 10.1016/j.ejvs.2005.08.028.

Meijer, W. T. *et al.* (2000) 'Determinants of Peripheral Arterial Disease in the Elderly: The

Rotterdam Study', *Archives of Internal Medicine*, 160(19), pp. 2934–2938. doi: 10.1001/ARCHINTE.160.19.2934.

Micheels, J., Aisbjorn, B. and Sorensen, B. (1984) 'Laser doppler flowmetry. A new non-invasive measurement of microcirculation in intensive care?', *Resuscitation*, 12(1), pp. 31–39. doi: 10.1016/0300-9572(84)90056-X.

Mittermayr, R. *et al.* (2012a) 'Extracorporeal shock wave therapy (ESWT) for wound healing: Technology, mechanisms, and clinical efficacy', *Wound Repair and Regeneration*, 20(4), pp. 456–465. doi: 10.1111/J.1524-475X.2012.00796.X.

Mittermayr, R. *et al.* (2012b) 'Extracorporeal shock wave therapy (ESWT) for wound healing: Technology, mechanisms, and clinical efficacy', *Wound Repair and Regeneration*, 20(4), pp. 456–465. doi: 10.1111/J.1524-475X.2012.00796.X.

Mizzi, A. *et al.* (2019) 'The progression rate of peripheral arterial disease in patients with intermittent claudication: A systematic review', *Journal of Foot and Ankle Research*, 12(1), pp. 1–9. doi: 10.1186/S13047-019-0351-0/TABLES/4.

Momsen, A. H. *et al.* (2009) 'Drug Therapy for Improving Walking Distance in Intermittent Claudication: A Systematic Review and Meta-analysis of Robust Randomised Controlled Studies', *Eur J Vasc Endovasc Surg*, 38, pp. 463–474. doi: 10.1016/j.ejvs.2009.06.002.

Moor Instruments (no date) *No Title*. Available at: https://www.moor.co.uk/products/monitoring/laser-doppler-monitor/.

Morgan, M. B. F. *et al.* (2001) 'Developing the Vascular Quality of Life Questionnaire: A new disease-specific quality of life measure for use in lower limb ischemia', *Journal of Vascular Surgery*, 33(4), pp. 679–687. doi: 10.1067/MVA.2001.112326.

Murabito, J. M. *et al.* (2002) 'Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study', *American Heart Journal*, 143(6), pp. 961–965. doi: 10.1067/mhj.2002.122871.

Naito, A., Honma, T. and Sekizawa, K. (2002) 'Quality of life in COPD patients', *Respiration and Circulation*, 50(3), pp. 241–245. doi: 10.1016/j.ejcdt.2012.08.012.

Ness, J., Aronow, W. S. and Ahn, C. (2000) 'Risk factors for symptomatic peripheral arterial disease in older persons in an academic hospital-based geriatrics practice', *Journal of the American Geriatrics Society*, 48(3), pp. 312–314. doi: 10.1111/J.1532-5415.2000.TB02652.X.

Newman, A. B. *et al.* (1993) 'Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group.', *Circulation*, 88(3), pp. 837–845. doi: 10.1161/01.CIR.88.3.837.

Newman, L. H. and Saltzman, B. (1991) 'Identifying risk factors in developmentof clinically significant post-shock-wave lithotripsy subcapsular hematomas', *Urology*, 38(1), pp. 35–38. doi: 10.1016/0090-4295(91)80009-V.

NICE (2011) 'Quality and Outcomes Framework Programme NICE cost impact statement Indicator

area: Peripheral arterial disease'.

NICE (2014) 'Overview | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE'.

NICE (2015) 'Type 2 diabetes in adults: management NICE guideline'. Available at: www.nice.org.uk/guidance/ng28 (Accessed: 22 October 2022).

NICE (2018) 'Clinical Guideline (CG147) Peripheral arterial disease: diagnosis and management', *NICE Guidelines*, (August 2012). Available at: https://www.nice.org.uk/guidance/cg147.

NICE (2019) 'Hypertension in adults: diagnosis and management NICE guideline'. Available at: www.nice.org.uk/guidance/ng136 (Accessed: 20 October 2022).

Nicolaï, S. P. A. *et al.* (2009) 'Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis', *Journal of vascular surgery*, 50(2), pp. 322–329. doi: 10.1016/J.JVS.2009.01.042.

Nishida, T. *et al.* (2004) 'Extracorporeal Cardiac Shock Wave Therapy Markedly Ameliorates Ischemia-Induced Myocardial Dysfunction in Pigs in Vivo', *Circulation*, 110(19), pp. 3055–3061. doi: 10.1161/01.CIR.0000148849.51177.97.

Nordanstig, J., Taft, C., *et al.* (2014) 'Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: One-year results of the invasive revascularization or not in intermittent claudication (IRONIC) trial', *Circulation*, 130(12), pp. 939–947. doi:

10.1161/CIRCULATIONAHA.114.009867.

Nordanstig, J., Broeren, M., *et al.* (2014) 'Six-minute walk test closely correlates to "real-life" outdoor walking capacity and quality of life in patients with intermittent claudication', *Journal of Vascular Surgery*, 60(2), pp. 404–409. doi: 10.1016/j.jvs.2014.03.003.

Norgren, L. *et al.* (2007) 'Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)', *Journal of Vascular Surgery*, 45(1), pp. S5–S67. doi: 10.1016/J.JVS.2006.12.037.

O'Banion, L. A. *et al.* (2023) 'Lack of patient-centered evaluation of outcomes in intermittent claudication literature', *Journal of Vascular Surgery*, 78(3), pp. 828–836. doi: 10.1016/j.jvs.2023.03.497.

Oi, K. *et al.* (2008) 'Extracorporeal Shock Wave Therapy Ameliorates Hindlimb Ischemia in Rabbits', *The Tohoku Journal of Experimental Medicine*, 214(2), pp. 151–158. doi: 10.1620/TJEM.214.151.

Pell, J. P. (1995) 'Impact of intermittent claudication on quality of life', *European Journal of Vascular and Endovascular Surgery*, 9(4), pp. 469–472. doi: 10.1016/S1078-5884(05)80018-8.

Petrofsky, J. *et al.* (2012) 'The effect of moist air on skin blood flow and temperature in subjects with and without diabetes', *Diabetes technology & therapeutics*, 14(2), pp. 105–116. doi: 10.1089/DIA.2011.0128.

Piepoli, M. F. *et al.* (2016) 'Guidelines: Editor's choice: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)', *European Heart Journal*, 37(29), p. 2315. doi: 10.1093/EURHEARTJ/EHW106.

