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Lower limb ischaemia and its treatment – the impact on physical function, balance and quality of life

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by

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The candidate confirms that the work submitted is hers and the appropriate credit has been given where reference has been made to the work of others.

Abstract

Improving functional outcomes of elderly, high risk, populations is of enormous public health importance with both high social and economic value. Lower limb ischaemia is a chronic and disabling condition with increasing prevalence among elderly populations and has been shown to be associated with impaired physical function and balance. The aim of this study was to investigate the impact of standard treatment, through angioplasty or exercise therapy, on clinical indicators of lower limb ischaemia, physical function, balance, falls risk and quality of life in patients with lower limb ischaemia.

Ankle brachial pressure index (ABPI) does not correlate with markers of physical function, balance and falls risk, whereas walking distances do correlate with physical function and falls. Angioplasty treatment leads to significant improvements in clinical indicators of lower limb ischaemia, markers of physical function that include an element of walking, history of falling or stumbling, fear of falling and quality of life. Balance is only slightly improved by angioplasty at 3 months following treatment. Supervised exercise programme treatment leads to significant improvements in walking distances but not ABPI, and physical function and a history of stumbles are improved. Balance is markedly improved at 3, 6 and 12 months from baseline. Quality of life improvements are seen at 3 and 6 months but not at 12 months from baseline.

This study highlights the high frequency of balance abnormalities among claudicants and recognises the link between balance abnormalities and falls risk. Treatment with either angioplasty or exercise improves markers of physical function, balance, falls risk and quality of life but there are differences between the 2 treatment effects. It is important that patients are thoroughly assessed in the wider context of their presentation and that treatment is targeted to the individual.

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Abbreviations

ABC	Activities-specific balance confidence scale
ABC-UK	Activities-specific balance confidence scale – UK
ABPI	Ankle brachial pressure index
ABPI-PE	Ankle brachial pressure index post exercise
BMI	Body mass index
BP	Blood pressure
CDP	Computerised dynamic posturography
CLAU-S	Claudication scale
COF	Centre of force
COG	Centre of gravity
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
EQ-5D	EuroQol
F	Female
FES	Falling efficacy scale
GFFM	Geriatric fear of falling measurement
IC	Intermittent claudication
ICD	Intermittent claudication distance
ICQ	Intermittent claudication questionnaire
IQR	Interquartile range
LREC	Local research ethical committee
M	Male
MCT	Motor coordination tests

MDT	Multidisciplinary team meeting
MWD	Maximum walking distance
N	No
NHP	Nottingham health profile
NHS	National health service
NICE	National institute for clinical excellence
NS	Non significant
OA	Osteoarthritis
P	Statistical significance value
PAD	Peripheral arterial disease
PAVK-86	Peripheral arterial occlusive disease 86
POMA	Performance oriented assessment of mobility
PREF	Preference score
PRWD	Patient reported walking distance
PTA	Percutaneous transluminal angioplasty
QALY	Quality adjusted life year
QOL	Quality of life
SEP	Supervised exercise programme
SF36	Short form 36
SF8	Short form 8
SIP	Sickness impact profile-intermittent claudication scale
SOM	Somatosensory score
SOT	Sensory organisation test
SPPB	Short physical performance battery

TASC	Transatlantic inter-society consensus
TIA	Transient ischaemic attack
TUG	Timed up and go test
VascuQol	Vascular quality of life scale
VEST	Vestibular score
VIS	Visual score
Y	Yes
ρ	Spearman rank correlation coefficient

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Supervised exercise improves balance in patients with intermittent claudication – presented at the 6th World Congress of Biomechanics, Singapore in August 2010.

Objective balance assessment in claudicants undergoing angioplasty – presented at the 22nd Congress of the International Society of Biomechanics, Cape Town, South Africa in July 2009.

Balance assessment in claudicants: High incidence of vestibular dysfunction –presented at the European Society for Cardio-Vascular Surgery (ESCVS), Warsaw, Poland in May 2009.

National Oral Presentations:

The impact of standard treatment on balance and physical function among claudicants – presented at the Vascular Society, Bournemouth in November 2010.

Objective balance assessment: Female claudicants perform poorly in computerized dynamic posturography – presented at the 1st International Conference of Computational and Mathematical Biomedical Engineering, Swansea in July 2009.

Predictors of falls and balance deficiencies in claudicants – Prize winning presentation at the Yorkshire Vascular Forum, Leeds in October 2009.

Poster Presentations:

Poor balance and physical function among elderly claudicants – is exercise the answer?
European Vascular Surgical Society, Oslo, Norway in September 2009.

Claudicants are at risk of balance problems and falling.
European Surgical Society, Nimes, France in May 2009.

1 Introduction

1.1 Aims

Intermittent claudication is the commonest presentation of lower limb ischaemia or peripheral arterial disease which is caused by atherosclerosis or occlusion of the arterial blood supply. It is a chronic, disabling condition with a prevalence of approximately 5% in over 50 year olds, increasing with age. Intermittent claudication typically presents with pain in the leg musculature on walking resulting in impaired walking distances and poor quality of life. Angioplasty and exercise therapy are the mainstays of treatment once risk factors have been modified. Pharmacological therapy is used in some cases but there is debate regarding efficacy. Surgery carries a high rate of morbidity and mortality and is reserved as a last resort in patients where symptoms cause an extreme impact on their quality life.

In addition, impaired physical function is prevalent among older patients with lower limb ischaemia, encompassing balance problems and increased falls risk. Functional morbidity carries huge financial and social costs and is thus an important issue to address with our ageing population. The identification and treatment of patient groups with poor lower limb function, especially those with poor physical function and impaired balance is a priority for both individuals and society as a whole, and attempts not only to improve function but also quality of life.

The aim of this study is to investigate the impact of standard treatment, through angioplasty or exercise therapy, on clinical indicators of lower limb ischaemia, physical function, balance, falls risk and quality of life in patients with lower limb ischaemia.

1.2 Peripheral arterial disease

1.2.1 Background

Peripheral arterial disease (PAD) is an occlusive disease of the arteries caused by atherosclerosis, most commonly of the lower limbs. PAD may be asymptomatic but symptoms become increasingly apparent with progressive arterial occlusion and are dependent on the site of vessel obstruction, the speed at which the vessel narrows (stenosis) or blocks (occlusion) and the adequacy of collateral blood flow.

The prevalence and incidence of PAD in the UK population has been the subject of much research but has proven difficult to ascertain due to the occurrence of asymptomatic disease. The Edinburgh Artery Study screened large random samples of the population between the ages of 55 and 74 using registers from general practices. This study identified symptomatic disease in nearly 5% of the population, major asymptomatic disease causing significant impairment to blood flow in 8% and further abnormalities among 16% (Fowkes *et al*. 1991). Recognised risk factors include male gender, increasing age, smoking, diabetes, hypertension, and dyslipidaemia (Norgren *et al*. 2007).

PAD can be classified as acute or chronic. Acute leg ischaemia can be defined as deterioration in the blood supply of a previously stable leg of less than 2 weeks duration, resulting in ischaemic pain at rest and/or other features of severe ischaemia, such as pallor, paralysis, paraesthesia, pulselessness (Earnshaw *et al*. 2006). The classification of acute limb ischaemia incorporates the viability of the limb and can be divided into viable (not

immediately threatened), threatened (which implies reversible ischaemia following treatment) and major irreversible ischaemia (which usually requires major amputation) (Rutherford *et al*. 1997).

Chronic leg ischaemia is also stratified by severity, but is simply divided by symptoms into intermittent claudication and critical ischaemia. Intermittent claudication (IC) is ischaemic pain, discomfort or weakness experienced in the leg muscles when the arterial supply is insufficient to meet the metabolic needs of the musculature during exercise. IC is most commonly experienced in the calf but may occur in the foot, thigh, hip or buttocks depending on the site of vessel occlusion and the muscle group this vessel supplies. Pain is experienced at a consistent walking distance and is alleviated by resting for 1-3 minutes. Further key features of IC include no pain at rest or on the first few steps of walking but pain that is worsened by walking uphill or walking quickly (McCollum and Ashleigh 2006).

IC tends to follow a benign course, perhaps due to the development of collateral vessels that contribute to lower limb vascularisation. The Basle study reported that at 5 years two thirds of surviving patients showed symptom improvement although 63% demonstrated progression of disease on angiography (Da Silva *et al*. 1979). The percentage of IC patients who progress to critical ischaemia is small. Despite 25% of IC patients experiencing progressive symptoms, only 5% will require revascularisation and only 1-2% will require major leg amputation. However of greater importance is that PAD acts as a marker for systemic atherosclerosis and thus there is an increased risk of cardiovascular events among

IC, with a 2-4% risk of non-fatal cardiovascular events in the first year following diagnosis and a 1-3% subsequent yearly incidence of non-fatal events (TASC 2000).
Critical ischaemia, however, is not a stable condition and requires prompt treatment to avoid the progression of tissue necrosis requiring amputation. Critical ischaemia encompasses ischaemic rest pain (severe pain in the toes or forefoot at rest) and tissue loss (either ischemic ulceration or gangrene). Critical ischaemia signifies that the blood supply to the limb is insufficient to meet the metabolic demands of the tissue at rest and thus requires urgent investigation and revascularisation (McCollum and Ashleigh 2006).

For all patients, investigations involve assessing the patient's cardiovascular risk factors and the extent of the presenting PAD. Usually claudicants are managed conservatively with risk factor modification, exercise advice and observation in the first instance. If claudication becomes disabling the patient would require further investigation. This commonly involves colour-flow duplex ultrasound imaging, magnetic resonance angiography or catheter angiography (an invasive technique using intravascular contrast media and serial X-rays to determine the location and extent of PAD).

The management of PAD extends from conservative treatment and risk factor modification, through pharmacological therapy, angioplasty and stenting to surgical treatments. Increasing severity of disease tends to require increasingly escalated management. Furthermore the potential risks and side effects of treatment also increase with more complex interventions. Deciding when to intervene in patients with IC is complex and is guided by the impact of their symptoms on their normal life, balanced with the risks of a given intervention for the individual.

1.2.2 Clinical indicators of lower limb ischaemia

1.2.2.1 Ankle Brachial Pressure Index

Insonation of the pedal pulses using a hand held Doppler ultrasound device is of use in identifying the presence and nature of arterial signals but is not a quantitative measurement. The Ankle Brachial Pressure Index (ABPI) is a simple bedside tool used to estimate blood flow to the lower extremity and compares the systolic blood pressure at the ankle with the brachial artery systolic pressure. ABPI is calculated using the following equation:

ABPI = highest ankle systolic pressure/highest brachial systolic pressure

Clinically, an ABPI of 1.0-1.2 is normal, <0.9 suggests arterial disease, and <0.3 suggests critical ischaemia. An ABPI of <0.9 has been shown to be up to 95% sensitive in detecting angiogram-positive disease (Bernstein and Fronek 1982; Vowden *et al* 1996).

1.2.2.2 Exercise challenge

Repeating ABPI post exercise can often reveal abnormalities not detected in limbs examined at rest. This usually occurs in patients with disease of the aorto-iliac arteries with collateralisation sufficient to produce pulses at rest. A simple bedside exercise test would be to stress the calf muscle by repeatedly rising onto "tiptoes" and returning the heel to the floor. An objective exercise test would be to ask the patient to walk on a treadmill and report the distance at which they experience pain and when they can no longer tolerate walking (maximum walking distance).

Mild IC is also indicated with a significant drop in ABPI post exercise testing, usually >20mmHg from resting ABPI (Rutherford *et al*. 1997).

1.2.2.3 Classification of ischaemia

Chronic lower limb ischaemia has two well-known classification systems: Fontaine (1954) and Rutherford (1997). The Fontaine classification system has four progressing stages as follows;

I Mild pain on walking

II Severe pain on walking (stage IIa >150m, stage IIb<150m)

III Rest pain, usually in the feet, which worsens on raising the limb

IV Tissue loss

The Rutherford classification system has superseded Fontaine as it requires further objective criteria in the assessment of each patient (Table 1.1).

Table 1.1 Rutherford classification of chronic lower limb ischaemia

Category	*Clinical description*	*Objective criteria*
0	Asymptomatic – no haemodynamically significant occlusive disease	Normal treadmill
1	Mild claudication	Completes treadmill test† Ankle pressure post exercise >50 mmHg but at least 20 mmHg lower than resting value
2	Moderate claudication	Between categories 1 and 3
3	Severe claudication	Cannot complete treadmill test† & Ankle pressure post exercise <50 mmHg
4	Ischaemic rest pain	Resting ankle pressure <40 mmHg
5	Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischaemia	Resting ankle pressure <60 mmHg, toe pressures <30mmHg
6	Major tissue loss – extending above the transmetatarsal (forefoot) level, i.e. functional foot no longer salvageable	Same as category 5

Categories 4, 5 and 6 are termed chronic critical ischaemia. †Rutherford treadmill test was five minutes at 2 mph on a 12% incline.

1.2.3 Role of angioplasty

Endovascular treatment of PAD is a rapidly evolving and proven therapeutic option and encompasses both balloon angioplasty (opening the lumen of the artery with a balloon) and arterial stenting. Stents are metallic tubes that exert a radial force on the vessel wall and stay *in situ* to maintain the vessel lumen. The indications for angioplasty are progressive and limiting IC preventing the patient from performing day to day activities and patients with critical ischaemia. Assessment, investigation and planning is paramount for all patients and discussion at a vascular multidisciplinary team meeting (MDT), which involves vascular surgeons and interventional radiologists, is important particularly in complex cases.

The distribution of PAD lesions are broadly divided into 3 anatomical regions; aorto-iliac, femoro-popliteal and crural disease, which has relevance for treatment. Lesions within each region have been further subdivided into TASC lesions A to D, indicating their suitability for endovascular treatment (Norgren *et al*. 2007);

A – represents a lesion which responds well to endovascular treatment

B – represents a lesion which, when treated endovascularly, yields good results but open surgical repair may be appropriate if there are multiple lesions in this area.

C – represents a lesion which responds better to open surgical repair but endovascular treatment may be suitable if they have a high operative risk

D – such lesions do not yield good enough results to justify endovascular as the initial treatment.

Crural vessel (below the knee) angioplasty is sometimes performed for patients with critical limb ischaemia as an initial salvage treatment, the aim of which is to restore in line blood flow to the foot. This is not a treatment for IC due to the increased risks associated with this procedure, particularly vessel spasm and acute closure. Given the systemic nature of atherosclerotic disease, patients often have multilevel disease, requiring treatment at more than one site (Ettles 2006).

Published data suggests lower limb angioplasty patency rates for femoropopliteal disease at 5 years range between12% and 68%, the best results being for patients with claudication and stenotic lesions (Hunink *et al*. 1994). For aortoiliac disease immediate technical success rate is as high as 96% for stenting procedures, but at 4 years patency rates are between 54% (for balloon angioplasty treatment of occlusion and 77% (for stent treatment of stensosis) (Bosch and Hunink 1997).

ABPI declines due to restenosis or occlusion at the original site of pathology or progression of disease at other sites. Restenosis has always been a technical challenge to angioplasty treatment and is caused by factors including elastic recoil following angioplasty, late vessel remodelling and neointimal hyperplasia. Neointimal hyperplasia is the physiological response to trauma to the vessel wall, occurring from 3-6 months after treatment and resulting in proliferation of the intimal lining of the vessel wall. Drug eluting stents are coated with a polymer matrix which controls the release of pharmaceutical agents aimed and maintaining patency. The SIROCCO trial used the immunosuppressant, Sirolimus (rapamycin) in comparison with bare nitinol stents for superficial femoral artery lesions.

The restenosis rate at 2 years was 22.9% for the sirolimus drug eluting stent and 21.1% for the bare nitinol stent (Duda *et al*. 2006)

1.2.4 Role of exercise therapy

A 2008 Cochrane review of randomised controlled trials using any exercise programme, has confirmed the role for exercise therapy in the treatment of IC showing improved walking ability by approximately 50% to 200% (Watson *et al*. 2008). Compared to usual care or placebo exercise leads to improvements in maximum walking times and distances without any improvement in ABPI. All studies recommended at least two weekly sessions of mostly supervised rather than unsupervised exercise. Classes lasted between 30 and 60 minutes and included walking and leg exercises or treadmill training. Beneficial effects were demonstrated following 3 months of supervised exercise (Watson *et al*. 2008).

An earlier meta-analysis demonstrated the clinical improvement possible with exercise therapy, with treadmill walking distance improvements of 122% (maximum treadmill walking distance) to 179% (treadmill walking distance where claudication pain begins) (Gardner and Poehlman 1995). This meta-analysis found that the key components among exercise programmes were;

- Session of > 30 minutes each
- 3 sessions per week
- Exercise programme duration of > 6months
- Walking focussed exercise programmes (Hiatt *et al*. 1994)
- Walking which induced near maximal pain.

Accounting for 85-90% of the variance in change in claudication distances was, in order of importance; near maximal pain, > 6 month duration and walking programmes rather than combination exercise programmes encompassing a variety of exercise modalities. Interestingly older patients (64-68 year olds) demonstrated greater increases in treadmill distances than their younger counterparts (58-63 year olds), although whether this was due to more severe disease was unclear.

Conversely it has been suggested that exercise to maximal pain may make PAD worse by inducing ischaemia and thus causing a local inflammatory and oxidative stress response (Tisi and Shearman 1998), which may promote atherosclerosis and have a deleterious effect on muscle function. However Tisi *et al*. (1997) confirmed a biochemical inflammatory response, but reported a reduction in inflammatory markers and improved symptoms following a 4 week supervised exercise programme with encouragement to continue exercising at home when compared to a non-exercise group.

Exercise intensity may not be important. Gardner *et al*. (2005) randomised claudicants to a low intensity (40% maximal exercise capacity) or high intensity (80%) groups for intermittent treadmill walking at near maximal pain in supervised sessions for 3 days a week and found no difference in efficacy provided that a similar volume of exercise is performed.

In terms of the type of exercise required, strength and resistance training alone or in combination with walking programmes has been studied. A randomised controlled trial of

29 patients who underwent 12 weeks (3 hours per week) of treadmill walking or lower limb strength training found the walking group improved in peak walking time twice as much as the strength group, and they also showed improvement in peak oxygen consumption and increased time to the onset of pain, findings which the strength group did not show. Sequential or concomitant strength and walking programmes showed similar improvements to treadmill walking alone (Hiatt *et al*. 1994).

Both supervised and unsupervised exercise programmes have been shown to be cost effective treatments both for primary and secondary prevention of cardiovascular disease (CVD) (Lowensteyn *et al*. 2000). Even with poor long term compliance, in the region of 30%, unsupervised exercise was highly cost effective at < 12,000 US$ per life year saved in both individuals with and without CVD. Supervised exercise programmes are intuitively more expensive. Even with an adherence of 50% in the first year following the exercise programme and 30% long term compliance, for all men with CVD and women with CVD (over 55 years old) and even for young men without CVD, such programmes are cost effective (between 20,000 and 40,000 US$ per life year saved). Lee *et al*. (2007) identified the cost per quality adjusted life year (QALY) over the first year following a 3 month exercise programme to be £1780/QALY. Given that the National Institute for Clinical Excellence (NICE) identify a cost-effective treatment as falling below £30,000/QALY, exercise appears to offer a highly cost-effective treatment option.

The proposed mechanisms of improved walking following exercise therapy are numerous (Stewart *et al*. 2002). Human studies demonstrating both improved collateral blood flow and clinical improvement are limited, with either no or moderate improvements in ABPI. It

is therefore proposed that mechanisms other than improved blood flow are responsible. Such mechanisms include;

- Increased aerobic capacity
- Improved muscle strength and endurance
- Improved walking ability through improved economy
- Improvements to the microcirculation, and endothelial function (Brendle *et al*. 2001)
- Improvements in the nature of blood flow, such as reduced viscosity

There is a paucity of data comparing exercise to angioplasty. The Cochrane review identified 2 studies separated by 16 years (Watson *et al*. 2008). These found that angioplasty produced a greater improvement in walking times and distances initially but this was not sustained at one year (Creasy *et al*. 1990), although improvements in angioplasty techniques over time may have made both treatments more comparable. In 2008 the MIMIC trial showed a sustained benefit in terms of walking distances for patients having undergone both angioplasty and exercise compared to those who had undergone exercise alone at 24 months from treatment (Greenhalgh *et al*. 2008).

TASC recommendations state that exercise therapy should be made available to all patients with peripheral arterial disease as an initial treatment strategy. They concur that the most effective sessions involve treadmill or track walking of sufficient intensity to induce IC pain, with rest periods over a 30 to 60 minute class conducted 3 times a week for 3 months (Norgren *et al*. 2007).

1.3 Physical function

1.3.1 Definition of physical function

"Physical function" can be defined as a complex, generalised measure of performance in various functional domains relevant to daily life, and as such is a reflection of overall health and the impact of disease on physical ability. Physical function requires multiple complementing and coexisting skills such as strength, proprioception, balance, freedom of movement and coordination and relies on adequately functioning neuromuscular systems in addition to an absence of pain and fear.

Physical function is particularly relevant to elderly populations. A large observational study of 1122 older patients without disability found those with the poorest lower extremity function at baseline were over 4 times as likely to have disability in both activities of daily living and mobility after 4 years of follow up as those with high performance scores on tests of walking speed, balance and functional strength (2.4 metre walk, repeated rising from a chair and standing balance) (Guralnik *et al*. 1995). This finding highlights the link between poor baseline physical function and potential future decline in older people.

Given the ageing nature of our population the burden of chronic disease such as PAD is set to continue, and concomitant rises in frailty, poor mobility and loss of independence associated with ageing are likely. Measuring functional decline and disability is important, particularly if this allows prediction of future demise to allow intervention.

The justification for an in depth assessment of physical function in patients with PAD, in addition to assessing walking distance or symptom improvement, is not only to ascertain problems with activities of daily living but to recognise patients at potential risk of the serious consequences of functional decline. Declining physical function is a predictor of future disability (Guralnik *et al*. 1995) and relates to falls risk (Tinetti *et al*. 1998). A core component of physical function is physical activity and this has alarmingly also been shown to be a predictor of all-cause mortality in PAD and IC (Garg *et al*. 2006; Gardner *et al*. 2008*a*).

1.3.2 The relationship between physical function and PAD

As previously described, PAD tends to be a disease of older people and therefore an elderly patient cohort is likely to experience the problems of declining physical function seen in otherwise healthy elderly people. Yet there is evidence to suggest there may be a greater association between physical function and PAD than merely that expected with aging.

Frailty or lack of physical function is associated with sub clinical cardiovascular disease (Newman *et al*. 2001) and an association between poor physical function and PAD, specifically, has been demonstrated in several large cross-sectional studies (Garg *et al*. 2006; McDermott *et al*. 2001). Given that walking impairment is the major symptomatic complaint of claudicants it follows that with increasing severity of PAD, determined by lower ABPI values, a correlation with deteriorating ambulatory function is seen. Patients with mild disease (high ABPI group, 0.76-0.9) performed significantly better than those with severe disease (low ABPI group, 0.36-0.5) over the 6-minute walk and had higher daily physical activity levels (Atkins *et al*. 2004). Such findings extend beyond just walking

related function. A multi-centre observational study of 740 individuals of whom 460 had PAD (33% with IC) found that lower ABPI values were associated with lower measures of functional strength and balance, in addition to poor ambulatory function (McDermott *et al*. 2002). Even among asymptomatic patients with low-normal (1.00 to 1.09) or borderline (0.9-0.99) ABPI values there is evidence of functional decline in a large prospective observational study (McDermott *et al*. 2009*b*), thus suggesting that the decline in function cannot be solely explained by pain when walking.

A potential pathological explanation for deteriorating physical function in patients with peripheral arterial disease is thought to be loss of strength consistent with ischaemic muscle changes. Histological analysis of gastrocnemius muscle from PAD patients has shown significantly increased evidence of angular fibres, indicative of chronic denervation, and significantly decreased type II muscle fibre area which is associated with greater strength deficits as type II fibres are larger, faster and stronger than type I fibres (Regensteiner *et al*. 1993).

Intuitively there are many other contributing factors which may account for poor performance among claudicants. Oka *et al*. performed a multiple regression analysis on data from 97 PAD patients to determine predictors of physical function, demonstrating; education, absolute walking distance, social support, arthritis and age to be the strongest predictors of physical function (Oka *et al*. 2004).

Deteriorating ABPI cannot therefore be relied on as a surrogate marker to detect declining physical function in a lower limb ischaemia population. This is supported by a study of

older males which found that despite no deterioration in ABPI, declines in walking function, physical activity, physical function (balance, lower limb functional strength and 4-metre walking velocity), and calf blood flow were noted over a period of 18 months follow up (Gardner *et al*. 2004).

The relationship between physical function and PAD is complex and not yet fully elucidated. Further understanding of how to identify patients at risk of deteriorating physical function is therefore important. Consequently identification of individuals with poor function allows targeted interventions towards those most in need and those most at risk of further decline. This may be particularly pertinent among patients with lower limb ischaemia as baseline functional performance has been shown to be a predictor for the rate of self-reported mobility loss among persons with PAD (hazard ratio 1.63, 95% CI 1.03 to 2.56) when compared to controls (McDermott *et al*. 2007).

1.3.3 Assessment of physical function

Physical function could be measured via a vast array of tests and assessments. Frailty, for example, has been assessed by measures of weight loss, low grip strength, low energy, slow gait speed and low physical activity (Newman *et al*. 2001). However there are many simple objective measures of physical function that could be used by any health care professional. Lower limb physical functional assessment is relevant to a cohort with lower limb disease.

To assess physical performance and to compile data on lower extremity function in non-disabled older people, Guralnik *et al*. (1995) used tests of standing balance, walking speed and the ability to rise from a chair. They assimilated their data to form a summary

performance score for each individual tested by dividing the results of their 5000 plus cohort into performance quartiles on each test. The validity of this summary score has been shown to correlate with an increasing of risk of admission to a nursing home and mortality with increasingly poor scores. The tests themselves incorporate assessment of balance, lower limb functional strength, and coordination. Such tests have been used in PAD patients in several studies (Arseven *et al*. 2007; Gardner and Montgomery 2001*b*; Gardner *et al*. 2004; McDermott *et al*. 2001; McDermott *et al*. 2002; McDermott *et al*. 2006;) and have been shown to be more strongly associated with physical activity levels during daily life than treadmill walking assessments (McDermott *et al*. 2008*b*).

Treadmill walking tests specifically for PAD have been discussed in Chapter 1.2 and are of relevance in measuring disease severity as well as physical function. Other walking tests are of value in the assessment of physical function such as the 6 minute walk test (McDermott *et al*. 2008*b*) which allows the individual to select their preferred walking velocity, thus offering a potentially more realistic portrayal of actual walking performance.

Balance is a key component of physical function and is explored in further detail in Chapter 1.4. Risk of falling is also intimately linked to poor physical function and this is expanded on in Chapter 1.5.

1.3.4 Exercise therapy and physical function

High levels of physical activity or exercise may be protective in preventing poor physical function in lower limb ischaemia. In a prospective cohort study of 417 patients with PAD, after adjusting for variables, found that patients who walked for exercise 3 or more times

per week, particularly if they exercise for more than 90 minutes per week, had a significantly smaller average annual decline in 6 minute walking distance compared to those who walked less frequently (McDermott *et al*. 2006). Despite an encouraging trend, there was no significant slowing of functional decline in other measures such as tandem balance and chair stand testing suggesting that these aspects of function may require different exercise training regimens.

A well conducted randomised controlled trial has demonstrated that even a short 5-week "circuit-style" exercise class performed twice weekly improved stepping balance, functional strength (sit to stand test), gait velocity and walking distance over six minutes, over those with no intervention in older mobility-impaired participants (mean age 74.9) (Sherrington *et al*. 2008*a*). There was no significant improvement in standing balance or lower limb strength, explained by a lack of strength training within the exercise classes. Modifications to the exercises performed or increasing the duration of the treatment may have demonstrated further functional improvement although this assumption is unproven.

Interventions aimed at improving physical activity levels are likely to be crucial in maintaining adequate physical function and preventing functional decline. Further research is required to delineate the exact components of an exercise regime that best suit individuals in terms of objective gains in physical function and the prevention of deterioration.

1.4 Balance

1.4.1 Background

Balance can be defined as the ability to maintain the body's centre of gravity over the base of support and is required for safe functional activity (Panzer *et al*. 1995) and thus the prevention of falls. Balance is both static and dynamic, requiring not only maintenance of position, but also postural control during transfer to a new base of support during voluntary activities such as walking (Howe *et al*. 2007) and overcoming involuntary perturbations to prevent falling.

Balance is complex, requiring interplay between different sensory systems, primarily somatosensory, visual and vestibular systems. The somatosensory system is responsible for proprioception and the awareness of the body's position in space. This is achieved through sensory pressure receptors and muscle and joint proprioceptors. The visual system enhances balance by orientating the body in space and providing information about the challenges or obstacles around. The vestibular system detects movement in space and triggers neuromuscular responses to rotations and translations experienced.

Impairment of balance occurs due to a wide range of aetiologies but the goal of management is to maintain function and minimise disability, particularly minimising the risk of falls and associated injury. Balance has recently been viewed as a learned neuro-motor skill rather than purely a reflex or reactive sense (Horak *et al*. 1997), which indicates potential for rehabilitation and improvement of balance.

1.4.2 The relationship between balance and PAD

The link between poor physical function and PAD was explored in section 1.3.2. Balance is one of the key components of physical function and therefore of specific relevance for further investigation. Suominen *et al*. (2008) established that older individuals with PAD exhibited a significantly increased amount of movement of their centre of pressure on standing, indicative of poor balance. Gardner and Montgomery (2001*a*) have shown that PAD patients have 28% shorter single leg stance times, 86% higher prevalence of stumbling and unsteadiness on walking and 73% more prevalent history of falling than non-PAD counterparts.

One explanation for poor balance in patients with PAD is similar to that for poor physical function, in that, PAD patients have ischaemic muscle changes that correspond with poor functional strength (Regensteiner *et al*. 1993) and poor motor neurone performance (Gardner and Montgomery 2001*a*). Whether the presence of PAD is indicative of central balance control impairment is difficult to ascertain, but the systemic atherosclerosis associated with PAD patients may cause central and cerebral changes which contribute to balance impairment.

1.4.3 Assessment of balance

The adequate assessment of balance begins with a clear patient history, including perceived balance problems and previous falling. Physical examination to elucidate coexisting medical conditions that affect balance is conducted followed by specific balance tests.

Romberg's test is a simple test to identify abnormal proprioception. The patient stands with their feet together and eyes closed. If instability is detected (swaying, falling or stepping) the test is positive (Clarke 1999).

Tinetti (1986) described the performance oriented assessment of mobility (POMA) assessment tool to quantify mobility problems in elderly patients. The balance component assesses 8 tasks such as sitting, standing and turning. Each task is scored out of 2 points with a maximum of 16 for the test, a higher score equates to better balance. POMA also includes a gait assessment with a maximum score of 12. Patients are stratified in terms of falls risk based on the combined score; ≤18 = high risk, 19-23 = moderate risk, ≥24-28 = low risk. The limitations of POMA are firstly, it is cognitively challenging with a number of instructions to be followed making it difficult for patients with cognitive impairment. Secondly it must not be considered to be a comprehensive falls assessment tool alone, as it does not account for all falls risk factors (Lewis and Shaw 2005).

Koch *et al*. (1994) showed high inter-rater reliability for a tool similar to the POMA tool for impairment and disability for community living older persons in which their balance assessment incorporates observing the patient conducting balance procedures during normal daily activities such as stand to sit, sit to stand, bending, reaching and carrying objects. The assessor records the number of attempt to complete the task, loss of balance, excessive leaning, unsafe positioning and the need for help or support. This tool also assesses strength, range of motion, gait and foot problems and is designed to be representative of activities of daily living but is not quantitative in terms of balance assessment. Berg balance score is a 56 point scale assessing similar functional tasks to the

POMA (Berg *et al*. 1992). The test is similarly cognitively challenging and takes approximately 20 minutes to complete which may induce fatigue and even IC pain in PAD patients.

Simple, quick and quantitative measures of balance are also described in the assessment of physical function and include the balance aspects of the summary performance score (Guralnik *et al*. 1995), for example the measurement of semi-tandem and full-tandem stance, and the Timed up and Go test (TUG) (Podsiadlo and Richardson 1995, Bohannon 2006). Tandem stance tests require the patient to stand with their heel of one foot beside the big toe of the other foot (semi-tandem) and the heel of one foot directly in front of the other foot (full-tandem) and loss of balance is recorded (Guralnik *et al*. 1995). The TUG test requires the patient to rise from a chair, walk 3 metres and turn, return and sit down again. The time taken to complete this is recorded and reference values have been determined to identify abnormal test scores (Bohannon 2006).

1.4.4 Computerised dynamic posturography

Computerised dynamic posturography (CDP) is the standard quantitative method for isolating and assessing the sensory and motor components of balance in the standing human (Black 2001). CDP testing is unique in that it measures a patient's postural sway by incorporating movement or perturbation of the support surface and is capable of isolating the contributions of different sensory components from the visual, vestibular and somatosensory systems and providing quantified data (Monsell *et al*. 1997). CDP incorporates aspects of clinical testing such as Rombergs, but has the unique advantage of providing quantitative data. This improves on simple clinical balance assessments in the

ability to perform repeated measurements to assess progress or response to treatment. CDP requires both sensory and motor impairment assessment and uses the Sensory Organisation Test (SOT) and motor coordination tests such as the Motor Control Test (MCT) (Black 2001). CDP, as described by Monsell *et al*. (1997) in their technology assessment for the American Academy of Otolaryngology-Head and Neck surgery Foundation, is based mostly on studies using the Equitest device manufactured by NeuroCom International, Clackamas, Oregon.

CDP measures the forces exerted by a patient standing on a platform, which is capable of movement controlled by the device's computer. Several test conditions exist to challenge the patient's mechanisms of postural control through alteration of somatosensory and visual input and consequently vestibular input. Data is compared with age matched control data to identify abnormalities.

Validity and reliability of CDP has been confirmed (Ford Smith *et al*. 1995; Monsell *et al*. 1997; Carter *et al*. 2001). The most reliable data from the SOT on test retest analysis is the composite score and the number of episodes of loss of balance (falls) during the test (Ford Smith *et al*. 1995).

Other similar tests include electronystagmography and rotational chair tests but both of these are limited to assessing visual and vestibular systems. Foam posturography (standing on a foam surface) can identify both normal and abnormal balance including patterns of abnormality but subtle abnormalities can be missed (Monsell *et al*. 1997).

There are a wide number of current and potential uses of CDP. Clinically CDP can determine whether or not a balance problem is present and if so whether the problem lies with sensory inputs, central integration or motor output, or indeed a combination of systems (Black 2001). For elderly and aging populations CDP is useful in the assessment of balance control and recovery of function. In particular CDP has been used in monitoring of balance rehabilitation programmes and to identify patients who fall from non-fallers (Whitney *et al*. 2006).

1.4.5 Exercise therapy and balance

A Cochrane review has concluded that exercise therapy improves balance when compared to usual activities in older people (Howe *et al*. 2007). Types of exercise interventions studied varied from walking and cycling to strengthening and resistance training, to specific balance training exercises, dance, yoga and tai chi. Of most benefit were interventions involving walking, balance training, coordination and functional exercises, muscle strengthening and combination sessions, and can be evaluated by indirect measures of balance such as single leg stance tests. However it is not clear as to whether the benefits of exercise therapy, which was typically a 3 month programme, are long lasting (Howe *et al*. 2007).

1.5 Falls

1.5.1 Falls and PAD

Risk factors for falls are multiple and include several domains of physical function, such as strength, and balance. The link between poor lower limb function or impaired balance and gait and falls risk is well recognised (Tinetti *et al*. 1988; Gardner and Montgomery 2001*a*). *Vice versa* known fallers have also demonstrated significantly poorer objective measures of ambulatory function, physical activity, lower limb functional strength (chair stand test), and impaired balance (single leg stance and full-tandem stance) (Gardner and Montgomery 2001*b*).

As PAD patients have been shown to have poor physical function an increased risk of falls would be expected although this has not been uniformly proven (Arseven *et al*. 2007). In a retrospective study of symptomatic patients, 26% of claudicants fell which differed significantly from 15% of controls ($P<0.001$). There was a significant relationship between falling and other aspects of poor physical function including balance, but ABPI was unrelated to falling (Gardner and Montgomery 2001*a*). A pilot study of 43 community dwelling older male claudicants which demonstrated functional decline despite no drop in ABPI also showed a significant increase in the percentage of patients reporting ambulatory stumbling and unsteadiness at 18 months (43% versus 28% at baseline) implying that men with PAD may experience gradual loss of stability over time which may increase their risk for falls. There was no perceived change in self-perceived health or reporting of symptoms over time, thus possibly rendering patients more susceptible to falls due to lack of insight towards their deterioration (Gardner *et al*. 2004).

1.5.2 Falls assessment

Most importantly all patients should be assessed on an individual basis in the wider context of their presentation with a full medical history and appropriate examination. If concerns are raised patients should be referred for a thorough falls assessment from an appropriate specialist.

The published guidelines for the prevention of falls in older persons by the American Geriatric Society advocates a simple assessment of falls risk as a screening tool, the timed "Up and Go test", (TUG) (American Geriatrics Society 2001); . During the TUG test the patient is observed and timed while he or she rises from a chair, walks 3 meters, turns and walks back and sits down again, with an abnormal result when the test completion is greater than 16 seconds (Figure 1.1) (Podsiadlo and Richardson 1991).

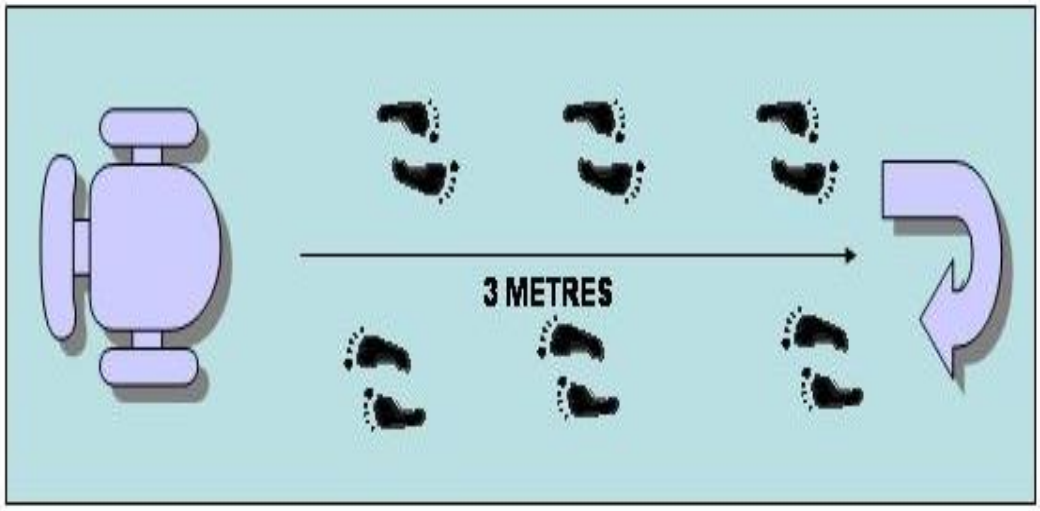


Figure 1.1 Timed Up and Go test (TUG)

The patient is observed and timed while he or she rises from a chair, walks 3 meters, turns and walks back and sits down again (Podsiadlo and Richardson 1991).

Assessment of falls and balance are closely linked in clinical balance and therefore there is overlap in their assessment. Chapter 1.4 concentrates on balance and its assessment, although several tests are described they are also used as measures of falls risk.

Fear of falling should also be considered in falls assessment as fear and activity avoidance are likely to significantly contribute to impaired quality of life. Fear of falling can be measured in a number of ways including: the Falling Efficacy Scale (FES), the Geriatric Fear of Falling Measurement (GFFM) and the Activities-Specific Balance Confidence Scale (ABC), which have all been shown to have strong internal consistency (Huang and Wang 2009). The ABC-UK assessment addresses more challenging balance tasks in its questioning and is specifically targeted at British participants (Parry *et al*. 2001).

1.5.3 Exercise therapy and falls

The role of exercise in the management of elderly persons aimed at reducing falls incidence has been explored in depth and both a Cochrane review (Gillespie *et al*. 2003) and more recent meta-analysis have concluded there is benefit of exercise on reducing falls rates (Sherrington *et al*. 2008*b*). This meta-analysis found that exercise reduced the rate of falling by 17% (44 trials with 9603 participants) with key recommendations being programs including a high total dose of exercise (>50 hours over the trial period) and challenging balance exercises (on one foot or with feet close together) (Sherrington *et al*. 2008*b*).

It seems timely that the crossover between research into elderly persons and patients with symptomatic and asymptomatic PAD is made, in terms of recognising and managing poor

physical function, to improve functional outcomes, particularly falls. Exercise, when specific and targeted has been shown to improve both symptoms of PAD but also falls risk among the elderly thus improving overall physical function.

Given that PAD patients are already exposed to increased morbidity and mortality associated with systemic atherosclerosis, poor functional outcomes and a possible increased risk of falls is an additional worrisome health burden for this population and a drive towards improving management including exercise training schemes for those at risk is paramount.

1.6 Quality of life

1.6.1 Quality of life and PAD

Patients with symptomatic PAD are known to have been shown to have impaired quality of life (QOL) with increasing severity of lower limb ischaemia corresponding to significant deterioration in QOL. Furthermore QOL improves with treatment (Chetter *et al*. 1999). Disease specific tools show greater sensitivity to symptomatic improvement following treatment (de Vries *et al*. 2005; Guidon and McGee 2010).

1.6.2 Measurement of quality of life

There are numerous measures of QOL, designed for generic and disease specific measurement. The Nottingham Health Profile (NHP), EuroQol (EQ-5D) and Short Form 36 (SF36) have been shown to be valid and reliable measures of generic QOL in PAD patients (Chetter *et al*. 1998). Domains examined are similar but specifically the NHP measures; energy, pain, emotional reaction, sleep, social isolation and physical mobility. The EQ-5D measures: mobility, self-care, usual activities, pain and anxiety/depression. Lastly, the SF36 measures: physical function, physical role, pain, general health, vitality, social functioning and mental health. SF36 is most sensitive to changes in psychological status and is therefore recommended as the most appropriate generic QOL assessment tool in PAD and for widespread use in vascular surgery to standardise reporting outcomes. More recently the Short Form 8 (SF8) when compared to SF36 has been found to be a valid and reliable measure, with the advantage of less questions and therefore rendering it easier and quicker to complete (Gulati *et al*. 2009).

There are a number of disease specific measures of QOL for PAD. The peripheral arterial occlusive disease 86 (PAVK-86) questionnaire (Bullinger *et al*. 1996) was validated in German and has 86 questions making it time consuming to complete. The IC questionnaire (ICQ) (Chong *et al*. 2002) is a 16 point questionnaire giving a single health domain. The sickness impact profile-IC scale (SIP) (Arfvidsson *et al*. 1993) and CLAU-S (Spengel *et al*. 1998) are both further disease specific measures for use in IC. The VascuQol is a 25 question assessment of limb ischaemia quality of life providing 5 domain scores (pain, activities, emotional, social and symptoms) (Morgan *et al*. 2001). VascuQol is unique in that it encompasses all lower limb ischaemia rather than just IC which is of increased value as symptoms progress towards severe lower limb ischaemia and has been shown to be more responsive than CLAU-S or SIP (Mehta *et al*. 2006). VascuQol has been recommended for assessment of disease specific QOL in PAD (de Vries *et al*. 2005; Mehta *et al*. 2006).

1.7 Hypothesis

The aim of this study is to investigate the impact of standard treatment, through angioplasty or exercise therapy, on clinical indicators of lower limb ischaemia including walking distances (both pain free and total walking distances), physical function, balance and quality of life in patients with lower limb ischaemia.

The specific research questions and hypotheses are:

1. Is increasing lower limb ischaemia associated with impairments of physical function and balance?

   Hypothesis 1: Prior to treatment, increasing severity of lower limb ischaemia will correlate with increasingly impaired physical function and balance.

2. What effect does angioplasty treatment have on outcome measures (i.e. clinical indicators of lower limb ischaemia, physical function, balance and quality of life) in patients with lower limb ischaemia?

   Hypothesis 2: Patients undergoing angioplasty treatment will demonstrate improved outcome measures after treatment.

3. What effect does exercise therapy treatment have on outcome measures (i.e. clinical indicators of lower limb ischaemia, physical function, balance and quality of life) in patients with lower limb ischaemia?

Hypothesis 3: Patients undergoing exercise therapy treatment will demonstrate improved outcome measures after treatment.

4. How do angioplasty and exercise therapy compare in the impact on outcome measures (i.e. clinical indicators of lower limb ischaemia, physical function, balance and quality of life) in patients with lower limb ischaemia?

