THE PROGNOSIS OF PATIENTS WITH INTERMITTENT CLAUDICATION: A PROSPECTIVE COHORT STUDY

Anabelle Mizzi

A dissertation submitted in fulfilment of the requirements for the Doctor of Philosophy degree at the Faculty of Health Sciences.

Faculty of Health Sciences

University of Malta

January 2021

Abstract

The prognosis of the lower limb in patients with intermittent claudication (IC) is considered to be relatively benign and it is assumed that only 5-10% deteriorate to critical limb ischaemia (CLI) over 5 years. The perceived benign prognosis supports the recommendation of conservative management for the vast majority of patients. However, for those who progress rapidly to severe ischaemia, such an approach may lead to delayed intervention and an increased risk of morbidity. Early identification of patients at high risk of deterioration may potentially guide clinical decision making for selection of an interventional management approach at diagnosis.

To test this hypothesis, four sequential studies were conducted with two primary foci. The first focus was to determine the rate of progression to CLI among patients with IC. The second was to determine whether prediction of impending rapid deterioration were possible, potentially allowing for an alternative management approach in high risk subgroups.

A systematic review of the literature (Study 1) indicated a relatively low risk of deterioration to critical ischaemia among patients with IC but the evidence is unclear. A retrospective study (Study 2) of local referral patterns of patients with IC provided the groundwork for the main studies. Subsequently, a prospective observational cohort study of consecutive patients newly referred to the vascular unit in the national hospital was conducted (Studies 3 and 4). This research aimed to explore the prognosis of the lower limb among patients with IC over two years and to identify predictive factors for deterioration to CLI. The identified independent predictors were used to design a patient-specific predictive model to stratify patients' risk of lower limb morbidity.

One hundred fifty participants (119 men, 31 women; mean age 69.7 years, SD 9.3) were recruited and assessed for PAD by ankle brachial index (ABI), toe-brachial index (TBI) and Doppler waveforms at baseline, 12 months and 24 months following enrolment. Duplex scans were accessed to confirm PAD and/or medial arterial calcification. Diabetes, hypertension, hyperlipidaemia and smoking history were present in >70% of the cohort.

Within two years 23.3% developed CLI and an additional 27.3% experienced significant haemodynamic deterioration (decline by ≥0.15 in ABPI and/or ≥0.1 TBI). Baseline ABPI ≤0.5, ABPI, TBPI, baseline TBPI ≤0.39, HbA1c and infrapopliteal artery disease were identified as independent predictors for the development of CLI within 2 years in patients with IC. A clinical patient-specific predictive model using the combined predictive value of baseline ABPI, TBPI and the presence of infrapopliteal artery disease was found to have a significant 'good level' predictive value for the development of CLI within two years (AUROC 0.82 p=<0.001).

This work demonstrated that the prognosis of the patient with IC may not be as benign as previously assumed. Using the proposed predictive model, patients may be stratified as requiring close haemodynamic monitoring or requiring prompt evaluation for revascularisation. This new knowledge may potentially support clinical decision making at initial diagnosis allowing for an individualised approach to management of patients with IC, aiming to reduce morbidity in this population.

Dedicated to my amazing parents

Acknowledgements

Firstly, I would like to thank my supervisors, who guided me throughout this journey of learning. Professor Cynthia Formosa, Head of Podiatry department, for her guidance and constant encouragement throughout the research. She provided important support when really needed and was instrumental to help me arrive to the final stages of the project. Professor Cathy Bowen, University of Southampton, who offered invaluable mentorship and helped me grow as a researcher in many different ways. I am immensely grateful for the opportunities, support and advice throughout my research. Thank you for the smiles and encouragement during difficult times. I am forever indebted to Professor Kevin Cassar, Lead vascular surgeon, from whom I learnt so much. This research would not have been possible without his support and profound insight. It was an honour and priveledge to work with such a great team.

I would also like to thank Professor Liberato Camilleri, Statistics and Operations Research, Faculty of Science, University of Malta. He kindly provided his expertise to increase my understanding of statistics and guided me in the selection and performance of the statistical analysis throughout the project.

I am grateful to all the patients who accepted to participate in my study, some of whom I can remember by name. This research would not have been possible without them and I sincerely hope that I have and will continue to help them in every way possible.

Finally, and most importantly, I wish to express my deepest gratitude to my family for their love and support throughout this journey. My now, 12-year old daughter, Katrina, thank you for waiting patiently for so many hours during my meetings with the statistician. For never complaining that I was studying in the weekends and for all the little notes and hugs of encouragement when you understood that I needed them. My husband, Stephen, for the continuous support and encouragement throughout these years, taking over so many things to allow me more time to work on my research. My love for you both has no end. I would like to thank my amazing parents, to whom I dedicate this work. You are my role models in life. You showed me the importance of honesty, empathy and respect towards others. I hope I can make you proud. Thank you to my in-laws, who were always there to offer their love and support.

Publications, peer reviewed abstracts and presentations

Conference presentations

Quantitative Pulsatility Index compared to Qualitative Spectral Doppler Waveform Analysis for diagnosis of Peripheral arterial disease in Diabetes Mellitus" 14th Staffordshire Conference on Clinical Biomechanics on 23rd April, 2016 in Staffordshire University, UK

The temporal progression and prognosis of intermittent claudication. A review of evidence – *College of Podiatry Conference, Liverpool November 2017*

Intermittent Claudication- Is this being misdiagnosed in the Primary Care Sector? *College of Podiatry Conference, Liverpool. November 2017*

The need for improvement in the diagnosis and management of patients with IC in primary care- *Primary Care Conference, Malta. October 2017*

A review of the temporal progression of intermittent claudication: Implications for the diabetic foot. Mizzi A, Cassar K, Bowen C and Formosa C. *Diabetes Uk Conference, London. March 2018*

Characteristics and treatment of patients with intermittent claudication. A comparison between UK and Maltese populations, *The College of Podiatry Conference, November 2018, Bournemouth, UK*

The patient with intermittent claudication in Primary care. A new model of patient care. *Primary Care Biennial Conference 2019. Dolmen Hotel, Malta*

Haemodynamics of the patient with intermittent claudication and diabetes, *Diabetes UK Conference, March 2019, Liverpool, UK.*

Diabetes increases the risk of deterioration to critical limb ischaemia in patients with intermittent claudication. *Diabetes UK. Glasgow. March 2020*

Peer reviewed abstracts and publications

Intermittent Claudication- Is this being misdiagnosed in the Primary Care Sector? Mizzi A, Cassar K, Bowen C and Formosa C.2018 *JFAR.* 11 (1): 1-125

The temporal progression and natural history of intermittent claudication. A review of current evidence. Mizzi A, Cassar K, Bowen C and Formosa C. 2018 *JFAR.* 11 (1): 1-125

A review of the temporal progression of intermittent claudication: Implications for the diabetic foot. Mizzi A, Cassar K, Bowen C and Formosa C. 2018. *Diabetic Medicine.* 35: 87

Intermittent claudication referral patterns in Malta, presented as a poster presentation and an oral presentation.2018. *Malta Medical Journal* (30): S.119

Characteristics and treatment of patients with intermittent claudication. A comparison between UK and Maltese populations. 2019 *Journal of foot and ankle research*. 12(1): 54