Pober, J. S., Min, W. and Bradley, J. R. (2009) 'Mechanisms of Endothelial Dysfunction, Injury, and Death', *Annual Review of Pathology: Mechanisms of Disease*, 4(1), pp. 71–95. doi: 10.1146/annurev.pathol.4.110807.092155.

Quick, C. R. G. and Cotton, L. T. (2005) 'The measured effect of stopping smoking on intermittent claudication', *British Journal of Surgery*, 69(Supplement_6), pp. S24–S26. doi: 10.1002/BJS.1800691309.

Rajan, V. *et al.* (no date) 'Review of methodological developments in laser Doppler flowmetry'. doi: 10.1007/s10103-007-0524-0.

Ramacciotti, E. *et al.* (2022) 'Rivaroxaban with Aspirin Versus Aspirin for Peripheral Arterial Disease and Intermittent Claudication. Rationale and Design of the COMPASS CLAUDICATION Trial', *Clinical and Applied Thrombosis/Hemostasis*, 28. doi: 10.1177/10760296211073922.

Ramalho, J. *et al.* (2016) 'Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update', *AJNR: American Journal of Neuroradiology*, 37(7), p. 1192. doi: 10.3174/AJNR.A4615.

Ratchford, E. V. (2017) ‘Medical management of claudication’, *Journal of Vascular Surgery*, 66(1), pp. 275–280. doi: 10.1016/j.jvs.2017.02.040.

Raza, A. *et al.* (2017) ‘Extracorporeal Shockwave Therapy for Peripheral Arterial Disease: A Review of the Potential Mechanisms of Action’, *Annals of Vascular Surgery*. Elsevier Inc., pp. 294–298. doi: 10.1016/j.avsg.2017.06.133.

Regensteiner, J. G. *et al.* (2016) ‘Functional Benefits of Peripheral Vascular Bypass Surgery for Patients with Intermittent Claudication’, *http://dx.doi.org/10.1177/000331979304400101*, 44(1), pp. 1–10. doi: 10.1177/000331979304400101.

Ritti Dias, R. M. *et al.* (2009) ‘Obesity Decreases Time to Claudication and Delays Post-Exercise Hemodynamic Recovery in Elderly Peripheral Arterial Disease Patients’, *Gerontology*, 55(1), pp. 21–26. doi: 10.1159/000155219.

Ross, R. (1999) ‘Atherosclerosis - An inflammatory disease’, *New England Journal of Medicine*, pp. 115–126. doi: 10.1056/NEJM199901143400207.

Roth, G. A. *et al.* (2020) ‘Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study’, *Journal of the American College of Cardiology*, 76(25), pp. 2982–3021. doi: 10.1016/J.JACC.2020.11.010.

Saggini, R. *et al.* (2008) ‘Extracorporeal Shock Wave Therapy for Management of Chronic Ulcers in the Lower Extremities’, *Ultrasound in Medicine and Biology*, 34(8), pp. 1261–1271. doi: 10.1016/j.ultrasmedbio.2008.01.010.

Sajobi, T. T. *et al.* (2018) ‘Trajectories of health-related quality of life in coronary artery disease’, *Circulation: Cardiovascular Quality and Outcomes*, 11(3). doi: 10.1161/CIRCOUTCOMES.117.003661.

Samet, J. M. (1991) ‘Health Benefits of Smoking Cessation’, *Clinics in Chest Medicine*, 12(4), pp. 669–679. doi: 10.1016/S0272-5231(21)00816-9.

Samet, J. M. (1992) ‘The health benefits of smoking cessation.’, *The Medical Clinics of North America*, 76(2), pp. 399–414. doi: 10.1016/S0025-7125(16)30359-5.

Sampson, U. K. A. *et al.* (2014) ‘Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010’, *Global Heart*. Elsevier B.V., pp. 145-158.e21. doi: 10.1016/j.gheart.2013.12.008.

Sata, M. (2006) ‘Role of circulating vascular progenitors in angiogenesis, vascular healing, and pulmonary hypertension: Lessons from animal models’, *Arteriosclerosis, Thrombosis, and Vascular Biology*, pp. 1008–1014. doi: 10.1161/01.ATV.0000206123.94140.f3.

Schaden, W. *et al.* (2007) ‘Shock Wave Therapy for Acute and Chronic Soft Tissue Wounds: A Feasibility Study’, *Journal of Surgical Research*, 143(1), pp. 1–12. doi: 10.1016/j.jss.2007.01.009.

Schmit, K. *et al.* (2014) ‘Comparative Effectiveness Review of Antiplatelet Agents in Peripheral Artery Disease’, *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, 3(6), p. 1330. doi: 10.1161/JAHA.113.001330.

Schnabel, M. J. *et al.* (2014) 'Antiplatelet and Anticoagulative Medication During Shockwave Lithotripsy', *https://home.liebertpub.com/end*, 28(9), pp. 1034–1039. doi: 10.1089/END.2014.0162.

Scott, I. C. A. and Kester, R. C. (1998) 'EDITORIAL An Introduction to Quality of Life Analysis: The New Outcome Measure in Vascular Surgery', *Eur J Vasc Endovasc Surg*, 15, pp. 4–6.

Serizawa, F. *et al.* (2012) 'Extracorporeal Shock Wave Therapy Improves the Walking Ability of Patients With Peripheral Artery Disease and Intermittent Claudication', *Circulation Journal*, 76(6), pp. 1486–1493. doi: 10.1253/CIRCJ.CJ-11-1216.

Siracuse, J. J. *et al.* (2012a) 'Long-term Results for Primary Bypass vs. Primary Angioplasty/Stent for Intermittent Claudication Due to Superficial Femoral Artery Occlusive Disease', *Journal of Vascular Surgery*, 55(4), p. 1001. doi: 10.1016/J.JVS.2011.10.128.

Siracuse, J. J. *et al.* (2012b) 'Long-term Results for Primary Bypass vs. Primary Angioplasty/Stent for Intermittent Claudication Due to Superficial Femoral Artery Occlusive Disease', *Journal of Vascular Surgery*, 55(4), p. 1001. doi: 10.1016/J.JVS.2011.10.128.

Song, P. *et al.* (2019) 'Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis', *The Lancet Global Health*, 7(8), pp. e1020–e1030. doi: 10.1016/S2214-109X(19)30255-4.