   Hypothesis 4: There will be no difference between angioplasty and exercise treatments in improving outcome measures.

2 Methods

2.1 Study design and patient recruitment

2.1.1 Study description

A prospective case series study was performed on an out-patient population in one geographical area to investigate the role of two treatment groups on physical function, balance and quality of life in patients with lower limb ischaemia. Patients for the two treatment groups (angioplasty and supervised exercise programme) were concurrently recruited from the district served by the Hull and East Yorkshire Teaching Hospitals National Health Service (NHS) Trust.

2.1.2 Ethical approval and permissions

Local Research Ethical Committee (LREC) approval for the study was granted in addition to approval from the Research and Development Departments of the University of Hull, and Hull and East Yorkshire Hospitals NHS Trust (LREC reference numbers 07/Q1105/12, 07/Q1105/13, 07/H1305/83). Patients, referred by the consultant vascular surgeon in charge of their care, volunteered and provided written informed consent at Hull Royal Infirmary to participate in the study.

2.1.3 Sample size calculations

Sample sizes calculated for each treatment arm were based on the composite equilibrium score from the Sensory Organisation Test (SOT) of the EquiTest System (NeuroCom,

Clackamas, OR, USA; see section 2.5). For the angioplasty treatment group, initial pilot data from 19 patients with a mean baseline SOT score of 59.8% (sd 24.8) was used. The minimum expected clinically significant improvement chosen was a score of 72.9% (sd 5.4), which represents the lowest normal mean score for NeuroCom healthy controls in the 70-79 year age category. The calculated sample size was 29 based on 80% power to detect this difference in the SOT means (difference of 13) using a paired t-test with a 0.05 two-tailed significance level. For the exercise group, the initial pilot data had a mean baseline score of 65.3% (sd 12.5) that required a calculated sample size required of 22 to detect a difference in means of 7.5. Assuming a 25% drop out rate from both groups the target samples were 37 for the angioplasty group and 28 for the supervised exercise group.

2.1.4 Study design

Patients underwent nine potential stages in the research study (Figure 2.1). The first three stages involved patient selection. Potential patients were identified at outpatient clinics by their consultant vascular surgeon and suitable treatment (angioplasty or supervised exercise) was assigned at this stage or following further discussion at the multi-disciplinary team meeting (MDT) comprising interventional radiologists and vascular surgeons. Subsequently a patient information sheet and letter of invitation was sent to the patient (Appendix 1). The second two stages of the study involved written informed consent and baseline data capture. The last four stages of the study involved the intervention and follow-up measurements conducted at 3, 6 and 12 months after commencing exercise treatment or undergoing angioplasty.

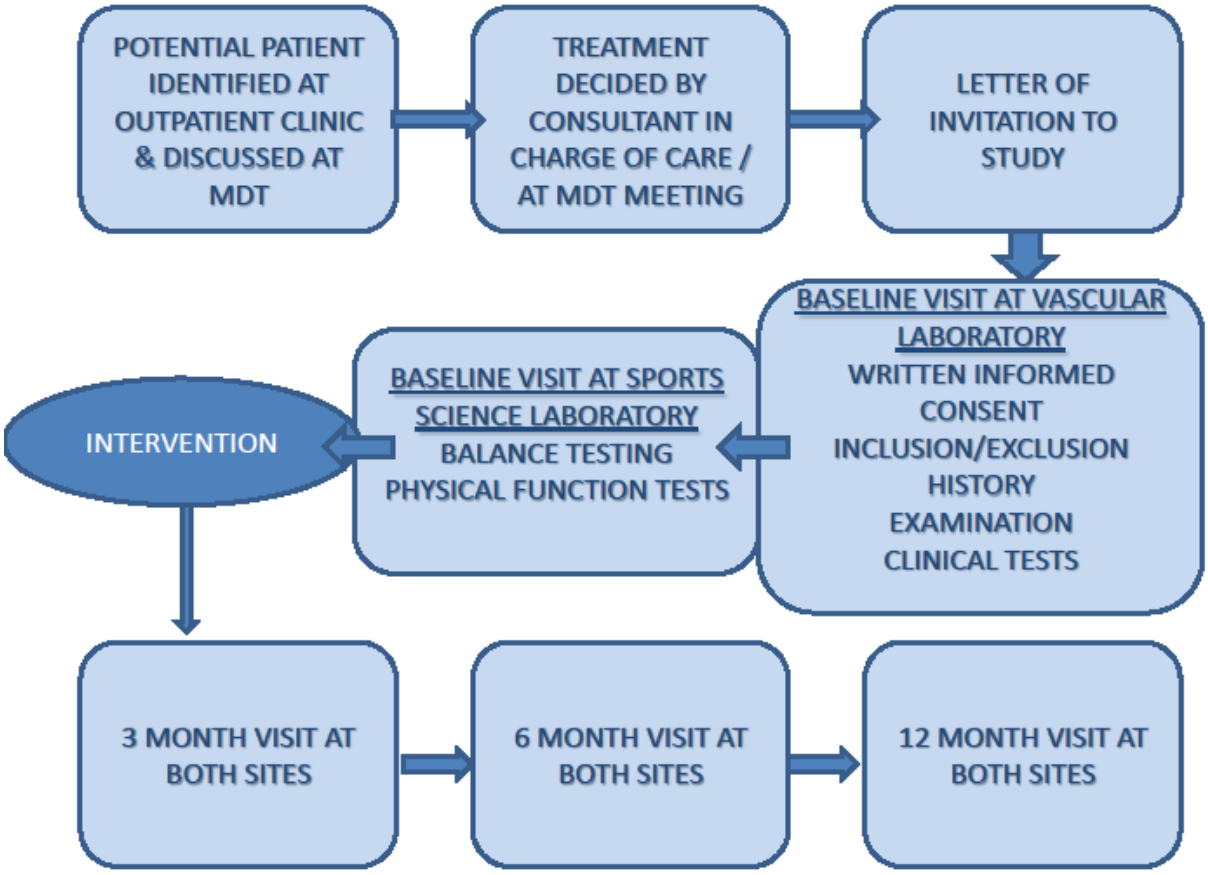


Figure 2.1 Flow diagram illustrating patient assessment and involvement in the study

MDT; multi-disciplinary team meeting comprising interventional radiologists and vascular surgeons

2.1.5 Patient selection

Potential patients identified by the study investigators at the vascular outpatient clinic at Hull Royal Infirmary, were confirmed as claudicants by clinical assessment in the clinic by the referring consultant. Confirmation was provided by documented current symptoms of intermittent claudication with an Ankle Brachial Pressure Index (ABPI) of $\leq$0.9 or >20 mmHg drop in ankle pressure post exercise testing (see section 2.3.1) or documented haemodynamically significant atherosclerosis on radiological imaging (angiogram or Duplex ultrasound).

2.1.6 Baseline visit 1 and inclusion/exclusion criteria

The baseline visit involved two stages. First, patients responding to the invitation visited the Vascular Laboratory at Hull Royal Infirmary where, at this initial appointment, written informed consent was obtained, and a detailed general medical and vascular surgical history was taken using a purpose designed proforma (Appendix 2). The following general inclusion/exclusion criteria were applied to all patients.

The inclusion criteria were: 1) confirmed as claudicants by the referring consultant following clinical assessment in out-patient clinic (section 2.1.5); 2) lived independently in the local community; 3) did not require assistance for general activities of daily living including shopping, cleaning and self-care; 4) over 50 years of age; 5) English speaking, and; 6) able to comply with simple study protocol instructions.

The exclusion criteria were: 1) inability to safely perform balance testing and to comply with the study protocol as determined by the referring consultant or study doctor (for

example; coexisting neurological or limiting cardio-respiratory or other significant medical problems); 2) significant peripheral neuropathy (Toronto clinical neuropathy score of >8 (Bril and Perkins 2002)); 3) life limiting conditions (such as active cancer); 4) mobility problems (such as major limb amputations, wheelchair use and hemiplegia), and; 5) dementia.

On confirmation of eligibility to the study, patients then underwent a thorough assessment both at the Vascular Laboratory and at the Sports Science Laboratory at the University of Hull (sections 2.2-2.5). Patients were seen at both locations within a 7 day period. Patient demographics were detailed in section 3.

2.2 Patient assessment

2.2.1 Medical history

A full medical history was performed by a study doctor to elucidate any serious co-morbidities as potential further exclusion criteria at baseline. This assessment was repeated at subsequent visits to identify any changes or potential exclusions during the study time period. Patients were specifically asked about any history of ischaemic heart disease, hypertension, hypercholesterolaemia or statin therapy, cerebrovascular disease, diabetes mellitus, arthritis, balance problems, neurological disease and smoking history (Appendix 2).

2.2.2 Medical examination

A full medical examination was conducted by a study doctor, including neurological examination and visual acuity assessment at 3 metres using a 3 metre Snellen (Turner and Blackwood 1998) chart. An assessment of peripheral neuropathy was made using the Toronto (Bril and Perkins 2002) scoring system (Table 2.1). Patients with a Toronto score of >8 were deemed as having moderate to severe peripheral neuropathy and were excluded from the study.

Simple anatomical measurements were taken. Circumferences of both calves were measured at the mid tibial point to assess any differences between symptomatic and asymptomatic legs. Height (wearing flat shoes) and weight (wearing light clothing) were measured and Body Mass Index (BMI) was calculated.

Table 2.1 Toronto clinical neuropathy scoring system

Symptom scores	*Reflex scores*	*Sensory test scores*
Foot	Knee reflexes	Pinprick
- Pain	Ankle reflexes	Temperature
- Numbness		Light touch
- Tingling		Vibration
- Weakness		Position sense
Ataxia		
Upper limb symptoms		

Sensory testing was performed on the great toe. Symptom scores were calculated as; present = 1, absent = 0. Reflex scores were calculated as; absent = 2, reduced = 1, normal = 0. Sensory test scores were calculated as; abnormal = 1, normal = 0. The maximum total score was 19.

2.3 Clinical indicators of lower limb ischaemia

The ankle brachial pressure index at rest (ABPI) was calculated using a hand held Doppler (Parks Medical Electronics, Inc. Oregon, USA). ABPI post exercise (ABPI-PE) was calculated for each patient immediately following the treadmill test (section 2.3). Post exercise the ankle pressure from the symptomatic leg was recorded and used to classify disease severity using the Rutherford criteria (Table 1.1) (Rutherford *et al*. 1997).

At baseline, and at months 3, 6 and 12, patients completed a modified Rutherford treadmill test involving walking at 1.6 mph at a 10 degree inclination for a maximum of 5 minutes. The test was modified by reducing the speed to 1.6 mph as the original 2 mph had been found in clinical practice to be too fast for a good proportion of our local population. The treadmill test was used to calculate the: intermittent claudication distance (ICD), which was the time when patients experienced the onset of their usual claudication pain, and; the maximum walking distance (MWD) when patients could walk no further. A small number of patients were unable to walk at 1.6 mph and were allowed to walk at slower speeds for safety purposes (1.0 mph or 1.2 mph). All patients were allowed to use handrails on the treadmill for balance. They were instructed not to hold themselves up or push down onto the handrails. Times (in seconds) were recorded at ICD and MWD, and converted into distances (in metres).

2.4 Physical function assessments

2.4.1 Short physical performance battery

Data were collected from the usual paced 4-metre walk, the chair stand test and semi tandem and tandem balance tests to derive scores for the short physical performance battery (SPPB) as a global measure of lower limb physical function (McDermott *et al*. 2007). Patients were assigned a score of 0 for each task they were unable to complete and scores of 1-4 were assigned for the remaining tasks, based upon quartiles of performance for over 6000 patients in the Established Populations for the Epidemiologic Study of the Elderly. Patients' scores were then added to obtain an overall score between 0 and 12 (Guralnik *et al*. 1995).

2.4.2 Four metre walk test

The time taken to walk in a straight line for 4 metres was measured in seconds and walking velocity in metres per second was calculated. Patients were asked to walk at their "usual" and then their "fastest" paces. Each walk was performed twice and the faster times were used for analyses (McDermott *et al*. 2008*b*).

2.4.3 Chair stand test

To assess functional lower limb strength and coordination to correlate with other measures of physical function assessment, patients were asked to sit in a straight backed chair (approximate seat height 42cm) with their arms folded across their chest and were requested to stand up and sit down five times as quickly as possible (Guralnik *et al*. 1995).

The total time taken to complete five chair stands was measured in seconds. This test was repeated after 3 minutes and the average score calculated.

2.4.4 Semi tandem and full tandem stance

To assess standing balance to correlate with dynamic balance test results, patients were asked to hold two standing positions each for a maximum of 30 seconds (Figure 2.2). The semi tandem position required the feet to be parallel, with the toes of one foot adjacent to and touching the heel of the opposite foot. The full tandem stance position requires one foot to be completely in front of the other but touching heel to toe (Guralnik *et al*. 1995). Duration of stance was recorded in seconds up to a maximum of 30 seconds.

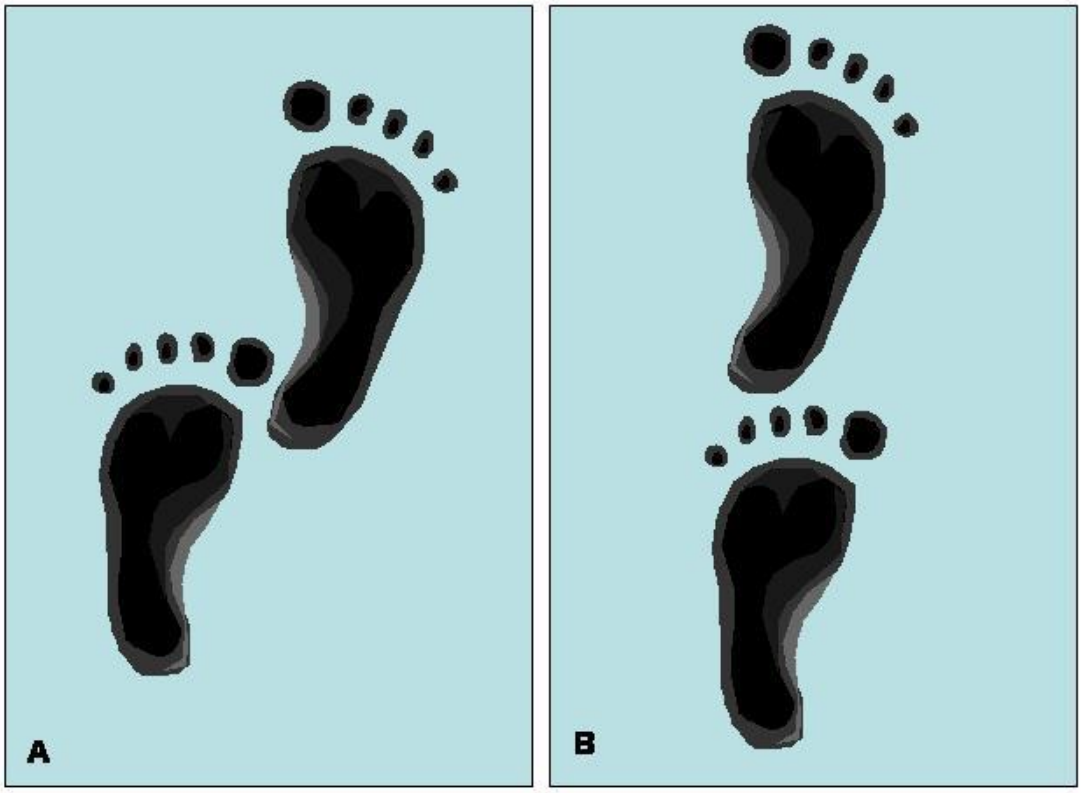


Figure 2.2 Semi tandem (A) and full tandem (B) stance

The semi tandem position required the feet to be parallel, with the toes of one foot adjacent to and touching the heel of the opposite foot. The full tandem stance position requires one foot to be completely in front of the other but touching heel to toe (Guralnik *et al*. 1995).

2.4.5 Hand grip strength

To assess general frailty and as a measurement of upper limb strength to correlate with lower limb tests, hand grip strength was assessed (Newman *et al*. 2001). Using a hand dynamometer (Takei Digital Display, Kogyu, Japan) (Figure 2.3), patients were asked to grip as tightly as possible, and the maximum grip strength was recorded in kilograms. Each hand was used three times and the average grip strength recorded. Hand dominance was also recorded.

Figure 2.3 Hand grip dynamometer

(Image taken from www.hab.co.uk). Patients were asked to grip as tightly as possible, and the maximum grip strength was recorded in kilograms.

2.4.6 Six minute walk test

Patients were asked to walk at their usual walking pace away and back over a 20 metre path. They were instructed to cover as much ground as possible during the 6 minute time period. During the test the distance and time at which intermittent claudication was first felt was recorded (ICD), which involved the patients alerting the researcher to the onset of their pain. The maximum walking distance (at which the patient could not walk any further) and time were also recorded (MWD and MWD time) (McDermott *et al*. 2008*b*). Distances were recorded to the nearest 5 metres.

2.5 Assessment of balance

2.5.1 Computerised Dynamic Posturography

CDP was undertaken using the EquiTest system (NeuroCom International Inc., Clackamas, OR, USA). This comprises a standing platform with dual force plates (Figure 2.4), which can undergo angular translations to tip the patient forwards (toes down) and backwards (toes up), termed "sway-referenced support". In addition the force plates can undergo linear translation to move the patient in an anterior or posterior direction. The patient's feet were centred on the force plates in a standard position facing a brightly coloured visual surround capable of movement relative to the patient (termed "sway-referenced surround") (Figure 2.4). The patient wore an appropriately sized safety harness throughout testing (Figure 2.4). The computer monitor within the visual surround was on during testing. Data were collected and analysed using NeuroCom International software (NeuroCom System Version 8.1.0., 1996-2006, NeuroCom International Inc.). The CDP comprised of the Sensory Organisation Test (SOT) and the Motor Control Test (MCT). If the patient was physically unable to continue with testing due to pain or fatigue CDP was terminated immediately.

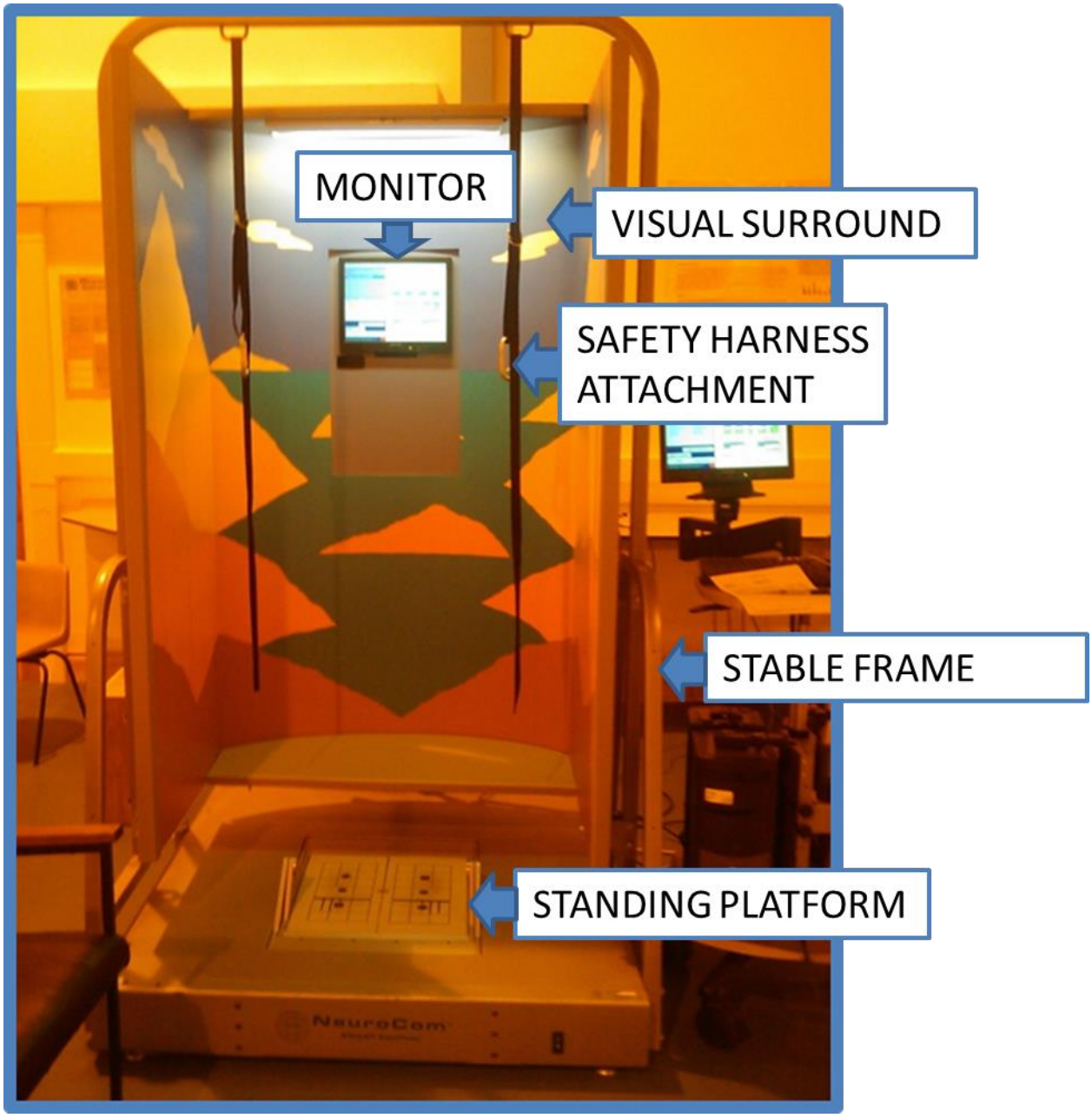


Figure 2.4 The NeuroCom EquiTest system

This comprises a standing platform with dual force plates, a visual surround capable of sway-referenced movement against a stable frame, a monitor and a safety harness.

Data captured using CDP was compared to the historical healthy controls from the NeuroCom database (Clackamas, OR, USA), which were stratified into three age groups: 20-59 years, 60-69 years and 70-79 years. For any patients over the age of 79 years their scores were compared to the 70-79 age group controls due to the absence of older age control data. Scores for both SOT and MCT which fell outside of those obtained by 95% of controls were described as abnormal i.e. those falling below the 5^{th} percentile. Historical controls had no symptoms or history of disequilibrium or motor problems, and specifically met the following criteria:

1. No current or past medical diagnosis or injury affecting balance
2. No medications affecting the central nervous system or known to affect balance/coordination
3. No symptoms of dizziness or lightheadedness
4. No symptoms suggestive of vestibular or neurologic disorders
5. No psychological disorders including depression
6. No history of two or more unexplained falls within the past 6 months
7. Normal vision with or without glasses

2.5.1.1 Sensory Organisation Test

The sensory organisation test (SOT) assesses the patients' ability to effectively use different sensory systems (somatosensory, visual and vestibular) to maintain balance during sensory conflict conditions. Sensory conflict situations were created by movement of the visual surroundings or standing platform in response to the patients' sway (calibrated sway referencing) either with the patients' eyes open or closed.

Sensory analysis

To identify functional impairment within each sensory system 6 different conditions were tested and compared (Figure 2.5). Before each condition, patients were provided with a brief explanation to clarify their expectations and to reduce any anxiety. Each sensory condition was repeated 3 times (3 trials), with each trial lasting for 20 seconds, and the mean data per condition was used. The measurements recorded were:

- The somatosensory score (SOM), which measures the patients' ability to use input from the somatosensory system or support surface to maintain balance, was calculated as a ratio of condition 2 to condition 1.
- The visual score (VIS), which identifies the patients' ability to use visual inputs to maintain balance, was calculated as a ratio of condition 4 to condition 1.
- The vestibular score (VEST), which assesses the patients' ability to use input from the vestibular system to maintain balance, was calculated as a ratio of condition 5 to condition 1.
- The preference score (PREF), which measures the degree to which a patient relies on visual information to maintain balance even if the visual information was inaccurate or incorrect, was calculated as the ratio of the sum of conditions 3 and 6 to the sum of conditions 2 and 5.

NeuroCom software indicates the normality or abnormality of each of these sensory components, meaning that even with a normal composite score, one or more aspects of balance may be abnormal when compared to NeuroCom historic control patients.

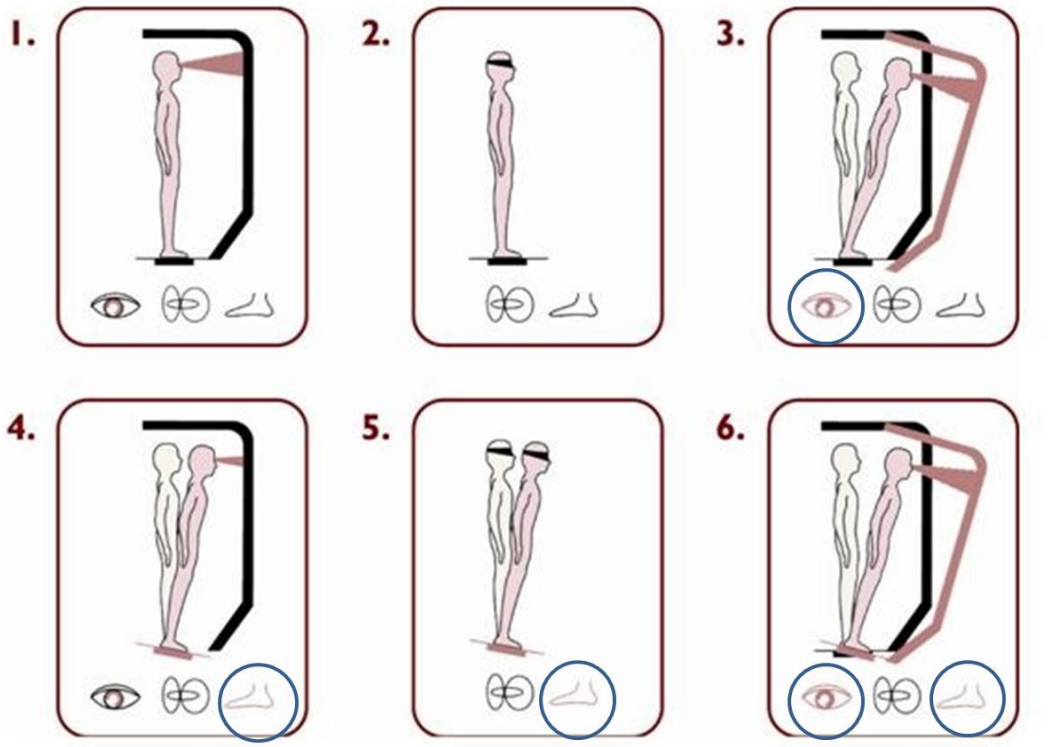


Figure 2.5 Six conditions used in the Sensory Organisation Test (SOT) using the NeuroCom

The sensory conditions were as follows; 1. Normal sensory input, 2. Absent visual input, 3. Inaccurate visual input, 4. Inaccurate somatosensory input, 5. Inaccurate somatosensory input and absent visual input, 6. Inaccurate visual and somatosensory inputs. The symbols  indicate which aspect of the sensory system (visual, vestibular or somatosensory, respectively) were receiving accurate (uncircled) or inaccurate (circled) inputs. If a symbol is not pictured for a condition then there is no input for that system e.g. conditions 2 and 5 require the patient to close their eyes thus removing a visual input. Figure used courtesy of NeuroCom® International, Inc.

Composite equilibrium SOT score

A healthy patient can exhibit an anterior to posterior sway over a total range of 12.5 degrees without losing balance (Nashner *et al*. 1989; NeuroCom 2001). The equilibrium score for each trial was calculated by comparing the difference between the patients calculated maximum displacement to the theoretical maximum and was expressed as a percentage, with 100 being perfect stability and 0 representing a fall. The composite equilibrium score provides a measure of overall performance in terms of postural stability during the test. It was calculated as a weighted average of the scores of all 6 conditions tested. The weighted average was the: average score for condition 1 added to the average score for condition 2 added to the scores of each trial of conditions 3-6, and this sum divided by 14. The composite equilibrium score was identified as abnormal when results were lower than scores of 95% of age matched, healthy control patients. For the composite SOT the minimum normal scores for each age group were 70% (20-59 year olds), 68% (60-69 year olds) and 64% (70-79 year olds) (NeuroCom 2001).

Movement strategies

Movement strategies were calculated by comparing the patient-generated horizontal shear force of the centre of gravity (COG) accelerations to the maximum possible shear of 25 lbs or 11.4 kg. Strategy scores were plotted in relation to the equilibrium score obtained for each patient. Data falling outside the expected range was described as an abnormal "hip strategy" or "ankle strategy". If a patient used a stepping strategy, i.e. they moved their feet, this trial would be categorised as a fall with a score of 0. Scores for each condition approaching 100 equate to a 100% reliance on the ankle strategy to maintain balance, whereas a score of 0 indicates 0% reliance on ankle strategy and therefore a hip strategy

was employed to maintain balance. This indicates a disproportionate reliance on either the ankle or the hip and upper body to maintain balance during the test and highlights discordance between the movement strategy being used and the degree of instability of the patient. Scores in between 0 and 100 represent a mixture of strategies (NeuroCom 2001).

SOT falls

A fall was recorded on the SOT test when the patient lost balance and needed to touch the walls of the visual surround, or take a step to regain balance, or when the test was stopped by the operator as the patient required stabilising using the harness. All falls were recorded and the condition on which the fall occurred was noted.

2.5.1.2 Motor Control Test

The motor control test (MCT) requires the patient to stand on the dual force plates where the patients' foot position was standardised and all patients were required to wear a safety harness. A brief and basic explanation of the test was given to patients just before the test started to ensure correct completion of the task and to minimise any anxiety. The force plates (AMTI, Advanced Mechanical Technology Inc, Watertown, MA, USA) measured 230x460mm and were connected by a pin joint that allowed the right and left plates to move separately and record independently the forces exerted by each leg on the support surfaces. The force plates were supported by 4 force transducers (strain gauges), mounted symmetrically on a supporting centre plate, which measure forces in three-dimensions. A fifth transducer bracketed to the centre plate beneath the pin joint allowed measurement of shear forces along the Y axis, i.e. parallel to the floor and anterior-posterior to the patient. The data were sampled at 100 Hz (NeuroCom 2001).

During the MCT test 9 translations occurred in a backward direction and 9 in the forward direction. This comprised of 3 small, 3 medium and 3 large force plate translations of the patients' centre of gravity graded as small, medium and large duration scaled to the patient's height (measured in inches) calculated as follows;

- Small translations: amplitude (inches) = 0.5 * (height÷72), and have a duration of 250ms
- Medium translations: amplitude (inches) = 1.25 * (height÷72), duration 300ms
- Large translations: amplitude (inches) = 2.25 * (height÷72), duration 400ms

The "centre of force" traces for each force plates were used to monitor the instantaneous level of muscular effort exerted about the ankle joint for each leg. These measurements were used to calculate weight symmetry, onset times (latency) and response strengths of the active force automatically generated by the patient (as defined below). Only data for medium and large translations were used for analysis.

Weight symmetry

Weight symmetry was measured by the distribution of total body weight over each leg during the force plate translations. Abnormal weight symmetries, towards the left or right leg, were recorded during both backward and forward graded translations of the force plate.

Response latency

Latency was the time in milliseconds between the onset of force plate translation and the initiation of the active force response of the leg. The NeuroCom measures the centre of

force (COF) trace during each translation and four multiple slope detection algorithms were used to determine the point at which the COF position first begins to change rapidly following translation. The MCT was repeated if no take-off points could be identified by any of the four search algorithms or if each algorithm defined a different take off point.

Response strength

The measurement of strength of response reflects the ability of the patient to produce a level of force appropriate for the degree of force plate linear translation. The response strengths were measured separately for each leg during each trial and normalised to body height and weight. Patients response strengths were measured and compared to NeuroCom historic control patients and documented as increased or reduced in one or both legs.

2.6 Assessment of falls

2.6.1 History of falls or stumbles

A history of falls and stumbles within the year preceding baseline visit 1 and at each subsequent visit was documented. A fall was defined as unintentionally coming to the ground or to another lower level, not as a result of an overwhelming hazard that would result in a fall by most young, healthy people (Tinetti *et al*. 1988). A stumble was defined as a near fall where the patient lost balance but was able to right themselves and prevent a true fall. Patients were asked their falls and stumbles history at each clinical assessment.

2.6.2 Fear of Falling

This was assessed using the 16-item Activities-specific Balance Confidence (ABC-UK) scale, demonstrated to be a valid and reliable measure of a fear of falling. Using a visual analogue scale patients score 16 scenarios analysing their confidence in performing tasks that may result in a fall. Each question was scored from 0 to 100, with 100 being total confidence and 0 being no confidence at all. The total score was an average of all 16 responses. Scenarios questioned increase in difficulty and range from "walking around the house" to, the most difficult being, "walking on an icy pavement" (Appendix 3) (Parry *et al*. 2001).

2.6.3 Timed Up and Go test

The Timed Up and Go test, (TUG) is a simple assessment of falls risk (Podsiadlo and Richardson 1995). During the TUG test the patient was observed and timed as they rise

from a standard chair (seat height 46cm, and arm height of 65cm), walk 3 meters, turn around and walk back to the chair and sit down again. An abnormal result was when time to complete the test was greater than age matched norms (Figure 1.1), specifically if they exceed: 9.0 seconds for 60-69 year olds, 10.2 seconds for 70-79 year olds and 12.7 for 80-99 year olds (Bohannon 2006).

2.7 Quality of life assessment

All patients were asked to complete three questionnaire assessments of their quality of life (QOL). Generic QOL was measured using both the Short Form-36 and Short Form-8, both known to be reliable and valid in the PAD population (Gulati *et al*. 2009). Disease specific QOL was measured using the Kings' Vascuqol questionnaire (Morgan *et al*. 2001).

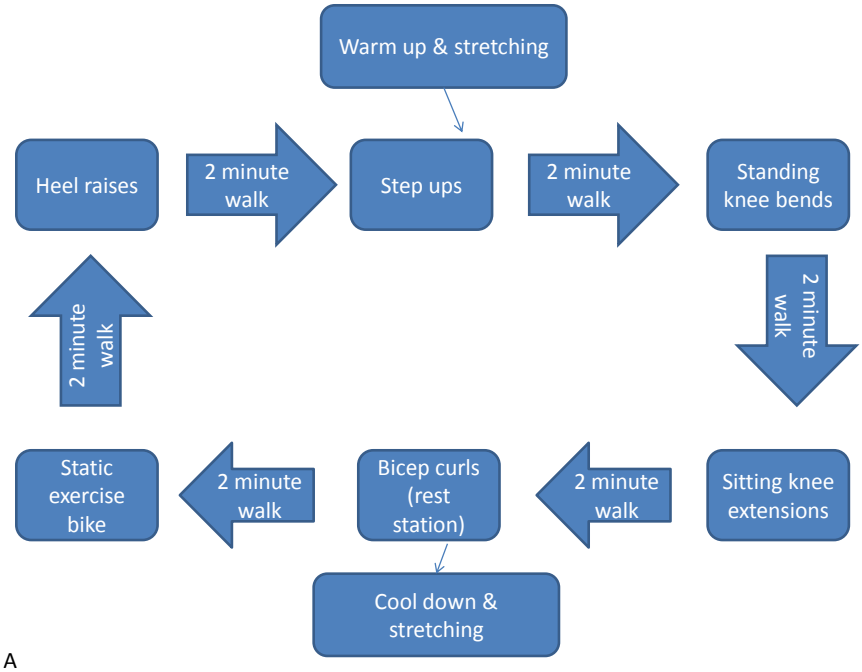
2.8 Intervention

2.8.1 Angioplasty

All angioplasties were performed in the interventional radiology suite of Hull Royal Infirmary in accordance with all clinical patients. The procedure was performed within a month of the baseline visit, and the follow up visits at 3, 6 and 12 months were performed at times measured from the angioplasty. Procedures were performed by interventional radiologists using local anaesthetic infiltration and femoral artery puncture in the groin. In addition to percutaneous transluminal balloon angioplasty, arterial stents were used where clinically indicated in lesions thought to be at high risk of primary failure or distal embolisation. Patients were admitted to the vascular ward on the morning of the procedure and discharged the following morning after overnight observation, vital sign monitoring and groin check by the clinical team.

2.8.2 Supervised Exercise Programme

The supervised exercise programme (SEP) took place on three afternoons per week for a period of 12 weeks (total course per patient = 36 sessions) from the baseline to 3-month visit. If patients missed a session due to illness or holiday they were allowed to make up the sessions at the end of the course. Each session lasted for a minimum of 30 minutes from 4pm on Mondays, Wednesdays and Fridays. SEP was conducted in groups of up to 12 patients and attendance was taken at each session. SEP was directed by the principal study doctor or other vascular research doctors. The SEP is described in (Figure 2.6), and all exercises were performed at a low intensity.



A

B

Warm up, cool down & stretching	1 minute of marching on the spot 1 minute of stepping side to side 1 minute of marching on the spot 2 minutes of walking Stretching – thigh, calf, hamstring, deltoid, hamstring
Heel raises	Holding onto wall bars for stability, standing on a step, rising onto ball of foot for 5 seconds then releasing and repeating for 2 minutes
Step ups	Using a 20cm high step, stepping on and off, alternating lead leg after 10 step ups. Repeated for 2 minutes.
Standing knee bends	While standing on one leg with support from parrallel hand rails the patient flexes and extends the weight bearing knee for 10 repetitions before changing legs. Repeated for 2 minutes.
Sitting knee extensions	Patients sit on a high stool with a 2kg weight strapped to the ankle and fully extend the knee and flex for 10 repetitions before changing legs. Repeated for 2 minutes.
Biceps curl (rest station)	Holding 2kg dumbells patients flex and extend their elbows for 2 minutes.
Static exercise bike	At self selected resistance at a target revolution per minute of 60-80, patient cycles on the bike for 2 minutes.

Figure 2.6 Structured exercise programme

A. Outline of each session during weeks 1-6, from week 7 an additional station was repeated each week until the patient completes 2 full circuits. B. Description of each station.

Each session began with a gentle 5 minute warm up and stretching and finished with 5 minutes of cool down with further stretching. The sessions comprised a circuit of 6 exercise stations each lasting for 2 minutes, which were alternated with 2 minutes of walking. Patients could perform the exercises in any order they preferred. After 6 weeks, for each additional week of the class completed, the patients repeated one exercise so that by week 12 they were completing 2 full circuits of the exercise stations.

2.8.3 Follow up

Assessments comprised repeating all tests and examinations performed at baseline (see sections 2.2-2.5) and were conducted at 3, 6 and 12 months after commencing the exercise programme or undergoing angioplasty.

2.9 Statistical analysis

Data sets were exported into SPSS v19.0 (IBM SPSS version 19) for statistical analysis. An alpha value of 0.05 was used to determine statistical significance in the data set. Data were checked for normality using a Shapiro-Wilks test, and as the majority were found to be not normally distributed non-parametric statistics were used throughout. Correlations were performed between clinical indicators of lower limb ischaemia and measures of physical function, balance and falls using Spearman rank correlation coefficient (ρ). To compare data within each group at different time points Wilcoxon signed ranks test was used for continuous data and Chi squared test for categorical data. To compare the angioplasty group with the exercise group the Mann Whitney U test was used at each time point.

3 Results

3.1 Correlation between lower limb ischaemia and physical function and balance

The first aim of this work was to explore whether worsening lower limb ischaemia is associated with impairments of physical function and balance. Table 3.1 shows the demographics and clinical indicators of lower limb ischaemia for the study population as a whole at baseline (Appendix 4). There were 98 patients with intermittent claudication included in the study and this comprised 67 males and 31 females.

Spearman rank correlation coefficient (ρ) was performed to assess whether there were any significant correlations. Both pre and post exercise ABPI demonstrated a significant correlation with semi tandem stance, but with no other measure of physical function or falls. These correlations with semi tandem stance were weak; pre exercise ABPI ($\rho = -.206$, $P = 0.043$), post exercise ABPI ($\rho = -.202$, $P = 0.049$). However treadmill ICD and MWD correlated well with almost all continuous measures of physical function and falls (Table 3.2). The subjective measure of patient reported walking distance only significantly correlated with the SPPB ($\rho = .306$, $P = 0.004$) and the chair stand test ($\rho = - .338$, $P < 0.001$).

Clinical indicators of lower limb ischaemia did not correlate well with measures of balance (Table 3.3). The only significant correlation found between pre exercise ABPI and balance was with the mean equilibrium score for condition 1 on the SOT ($\rho = .240$, $P = 0.018$). There were no significant correlations found between post exercise ABPI, treadmill ICD or MWD and measures of balance. ABPI both pre and post exercise did not show any signifcant correlation with any measure of falls. However significant correlations between both ABC-UK score and TUG score were seen with ICD and MWD (Table 3.3).

Table 3.1 Patient demographics at baseline for all study patients

	All Patients
Number	98
Age (years)	
- **Median (IQR)**	69 (64-75)
Age group (N)	
- **20-59 years**	12
- **60-69 years**	40
- **70-79 years**	34
- **80+ years**	12
Gender (N)	M:67 F:31
Medical history (N)*	
- **Ischaemic heart disease (Y/N)**	42 / 55
- **Hypertension (Y/N)**	71 / 26
- **On statin therapy (Y/N)**	79 / 18
- **CVA or TIA (Y/N)**	18 / 79
- **Diabetes (Y/N)**	24 / 73
- **Smoker (current / ex / never)**	27 / 56 / 14
- **OA lower limb / other / none**	34 21 / 42
Height (cm) Median (IQR)	167 61-173)
Weight (kg) Median (IQR)	78 69-91)
BMI (kg/m^2) Median (IQR)	28 (26-31)
Visual acuity	
- **6/6 or 6/9**	53
- **6/12**	13
- **worse than 6/12**	14
Pre exercise ABPI - median (IQR)	
- **Right leg**	0.79 (0.64-0.94)
- **Left leg**	0.79 (0.58-0.93)
- **Symptomatic leg**	0.69 (0.55-0.86)
Post exercise ABPI - median (IQR)	
- **Right leg**	0.46 (0.28-0.75)
- **Left leg**	0.53 (0.24-0.84)
- **Symptomatic leg**	0.32 (0.22-0.52)
Post exercise ankle pressure (mmHg)	52 (38-82)
Rutherford categories (N)	
- **Mild claudication**	5
- **Moderate claudication**	52
- **Severe claudication**	38
Treadmill ICD (m) Median (IQR)	39.5 (24.75-60.38)
Treadmill MWD (m) Median (IQR)	74.7(47.43-129)
PRWD (m) Median (IQR)	135 (90-274)

Values are expressed as median (IQR, interquartile range) or as numbers (N). M (male), F (female), BMI (body mass index). * 1 subject did not declare their medical history and therefore there is one set of missing data throughout the medical history section. Yes / No. (Y/N). Cerebrovascular accident (CVA), transient ischaemic attack (TIA). Osteoarthritis (OA). Visual acuity fractions; 6/6 is normal vision, 6/9 indicated that at 6 metres the smallest row of letters the tested eye can discern would be what a normal eye can read at 9 metres, this applies to 6/12 but represents what a normal eye can read at 12 metres. ABPI (ankle brachial pressure index, ICD (intermittent claudication distance), MWD (maximum walking distance), PRWD (patient reported walking distance).

Table 3.2 Physical function correlated with treadmill walking distances at baseline

	All Patients	ICD correlation	MWD correlation
Short performance physical battery - median (IQR)	10 (9-11)	**ρ = .455 P < 0.001**	**ρ = .544 P < 0.001**
- **0-6 (N)**	6		
- **7-9 (N)**	34		
- **10-12 (N)**	55		
- **missing**	3		
4 metre walk at usual pace (m/s)			
- **Median (IQR)**	1.01 (0.84-1.15)	**ρ = .423 P < 0.001**	**ρ = .503 P < 0.001**
4 metre walk at fastest pace (m/s)			
- **Median (IQR)**	1.07 (1.33-1.54)	**ρ = .413 P < 0.001**	**ρ = .517 P < 0.001**
Chair stand test (s)			
- **Median (IQR)**	14.86 (11.73-19.07)	**ρ = - .406 P < 0.001**	**ρ = - .440 P < 0.001**
Semi tandem stance (s) – median (IQR)	30 (30-30)	**ρ = .263 P = 0.012**	**ρ = .339 P = 0.001**
- **< 10 seconds (N)**	6		
- **10-29 seconds (N)**	12		
- **30 seconds (N)**	79		
- **missing**	1		
Full tandem stance (s) – median (IQR)	30 (12.99-30)	ρ = .145 P = 0.174	**ρ = .282 P = 0.006**
- **< 10 seconds (N)**	16		
- **10-29 seconds (N)**	26		
- **30 seconds (N)**	55		
- **missing**	1		
Handgrip strength (kg) – median (IQR)			
- **Right hand**	30.9 (19.8-39.6)	ρ = .215 P = 0.069**ρ = .277, P = 0.018**	**ρ = .312, P = 0.006**
- **Left hand**	29.9 (19.1-36.8)		**ρ = .377, P = 0.001**
6 minute walk – median (IQR)			
- **ICD distance (m)**	100 (60-160)	**ρ = .570, P < 0.001**	**ρ = .543, P < 0.001**
- **MWD distance (m)**	240 (160-400)	**ρ = .385, P < 0.001**	**ρ = .513, P < 0.001**
- **ICD time (s)**	58.5 (92.5-135.5)	**ρ = .528, P < 0.001**	**ρ = .472, P < 0.001**
- **MWD time (s)**	221 (132.5-360)	**ρ = .277, P = 0.010**	**ρ = .389, P < 0.001**

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance, MWD (maximum walking distance). ρ (Spearman rank correlation coefficient), NS (non significant). P values are given and highlighted in **bold** if significant (P< 0.05).