Haemodynamics of the patient with intermittent claudication and diabetes, *Diabetic medicine*. 2019. 36 (1): 1-185

The progression rate of peripheral arterial disease in patients with intermittent claudication. A systematic review. 2019 *Journal of foot and ankle research.* 12(1): 40

Diabetes increases the risk of deterioration to critical limb ischaemia in patients with intermittent claudication. 2020 *Diabetic Medicine* 37(10):S1

TABLE OF CONTENTS

CHAPTER THREE

METHODOLOGY – IDENTIFYING THE PHILOSOPHICAL APPROACH

CHAPTER SIX

CHARACTERISTICS OF PATIENTS WITH IC. A CROSS-SECTIONAL PROSPECTIVE COHORT OBSERVATIONAL STUDY (STUDY 3)

CHAPTER EIGHT

DISCUSSION AND CONCLUSIONS

List of tables

List of figures

List of Appendices

CHAPTER ONE

Framing the thesis

1.1 Introduction

This research sought to evaluate the prognosis of patients with symptoms of intermittent claudication (IC). The idea emerged from personal clinical experience as a podiatrist running a vascular clinic in a primary care setting where I noted wide variations in the rate of progression of peripheral arterial disease (PAD) in patients presenting with this condition. Despite similar symptom presentation in this specific population, some patients remained with relatively stable symptoms, while others progressed rapidly to critical limb ischaemia (tissue loss and rest pain) in the affected limb, resulting in significant morbidity and even mortality.

Diversity in disease progression is well recognised in patients with IC (V. Aboyans et al., 2006; M. S. Conte et al., 2015) and is a source of clinical uncertainty surrounding the prognosis of the individual patient, causing difficulty in the selection of management at initial presentation (Soden et al., 2017). Despite extensive research on PAD (V. Aboyans et al., 2012; V. Aboyans et al., 2018; M. H. Criqui et al., 2008; Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014; J. G. Regensteiner et al., 2008), there is inadequate evidence to accurately predict who is more likely to deteriorate. Recommended management is generally conservative for the vast majority of patients (2011 Writing group members et al., 2011; M. S. Conte et al., 2015; Gerhard-Herman et al., 2017). Early revascularisation in patients with IC is recommended only when the symptoms are lifestyle limiting (M. S. Conte et al., 2015). Therefore, investigating the prognostic factors for deterioration could assist in the early identification of those patients who are more likely to deteriorate. This would allow for a more informed clinical decision for selection of treatment at diagnosis, improving management of IC, potentially guiding decisions for early intervention and lead to a reduction in amputation risk and mortality in this population (M. S. Conte et al., 2019).

This chapter provides a brief background to the subject area of this thesis, namely peripheral arterial disease and intermittent claudication, encompassing the personal clinical experiences that have led to this research. A broad overview of the risk factors associated with symptoms of IC, making particular reference to the Maltese context where this study took place, is

presented. The current knowledge related to the progression of PAD in patients presenting with this condition is also introduced. The prognosis of IC will be further explored in the next chapters, followed by a description of the research methodology and subsequent presentation of the sequential studies presented in this thesis.

1.2 Peripheral arterial disease

Peripheral arterial disease (PAD) is a condition characterized by blockage or narrowing of one or more of the main arteries, most commonly the superficial femoral artery in the thigh or the common and external iliac arteries (Mahé et al., 2015) in the lower abdomen which carry blood to the legs and arms (NICE, 2011). It is the most prevalent chronic disease in the developed world and is rapidly increasing in importance in the developing world (M. S. Conte et al., 2019; F. G. R. Fowkes et al., 2013; Song et al., 2019). The prevalence of PAD has been estimated in several epidemiological studies (V. Aboyans et al., 2018; M. H. Criqui & Aboyans, 2015) and found to be in the range of 3-10% in the general population, increasing to 15-20% in individuals over 70 years of age and up to 26% in persons with diabetes mellitus (C. Formosa et al., 2012; Thiruvoipati et al., 2015). With longer life expectancy, the prevalence of PAD is increasing, presenting an important public health challenge (Song et al., 2019).

Peripheral arterial disease is commonly caused by atherosclerotic plaques which cause stenoses or occlusion in the arteries resulting in reduced blood flow to the extremities and is the third leading cause of vascular morbidity, after coronary heart disease and stroke (F. G. R. Fowkes et al., 2013). Approximately 80% of patients with PAD are asymptomatic and it is estimated that about 20-35% complain of exertional leg pain known as intermittent claudication (A. T. Hirsch et al., 2001; Hooi et al., 2001).

1.3 Intermittent claudication

Intermittent claudication (IC) is the most common symptom of lower extremity PAD and is defined as pain, cramping or aching in the calf, thighs or buttocks exacerbated by walking and relieved by rest (V. Aboyans et al., 2018). The prevalence of IC among the general population is not clear in the literature but is thought to be approximately 3% in people aged 40 years, increasing to almost 20% in individuals over 65 years of age (Diehm et al., 2004). Intermittent claudication is associated with adverse outcomes, since patients with IC have a higher risk of

foot deterioration with worsening symptoms and also a higher risk of suffering a heart attack or stroke than patients with PAD who do not have IC (M. H. Criqui et al., 1992; M. H. Criqui et al., 2008; Muluk et al., 2001).

The progression of PAD in the symptomatic limb can be divided into three categories: i) those who remain stable ii) those who improve and iii) those who develop progressive limb ischaemic symptoms (5-10%), (C. Diehm et al., 2009), commonly described as critical limb ischaemia (CLI) with rest pain (pain in the feet at rest), ulceration, gangrene and amputation (Weitz et al., 1996). Although for most patients with IC, the major fear is amputation, existing literature reports that the fate of the affected leg in terms of limb loss is generally favourable, with an amputation rate of less than 2% being reported in the literature (Norgren et al., 2007). To date, because statistically, the proportion of claudicants who develop CLI is relatively small, IC is generally described as *'benign'* and treatment for patients with IC often does not include revascularisation (Rooke et al., 2012). The perceived benign prognosis has been the foundation of management guidelines for patients presenting with IC. First line treatment is conservative and involves administration of preventive medication, smoking cessation (if needed) and exercise (A. T. Hirsch et al., 2001).

1.3.1 Management of the patient with IC

Vascular care and management of patients with PAD is principally guided by The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) (Norgren et al., 2007) which was compiled through the cooperation between medical, surgical, cardiovascular, vascular radiology and cardiology societies in Europe, North America, Asia, Africa and Australia. This document is periodically updated based on important new evidence which may influence practice.