Steffel, J. *et al.* (2020) 'The COMPASS Trial: Net Clinical Benefit of Low-Dose Rivaroxaban plus Aspirin as Compared with Aspirin in Patients with Chronic Vascular Disease', *Circulation*, pp. 40–48. doi: 10.1161/CIRCULATIONAHA.120.046048.

Stoner, M. C. *et al.* (2016) 'Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease', *Journal of Vascular Surgery*, 64(1), pp. e1–e21. doi: 10.1016/j.jvs.2016.03.420.

Tara, S. *et al.* (2014) 'Low-energy Extracorporeal Shock Wave Therapy Improves Microcirculation Blood Flow of Ischemic Limbs in Patients with Peripheral Arterial Disease: Pilot Study', *Journal of Nippon Medical School*, 81(1), pp. 19–27. doi: 10.1272/JNMS.81.19.

Tarride, J. E. *et al.* (2009) 'A review of the cost of cardiovascular disease', *Canadian Journal of Cardiology*, 25(6), pp. e195–e202. doi: 10.1016/S0828-282X(09)70098-4.

Tepeköylü, C. *et al.* (2013) 'Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: Implications for angiogenesis and vasculogenesis', *Journal of Thoracic and Cardiovascular Surgery*, 146(4), pp. 971–978. doi: 10.1016/j.jtcvs.2013.01.017.

Tew, G. A. *et al.* (2020) 'Infographic. Exercise for intermittent claudication', *British Journal of Sports Medicine*, 54(23), pp. 1443–1444. doi: 10.1136/BJSPORTS-2019-101930.

Thiel, M. (2001) 'Application of Shock Waves in Medicine', *Clinical Orthopaedics and Related Research*, 387, pp. 18–21.

Trikkalinou, A., Papazafiropoulou, A. K. and Melidonis, A. (2017) 'Type 2 diabetes and quality of life', *World Journal of Diabetes*, 8(4), p. 120. doi: 10.4239/wjd.v8.i4.120.

Tsai, J. C. *et al.* (2002) 'The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease', *Journal of Internal Medicine*, 252(5), pp. 448–455. doi: 10.1046/J.1365-2796.2002.01055.X.

Vaidya, A. *et al.* (2018) 'Comparison of EQ-5D and SF-36 in untreated patients with symptoms of intermittent claudication', *https://doi.org/10.2217/cer-2017-0029*, 7(6), pp. 535–548. doi: 10.2217/CER-2017-0029.

Vongsavan, N. and Matthews, B. (1993) 'Some aspects of the use of laser Doppler flow meters for recording tissue blood flow', *Experimental physiology*, 78(1), pp. 1–14. doi: 10.1113/EXPPHYSIOL.1993.SP003664.

De Vries, M. *et al.* (2005) 'Comparison of generic and disease-specific questionnaires for the assessment of quality of life in patients with peripheral arterial disease', *Journal of Vascular Surgery*, 41(2), pp. 261–268. doi: 10.1016/j.jvs.2004.11.022.

Wang, C. J. (2012) 'Extracorporeal shockwave therapy in musculoskeletal disorders', *Journal of Orthopaedic Surgery and Research*, 7(1), p. 11. doi: 10.1186/1749-799X-7-11.

Ware, J. E. *et al.* (1993) 'SF-36 Health Survey Manual and Interpretation Guide', *Boston New England Medical Centre*. Available at: http://www.mendeley.com/catalog/sf-36-health-survey-manual-interpretation-guide/ (Accessed: 23 September 2013).

Watanabe, T. *et al.* (2004) 'Near-Infrared Spectroscopy with Treadmill Exercise to Assess Lower Limb Ischemia in Patients with Atherosclerotic Occlusive Disease', *Surgery Today 2004 34:10*,

34(10), pp. 849–854. doi: 10.1007/S00595-004-2833-2.

Wawruch, M. *et al.* (2019) 'Patient-Associated Characteristics Influencing the Risk for Non-Persistence with Statins in Older Patients with Peripheral Arterial Disease', *Drugs & Aging 2019 36:9*, 36(9), pp. 863–873. doi: 10.1007/S40266-019-00689-2.

Wawruch, M. *et al.* (2021) 'Non-Persistence With Antiplatelet Medications Among Older Patients With Peripheral Arterial Disease', *Frontiers in Pharmacology*, 12, p. 687549. doi: 10.3389/FPHAR.2021.687549/FULL.

WHO (2013) 'Global action plan for the prevention and control of noncommunicable diseases 2013-2020.', *World Health Organization*, p. 102. doi: 978 92 4 1506236.

WHO (no date) *WHOQOL - Measuring Quality of Life| The World Health Organization*. Available at: https://www.who.int/tools/whoqol (Accessed: 23 October 2022).

Wightman, J. M. and Gladish, S. L. (2001) 'Explosions and blast injuries', *Annals of Emergency Medicine*, 37(6), pp. 664–678. doi: 10.1067/mem.2001.114906.

Wikipedia (2006) *File:Endothelial dysfunction Atherosclerosis.png - Wikimedia Commons*. Available at: https://commons.wikimedia.org/wiki/File:Endothelial_dysfunction_Atherosclerosis.png (Accessed: 31 October 2022).

Wikipedia (2013a) *File:2129ab Lower Limb Arteries Anterior Posterior.jpg - Wikimedia Commons*. Available at:

https://commons.wikimedia.org/wiki/File:2129ab_Lower_Limb_Arteries_Anterior_Posterior.jpg (Accessed: 31 October 2022).

Wikipedia (2013b) *File:Artery.svg - Wikimedia Commons*. Available at: https://commons.wikimedia.org/w/index.php?curid=25179416 (Accessed: 31 October 2022).

Winsor, T. *et al.* (1989) 'Influence of local and environmental temperatures on cutaneous circulation with use of laser Doppler flowmetry', *Angiology*, 40(5), pp. 421–428. doi: 10.1177/000331978904000501.

Wong, P. F. *et al.* (2011) 'Antiplatelet agents for intermittent claudication', *Cochrane Database of Systematic Reviews*, (11). doi: 10.1002/14651858.CD001272.PUB2/MEDIA/CDSR/CD001272/IMAGE_N/NCD001272-CMP-002-13.PNG.

El Yamany, M., Mohamed, H. and Kamel, M. (2020) 'Outcome after angioplasty versus bypass surgery in patients with superficial femoral artery lesions', *The Egyptian Journal of Surgery*, 39(1), p. 138. doi: 10.4103/EJS.EJS_147_19.