Table 3.3 Balance and falls correlated with treadmill walking distances at baseline

	All Patients	ICD correlation	MWD correlation
SOT composite score			
- **Median (IQR)**	68 (57.5-76)	ρ = .069, P = 0.520	ρ = .059, P = 0.571
SOT mean trial score for each condition			
- **Median (IQR)**			
- **Condition 1**	94.67 (93.00-95.66)	ρ = .073, P = 0.492	ρ = .184, P = 0.76
- **Condition 2**	90.33 (86.92-92.75)	ρ = .115, P = 0.279	ρ = .022, P = 0.832
- **Condition 3**	88.67 (83.25-92.33)	ρ = .029, P = 0.785	ρ = -.060, P = 0.565
- **Condition 4**	81.17 (70.33-85.67)	ρ = .208, P = 0.059	ρ = .159, P = 0.126
- **Condition 5**	47.33 (22.33-61.42)	ρ = .051, P = 0.635	ρ = .062, P = 0.550
- **Condition 6**	41.34 (14.34-60.58)	ρ = .041, P = 0.699	ρ = .048, P = 0.649
MCT composite score			
- **Median (IQR)**	141 (134-150)	ρ = .128, P = 0.232	ρ = .047, P = 0.658
ABC-UK score			
- **Median (IQR)**	80.6 (64.6-92.75)	**ρ = .419, P < 0.001**	**ρ = .335, P = 0.001**
Timed Up and Go test score (s)			
- **Median (IQR)**	9.16 (7.49-11.18)	**ρ = .450, P < 0.001**	**ρ = .494, P < 0.001**

Values are expressed as median (IQR, interquartile range). SOT (sensory organisation test), MCT (motor control test), ABC-UK (activities-specific balance confidence scale). ICD (intermittent claudication distance, MWD (maximum walking distance). ρ (Spearman rank correlation coefficient), NS (non significant). P values are given and highlighted in **bold** if significant (P< 0.05).

3.2 The effect of percutaneous transluminal angioplasty on outcome measures

The second aim of this work was to investigate the effect of angioplasty treatment on clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life in patients with lower limb ischaemia.

3.2.1 Patient demographics

Table 3.4 shows the basic demographics for the angioplasty group. There were 47 patients who underwent angioplasty, with a median age of 69 (IQR 63-76). The majority of patients were male (N = 33) with 14 females included.

Table 3.4 Patient demographics at baseline for the angioplasty group

	Angioplasty
Number	47
Age (years)	
- **Median (IQR)**	69 (63-76)
Age group (N)	
- **20-59 years**	6
- **60-69 years**	21
- **70-79 years**	13
- **80+ years**	7
Gender (N)	M:33 F:14
Medical history (N)	
- **Ischaemic heart disease (Y/N)**	20 / 27
- **Hypertension (Y/N)**	32 / 15
- **On statin therapy (Y/N)**	35 / 12
- **CVA or TIA (Y/N)**	10 / 37
- **Diabetes (Y/N)**	9 / 38
- **Smoker (current / ex / never)**	12 / 29 / 6
- **OA lower limb / other / none**	20 / 10 / 17
- **Previous vascular intervention**	
- **- same leg angioplasty**	8
- **- other leg angioplasty**	6
- **- same leg surgery**	1
- **- other leg surgery**	0
- **- none**	26
- **- unknown**	6
Height (cm)	
- **Median (IQR)**	169 (159-173)
Weight (kg)	
- **Median (IQR)**	80 (69-93)
BMI (kg/m^2)	
- **Median (IQR)**	28 (25-31)
Visual acuity	
- **6/6 or 6/9**	33
- **6/12**	4
- **worse than 6/12**	4
- **unknown**	6

Values are expressed as median (IQR, interquartile range) or as numbers (N). M (male), F (female), BMI (body mass index). Yes / No. (Y/N). Cerebrovascular accident (CVA), transient ischaemic attack (TIA). Osteoarthritis (OA). Visual acuity fractions; 6/6 is normal vision, 6/9 indicated that at 6 metres the smallest row of letters the tested eye can discern would be what a normal eye can read at 9 metres, this applies to 6/12 but represents what a normal eye can read at 12 metres.

3.2.2 Clinical indicators of lower limb ischaemia

Clinical indicators of lower limb ischaemia were assessed for patients in the angioplasty group at baseline and were compared to values at each of the other time points (3, 6 and 12 months) (Appendix 5). From baseline there was a significant improvement in both pre and post exercise ABPI of the symptomatic leg at 3 months (baseline pre exercise ABPI 0.78 (0.61-0.92) improved to 0.90 (0.77-0.99) Figure 3.1) and post exercise 0.38 (0.25-0.63) improved to 0.63 (0.43-0.82), (Figure 3.2). The improvement from baseline persists post exercise (Figure 3.2) but not pre exercise, where the ABPI deteriorated between 3 and 12 months (Figure 3.1).

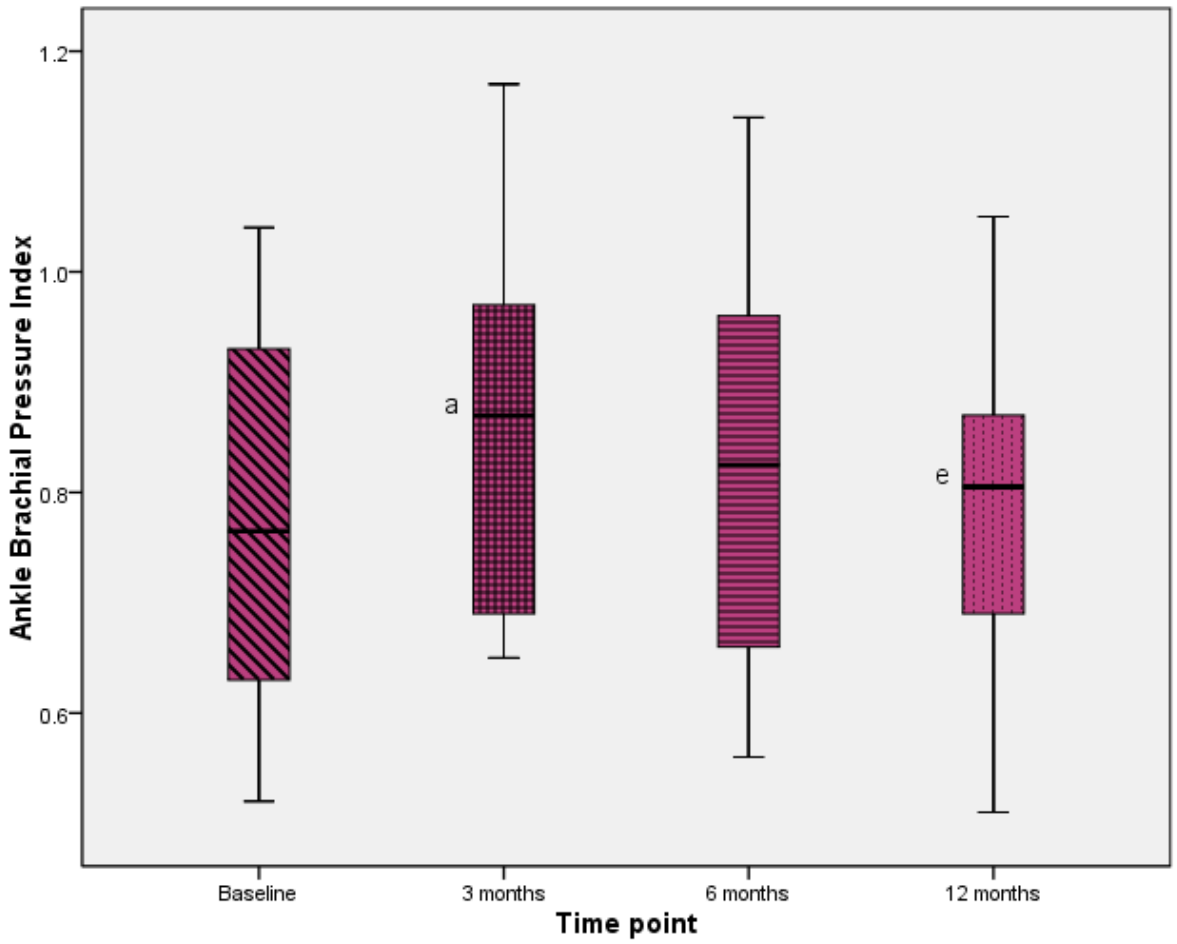


Figure 3.1 Pre exercise ankle brachial pressure index (ABPI) at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range, thick horizontal lines represent the median and whiskers represent the range. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a". A significant deterioration between 3 months and 12 months is indicated by "e".

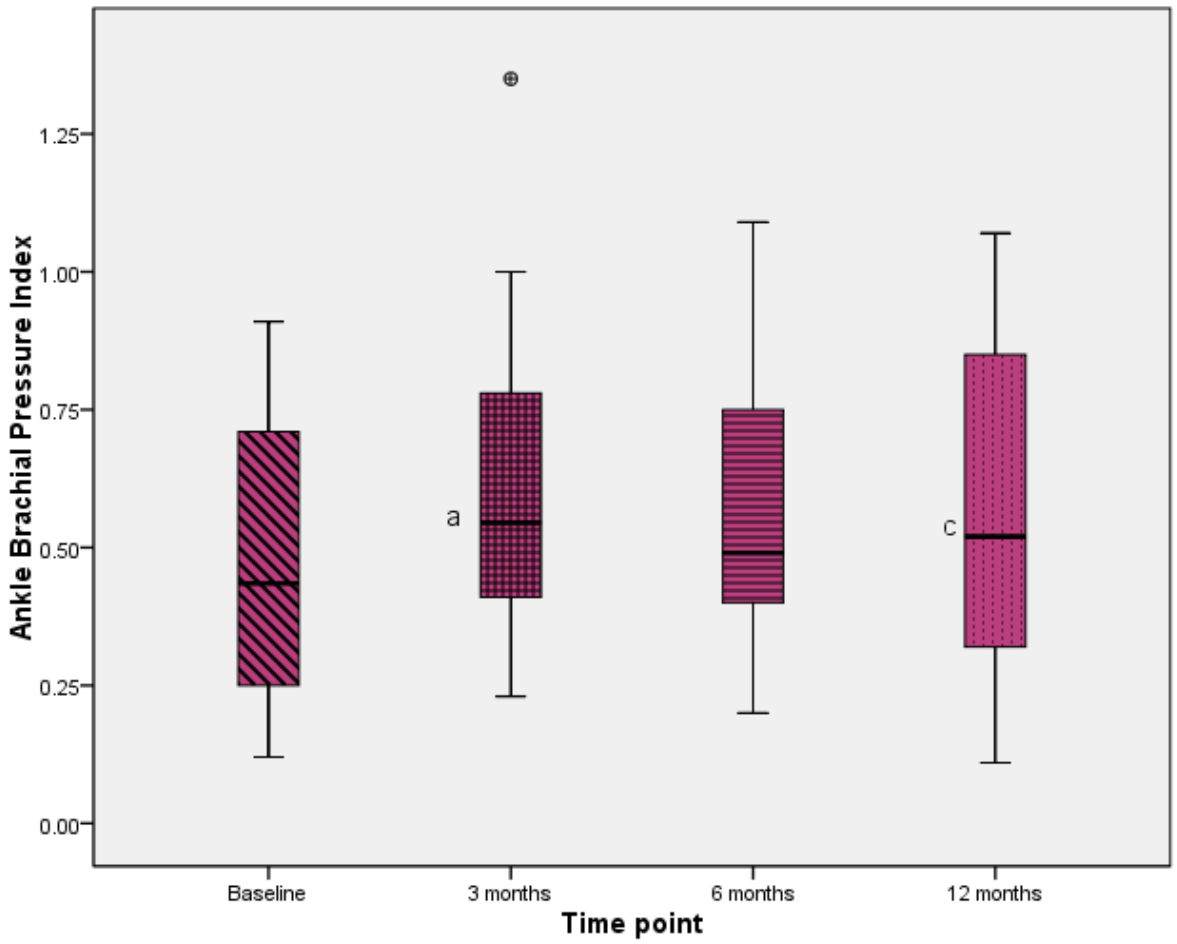


Figure 3.2 Post exercise ankle brachial pressure index (ABPI) at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range, the thick horizontal lines represent the median and whiskers represent the range with outliers represented by circles. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a". A significant improvement persisting between baseline and 12 months is indicated by "c".

Walking distances improved following angioplasty. Figure 3.3 shows a significant improvement from baseline to 3 months in ICD distance on the treadmill. There was a further significant improvement from 3 to 6 months and from baseline to 6 months. At 12 months there was no longer a significant difference to baseline but there remained a significant improvement when compared to 3 months. At baseline there is very little range in the ICD achieved by the study cohort, however after treatment, and particularly at 12 months, there is a much greater range in walking distances achieved.

Maximum walking distances on the treadmill also improved following angioplasty. Figure 3.4 shows that there was a significant improvement between baseline and each of the individual time points following angioplasty (3, 6 and 12 months). Patient reported walking distances also improved from baseline to each of the individual time points ($P < 0.05$) (Appendix 5).

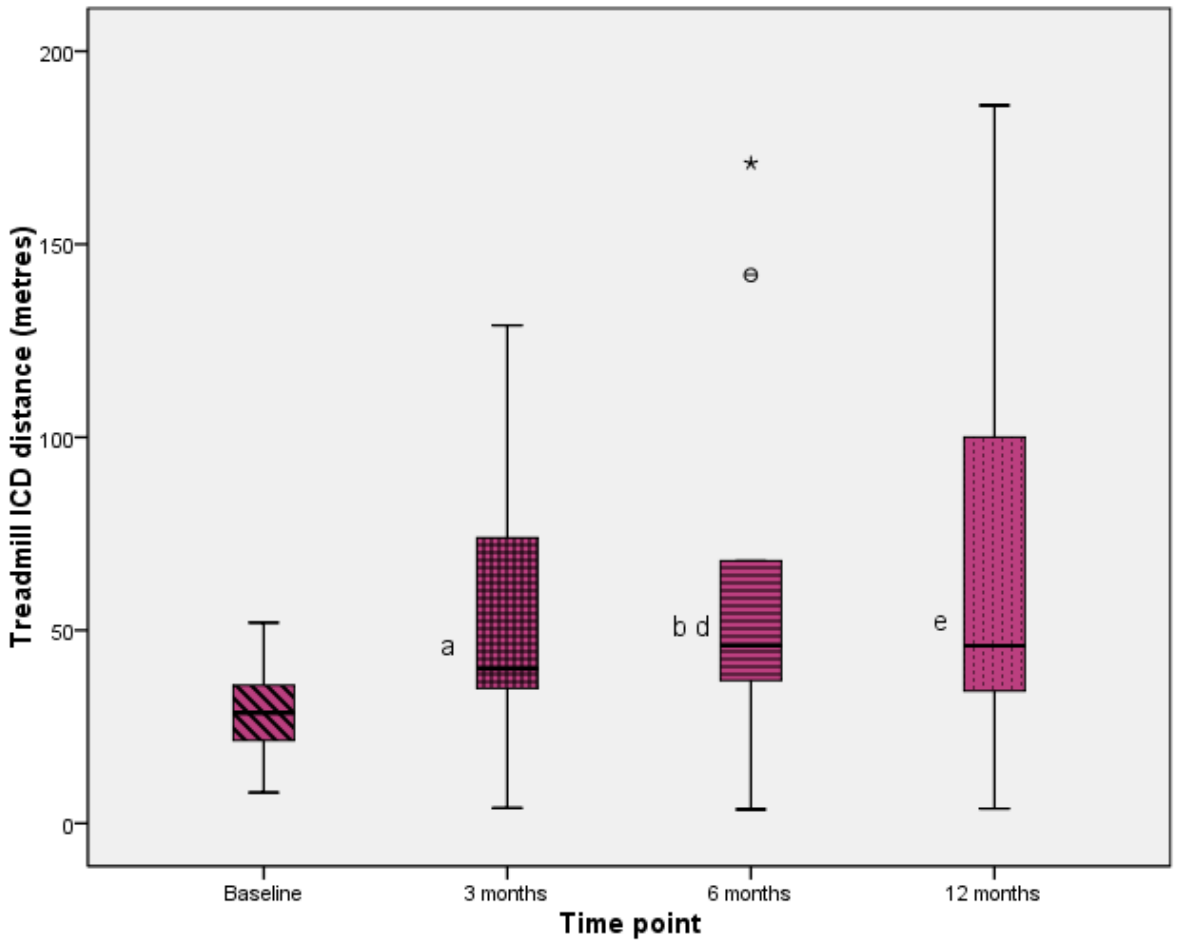


Figure 3.3 Treadmill intermittent claudication distance (ICD) at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a" and between baseline and 6 months is indicated by "b". Further significant improvements between 3 months and 6 months and 3 months and 12 months are indicated by "d" and "e" respectively.

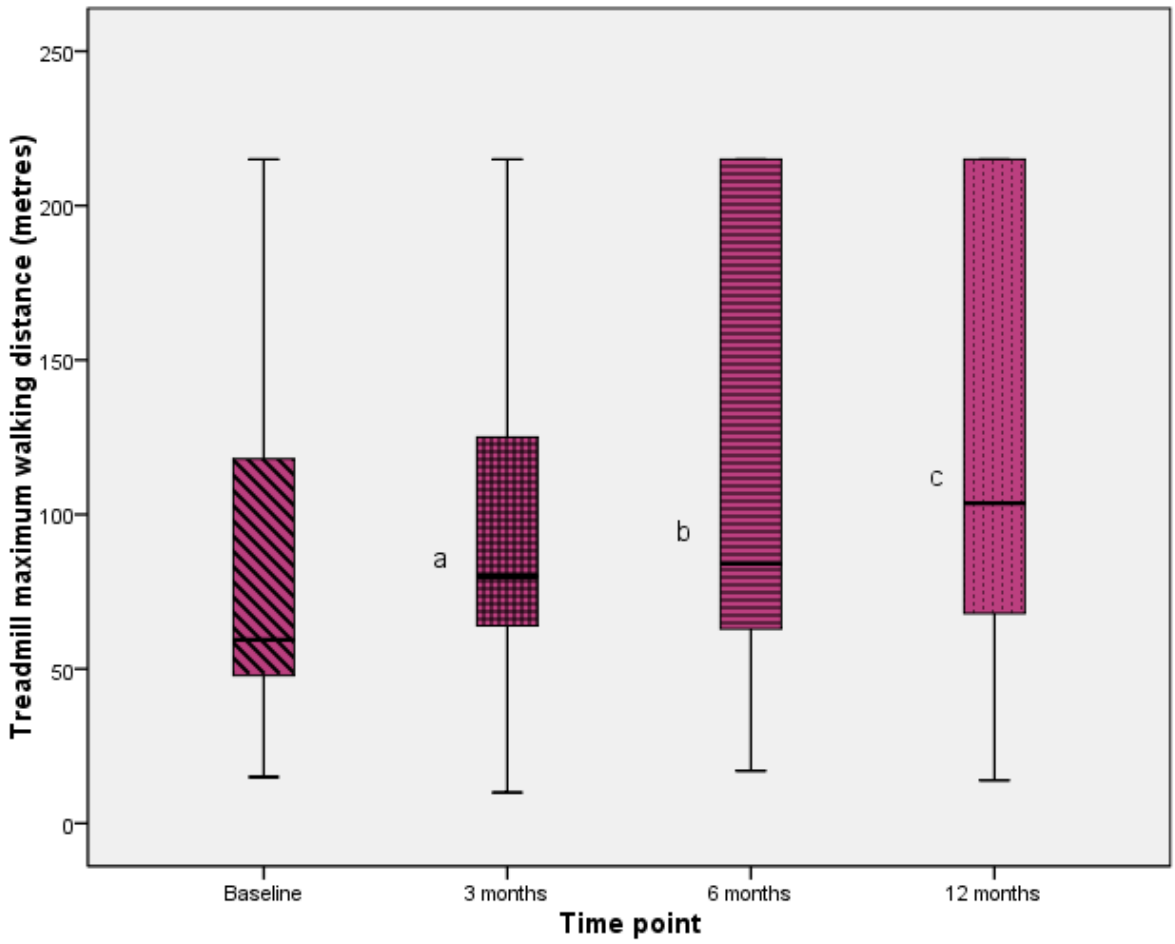


Figure 3.4 Treadmill maximum walking distance (MWD) at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a". A significant improvement persisting between baseline and 6 months is indicated by "b" and a significant difference between baseline and 12 months is represented by "c".

3.2.3 Effect of angioplasty on markers of physical function

The short performance physical battery scores (SPPB) were derived from the usual paced 4-metre walk, the chair stand test and the semi and full tandem balance tests. The scores can range between 0 and 12, with 12 being the best score possible. There was a significant improvement between baseline and 3 months scores for the angioplasty group, with a median of 9 (IQR 8-11) compared to a median of 10 (IQR 9-12) at 3 months ($P = 0.011$). The significant improvement was maintained at 6 (median of 10.5 (IQR 8-11)) and 12 months (median of 10 (IQR 9-11)) ($P = 0.001$ and $P = 0.002$ respectively) (Appendix 6).

Following angioplasty there were significant improvements in the 4 metre walk speed at usual pace from baseline to 6 and 12 months and at fastest pace, from baseline to 3, 6 and 12 months in turn ($P < 0.05$) (Table 3.5). The chair stand test results improved significantly between baseline and 3 months and baseline and 6 months. The improvement was not maintained and a significant deterioration was noted between baseline and 12 months (Table 3.6) (Appendix 6).

Table 3.5 Four metre walk speeds at usual and fastest pace for angioplasty patients

	Baseline	**3 months**	**6 months**	**12 months**
Usual pace (m/s) **Median (IQR)**	1.00 (0.74-1.15)	1.05 (0.83-1.19)	1.02 (0.83-1.15)*	1.03 (0.81-1.19)*
Fastest pace (m/s) **Median (IQR)**	1.31 (0.93-1.53)	1.36 (1.03-1.56)*	1.33 (0.96-1.48)*	1.27 (1.00-1.60)*

Values are expressed as median (IQR, interquartile range). Time points post angioplasty were compared using the Wilcoxon signed ranks test and a P value of < 0.05 is indicated by * when compared to baseline.

Table 3.6 Chair stand test for angioplasty patients

	Baseline	**3 months**	**6 months**	**12 months**
Chair stand test (s)	17.02	13.53	13.5	13.27
median (IQR)	(12.31-20.55)	(9.82-16.2)*	(11.16-16.54)*	(11.91-22.08)**

Values are expressed as median (IQR, interquartile range). Time points post angioplasty were compared using the Wilcoxon signed ranks test and a P value of < 0.05 is indicated by * when compared to baseline. A significant change is noted between 6 and 12 months by**.

There was no significant difference in semi tandem and full tandem stance between baseline and 3 and 6 months (score 0-30 seconds; worst to best). However between baseline and 12 months there was a significant improvement in both semi tandem stance (median 30 seconds (IQR 19.4-30) improving to 30 (30-30)) and full tandem stance times (median 29 seconds (IQR 8.9-30) improving to 30 (11.1-30)), ($P < 0.05$) (Appendix 6).

Hand grip strength did not alter significantly across the study period in the angioplasty group except for 2 time points. There was a significant improvement in right hand grip between baseline and 6 month but deterioration was noted between baseline and 12 months for the left hand grip strength (Appendix 6).

The angioplasty group showed significant improvements in walking distances determined using the six minute walk test following treatment (Figures 3.5 and 3.6). In terms of time until onset of claudication (ICD time), there were only significant improvements between baseline and 3 months and baseline and 6 months (Appendix 6). The maximum time patients were able to walk (MWD time) also improved significantly between baseline and 3 months and baseline and 6 months. There was a further significant improvement in maximum walking time between 3 and 6 months.

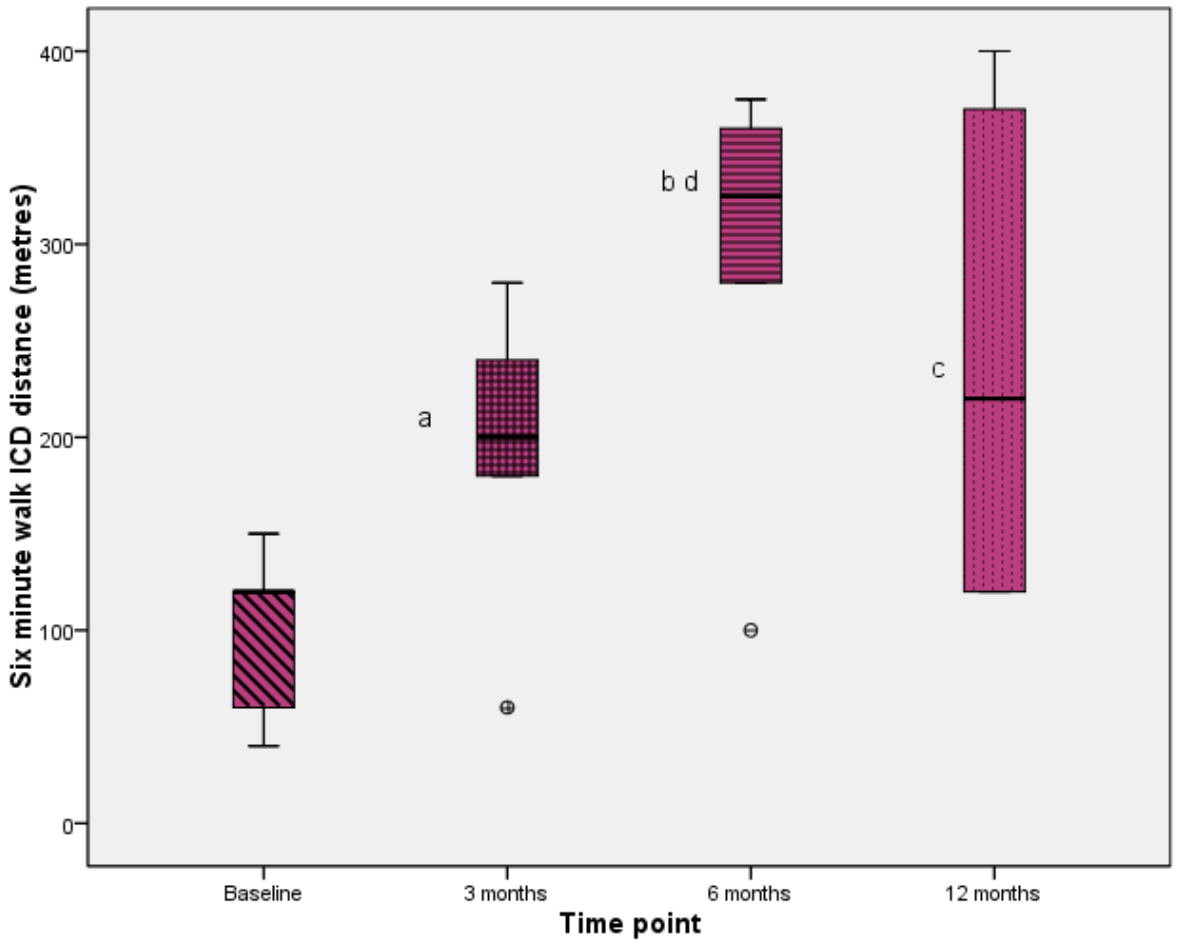


Figure 3.5 Six minute walk test intermittent claudication walking distance (ICD) at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). Significant improvements between baseline and 3 months, 6 months and 12 months are indicated by "a", "b" and "c" respectively. A further significant improvement between 3 and 6 months is indicated by "d".

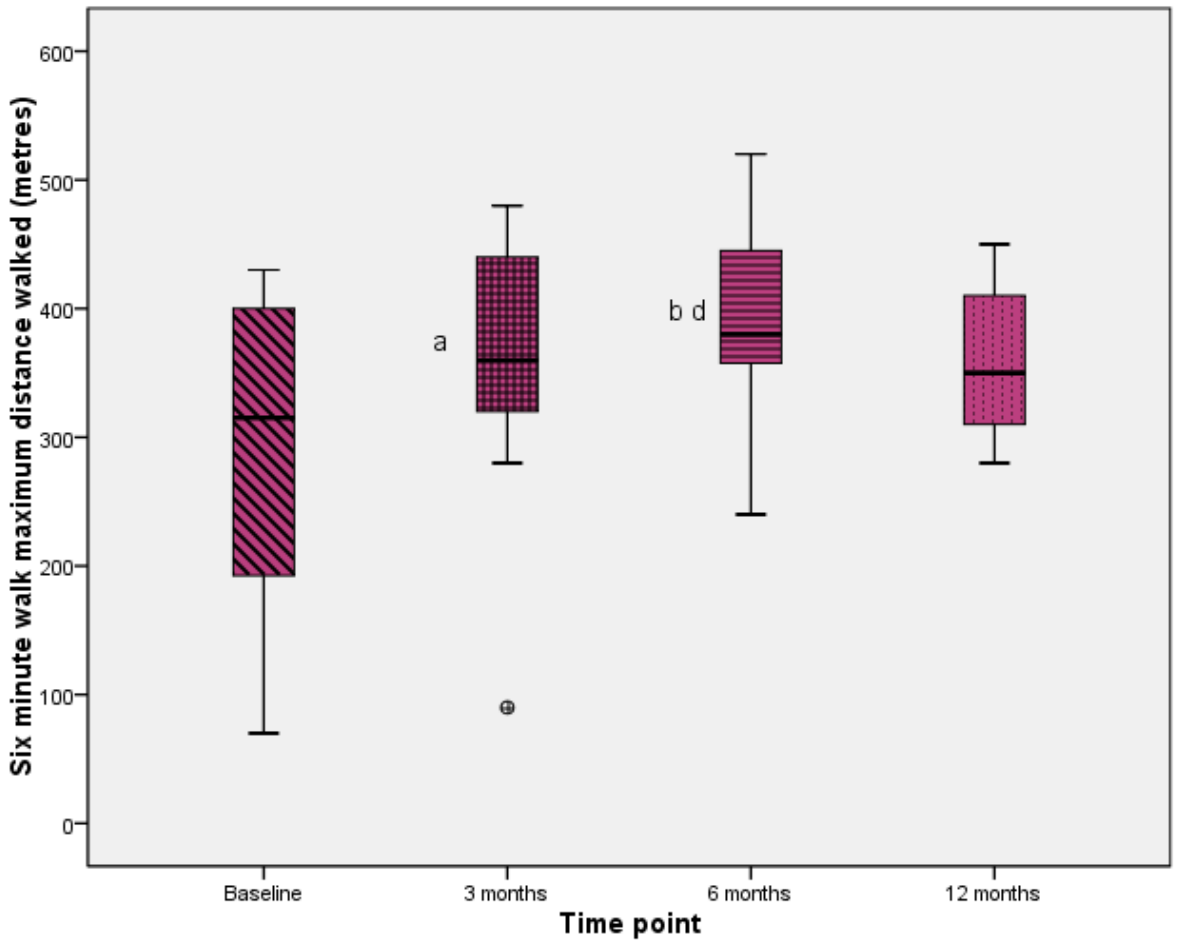


Figure 3.6 Six minute walk test maximum walking distance (MWD) at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a".A significant improvement persisting between baseline and 6 months is indicated by "b". A further significant improvement between 3 and 6 months is indicated by "d".

3.2.4 Effect of angioplasty on measures of balance

After angioplasty there was no significant improvement in the proportion of patients who passed the Sensory Organisation Test (SOT) (Appendix 7). The median SOT composite scores improved significantly between baseline and 3 months as shown in Figure 3.7. There was no other significant change between groups. There was a significant correlation between composite SOT scores and age at 3 months ($\rho = -0.369$, $P = 0.017$). This was not maintained at 6 or 12 months (6 months $\rho = -0.238$, $P > 0.05$, 12 months $\rho = -0.326$, $P > 0.05$).

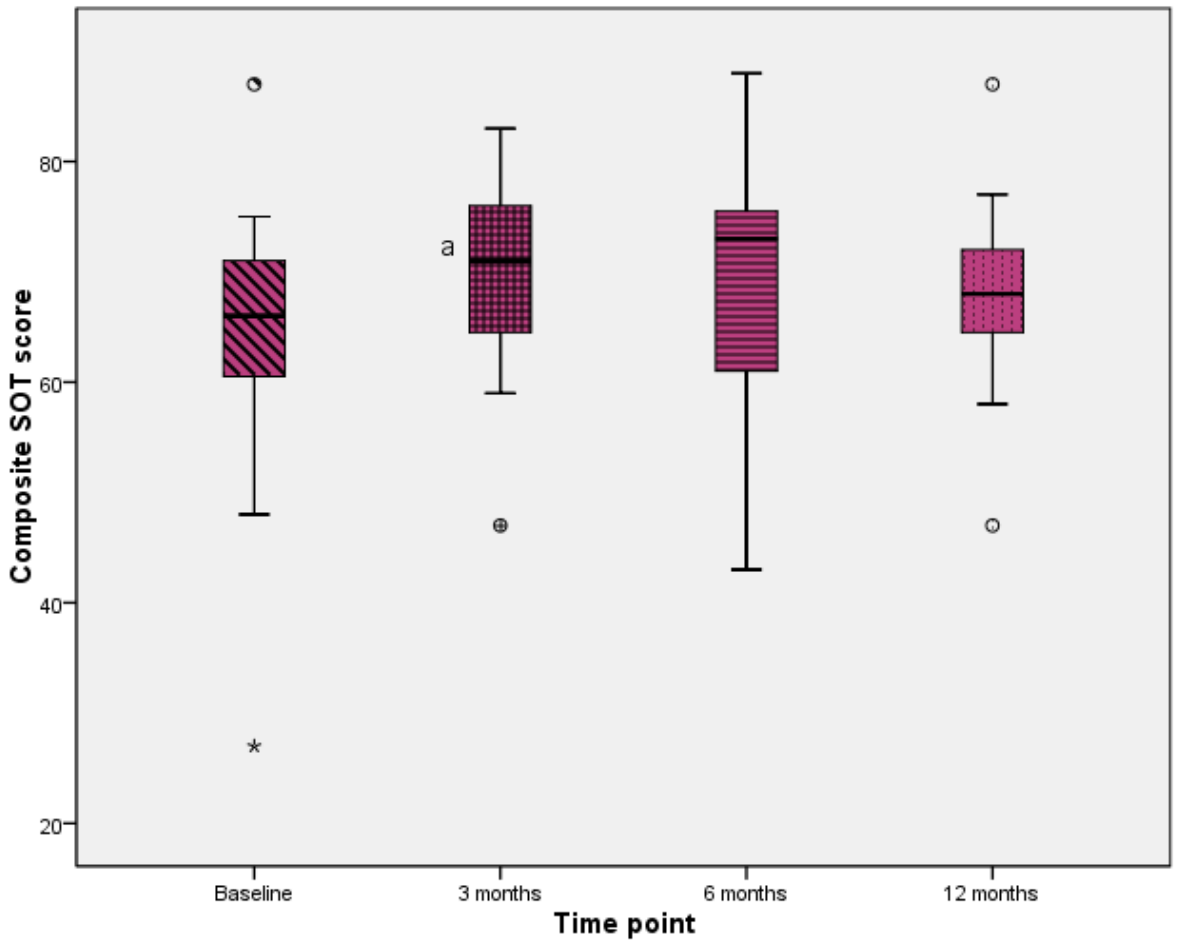


Figure 3.7 Composite sensory organisation test (SOT) scores at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a".

When scores for the individual conditions were assessed there was no significant change between any time points except during condition 4 of the SOT (where the somatosensory input was altered as the standing platform moved). There were significant improvements from baseline at 3, 6 and 12 months during condition 4 (Figure 3.8).

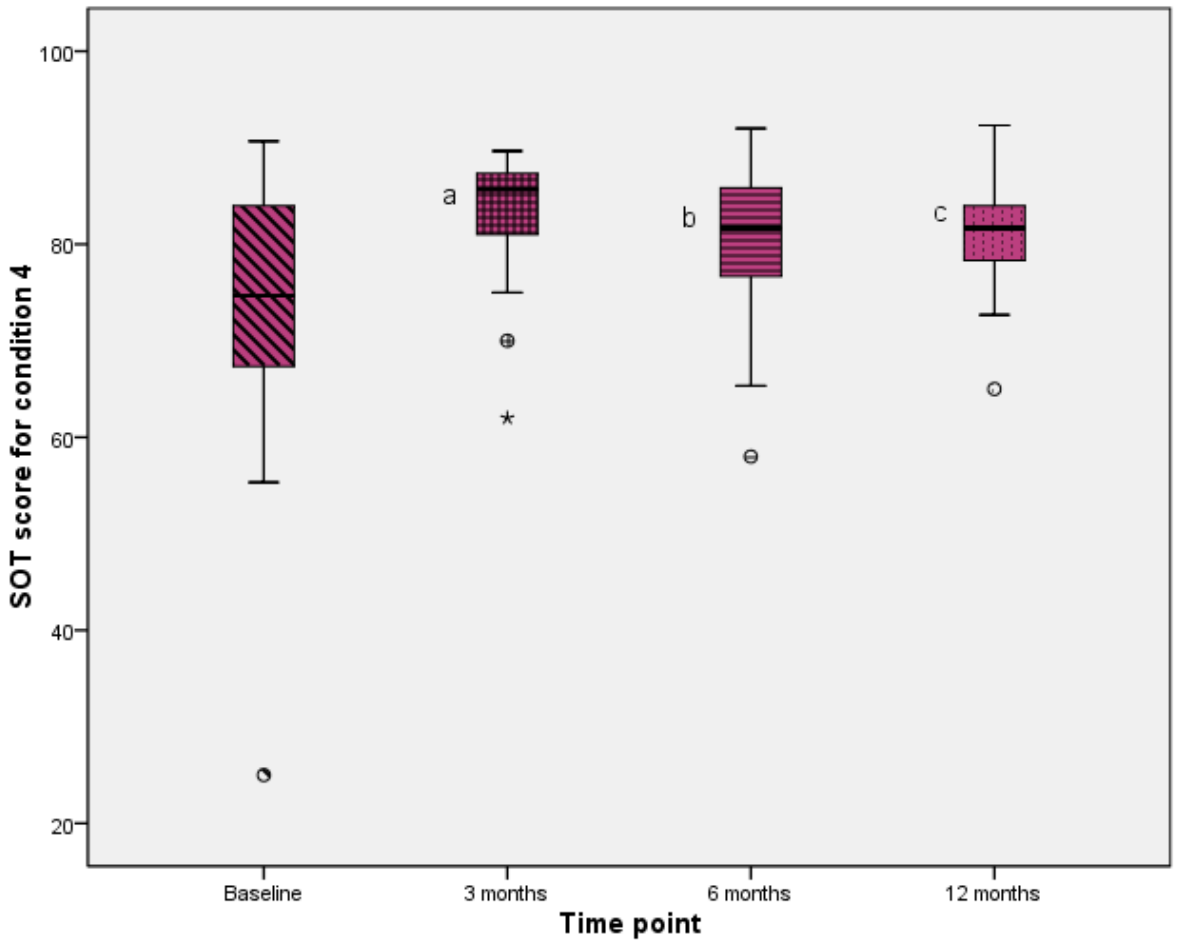


Figure 3.8 Sensory organisation test (SOT) score for condition 4 at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a".A significant improvement persisting between baseline and 6 months is indicated by "b" and between baseline and 12 months is indicated by "c".

There was no difference between time points in terms of the sensory breakdown analysis. Hip strategy was employed differently between baseline and 12 months (Appendix 7). The motor control test latency outcome did not improve across the study period for the angioplasty group. MCT composite scores improved significantly between 3 and 12 months and 6 and 12 months (Appendix 7).

3.2.5 Effect of angioplasty on falls incidence and risk of falling

At baseline 12 of the 47 patients reported a history of falls and 12 reported a history of stumbles. There was a significant reduction in the number of patients reporting falls and stumbles at 3 months (3 and 7 patients respectively) but no other significant differences were found between any other time points (Appendix 8). There was a significant improvement in Activities-specific Balance Confidence (ABC-UK) score between baseline and 3 months but there were no other significant changes across the time period as shown in Figure 3.9.

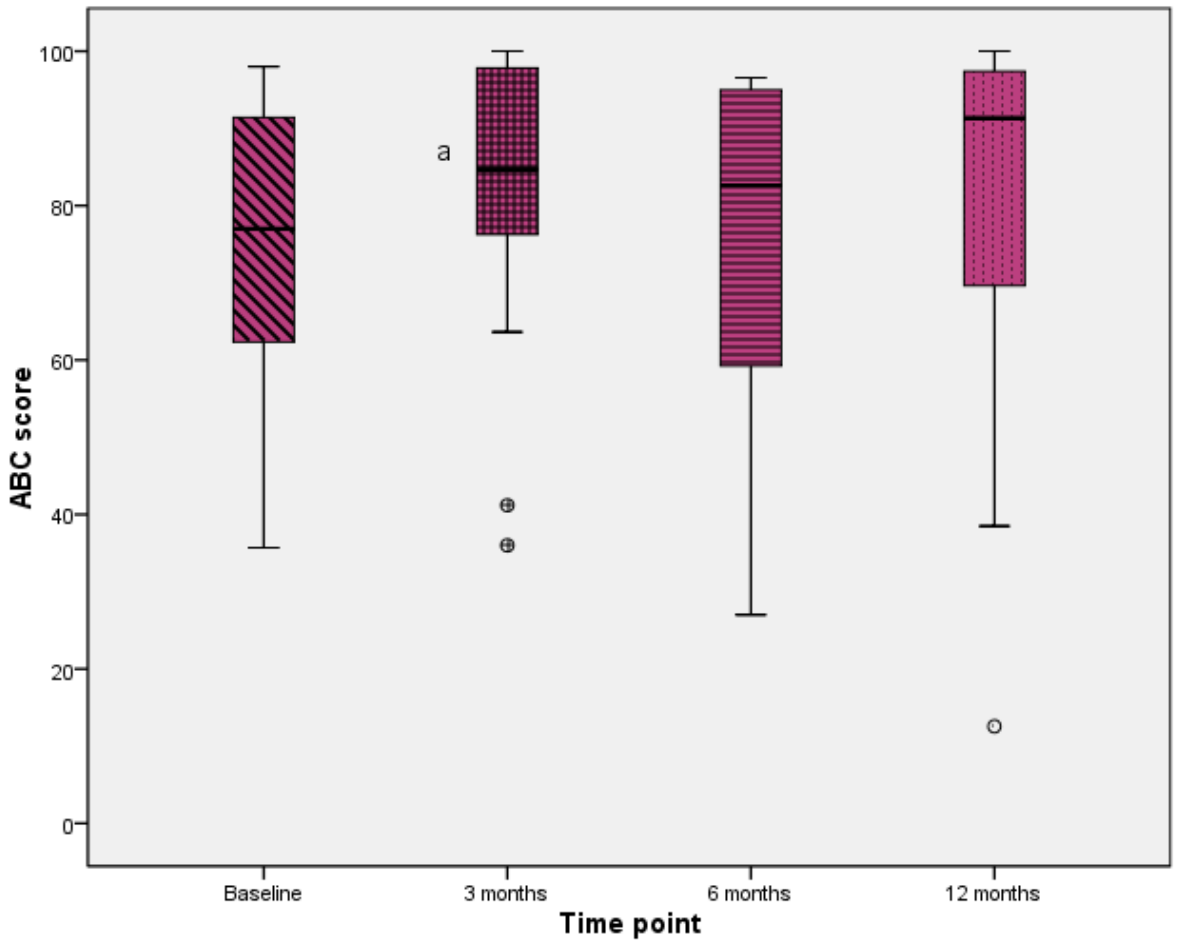


Figure 3.9 Activities-specific balance confidence scale (ABC-UK) score at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a".