In the latest update, TASC II guidelines (Jaff et al., 2015) recommend that in the initial stages of the disease, the goal of management of IC should primarily address improvement of symptoms and the systemic impact of the disease through risk factor control, aimed at reducing the risk of subsequent cardiovascular events (Dormandy & Rutherford, 2000). Ample evidence (V. Aboyans et al., 2018; Mc Grae McDermott et al., 2002; Rooke et al., 2012; Y. Zhang et al., 2016) identifies the primary risk factors for the development and progression of PAD, which include diabetes mellitus, smoking, hypertension, obesity, hyperlipidaemia and impaired renal

function. Due to the generally perceived benign prognosis of the lower limb in IC, where symptoms remain stable in 85% of the patients, current care guidelines for first line treatment therefore principally include medical therapy (Gerhard-Herman et al., 2017) (lipid lowering drugs, antiplatelet agents and blood pressure control (Hess et al., 2017)) together with lifestyle modifications (exercise) (Wisloff et al., 2007), and smoking cessation (Armstrong et al., 2014; Kalbaugh et al., 2018; Quick & Cotton, 1982)). On the other hand, interventional treatment, such as endovascular or open revascularisation are only recommended when the claudication significantly interferes with the patients' quality of life or when the symptoms fail to improve with conservative treatment and the disease progresses to CLI (Norgren et al., 2007). While recent updates in TASC II guidelines (Jaff et al., 2015) recommend revascularisation in some cases of severe disease, there still remains a large majority of patients for whom conservative management is recommended. As discussed in the following sections, this approach is widely practised both locally and internationally, but is not founded on strong evidence and further data to support clinical decision making is required.

1.4 The local context

Malta is a European country comprising of an archipelago with an area of 316 km^2, having a total population of 514,564 (NSO Malta, 2020). It is geographically located 166Km south of Sicily, and is typically Mediterranean. Being a small island, there is one national major hospital where all specialist services are located, including the vascular surgery unit which is the only one available for the whole country. Additionally, there are nine district primary care clinics dispersed geographically around the island where general practitioner and allied health services, including podiatry, are provided.

While life expectancy in Malta is higher than the average in the European union (82.01 years and 80.8 years respectively) (Azzopardi Muscat et al., 2017), the leading cause of mortality in both men and women, is cardiovascular disease, accounting for two out of every five deaths [euro.who.int – State of health in the EU. Malta country health profile 2019]. The high rate of cardiovascular death is possibly due to the genetic predisposition of this specific population to major risk factors associated with cardiovascular disorders and PAD (Cuschieri et al., 2016; C. Formosa et al., 2011), most specifically, diabetes mellitus.

The prevalence of diabetes in Malta is approximately 10.4% and is one of the highest in Western Europe (Cuschieri, 2020) and it may be in part responsible for the increased incidence of patients with cardiovascular and atherosclerotic diseases in this population [health.gov.mt, 2015]. Additionally, recent reports indicate that 21.5% of the Maltese adult population are smokers, also among the highest in Europe [euro.who.int – State of health in the EU. Malta country health profile 2019]. Both smoking and diabetes are associated with more than 7 fold increased risk of development of PAD (V. Aboyans et al., 2006; Kalbaugh et al., 2018; Rooke et al., 2011). Furthermore, Malta also has one of the highest obesity rates in Europe with approximately 70% of the population being overweight or obese (World Health Organization, 2016). The high obesity rate has been related to a shift from a typically Mediterranean diet to higher consumption of carbohydrates in the last two decades [ec.europa.eu –The Maltese food basket]. Hypertension and diabetes, which are two main risk factors for cardiovascular events and PAD (V. Aboyans et al., 2018; F. G. R. Fowkes et al., 2013; Joosten et al., 2012) are highly associated with obesity, linked through complex biological mechanisms (Jiang et al., 2016), thus further increasing their prevalence among this population.

These statistics indicate that the Maltese population is at an increased risk not only of cardiovascular events such as myocardial infarction (Kumbhani et al., 2011) but also of lower limb events, including ulceration, gangrene and amputation together with impaired quality of life (J. G. Regensteiner et al., 2008). Such adverse events place a huge economic burden on the country, the healthcare system, the patients and their families (F. G. R. Fowkes et al., 2013), highlighting the need for further research aimed at reducing their negative impact.

While the increased prevalence of cardiovascular risk factors among the Maltese population is known, the prevalence of patients with IC in Malta, patient characteristics and the treatment outcomes and are not yet well-documented. To date there is no national prospective registry of patients with IC or PAD in Malta. Furthermore, no local research studies have been conducted which sought to explore the characteristics and risk factors of patients with IC who are referred to the Vascular surgery department in Malta. This lack of data in Malta may be attributed to several factors, such as fragmentation of documentation and sub-optimal referral systems (Chetcuti et al., 2009), which are further explained in the following sections discussing the healthcare system in Malta.

1.4.1 The health care system in Malta

Healthcare in Malta is administered and funded by the central government and is free at point of delivery, supported through taxpayers' funding (Azzopardi Muscat et al., 2017). In Malta, patients seeking medical help, have the opportunity to attend a public funded Primary health care clinic, of which there are nine dispersed around the island, making accessibility easy. The patient with IC is at liberty of choosing whether to seek help from a general practitioner (GP) or a podiatrist through a self referral system (Azzopardi Muscat et al., 2017). The choice of health practitioner, however, often determines the referral route pursued, as described in further detail in the retrospective review of referral pathways presented later in this thesis (Chapter 4, Study 2).

Patients who require referral to a vascular surgeon for further expert assessment and consideration of revascularisation are referred to the Vascular unit located within the national hospital. Patients who attend any government healthcare facility are registered by a unique personal identification number onto a clinical patient administration system. This is a digitized register which stores patient demographics and patient appointments. Clinical data for patients attending the vascular surgery unit are kept in an additional database where further information such as duplex scan reports (eg: location and size of arterial occlusion, areas of calcification), treatment plans and review notes are recorded. This makes it possible to follow patients over time and to cross link data from the hospital register and specialist databases. During the initial phases of this research, ethical approval (Appendix 1) was sought in order to be able to access the required registers and databases for data collection during the study.

For the management of the patient with IC in Malta, vascular surgeons follow recommendations by the TASC II guidelines (Jaff et al., 2015). Referred patients are assessed at the vascular surgery unit where evidence of PAD is confirmed using duplex ultrasound scanning in an outpatient setting. Depending on the severity of their condition, patients who are not offered revascularisation, are discharged with an open appointment (to contact the vascular unit if ulceration/ rest pain occurs) or given a review appointment at the outpatient department once secondary risk factor control is instituted. Patients are referred to smoking cessation programs and advised to exercise. A supervised exercise programme is currently lacking in Malta, therefore patients cannot be referred as recommended in the guidelines.

As discussed further in the following section, while the local approach to the management of patients with IC follows international recommendations, there is insufficient information in published guidelines to support informed clinical decision making at initial diagnosis.

1.5 Identification of the literature gap and justification of the study

1.5.1 The literature gap

At initial diagnosis, following international guidelines (M. S. Conte et al., 2019; Jaff et al., 2015), a conservative approach is implemented through medical control of known cardiovascular risk factors and advice on life-style changes. After a review period, the therapeutic effect is evaluated and if no improvement is achieved, then an endovascular, surgical or hybrid approach is recommended, provided that the patient is fit and the current symptoms are lifestyle limiting as perceived by the patient (M. S. Conte et al., 2015; Hess et al., 2017). Such a decision is made after taking into consideration various factors which are centered around the patient's perception of disability, the type of intervention most beneficial to the patient over their anticipated life-span, the complexity of the procedure and associated risks (Simons et al., 2012), availability of vein conduit in case of bypass procedures and multiple other factors (M. S. Conte et al., 2019). Clinical decision making is difficult due to the complexities surrounding the individual estimates of morbidity (M. S. Conte et al., 2019; Norgren et al., 2007), particularly since risk of deterioration in a patient with IC cannot be predicted with the available evidence (Norgren et al., 2007).