Yoder, M. C. (2012) 'Human Endothelial Progenitor Cells', *Cold Spring Harbor Perspectives in Medicine*, 2(7). doi: 10.1101/CSHPERSPECT.A006692.

# Appendices

## Appendix 1 – Prizes arising from this work

1. Short paper of Distinction – ASGBI Virtual Conference 2021
2. Short listed for BJS Prize Presentation – Vascular Society of Great Britain and Ireland Annual Scientific Meeting 2020

## Appendix 2 – Presentations to learned societies arising from this work

"A double-blind, placebo-controlled, randomised trial of extracorporeal shockwave therapy as a novel treatment for intermittent claudication."

Oral presentation at:

1. Vascular Society of Great Britain and Ireland Annual Scientific Meeting 2020
2. Charing Cross International Symposium 2021
3. Association of Surgeons of Great Britain and Ireland Virtual Conference 2021
4. Surgical Research Society Annual Meeting 2022
5. European Society of Vascular Surgery Annual Meeting 2022

## Appendix 3 – Quality of life measures Table

| | Intervention Group | Control Group | p value |
|---|---|---|---|
| **Baseline** | | | |
| SF-36 PF | 36.5 (30.8 – 44.2) | 33.0 (26.9 – 38.9) | 0.047 |
| SF-36 RP | 39.1 (31.3 – 48.2) | 37.0 (30.2 – 43.1) | 0.183 |
| SF-36 BP | 38.2 (30.6 – 43.5) | 38.2 (30.6 – 42.2) | 0.320 |
| SF-36 GH | 43.2 (35.2 – 50.8) | 38.4 (30.8 – 47.5) | 0.067 |
| SF-36 VT | 46.7 (40.7 – 49.6) | 43.7 (32.5 – 49.6) | 0.164 |
| SF-36 SF | 42.3 (32.3 – 53.6) | 42.3 (32.3 – 47.3) | 0.063 |
| SF-36 RE | 45.7 (31.8 – 56.2) | 42.2 (28.3 – 56.2) | 0.335 |
| SF-36 MH | 50.9 (42.4 – 58.7) | 45.6 (37.8 – 56.1) | 0.114 |
| SF-36 PCS | 36.1 (31.3 – 41.7) | 34.0 (27.6 – 39.8) | 0.086 |
| SF-36 MCS | 49.5 (43.1 – 58.3) | 45.6 (35.4 – 56.4) | 0.156 |
| EQ-5D VAS | 0.66 (0.53 – 0.68) | 0.65 (0.38 – 0.66) | 0.149 |
| VascuQol | 4.4 (3.33 – 5.5) | 4.2 (3.2 – 4.8) | 0.134 |
| **4-week follow up** | | | |
| SF-36 PF | 39.4 (32.6 – 44.6) | 36.5 (28.8 – 44.2) | 0.106 |
| SF-36 RP | 40.3 (34.7 – 52.7) | 39.2 (32.5 – 48.2) | 0.114 |
| SF-36 BP | 42.2 (37.3 – 51.5) | 38.2 (34.2 – 46.3) | 0.186 |
| SF-36 GH | 43.7 (38.7 – 53.2) | 38.0 (33.2 – 46.1) | **0.004** |
| SF-36 VT | 49.6 (45.9 – 55.6) | 46.7 (34.8 -55.6) | **0.034** |
| SF-36 SF | 47.3 (37.3 – 57.3) | 42.3 (37.3 – 52.3) | 0.369 |
| SF-36 RE | 49.2 (35.3 – 56.2) | 42.2 (31.8 – 56.2) | 0.256 |
| SF-36 MH | 56.1 (42.4 – 58.7) | 50.9 (40.4 – 58.7) | 0.192 |

| | | | |
|---|---|---|---|
| SF-36 PCS | 39.7 (33.9 – 44.5) | 35.9 (31.0 – 40.2) | **0.018** |
| SF-36 MCS | 53.5 (43.5 – 60.0) | 49.3 (40.6 – 59.3) | 0.271 |
| EQ-5D VAS | 0.66 (0.60 – 0.69) | 0.66 (0.36 – 0.69) | **0.034** |
| VascuQol | 5.3 (4.2 – 5.9) | 4.8 (3.9 – 5.6) | 0.142 |
| **8-week follow up** | | | |
| SF-36 PF | 42.2 (31.2 – 46.1) | 36.5 (30.3 – 42.7) | 0.079 |
| SF-36 RP | 39.2 (32.5 – 52.1) | 39.2 (30.2 – 43.7) | 0.135 |
| SF-36 BP | 42.2 (34.2 – 49.9) | 38.2 (34.2 – 46.3) | 0.173 |
| SF-36 GH | 43.7 (36.2 – 50.8) | 40.4 (33.2 – 48.4) | 0.142 |
| SF-36 VT | 49.6 (38.5 – 55.6) | 43.7 (37.7 – 49.6) | 0.088 |
| SF-36 SF | 47.3 (37.3 – 57.3) | 42.3 (37.3 – 52.3) | 0.166 |
| SF-36 RE | 45.7 (31.8 – 56.2) | 42.2 (35.3 – 56.2) | 0.658 |
| SF-36 MH | 53.5 (43.0 – 58.7) | 48.3 (37.8 – 58.7) | 0.366 |
| SF-36 PCS | 41.2 (35.9 – 46.0) | 35.9 (30.7 – 40.9) | 0.327 |
| SF-36 MCS | 52.6 (39.9 – 59.0) | 47.2 (39.7 – 57.5) | 0.531 |
| EQ-5D VAS | 0.66 (0.60 – 0.69) | 0.66 (0.50 – 0.66) | 0.102 |
| VascuQol | 5.2 (3.8 – 5.8) | 4.6 (3.8 – 5.3) | 0.084 |
| **12-week follow up** | | | |
| SF-36 PF | 41.3 (31.2 – 46.1) | 34.6 (28.8 – 42.7) | **0.033** |
| SF-36 RP | 41.4 (32.5 – 48.2) | 39.2 (32.5 – 48.2) | 0.384 |
| SF-36 BP | 40.2 (34.2 – 46.7) | 38.2 (30.6 – 46.7) | 0.484 |
| SF-36 GH | 44.4 (35.6 – 50.8) | 38.0 (33.2 – 46.1) | 0.059 |
| SF-36 VT | 49.6 (40.0 – 55.6) | 43.7 (37.7 – 52.6) | 0.202 |
| SF-36 SF | 47.3 (32.3 – 57.3) | 42.3 (37.3 – 47.3) | 0.306 |

| | | | |
|---|---|---|---|
| SF-36 RE | 45.7 (35.3 – 56.2) | 42.2 (28.3 – 56.2) | 0.424 |
| SF-36 MH | 52.2 (40.4 – 58.7) | 48.3 (40.4 – 56.1) | 0.282 |
| SF-36 PCS | 40.8 (33.5 – 45.4) | 36.6 (31.4 – 43.7) | 0.123 |
| SF-36 MCS | 48.7 (39.4 – 58.6) | 46.4 (37.7 – 57.4) | 0.465 |
| EQ-5D VAS | 0.66 (0.59 – 0.69) | 0.66 (0.50 – 0.67) | 0.671 |
| VascuQol | 4.9 (3.9 – 5.9) | 4.9 (3.6 – 5.5) | 0.478 |