TUG test scores improved after treatment and continued to improve at each visit when compared to baseline. There was also a significant improvement between 3 and 6 months in TUG scores, Figure 3.10. The proportion of patients who passed the TUG scores when age adjusted, also significantly improved at 3 and 12 months compared to baseline (Appendix 8).

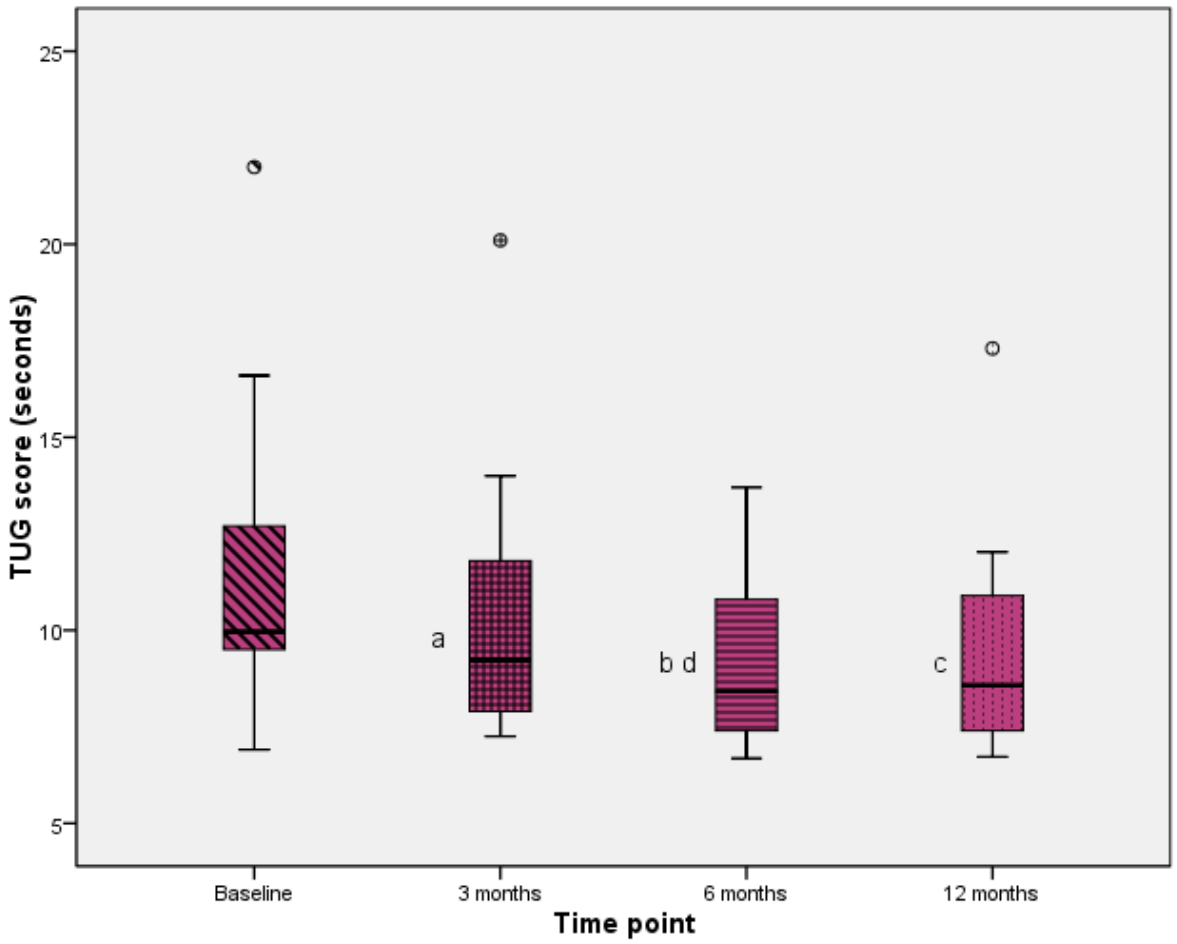


Figure 3.10 Timed up and go test (TUG) score at baseline, 3, 6 and 12 months for the angioplasty group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a" , baseline and 6 months by "b" and baseline and 12 months by "c". A further significant improvement between 3 and 6 months is indicated by "d".

3.2.6 Effect of angioplasty on patient reported quality of life

Table 3.7 indicates the improvements recorded in QOL after angioplasty. The disease specific VascuQol quality of life measure showed improvement in every domain at 3, 6 and 12 months when compared to baseline. Short form 36 indicated significant changes from baseline 14 times whereas short form 8 showed 11 significant changes from baseline as indicated by the shaded results in Table 3.7. The VascuQol showed improvements in the social domain which was not seen with SF36. Despite improvements in physical function, no improvement in general health was seen with SF36 or SF8.

Table 3.7 Quality of life data for the angioplasty group

	Baseline	3 months	6 months	12 months	P
SF36					
- **Physical function**	35 (28.75-50)	55.5 (37.5-80)	52.5 (35-71.25)	52.5 (33.75-80)	**[a,b]<0.001, [c]0.001**
- **Role physical**	0 (0-50)	50 (0-100)	25 (0-100)	0 (0-100)	**[a]<0.001, [b]0.046,** [c]0.056
- **Bodily pain**	36.5 (31-51)	62 (41-77)	41 (31-88)	46 (23.5-62)	**[a]<0.001,[b]0.019,** [c]0.290
- **General health**	47 (35-69.5)	57 (38.5-72)	45 (35-67)	46 (28.75-72)	[a]0.202, [b]0.459, [c]0.922
- **Vitality**	50 (30-65)	60 (42.5-75)	55 (38.75-70)	50 (40-75)	**[a]0.008,[b]0.011,[c]0.013**
- **Role emotional**	50 (33.3-87.5)	100 (16.65-100)	79.35 (0-100)	66.7 (0-100)	**[a]0.024,** [b]0.431, [c]0.352
- **Mental health**	67.35 (48-100)	76 (62-88)	80 (52-92)	76 (56-84)	[a]0.270, [b]0.338, [c]0.352
- **Social function**	73.5 (50-87.63)	75 (50-100)	75 (50-100)	62.5 (50-90.63)	[a]0.208, [b]0.331, [c]0.383
- **Physical summary**	30.1 (25.2-33.9)	41.8 (27.75-48.95)	31.8 (27.4-48.55)	32.3 (24.05-48.6)	**[a]<0.001,[b]0.001, [c]0.010**
- **Mental summary**	51.2 (40.3-60.9)	52.7 (42.85-60.7)	51.2 (39.85-59.7)	51.4 (41.05-57.7)	[a]0.287, [b]0.313, [c]0.456
VascuQol					
- **Pain**	4.0 (2.75-4.63)	5.63 (3.94-6.56)	5.25 (3.75-6.25)	5 (3.75-6)	**[a,b,c]<0.001**
- **Social**	4.0 (3.5-5.5)	6.5 (4.38-7)	6.5 (4-7)	6 (4.5-6.5)	**[a]<0.001, [b]0.008, [c]0.003**
- **Activities**	3.63 (3.19-4.32)	5.44 (3.72-6.88)	5.25 (3.38-6.13)	4.25 (3.38-6.13)	**[a,b]<0.001, [c]0.002**
- **Symptoms**	4.75 (4-5.75)	6 (5.25-6.75)	5.75 (4.5-6.5)	5.75 (4.75-6.25)	**[a,b,c]<0.001**
- **Emotional**	4.57 (3.57-5.5)	6.36 (4.43-7)	6.14 (4.29-6.86)	6 (4.43-6.86)	**[a,b,c]<0.001**
- **Total**	4.32 (3.22-5.02)	5.9 (4.19-6.66)	5.68 (3.96-6.36)	5.2 (4.08-6.32)	**[a,b,c]<0.001**
SF8					
- **Physical function**	30.3 (30.3-40.1)	40.1 (30.3-48.3)	40.1 (30.3-48.3)	40.1 (30.3-48.3)	[a]0.425, **[b]0.006, [c]0.037**
- **Role physical**	38.7 (28.3-46.9)	3.87 (28.3-46.9)	38.7 (38.7-54)	38.7 (28.3-46.9)	[a]0.781, **[b]0.006,** [c]0.161
- **Bodily pain**	40.1 (31.5-40.1)	40.1 (40.1-53.4)	40.1 (40.1-53.4)	40.1 (31.5-47.7)	[a]0.306,**[b]0.017,** [c]0.860
- **General health**	38.4 (38.4-46.4)	38.4 (38.4-46.4)	38.4 (38.4-46.4)	38.4 (34.05-46.4)	[a]0.838, [b]0.075, [c]0.639
- **Vitality**	45.2 (45.2-55.6)	45.2 (35.8-55.6)	45.2 (35.8-45.2)	45.2 (45.2-55.6)	[a]0.375, [b]0.857, [c]0.253
- **Role emotional**	45.7 (32.85-52.4)	48.3 (38.1-52.4)	52.4 (38.1-52.4)	45.7 (38.1-52.4)	**[a]0.046, [b]0.032,** [c]0.145
- **Mental health**	49.6 (36.55-56.80)	49.6 (46.9-56.8)	49.6 (41.5-56.8)	49.6 (41.5-56.8)	**[a]0.037,** [b]0.093, [c]0.138
- **Social function**	40.4 (29.5-49.5)	49.5 (29.5-55.3)	40.4 (40.4-55.3)	40.4 (40.4-55.3)	[a]0.525, **[b]0.035, [c]0.007**
- **Physical summary**	34.65 (29.18-40.38)	40.7 (33.7-49.33)	36.5 (32.4-50.1)	38.6 (26.9-48.9)	**[a]0.005, [b]0.001,** [c]0.135
- **Mental summary**	46.3 (38.58-57.38)	52.85 (44.18-56.98)	52.4 (40.8-57.5)	49.7 (40.5-54.7)	[a]0.082, [b]0.548, [c]0.282

Values are expressed as median (IQR, interquartile range). Each time point was compared to baseline using Wilcoxon signed ranks test. P values are shown and highlighted in bold if <0.05. [a]Wilcoxon 0-3, [b]Wilcoxon 0-6,[c]Wilcoxon 0-12. SF36 (Short Form 36), SF8 (Short Form 8). Significant improvements from baseline indicated by highlighted text.

3.3 The effect of a supervised exercise programme on outcome measures

The third aim of this work included investigating the effect of a supervised exercise programme (SEP) on clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life in patients with lower limb ischaemia.

3.3.1 Patient demographics

Table 3.8 shows the basic demographics for the angioplasty group. There were 51 patients who participated in SEP, with a median age of 70 (IQR 64-74). The majority of patients were male (N = 34) with 17 females included.

Table 3.8 Patient demographics at baseline for the SEP group

	SEP
Number	51
Age (years)	
- **Median (IQR)**	70 (64-74)
Age group (N)	
- **20-59 years**	6
- **60-69 years**	19
- **70-79 years**	21
- **80+ years**	5
Gender (N)	
- **M**	34
- **F**	17
Medical history (N)	
- **Ischaemic heart disease (Y/N)**	22 / 28
- **Hypertension (Y/N)**	38 / 11
- **On statin therapy (Y/N)**	44 / 6
- **CVA or TIA (Y/N)**	8 / 42
- **Diabetes (Y/N)**	15 / 35
- **Smoker (current / ex / never)**	15 / 27 / 8
- **OA lower limb / other / none**	14 / 11 / 25
- **Previous vascular intervention**	
- **- same leg angioplasty**	10
- **- other leg angioplasty**	2
- **- same leg surgery**	2
- **- other leg surgery**	2
- **- none**	30
- **- unknown**	5
Height (cm)	
- **Median (IQR)**	167 (162-173)
Weight (kg)	
- **Median (IQR)**	77 (68-86)
BMI (kg/m^2)	
- **Median (IQR)**	27.7 (25.63-30.4)
Visual acuity	
- **6/6 or 6/9**	20
- **6/12**	9
- **worse than 6/12**	10
- **unknown**	12

Values are expressed as median (IQR, interquartile range) or as numbers (N). SEP (structured exercise programme), M (male), F (female), BMI (body mass index). Yes / No. (Y/N). Cerebrovascular accident (CVA), transient ischaemic attack (TIA). Osteoarthritis (OA). Visual acuity fractions; 6/6 is normal vision, 6/9 indicated that at 6 metres the smallest row of letters the tested eye can discern would be what a normal eye can read at 9 metres, this applies to 6/12 but represents what a normal eye can read at 12 metres.

3.3.2 Clinical indicators of lower limb ischaemia

Ankle Brachial Pressure Index (ABPI) did not significantly alter across the study period in the SEP group as shown in Figures 3.11 and 3.12.

Walking distances did improve following exercise. The treadmill ICD distance improved significantly between baseline and 3 months and baseline and 6 months (Figure 3.13). The maximum walking distance on the treadmill (MWD) improved significantly between baseline and 3 months (Figure 3.14). Patient reported walking distances also improved from baseline to each of the individual time points (3, 6 and 12 months) ($P < 0.05$) (Appendix 9).

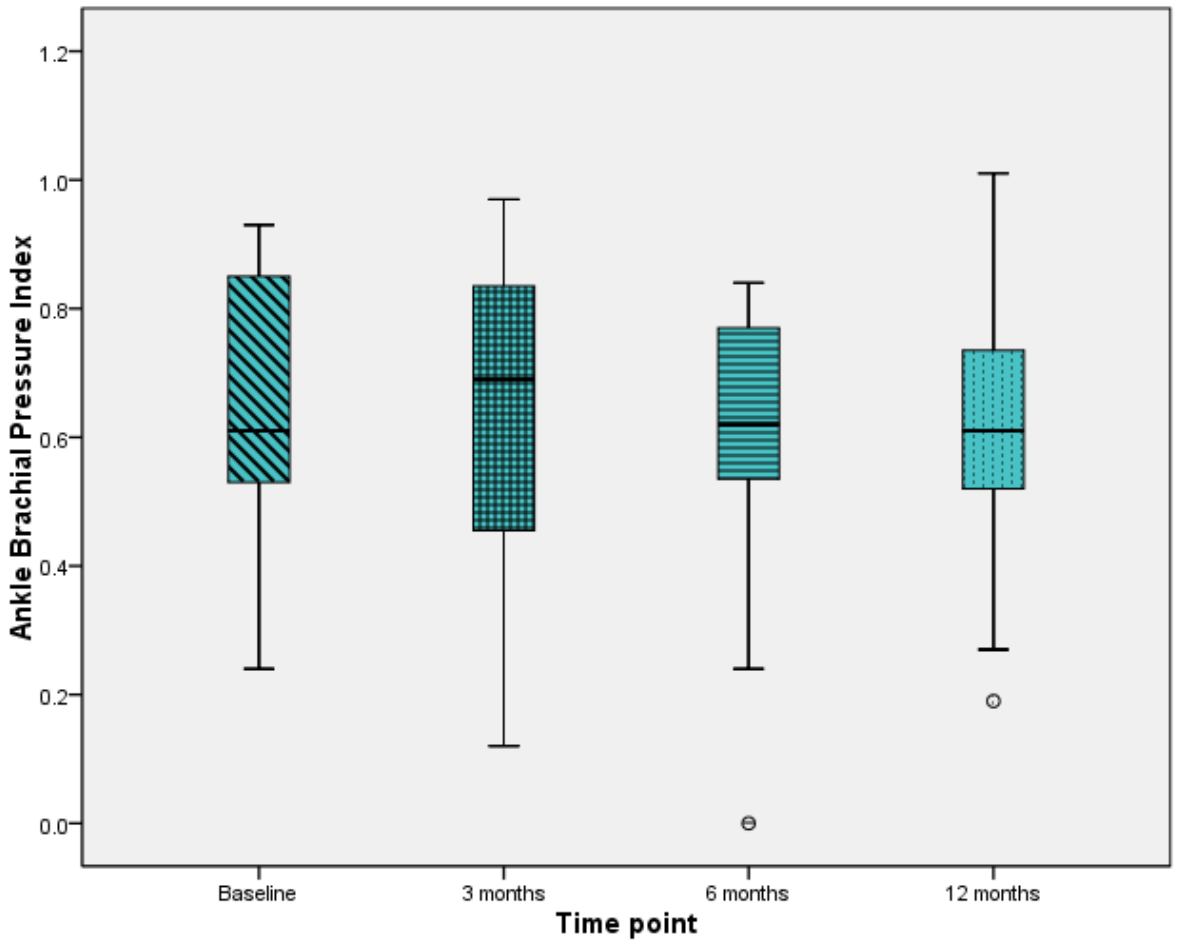


Figure 3.11 Pre exercise ankle brachial pressure index (ABPI) at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). There were no significant differences between any of the time points. SEP (structured exercise programme).

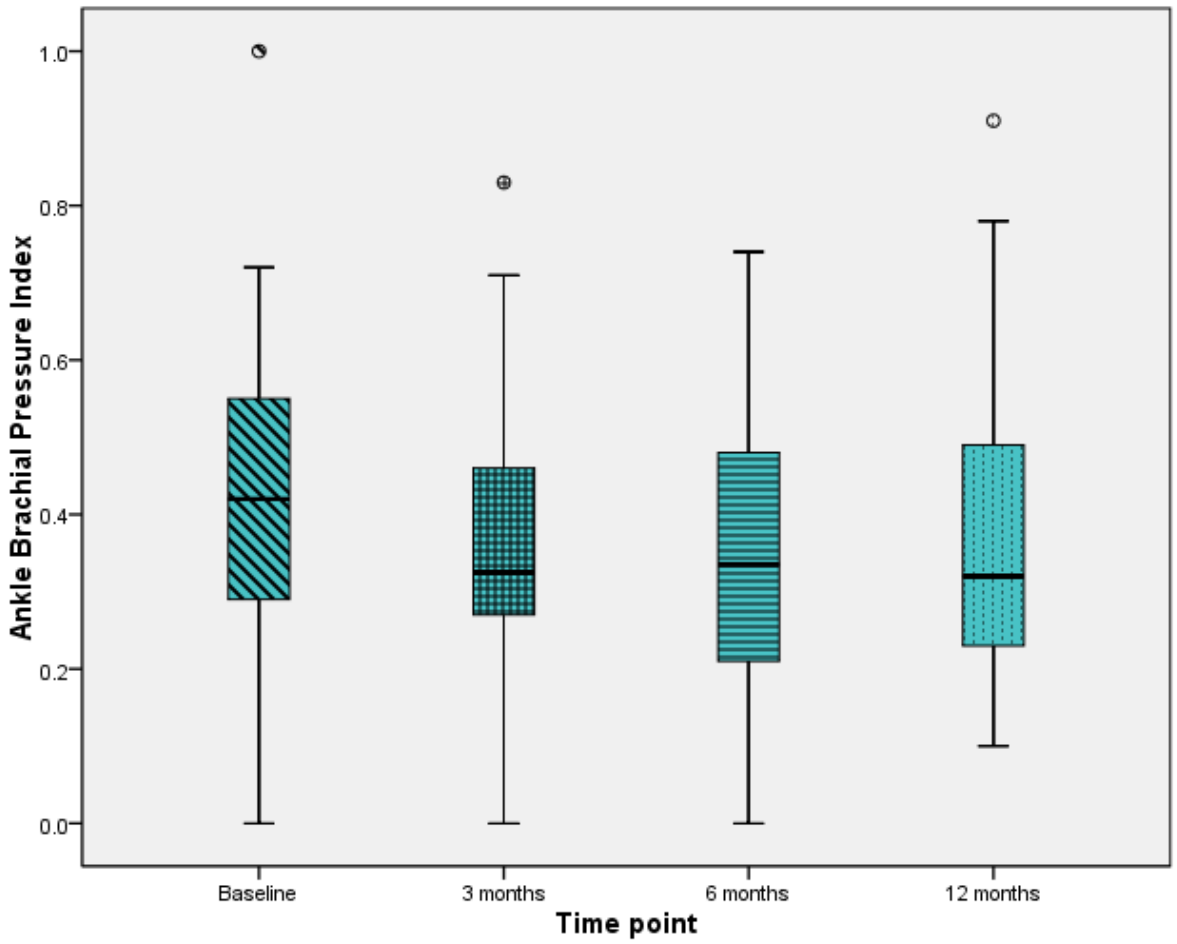


Figure 3.12 Post exercise ankle brachial pressure index (ABPI) at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). There were no significant differences between any of the time points. SEP (structured exercise programme).

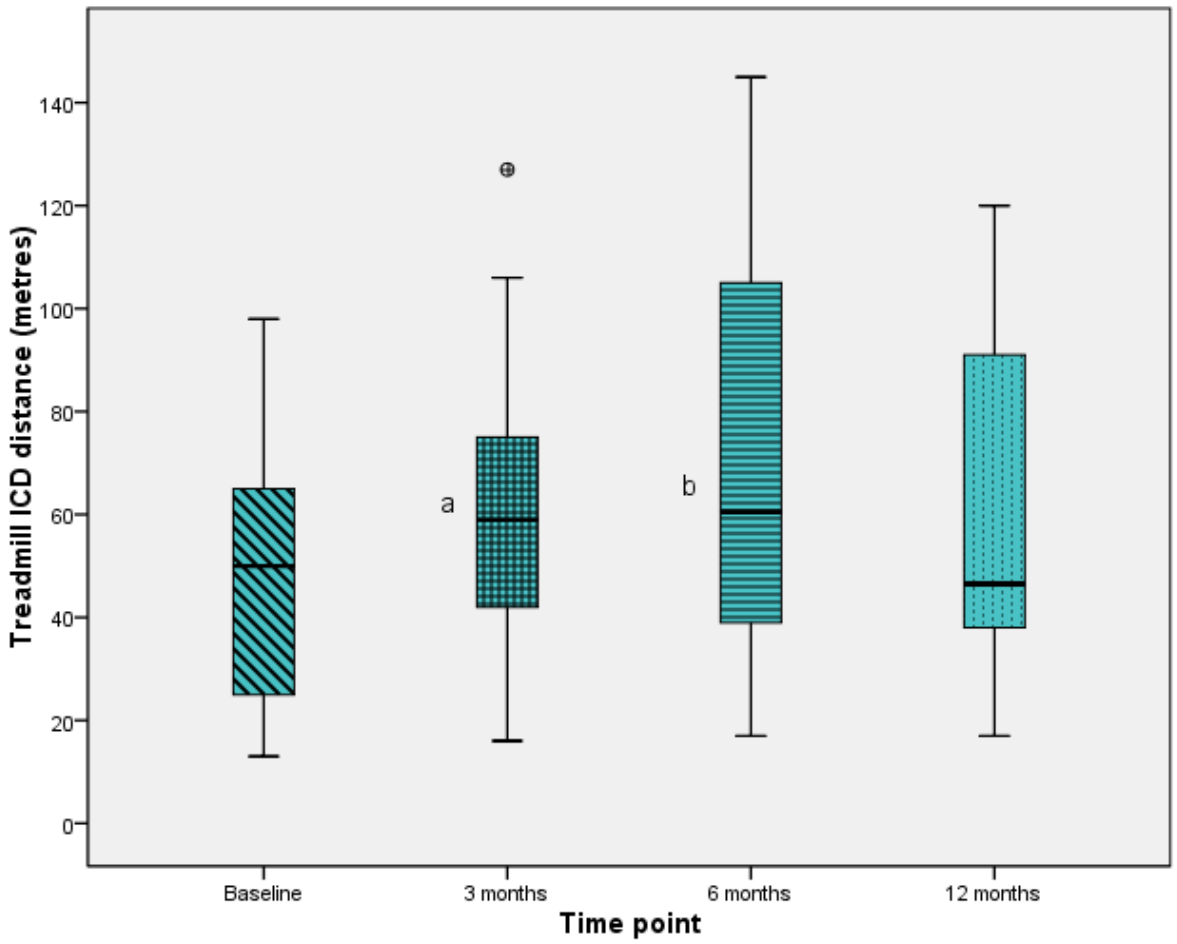


Figure 3.13 Treadmill intermittent claudication distance (ICD) at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a" and between baseline and 6 months by "b". SEP (structured exercise programme).

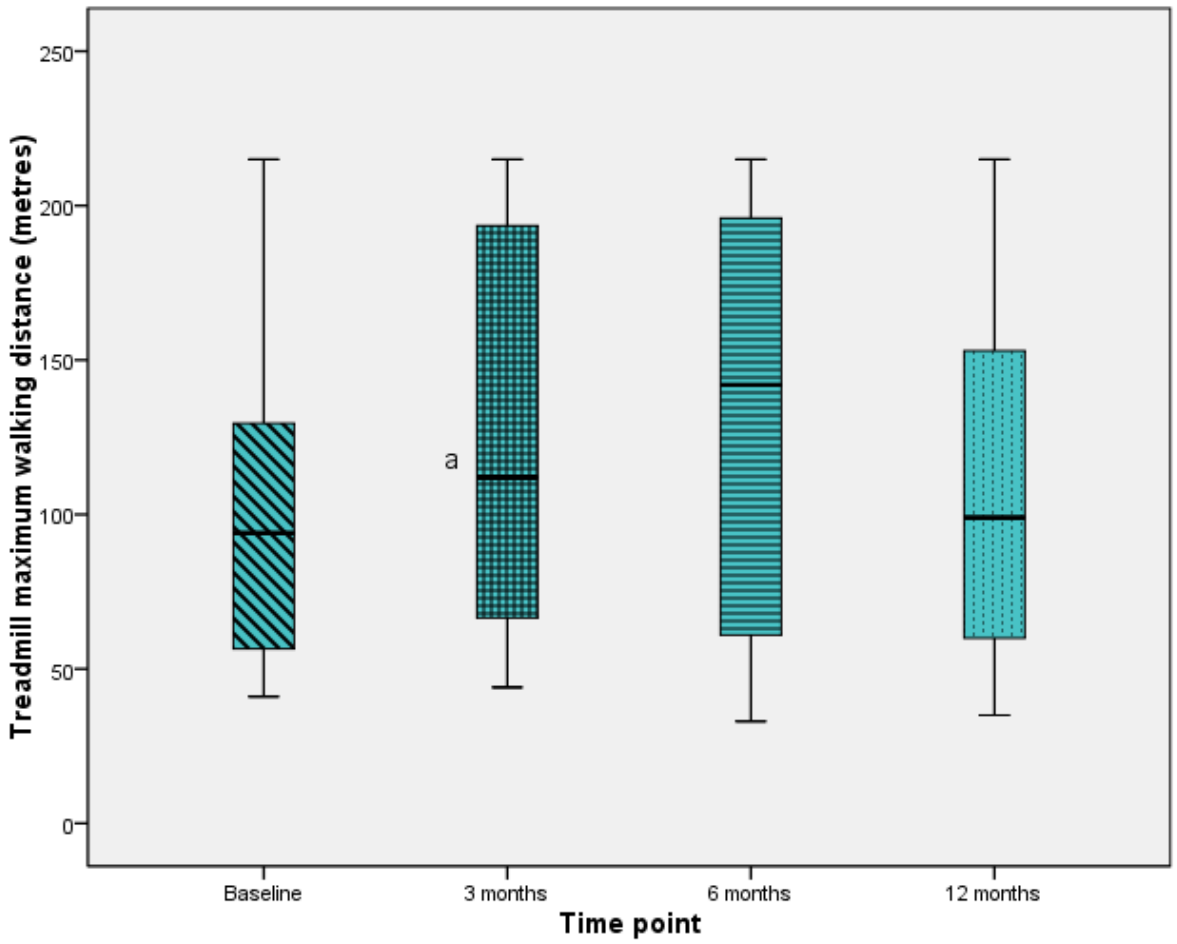


Figure 3.14 Treadmill maximum walking distance (MWD) at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a". SEP (structured exercise programme).

3.3.3 Effect of a SEP on markers of physical function

The short performance physical battery scores (SPPB) were derived from the usual paced 4-metre walk, the chair stand test and the semi and full tandem balance tests (score 0-12; worst to best). For the SEP group, a significant improvement was noted between baseline and 3 months, with a median of 10 (IQR 9-11.25) at baseline compared to a median of 11 (IQR 10-12) at 3 months (P = 0.005). This improvement was not maintained at later time points (Appendix 10).

Patients performed much better on the 4 metre walk test at both usual and fastest pace after SEP treatment. Significant improvements were seen at 3 and 6 months, compared to baseline, for both paces and at 12 months a further improvement was noted from baseline for the usual paced 4 metre walk (Table 3.9). There was no significant change in chair stand test results at any time point after SEP treatment, despite faster 4 metre walk test results (Appendix 10).

Table 3.9 Four metre walk speeds at usual and fastest pace for the SEP group

	Baseline	3 months	6 months	12 months
Usual pace (m/s) **Median (IQR)**	1.03 (0.92-1.16)	1.11 (1.04-1.27)*	1.15 (1.00-1.31)*	1.16 (0.98-1.37)*
Fastest pace (m/s) **Median (IQR)**	1.39 (1.14-1.60)	1.43 (1.26-1.64)*	1.45 (1.20-1.75)*	1.52 (1.12-1.81)

Values are expressed as median (IQR, interquartile range). Time points were compared using the Wilcoxon signed ranks test and a significant P value of <0.05 is indicated by * when compared to baseline. SEP (structured exercise programme).

Semi tandem and full tandem stance times were not significantly different from baseline at any of the time points. However, full tandem stance times significantly deteriorated between 3 and 12 months and 6 and 12 months (Appendix 10).

Hand grip strength deteriorated significantly between baseline and 3 months for SEP patients in both hands. This deterioration was maintained at 6 months in the left hand only but at 12 months there was no difference in hand grip strength when compared to baseline (Appendix 10).

The SEP group showed significant improvements in walking distances during the six minute walk test following treatment at 3 and 6 months (Figures 3.15 and 3.16). Maximum walking distance deteriorated between 3 and 12 months (Figure 3.16). In terms of time until the onset of claudication (ICD time) there was only a significant improvement between baseline and 3 months. The maximum time patients were able to walk (MWD) did not change during the study period (Appendix 10).

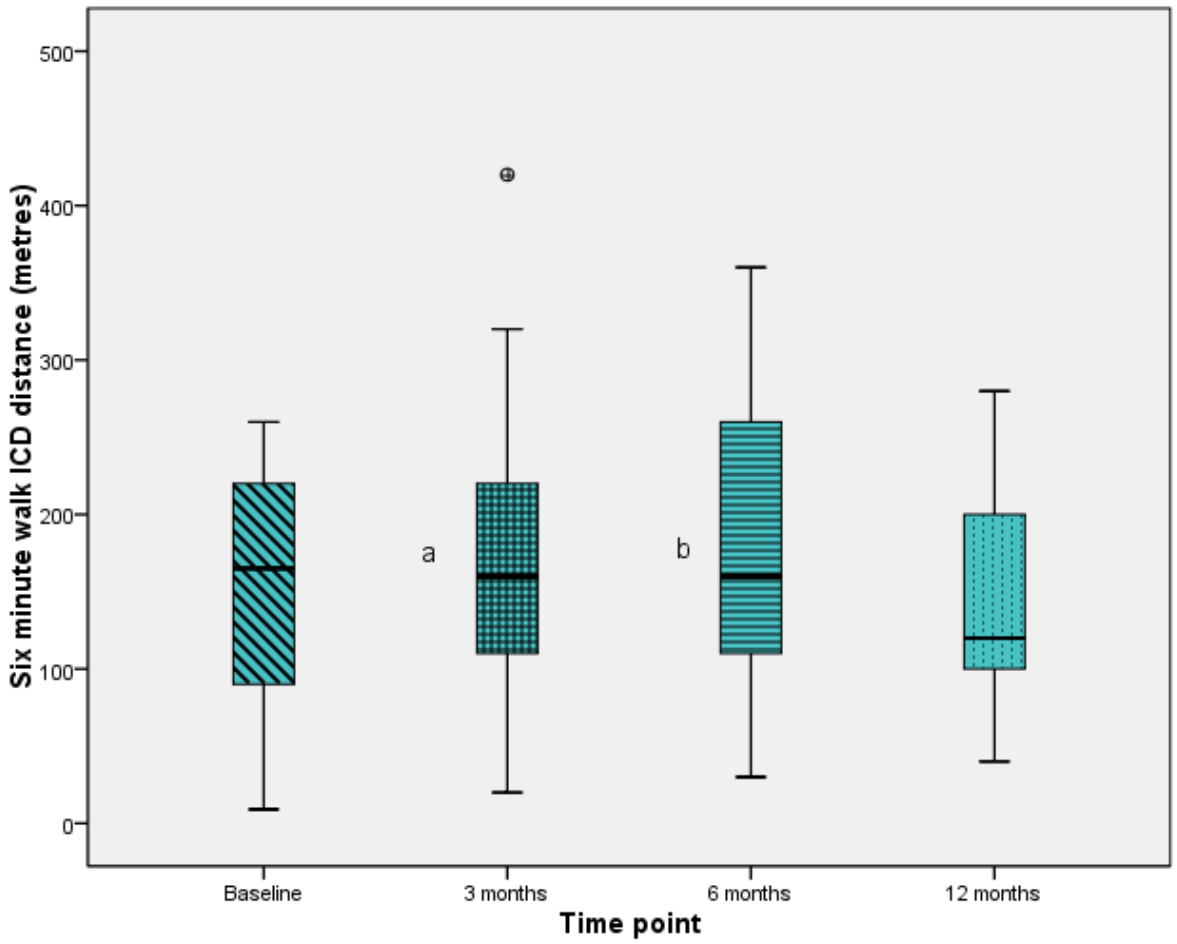


Figure 3.15 Six minute walk intermittent claudication distance (ICD) at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a" and between baseline and 6 months is indicated by "b". ICD (intermittent claudication distance); SEP (structured exercise programme).

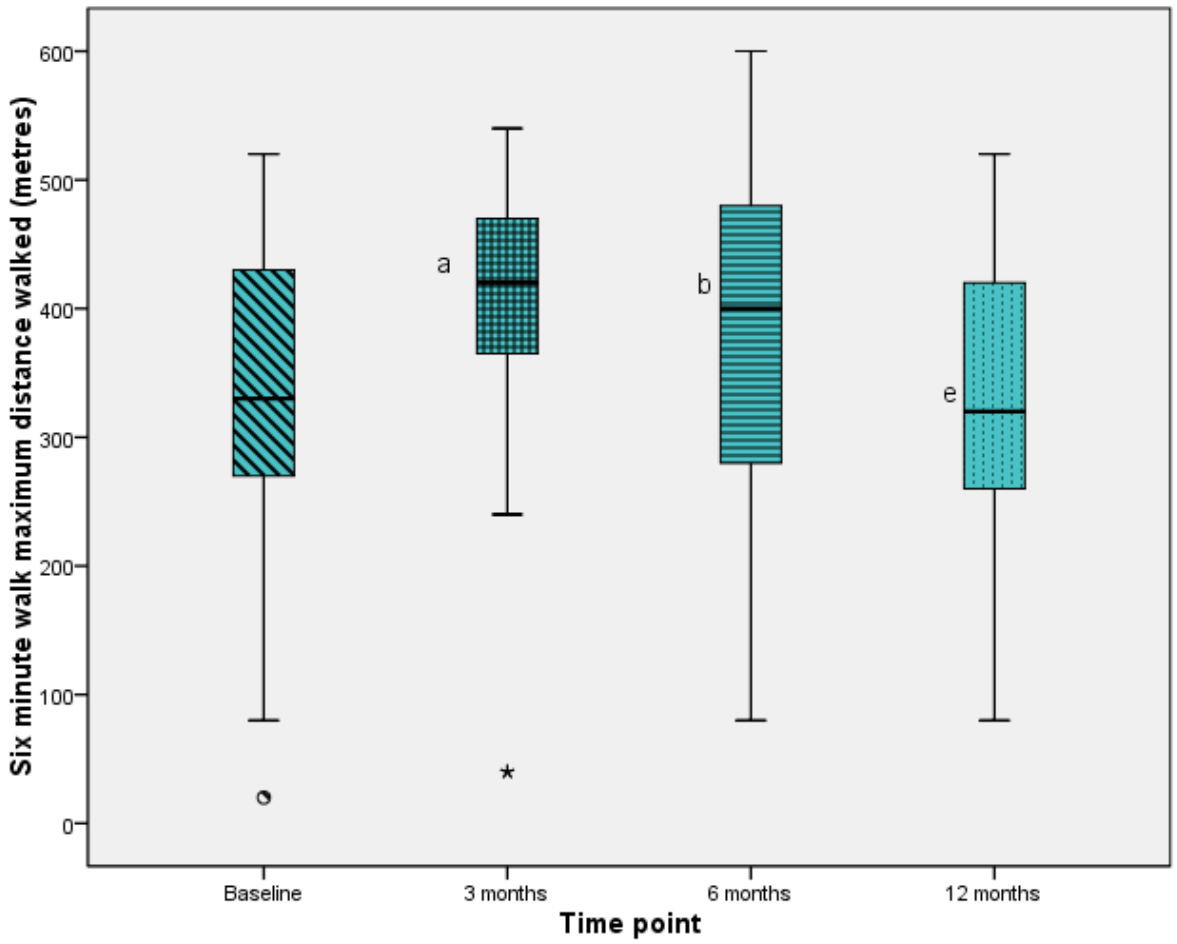


Figure 3.16 Six minute walk maximum walking distance (MWD) at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a" and between baseline and 6 months is indicated by "b". A significant deterioration is indicated by "e" between 3 months and 12 months. SEP (structured exercise programme).

3.3.4 Effect of SEP on measures of balance

Following SEP there was a significant improvement in the proportion of patients who passed the Sensory Organisation Test (SOT) at all 3 time points when compared to baseline ($P < 0.05$) (Appendix 11). The median SOT composite score improved significantly between baseline and all 3 time points as shown in Figure 3.17. There was no significant correlation between composite SOT scores and age at any time point (3 months $\rho = -0.177$, $P > 0.05$, 6 months $\rho = -0.332$, $P > 0.05$, 12 months $\rho = -0.316$, $P > 0.05$).

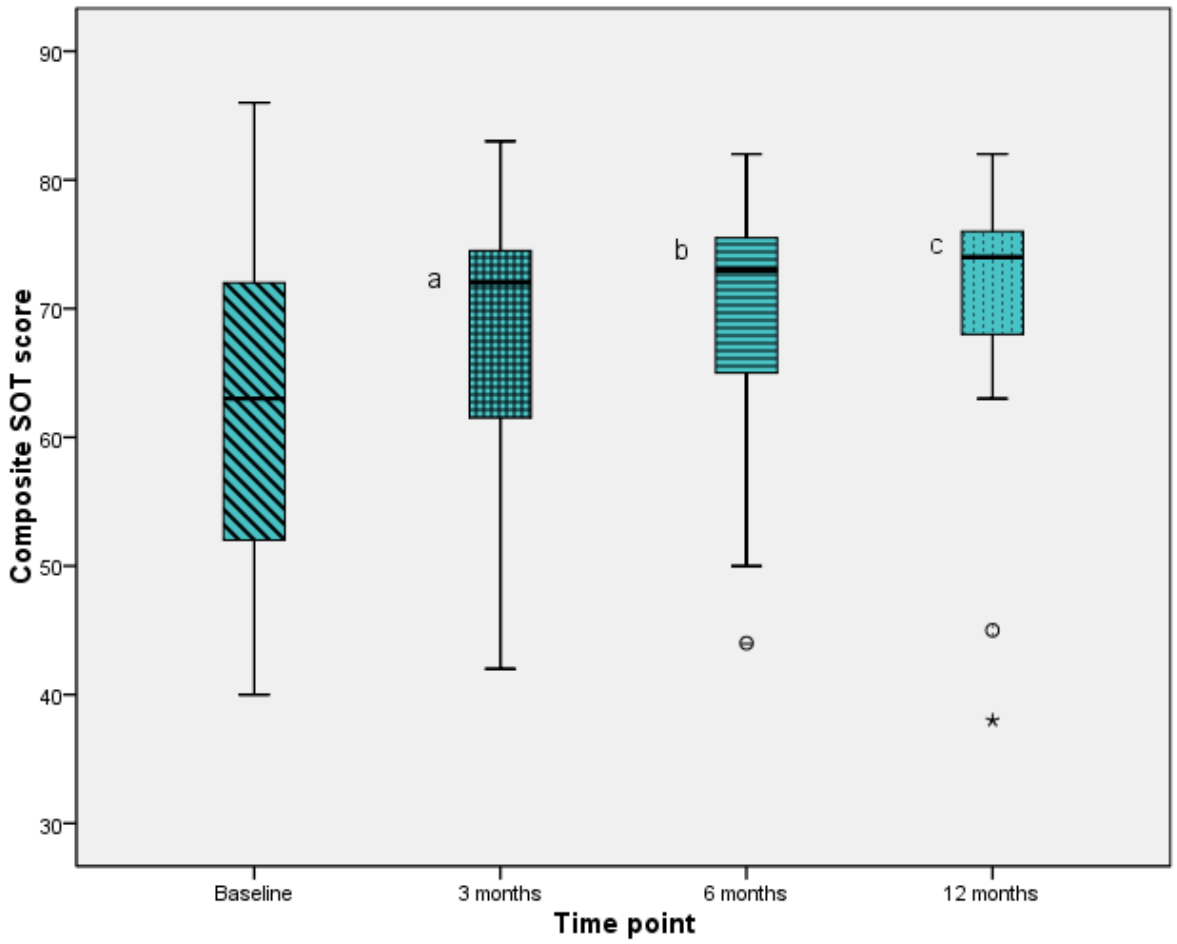


Figure 3.17 Composite sensory organisation test (SOT) scores at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). Significant improvements between baseline and 3 months are indicated by "a" and between baseline and 6 months by "b" and between baseline and 12 months by "c". SOT (sensory organisation test); SEP (structured exercise programme).

When individual conditions were analysed there was no improvement seen between baseline and 3, 6 or 12 months in conditions 1, 2 and 3. However a significant improvement was seen in condition 4 between baseline and 3 and baseline and 6 months (Figure 3.18). For conditions 5 and 6 significant improvements were seen between baseline and all 3 time points (Figures 3.19 and 3.20). In addition significant improvements were seen between 3 and 12 months for condition 5, and 6 and 12 months for condition 6 (Appendix 11).

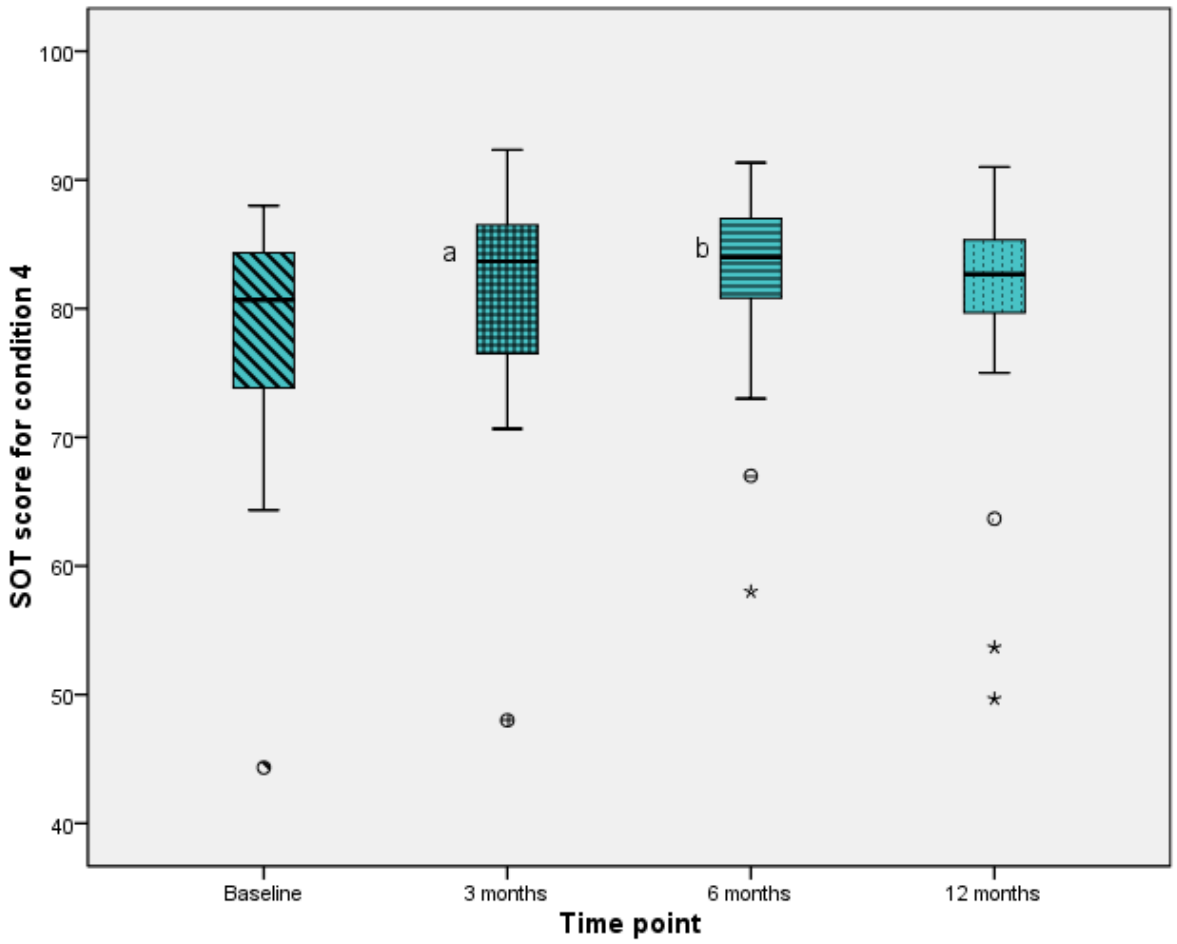


Figure 3.18 Sensory organisation test (SOT) score for condition 4 at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). Significant improvements between baseline and 3 months are indicated by "a" and between baseline and 6 months indicated by "b". SEP (structured exercise programme).