Although the practice of applying conservative management at diagnosis is well established (Mohler et al., 2008), current evidence does not provide enough knowledge to predict the risk of deterioration for each individual case (Norgren et al., 2007). Risk prediction, or prognosis of a condition is required for optimal choice of management strategies (Djulbegovic et al., 2011). However, in order to determine the prognosis of a condition, knowledge of disease progression and knowledge of factors which may influence this progression are required (Norgren et al., 2007). As shown in brief in the following paragraphs and in further detail in Chapter Two, for the patient with IC, these two elements of information, required for the understanding of the prognosis of IC, are not clear in the literature.

Following review of published reports related specifically to the progression of arterial disease in IC, the risk of deterioration to critical limb ischaemia (CLI) varies widely, ranging from 1.4% per year to 21% within 5 years of diagnosis (Aquino et al., 2001; Jelnes, Gaardsting, Hougaard Jensen, Baekgaard, Tonnesen, & Schroeder, 1986; Jensen et al., 2006; Kumakura et al., 2016; Naschitz et al., 1988; B. Sigvant et al., 2007). The wide variation could mainly be attributed to differences in risk factor prevalence, population characteristics, definition of CLI as the outcome measure, baseline inclusion criteria and study design used in the respective studies (Bitar & Garcia, 2010). In recently published management guidelines, it was in fact stated that for the patient with IC, reliable data on the epidemiology of CLI is lacking and estimates can be highly misleading (M. S. Conte et al., 2019) because progression is likely underestimated in published reports (B. Sigvant et al., 2016). The lack of evidence and possible underestimation of deterioration is confirmed in a systematic review (Mizzi et al., 2019) completed and published in the initial phase of this thesis which is presented in Chapter Four, Study 1.

The second important identified gap in knowledge related to the prognosis of the individual patient with IC, is identification of predictors of deterioration (Norgren et al., 2007). There is an abundance of research in published literature (F. G. R. Fowkes et al., 2013; Joosten et al., 2012; Khawaja & Kullo, 2009; Ortmann et al., 2012) which identified factors associated with deterioration of PAD - mainly diabetes, smoking, hypertension and hyperlipidaemia (V. Aboyans et al., 2006). However, this knowledge is not specific to patients with IC but refers to both symptomatic and asymptomatic PAD patients. Most predictive research in IC patients is focused either on predicting mortality and major adverse cardiovascular events (Arboix et al., 2004; C. Diehm et al., 2009; Gardner et al., 2008; Sartipy et al., 2018) or on predicting outcomes following revascularisation (Kalbaugh et al., 2018; Miura et al., 2014; Stone et al., 2014; Taft et al., 2004). For the patient with IC, efforts to establish predictors to help identify patients at risk of adverse lower limb events at initial diagnosis, is limited (Smolderen et al., 2015). There is some evidence indicating that an ankle-brachial pressure index of <0.5 or a low ankle pressure (40-60mmHg) is positively associated with risk of progression to severe ischaemia (Norgren et al., 2007) but the data is derived from secondary analysis of larger trials of PAD patients (J. M. Murabito et al., 2002; J. M. Murabito et al., 1997). Therefore, knowledge of factors that can predict deterioration to CLI has not yet been thoroughly quantified in IC patients (Tripathi & Verma, 2014).

With this limited evidence to objectively predict progression of arterial disease in a patient presenting with IC, it is at present difficult to identify those patients at highest risk of developing CLI (M. S. Conte et al., 2019; Norgren et al., 2007). This lack of evidence prevents identification of patients who are likely to benefit from more prompt aggressive interventions (Tripathi & Verma, 2014). This uncertainty, together with the perceived benign prognosis of the affected limb justifies the clinical recommendations of conservative management as first line treatment for the majority of patients presenting with IC (Jaff et al., 2015), but it is an approach which may be inadequate for those who are at risk of developing progressive ischaemic limb or life threatening events. Delaying revascularisation in a high risk patient cohort may lead to poorer outcomes due to delayed intervention and possible loss of less risky endovascular options (M. S. Conte et al., 2019; Ferrari et al., 2004; Wolosker et al., 2003).

The current inability to reliably and prospectively identify patients who would have a poor prognosis following conventional medical treatment highlights the need for further work in this field. New data would be required for the possible development of clinical algorithms and risk stratification methods of patients who are likely to develop CLI, to assist clinicians in advising patients about potentially risky interventions to revascularise the limb and prevent CLI. Evidence that enables clinicians to predict the benefit:risk ratio on an individual patient basis in this patient group would be a major step towards providing patient centered and patient specific advice based on sound and robust evidence rather than clinician preferences. It is hoped that this new data would provide further knowledge to underpin a review in approach to treatment of patients with IC with the ultimate aim of reducing limb loss and mortality in this group of patients.

1.5.2 Justification of the study

The justification for this research is to address the current gaps in the current literature with regards to the prognosis of patients with IC at initial diagnosis and to provide robust data to inform and add to the body of knowledge to help guide physicians in clinical decisions and prevent deterioration to CLI. The literature highlights the increase in risk of adverse cardiovascular events in patients with IC compared to age matched controls (Muluk et al., 2001) but the risk is increased further in those with critical limb ischaemia (Brass & Hiatt, 2006). For the patient with IC, prevention of deterioration to CLI is crucial, because the

prognosis of CLI is unfavourable, for both life and lower limb outcomes (M. S. Conte et al., 2019).

Once CLI develops, prognosis is very poor with a 1-year mortality rate of 25% (Anand et al., 2018) which increases to 45% in those who undergo major amputation (Kristensen et al., 2012). Furthermore, in terms of the lower limb, unless revascularisation is established, the development of CLI is associated with poor prognosis, with a 200-fold increased risk of amputation and a 3-fold increased risk of mortality, highlighting that prevention of deterioration is paramount (Anand et al., 2018).

While revascularisation is known to improve functional capacity and quality of life, with subsequent improvement in control of atherosclerotic risk factors further leading to reduction in major adverse cardiovascular events (Fakhry et al., 2018; Mazari et al., 2017; McDermott et al., 2001; McDermott et al., 2004), this is currently not recommended primary management for the vast majority of patients presenting with IC, due to the evidence gaps previously highlighted. There is currently insufficient evidence to enable the prediction of which patients with IC will progress to CLI and therefore who would benefit from early intervention (Norgren et al., 2007; Tripathi & Verma, 2014). In those at risk, this approach may result in delayed treatment and loss of opportunity for early endovascular or surgical therapy which may be more effective (Wolosker et al., 2003). As time passes, clinical deterioration is more likely and the possibility for successful revascularisation is often significantly compromised (M. S. Conte et al., 2019). Exploring the possibility of identifying predictive factors which can be used for early identification of patients who are more likely to deteriorate and potentially guide the clinical making for selection of appropriate treatment is therefore important and justifies the need for this research.