Key:

PF – Physical Function

RP – Role Physical

BP – Bodily Pain

GH – General Health

VT – Vitality

SF – Social Functioning

RE – Role Emotional

MH – Mental Health

PCS – Physical Component Summary

MCS – Mental Component Summary

**Appendix 4 – Patient Information Leaflet**

# Extracorporeal shockwave therapy in lower limb intermittent claudication

## A randomised clinical trial to assess the effectiveness of extracorporeal shockwave therapy for lower limb intermittent claudication

## Patient information sheet

**Part 1**

### Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Feel free to talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen next if you decide to take part.

- Part 2 gives you more detailed information about the conduct of the study.

### You are being asked to take part in this study because:

You have been referred to the Vascular Department with pain in your calf muscles due to poor circulation known as intermittent claudication. Intermittent claudication can be painful and affect your quality of life. As a result new treatments are being investigated to see if we can improve your symptoms and improve your quality of life.

## What is the purpose of the study?

Your consultant believes you may be a suitable participant for a research study being carried out at Hull Royal Infirmary. The study is being carried out by a Research Fellow attached to the Department of Vascular Surgery, undertaking a research degree at Hull University.

You have been invited to take part in a clinical trial to see if using a device called the Piezowave 2 can improve the blood supply to your calf and to see if this improves your walking ability and improve your quality of life. The device is widely used for a variety of indications such as chronic painful muscular tensions, Plantarfasciitis and Tennis elbow. This is a trial of that same device 'off license' in order to assess the effects when used for a different reason, that being pain caused by reduced blood flow to the muscles.

Some patients, chosen at random, will receive a "sham treatment" which uses the same equipment but with the power turned off. This allows us to determine whether the effect of the treatment is psychological as well as physical. You will not be able to tell which treatment you have received.

To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss the study or ask any questions.

## Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to participate you will be given this information sheet to keep and be asked to sign a Consent form. You are still free to withdraw at any time and without giving a reason. Your non-participation or dropping out of the study will not affect your planned treatment and care in any way.

## Before you can begin the study

You may read the full study protocol as well as this Patient Information Sheet, which gives you many details about the study. The recruiting Investigator will tell you about any potential adverse events that could occur in this study. You will be told exactly what the study entails and what will be required of you. You are encouraged to ask questions of the Investigators conducting the recruitment interview until you are satisfied that you fully understand the nature of the study and the requirements.

## What happens in the study?

If you think you might be interested in taking part in the study, you will have a short interview with one of the Researchers so we can collect some details from you and make sure you are eligible to join in the trial.

Once you are enrolled in the trial we will ask you to complete short questionnaires and we will perform a physical examination, which will include an assessment of your walking.

The study and tests will take place in a clinical room at Hull Royal Infirmary. A maximum of 9 treatments will be given (three times per week for 3 weeks). Each treatment with the device lasts only a matter of minutes.

When you attend for the therapy with the device;

- You will be asked to fill in some short questionnaires before and after the treatment.
- You will have your blood pressure and heart rate measured before the treatment.
- During the treatment, there will be video recording of the blood flow in your leg. It will be done using a non-contact device which uses laser technology to assess any change in blood flow during the treatment.

Walking assessments and follow up appointments;

- Before the first treatment begins you will be asked to walk on a treadmill for several minutes. You will be asked to tell the person supervising you when you experience any pain. If you cannot tolerate walking any further we will stop machine and you will be able to sit down.
- There will be a walking assessment on the treadmill at the week 4, 8 and 12 week follow up appointments. This means a total of 4 times on the treadmill which will allow us to see if your walking has improved.

Leg blood flow assessments;

- Laser Doppler scan looks at skin blood flow using a small probe which is attached to your foot. Scan is safe and painless. Scan will be used to look at the blood flow in your leg before the first treatment and the follow up appointments at 4, 8, and 12 weeks.
- 10ml of blood (one tablespoon) will be taken from a vein in the groin of each leg (at the top of the leg in the crease). This is to look for markers in the blood which can encourage the growth of new blood vessels. Blood will be taken on your first visit (baseline assessment), after the first treatment, after the sixth treatment and on the first follow up (Week 4).

**What will happen to the samples I provide?**

After the blood samples are taken from the leg, they will be frozen and initially stored in a freezer in the pathology department of the Hull Royal Infirmary.

The blood samples will then be transferred to the laboratories at the Hull York Medical School (University of Hull) where they will also be stored in a secured freezer. The samples will then undergo a variety of tests to understand the mechanisms of action of shockwave therapy. The blood samples will be disposed under the Human Tissue Authority after the tests.

**Are there any risks to participating in the study?**

Taking part in the trial will not otherwise alter any treatment which your doctor has advised. The device has been used for many years for various other reasons and is deemed safe although potential risks could include pain, itching, redness of skin, bruising or bleeding. Due to the potential bruising or bleeding risk, those with a blood clotting disorder will not be included in the trial.

**What are the possible benefits of taking part?**

This study may improve your walking ability and you may experience some pain relief. As a consequence you may notice an improvement in your quality of life.

**Could I come to any harm if I take part in the study?**

All of the previous work using the system was found to be safe. If you feel unacceptable levels of discomfort during the study or you simply do not wish to continue, then we will stop the tests immediately.

You may be withdrawn from the study if the doctors feel it is best for you or if you do not comply with the requirements of the study.

If during the health screening tests any abnormal results are found, you will be immediately referred for clinical review as appropriate.

There are very few risks involved in using this type of equipment and the device is already used for a number of other problems such as joint pains.

**What happens when the research study stops?**

When the study is complete, you will continue to be followed up by the vascular team as planned. Continued treatment with the shockwave device cannot be guaranteed following the conclusion of the trial.