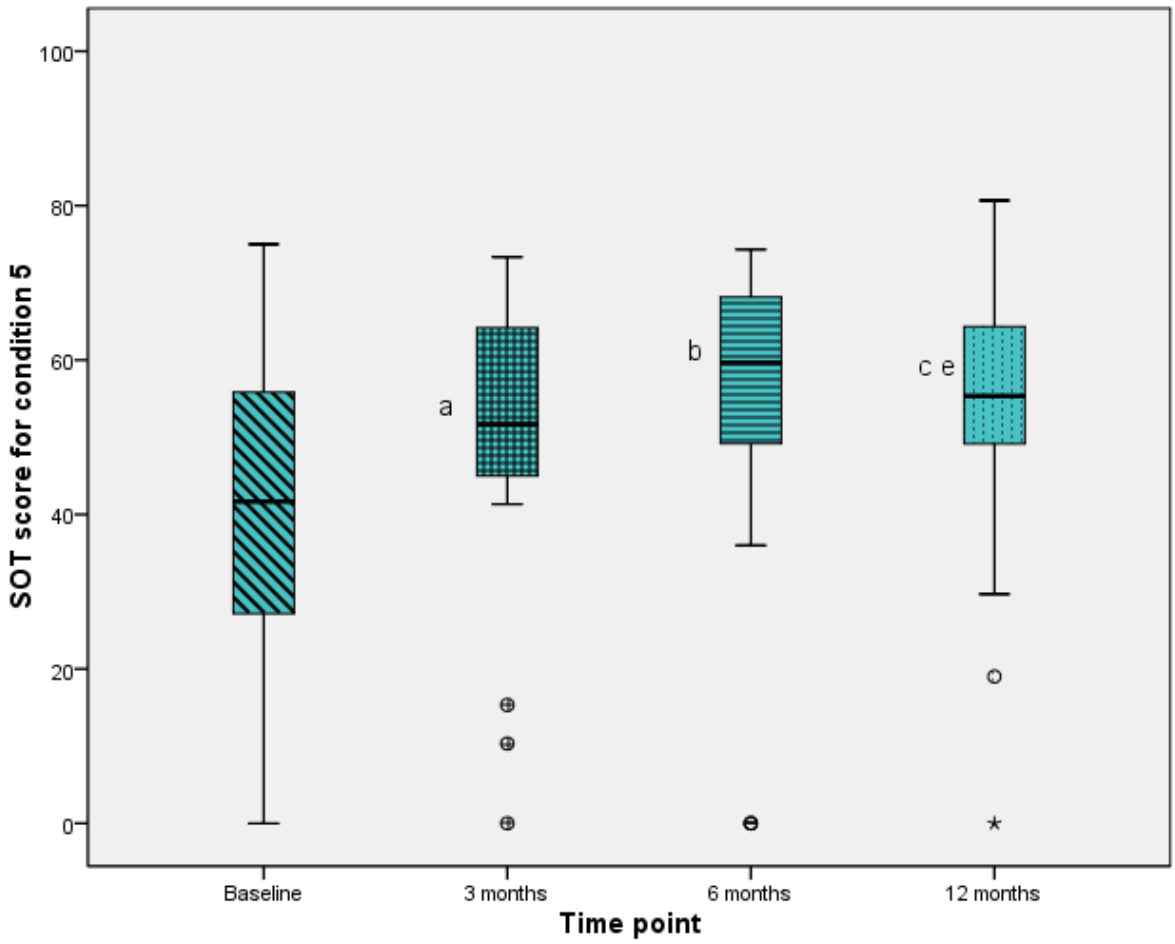


Figure 3.19 Sensory organisation test (SOT) score for condition 5 at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). Significant improvements between baseline and 3 months are indicated by "a" and between baseline and 6 months is indicated by "b" and baseline and 12 months by "c". There was also a significant improvement between 3 and 12 months indicated by "e". SEP (structured exercise programme).

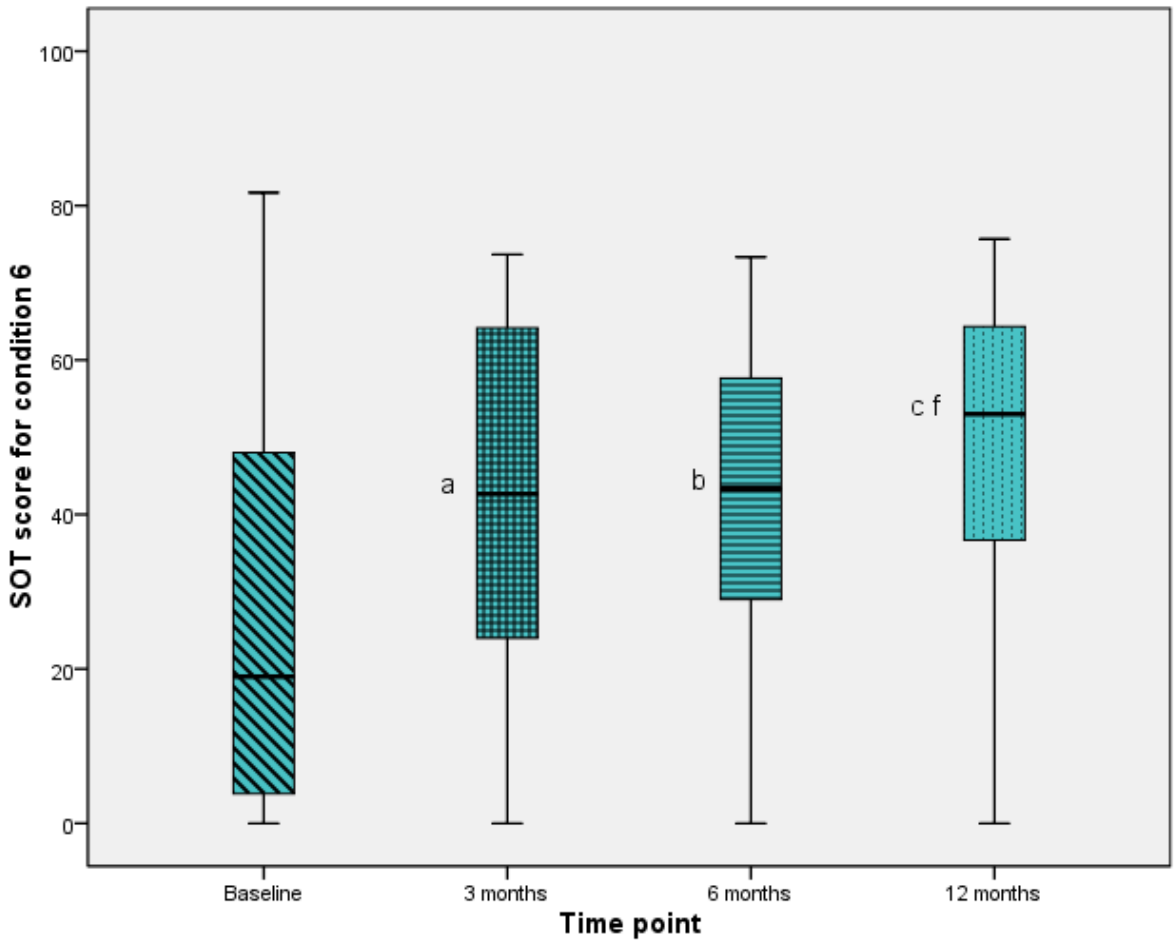


Figure 3.20 Sensory organisation test (SOT) score for condition 6 at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). Significant improvements between baseline and 3 months are indicated by "a" and between baseline and 6 months is indicated by "b" and baseline and 12 months by "c". There was also a significant improvement between 6 and 12 months indicated by "f". SEP (structured exercise programme).

The SOT analysis was further divided into sensory components. Over the study period there was no difference in the proportion of patients passing the somatosensory, visual or preferential analysis. However there were significant improvements in the proportion of patients passing the vestibular analysis between baseline and all 3 time points ($P < 0.05$, Appendix 11). There was no difference in falls during the SOT or in any aspect of the MCT throughout the study period in the SEP group.

3.3.5 Effect of SEP on falls incidence and risk of falling

At baseline 8 patients reported a history of falls and 18 reported a history of stumbles (total n = 51). There was no significant difference in the number of patients reporting a history of falls over the study period from the SEP group, although there was a significant decrease in the number reporting stumbles between baseline (n=18) and 3 months (n=7) ($P < 0.05$) (Appendix 12).

There was no significant difference in ABC-UK score across the study period. The TUG test was performed significantly faster at 3, 6 and 12 months when compared to baseline (Figure 3.21) although there was no significant difference in the proportion of patients passing the TUG based on their age adjusted scores (Appendix 12).

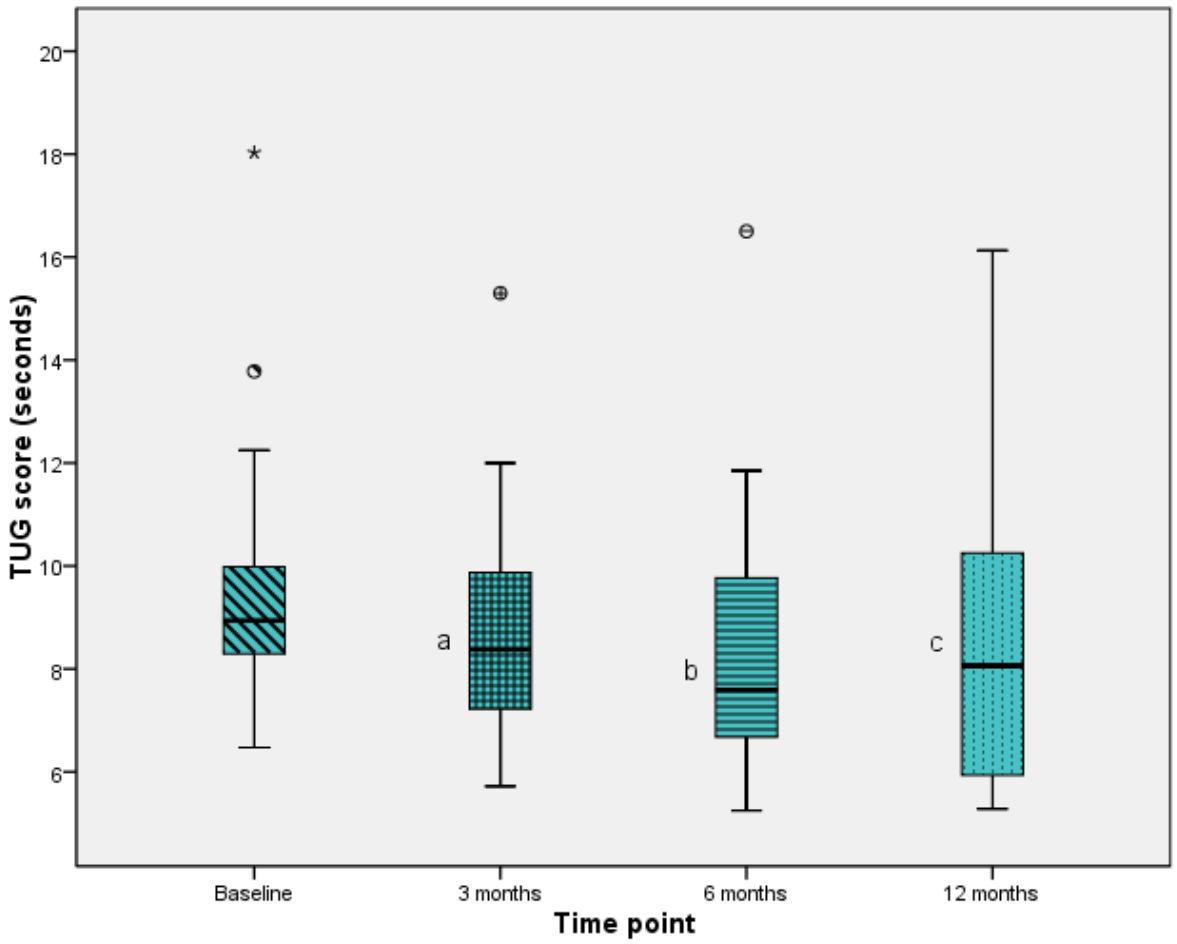


Figure 3.21 Timed up and go test (TUG) score at baseline, 3, 6 and 12 months for the SEP group

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Each time point was compared to another using Wilcoxon signed ranks test ($P < 0.05$). A significant improvement between baseline and 3 months is indicated by "a" , baseline and 6 months by "b" and baseline and 12 months by "c". One extreme outlier was excluded from the figure (TUG score >20 at baseline and >60 at 3 months) but not from the analysis. SEP (structured exercise programme).

3.3.6 Effect of SEP on patient reported quality of life

Table 3.10 indicates the improvements recorded in quality of life after SEP. Improvements in physical domains were noted at 3 and 6 months but no significant improvements were seen at 12 months when compared to baseline. No emotional or social domain scores improved in either SF8 or SF36, however significant improvements in the emotional domain scores of VascuQol were seen at 3 and 6 months, and an improvement in social domain scores was seen at 6 months (Table 3.10). Short form 36 indicated significant changes from baseline 8 times whereas short form 8 showed 5 significant changes from baseline as indicated by the shaded results in Table 3.10.

Table 3.10 Quality of life data for the SEP group

	Baseline	3 months	6 months	12 months	P
SF36					
- **Physical function**	45 (33.75-55)	49.94 (35-60)	52.5 (25-60)	45 (22.5-62.5)	[a]**0.029,** [b]**0.038,** [c]0.985
- **Role physical**	0 (0-56.25)	25 (0-100)	12.5 (0-100)	0 (0-87.5)	[a]**0.009,** [b]**0.039**, [c]0.072
- **Bodily pain**	42 (41-64)	56.5 (38.75-74)	56.5 (38.5-76.5)	42 (31-67)	[a]**0.015,** [b]**0.016,** [c]0.077
- **General health**	55 (41-68.5)	53.5 (39.25-67)	51 (38.75-67)	47 (43.5-69.5)	[a]0.893. [b]0.992, [c]0.722
- **Vitality**	55 (40-65)	60 (45-65)	60 (40-71.25)	55 (40-57.5)	[a] [a]0.186. [b]0.135, [c]0.570
- **Role emotional**	75 (50-100)	100 (33-100)	66.7 (24.75-100)	66.7 (16.65-100)	[a]0.301. [b]0.294,
- **Mental health**	100 (33.3-100)	76 (63-92)	84 (67-92)	76 (62-84)	[c]0.456[a]0.926. [b]0.575,
- **Social function**	78 (71-92)	87.5 (59.38-100)	87.5 (62.5-100)	75 (62.5-100)	[c]0.881[a]**0.015,** [b]**0.020,**
- **Physical summary**	31.9 (25.55-37.3)	35.3 (27.2-42.35)	35.7 (25.28-41)	30.4 (24.55-40.05)	[c]0.177[a]0.904. [b]0.694, [c]0.955
- **Mental summary**	56.7 (46.45-62.1)	56.8 (48.75-60.6)	57.3 (41.3-60.33)	54 (44.65-57.55)	
VascuQol					
- **Pain**	4.25 (3.5-5.25)	5 (3.56-5.5)	5.0 (3.63-5.88)	4.75 (4-5.5)	[a]**0.010,** [b]**0.018**, [c]0.079
- **Social**	5.5 (4-6.5)	5.88 (4.63-6.5)	6.0 (4.5-7)	6.0 (3.5-7)	[a]0.088, [b]**0.026,** [c]0.358
- **Activities**	4.13 (3.47-5)	4.63 (4.25-5.72)	4.63 (3.88-5.44)	4.13 (3.32-5.5)	[a]**0.001,** [b]**0.002,** [c]0.212
- **Symptoms**	5.5 (4.94-6.06)	5.63 (5-6.25)	6.0 (5.13-6.38)	5.75 (5-6.25)	[a]0.760, [b]0.347, [c]0.207
- **Emotional**	5.14 (4.68-5.86)	5.71 (4.75-6.29)	5.71 (4.78-6.57)	5.71 (4.43-6.57)	[a]**0.009,** [b]**0.028,** [c]0.230
- **Total**	4.84 (4.13-5.35)	5.22 (4.64-5.88)	5.4 (4.38-5.9)	5.08 (3.98-5.94)	[a]**0.005,** [b]**0.011,** [c]0.159
SF8					
- **Physical function**	40.1 (30.3-42.15)	40.1 (40.1-48.3)	40.1 (30.3-48.3)	40.1 (30.3-48.3)	[a]**0.044,** [b]**0.010,** [c]0.132
- **Role physical**	38.7 (38.7-46.9)	42.8 (38.7-46.9)	42.8 (38.7-48.68)	38.7 (33.5-46.9)	[a]0.541, [b]0.072, [c]0.722
- **Bodily pain**	40.1 (40.1-47.7)	43.9 (40.1-53.4)	40.1 (40.1-53.4)	40.1 (40.1-50.55)	[a]**0.017**, [b]0.105, [c]0.122
- **General health**	46.4 (38.4-46.4)	46.4 (38.4-46.4)	42.4 (38.4-46.4)	46.4 (38.4-46.4)	[a]0.263, [b]0.861, [c]0.353
- **Vitality**	45.2 (45.2-55.6)	45.2 (45.2-55.6)	45.2 (45.2-55.6)	45.2 (45.2-45.2)	[a]**0.037**,[b]0.319, [c]0.785
- **Role emotional**	52.4 (38.1-52.4)	49.05 (45.7-52.4)	45.7 (38.1-52.4)	45.7 (38.1-52.4)	[a]0.935, [b]0.743, [c]0.782
- **Mental health**	49.6 (41.5-56.8)	49.6 (41.5-56.80)	49.6 (49.6-56.8)	49.6 (41.5-56.8)	[a]0.688, [b]0.304,
- **Social function**	49.5 (40.4-55.3)	49.5 (40.4-55.3)	49.5 (40.4-55.3)	49.5 (40.4-55.3)	[c]0.720[a]0.222, [b]0.064,
- **Physical summary**	39.25 (30.7-44.2)	41.35 (35.4-47.5)	40.65 (34.2-46.38)	39.2 (30.2-46.2)	[c]0.125 [a]**0.003**, [b]0.120, [c]0.114
- **Mental summary**	53.4 (42.48-59)	54.1 (44.98-58.83)	52.2 (46.13-57.48)	51.9 (43.75-56.40)	[a]0.312, [b]0.521, [c]0.972

Values are expressed as median (IQR, interquartile range). Each time point was compared to baseline using Wilcoxon signed ranks test. P values are shown and highlighted in bold if <0.05. [a]Wilcoxon 0-3, [b]Wilcoxon 0-6,[c]Wilcoxon 0-12. SF36 (Short Form 36), SF8 (Short Form 8). Significant improvements from baseline indicated by highlighted text.

3.4 Comparison between the effects of angioplasty and exercise therapy

The final aim of this work was to compare the effects of both angioplasty and exercise treatments on clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life in patients with lower limb ischaemia.

3.4.1 Baseline data

Initially a comparison was made between the angioplasty and the exercise groups to determine, whether at baseline, there were any important differences. There was no significant difference between the 2 groups in terms of basic demographics; age, gender, medical history, height, weight or BMI ($P > 0.05$) (Appendix 4).

There were, however, significant differences between the 2 groups in clinical indicators of lower limb ischaemia at baseline. The exercise group had worse ankle brachial pressure index (ABPI) results both pre and post exercise ($P < 0.05$) (Figure 3.22, Appendix 13). Despite their post exercise ankle pressure and ABPI results, the angioplasty group walked for shorter distances before the onset of pain (intermittent claudication distance, ICD) compared to the exercise group at baseline (Appendix 13). There was no difference in maximum walking distance (MWD) on the treadmill, or in patient reported walking distance (PRWD) (Appendix 13).

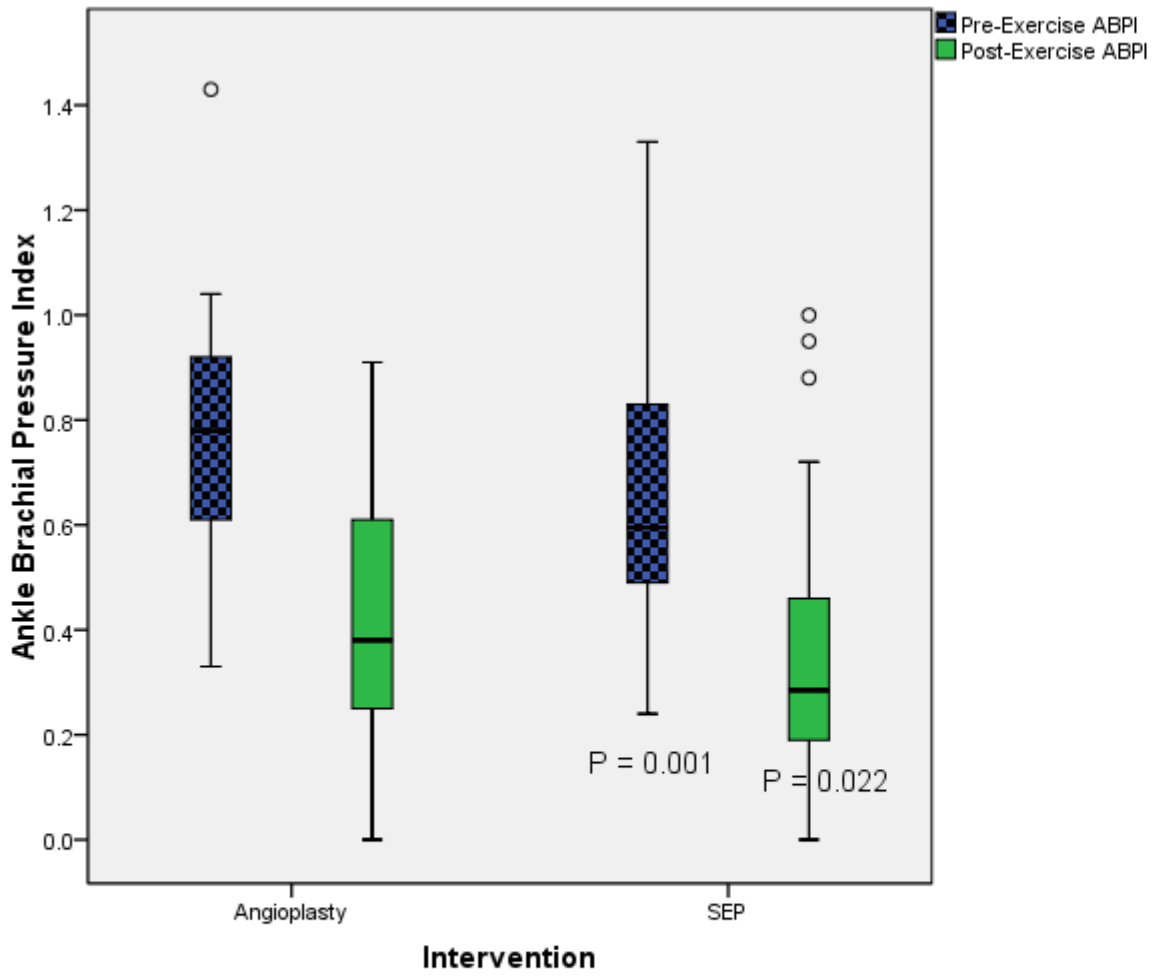


Figure 3.22 Ankle brachial pressure index at baseline for the angioplasty and SEP groups

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test and P values are given for each variable.

The short performance physical battery scores were derived from the usual paced 4-metre walk, the chair stand test and the semi and full tandem balance tests. The scores can range between 0 and 12, with 12 being the best score possible. There was a significant difference at baseline between the angioplasy and exercise groups, with a median of 9 (IQR8-11) for the angioplasty and a higher median score of 10 (IQR 9-11) for the exercise group (P = 0.007) (Figure 3.23, Appendix 14).

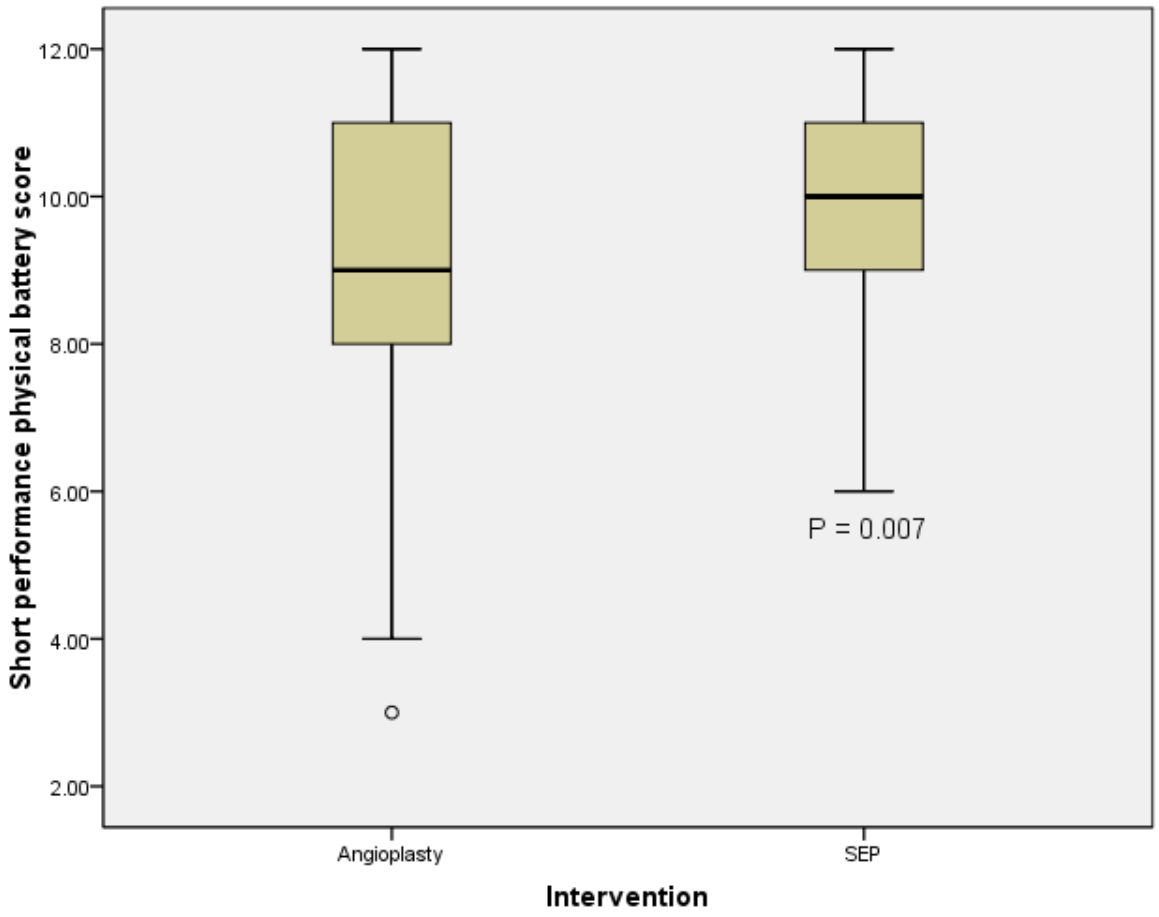


Figure 3.23 Short performance physical battery score at baseline for the angioplasty and SEP groups

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test and P values are given.

The 4 metre walk at usual pace and at fastest pace were not significantly different between the angioplasty and exercise groups. The chair stand test was significantly worse for the angioplasty group at baseline, with a median time of 17 seconds (IQR 12-21) compared to 14 seconds (IQR 11-17) for the exercise group ($P = 0.044$). The semi tandem stance was poorer for the angioplasty group (angioplasty: median 30 seconds (IQR 19-30), exercise: median 30 seconds (IQR 30-30) $P = 0.004$) but there was no significant difference in full tandem stance times between groups. There was no significant difference in hand grip strength between the angioplasty and exercise groups. During the six minute walk test the angioplasty group demonstrated shorter intermittent claudication distances ($P < 0.05$) and more rapidly reached the onset of intermittent claudication compared to the exercise group ($P < 0.05$) (Figure 3.24). However there was no significant difference between the two groups in maximum walking distance or the time when maximum walking distance was achieved (Appendix 14).

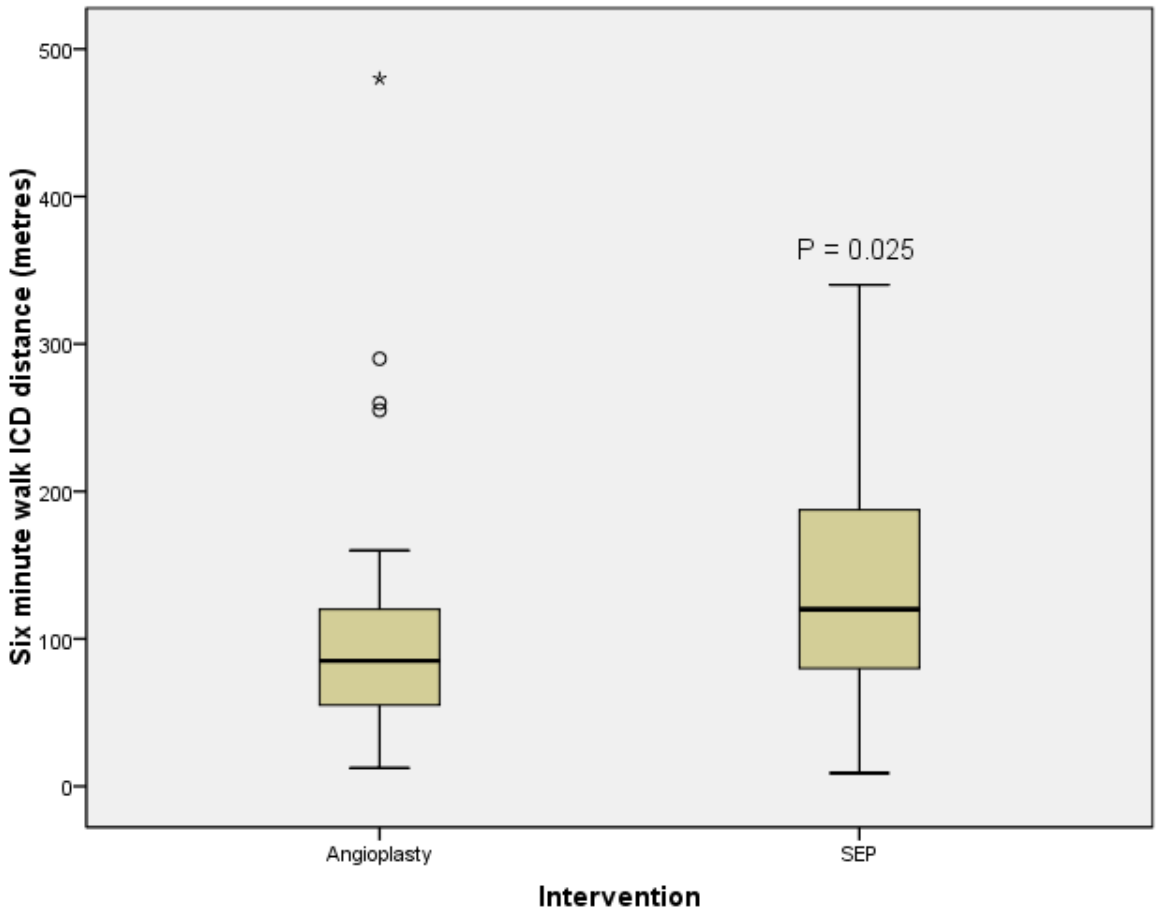


Figure 3.24 Six minute walk intermittent claudication distance at baseline for the angioplasty and SEP groups

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test and P values are given.

At baseline 46 of the 98 patients tested failed the Sensory Organisation Test (SOT) (Appendix 15). Scores range from 0-100 (worst to best). There was no significant difference between the angioplasty or exercise groups. The median SOT composite score for the whole population tested was 68 (IQR 58-76), for the angioplasty group was 70 (IQR 61-79) and for the exercise group was 65 (IQR 54-75), ($P > 0.05$) (Figure 3.25). Scores for each of the 6 SOT conditions were assessed. The angioplasty group performed significantly worse in condition 3 (inaccurate visual input as the visual surround moves relative to the patient), yet there was no difference between groups for the other conditions tested. The sensory analysis breakdown showed that all claudicants performed poorly in vestibular testing with less than half of patients (46 of the 98 patients) passing the vestibular assessment. This was significantly different between the groups with 60% (28 of 47) passing the vestibular assessment in the angioplasty group and 35% (18 of 52) passing in the exercise group ($P = 0.012$). Exercise patients were found to fall on the SOT test significantly more often (35 of the 52) than the angioplasty patients (20 of 47, $P = 0.009$) and an abnormal ankle strategy was employed more often by the SEP group (31 vs 11, $P <0.001$). The Motor Control Test (MCT) was performed well by claudicants with weight symmetry, latency and response strength being normal in over 70% of patients. There was no significant difference between groups in any outcome except response strength to forward translations,where exercise patients performed better than angioplasty patients, $P = 0.005$, (exercise: 43 passed and 7 failed, angioplasty: 28 passed and 18 failed) (Appendix 15).

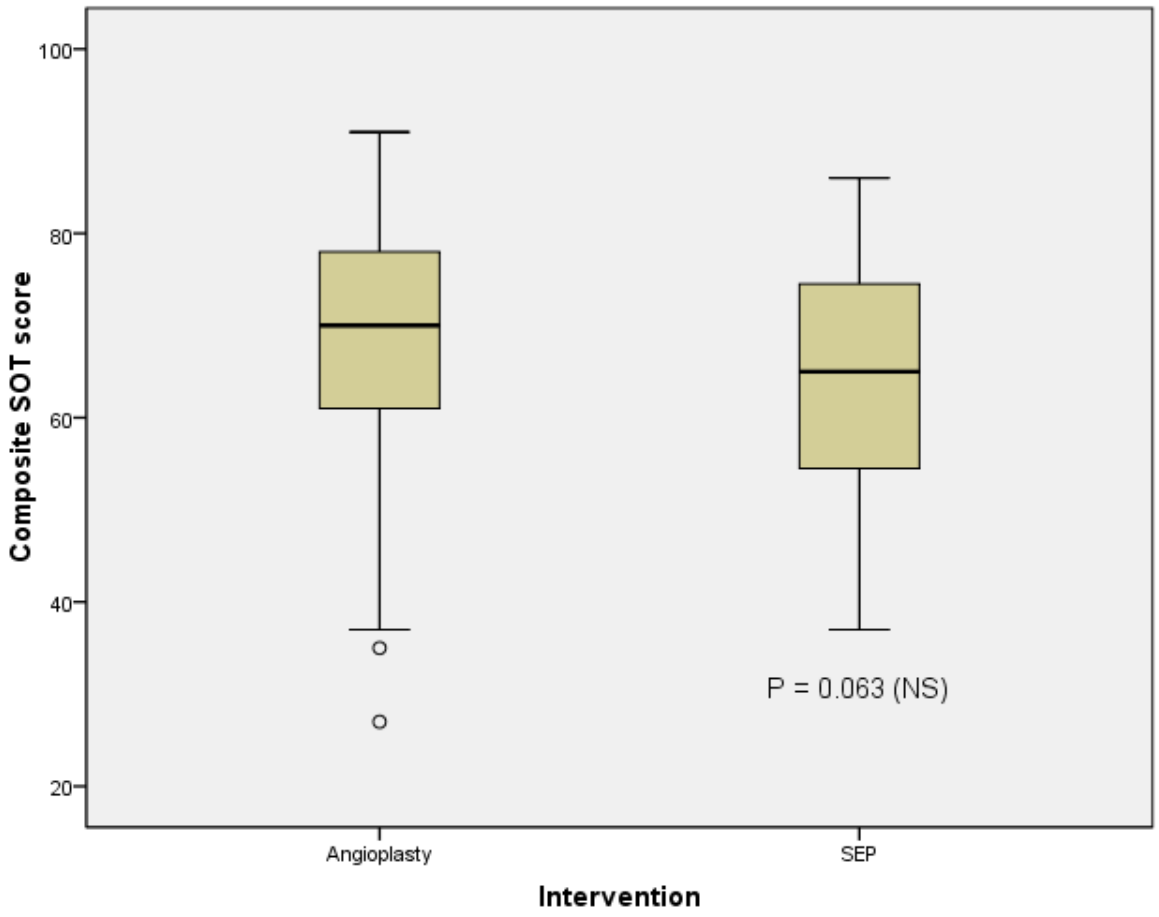


Figure 3.25 Composite sensory organisation test (SOT) scores at baseline for the angioplasty and SEP groups

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test and P values are given. Non significance is highlighted by (NS) if $P > 0.05$.

Normal and abnormal balance groups (those that passed or failed composite SOT) were compared. There was no difference in age, comorbidities or height, weight and bmi between those with normal or abnormal balance. However there was a much higher proportion of female patients in the abnormal balance group, of 31 females only 11 passed, whereas 41 males of 67 passed (P = 0.018). There was no difference between normal and abnormal balance groups, in any of the clinical indicators of lower limb ischaemia. In terms of physical function, those with abnormal balance had significantly longer times to claudication during the 6 minute walk test (median 113 minutes, IQR 85-154 mins) compared to those with normal balance (median 66 minutes, IQR 53-117 mins), P = 0.007). There was no difference in falls history or quality of life between the 2 balance groups.

In all patients there was a history of falls from 20 patients and a history of stumbles from 30 patients. There was no significant difference in falls history or history of stumbling between the angioplasty and exercise groups at baseline. The median Activities-specific Balance Confidence (ABC-UK) score for the cohort was 80.6% (IQR 64.6-92.8) where 100% would be no fear at all. There was no significant difference at baseline between the ABC-UK score for angioplasty or exercise patients.

The median Timed Up and Go (TUG) test score for the cohort was 9.16 seconds (IQR 7.49-11.18) with no signifcant difference at baseline between the angioplasty or exercise patients (Figure 3.26, Appendix 16). However once TUG scores were adjusted by age there was a significant difference between the pass and fail rates between groups. Overall 58 of the 98

patients passed the TUG test based on age adjusted normative values. Angioplasty patients performed significantly worse than exercise patients in terms of age adjusted pass fail rates with 21 of 47 passing compared to 37 of 52 exercise patients passing (P = 0.005) (Appendix 16).

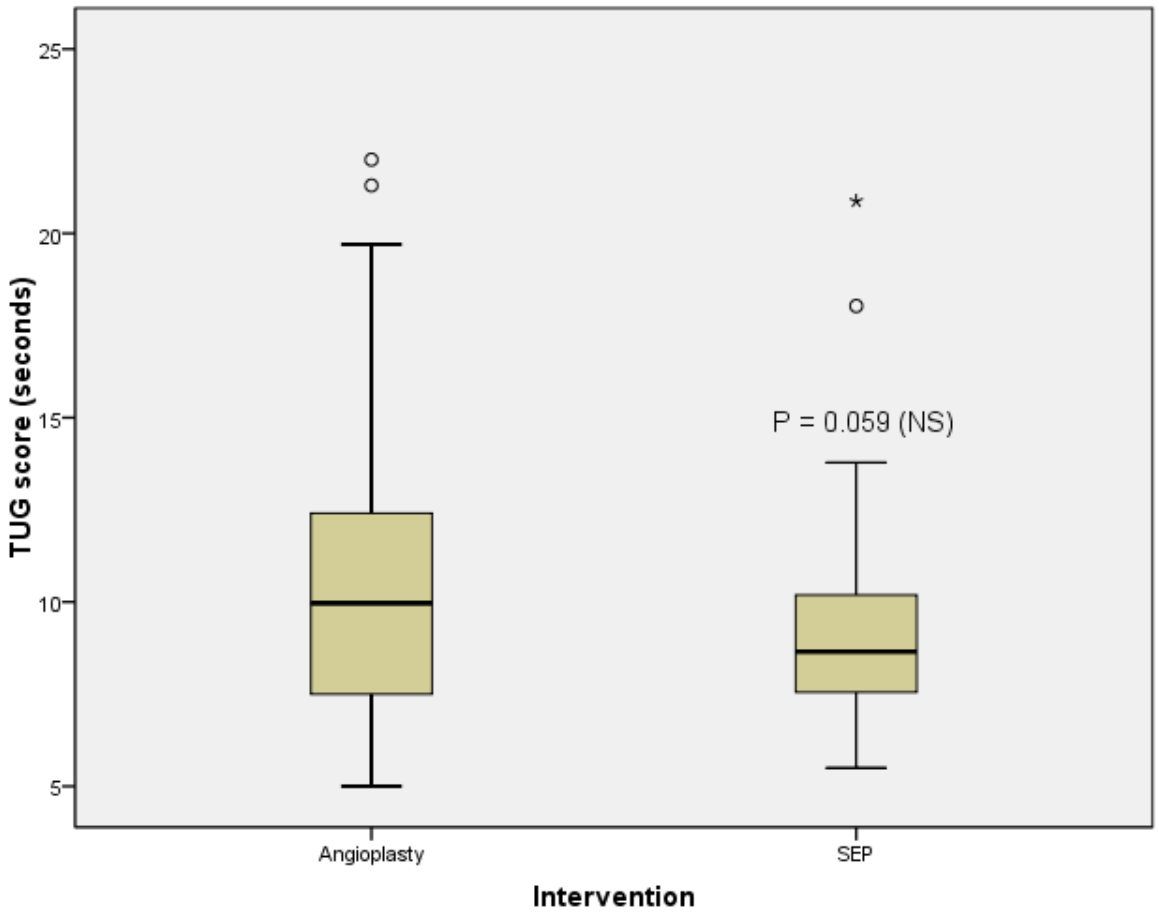


Figure 3.26 Timed up and go test (TUG) scores at baseline for the angioplasty and SEP groups

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test and P values are given. Non significance is highlighted by (NS) if $P > 0.05$.

The angioplasty group demonstrated poorer quality of life than the exercise group in multiple domains from the Short Form 36, VascuQol and Short Form 8 at baseline (Figure 3.27, Appendix 17).

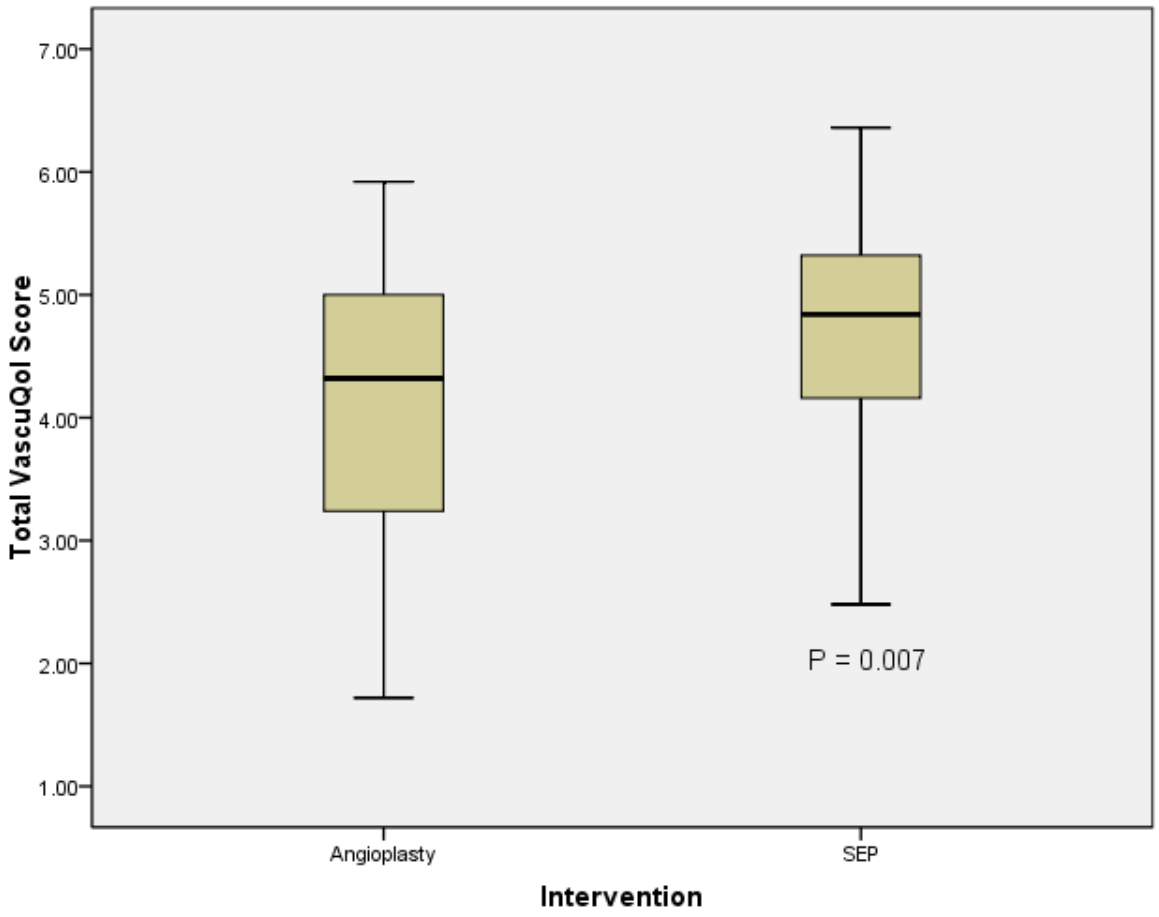


Figure 3.27 Total VascuQol quality of life score at baseline for the angioplasty and SEP groups

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test and P values are given. Non significance is highlighted by (NS) if $P > 0.05$.