This gap in knowledge prompted the need for the current work, highlighting the necessity for new evidence to identify those patients who are more likely to progress to CLI and to establish the temporal progression of the disease so that timely intervention can be provided. Timely revascularisation is key, when the patient's general fitness is likely to be better due to younger age and fewer comorbidities, resulting in lower perioperative risks than when performed at a more advanced age and advanced stage of the disease (Salas et al., 2004; Siracuse et al., 2014). In addition, delaying intervention is associated with the need for more complex and invasive procedures due to progression of the disease which translates into a higher risk in a frailer

patient. It is hoped that knowledge derived from this thesis related to the prognosis of IC could help support the clinical decision for preventive intervention in patients presenting with IC, identified as being at high risk of deterioration to CLI, leading to the desired outcome of reduced lower limb morbidity, better quality of life and possibly improved survival in this population.

This information could support better estimation of the patient risk for subsequent events and may provide clinicians with an efficient way to stratify deterioration risk at initial diagnosis of IC. Risk-stratification of IC patients may be clinically useful to support choice of management, whether to apply a conservative approach, adding a more intensive follow-up approach or whether more aggressive treatment should be considered.

1.7 Development of the research question

The clinical uncertainty related to the prognosis of the patient with IC which does not allow for informed clinical decision making at diagnosis, highlights the need for further evidence which would help in identifying those patients who would benefit from preventive intervention. Further research evaluating the possibility of identifying a pattern of characteristics and risk factors of those patients with IC who progress to develop CLI is required. The identification of predictive factors can be used to identify patients who are likely to have poor outcomes with conservative treatment alone and to forewarn physicians of the possible need of preventive intervention.

Revascularisation improves lower limb perfusion, reduces symptoms (West et al., 2012) and would allow the patient to be more mobile which has been shown to result in better control of atherosclerosis risk factors, thus reducing the risk of adverse events (Iso & Suzuki, 2015; Spannbauer, Chwała, Ridan, Berwecki, Mika, Kulik, Berwecka, & Szewczyk, 2019a). Additionally, early intervention, that is, when the patient is younger with fewer comorbidities and before progression of PAD occurs, will result in reduced perioperative risks with the additional possibility of performing less technically challenging interventions since the disease is at a less advanced stage (Salas et al., 2004; Siracuse et al., 2014). Intervening before the onset of gangrene or deep ulceration would also mean that there is less risk of minor foot amputation and loss of digits (Anand et al., 2018). Minor foot amputations (amputations below ankle) are associated with reduced mobility, reduced stability (Guest et al., 2019) and increased

risk for further ulceration due to abnormal plantar pressures (Motawea[1] et al., 2015) often resulting in the patient requiring specific footwear to reduce risks of further ulceration (Yonclas & O'donnell, 2005).

This research is intended to provide prognostic information related to the identification of patients with IC who are more likely to develop CLI. It is planned that once the prognostic factors for deterioration to CLI are established, a patient-specific predictive algorithm of the risk of developing CLI will be developed with the aim of reducing risk of amputation and improving quality of life and long-term outcomes in patients living with IC. Currently, while predicitive algorithims to stratify risk exist for patients with CLI (Kodama et al., 2018), there are none available for patients with IC. Information gained from this research could mean fewer foot complications due to timely revascularization and possibly a reduced morbidity for the patients with IC.

1.7.1 The research aim

This research aims to identify predictors for the progression of PAD to CLI among patients presenting with IC and use the identified predictive factors to develop a novel patient-specific predictive algorithm to help stratify the predictive risk for CLI and define the likely prognosis.

1.7.2 The thesis research question and hypotheses

In order to reach the aim of this thesis, the following research question was proposed:

> *Is there a pattern of predictive patient factors among patients with IC which identifies patients at risk of deterioration to CLI within two years?*

The research objectives were:

- *To determine risk factor prevalence, patient characteristics of patients presenting with IC*
- *To identify predictive risk factors for deterioration from IC to CLI and the effect of different combinations of risk factors*
- *To develop a novel predictive algorithm for identifying patients at high risk of deteriorating to CLI within two years*

The research hypotheses were:

H_1: there is a pattern of predictive factors among patients with IC which identifies patients at risk of deterioration to CLI within two years

H_0 : there is no pattern of predictive factors among patients with IC which identifies patients at risk of deterioration to CLI within two years

1.8 The structure of this thesis

In order to achieve the main aim of the study and answer the thesis research question posed, this research was developed around a series of quantitative investigations that built sequentially within the critical realist pathway, each with study-specific objectives presented in separate chapters in this thesis. This thesis was completed in three phases.

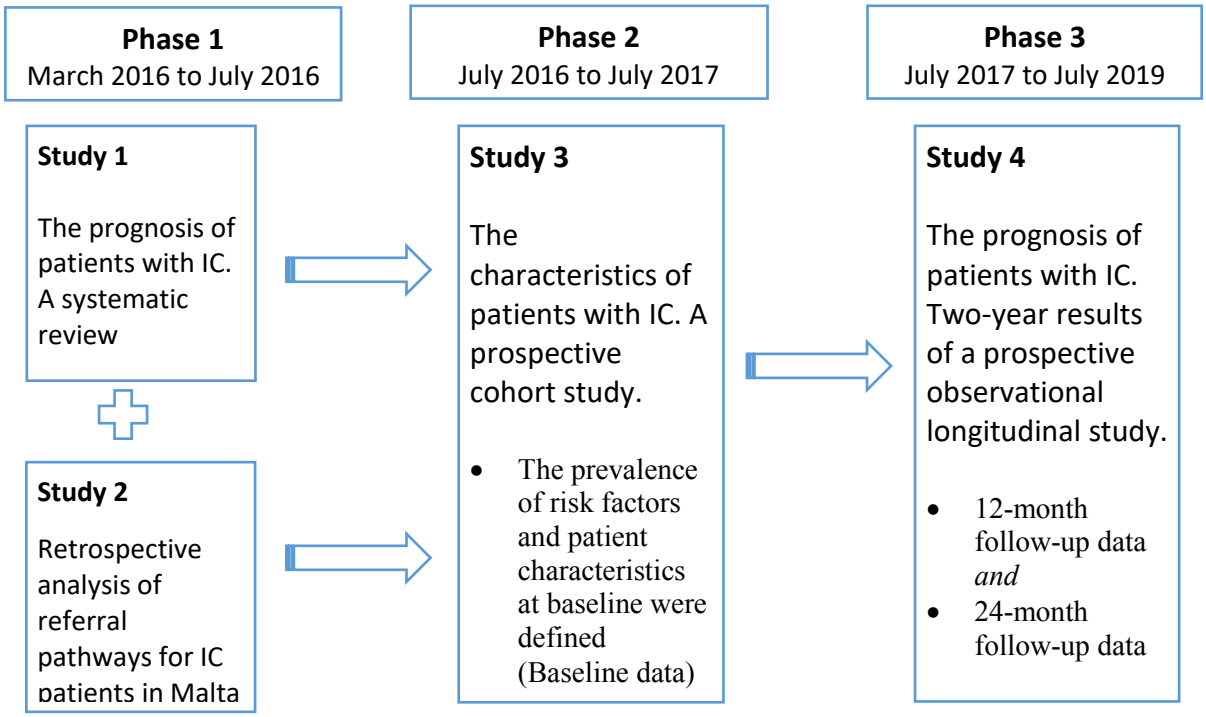


Figure 1.1 Flow diagram of thesis studies

Phase 1 of the thesis established the groundwork for the main study. During the first phase, the current knowledge in the literature related to the progression rate of PAD among patients with IC was explored through a systematic review **(Study 1)**. Through robust analysis, this study

confirmed the literature gap and provided the underpinning justification for the design of the main study in which prognostic factors in PAD progression were investigated. Additionally, during the first phase of the research, to determine the scale of the problem and feasibility for conducting the main investigation (studies 3 and 4), the annual incidence rate of patients with IC referred for revascularisation at the national vascular unit and the service pathways employed were explored through a retrospective study of referral pathways in Malta **(Study 2)**. This study draws on retrospective data from electronic databases within the Vascular unit in the general hospital to determine the incidence of the potential participant population for the planned research while also illustrating the clinical referral pathways employed for specialist intervention.