**What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

If you have a complaint, please contact Dr Paris Limin Cai in the first instance. If you feel any significant discomfort or distress during the investigations, you must say so and we will stop the tests immediately at any time. A contact number for complaints will be given.

**Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

**Contact Details:**

If you require any further information please contact:

Research team contact;

Dr Paris Limin Cai,

Clinical Research Fellow,

Academic Vascular Surgery Unit,

Vascular Laboratory,

First Floor Tower Block, Hull Royal Infirmary,

Hull.

HU3 2JZ

Tel: 01482 674643

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

## Part 2

### What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

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

If you withdraw from the study you will continue to receive your normal NHS care and we may use the data collected up to your withdrawal.

### What if there is a problem?

If you have a concern about any aspect of this trial, you should first ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain, you can do this via the NHS Complaints Procedure. Details can be obtained from;

**Ms Janet Austin, Head of Complaints Department, Hull Royal Infirmary.**

**Tel: 01482 605284**

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Hull and East Yorkshire Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. In the highly unlikely event that you suffer from injury or illness as a result of participation in this study, indemnity will be provided by the Hull and East Yorkshire hospitals NHS Trust. Compensation will be by the usual NHS procedures.

**Will my taking part in this study be kept confidential?**

All the information obtained about you in the course of the study is confidential and will be stored on secure servers in the vascular laboratory within Hull Royal Infirmary. The investigators performing the study and a study Monitor will have access to the data collected in this study. They may also be looked at by representatives of regulatory authorities and by authorised people from Hull Royal Infirmary to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

**What will happen to the results of the research study?**

The results of this study may be published or presented at meetings. You will not be identified in any report / publication or presentation. We would be happy to supply you with a copy of the results on request.

**Who is organising and funding the study?**

This study is organised and funded through the Academic Vascular Surgery Unit, Hull Royal Infirmary.

**Who has reviewed this study?**

The ethics behind this study have been reviewed and supported by the National Research Ethics Service Committee. (NRES Committee East of England - Cambridge East)

## Further information/independent advice

Independent advice regarding this study or any other aspect of your care can be obtained from the Patients Advisory Liaison Service (PALS) using the details below;

**PALS Office, Main Reception, Hull Royal Infirmary, Anlaby Road, HULL, HU3 2JZ**

**Tel. 01482 623065**

**Fax: 01482 622252**

Email: pals@hey.nhs.uk

## What happens next?

Please discuss this information with your family, friends or GP if you wish. Any questions can be answered then or please do not hesitate to contact the research team on the number below. Thank you very much for taking the time to read this information sheet and considering taking part in our research.

Academic Vascular Surgery Unit,

Vascular Laboratory,

Hull Royal Infirmary,

Hull. HU3 2JZ

Tel: 01482 674643

## Appendix 5 – Consent Form

**Consent to participate in:**

**A randomised clinical trial to assess the effectiveness of extracorporeal shockwave therapy for lower limb intermittent claudication**

**Short title; Extracorporeal shockwave therapy in lower limb intermittent Claudication**

Please affix
Pt. Details sticker

| | Participants Initials |
|---|---|
| I confirm that I have been given adequate time to read and understand all of the patient information relating to the trial (Patient information sheet). I have had the opportunity to ask any questions and have understood the responses. | |
| I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records | |
| I understand that participation in the trial is entirely voluntary and that I have the right to withdraw at any time without giving my reasons. | |
| I consent to my general practitioner being informed of my participation in the trial. | |
| I agree to take part in the study | |
| I consent to have details stored in the trial database and understand that my details will not be available to anyone other than the research staff or database administrator. | |
| I consent to my details being kept in the database and being updated further after the trial ends to help with future research and studies subject to approval by a research ethics Committee. | |
| I would be happy to be contacted in the future about follow up at 12 months and at the 5 year period. | |
| I consent to have video recording of leg blood flow during the treatments. | |
| I consent to giving blood samples during the trial for use in evaluating the mechanism of actions of shockwaves therapy. | |
| I understand that the results of the study may be presented at medical conferences and published in medical literature in an anonymous form. No identifiable details will be released to anyone outside of the research team without my permission. | |

Participant: Name_____ date__/__/__ Signature _____

Researcher: Name_____ date__/__/__ Signature_____

# Appendix 6 – EQ-5D-3L

## Extracorporeal shockwave therapy in lower limb intermittent claudication

**A randomised clinical trial to assess the effectiveness of extracorporeal shockwave therapy for lower limb intermittent claudication**

Appendix 7: EQ5D

**Sponsor:**

James Illingworth,

Hull and East Yorkshire Hospitals NHS Trust, R&D Department, Office 13, 2nd Floor Daisy Building, Castle Hill Hospital, Castle Rd, Cottingham, East Yorkshire HU16 5JQ.


**Funder:**

Academic Department of Vascular Surgery, Hull Royal Infirmary

Study ID Number __ __ __ __ __ __

# Quality of Life: EQ5D

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Completed at: Baseline ☐

4 weeks ☐ 8 weeks ☐ 12 weeks ☐

**Mobility**

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

**Self-Care**

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

**Usual Activities** (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

**Pain/Discomfort**

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

**Anxiety/Depression**

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

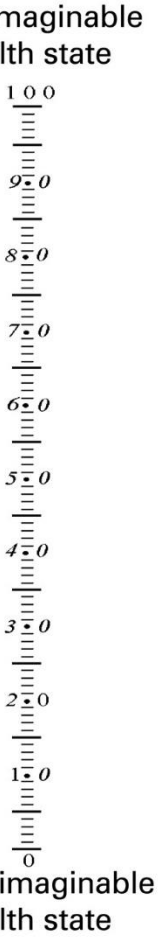
Visual Analogue Scale

Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box to the point on the scale that indicates how good or bad your health state is today.

Your own health state today



## Appendix 7 – SF-36

# Extracorporeal shockwave therapy in lower limb intermittent claudication

### A randomised clinical trial to assess the effectiveness of extracorporeal shockwave therapy for lower limb intermittent claudication

Appendix 8: SF-36 Questionnaire

**Sponsor:**

James Illingworth,

Hull and East Yorkshire Hospitals NHS Trust, R&D Department, Office 13, 2nd Floor Daisy Building, Castle Hill Hospital, Castle Rd, Cottingham, East Yorkshire HU16 5JQ.