3.4.2 Post treatment comparison between angioplasty and exercise

Sections 3.2 and 3.3 individually discuss the effect of treatment for the angioplasty group and the SEP group respectively. This study was a pragmatic observational study and as such there were obvious differences between groups at baseline as highlighted above. However, these were only evident in certain outcome measures and as such the groups are comparable for a number of other measures. As such, a comparison between groups was undertaken post intervention for both treatment groups (angioplasty and exercise) at each of the time points. The variables used were chosen as they had identified the greatest improvements in either the angioplasty or exercise groups after treatment from each of the different categories of outcomes measured (clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life) (Table 3.11).

Pre exercise ABPI and treadmill ICD were used as measures of ischaemia. It had been highlighted at baseline that the angioplasty group had better pre exercise ABPI but worse treadmill ICD compared to the SEP group. The angioplasty group showed improvements in ABPI whereas the SEP group had a stable median ABPI and therefore the significant difference between the two groups persisted at each time point (Figure 3.28, Table 3.11). ICD also significantly improved after angioplasty, and despite no improvement in ABPI, the SEP group also showed a significant improvement at 3 and 6 months. There was a significant difference between the two groups at baseline and 3 months for treadmill ICD (greater ICD for the SEP group), but by 6 months the improvement made by the angioplasty group made the difference non significant and this persisted at 12 months (Figure 3.29, Table 3.11).

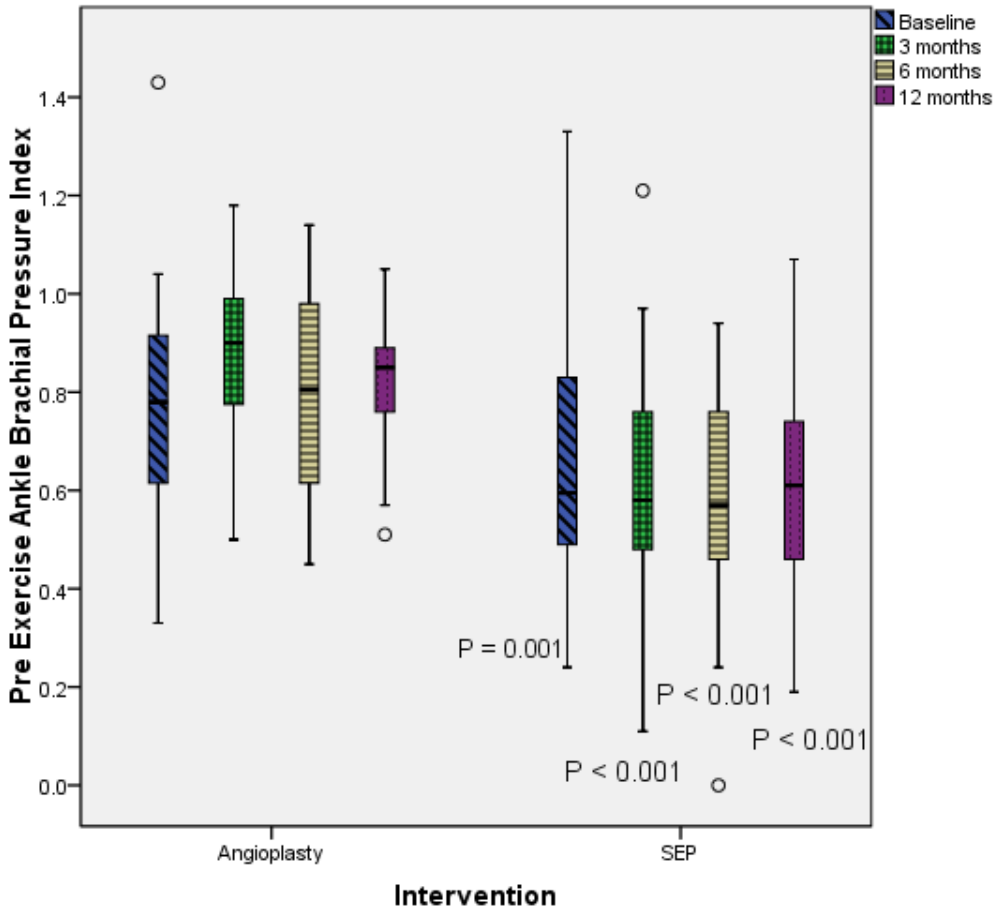


Figure 3.28 Pre exercise ankle brachial pressure index (ABPI) for the angioplasty and SEP groups at each study time point

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test at each time point. P values are given under the SEP box for each comparison with angioplasty. Non significance is highlighted by (NS) if $P > 0.05$.

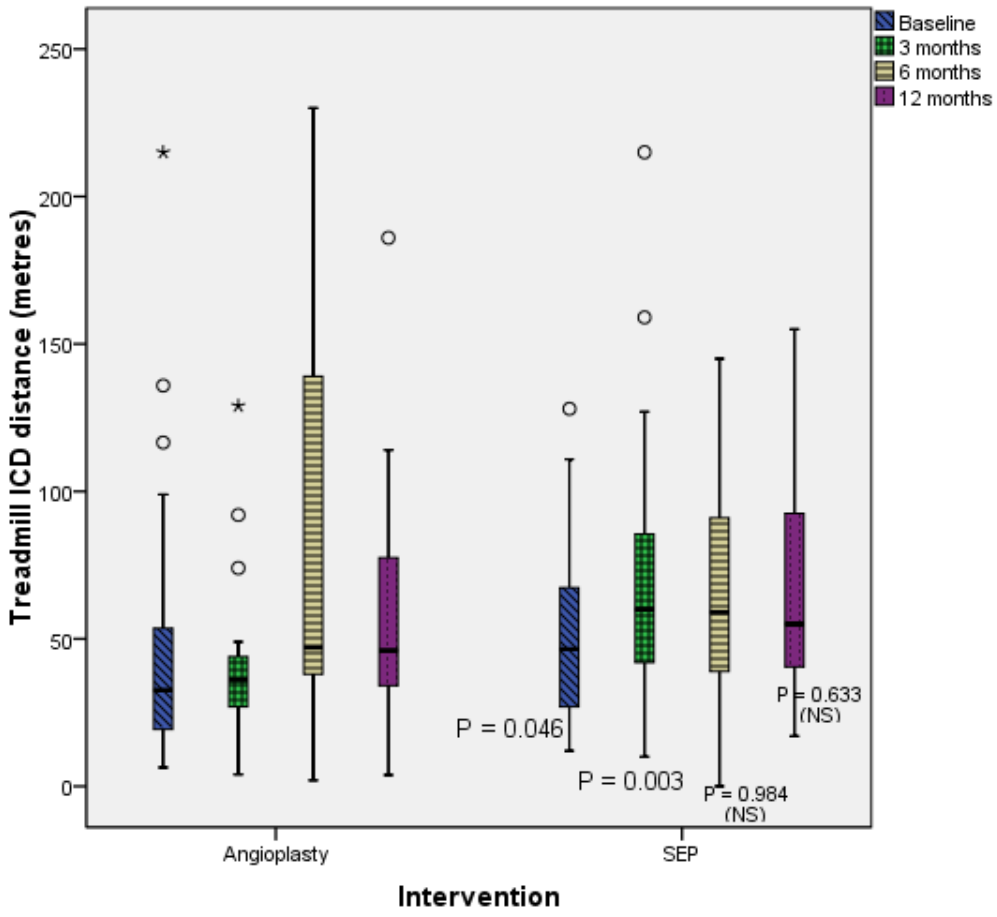


Figure 3.29 Treadmill intermittent claudication distance (ICD) for the angioplasty and SEP groups at each study time point

Boxes represent the interquartile range and the thick horizontal lines represent the median, whiskers represent the range with outliers represented by circles and extreme outliers as stars. Exercise and angioplasty groups were compared to another using Mann Whitney U test at each time point. P values are given under the SEP box for each comparison with angioplasty. Non significance is highlighted by (NS) if $P > 0.05$.

The short performance physical battery (SPPB) score was used as a measure of physical function as this encompassed both the walking and simple balance tests. At baseline there was a significant difference between the two groups, with the SEP group performing better (Figure 3.23). The difference between the groups diminished after treatment and was no longer significant at 3, 6 or 12 months due to the improvements made by the angioplasty group (Table 3.11).

Balance and falls risk were not significantly different between the two treatment groups at baseline and this non significant difference was maintained at each of the time points post treatment (Table 3.11). However the median composite SOT scores were higher in the angioplasty group until 12 months when the SEP group had a higher median score.

Quality of life was significantly better for the SEP group at baseline compared to the angioplasty group, although following treament the significance was reversed as the angioplasty data improved alongside that of the SEP group (Table 3.11).

Table 3.11 Comparison between angioplasty and exercise groups over time

Variable	Time point	Angioplasty group	Exercise group	P
Pre exercise ABPI (symptomatic leg)	Baseline	**0.78 (0.61-0.92)**	0.60 (0.49-0.83)	0.001
	3 months	**0.90 (0.77-0.99)**	0.58 (0.48-0.77)	<0.001
	6 months	**0.81 (0.61-0.99)**	0.57 (0.44-0.77)	<0.001
	12 months	**0.85 (0.76-0.90)**	0.61 (0.45-0.75)	<0.001
Treadmill ICD	Baseline	32.6 (19.13-53.95)	**46.5 (27-68.03)**	0.046
	3 months	36.0 (26.5-45.25)	**60.0 (42.0-85.75)**	0.003
	6 months	47.0 (37.5-140.5)	**59.0 (38.0-95.5)**	NS (0.984)
	12 months	46 (34.0-78.0)	**55.0 (39.25-93.25)**	NS (0.633)
SPPB	Baseline	9 (8-11)	**10 (9-11.25)**	0.007
	3 months	10 (9-12)	**11 (10-12)**	NS (0.153)
	6 months	10.5 (8.75-11)	**11 (10-11)**	NS (0.296)
	12 months	10 (9-11)	**10 (9.5-12)**	NS (0.135)
SOT composite score	Baseline	**70 (61-79)**	65 (54-75)	NS (0.063)
	3 months	**73 (64.75-82)**	69 (60.5-77.5)	NS (0.151)
	6 months	**74 (61-76.5)**	73 (66-78)	NS (0.754)
	12 months	68 (62.5-76)	**74 (68-77)**	NS (0.161)
TUG score	Baseline	10.13 (7.50-12.50)	**8.65 (7.44-10.19)**	NS (0.059)
	3 months	8.70 (7.04-10.97)	**7.48 (6.80-9.64)**	NS (0.213)
	6 months	9.25 (7.57-10.58)	**8.03 (6.69-9.75)**	NS (0.095)
	12 months	8.29 (7.20-11.43)	**8.06 (5.87-10.47)**	NS (0.207)
Total VascuQol score	Baseline	4.32 (3.22-5.02)	**4.84 (4.13-5.35)**	0.007
	3 months	**5.9 (4.19-6.66)**	5.22 (4.64-5.88)	NS (0.055)
	6 months	**5.68 (3.96-6.36)**	5.4 (4.38-5.9)	NS (0.532)
	12 months	**5.2 (4.08-6.32)**	5.08 (3.98-5.94)	NS (0.611)

Values are all expressed as median (IQR, interquartile range). Angioplasty and exercise groups were compared at each time point using Mann Whitney U test (MWU) and P values are shown if < 0.05 or if > 0.05 expressed as non significant (NS), with P values given in brackets. Data highlighted in **bold** indicates a better result than the other group. ABPI (ankle brachial pressure index), SPPB (short physical performance battery score), SOT (sensory organisation test), TUG (timed up and go test), VascuQol (disease specific quality of life measure).

4 Discussion

The discussion is structured according to the format of the results chapter, beginning with a discussion of the correlation between lower limb ischaemia and physical function and balance. Secondly the effects both treatment arms (angioplasty and exercise) are discussed and lastly the comparison between the angioplasty and exercise groups is made. Limitations and future directions are also discussed in this chapter.

4.1 Correlation between lower limb ischaemia and physical function and balance

The initial aim of this work was to explore the hypothesis that prior to treatment; increasing severity of lower limb ischaemia will correlate with increasingly impaired physical function and balance. Yet in this study worsening lower limb ischaemia, as determined by lower ABPI, did not translate into worsening physical function, balance or falls risk. However treadmill walking distances, as a measure of lower limb ischaemia, were found to correlate much more accurately with almost all measures of physical function and falls, but not objective measures of balance.

It has previously been recognised in the literature that there is an association between lower limb ischaemia and poor physical function (Gardner *et al*. 2004), and even in asymptomatic

patients with low-normal (1.00 to 1.09) or borderline (0.9-0.99) ABPI values, a decline in physical function has been found (McDermott *et al*. 2009). However, as with the findings in this study (section 3.1), ABPI itself has not been found to be a reliable marker of poor physical function (Atkins and Gardner 2004), suggesting that the degree of limb ischaemia alone is not the only causative factor for poor function in this cohort of patients. An alternative explanation for poor function may be reduced physical activity and it has been demonstrated that daily physical activity levels are a more significant factor in determining physical function (Atkins and Gardner 2004) rather than ABPI.

Simple tests of balance have previously also indicated a specific connection between PAD and poor balance (Suominen *et al*. 2008) but no significant correlation between ABPI or walking distances and objective balance measures have been found. Worsening ABPI has been previously found to be unrelated to falls risk (Gardener and Montgomery 2001a). This suggests that in claudicants, walking distance impairment or physical function impairment may be better predictors of falls risk and balance than arterial disease severity, as found in this work. Those with more severe disease as measured by ABPI may still have good function in terms of walking (Appendix 13) which enables them to keep up a more active, exercise rich lifestyle which leads to reduced falls risk through a training effect.

The walking related clinical indicators of lower limb ischaemia, ICD and MWD, correlated well with all measures of physical function (e.g. MWD correlated with SPPB, $\rho = .544$, $P < 0.001$). PRWD was a less useful indicator and therefore treadmill tests may be of increased value in confirming or identifying those at risk of poor physical function. It seems logical

that the distance an individual can walk, both without pain (ICD) and before stopping (MWD), will relate to their performance in measures of physical function. Most measures require an individual to walk, if only for a short time and if walking is painful it is likely that such pain will impair the individuals' ability to complete the functional task. Moreover if an individual avoids walking, for fear of inducing pain, they will likely become less accustomed to performing tasks involving walking and their muscle strength will diminish through lack of training. The explanation for both poor physical function and balance may rest in ischaemic muscle changes causing muscle atrophy and poor functional strength and consequent poor motor neurone performance. Regensteiner *et al*. (1993) found PAD patients had gastrocnemius muscle changes which correlated with functional strength and with peak walking time on the treadmill. The histological changes consisted of a reduction in the cross sectional area of type II muscle fibres and muscle denervation. They also found that those with less severe PAD (mild claudicants) did not demonstrate changes in morphology of skeletal muscle but all PAD patients showed evidence of denervation. Muscle denervation severity has been shown to correlate with the severity of vascular disease (England *et al*. 1992) and that denervation caused by ischaemia is one of the contributory factors to poor performance. Muscle biopsies were not taken in this current study but this may prove an interesting area of future research particularly to compare the differences in PAD patients at baseline, their response to treatment and their correlation with physical ability.

The maximum walking distance correlated with hand grip strength, which cannot be directly explained by mechanisms resulting from reduced lower limb blood flow or muscle denervation. It seems from this study that a decline in physical function affects the whole

body, or at least the upper limbs, despite there being no known pathology in that location. The explanation may be related to training and that a lack of walking has a knock on effect on lack of whole body activities which would otherwise maintain upper limb function, such as carrying shopping or household chores. This conclusion is in contrast to that of McDermott *et al*. (2008a) who found no association between PAD and upper limb strength, although they used ABPI as a marker of PAD rather than walking distance. The contrast in conclusions may have occurred because of this difference in methodology. The current study correlated both ABPI and walking distances with hand grip strength, ABPI was not found to correlate, but MWD correlated with both right ($\rho = .312$, $P = 0.006$) and left hand grip strength ($\rho = .377$, $P = 0.001$).

This study confounds previous findings that walking distance may be a useful predictor of impaired physical function. A significant correlation between walking distances and falls risk was also found. Previous studies have had conflicting results in that PAD is both associated with a higher (Gardner and Montgomery 2001a) and lower risk of falling (Arseven *et al*. 2007), but what these studies have not specifically correlated is claudication treadmill walking distances with measures of falls risk. As individuals are able to walk less and less far due to pain, they are likely to be at increased risk of falls for the same reasons as poor balance and impaired physical function. Lack of muscle strength and training may again contribute to falls risk. In the study that found a lower risk of falling it was hypothesised that reduced levels of physical activity and avoidance of walking may account for reduced falls risk due to there being less opportunity to fall (Arseven *et al*. 2007). Arseven *et al*. (2007) conducted their study prospectively and while there are certainly advantages of a prospective study in that falls should be reported more reliably, the

prospective design may have impacted on their results by patients' awareness of falls risk being triggered and thus them purposefully avoiding falls risk situations. Correlation with daily physical activity either subjectively, through patient diaries or objectively through devices such as pedometers, may identify a link between physical activity levels and falls frequency.

The implications from the initial part of this study for PAD patients are that clinicians cannot rely on ABPI as an indication of an individual's level of performance, physical function, balance or falls risk. There must be other aspects of their assessment to identify potential deficits in these areas. Asking patients how far they can walk is notoriously unreliable in terms of actual distance a patient is able to walk (Watson *et al.* 1997). However it may still be a useful question for a clinician to ask as this study did find a correlation between patient reported walking distance (PRWD) and two measures of physical function, the SPPB and the chair stand test. Without access to a treadmill this may supplement the history taking in terms of identifying potential functional impairment. A simple treadmill test will not only give a useful and objective measure of walking distance but has been found in this study to correlate well with physical function performance and falls risk on many different measures. It may be appropriate, then to target such individuals with poorer walking distances with treatment measures designed not only to improve their ABPI but to improve walking distance, physical function and falls risk.

4.2 Angioplasty data

The second aim of this work was to investigate the hypothesis that patients undergoing angioplasty treatment will demonstrate improvements in clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life in patients with lower limb ischaemia.

4.2.1 Clinical indicators of lower limb ischaemia

Following angioplasty treatment, as expected, patients were found to have a significant improvement in ABPI at 3 months when compared to baseline. This is explained as angioplasty restores inflow and consequently improves pressure in the lower limb arterial tree. However early success did not persist long term. Even at 6 months our data shows no significant improvement in resting ABPI from baseline (Figure 3.1). Yet post treadmill exercise ABPI did continue to show an improvement at 12 months (Figure 3.2). It might be assumed that either; restenosis, occlusion or disease progression at other sites may occur to account for the decline in resting ABPI. Why post exercise ABPI continued to improve while resting ABPI deteriorated was not explored in this study but may be as a result of partially failed angioplasty resulting in altered haemodynamics due to incomplete restoration of the vessel lumen (Rutherford *et al*. 1997). ABPI was used as a surrogate marker of radiological success rather than Duplex ultrasound as this imaging modality is not routinely used to follow up angioplasty treatment sites.

Smoking plays an important part in disease progression and restenosis (Jonason and Ringqvist 1985). At baseline 25% of angioplasty patients and 29% of exercise patients were current smokers, a difference which was not statistically significant (compared to 20% of the general population in 2010, Office for National Statistics 2012). Smoking rates at later visits were not explored but all patients were given advice to stop smoking. It may be that continued smoking had a part to play in late angioplasty failure rates. In addition the adherence to statin and antiplatelet therapy was assessed at baseline but not at later visits. Those patients not on statins or antiplatelet agents were advised to contact their GP to ensure secondary prevention measures were addressed; in addition it is standard practice to put the need for aspirin and statin in a letter to the GP from the initial clinical visit.

Coupled with improvements in ABPI there were significant improvements in walking distances (both ICD and MWD) at 3 months compared to baseline. It follows that revascularisation and treatment of the occluded or stenosed vessel would result in an improved ability to walk, as the causative factor for claudication has been successfully treated. Despite the return to baseline in ABPI, ICD distances on the treadmill were not only maintained but showed significant improvement even from the 3 month data at both 6 and 12 months. MWD distances improved from baseline to each of the time points and there was also a statistically significant improvement in patient reported walking distances. This is hugely encouraging in that although a degree of restenosis or disease progression may occur this does not necessarily translate into a return to baseline in symptoms. The explanation for this may lie in the fact that once treated, the angioplasty group were then able to walk and improve their tolerance to ischaemia and in effect they produced an exercise therapy result themselves. McDermott *et al*. 2006 found that PAD patients who

exercised for 3 or more times a week demonstrated smaller annual declines in walking tests (6 minute walk, 4 metre walk tests) suggesting that self-directed exercise (> 3 times a week) has a potential benefit on walking function, compared to less frequent exercise. Objective assessment of physical activity, by using exercise diaries or pedometers, may have proven this link to increased physical activity in the current study.

4.2.2 Physical function

The short performance physical battery scores (SPPB), which involve walking tests, improved significantly for the angioplasty group between baseline and 3 months. This improvement was maintained at the 6 and 12 month visits. When broken down into the components of SPPB, significant improvements were seen in all areas of the test. Standing balance did improve, but only at 12 months was there a significant improvement from baseline in the semi tandem and full tandem stance times. Given the improvements seen in ABPI and treadmill walking, the tests involving an element of walking should and did improve following treatment. The improvements were maintained, which as with treadmill walking, indicates that once able to walk post angioplasty patients must continue to exercise to a degree which allows preservation of walking function, despite declining ABPI. As described above McDermott *et al*. (2006) showed a decline in deterioration in the walking tests of physical function used in the present study (6 minute walk, 4 metre walk tests) among patients who reported a higher frequency of self-directed walking exercise. The decline in function could be explained in their group as their patients had not undergone angioplasty treatment or formal exercise treatment, as with this current study (sections 3.2.3 and 3.3.3). Yet the fact that the decline in function was less than that

observed among patients who exercised less than 3 times a week suggests continuing to exercise through walking has a positive effect on PAD patients rather than not walking. The implication is that encouraging self-directed exercise in all patients as an additional treatment should be promoted, not only to improve claudication symptoms but to improve global physical function. The vascular adage "stop smoking and keep walking" has relevance for function as well as symptom improvement.

It could be implied that improvement noted in standing balance at 12 months is due to exercise effects rather than revascularisation as there was no improvement early post treatment. Certainly exercise has been proven to improve balance (Howe *et al*. 2007), but angioplasty treatment and balance has not been previous studied. This study did not confirm that angioplasty patients were taking more exercise post treatment, it is an assumed effect of successful treatment and further work to confirm or refute increased levels of exercise would be of benefit.

There was no discernible pattern or explanation for the two significant changes noted in hand grip strength (Appendix 6) and the clinical relevance of these findings may be minimal. The changes may have been related to increased exercise and physical function but the decline seen in left hand grip is more difficult to explain. The left hand was non-dominant hand in 88% of patients and therefore the decline in function may be related to lack of use but is not proven.

As expected, 6 minute walking distances at all times points were significantly improved compared to baseline, except for the maximum walking distance at 12 months (Figures 3.5 and 3.6). Time taken until claudication arose, and maximum walking times were also recorded. Angioplasty patients were able to walk for longer both pain free and with pain after treatment (ICD time and MWD time respectively) and this was significant at 3 and 6 months compared to baseline. There was a further significant improvement in maximum walking time between 3 and 12 months. This suggests that at 12 months patients were not covering the same distances but were walking for longer and therefore had possibly adapted slower walking speeds to cope with restenosis or deteriorating disease as indicated by a decline in ABPI to near baseline levels. Mockford *et al*. (2010) demonstrated that patients make significant temporospatial gait adaptations to claudication pain such as; reduced walking speed, reduced step frequency and increased time spent in the double support phase of gait, with the onset and progression of pain. It may have been that at 12 months patients had a degree of recurrent symptoms that were induced during the 6 minute walk and therefore explaining the reduction in walking distance but increase in walking time. This is supported by the decline in median ICD between 6 and 12 months and the wide variability in ICD recorded at 12 months (Figure 3.5).

4.2.3 Balance

As with standing balance, great improvements in CDP balance were not seen in angioplasty patients post treatment. There was no improvement in the proportion of patients who passed the SOT, although the median composite SOT score improved significantly between baseline and 3 months. This may be a function of improved vascular supply and more

closely related to ABPI in this group, than to walking distances as improvements followed the same pattern of significant change (Figures 3.1 and 3.7). It seems that on-going improved walking distances did not impact on balance in this group as SOT scores showed no significant improvement at 6 or 12 months (Figure 3.7). No previous work has studied the effect of lower limb angioplasty on balance but exercise has been shown to improve objective markers of balance such as SOT scores (Wallmann *et al*. 2009; Alpert *et al*. 2009). In the previous section it was hypothesised that improvements in physical function beyond 3 months may be due to patients engaging in self-directed exercise to maintain function. If this is the case, it seems that the exercise undertaken is not sufficient or appropriate to improve balance. Exercise programmes aimed at improving balance do not necessarily recommend walking. Sherrington *et al*. (2008*b*) found that the most successful programmes for minimising falls did not include walking and an explanation may be that walking takes time away from balance challenging exercises which have a greater effect on falls reduction. Education for patients aimed at improving global function after angioplasty intervention should include self-directed exercise ("stop smoking and keep walking") but should also include measures to improve balance and physical function. Exactly which exercises will benefit this group most has not yet been clarified.

Condition 4 of the SOT involves the base plate rotating (angular translations) and therefore requires the patient to engage their calf musculature to maintain their stability. This section of the SOT did show significant improvements from baseline at 3, 6 and 12 months. This may be a reflection of both improved vascular supply and improved muscle conditioning with increased levels of exercise once angioplasty patients were able to walk. The sensory analysis was not affected by treatment at any of the time points.

The MCT latency outcome did not change over the study period. The composite MCT score improved between 3 and 12 months, and 6 and 12 months. This is difficult to explain by either improved vascular flow or by increased levels of exercise, unless it is a delayed effect as improvements were not seen between baseline and 3 months. This finding may not be related to revascularisation but to an event after treatment, such as an exercise effect occurring once patients are able to walk pain free. Another explanation may revolve around possible improvements in muscle structure or muscle denervation after angioplasty. The severity of muscle denervation correlates with the severity of vascular disease (England *et al*. 1992) and denervation should be associated with poor performance on the MCT test. It should follow that if neuromuscular function improves with improving vascular disease, MCT performance may also improve. These suggested changes in muscle histology may take longer to manifest, which would explain a delay in improvement.

4.2.4 Falls

The number of falls and stumbles reported by patients fell at 3 months compared to baseline but no other changes were seen. This is likely to be due to improved walking ability and to greater confidence post revascularisation. Confidence did improve at 3 months as measured by a significant improvement in Activities-specific Balance Confidence (ABC-UK) score (baseline: 79.56 (IQR 53.92-90.72), 3 months: 87.60 (IQR 73.84-97.26) $P < 0.001$), although this improvement was not maintained at later time points. This may reflect the sudden improvement seen in walking distances with angioplasty revascularisation and may translate into improved confidence with falls related activities due to more confident walking. This finding is supported by Gardner and

Montgomery's (2001) observation that self-reported ambulatory function relates to measures of falls. In the present study confidence declined at 6 months back to baseline levels. This decline in confidence at 6 months matches the return to baseline seen in SOT scores at 6 months, highlighting the link between balance and falls risk (American Geriatrics Society 2001). As with SOT, ABC-UK scores may be more closely related to ABPI or the consequences of improved lower limb perfusion rather than related to improved walking distances.

The TUG test is a recommended assessment for falls risk (American Geriatrics Society 2001). As seen with some measures of physical function, TUG test scores improved after treatment and continued to improve at each visit when compared to baseline (Figure 3.10). The TUG test is again a walking test and therefore improved walking ability is likely to lead to improved TUG times. This is an encouraging finding in that angioplasty treatment may lead to a reduction in falls risk through improvements in walking function, demonstrated by TUG improvements.

4.2.5 Quality of Life

As expected there were significant improvements in quality of life following angioplasty treatment. The disease specific VascuQol quality of life measure showed improvement in every domain at 3, 6 and 12 months when compared to baseline. The literature has long since recognised that patients with symptomatic PAD have impaired quality of life and that such impairments improve with treatment (Chetter *et al*. 1999). It has also been acknowledged that disease specific tools such as the VascuQol are more sensitive to

improvements following treatment (de Vries *et al*. 2005). In this study VascuQol did identify improvements in non-physical domains not identified by generic QOL measures and therefore it seems appropriate to use this tool in PAD populations.

Quality of life assessment was included in this study to assist in identifying global factors associated with physical function and balance impairment, and falls risk. It may be prudent in the future to combine quality of life assessment with assessment of physical function and falls risk targeting improvements in patients' perception of their lives as well as in diminishing objective falls risk. Improving an individuals' physical function alone without consequent improvements in quality of life might be perceived as of little value for some individuals. It may be possible to construct further quality of life tools that are even better targeted to physical function, balance and falls risk related quality of life.

4.3 Exercise data

In addition to angioplasty treatment, the effects of a structured exercise programme on clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life in patients with lower limb ischaemia were examined hypothesising that patients undergoing exercise therapy will demonstrate improved outcome measures after treatment.

4.3.1 Clinical indicators of lower limb ischaemia

Ankle Brachial Pressure Index (ABPI) did not significantly alter across the study period in the SEP group, and this was to be expected. SEP does not revascularise the limb and therefore major changes in blood flow to affect ABPI do not occur (Watson *et al* 2008). Despite not improving ABPI, exercise treatment has been previously proven to be of value in improving walking ability (Watson *et al*. 2008). In this study, objective walking distances did improve following exercise. The treadmill ICD distance improved significantly between baseline and 3 months and baseline and 6 months (Figure 3.13) and the maximum walking distance on the treadmill improved significantly between baseline and 3 months (Figure 3.14). Patient reported walking distances also improved from baseline to each of the individual time points (3, 6 and 12 months) (Appendix 9).

The mechanisms thought to be involved in improving walking distances include not only improvements to collateral blood flow but increased aerobic capacity, improved muscle strength and endurance, improved walking economy, improvements to endothelial function

and the microcirculation and improvements in the nature of blood flow (Stewart *et al*. 2002; Brendle *et al*. 2001). Muscle biopsies were not taken in the current study but would be an interesting avenue of future research, particularly after treatment and to compare treatment effects.

4.3.2 Physical function

With improved walking distances an improvement in measures of physical function is expected. At 3 months many aspects of physical function had improved (SPPB, 4 metre walk test at usual and fastest pace, and 6 minute walking distances and times, Appendix 10). All of these tests involve an element of walking and therefore as the SEP patients improved their walking distances, it follows that the measures of physical function directly involving walking should also improve. McDermott *et al*. (2009*a*) have also investigated the effect of exercise on function, although they only found improvements in the 6 minute walk test rather than in SPPB. This may have been due to the nature of their exercise programmes which were either treadmill walking based or resistance training based. The SEP group in this study took part in a circuit based programme involving walking and strength training stations and the combination seems to show better gains in terms of function.

However the chair stand test and semi and full tandem balance tests did not improve with exercise treatment in this study. This may be a reflection of not specifically training to improve these elements of physical function in the exercise programme. McDermott *et al*. (2009*a*) found an improvement in stair climbing ability with their resistance programme not

found with their walking programme. It seems that in this study the strength training aspects of the SEP programme were not sufficient to produce a meaningful improvement in the chair stand test, which requires good quadriceps function.

The physical function indicators suggest that balance may also not have been adequately trained in this study as semi and full tandem balance did not improve. However these tests of standing balance were not very sensitive in that at baseline most patients were able to complete both tests (semi tandem N = 79 and full tandem N = 55). This finding was also noted by Sherrington *et al*. (2008*a*) who observed improvements in step balance tests, sit to stand, gait, and the 6 minute walk after circuit style exercise but no significant change in semi tandem or tandem stance.

Furthermore, hand grip strength deteriorated with the SEP programme. Both the right and left hand grip strength deteriorated between baseline and 3 months, and this significant deterioration remained at 6 months in the left hand (Appendix 10). Upper limb function was not a priority for the SEP programme but there was a 2 minute upper limb station within the programme, aimed at providing a rest for the legs while giving patients a focus by performing biceps curls (Figure 2.6). This station was not intended to produce improvements in hand grip strength. However the promotion of general health through SEP could have led to an increased uptake of self-directed exercise and therefore perhaps a reduction in general frailty demonstrated by improved hand grip strength. This did not appear to be the case with this patient group and rather than any improvement, a deterioration was seen during the SEP course. The explanation may be that the SEP patients

were so focussed on their symptomatic lower limbs that they ignored potentials for improving their whole body function and specifically their hand grip strength during the initial 3-6 months of the study. Given that there were no longer term significant differences in grip strength from baseline, it may be that as the SEP finished, and particularly for those who had improved their walking ability, patients were then able to consider improving their general health and therefore grip strengths returned to baseline levels. Of note the overwhelming right hand dominance of the study population (88%) implies that the right hand would be prioritised for everyday functional tasks and that decline in function should be less apparent in the right hand. This fits with no deterioration from baseline at 6 months in the right hand grip strength but an on-going decline in the left hand at this time point.

4.3.3 Balance

Interestingly, although the simple static measures of balance semi tandem and tandem stance did not improve after SEP, this study found an improvement in CDP balance post treatment. The proportion of patients who passed the Sensory Organisation Test (SOT) (Appendix 11) and the mean composite score for SOT improved significantly at all 3 time points after treatment (Figure 3.17), when compared to baseline. Exercise treatment has previously been shown to improve balance particularly when programmes involve a combination of interventions including walking, balance training and functional exercises (Howe *et al*. 2007) and in particular have resulted in objective improvements in SOT scores (Wallmann *et al*. 2009; Alpert *et al*. 2009). The exercise programme in this study, however, was not specifically aimed at balance. In fact it was not altered at all from the standard supervised exercise programme offered to claudicants at this NHS trust, in order not to

deviate from standard treatment. This is hugely encouraging and with further improvements to the exercise programme it may be that more gains can be made in terms of balance improvement with potential consequent improvements in function and falls risk.

When individual conditions of the SOT were analysed, there was a significant improvement noted at 3 and 6 months for condition 4 and a significant improvement at all 3 time points for conditions 5 and 6. Furthermore, improvements continued to occur after the exercise programme had finished in condition 5 (significant improvement from 3 to 12 months) and condition 6 (significant improvement from 6 to 12 months). Conditions 4, 5 and 6 are the most challenging of the SOT, with therefore more room for improvement in scores. In condition 4 the platform rotates via angular translations (Figure 2.5) and the individual must engage their lower limb musculature to stabilise themselves. The same occurs in condition 5 but the individual also has their eyes closed, thus removing visual feedback and leaving vestibular and somatosensory systems to cope with the perturbation. Condition 6 involves both the standing platform and the visual surround moving thus giving incorrect somatosensory and visual input and requiring an accurate vestibular system to trigger the correct response from the lower limb musculature to maintain an upright stance. The improvements seen in these 3 conditions after SEP suggests that SEP affords more than just an improvement in lower limb muscular function that could be obtained by walking. These same improvements were not seen in angioplasty patients, suggesting that the SEP may challenge and even train balance or the vestibular system to some degree in addition to improving leg function. This may result from activities as simple as stretching in the warm up phase whereby claudicants stood on one leg and stretched their quadriceps by holding the contralateral ankle behind them at the base of their gluteals. As described in previous

sections histological muscle changes may account for improvements seen in balance, particularly of interest would be changes to muscle denervation in terms of responding to perturbations. Muscle biopsies after exercise treatment in PAD populations have not been carried out either in this study or in the published literature, although may give information about the mechanism of improvement in balance after exercise treatment.

Although the NeuroCom does not give a diagnosis or a specific system impairment it computes sensory ratios between the average condition scores on specific paired results i.e. for vestibular function condition 5 and condition 1 are paired, a low score implies that the patient is unable to utilise vestibular cues (NeuroCom 2001). The sensory breakdown analysis confirms that improvements were found in vestibular component of balance assessment between baseline and 3 months. A significantly higher proportion of patients passed the vestibular analysis at 6 and 12 months compared to baseline. There was no difference in falls during the SOT or in any aspect of the MCT throughout the study period in the SEP group. Therefore the improvements noted with angioplasty were not found in the SEP group suggesting revascularisation may be aiding the neuromuscular component of balance. This study found significant objective improvements in balance outcome measures with SEP, not seen with angioplasty treatment suggesting that exercise therapy may be an effective treatment for those claudicants with impaired balance.

4.3.4 Falls

SEP patients did not report a significant change in falls history over the study period. However there was a significant improvement in the number reporting stumbles between

baseline and 3 months. Exercise programmes have been found to be effective preventative treatments for fallers in reducing falls rates (Gillespie *et al*. 2003; Sherrington *et al*. 2008*b*) and perhaps more of a reduction in falls history would be expected. The limitation of questioning patients retrospectively is that they may not adequately recall falls events or even the timing of falls therefore falls may be both under reported or inaccurately reported in relation to the treatment period. A future study could use a diary system of documentation or send out reminder cards to patients on a frequent basis to trigger accurate reporting (Arseven *et al*. 2007). Although prospective triggering of a potential falls risk may lead to behaviour aimed avoiding potential situations which may cause a fall that would otherwise be undertaken.

Fear of falling did not drop with the exercise programme as there was no significant difference in ABC-UK scores across the study period (Appendix 12). Despite the fact that this group reported less stumbles, perhaps the improvements were gradual and therefore any possible improvements in confidence were not perceived by individuals in the SEP group.

The TUG test was performed significantly faster at 3, 6 and 12 months when compared to baseline (Figure 3.21), which as with other walking tests, may be a reflection of improved walking ability after the SEP treatment. This confounds results from a previous study showing improvements in TUG scores with exercise therapy in a non-PAD population (Jacobson *et al*. 2011). TUG is recommended as a screening tool for falls risk (American Geriatrics Society 2001; Rao 2005) and thus improving TUG scores can be seen as an

encouraging marker of potential reduced falls risk after SEP and is comparable to the improvement seen with angioplasty.

4.3.5 Quality of life

Quality of life improvements were noted for the SEP group but were not sustained at 12 months (Table 3.10). Disease specific VascuQol was a more sensitive measure of quality of life, as expected (de Vries *et al*. 2005; Mehta *et al*. 2006). VascuQol has been shown to correlate better with clinical indicators of lower limb ischaemia in patients with PAD both pre and post treatment (angioplasty and exercise) than generic QOL tools (Mazari *et al*. 2010).

No emotional or social domain scores improved in either SF8 or SF36, however significant improvements in the emotional domain scores of VascuQol were seen at 3 and 6 months, and an improvement in social domain scores was also seen at 6 months. It is not surprising that at 12 months quality of life in the SEP group reverted back to baseline, in that treadmill and six minute walking distances were not significantly different at 12 months compared to baseline. Once the primary symptom of claudication was not significantly improved it follows that quality of life would also deteriorate. No gains in function with falls risk or balance had enough impact on quality of life to make any significant difference. Perhaps a more balance orientated QOL measure would have identified small changes had these been present.

4.4 Comparison between the effects of angioplasty and exercise therapy

The final aim of this work was to compare the effects of both angioplasty and exercise treatments on clinical indicators of lower limb ischaemia, physical function, balance, falls and quality of life in patients with lower limb ischaemia. It was hypothesised that there would be no difference between angioplasty and exercise treatments in improving outcome measures.

4.4.1 Baseline data

This was not a randomised study as patients were referred for either angioplasty or exercise treatment based on their symptoms, disease morphology and previous treatment. Full clinical assessment and treatment planning was carried out by the referring Consultant Vascular Surgeon prior to study inclusion. Therefore the 2 patient groups on inclusion into the study were different, requiring different treatments for their peripheral arterial disease. The 2 groups were compared in detail at baseline to identify differences which may explain differing responses to treatment. In terms of basic demographics they were comparable in terms of age, gender, medical history, height, weight and BMI.

4.4.1.1 Clinical indicators of lower limb ischaemia

Those patients who were referred for exercise had poorer baseline vascular function in terms of ankle brachial pressure indices both pre and post treadmill exercise, although were able to walk further on the treadmill before complaining of pain (intermittent claudication distance) than their angioplasty peers. Both groups walked for a similar maximum distance and both reported similar patient reported walking distances (Appendix 13).

It might be expected that a poorer ABPI should correlate with a shorter walking distance before the onset of pain; however this was not the case in this study and is well recognised (Da Silva *et al*. 1979; Gardner *et al*. 2008*b*). ABPI values are not absolute indicators for treatment; moreover treatment planning is based on symptoms and patient determined quality of life factors, balanced with risk and potential benefit of intervention. Both clinical and patient based factors are recommended assessment criteria for claudicants (Norgren *et al*. 2007). It is known that claudication is often a stable condition without significant deterioration in symptoms over time in the majority of patients. This may be due to collateral vessel development which is difficult to measure objectively and is not measureable by ABPI. The Basle study reported that at 5 years two thirds of surviving patients showed symptom improvement although 63% demonstrated progression of disease on angiography (Da Silva *et al*. 1979). ABPI alone is therefore not a good indicator of walking function, as found in this work.

Demonstrating a significant difference in clinical indicators of lower limb ischaemia, in particular ABPI and walking distances, between the two groups studied suggests a different

morphology of disease. The study patients were not classified at baseline in terms of pattern of disease, nor did they all undergo investigation using the same imaging modality prior to referral and therefore disease morphology was not retrospectively analysed.

4.4.1.2 Physical function

Walking and physical function are intimately related and most of the measures of physical function required patients to walk. This may explain the poorer performance from angioplasty patients compared to exercise patients given that they suffered from claudication related pain on walking at shorter distances. Although not all physical function tests require a walk long enough to induce pain, a poorer tolerance to walking in general may lead to poorer overall physical function through lack of exercise. Not explained by walking, standing balance was also poorer in angioplasty patients, suggesting that those patients who are less able to walk may have impaired muscle strength and consequently balance.

4.4.1.3 Balance

In objective balance assessment using CDP, this study demonstrated that global balance abnormalities are extremely common in claudicants occurring in 47% of this study population compared to 5% of NeuroCom control patients (NeuroCom 2001). Despite the finding that angioplasty patients performed worse in standing balance tests there was no difference between exercise and angioplasty groups in terms of their CDP scores. Poor balance was particularly evident in the sensory analysis breakdown at baseline with 53% of

patients failing the vestibular assessment. None of the patients recruited complained of balance problems and all led functionally independent lives. Therefore the detection of a potential risk factor for falls in an asymptomatic group of vascular patients, such as this cohort, highlights the common nature of balance problems and the lack of awareness among patients. This has been shown in other studies, Cohen *et al*. (1996) tested 94 independently-living healthy control subjects who were all able to perform self-care tasks unaided and among their population SOT scores did vary, even to the extent of being abnormal in some patients, despite a lack of symptoms. Acknowledging that people may be functionally independent but still have abnormal balance scores is important. Abnormal balance assessment may be seen as a warning sign of potential future problems and that these are the very people to target in order to prevent or minimise further decline, falls risk and serious injury. Given that coupled with poorer physical function, intervention to improve balance is particularly pertinent. Indeed current functional competence may allow patients the freedom to participate in programmes to improve stability and may also directly motivate patients to maintain their current state of independence. Furthermore balance is thought to deteriorate with age and this has been objectively demonstrated by decreasing SOT scores among older populations with a continued deterioration even into the ninth decade (Cohen *et al*. 1996). This study, however, showed no significant correlation between composite SOT scores and age at baseline, suggesting factors other than age had greater influence over SOT than age. This also indicates that age alone is not necessarily a risk factor for balance in claudicants and should be considered along with functional performance.