Phase 2 of this thesis explored the characteristics and treatments of patients with IC through a prospective registry of patients with IC **(Study 3)** in order to provide insight into the patient characteristics of this population. During this phase of the thesis, the characteristics of the patient with IC in Malta were defined since this information was currently lacking. This deficiency may be a potential hindrance to the formulation of specific preventive plans such as establishing lifestyle clinics and supervised exercise programs or having enough availability of medication (statins and anti-platelets) (Bevan & White Solaru, 2020) which are provided free to those at risk (Azzopardi Muscat et al., 2017). The prospective registry included newly referred consecutive patients with IC, comprised the recruited participants for study 4 and provided the baseline characteristics of the participant group.

Phase 3 of the thesis investigated the progression of PAD in patients with IC and evaluated prognostic factors related to the outcomes of patients after 2 years. This was achieved through a prospective observational longitudinal study **(Study 4)**. Patterns of predictive factors among participants who progressed to CLI were investigated. This enabled the development of a novel patient-specific algorithm of predictive factors to allow for the identification of patients more likely to deteriorate to CLI and therefore benefit from early intervention.

1.9 Presentation of this thesis

Chapter One: This chapter presents the background to the research topic and provides the context of the study. It describes the influences from clinical practices on the researcher which led to the development of the research question and describes the design of the thesis.

Chapter Two: This chapter provides a comprehensive review of the current literature related to peripheral arterial disease and more specifically intermittent claudication. It presents an overview of the epidemiology, risk factors, complications and current treatment guidelines for patients with IC in terms of revascularisation and conservative management. This chapter also presents and justifies methods used for the diagnosis of IC including analysis techniques employed for vascular assessment which were used throughout this research project.

Chapter Three: Methodology. This chapter presents the overall philosophical approach together with the justification of the methodological design applied in this thesis. It describes how a series of quantitative investigations built iteratively towards the aim of this research project.

Chapter Four: This chapter presents the preliminary work completed as a foundation to the main study of this research. The two review studies presented in this chapter provided the groundwork for this research. 'The progression of PAD in patients with IC. A systematic review' **(Study 1)**. This systematic review explored the current knowledge related to the temporal progression of PAD in patients with IC. The second study, 'A retrospective review of referral pathways in Malta' **(Study 2)**, presents the initial background work done in this research, analyzing the incidence of referrals of patients with IC in Malta and revealed the referral pathways employed within the health service while drawing attention to possible improvements within the local clinical pathways.

Chapter Five: This chapter presents the methods employed for data collection of the prospective studies (study 3 and study 4). It describes the recruitment processes, methods for haemodynamic analysis and collection of all the data pertaining to both studies. The ethical considerations employed in this thesis are also presented. In this chapter, the general methods including vascular assessment techniques, outcome measures, definitions and analysis applied throughout the research are discussed.

Chapter Six: 'The characteristics of patients with IC' **(Study 3)**. This chapter presents a prospective cross-sectional observational study of patients with IC and analyses the baseline patient characteristics of the recruited participants. This study explores and compares the characteristics and medication regime of the study population with similar populations in other countries drawn from previously published studies through statistical analysis of the data.

Chapter Seven: 'The prognosis of patients with IC' **(Study 4)**. This chapter presents a prospective longitudinal observational study investigating the progression of PAD and the outcomes of patients with IC over two years. Predictive factors for deterioration were assessed by regression analysis and are discussed in this chapter. A novel patient-specific predictive algorithm is presented and discussed within the context of the clinical contribution towards the management approach of patients with IC. The analysis under the receiver-operator characteristic (AUROC) curve method was applied to evaluate the performance of the predictive algorithm.

Chapter Eight: This chapter presents the discussion and conclusions drawn from this research. Potential limitations throughout the work are discussed and suggestions for future research are also presented in this chapter.

CHAPTER TWO

The literature Review

'More than a century has passed since Brodie (1846) first described in man the symptom complex which we now call intermittent claudication. He clearly recognised its association with obliterative arterial disease of the main arteries of the lower limbs, and he pointed out that it was frequently a premonitory symptom of what was then called 'senile gangrene'. Although we still recognise these associations there is little reliable information about the prognostic significance of intermittent claudication'.

(Richards, 1957, p.1093)

2.1 Introduction

This chapter provides an overview of previous research on intermittent claudication [IC] and its prognosis. It introduces the framework for the main study that comprises the main focus of the research described in this thesis. Reviewing previous work helped to scope out key data collection requirements for the research to be conducted and helped form the study design. The appreciation of previous work also helped to provide direction and perspective to this thesis. Through critical analysis of previous works, this literature review provided an opportunity to identify important biases to be addressed during the design process of this research.

There is an extensive amount of literature regarding both peripheral arterial disease [PAD] and IC dating back to the 1950s (Richards, 1957; Spaulding, 1956) and a synthesis of published works in this chapter provides an overview of the research topic. This narrative critical review of previous research was conducted to provide a better understanding of the condition and establish what is known about its management, while also setting the background to the research in this thesis. Existing research has founded several published international guidelines and clinical recommendation documents pertaining to the management of IC (M. S. Conte et al., 2019; European Stroke Organisation et al., 2011; Hess et al., 2017; Rooke et al., 2011). However, although published guidelines are established on knowledge related to disease progression, prognostic evidence for the patient with IC is still unclear. The insufficient

evidence in existing published research specific to the prognosis of the individual patient with IC justified the need of the research described in this thesis.

2.1.1 Search strategy

The search strategy conducted for this review included both electronic and non-electronic searches as a source of information. The main search engine that was utilised was HyDi, which is a search gateway provided by the University of Malta. The search facility incorporates searches from several subscribed databases including EBSCO, PubMed, ProQuest and Ovid (Medline) and enabled advanced searches for both online and print library sources. Online search in other databases including Science Direct, Cochrane, Scopus and Google Scholar were employed. Grey literature was also searched for guidelines, guidance articles and reviews.

There were no limits to date of publication since historical articles were of interest. Although literature searches were conducted in the English language, HyDi also provided articles published in foreign languages that were translated into English. Therefore, no limitation for language was applied in the search.