**Funder:**

Academic Department of Vascular Surgery, Hull Royal Infirmary

Study ID Number __ __ __ __ __ __

# Your Health and Well-Being

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

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Completed at: Baseline ☐

4 weeks ☐ 8 weeks ☐ 12 weeks ☐

**For each of the following questions, please tick the one box that best describes your answer.**

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

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ▼ | ▼ | ▼ | ▼ | ▼ |
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

| Much better now than one year ago | Somewhat better now than one year ago | About the same as one year ago | Somewhat worse now than one year ago | Much worse now than one year ago |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports | ☐ 1 | ☐ 2 | ☐ 3 |
| b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐ 1 | ☐ 2 | ☐ 3 |
| c Lifting or carrying groceries | ☐ 1 | ☐ 2 | ☐ 3 |
| d Climbing <u>several</u> flights of stairs | ☐ 1 | ☐ 2 | ☐ 3 |
| e Climbing <u>one</u> flight of stairs | ☐ 1 | ☐ 2 | ☐ 3 |
| f Bending, kneeling, or stooping | ☐ 1 | ☐ 2 | ☐ 3 |
| g Walking <u>more than a mile</u> | ☐ 1 | ☐ 2 | ☐ 3 |
| h Walking <u>several hundred yards</u> | ☐ 1 | ☐ 2 | ☐ 3 |
| i Walking <u>one hundred yards</u> | ☐ 1 | ☐ 2 | ☐ 3 |
| j Bathing or dressing yourself | ☐ 1 | ☐ 2 | ☐ 3 |

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

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Cut down on the amount of time you spent on work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b Accomplished less than you would like | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c Were limited in the kind of work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d Had difficulty performing the work or other activities (for example, it took extra effort) | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

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

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Cut down on the amount of time you spent on work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b Accomplished less than you would like | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c Did work or other activities less carefully than usual | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**

| Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

| None | Very mild | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 |

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

| Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

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

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Did you feel full of life? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b Have you been very nervous? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c Have you felt so down in the dumps that nothing could cheer you up? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d Have you felt calm and peaceful? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| e Did you have a lot of energy? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| f Have you felt downhearted and low? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| g Did you feel worn out? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| h Have you been happy? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| i Did you feel tired? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

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

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**11. How TRUE or FALSE is <u>each</u> of the following statements for you?**

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a | I seem to get ill more easily than other people | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b | I am as healthy as anybody I know | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c | I expect my health to get worse | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d | My health is excellent | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

***Thank you for completing these questions!***

## Appendix 8 – VascuQul

# Extracorporeal shockwave therapy in lower limb intermittent claudication

### A randomised clinical trial to assess the effectiveness of extracorporeal shockwave therapy for lower limb intermittent claudication

Appendix 4: VascuQol Questionnaire

**Sponsor:**

James Illingworth,

Hull and East Yorkshire Hospitals NHS Trust, R&D Department, Office 13, 2nd Floor Daisy Building, Castle Hill Hospital, Castle Rd, Cottingham, East Yorkshire HU16 5JQ.


**Funder:**

Academic Department of Vascular Surgery, Hull Royal Infirmary

Study ID Number __ __ __ __ __ __

VascuQol Questionnaire

**(To be completed by the patient at follow-up. Please complete text in BLOCK CAPITALS, tick the appropriate box.)**

Date of Completion: ☐☐/☐☐/☐☐ (dd/mm/yy)

Completed at: Baseline ☐

4 weeks ☐ 8 weeks ☐ 12 weeks ☐

**Instructions**: These questions ask you how you have been affected by poor circulation to your legs over the last two weeks.

You will be asked about the symptoms you have had, the way that your activities have been affected and how you have been feeling.

Please read each bit of the answer and then tick the one that applies best to you.

If you are unsure about how to answer a question, please give the best answer you can.

There is no right or wrong answer.

**Please answer every question. Thank you.**

**1**. In the last two weeks **I have had pain in the leg (or foot) when walking** ……

*(tick one)*

| | |
|---|---|
| 1. All of the time | ☐ 1 |
| 2. Most of the time | ☐ 2 |
| 3. A good bit of the time | ☐ 3 |
| 4. Some of the time | ☐ 4 |
| 5. A little of the time | ☐ 5 |
| 6. Hardly any of the time | ☐ 6 |
| 7. None of the time | ☐ 7 |

**2**. In the last two weeks **I have been worried that I might injure my leg** ……

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

3. In the last two weeks **cold feet have given me** …….

*(tick one)*

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3
4. A moderate amount of discomfort or distress ☐ 4
5. Some discomfort or distress ☐ 5
6. Very little discomfort or distress ☐ 6
7. No discomfort or distress ☐ 7

4. In the last two weeks, because of the poor circulation to my legs, **my ability to take exercise or to play any sports has been** …..

*(tick one)*

1. Totally limited, couldn't exercise at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

5. In the last two weeks **my legs have felt tired or weak** …..

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

6. In the last two weeks, because of the poor circulation to my legs, **I have been restricted in spending time with my friends or relatives** …..

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

7. In the last two weeks **I have had pain in the foot (or leg) after going to bed at night** …..

*(tick one)*

| | |
|---|---|
| 1. All of the time | ☐ 1 |
| 2. Most of the time | ☐ 2 |
| 3. A good bit of the time | ☐ 3 |
| 4. Some of the time | ☐ 4 |
| 5. A little of the time | ☐ 5 |
| 6. Hardly any of the time | ☐ 6 |
| 7. None of the time | ☐ 7 |

8. In the last two weeks **pins and needles or numbness in my leg (or foot)** have caused me ….

*(tick one)*

| | |
|---|---|
| 1. A very great deal of discomfort or distress | ☐ 1 |
| 2. A great deal of discomfort or distress | ☐ 2 |
| 3. A good deal of discomfort or distress | ☐ 3 |
| 4. A moderate amount of discomfort or distress | ☐ 4 |
| 5. Some discomfort or distress | ☐ 5 |
| 6. Very little discomfort or distress | ☐ 6 |
| 7. No discomfort or distress | ☐ 7 |

9. In the last two weeks **the distance I can <u>walk has improved</u>** …..

*(tick one)*

| | |
|---|---|
| 1. Not at all (tick this if distance is unchanged or has decreased) | ☐ 1 |
| 2. A little | ☐ 2 |
| 3. Somewhat | ☐ 3 |
| 4. Moderately | ☐ 4 |
| 5. A good deal | ☐ 5 |
| 6. A great deal | ☐ 6 |
| 7. A very great deal | ☐ 7 |