The explanation for impaired balance, as with physical function, is likely to be multifactorial. Particularly older claudicants often have multiple co-morbidities which may result in confounding reasons for impaired balance. Patients in this study were selected to be older (>50 years of age) in order to gain information on an age group known to be at high risk of falls, however, no significant variation in co-morbidities was observed between patients with abnormal and normal balance in our study population. Impaired muscle function among claudicants is likely to be a significant contributing factor. One explanation for poor balance in patients with PAD is similar to that for poor physical function, in that, PAD patients have ischaemic muscle changes that correspond with histological muscle changes and poor functional strength (Regensteiner *et al*. 1993). Whether the presence of PAD is indicative of central balance control impairment is difficult to ascertain, but the systemic atherosclerosis associated with PAD patients may cause central and cerebral changes which contribute to balance impairment.

Whether impaired balance can be directly attributed to peripheral vascular disease remains unproven, but potential avenues of research must include central causes such as small and large vessel cerebrovascular disease and peripheral causes such as proprioceptive pathways and muscle weakness limiting the adaptive response.

Claudicants may be expected to have a higher frequency of somatosensory balance abnormality due to peripheral neuropathy and impaired sensation as a reflection of their vascular disease, particularly those with diabetes (who exhibited no significantly increased rate of abnormal balance). Rather than predominantly somatosensory dysfunction, this

study identified a high incidence of balance abnormalities secondary to vestibular dysfunction in patients with claudication (Appendix 15). The functional impact of an impaired vestibular score on a firm support surface in the presence of normal vision is negligible, as other systems will compensate. Conversely, on irregular surfaces and in conditions of low lighting such patients will experience instability. This is hugely significant for elderly, falls risk patients in situations such as getting out of bed at night, and when out of the house walking on irregular paving. The high incidence of vestibular dysfunction in this group was unexpected as a direct aetiological link between vestibular dysfunction and peripheral arterial disease has not previously been established. However, among people with balance disorders, vestibular dysfunction is common and represents up to 50% of cases (Cohen *et al*. 1996). While our high rate of vestibular dysfunction may be a reflection of the spectrum of balance dysfunction within society, it may also be linked to high rates of systemic atherosclerosis including micro vascular disease among claudicants. Vestibular dysfunction has previously been linked to atherosclerosis, in particular vertebrobasilar insufficiency (Alekseeva 2004) although research in this area is sparse. The purpose of the SOT and indeed this work was to highlight a potential area of deficiency rather than to offer an absolute diagnosis. The sensory analysis results must be interpreted with the clinical assessment of each individual.

Of further note we found a significant difference between male and female claudicants in terms of balance scores. Overstall *et al*. (1977) measured anterior-posterior sway using an ataxiameter on 306 elderly people noting an increase in sway with age and in particular, increased sway among women. They suggested a decline in central postural control and loss of proprioceptive information with age and hypothesised that women's increased sway

may be a function of body weight to muscle mass ratio. The present study did not specifically focus on the difference between male and female claudicants though there was no difference in height, weight or BMI found between different balance outcomes. Future work on elucidating the aetiology of abnormal balance and the difference between the genders will be of use in developing targeted treatments to allow functional improvement.

The Motor Control Test (MCT) was performed well at baseline. Less than 30% of claudicants showed abnormalities in weight symmetry and latency, indicating that despite having one poorer functioning limb they were able to distribute their weight evenly during the MCT and were able to react in a timely fashion. Prolonged latency times have been associated with peripheral neuropathy and delayed central nervous system processing secondary to ageing or cerebral atrophy (Horak *et al*. 1997). A strong correlation has been described between short MCT latency time and the ability to recover from sudden minor slips (Lockhart 2002), thus these were positive findings for the claudicants in the current study in that they were able to recover from or respond quickly to perturbations. In addition, it also suggests, that abnormal MCT latency was not a strong contributing factor to impaired balance and increased risk of falls in claudicants.

The incidence of abnormally weak response strength during MCT testing was 19% for backward translations (n = 18) and 26% for forward translations (n = 25) among our subjects. The functional impact of poor response strength is likely to be significant; in that a poor response strength result from either leg suggests difficulty in recovering from instability, such as that which occurs when stumbling. Thus, even with adequate latency

timing, if the response strength is suboptimal a patient may still be susceptible to falling. The relationship between response strength and latency to exercise training is not known, particularly in this patient group. It may be hypothesised that strength training, for example, would be associated with improvements in response strength results. There was no significant difference between angioplasty and SEP groups in any outcome on the MCT except response strength to forward translations, where exercise patients performed better. The reason for this finding is unclear and identifying the causes of differences between 2 such groups may be an avenue for future research. It may be related to tolerance to ischaemia or as a reflection of poorer function.

4.4.1.4 Falls history

Falls history was frequent among this study group with 20/98 patients having fallen in the previous year and no significant difference between the 2 groups. This may be expected given the findings of impaired balance and previous studies which have indicated higher falls risk in PAD (Gardner and Montgomery 2001*a*). Impaired composite SOT scores have been demonstrated to be useful in identifying not only patients with balance disorders but also those at risk of falling with two papers confirming a relationship between poor SOT scores and a history of falling (Wallmann 2001; Whitney *et al*. 2006). The relevance of poor balance and increased falls risk is of prime concern among the elderly, as they, with potentially a multitude of other contributory risk factors, are more susceptible to morbidity associated with falls.

Conversely the ABC-UK scores for the baseline population were good and again no difference was found between either treatment group. This is perhaps more worrying as a lack of insight may give rise to increased risk. This has been noted previously in a study of 43 community dwelling elderly men who experienced a decline in walking function, physical activity and function as well as an increase in the incidence of self-reported ambulatory stumbling and unsteadiness over 18 months of follow up. Perhaps of greater concern in that particular study, was the lack of change in self-perceived health status over time, suggesting a lack of awareness of their deterioration thus rendering patients more susceptible to potential instability and falls (Gardner *et al*. 2004). At baseline the falls history data was collected retrospectively and thus it is not possible to predict future falls from this data, but instead offer comment on the relationship between balance and our patients' retrospective falls history. While improving a risk factor does not guarantee a reduction in falls or improved outcome, it can be argued that the identification of a risk factor by such means as objective balance assessment offers a useful tool in directing therapy towards those at potential risk.

The TUG test was the other measure of falls risk examined in this study and there were no immediate differences between the 2 groups, although on further analysis angioplasty patients performed significantly worse than exercise patients in terms of age adjusted pass fail rates with 21 of 47 passing compared to 37 of 52 exercise patients passing. The explanation for this finding at baseline is likely to be similar to that of the walking measures of physical function, in that the TUG test requires patients to walk and therefore those that are better able to walk comfortably are the exercise patients.

4.4.1.5 Quality of life

At baseline this cohort demonstrated, as expected, poor QOL in physical domains but also in measures of activities. Angioplasty patients reported poorer QOL and this may reflect the fact that they are due to undergo a procedure which is in part indicated for poor quality of life and the inability to perform activities important to their lives which require pain free walking.

4.4.2 Post treatment comparison between angioplasty and exercise

Pre exercise ABPI and treadmill ICD were used as measures of ischaemia in comparing the effects of both treatments at 3, 6 and 12 months. The significant differences highlighted at baseline were that the angioplasty group had better pre exercise ABPI but worse treadmill ICD compared to the SEP group. As expected the angioplasty group improved in terms of ABPI whereas the SEP group had stable ABPI and therefore the significant difference between the groups was maintained as the difference between the 2 groups increased further. The explanation for this difference after treatment is that angioplasty revascularised the limb allowing improved blood flow but exercise treatment enables better tolerance of ischaemic conditions without drastically affecting blood flow and hence blood pressure.

Gains were made by both groups in terms of walking distance post treatment justifying both as acceptable treatments for claudication. Despite differences at baseline the improvements made by the angioplasty group made any difference between them non-significant at 6 and 12 months as the angioplasty group were able to match the exercise

group in terms of walking distance. Angioplasty treatment gave rise to greater improvements in walking distance due to the success of initial revascularisation, however ABPI were not maintained at the later time points and therefore the continued improvements must be due to an exercise effect in this group. It may be that once able to walk they continued to walk and exercise enough to improve walking function further.

The short performance physical battery (SPPB) score was used as a measure of physical function and at baseline the SEP group performed significantly better. However likely due to the improvements made in walking the difference between the two groups was eliminated at 3, 6 and 12 months.

Balance and falls risk were not significantly different between the two treatment groups at baseline and this non-significant difference was maintained at each of the time points post treatment. However the patterns of improvements made by both groups were different as explored in the previous 2 sub sections.

Quality of life was significantly better for the SEP group at baseline compared to the angioplasty group, although following treatment the significance was reversed as the angioplasty data improved alongside that of the SEP group. The better quality of life noted by the exercise group at baseline may reflect their improved walking function and this may then explain why the angioplasty group, as their walking function improved to the same level of that of SEP, also showed similar quality of life scores as the study progressed. The

MIMIC trial compared angioplasty with no angioplasty for patients who had already participated in a structured exercise programme and found that there was no improvement in SF36 quality of life scores for patients with femoropopliteal disease but a significant improvement in the physical score of SF36 for the angioplasty group in patients with aortoiliac disease (Greenhalgh *et al*. 2008).

This study acknowledges that the comparisons made between the 2 treatment groups are primarily observational. The study was non-randomised and identified clear differences between the 2 groups at baseline therefore a strict comparison of treatment effects was not possible. It is, however, possible to comment on the progress of the 2 distinct groups, as has been done, and to reiterate that both treatments have their place. This study is not designed to recommend one treatment over another but to investigate potential concomitant improvements in physical function, balance and falls, as have been demonstrated, after treatment.

4.5 Delimitations and limitations

There are several important delimitations and limitations to discuss with this study, all of which have been alluded to in the main discussion. These are as follows;

- This study was non-randomised and therefore a direct comparison between exercise and angioplasty treatment effects cannot be used to imply the superiority of one treatment. This study was aimed at every day vascular practice and therefore patients were recruited after a clinical decision regarding best treatment had been made. Randomization of this cohort would have been unethical in that the some patients would have been better served by a particular treatment modality in the first instance.

- The spread of disease severity within the study was not uniform. There were only 5 mild claudicants recruited and 39 severe claudicants. This is, however, representative of treatment patterns in daily vascular practice.

- The pattern of arterial disease was not recorded or followed up. There may have been useful differences found between aortoiliac and femoropopliteal disease in terms of outcomes.

- Radiological success was not measured after angioplasty due to the risks of an unnecessary radiological procedure, however, Duplex imaging may have highlighted success rate to some degree. ABPI was used as a surrogate marker for radiological success.

- The history of falls and stumbles reported by patients may have been improved by documentation aids given to the patients such as a diary or reminder cards.

- Smoking rates were not recorded at follow up visits, which may have identified a risk factor for restenosis/occlusion or disease progression and hence treatment failure.

- Not all patients referred for exercise took up the structured exercise class (125 invited and 51 were enrolled into the trial). Many patients declined to participate for a number of reasons including transport availability to the class. Once they had begun the SEP the drop-out rate from the classes was less than 10%.

- There was a drop-out rate from both groups throughout the study, and at 12 months 18 patients had dropped out of the angioplasty group and 28 from the exercise group (Appendix 18).

- This work contains multiple statistical comparisons and therefore there is a violation of the familywise error rate. This will result in an increased likelihood that statistical significance will appear where there may be no clinical significance due to the large number of tests performed (i.e. a type I error). There are several methods to adjust for multiple testing, which include the Bonferroni and Holm methods (Aickin and Gensler 1996) which reduce the type I error rate. There have been several cautions proposed to such adjustments, most notably that the reduced type I error rate leads to the converse occurring, i.e. that there is an increased type II error rate (Perenger 1998). In this particular study, no adjustment was used partially owing to the massive type II error rate inflation that would occur from the large number of variables analysed. In addition, this study was powered for the primary hypotheses to compare baseline to 3 months; combining these two time points with the other two time points (i.e. 6 and 12 months) would require greater sample sizes. As this comparison was not powered for in this study, it is likely to be underpowered, particularly with the addition of the multiple testing corrections. As such, in all cases

significant and non-significant findings are also interpreted for clinical meaning and significant differences of no or uncertain clinical relevance have been discussed and discarded appropriately.

4.6 Future directions

Specific randomised controlled trials (RCT) to consider would include the randomisation of patients with the same morphology of disease to each treatment arm. As previously discussed, in this study there were patients who were more suitable for angioplasty as a first line treatment and therefore randomisation was not appropriate for this cohort. However it would be possible to design a study specifically for patients who would be suitable for either treatment to then be randomised to determine treatment effect. Furthermore, an alternative RCT would be for patients having undergone angioplasty to then be randomised to SEP or no SEP to identify any cumulative benefit of both treatments, or an additional benefit of SEP.

A future study investigating the impact of standard treatment on clinical indicators of lower limb ischaemia, physical function, balance, falls risk and quality of life in patients with critical limb ischaemia would be of interest and may demonstrate even further gains in terms of function. The most suitable RCT for this cohort may be to randomise patients after angioplasty to SEP or no SEP and assess function accordingly.

Furthermore, modifications to the standard supervised exercise programme for claudicants could be made aimed at improving the gains in balance and physical function seen with the current programme. This might involve more targeted balance stations and more work to improve lower limb functional strength. This study proposed that one explanation for

improved function despite no improvement in ABPI from baseline among both angioplasty and exercise patients may result from improved levels of physical activity. Correlation with daily physical activity, either subjectively by asking patients directly or objectively, by measuring activity through accelerometers, pedometers and other devices, may confirm or refute this hypothesis.

Other key areas of interest for the future work centre on the possible explanations for treatment effects. Histological examination of muscle biopsies pre and post treatment may identify changes brought on by exercise and angioplasty, and indeed differences between the 2 treatments. This would not be a straight forward study as muscle biopsies can be painful and patients may be reluctant to participate in that aspect of the study. Specifically to examine the reasons for improvement in balance with exercise treatment, central causes of balance function should be researched including concomitant cerebrovascular disease.

4.7 Conclusion

This study highlights the impairments in physical function and balance among claudicants and recognises the link between balance abnormalities and falls risk. The relevance of balance and falls risk assessment specifically to vascular surgery has been clearly demonstrated by this study and this should act as a basis for on-going research to improve the functional outcome of vascular patients as well as purely improving their walking distance. The impact of research to improve functional outcome has the potential to be huge given our increasingly elderly population and improved survival into older age.

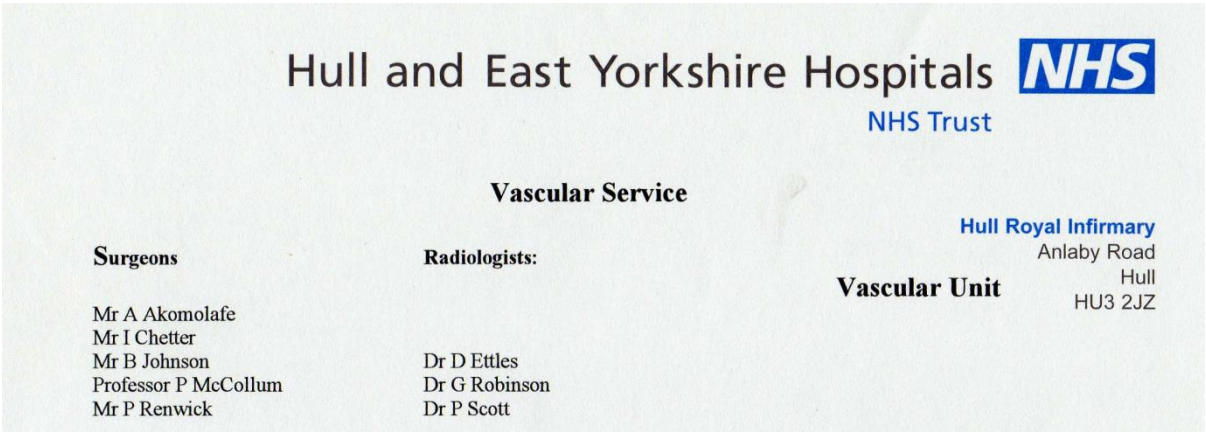
This study alone does not offer a definitive answer to improving function. However it was found that treatment, either through angioplasty or a structured exercise programme, led to improvements in many of the measures of clinical indicators of lower limb ischaemia, physical function, balance, falls risk and quality of life in patients with lower limb ischaemia. Interestingly there were differences between the two treatment groups, in that angioplasty led to significant improvements in clinical indicators of lower limb ischaemia, markers of physical function that include an element of walking, history of falling or stumbling, fear of falling and quality of life, but improvements in balance were minimal. Balance was only slightly improved by angioplasty at 3 months following treatment. Exercise, however, led to marked improvements in balance throughout the year from baseline, with also significant improvements in walking distances, physical function and a history of stumbles. Quality of life improvements were seen at 3 and 6 months but not at 12 months from baseline in the exercise group.

As has been discussed, the study was not randomised and therefore direct comparisons between the two treatment arms are limited. Future work, including randomising patients with similar disease morphology will improve the evidence for or against angioplasty and exercise in improving functional outcome. As some variables in this study did not improve with treatment, this work could be extended to study patients with critical limb ischaemia in whom additional functional gains might be expected given a poorer functional starting point.

Falls risk and declining physical function will be an ever concerning issue with our ageing population. Therefore recognising patients at risk in all medical specialities and allied health disciplines will hopefully allow improvements in prevention, targeted treatment and consequent improvements in quality of life for those at risk.

Appendices

Appendix 1. Patient letter and information sheet



21st January 2010

Mr xx

Dear Mr xx,

I am writing to you to invite you to take part in a research study that we are undertaking in the Academic Vascular Unit at Hull Royal Infirmary. You are invited to take part in the trial because you have reduced circulation to your legs that causes pain when you walk and you are going to undergo treatment to try and improve the circulation. There is no compulsion for you to take part. I enclose an information sheet that tells you all about the trial. If you require any information then do not hesitate to contact me on 01482675523 or 07736275213. If you wish to take part in the study then please complete the tear off slip at the bottom of this letter and return it in the stamped address envelope.

Kind regards,

Miss Katherine Mockford
Clinical Research Fellow in Vascular Surgery

Name:

I wish / do not wish (please delete) to take part in the "The role of treatment on balance and stability in patients with intermittent claudication." study.

PATIENT/SUBJECT INFORMATION LEAFLET

The role of treatment on balance and stability in patients with intermittent claudication: A pilot study.

You are 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 and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?
Patients with pains in their legs on walking caused by problems with their circulation (known as intermittent claudication) are more likely to experience a fall due to poor balance. Falls are associated with reduced mobility and a lower quality of life. No one knows what causes patients with intermittent claudication to fall and whether standard treatments aimed at improving the circulation and subsequently distances that you can walk also improve the balance of patients with poor circulation. Therefore, the goal of this study is to assess whether standard forms of treatment in patients with poor circulation to their legs improve balance and stability.

Why have I been invited?
You have been invited to participate in this study because you suffer from poor circulation to your legs (intermittent claudication) and the consultant in charge of your care in discussion with you has arranged for you to undergo either exercise treatment, or stretching of your arteries with a balloon (also known as angioplasty) or surgery to try and improve the distances that you can walk. The exercise programme consists of three sessions per week over a three months period and each session lasts for no more than one hour.

What will happen if I decide to take part?
If you decide to take part in this study, you will be invited to the Vascular Laboratory at Hull Royal Infirmary and the Human Performance Laboratory in the Department of Sport, Health and Exercise Science at the University of Hull, Cottingham. If you do not have your own transportation, it will be arranged for you by the Vascular Laboratory.

When you arrive at the Vascular Laboratory, you will be asked to complete some questionnaires. These questionnaires are used to rate your perceived fear of falling, balance confidence and quality of life. You will also be asked to perform a number of walking tests performed at your own speed well as a test of your ability to stand up from a chair. One of the walking test is a treadmill test. This forms part of the normal assessment that you would undertake even if you were not in this study. You will also be asked to walk on the treadmill for a maximum of 5 minutes at a slow pace. The tests will be undertaken at the same time as your routine visit to the vascular laboratory for the assessment of your circulation.

The second part of the assessment will take place at the University of Hull. You will complete a number of short tests on a platform that measures your balance control. For your own safety, you will be fitted with a security harness around your torso and waist. By

wearing a harness, the performance environment in which you will undertake the testing protocol is much safer. We will need to place some stickers on your legs to assess nerve and muscle function. They are small (about the size of a large postage stamp) but require a hair free area for best function. This means that if you are male you may need to shave a very small patch of hair from your lower leg so that the sticker will stick. You will be asked to bring a pair of shorts, comfortable shoes (no high heels!) and t-shirt. Shorts will be provided if you do not have a pair. If you do not have your own transportation, it will be arranged for you by the University. You will be reimbursed for the cost of travel to and from the University of Hull if you use your own transport.

Only if you have been recommended to undergo an exercise training programme, this will involve three visits per week to the physiotherapy gym at Hull Royal Infirmary over a three months period with each session lasting no more than one hour. The session is run by a physiotherapist with a doctor present and the exercises are started lightly initially and increased as time goes on. The exercise training is not standard treatment in the NHS but results from studies already performed in Hull have found encouraging results with regard to improving walking distances and quality of life.

What do I have to do?
To take part in this study, you will need to visit the both the Vascular Laboratory at Hull Royal Infirmary as part of your normal vascular assessment which will take approximately one hour and the Human Performance Laboratory at the University of Hull for approximately 30 minutes.
These assessments will be undertaken prior to your treatment and then at 3, 6 and 12 months after your treatment. This results in a total of four visits to both sites over a year long period.

Do I have to take part?
Participation in this study is entirely voluntary.
You may refuse to participate or withdraw from the study at any time. You do not need to tell the researchers why you do not want to take part. If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. If you choose to withdraw or not to participate, your decision will in no way affect your future treatment. It may be that the investigator or sponsor of the study consider that it is in your interests to withdraw you or stop the study altogether.

Are there any risks involved?
Appropriate safety measures will be taken at all times. Very occasionally, you may get a feeling that you are going to fall when performing the balance tests at the Human Performance Laboratory but the safety harness will hold you up.

Are there any costs involved?
No

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to

withdraw 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.

What happens when the research study stops?
When the study is complete, you will if required be referred back to your original vascular surgeon for continued management.

What if something goes wrong?
In the 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 the study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. If you consent to participate in the trial we will inform your GP unless this is against your wishes.

What will happen to the results of the research study?
The overall results will be published in leading scientific and medical journals in approximately 3 years. Your confidentiality will be preserved in all published articles.
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 funded by the academic vascular unit, hull royal infirmary.

Who has reviewed this study?
The ethics behind this study have been reviewed and supported by the South Humber Local Research Ethics Committee.

Thank you for taking the time to read this information sheet and consenting to participate in the study. You will be given a copy of this information sheet and a copy of your consent to participate form. If you have any further queries or questions please don't hesitate to contact Miss Katherine Mockford (Clinical Research Fellow in Vascular Surgery; telephone number 01482675523 / 07736275213).

Thank you.

Appendix 2. Data collection proforma, consent form and letters

Initial Assessment

Date of assessment:

Study Patient ID:			
Surname:		**Forename:**	
DOB:		**Age:**	
Unit Number:			

Intervention:	Single Visit	PTA SEP	Surgery

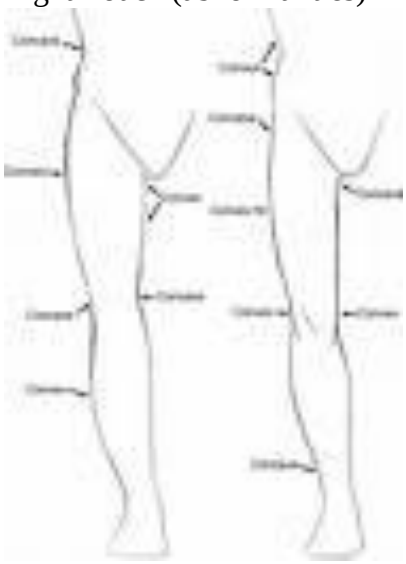
Risk factors:	**Specify Hx**		**Medication**
IHD / MI			
Hypertension			
Hypercholesterolaemia			
Cerebrovascular disease			
Diabetes mellitus			
Smoking			
OA			
Neurological disease			
Other medical history			
Other medication			
Allergies			

Clinical Examination
Initial Assessment
Date of assessment:

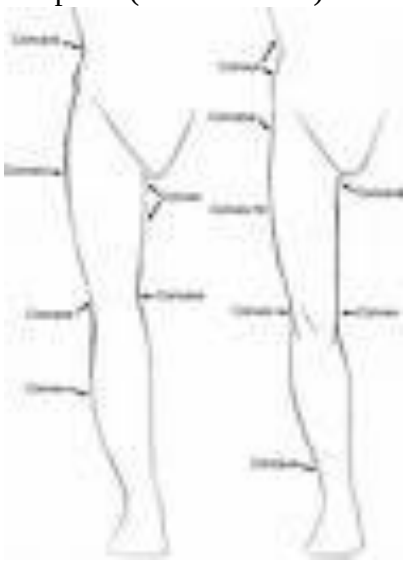
Study Patient ID:			
Pulse:		Visual Acuity Rt	
Systolic BP		Visual Acuity Lt	
Diastolic BP			
	Right	Left	
Femoral			
Popliteal			
Dorsalis Pedis			
Posterior Tibial			
Ankle Pressure			
ABPI pre exercise			
Ankle pressure post			
ABPI post exercise			
Treadmill ICD			
Treadmill MWD			
PRWD			
Height			
Weight			
BMI			

Neurological Assessment

Light Touch (abnormalities)



Pin prick (abnormalities)



Power	Right	Left
Hip Flexors		
Hip Extensors		
Knee Flexors		
Knee Extensors		
Ankle Dorsiflexion		
Ankle Plantarflexion		

Reflex	Right	Left
Knee		
Ankle		
Plantar		

Other neurological deficiencies

Hand grip strength	Right	Left
1		
2		
3		
Mean		

Skin Thickness Measurement

	1	2	3	mean
Triceps				
Biceps				
Suprailiac				

Mid-calf circumference (cm)

Right

Left

Table 1— Toronto Clinical Neuropathy Score

Symptom scores	Reflex scores	Sensory test scores
Foot pain	Knee reflexes	Pinprick
Numbness	Ankle reflexes	Temperature
Tingling		Light touch
Weakness		Vibration
Ataxia		Position sense
Upper limb symptoms		

Symptom scores: present = 1, absent = 0; reflex scores: absent = 2, reduced = 1, normal = 0; sensory test scores: abnormal = 1, normal = 0; total scores range from normal = 0 to maximum of 19.

Outcome Measures
Initial Assessment
Date of assessment:

Quality of life scores		Functional Assessments	
SF 36			
PF		Chair stand test (time - s)	
RP			
BP		Semi tandem	
GH		Full tandem	
V			
RE			
MH			
SF			
PS			
MS			
VascuQol			
Activity		Other	
Symptoms		Overall	
Pain			
Emotional			

Chair Stand Test

Using a standard chair with arms and with a seat height of approximately 17 inches for all assessments, regardless of the height of the subject. Place the back of the chair against a wall to prevent movement during the test. The patient is instructed to sit as far back as possible in the chair seat. They are then asked to stand up one time and sit down, returning completely to the correct starting position. The time taken to perform 5 repetitions is recorded. Two trials are performed separated by three minutes.

Outcome Measures
Initial Assessment
Date of assessment:

Activities-specific Balance Confidence (ABC-UK) Scale	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
Overall %	

Fall in last year	Yes	No	
Stumble in last year	Yes	No	

Fall: Unintentionally coming to rest in the ground or at some other level not as a result of an overwhelming hazard that would result in a fall by most young healthy people.

Stumble: Loss of balance that was restored before a fall occurred.
Unsteadiness: Routine or regular sense of difficulty with balance while walking.

Data collected from Uni of Hull Site

1. **Equitest**
2. **TUG test**
3. **4 metre walk velocity**
4. **Walking distance (6 minute walk)**

TUG test	**Time (s)**
1	
2	
3	
Best	
ICD	
Time	
Distance	
MWD	
Time	
Distance	
Four metre walk velocity test	
Usual speed	
Fastest speed	

Timed, Up, and Go Test (TUG)

The timed "Up & Go" test measures, in seconds, the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm, arm height 65 cm), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear. No physical assistance is given.

The 4 Meter Walking Velocity Test

Walking velocity is measured with a 4-meter walk performed at usual pace and at fastest pace. Each walk is performed twice. The faster walk in each pair is used in analyses.

Patient ID number;

Consent Form

Title of project;
The role of treatment on balance and stability in patients with intermittent claudication.

Names of researchers;
Prof. PT McCollum MCh, FRCS. Professor of Vascular Surgery. Hull and East Yorkshire NHS Trust
Mr IC Chetter MBChB FRCS. Senior Lecturer in Vascular Surgery. Hull and East Yorkshire NHS Trust
Mr Patrick Coughlin MRCS. SpR in Vascular Surgery, Vascular Surgery, Hull and East Yorkshire NHS Trust.
Miss K Mockford, MRCS Research Fellow in Vascular Surgery, Vascular Surgery, Hull and East Yorkshire NHS Trust.

Contact Address:
Academic Vascular Unit
Ward 100, Hull Royal Infirmary
Anlaby Road, Hull HU3 2JZ

Telephone No: 01482 674643
Fax No: 01482 675665

Treatment arm (please circle): Exercise Angioplasty Surgery

Please initial box

1 I confirm that I have read and understand the information sheet dated for the above study and have had the opportunity to ask questions. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3 I agree to take part in the above study. ☐

_____ _____ _____
Name of Subject (BLOCK CAPITALS) Date Signature

_____ _____ _____
Name of Person taking consent Date Signature

_____ _____ _____
Researcher/witness Date Signature

1 for patient, 1 for researcher, 1 to be kept with hospital notes

Hull and East Yorkshire Hospitals NHS
NHS Trust

Vascular Service

Surgeons

Mr A Akomolafe
Mr I Chetter
Mr B Johnson
Professor P McCollum
Mr P Renwick

Radiologists:

Dr D Ettles
Dr G Robinson
Dr P Scott

Vascular Unit

Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ

LETTER TO PATIENT'S GP

Date 29/07/2013

Dear Dr xxxxxx

Re: <*Patient Name and Address*>.
…….
…….

The role of treatment on balance and stability in patients with intermittent claudication.

I am writing to inform you that your patient has been enrolled into the above research study.
The consultant in charge of their case has following discussion advised your patient to undergo exercise training, angioplasty, surgery (delete as required) to help improve the symptoms that they have in their legs. Patients with intermittent claudication are known to have poor balance and stability that predispose to falls. Falls are associated with decreased independence and mobility and a lower quality of life. Virtually no studies have investigated the effect of intervention in claudicants upon balance and stability. Therefore, the goal of this project is to determine the role of intervention upon balance and stability in claudicants. There will be no deviation from standard treatment and patients will be recruited following a decision to treat has been made.
The study will collect data on walking distance (both patient reported and treadmill) as well as assessing balance using a well validated questionnaire. Quality of life indicators specific to this group of individuals will also be considered using validated questionnaires. Performance data will be collected when the participant visits the Human Performance Laboratory in the Department of Sport, Health and Exercise Science at the University of Hull. The study length is one year with visits prior to and at 3, 6 and 12 months after intervention. If you have any questions regarding any of the above, please feel free to contact me on 01482 466212.

Yours sincerely,

Miss Katherine Mockford
Clinical Research Fellow Vascular Surgery
Academic Vascular Unit

Hull and East Yorkshire Hospitals NHS
NHS Trust

Vascular Service

Surgeons

Mr A Akomolafe
Mr I Chetter
Mr B Johnson
Professor P McCollum
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Radiologists:

Dr D Ettles
Dr G Robinson
Dr P Scott

Vascular Unit

Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ

Mr.
Consultant Vascular Surgeon
Hull Royal Infirmary
Hull

29 July 2013

Dear Mr.

Re: DOB: Unit Number:

The above patient who is due to undergo an angioplasty underwent an assessment prior to angioplasty in the "The role of treatment on balance and stability in patients with intermittent claudication." study. The following measurements were obtained.

Treadmill ICD		metres
Treadmill MWD		metres
Pre ABPI:	Right	Left
Post ABPI:	Right	Left

This patient will be seen again in three months after the PTA as part of this study. Many thanks for allowing this patient to take part. Please find enclosed a copy of the consent form for the hospital notes.

Kind Regards

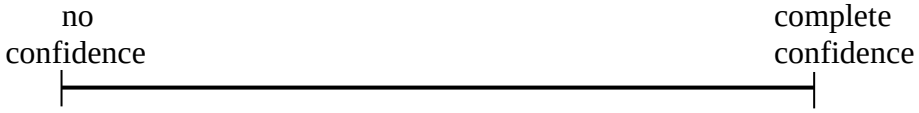
Miss Katherine Mockford
Clinical Research Fellow Vascular Surgery
Academic Vascular Unit

Appendix 3. Activities-specific Balance Confidence (ABC-UK) Scale

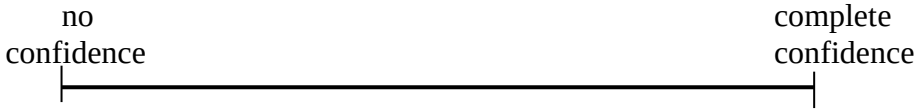
Instructions
As you read each statement, remember there is no right or wrong answer. Just think about how confident you are to execute each activity. Do this by making a mark through the line anywhere along the line from 'no-confidence' to 'complete confidence'.

(1) Walk around the house

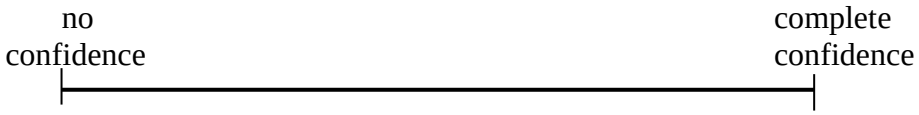
(2) Go up and down stairs



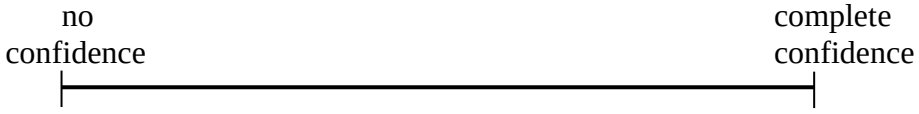
(3) Pick up a slipper from the floor



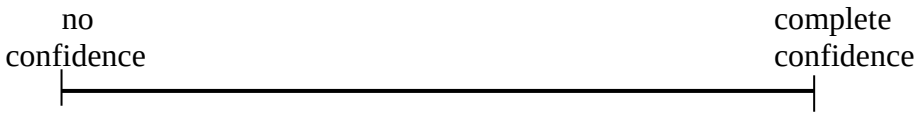
(4) Reach at eye level



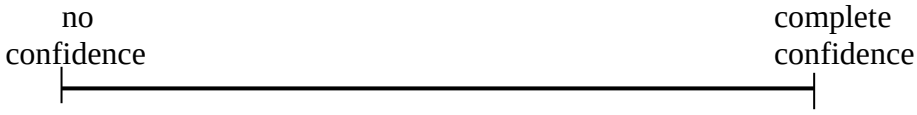
(5) Reach on tiptoes



(6) Stand on a chair to reach

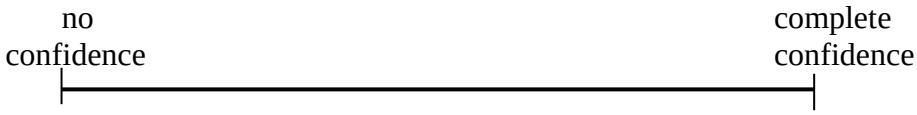


(7) Sweep the floor



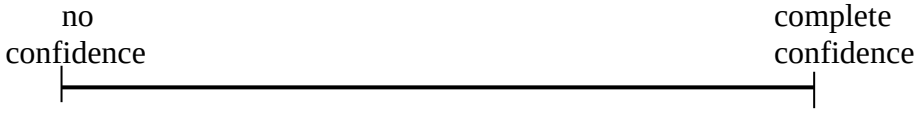
(8) Walk outside to a nearby car

(9) Get in/out of a car

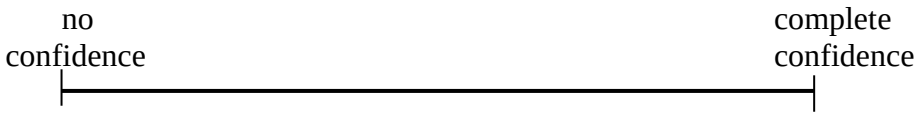


(10) Walk across a car park to the shops

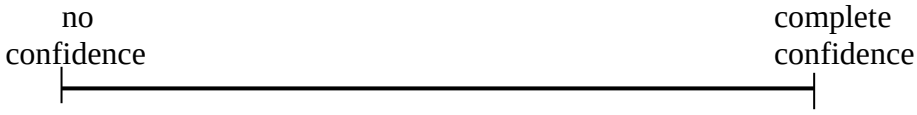
(11) Walk up and down ramp



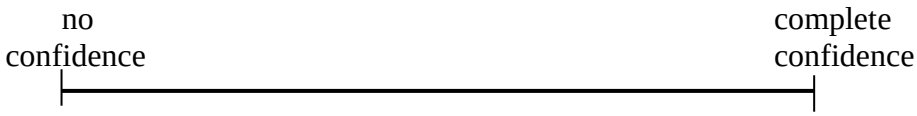
(12) Walk in a crowded shopping centre



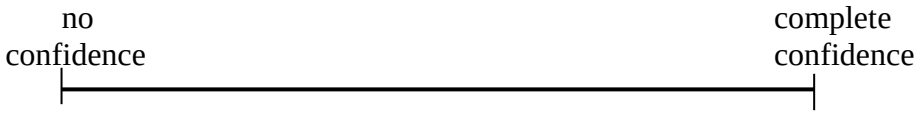
(13) Walk in a crowd/ be bumped



(14) Travel on an escalator holding the rail



(15) Travel on an escalator not holding a rail



(16) Walk on an icy pavement

Appendix 4. Patient demographics at baseline

	All patients	Angioplasty	Exercise	P
N	98	47	51	
Age (years)				
- **Median (IQR)**	69 (64-75)	69 (63-76)	70 (64-74)	0.817 NS
Age group (years)				0.683
- 20-59	12	6	6	NS
- 60-69	40	21	19	
- 70-79	34	13	21	
- $\geq$ 80	12	7	5	
Gender				0.708
- **M**	67	33	34	NS
- **F**	31	14	17	
IHD				0.647
- **None**	55	27	28	NS
- **MI**	18	6	12	
- **Angina**	10	7	3	
- **Other**	14	7	7	
- **unknown**	1	0	1	
Hypertension				0.273
- **No**	26	15	11	NS
- **Yes**	70	32	38	
- **unknown**	1	0	2	
Cholesterol management				0.088
- **on statin**	79	35	44	NS
- **no statin**	18	12	6	
- **unknown**	1	0	1	
CVA				0.654
- **none**	79	37	42	NS
- **TIA**	8	5	3	
- **CVA**	10	5	5	
- **unknown**	1	0	1	
Diabetes				0.195
- **none**	73	38	35	NS
- **diet controlled**	4	2	2	
- **tablet controlled**	16	7	9	
- **insulin controlled**	4	0	4	
- **unknown**	1	0	1	
Smoking				0.475
- **never smoked**	14	6	8	NS
- **ex-smoker**	56	29	27	
- **current smoker**	27	12	15	
- **unknown**	1	0	1	
Osteoarthritis				0.188
- **none**	42	17	25	NS
- **back**	16	8	8	
- **lower limb**	34	20	14	
- **upper limb**	5	2	3	
- **unknown**	1	0	1	
Hip or knee replacement				0.699
- **none**	92	45	47	NS
- **yes**	5	2	3	
- **unknown**	1	0	1	
Previous vascular Interventions				0.550
- **none**	56	26	30	NS
- **same leg angioplasty**	18	8	10	
- **other leg angioplasty**	8	6	2	
- **other leg surgery**	3	1	2	

- **same leg surgery**	2	0	2	
- **unknown**	11	6	5	
Visual acuity				0.070
- **6/9 or 6/6**	53	33	20	NS
- **6/12**	13	4	9	
- **Worse**	14	4	10	
- **missing**	18	6	12	
Height				0.887
- **Median**	167	169	167	NS
- **(IQR)**	(161-173)	(159-173.3)	(162-173)	
Weight				0.700
- **Median**	78.25	80	77	NS
- **(IQR)**	(69-90.75)	(69-92.5)	(68-86)	
BMI				0.665
- **Median**	28.21	28.41	27.7	NS
- **(IQR)**	(25.54-30.61)	(25.35-31.1)	(25.63-30.4)	

Values are expressed as median (IQR, interquartile range) or as numbers (N). M (male), F (female), BMI (body mass index). * 1 subject did not declare their medical history and therefore there is one set of missing data throughout the medical history section. Yes / No. (Y/N). Cerebrovascular accident (CVA), transient ischaemic attack (TIA). Osteoarthritis (OA). Visual acuity fractions; 6/6 is normal vision, 6/9 indicated that at 6 metres the smallest row of letters the tested eye can discern would be what a normal eye can read at 9 metres, this applies to 6/12 but represents what a normal eye can read at 12 metres. Exercise and angioplasty groups were compared using Mann Whitney U test and P values are given. If P > 0.05 non significance is also expressed as NS.