Related search terms were identified through extensive reading related to the field of PAD and IC and were combined using Boolean operators which were supported by HyDi. The search included key words relating to four domains

1) 'peripheral arterial disease', including alternative terms such 'peripheral vascular disease', 'peripheral occlusive disease', 'peripheral atherosclerotic disease' and corresponding acronyms (such as PAD, PVD, POAD, LEAD)
2) 'Intermittent claudication' including alternative terms such as 'chronic lower limb ischaemia', 'symptomatic PAD', 'non-threatening lower limb ischaemia', 'claudicant'
3) 'prognosis' including alternative terms such as 'prognostic', 'predictive', 'progression'
4) 'management' and alternative terms such as 'treatment', 'revascularisation', 'therapy', 'intervention', 'management guidelines'. Supplementary key terms were added when specific information was required including 'diagnosis', 'epidemiology', 'definition', 'pathophysiology' and 'incidence'.

This chapter presents a comprehensive review of the epidemiology, risk factors and classification of IC due to PAD. The current diagnostic techniques, management as well as knowledge related to the natural history of IC are also discussed. Although this search was performed in the initial phase of this research, continuous updating of the literature was conducted until submission of this thesis.

2.2 Peripheral arterial disease

Peripheral arterial disease (PAD) is the preferred term for the occlusion (stenosis) of one or more arteries (Hiatt et al., 2008) of the arterial network that supplies the brain, visceral organs and limbs but excludes coronary arteries (A. T. Hirsch, Haskal, Hertzer, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Halperin et al., 2006). Numerous physiological processes can contribute to the development of arterial stenosis including vasculitis, dysplastic disorders, degenerative diseases and atherosclerosis. Atherosclerosis is however the most common disease process causing PAD (American College of Cardiology Foundation et al., 2010). Atherosclerosis is a systemic process in nature therefore (Levey et al., 2003), although the term PAD is often used to refer to lower extremity arterial disease, it includes a large series of disorders affecting several arterial beds making patients with PAD at a higher risk not only of lower limb morbidity but also for myocardial infarction [MI], stroke and all-cause mortality (Anand et al., 2018). Although it is unlikely that lower extremity PAD is a direct cause of atherosclerotic diseases affecting the heart or the brain, its diagnosis may serve as a marker for underlying atherosclerotic susceptibilities affecting other vascular beds. This relationship has an important clinical value to the extent that PAD has prognostic significance independent of other known risk factors (M. H. Criqui et al., 2008).

Following several epidemiologic studies, PAD prevalence has been estimated to lie within the range of 3-10% in the general population below the age of 70, increasing to 15-20% in persons over 70 years of age (M. H. Criqui & Aboyans, 2015; F. G. Fowkes et al., 1991; E. Selvin & Erlinger, 2004). As a result of an increase in longevity, a rise in prevalence was observed between the years 2000 and 2010 resulting in an estimated affected number of more than a quarter of a billion people worldwide, of whom 40 million were in Europe (F. G. R. Fowkes et al., 2013). In an updated systematic review of population based studies, the estimated

prevalence was 5.56% in people aged 25 years or older, leading to a global estimate of 236.63 million people having PAD (Song et al., 2019).

Despite its prevalence and importance, PAD is poorly understood by the general public (A. T. Hirsch et al., 2007) and underdiagnosed in primary care, leading to under-treatment of the condition (A. T. Hirsch et al., 2001; J. G. Regensteiner et al., 2008). In part, the reason is due to frequent absence of symptoms or atypical manifestations of the disease, with only 25-35% of patients experiencing the hallmark symptom of PAD, which is intermittent claudication [IC] (Hoeks et al., 2007). Limited exposure to PAD, its risk factors, preventive measures and complications in medical school curricula has also been associated with suboptimal knowledge of general practitioners with regards to identifying the clinical signs of the disease (AlHamzah et al., 2019).

While both symptomatic and asymptomatic PAD increase the risk of cardiovascular events (Bianchi et al., 2007; M. S. Conte et al., 2015), patients with IC are at a heightened risk of suffering an MI, stroke and vascular morbidity when compared with patients without symptoms (V. Aboyans et al., 2018; C. Diehm et al., 2009; Kollerits et al., 2008).

2.2.1 Increased risk in symptomatic PAD

Patients with symptomatic PAD are at increased risk of major adverse cardiovascular events compared to patients with PAD who do not manifest symptoms (K. Cassar, 2006; M. H. Criqui et al., 2008; Sartipy et al., 2018) and the risk of mortality is double that observed in the general population (Sartipy et al., 2018). A long-term follow up of patients with symptomatic PAD indicated that approximately 30% will suffer a cardiovascular event within 5 years (Rantner et al., 2017). A three-year follow-up study of patients with IC (Bonaca et al., 2013) showed that 12% suffered a major adverse cardiovascular event [MACE], including stroke, myocardial infarction and death, while 4% had acute lower limb ischaemia. After revascularisation, the risk of suffering a MACE among patients with IC significantly increased when compared to patients with asymptomatic PAD with an adjusted hazard ratio [HR] of 1.29 (95% confidence interval [CI]) (B. Sigvant et al., 2016). Lower limb morbidity is also worse in symptomatic PAD compared to those without symptoms. A long-term follow-up study reported a cumulative incidence of PAD deterioration over 5 years of 7% in patients with asymptomatic PAD, while

for patients with IC the 5-year cumulative incidence for PAD deterioration was 21% (Sartipy et al., 2018).

Symptomatic PAD profoundly affects the patient's ability to walk or exercise and as a result is associated with a reduced quality of life (Dumville et al., 2004; J. Nordanstig et al., 2014; J. G. Regensteiner et al., 2008). The symptoms can resolve spontaneously, remain stable for several years or may progress rapidly to develop critical limb ischaemia (CLI) (S. M. Conte & Vale, 2018). For those who progress to CLI, prognosis for life and limb is poor with high rates of morbidity and mortality (Anand et al., 2018; Cascini et al., 2020; Meshkin et al., 2020). Consequently, together with its pronounced risk for morbidity and mortality, management of IC is an important health problem (Kollerits et al., 2008; OECD., 2018; Vogel et al., 2009). The main objectives of this review is to evaluate the evidence surrounding the current recommended management approach for patients with IC and to identify risk factors associated with progression of the PAD in this group of patients.

2.3 Intermittent claudication

Intermittent claudication is the most common symptomatic expression of PAD (K. Cassar, 2006) and is defined as cramping, discomfort, fatigue or aching occurring in the calves, thighs or buttocks, which is reproducibly produced due to exercise-induced ischaemia and is relieved by rest within ten minutes (Moyer & U.S. Preventive Services Task Force, 2013).

The first mention of this syndrome, described as 'progressive limping and lameness' was by Bouley (Bouley, 1831), a veterinary surgeon. Through the post-mortem of a horse he discovered that the femoral arteries of the limb which exhibited a limp, were completely occluded by a fibrous blood clot. In humans this symptom was first described by Brodie (Brodie, 1846) and later defined as *intermittent claudication* by Charcot (Charcot, 1858) who associated IC with occlusion of the iliac artery. While earlier scientists erroneously attributed the symptom as a consequence to vasospasm factors up to the 1940s (Lindqvist, 1945; WÜ, 1898) today it is known that the pathophysiology of claudication, is complex and occurs due to limitations of blood flow during exercise with associated metabolic, neurological and inflammatory effects (K. J. Stewart et al., 2002).