10. In the last two weeks, because of the poor circulation to my legs, **my ability to walk has been**

*(tick one)*

| | |
|---|---|
| 1. Totally limited, couldn't walk at all | ☐ 1 |
| 2. Extremely limited | ☐ 2 |
| 3. Very limited | ☐ 3 |
| 4. Moderately limited | ☐ 4 |
| 5. A little limited | ☐ 5 |
| 6. Only very slightly limited | ☐ 6 |
| 7. Not at all limited | ☐ 7 |

11. In the last two weeks **being (or becoming) housebound has been a concern of mine** …..

*(tick one)*

1. A very great deal ☐ 1
2. A great deal ☐ 2
3. A good deal ☐ 3
4. Moderately ☐ 4
5. Somewhat ☐ 5
6. A little ☐ 6
7. Not at all ☐ 7

12. In the last two weeks **I have been concerned about having poor circulation to my legs** …..

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

13. In the last two weeks **I have had pain in the foot (or leg) when I am at rest** …..

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

14. In the last two weeks, because of the poor circulation to my legs**, my ability to climb stairs has been** …..

*(tick one)*

1. Totally limited, couldn't climb stairs at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

15. In the last two weeks, because of the poor circulation to my legs**, my ability to take part in social activities has been** …..

*(tick one)*

1. Totally limited, couldn't socialise at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

16. In the last two weeks, because of the poor circulation to my legs**, my ability to perform routine household work has been** …..

*(tick one)*

1. Totally limited, couldn't perform housework at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

17. In the last two weeks **ulcers in the leg (or foot) have given me pain or distress** …..

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time (tick this if you do not have leg ulcers) ☐ 7

18. Because of poor circulation to my legs, **the overall range of activities that I would have liked to do in the last two weeks has been** …..

*(tick one)*

1. Severely limited – most activities not done ☐ 1
2. Very limited ☐ 2
3. Moderately limited – several activities not done ☐ 3
4. Slightly limited ☐ 4
5. Very slightly limited – very few activities not done ☐ 5
6. Hardly limited at all ☐ 6
7. Not limited at all – have done all the activities that I wanted to ☐ 7

19. In the last two weeks **the poor circulation to the legs have made me feel frustrated** …..

*(tick one)*

| | |
|---|---|
| 1. All of the time | ☐ 1 |
| 2. Most of the time | ☐ 2 |
| 3. A good bit of the time | ☐ 3 |
| 4. Some of the time | ☐ 4 |
| 5. A little of the time | ☐ 5 |
| 6. Hardly any of the time | ☐ 6 |
| 7. None of the time | ☐ 7 |

20. In the last two weeks **when I do get pain in my leg (or foot) it has given me** ….

*(tick one)*

| | |
|---|---|
| 1. A very great deal of discomfort or distress | ☐ 1 |
| 2. A great deal of discomfort or distress | ☐ 2 |
| 3. A good deal of discomfort or distress | ☐ 3 |
| 4. A moderate amount of discomfort or distress | ☐ 4 |
| 5. Some discomfort or distress | ☐ 5 |
| 6. Very little discomfort or distress | ☐ 6 |
| 7. No discomfort or distress | ☐ 7 |

21. In the last two weeks **I have felt guilty about relying on friends or relatives** …..

*(tick one)*

| | |
|---|---|
| 1. All of the time | ☐ 1 |
| 2. Most of the time | ☐ 2 |
| 3. A good bit of the time | ☐ 3 |
| 4. Some of the time | ☐ 4 |
| 5. A little of the time | ☐ 5 |
| 6. Hardly any of the time | ☐ 6 |
| 7. None of the time | ☐ 7 |

22. In the last two weeks, because of the poor circulation to my legs**, my ability to go shopping or carry bags has been** …..

*(tick one)*

| | |
|---|---|
| 1. Totally limited, couldn't go shopping at all | ☐ 1 |
| 2. Extremely limited | ☐ 2 |
| 3. Very limited | ☐ 3 |
| 4. Moderately limited | ☐ 4 |
| 5. A little limited | ☐ 5 |
| 6. Only very slightly limited | ☐ 6 |
| 7. Not at all limited | ☐ 7 |

23. In the last two weeks **I have worried I might be in danger of losing a part of my leg or foot**

*(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

24. In the last two weeks **the distance I can walk <u>has become less</u>** …..

1. A very great deal ☐ 1
2. A great deal ☐ 2
3. A good deal ☐ 3
4. Moderately ☐ 4
5. Somewhat ☐ 5
6. A little ☐ 6
7. Not at all – tick if distance is unchanged or has increased ☐ 7

25. In the last two weeks **I have been depressed about the poor circulation to my legs** …..

*(tick one)*

| | |
|---|---|
| 1. All of the time | ☐ 1 |
| 2. Most of the time | ☐ 2 |
| 3. A good bit of the time | ☐ 3 |
| 4. Some of the time | ☐ 4 |
| 5. A little of the time | ☐ 5 |
| 6. Hardly any of the time | ☐ 6 |
| 7. None of the time | ☐ 7 |

Thank you for completing this questionnaire

## Appendix 9 – Letter to GP

Academic Vascular Surgery Unit

University of Hull/ Hull Royal Infirmary

Hull And East Yorkshire Hospitals NHS Trust

Anlaby Road

Hull HU3 2JZ

Tel: 01482 674643

Study investigator/contact: Dr Paris Cai

Email: paris.cai@hey.nhs.uk

**Date:**

**Dear Doctor**

**Re: Pt name:**

**Hospital Number:**

**DOB:**

# Extracorporeal shockwave therapy in lower limb intermittent claudication

### A randomised clinical trial to assess the effectiveness of extracorporeal shockwave therapy for lower limb intermittent claudication

This patient of yours has kindly agreed to participate in the above research study.

We do not expect this research to impact on any other aspect of their care but wished to keep you informed.

Should your patient have any queries regarding the trial that you do not feel able to answer or should you wish to know more about the trial yourself, please do not hesitate to contact the research team using the details above.

Yours sincerely,

Dr Paris Cai

Vascular research fellow

# Appendix 10 – Letter to Consultant Vascular Surgeon

**Dear Mr.**

Consultant Vascular Surgeon

HRI

**Date:**

**Re:**

**Case number:**

I have today reviewed the above patient for consideration for the Shockwave Trial for claudication. Mr. is willing and has been recruited to the trial for his **left** leg intermittent claudication. Please do not hesitate to contact me if you have any questions and I look forward to receiving more referrals from you.

Yours Sincerely,

Dr Paris Cai
Vascular Research Fellow
Vascular Department
Tower Block
Hull Royal Infirmary
Tel: 01482 674643