Appendix 5. Clinical indicators of lower limb ischaemia for angioplasty patients

	Baseline N=47	3 months	6 months	12 months	P
Pre exercise ABPI *median (IQR)*					[a]**0.001**
- **Right leg**	0.87 (0.72-1.00)	0.96 (0.87-1.07)	0.96 (0.70-1.13)	0.89 (0.83-1.00)	[b]0.091
- **Left leg**	0.86 (0.69-0.95)	0.93 (0.86-1.03)	0.85 (0.68-1.07)	0.87 (0.77-0.99)	[c]0.311
- **Symptomatic leg**	0.78 (0.61-0.92)	0.90 (0.77-0.99)	0.81 (0.60-0.99)	0.85 (0.76-0.90)	[d]0.306
					[e]**0.026**
					[f]0.856
Post exercise ABPI					[a]**0.002**
- **Right leg**	0.52 (0.31-0.84)	0.78 (0.54-1.03)	0.66 (0.44-1.00)	0.84 (0.51-0.94)	[b]0.078
- **Left leg**	0.67 (0.39-0.89)	0.78 (0.56-0.92)	0.63 (0.48-1.00)	0.70 (0.50-0.86)	[c]**0.035**
- **Symptomatic leg**	0.38 (0.25-0.63)	0.63 (0.43-0.82)	0.47 (0.40-0.73)	0.60 (0.40-0.86)	[d]0.192
					[e]0.162
					[f]0.841
Post exercise ankle pressure (mmHg)	66 (42-108)	98 (70-129)	80 (61-113)	80 (54-128)	[a]**0.015**
					[b]0.157
					[c]0.139
					[d]0.148
					[e]**0.036**
					[f]0.575
Rutherford categories *N*					
- **No claudication**	0	17	4	7	
- **Mild claudication**	4	5	5	3	
- **Moderate claudication**	28	14	13	15	
- **Severe claudication**	13	5	2	3	
- **Missing**	2	6	23	19	
Treadmill completion *N*					
- **Claudication felt during test**	41	18	17	19	
- **No claudication felt**	1	15	4	7	
- **Test stopped prematurely**	2	6	3	2	
- **Claudication stopped test**	37	18	13	15	
- **Test completed**	5 (4 with pain)	15	7	9	
Treadmill ICD (m) *median (IQR)*	32.6 (19.13-53.95)	36 (26.5-45.25)	47 (37.5-140.5)	46 (34-78)	[a]**0.015**
					[b]**0.002**
					[c]0.052
					[d]**0.041**
					[e]**0.012**
					[f]0.575
Treadmill MWD (m)	62.9 (39.48-123.75)	112 (64-215)	85 (59.25-215)	104.5 (68.25-215)	[a]**0.001**
					[b]**0.003**
					[c]**0.007**
					[d]0.102
					[e]0.089
					[f]0.198
PRWD (m)	136 (90-370)	888 (247.5-888)	650 (210-888)	450 (90-888)	[a]**<0.001**
					[b]**0.001**
					[c]**0.030**
					[d]0.859
					[e]0.859
					[f]0.635

Values are expressed as median (IQR, interquartile range) or as numbers (N). ABPI (ankle brachial pressure index, ICD (intermittent claudication distance), MWD (maximum walking distance), PRWD (patient reported walking distance). Each time point was compared to another using the Wilcoxon signed ranks test and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 6. Physical function for angioplasty patients

	Baseline	3 months	6 months	12 months	P
Short performance physical battery					[a]**0.011** [b]**0.001** [c]**0.002** [d]0.438 [e]0.882 [f]0.593
(Median, IQR)	9 (8-11)	10 (9-12)	10.5 (8.75-11)	10 (9-11)	
- **0-6 (N)**	5	3	1	1	
- **7-9**	21	9	8	12	
- **10-12**	19	30	13	16	
- **missing**	2	5	25	18	
4 metre walk at usual pace (m/s) **- Median, IQR**	1.00 (0.74-1.15)	1.05 (0.83-1.19)	1.02 (0.83-1.15)	1.03 (0.81-1.19)	[a]0.133 [b]**0.002** [c]**<0.001** [d]0.139 [e]**0.004** [f]0.149
4 metre walk at fastest pace (m/s) **- Median, IQR**	1.31 (0.93-1.53)	1.36 (1.03-1.56)	1.33 (0.96-1.48)	1.27 (1.00-1.60)	[a]**0.026** [b]**0.003** [c]**0.002** [d]**0.020** [e]**0.003** [f]0.602
Chair stand test (s) **- Median, IQR**	17.02 (12.31-20.55)	13.53 (9.82-16.2)	13.5 (11.16-16.54)	13.27 (11.91-22.08)	[a]**0.004** [b]**0.002** [c]0.315 [d]0.394 [e]0.107 [f]**0.016**
Semi tandem stance (N)					[a]0.118 [b]0.314 [c]**0.041** [d]0.600 [e]0.917 [f]0.600
- **< 10 s**	6	5	2	3	
- **10-29 s**	8	2	3	2	
- **30 s**	33	37	20	24	
- **missing**	0	3	22	18	
(Median, IQR) (s)	30 (19.4-30)	30 (30-30)	30 (30-30)	30 (30-30)	
Full tandem stance (N)					[a]0.446 [b]0.363 [c]**0.010** [d]0.959 [e]0.778 [f]0.158
- **< 10 s**	12	10	6	6	
- **10-29 s**	12	5	5	5	
- **30 s**	23	29	14	18	
- **missing**	0	3	22	18	
(Median, IQR) (s)	29 (8.9-30)	30 (11.66-30)	30 (10.02-30)	30 (11.1-30)	
Handgrip strength (kg) - **Right hand** **(Median, IQR)**	26.24 (18.61-40.4)	31.8 (22.55-40.44)	26.9 (18.84-37.32)	28.64 (22.07-36.73)	[a]0.548 [b]0.075 [c]0.234 [d]0.451 [e]**0.006** [f]0.287
Handgrip strength (kg) - **Left hand** **(Median, IQR)**	29.05 (18.12-37.63)	30.47 (21.92-38.58)	26.97 (15.9-38.2)	27.6 (20.92-36.22)	[a]0.130 [b]0.249 [c]**0.010** [d]0.551 [e]0.054 [f]0.862
6 minute walk - **ICD distance (m)**	85 (52.5-120)	140 (45-190)	200 (110-323)	160 (100-210)	[a]**0.015** [b]**0.002** [c]**0.043** [d]**0.021** [e]0.312 [f]0.726
- **MWD distance (m)**	200 (120-380)	360 (170-440)	358 (200-440)	335 (170-415)	[a]**0.001** [b]**0.001** [c]0.211 [d]**0.008** [e]0.365 [f]0.814
- **ICD time (s)**	78.5 (56.25-109.25)	110 (57-164)	210 (116-255)	140 (105-196)	[a]**0.008** [b]**0.004** [c]0.078 [d]0.091 [e]0.213 [f]0.397
- **MWD time (s)**	196 (111.5-330)	204 (300-360)	300 (224-360)	300 (188-360)	[a]**0.005** [b]**0.005** [c]0.199 [d]0.043

					[e]0.479 [f]0.933

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance), MWD (maximum walking distance). Each time point was compared to another using the Wilcoxon signed ranks test and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 7a. Balance assessment for angioplasty patients

	Baseline	3 months	6 months	12 months	P
Sensory organisation test					[a,b,c,d,e,f]NS
- **Pass**	29	30	15	19	
- **Fail**	18	12	7	10	
- **Missing**	0	5	25	18	
SOT composite score Median (IQR)	70 (61-79)	73 (65-82)	74 (62.5-77.75)	68 (32.5-76)	[a]0.033 [b,c,d,e,f]NS
SOT mean trial score for each condition					
- **Condition 1**	95 (93-96)	95.33 (92.92-95.75)	94.5 (92.5-95.84)	95 (91.84-95.67)	[a,b,c,d,e,f]NS
- **Condition 2**	91.33 (85.67-93.33)	90.5 (88.25-93.42)	91.67 (85.59-93.42)	90.33 (87.5-93.67)	[a,b,c,d,e,f]NS
- **Condition 3**	89.66 (83.33-94.33)	89.67 (85.59-94.33)	88.5 (84.75-91.84)	88.33 (82.84-91)	[a,b,c,d,e,f]NS
- **Condition 4**	82 (66-85.67)	85.84 (81.25-88.08)	83.5 (77.17-88.08)	81.67 (75.33-86)	* (see below)
- **Condition 5**	56 (22.33-66)	57 (46.75-69)	54.67 (48.42-65.59)	51.67 (37.5-61.33)	[b,c,d,e,f,g]NS
- **Condition 6**	42 (17.66-63.37)	48.34 (19.50-64.42)	52.84 (20.08-69.67)	46 (23.5-58.5)	[b,c,d,e,f,g]NS
Median (IQR)					* [a]0.009, [b]0.012, [c]0.038, [d]0.039, [e,f]NS
SOT Sensory analysis (N)					
- **Somatosensory**	39 / 8	40 / 2	20 / 2	25 / 4	[a,b,c,d,e,f]NS
- **Visual**	35 / 11	37 / 5	19 / 3	24 / 5	[a,b,c,d,e,f]NS
- **Vestibular**	28 / 18	30 / 12	15 / 7	17 / 12	[a,b,c,d,e,f]NS
- **Preferential**	40 / 6	34 / 8	16 / 6	26 / 3	[a,b,c,d,e,f]NS
Pass/fail					
SOT falls (N)					
- **Any falls**	27 / 20	22 / 20	13 / 9	17 / 12	[a,b,c,d,e,f]NS
- **Abnormal hip strategy**	33 / 14	34 / 8	19 / 3	28 / 1	[a,b,d,e,f]NS, [c]0.005
- **Abnormal ankle strategy**	40 / 11	24 / 18	15 / 7	17 / 12	[a,b,c,d,e,f]NS
No/Yes					
Motor control test – weight symmetry (N)					
- **To backwards Translations**	44 / 2 (1 missing)	38 / 3 (6 missing)	18 / 4	25 / 2	[a,b,c,d,e,f]NS
- **To forwards Translations**	44 / 2 (1 missing)	39 / 2	20 / 2	24 / 3	[a,b,c,d,e,f]NS
Normal / abnormal					
Motor control test – latency (N)					
- **Normal / abnormal**	38 / 8 (1 missing)	38 / 2	18 / 4	24 / 4	[a,b,c,d,e,f]NS
Motor control test – response strength (N)					
- **To backwards Translations**	39 / 7 (1 missing)	34 / 7	21 / 2	26 / 1	[a,b,c,d,e,f]NS
- **To forwards Translations**	28 /18 (1 missing)	28 / 13	14 / 8	21 / 6	[a,b,c,d,e,f]NS
Normal / abnormal					
MCT composite score Median (IQR)	142 (134-151)	145 (135.5-149)	146.5 (135-151.25)	140.5 (136-148)	[a,b,c,d]NS [e]0.004 [f]0.043

Values are expressed as median (IQR, interquartile range) or as numbers (N). Each time point was compared to another using the Wilcoxon signed ranks test (continuous data) Chi squared test (categorical data) and a P value of > 0.05 is expressed as NS (non-significant). P values of < 0.05 are given. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 7b. Balance assessment for angioplasty patients with specified P values

	Baseline	3 months	6 months	12 months	P
Sensory organisation test - **Pass** - **Fail** - **Missing**	 29 18 0	 30 12 5	 15 7 25	 19 10 18	[a]0.333 [b]0.602 [c]0.738 [d]0.787 [e]0.596 [f]0.842
SOT composite score Median (IQR)	70 (61-79)	73 (65-82)	74 (62.5-77.75)	68 (32.5-76)	**[a]0.033** [b]0.154 [c]0.965 [d]0.678 [e]0.615 [f]0.463
SOT mean trial score for each condition - Condition 1 Median (IQR)	95 (93-96)	95.33 (92.92-95.75)	94.5 (92.5-95.84)	95 (91.84-95.67)	[a]0.822 [b]0.466 [c]0.478 [d]0.811 [e]0.515 [f]0.333
SOT mean trial score for each condition - Condition 2 Median (IQR)	91.33 (85.67-93.33)	90.5 (88.25-93.42)	91.67 (85.59-93.42)	90.33 (87.5-93.67)	[a]0.521 [b]0.088 [c]0.767 [d]0.601 [e]0.753 [f]0.962
SOT mean trial score for each condition - Condition 3 Median (IQR)	89.66 (83.33-94.33)	89.67 (85.59-94.33)	88.5 (84.75-91.84)	88.33 (82.84-91)	[a]0.291 [b]0.808 [c]0.201 [d]0.433 [e]0.076 [f]0.231
SOT mean trial score for each condition - Condition 4 Median (IQR)	82 (66-85.67)	85.84 (81.25-88.08)	83.5 (77.17-88.08)	81.67 (75.33-86)	**[a]0.009** **[b]0.012** **[c]0.038** **[d]0.039** [e]0.124 [f]0.831
SOT mean trial score for each condition - Condition 5 Median (IQR)	56 (22.33-66)	57 (46.75-69)	54.67 (48.42-65.59)	51.67 (37.5-61.33)	[a]0.050 [b]0.573 [c]0.788 [d]0.272 [e]0.390 [f]0.642
SOT mean trial score for each condition - Condition 6 Median (IQR)	42 (17.66-63.37)	48.34 (19.50-64.42)	52.84 (20.08-69.67)	46 (23.5-58.5)	[a]0.317 [b]0.341 [c]0.946 [d]0.670 [e]0.584 [f]0.570
SOT Sensory analysis (N) - Somatosensory Pass/fail	39 / 8	40 / 2	20 / 2	25 / 4	[a]0.068 [b]0.383 [c]0.708 [d]0.497 [e]0.179 [f]0.606
SOT Sensory analysis (N) - Visual Pass/fail	35 / 11	37 / 5	19 / 3	24 / 5	[a]0.145 [b]0.327 [c]0.492 [d]0.842 [e]0.525 [f]0.726
SOT Sensory analysis (N) - Vestibular Pass/fail	28 / 18	30 / 12	15 / 7	17 / 12	[a]0.297 [b]0.559 [c]0.846 [d]0.787 [e]0.262 [f]0.484

SOT Sensory analysis (N) - **Preferential** **Pass/fail**	40 / 6	34 / 8	16 / 6	26 / 3	[a]0.442 [b]0.150 [c]0.726 [d]0.450 [e]0.319 [f]0.116
SOT falls (N) - **Any falls** **No/Yes**	27 / 20	22 / 20	13 / 9	17 / 12	[a]0.632 [b]0.897 [c]0.919 [d]0.609 [e]0.603 [f]0.973
SOT falls (N) - **Abnormal hip strategy** **No/Yes**	33 / 14	34 / 8	19 / 3	28 / 1	[a]0.241 [b]0.147 **[c]0.005** [d]0.586 [e]0.052 [f]0.484
SOT falls (N) - **Abnormal ankle strategy** **No/Yes**	24 / 23	24 / 18	15 / 7	17 / 12	[a]0.566 [b]0.181 [c]0.521 [d]0.389 [e]0.901 [f]0.484
Motor control test – weight symmetry (N) - **To backwards Translations** **Normal / abnormal**	44 / 2 (1 missing)	38 / 3 (6 missing)	18 / 4	25 / 2	[a]0.550 [b]0.060 [c]0.579 [d]0.191 [e]0.989 [f]0.253
Motor control test – weight symmetry (N) - **To forwards Translations** **Normal / abnormal**	44 / 2 (1 missing)	39 / 2	20 / 2	24 / 3	[a]0.906 [b]0.437 [c]0.269 [d]0.513 [e]0.335 [f]0.816
Motor control test – latency (N) - **Normal / abnormal**	38 / 8 (1 missing)	38 / 2	18 / 4	24 / 4	[a]0.074 [b]0.936 [c]0.725 [d]0.093 [e]0.184 [f]0.709
Motor control test – response strength (N) - **To backwards Translations** **Normal / abnormal**	39 / 7 (1 missing)	34 / 7	21 / 2	26 / 1	[a]0.814 [b]0.448 [c]0.128 [d]0.355 [e]0.094 [f]0.459
Motor control test – response strength (N) - **To forwards Translations** **Normal / abnormal**	28 /18 (1 missing)	28 / 13	14 / 8	21 / 6	[a]0.471 [b]0.826 [c]0.138 [d]0.709 [e]0.394 [f]0.276
MCT composite score Median (IQR)	142 (134-151)	145 (135.5-149)	146.5 (135-151.25)	140.5 (136-148)	[a]0.678 [b]0.862 [c]0.149 [d]0.794 **[e]0.004** **[f]0.043**

Values are expressed as median (IQR, interquartile range) or as numbers (N). Each time point was compared to another using the Wilcoxon signed ranks test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 8. Falls assessment for angioplasty patients

	Baseline	3 months	6 months	12 months	P
History of falls (no/yes) (N)	33 / 12 (2 missing)	36 / 3 (8 missing)	16 / 4 (missing 27)	19 / 6 (missing 22)	[a]0.024 [b]0.565 [c]0.807 [d]0.166 [e]0.067 [f]0.748
History of stumbles (no/yes) (N)	18 / 12 (17 missing)	32 / 7 (8 missing)	16 / 3 (missing 28)	16 / 8 (missing 23)	[a]0.042 [b]0.073 [c]0.614 [d]0.838 [e]0.164 [f]0.190
ABC-UK score Median (IQR)	79.56 (53.92-90.72)	87.60 (73.84-97.26)	78 (58.63-94.80)	81.07 (61.84-96.92)	[a]**<0.001** [b]0.073 [c]0.387 [d]0.100 [e]0.191 [f]0.587
Timed Up and Go test score Median (IQR)	10.13 (7.5-12.5)	8.7 (7.04-10.97)	9.25 (7.565-10.575)	8.29 (7.2-11.43)	[a]**<0.001** [b]**<0.001** [c]**<0.001** [d]**0.005** [e]0.061 [f]0.089
Timed Up and Go test age adjusted pass/fail (N)	21 / 26	27 / 14 (6 missing)	14 / 8 (25 missing)	20 / 9 (18 missing)	[a]**0.047** [b]0.142 [c]**0.039** [d]0.860 [e]0.785 [f]0.689

Values are expressed as median (IQR, interquartile range) or as numbers (N). Each time point was compared to another using the Wilcoxon signed ranks test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 9. Clinical indicators of lower limb ischaemia for exercise patients

	Baseline N=51	**3 months**	**6 months**	**12 months**	**P**
Pre exercise ABPI *median (IQR)*					[a]0.463 [b]0.502
- **Right leg**	0.74 (0.61-0.89)	0.69 (0.54-0.89)	0.77 (0.53-0.89)	0.74 (0.63-0.96)	[c]0.085
- **Left leg**	0.64 (0.51-0.89)	0.68 (0.54-0.88)	0.63 (0.44-0.83)	0.64 (0.45-0.95)	[d]0.939
- **Symptomatic leg**	0.60 (0.49-0.83)	0.58 (0.48-0.77)	0.57 (0.44-0.77)	0.61 (0.45-0.75)	[e]0.273 [f]0.601
Post exercise ABPI					[a]0.203
- **Right leg**	0.43 (0.26-0.69)	0.38 (0.27-0.57)	0.40 (0.26-0.70)	0.57 (0.43-0.87)	[b]0.108
- **Left leg**	0.38 (0.20-0.67)	0.32 (0.20-0.64)	0.33 (0.11-0.59)	0.36 (0.18-0.80)	[c]0.616
- **Symptomatic leg**	0.29 (0.19-0.47)	0.30 (0.20-0.40)	0.28 (0.11-0.42)	0.32 (0.18-0.56)	[d]0.657 [e]0.537 [f]0.080
Post exercise ankle pressure (mmHg)	47 (32-72)	45 (31-67)	40 (20-67)	43 (33-90)	[a]0.313 [b]0.199 [c]0.809 [d]0.764 [e]0.776 [f]0.764
Rutherford categories *N*					
- **No claudication**	0	0	1	1	
- **Mild claudication**	1	2	0	1	
- **Moderate claudication**	24	24	14	10	
- **Severe claudication**	26	23	20	10	
- **Missing**	0	2	16	29	
Treadmill completion *N*					
- **Claudication felt during test**	48	42	32	20	
- **No claudication felt**	0	2	0	0	
- **Test stopped prematurely**	2	1	2	1	
- **Claudication stopped test**	44	42	23	13	
- **Test completed**	4	2	5	5	
Treadmill ICD (m) *median (IQR)*	46.5 (27-68.03)	60 (42-85.75)	59 (38-95.5)	55 (39-93)	[a]**<0.001** [b]**0.005** [c]0.070 [d]0.866 [e]0.271 [f]0.130
Treadmill MWD (m)	91.55 (52.75-129.25)	111 (61-178)	105 (52-163)	105 (65-203)	[a]**0.004** [b]0.137 [c]0.467 [d]0.784 [e]0.227 [f]0.162
PRWD (m)	100 (90-182.5)	190.5 (67.25-400)	230.5 (136-400)	180 (60-866)	[a]**0.002** [b]**0.001** [c]**0.026** [d]0.239 [e]0.959 [f]0.484

Values are expressed as median (IQR, interquartile range) or as numbers (N). ABPI (ankle brachial pressure index, ICD (intermittent claudication distance), MWD (maximum walking distance), PRWD (patient reported walking distance). Each time point was compared to another using the Wilcoxon signed ranks test and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 10. Physical Function for exercise patients

	Baseline	3 months	6 months	12 months	P
Short performance physical battery (median, IQR) - **0-6 (N)** - **7-9** - **10-12** - **missing**	10 (9-11.25) 1 13 36 1	11 (10-12) 1 8 40 1	11 (10-11) 1 6 28 16	10 (9.5-12) 0 5 16 30	[a]**0.005** [b]0.137 [c]0.266 [d]1.000 [e]0.803 [f]0.527
4 metre walk at usual pace (m/s) Median, IQR	1.03 (0.92-1.16)	1.11 (1.04-1.27)	1.15 (1.00-1.31)	1.16 (0.98-1.37)	[a]**<0.001** [b]**<0.001** [c]**0.001** [d]0.085 [e]0.455 [f]0.313
4 metre walk at fastest pace (m/s) Median, IQR	1.39 (1.14-1.60)	1.43 (1.26-1.64)	1.45 (1.20-1.75)	1.52 (1.12-1.81)	[a]**0.048** [b]**0.021** [c]0.050 [d]0.116 [e]0.717 [f]0.313
Chair stand test (s) Median, IQR	13.81 (10.94-16.92)	12.57 (10.36-16.35)	12.99 (11.35-15.98)	14.05 (10.21-16.14)	[a]0.196 [b]0.108 [c]0.355 [d]0.101 [e]0.985 [f]0.709
Semi tandem stance (N) - **< 10 s** - **10-29 s** - **30 s** - **missing** **Median, IQR**	 0 4 46 1 30 (30-30)	 0 1 49 1 30 (30-30)	 0 1 34 16 30 (30-30)	 0 3 19 29 30 (30-30)	[a]0.343 [b]0.465 [c]0.893 [d]0.317 [e]0.715 [f]0.715
Full tandem stance (N) - **< 10 s** - **10-29 s** - **30 s** - **missing** **Median, IQR**	 4 14 32 1 30 (15.62-30)	 4 9 37 1 30 (28.89-30)	 1 7 27 16 30 (30-30)	 4 5 13 29 30 (16.25-30)	[a]0.403 [b]0.078 [c]0.169 [d]0.266 [e]**0.043** [f]**0.021**
Handgrip strength (kg) - **Right hand** **(Median, IQR)**	31.64 (20.70-39.22)	30.79 (21.13-36.98)	33.87 (26.10-39.47)	33.67 (21.00-37.88)	[a]**0.004** [b]0.443 [c]0.532 [d]0.155 [e]0.865 [f]0.191
Handgrip strength (kg) - **Left hand** **(Median, IQR)**	30.83 (19.54-36.79)	28.34 (17.50-35.38)	28.77 (22.73-35.50)	31.67 (17.83-35.44)	[a]**<0.001** [b]**0.003** [c]0.118 [d]0.986 [e]0.865 [f]0.887
6 minute walk - **ICD distance (m)**	120 (80-195)	160 (100-225)	160 (120-240)	137 (93.5-162)	[a]**0.003** [b]**0.039** [c]0.959 [d]0.483 [e]0.274 [f]0.177
- **MWD distance (m)**	280 (160-400)	370 (180-430)	360 (270-460)	351 (247.5-360)	[a]**0.003** [b]**0.003** [c]0.972 [d]0.945 [e]**0.017** [f]0.077
- **ICD time (s)**	111 (60.75-157)	113 (88.5-186.5)	125 (99.5-196)	165 (120-200)	[a]**0.034** [b]0.113 [c]0.456 [d]0.259 [e]0.256 [f]0.569
- **MWD time (s)**	244 (146-360)	314 (162-360)	311 (237-360)	340 (270-430)	[a]0.071 [b]0.128 [c]0.756

					[d]0.926 [e]0.198 [f]0.363

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance), MWD (maximum walking distance). Each time point was compared to another using the Wilcoxon signed ranks test and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 11a. Balance assessment for exercise patients

	Baseline	3 months	6 months	12 months	P
Sensory organisation test					[a]0.025 [b]0.007
- **Pass**	23	33	26	20	[c]<0.001
- **Fail**	28	16	9	3	[d,e,f]NS
- **Missing**	0	2	16	28	
SOT composite score Median (IQR)	65 (54-75)	69 (60.5-77.5)	73 (66-78)	74 (68-77)	[a]0.018 [b]0.013 [c]0.007 [d,e,f]NS
SOT mean trial score for each condition					
- **Condition 1**	94.67 (92.67-95.33)	94.33 (92.15-95.33)	94.33 (93-94.67)	94 (93-95)	[a,b]NS, [c]0.032, [d,e,f]NS
- **Condition 2**	89.67 (87-92)	89.33 (86.84-92)	90.33 (88.33-92.33)	90.33 (88.33-92)	[a-f]NS
- **Condition 3**	87.33 (83-91)	89 (83-91.67)	90.33 (86.33-92)	89 (84.67-90.67)	[a-f]NS
- **Condition 4**	81 (73-85.67)	84.66 (78.5-87.67)	84 (79.33-87.67)	83 (78.67-87)	[a]0.002, [b]0.035, [c,d,e,f]NS
- **Condition 5**	39.66 (22.33-58)	51 (39.17-62.83)	59.67 (40.67-69)	55.33 (48-63.67)	* (see below)
- **Condition 6**	39.66 (12-55)	43.33 (24-64.67)	44.33 (29.33-63)	53 (40.33-66.67)	** (see below)
Median (IQR)					* [a]0.005, [b]0.009,[c]0.003, [d]NS [e]0.044, [f]NS ** [a]0.014, [b]0.023, [c]0.004, [d,e]NS, [f]0.009
SOT Sensory analysis					
- **Somatosensory**	47 / 4	46 / 3	35 / 0	23 / 0	[a-f]NS
- **Visual**	39 / 12	44 / 5	28 / 7	20 / 3	[a-f]NS
- **Vestibular**	18 / 33	28 / 21	24 / 11	17 / 6	[a]0.028, [b]0.002, [c]0.002,[d,e,f]NS
- **Preferential Pass/Fail**	42 / 9	40 / 9	31 / 4	21 / 2	[a-f]NS
SOT falls					
- **Any falls no/yes**	16 / 35	22 / 26	17 / 18	12 / 11	[a-f]NS
- **Abnormal hip strategy no/yes**	40 / 11	39 / 8	28 / 7	19 / 4	[a-f]NS
- **Abnormal ankle strategy no/yes**	20 / 31	25 / 22	19 / 16	12 / 11	[a-f]NS
Motor control test – weight symmetry					
- **To backwards Translations**	44 / 6 (1 missing)	42 / 5 (4 missing)	31 / 3 (17 missing)	21 / 1 (29 missing)	[a-f]NS
- **To forwards Translations**	45 / 5 (1 missing)	44 / 3 (4 missing)	31 / 3 (17 missing)	21 / 1 (29 missing)	[a-f]NS
Normal / abnormal					
Motor control test – latency	44 / 6 (1 missing)	42 / 5 (4 missing)	32 / 2 (17 missing)	21 / 1 (29 missing)	[a-f]NS
- **Normal / abnormal**					
Motor control test – response strength					
- **To backwards Translations**	39 / 11 (1 missing)	38 / 8	28 / 6	20 / 2	[a-f]NS
- **To forwards Translations**	43 / 7 (1 missing)	38 / 8	29 / 5	18 / 4	[a-f]NS
Normal / abnormal					
MCT composite score Median (IQR)	141 (133.5-149.25)	140 (131-147)	141.5 (135.75-149)	144.5 (134.75-150.5)	[a-f]NS

Values are expressed as median (IQR, interquartile range) or as numbers (N). Each time point was compared to another using the Wilcoxon signed ranks test (continuous data) Chi squared test (categorical data) and a P value of > 0.05 is expressed as NS (non-significant). P values of < 0.05 are given. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 11b. Balance assessment for exercise patients with specified P values

	Baseline	3 months	6 months	12 months	P
Sensory organisation test - **Pass** - **Fail** - **Missing**	 23 28 0	 33 16 2	 26 9 16	 20 3 28	[a]**0.025** [b]**0.007** [c]**<0.001** [d]0.493 [e]0.078 [f]0.244
SOT composite score Median (IQR)	65 (54-75)	69 (60.5-77.5)	73 (66-78)	74 (68-77)	[a]**0.018** [b]**0.013** [c]**0.007** [d]0.314 [e]0.112 [f]0.076
SOT mean trial score for each condition - **Condition 1 Median (IQR)**	94.67 (92.67-95.33)	94.33 (92.15-95.33)	94.33 (93-94.67)	94 (93-95)	[a]0.682 [b]0.587 [c]**0.032** [d]0.194 [e]0.413 [f]0.354
SOT mean trial score for each condition - **Condition 2 Median (IQR)**	89.67 (87-92)	89.33 (86.84-92)	90.33 (88.33-92.33)	90.33 (88.33-92)	[a]0.575 [b]0.200 [c]0.915 [d]0.893 [e]0.614 [f]0.513
SOT mean trial score for each condition - **Condition 3 Median (IQR)**	87.33 (83-91)	89 (83-91.67)	90.33 (86.33-92)	89 (84.67-90.67)	[a]0.246 [b]0.108 [c]0.770 [d]0.141 [e]0.588 [f]0.821
SOT mean trial score for each condition - **Condition 4 Median (IQR)**	81 (73-85.67)	84.66 (78.5-87.67)	84 (79.33-87.67)	83 (78.67-87)	[a]**0.002** [b]**0.035** [c]0.068 [d]0.943 [e]0.972 [f]0.219
SOT mean trial score for each condition - **Condition 5 Median (IQR)**	39.66 (22.33-58)	51 (39.17-62.83)	59.67 (40.67-69)	55.33 (48-63.67)	[a]**0.005** [b]**0.009** [c]**0.003** [d]0.221 [e]**0.044** [f]0.370
SOT mean trial score for each condition - **Condition 6 Median (IQR)**	39.66 (12-55)	43.33 (24-64.67)	44.33 (29.33-63)	53 (40.33-66.67)	[a]**0.014** [b]**0.023** [c]**0.004** [d]0.660 [e]0.191 [f]**0.009**
SOT Sensory analysis (N) - **Somatosensory Pass/fail**	47 / 4	46 / 3	35 / 0	23 / 0	[a]0.736 [b]0.090 [c]0.167 [d]0.136 [e]0.225 [f]0.999
SOT Sensory analysis (N) - **Visual Pass/fail**	39 / 12	44 / 5	28 / 7	20 / 3	[a]0.076 [b]0.698 [c]0.299 [d]0.206 [e]0.721 [f]0.493
SOT Sensory analysis (N) - **Vestibular Pass/fail**	18 / 33	28 / 21	24 / 11	17 / 6	[a]**0.028** [b]**0.002** [c]**0.002** [d]0.288 [e]0.171 [f]0.662

SOT Sensory analysis (N) - **Preferential** **Pass/fail**	42 / 9	40 / 9	31 / 4	21 / 2	[a]0.925 [b]0.429 [c]0.316 [d]0.386 [e]0.288 [f]0.738
SOT falls (N) - **Any falls** **No/Yes**	16 / 35	22 / 26	17 / 18	12 / 11	[a]0.139 [b]0.107 [c]0.088 [d]0.805 [e]0.617 [f]0.789
SOT falls (N) - **Abnormal hip strategy** **No/Yes**	40 / 11	39 / 8	28 / 7	19 / 4	[a]0.569 [b]0.861 [c]0.679 [d]0.730 [e]0.969 [f]0.804
SOT falls (N) - **Abnormal ankle strategy** **No/Yes**	20 / 31	25 / 22	19 / 16	12 / 11	[a]0.165 [b]0.168 [c]0.298 [d]0.921 [e]0.936 [f]0.875
Motor control test – weight symmetry (N) - **To backwards Translations** **Normal / abnormal**	44 / 6 (1 missing)	42 / 5 (4 missing)	31 / 3 (17 missing)	21 / 1 (29 missing)	[a]0.833 [b]0.644 [c]0.325 [d]0.787 [e]0.403 [f]0.544
Motor control test – weight symmetry (N) - **To forwards Translations** **Normal / abnormal**	45 / 5 (1 missing)	44 / 3 (4 missing)	31 / 3 (17 missing)	21 / 1 (29 missing)	[a]0.518 [b]0.857 [c]0.440 [d]0.679 [e]0.761 [f]0.544
Motor control test – latency (N) - **Normal / abnormal**	44 / 6 (1 missing)	42 / 5 (4 missing)	32 / 2 (17 missing)	21 / 1 (29 missing)	[a]0.833 [b]0.358 [c]0.325 [d]0.452 [e]0.403 [f]0.828
Motor control test – response strength (N) - **To backwards Translations** **Normal / abnormal**	39 / 11 (1 missing)	38 / 8	28 / 6	20 / 2	[a]0.571 [b]0.626 [c]0.190 [d]0.976 [e]0.366 [f]0.372
Motor control test – response strength (N) - **To forwards Translations** **Normal / abnormal**	43 / 7 (1 missing)	38 / 8	29 / 5	18 / 4	[a]0.648 [b]0.928 [c]0.650 [d]0.748 [e]0.936 [f]0.729
MCT composite score Median (IQR)	141 (133.5-149.25)	140 (131-147)	141.5 (135.75-149)	144.5 (134.75-150.5)	[a]0.975 [b]0.364 [c]0.931 [d]0.243 [e]0.981 [f]0.304

Values are expressed as median (IQR, interquartile range) or as numbers (N). Each time point was compared to another using the Wilcoxon signed ranks test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 12. Falls assessment for exercise patients

	Baseline	3 months	6 months	12 months	P
History of falls (no/yes)	42 / 8 (1 missing)	44 / 6 (1 missing)	31 / 4 (16 missing)	19 / 4 (28 missing)	[a]0.564 [b]0.551 [c]0.882 [d]0.936 [e]0.533 [f]0.519
History of stumbles (no/yes)	32 / 18 (1 missing)	42 / 7 (2 missing)	25 / 8 (18 missing)	16 / 6 (29 missing)	**[a]0.013** [b]0.258 [c]0.469 [d]0.253 [e]0.191 [f]0.800
ABC-UK score Median (IQR)	82.47 (69.21 – 94.09)	84.19 (63.63-93.25)	83.25 (68.28-94.64)	84.19 (58.76-92.60)	[a]0.368 [b]0.514 [c]0.414 [d]0.348 [e]0.848 [f]0.446
Timed Up and Go test score (s) Median (IQR)	8.65 (7.44-10.19)	7.48 (6.8-9.6)	8.03 (6.69-9.75)	8.06 (5.87-10.47)	**[a]0.001** **[b]0.011** **[c]0.023** [d]0.059 [e]0.092 [f]0.862
Timed Up and Go test age adjusted pass/fail	37 / 14	42 / 8	28 / 7	20 / 6	[a]0.163 [b]0.429 [c]0.679 [d]0.634 [e]0.450 [f]0.772

Values are expressed as median (IQR, interquartile range) or as numbers (N). Each time point was compared to another using the Wilcoxon signed ranks test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**. Time points compared are as follows: [a]baseline compared to 3 months, [b]baseline compared to 6 months, [c]baseline compared to 12 months, [d]3 months compared to 6 months, [e]3 months compared to 12 months and [f]6 months compared to 12 months.

Appendix 13. Clinical indicators of lower limb ischaemia at baseline

	All	Angioplasty	Exercise	P
Pre exercise ABPI				
- **Right leg**	0.79 (0.64-0.94)	0.87 (0.72-1.00)	0.74 (0.61-0.89)	**0.009**
- **Left leg**	0.79 (0.58-0.93)	0.86 (0.69-0.95)	0.64 (0.51-0.89)	**0.008**
- **Symptomatic leg**	0.69 (0.55-0.86)	0.78 (0.61-0.92)	0.60 (0.49-0.83)	**0.001**
Post exercise ABPI				
- **Right leg**	0.46 (0.28-0.75)	0.52 (0.31-0.84)	0.43 (0.26-0.69)	0.107
- **Left leg**	0.53 (0.24-0.84)	0.67 (0.39-0.89)	0.38 (0.20-0.67)	**0.003**
- **Symptomatic leg**	0.32 (0.22-0.52)	0.38 (0.25-0.63)	0.29 (0.19-0.47)	**0.022**
Treadmill ICD (m)	39.5 (24.75-60.38)	32.6 (19.13-53.95)	46.5 (27-68.03)	**0.046**
Treadmill MWD (m)	74.7 (47.43-129)	62.9 (39.48-123.75)	91.55 (52.75-129.25)	0.225
PRWD (m)	135 (90-274)	136 (90-370)	100 (90-182.5)	0.348

Values are expressed as median (IQR, interquartile range). Exercise and angioplasty groups were compared using Mann Whitney U test and P values are given. Significant P values of < 0.05are highlighted in **bold**.

Appendix 14. Physical Function at baseline

	All	Angioplasty	Exercise	P
Short performance physical battery (median, IQR)	10 (9-11)	9 (8-11)	10 (9-11.25)	**0.007**
- **0-6 (N)**	6	5	1	
- **7-9**	34	21	13	
- **10-12**	55	19	36	
- **missing**	3	2	1	
4 metre walk at usual pace (m/s) Median, IQR	1.01 (0.84-1.15)	1.00 (0.74-1.15)	1.03 (0.92-1.16)	0.169
4 metre walk at fastest pace (m/s) Median, IQR	1.07 (1.33-1.54)	1.31 (0.93-1.53)	1.39 (1.14-1.60)	0.112
Chair stand test (s) Median, IQR	14.86 (11.73-19.07)	17.02 (12.31-20.55)	13.81 (10.94-16.92)	**0.044**
Semi tandem stance (N)				
- **< 10 s**	6	6	0	
- **10-29 s**	12	8	4	
- **30 s**	79	33	46	
- **missing**	1	0	1	
Median, IQR	30 (30-30)	30 (19.4-30)	30 (30-30)	**0.004**
Full tandem stance (N)				
- **< 10 s**	16	12	4	
- **10-29 s**	26	12	14	
- **30 s**	55	23	32	
- **missing**	1	0	1	
Median, IQR	30 (12.99-30)	29 (8.9-30)	30 (15.62-30)	0.055
Handgrip strength (kg)				
- **Right hand**	30.9 (19.8-39.6)	26.24 (18.61-40.4)	31.64 (20.7-39.22)	0.467
- **Left hand**	29.9 (19.1-36.8)	29.05 (18.12-37.63)	30.83 (19.54-36.79)	0.918
Median, IQR				
6 minute walk				
- **ICD distance (m)**	100 (60-160)	85 (52.5-120)	120 (80-195)	**0.025**
- **MWD distance (m)**	240 (160-400)	200 (120-380)	280 (160-400)	0.243
- **ICD time (s)**	58.5 (92.5-135.5)	78.5 (56.25-109.25)	111 (60.75-157)	**0.018**
- **MWD time (s)**	221 (132.5-360)	196 (111.5-330)	244 (146-360)	0.205
Median, IQR				

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance), MWD (maximum walking distance). Exercise and angioplasty groups were compared using the Mann Whitney U test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**.

Appendix 15. Balance at baseline

	All	Angioplasty	Exercise	P
Sensory organisation test				0.100
- **Pass**	52	29	23	
- **Fail**	46	18	28	
- **Missing**	0	0	0	
SOT composite score Median (IQR)	68 (57.5-76)	70 (61-79)	65 (54-75)	0.063
SOT mean trial score for each condition	94.67 (93-95.66)	95 (93-96)	94.67 (92.67-95.33)	0.448
- **Condition 1**	90.33 (86.92-92.75)	91.33 (85.67-93.33)	89.67 (87-92)	0.123
- **Condition 2**	88.67 (83.25-92.33)	89.66 (83.33-94.33)	87.33 (83-91)	**0.042**
- **Condition 3**	81.17 (70.33-85.67)	82 (66-85.67)	81 (73-85.67)	0.963
- **Condition 4**	47.33 (22.33-61.42)	56 (22.33-66)	39.66 (22.33-58)	0.070
- **Condition 5**	41.34 (14.34-60.58)	42 (17.66-63.37)	39.66 (12-55)	0.254
- **Condition 6 Median (IQR)**				
SOT Sensory analysis				
- **Somatosensory pass/fail**	86 / 12	39 / 8	47 / 4	0.168
- **Visual pass/fail**	74 / 23 (1 missing)	35 / 11	39 / 12	0.965
- **Vestibular pass/fail**	46 / 51 (1 missing)	28 / 18	18 / 33	**0.012**
- **Preferential pass/fail**	82 / 15 (1 missing)	40 / 6	42 / 9	0.533
SOT falls				
- **Any falls no/yes**	43 / 55	27 / 20	16 / 35	**0.009**
- **Abnormal hip strategy no/yes**	73 / 25	33 / 14	40 / 11	0.354
- **Abnormal ankle strategy no/yes**	44 / 54	40 / 11	20 / 31	**<0.001**
Motor control test – weight symmetry				
- **To backwards Translations**	88 / 8 (2 missing)	44 / 2 (1 missing)	44 / 6 (1 missing)	0.178
- **To forwards Translations Normal / abnormal**	89 / 7 (2 missing)	44 / 2 (1 missing)	45 / 5 (1 missing)	0.290
Motor control test – latency				
- **Normal / abnormal**	82 / 14 (2 missing)	38 / 8 (1 missing)	44 / 6 (1 missing)	0.457
Motor control test – response strength				
- **To backwards Translations**	78 / 18 (2 missing)	39 / 7 (1 missing)	39 / 11 (1 missing)	0.311
- **To forwards Translations Normal / abnormal**	71 / 25 (2 missing)	28 /18 (1 missing)	43 / 7 (1 missing)	**0.005**
MCT composite score Median (IQR)	141 (134-150)	142 (134-151)	141 (133.5-149.25)	0.828

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance), MWD (maximum walking distance). Exercise and angioplasty groups were compared using the Mann Whitney U test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**. SOT (sensory organisation test).

Appendix 16. Falls assessment at baseline

	All	Angioplasty	Exercise	P
History of falls (no/yes)	75 / 20 (3 missing)	33 / 12 (2 missing)	42 / 8 (1 missing)	0.203
History of stumbles (no/yes)	50 / 30 (18 missing)	18 / 12 (17 missing)	32 / 18 (1 missing)	0.720
ABC-UK score Median (IQR)	80.6 (64.6-92.75)	79.56 (53.92-90.72)	82.47 (69.21 – 94.09)	0.110
Timed Up and Go test score (s) Median (IQR)	9.16 (7.49-11.18)	10.13 (7.5-12.5)	8.65 (7.44-10.19)	0.059
Timed Up and Go test age adjusted pass/fail	58 / 40	21 / 26	37 / 14	**0.005**

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance), MWD (maximum walking distance). Exercise and angioplasty groups were compared using the Mann Whitney U test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**.

Appendix 17. Quality of life at baseline

	All	Angioplasty	Exercise	P
SF36				
- **Physical function**	40 (30-50)	35 (28.75-50)	45 (33.75-55)	**0.04**
- **Role physical**	0 (0-50)	0 (0-50)	0 (0-56.25)	0.897
- **Bodily pain**	41 (31-51.75)	36.5 (31-51)	42 (41-64)	**0.03**
- **General health**	52 (40-67.75)	47 (35-69.5)	55 (41-68.5)	0.435
- **Vitality**	50 (40-65)	50 (30-65)	55 (40-65)	0.192
- **Role emotional**	66.7 (37.5-100)	50 (33.3-87.5)	75 (50-100)	**0.018**
- **Mental health**	76 (33.35-100)	67.35 (48-100)	100 (33.3-100)	0.223
- **Social function**	76 (60-88)	73.5 (50-87.63)	78 (71-92)	**0.043**
- **Physical summary**	31.3 (25.3-36.25)	30.1 (25.2-33.9)	31.9 (25.55-37.3)	0.228
- **Mental summary**	52.9 (44.78-61.38)	51.2 (40.3-60.9)	56.7 (46.45-62.1)	0.209
VascuQol				
- **Pain**	4.25 (3.25-4.75)	4.0 (2.75-4.63)	4.25 (3.5-5.25)	0.106
- **Social**	4.5 (3.5-6)	4.0 (3.5-5.5)	5.5 (4-6.5)	**0.008**
- **Activities**	3.88 (3.25-4.63)	3.63 (3.19-4.32)	4.13 (3.47-5)	**0.009**
- **Symptoms**	5.25 (4.25-6.00)	4.75 (4-5.75)	5.5 (4.94-6.06)	**0.009**
- **Emotional**	5.0 (4.14-5.71)	4.57 (3.57-5.5)	5.14 (4.68-5.86)	**0.030**
- **Total**	4.6 (3.64-5.12)	4.32 (3.22-5.02)	4.84 (4.13-5.35)	**0.007**
SF8				
- **Physical function**	40.1 (30.3-40.1)	30.3 (30.3-40.1)	40.1 (30.3-42.15)	0.125
- **Role physical**	38.7 (28.3-46.9)	38.7 (28.3-46.9)	38.7 (38.7-46.9)	0.060
- **Bodily pain**	40.1 (40.1-47.7)	40.1 (31.5-40.1)	40.1 (40.1-47.7)	0.085
- **General health**	42.4 (38.4-46.4)	38.4 (38.4-46.4)	46.4 (38.4-46.4)	**0.050**
- **Vitality**	45.2 (45.2-55.6)	45.2 (45.2-55.6)	45.2 (45.2-55.6)	0.503
- **Role emotional**	45.7 (38.1-52.4)	45.7 (32.85-52.4)	52.4 (38.1-52.4)	**0.013**
- **Mental health**	49.6 (41.5-56.8)	49.6 (36.55-56.80)	49.6 (41.5-56.8)	**0.049**
- **Social function**	40.4 (40.4-49.5)	40.4 (29.5-49.5)	49.5 (40.4-55.3)	**0.023**
- **Physical summary**	36.8 (30.03-42.63)	34.65 (29.18-40.38)	39.25 (30.7-44.2)	**0.043**
- **Mental summary**	51.25 (40.33-58.53)	46.3 (38.58-57.38)	53.4 (42.48-59)	**0.037**

Values are expressed as median (IQR, interquartile range) or as numbers (N). ICD (intermittent claudication distance), MWD (maximum walking distance). Exercise and angioplasty groups were compared using the Mann Whitney U test (continuous data) or Chi squared test (categorical data) and P values are given. Significant P values of < 0.05 are highlighted in **bold**.

Appendix 18. Number of patients at each visit

	Angioplasty	**Exercise**
Baseline (N)	47	51
3 months (N)	42	49
6 months (N)	22	35
12 months (N)	29	23

(N) Number of patients who attended for follow up in each group at the 4 study time points.

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