An understanding of the arterial anatomy of the lower extremity (Figure 2.1) where symptoms are involved, may guide diagnosis and treatment plans, since the anatomical site of the stenosis or occlusion is associated with the symptomatic muscle group (Rooke et al., 2012). For example, pain in the calf muscles is generally associated with occlusive disease in the superficial femoral and popliteal arteries, while disease in the tibial arteries may result in calf pain or, although uncommon, foot pain and numbness (A. T. Hirsch, Haskal, Hertzer, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Halperin et al., 2006). The primary sites of stenosis involved with IC symptoms are most common in the femoral and popliteal arteries (80-90% of patients), followed by the tibial and peroneal arteries (40-50%) and the aorta and iliac arteries (30%) (Meru et al., 2006).

However, identification of the site of symptoms is insufficient for diagnosis as IC due to PAD needs to be distinguished from other conditions which may cause similar symptoms of leg pain

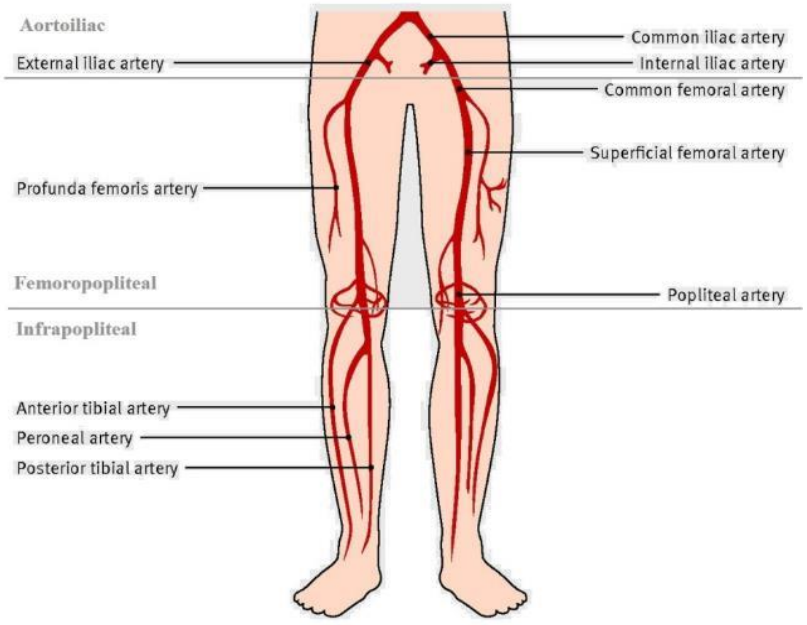


Figure 2.1 Anatomy of the Peripheral arteries**.** Adapted from Peach et al. (2012).

during exertion (Carman & Fernandez, 2000). These include severe venous obstructive disease, chronic compartment syndrome, lumbar disease, spinal stenosis, osteoarthritis and inflammatory muscle disease (K. Cassar, 2006; Dormandy & Rutherford, 2000). The appropriate diagnosis of IC due to PAD is important as it guides management choices (C. Diehm et al., 2009; A. T. Hirsch, Haskal, Hertzer, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith,

Adams, Anderson, Faxon, Fuster, Gibbons, Hunt et al., 2006) as discussed in further detail in section 2.6. Additionally, since not all patients with PAD experience symptoms of IC the reported prevalence may be influenced by the diagnostic methods applied (McDermott et al., 2001) as further discussed in section 2.4.1.

2.4 The clinical pathway for diagnosis of IC

Patients with IC often first seek medical help in primary care clinics (Argyriou et al., 2013; Davies et al., 2017) and depending on the health care system, advice is sought either from a general practitioner or a health care professional such as a physiotherapist or a podiatrist. Despite the utility of the symptom of classic claudication used to identify PAD, it can be misleading in cases of neurological origin of the symptom. For this reason, questionnaires, which were previously used in studies as diagnostic tools, may be unreliable and adjunct vascular analysis is required.

Diagnosis of symptomatic PAD within the clinical context therefore includes a detailed medical history, clinical examination and vascular tests which are essential to distinguish the IC due to PAD from other conditions that may cause leg pain (V. Aboyans et al., 2018). Guidelines recommend physical examination for the presence of diminished pulses of the common femoral, popliteal, posterior tibial and dorsalis pedis arteries and haemodynamic analysis by ABPI in patients suspected of having PAD (Bevan & White Solaru, 2020; Marbach et al., 2020). Imaging modalities such as duplex ultrasound are also viable diagnostic tools, but not commonly available in a primary care clinical context. Symptom severity may be established using validated questionnaires or treadmill testing, which is also not easily available in routine clinics but more commonly used in research. The different methods of vascular assessment methods for diagnosis of IC are further discussed in section 2.4.1.

2.4.1 Haemodynamic analysis

According to international guidelines (M. S. Conte et al., 2019), the diagnosis of PAD in an outpatient setting includes the assessment of Doppler waveforms and the measurement of the ABPI. A further assessment by TBPI is advocated in patients who have abnormally high ABPI

or who are known to have calcified arteries. The assessment modalities for diagnosis of PAD are each discussed in detail in sections 2.4.1.1 to 2.4.1.4.

2.4.1.1 The Ankle brachial pressure index

The ankle-brachial pressure index (ABPI) is the ratio of the ankle pressure divided by the brachial pressure and is determined by measuring the systolic pressure of the dorsalis pedis, the posterior tibial artery and the brachial systolic blood pressure detected by continuous wave Doppler with the patient in a supine position. The protocol on how to perform the actual test has been clearly defined (V. Aboyans et al., 2012) and was adopted in this research. The protocol is summarised in Chapter Five table 5.1. The ABPI is a useful clinical tool for measuring ankle perfusion and diagnosing PAD (V. Aboyans et al., 2018) and it is also a marker for cardiovascular disease (Anand et al., 2018).

Normal values of ABPI range from 0.9 to 1.39 and an ABPI of 0.9 or lower is one of the main diagnostic tools used in the clinical setting for diagnosing PAD (M. S. Conte et al., 2019). Low values of ABPI are predictive of risk of subsequent cardiovascular events (Hajibandeh et al., 2017) and the test provides an indication of severity of PAD and urgency of referral. It is widely used by a variety of healthcare professionals in primary settings because it is a non-invasive measure of PAD and can be performed by trained healthcare professionals in a clinical setting (M. S. Conte et al., 2019; Davies et al., 2017). Despite its widespread advocated use, ABPI has important limitations which impact its reliability.

Firstly, the reliability of the test is operator dependant since it requires expertise in the use and interpretation of Doppler waveforms when detecting the pulse of the pedal arteries (Kim et al., 2020; P. E. Tehan & Chuter, 2015). Highly trained clinicians are more likely to report accurate ABPI measurements compared to less trained physicians (V. Aboyans & Lacroix, 2007). Secondly, in cases when the ankle arteries are calcified, often manifested in patients with medial calcinosis, diabetes mellitus, end stage renal disease or smokers, the artery is incompressible despite cuff inflation >250mmHg, or systolic pressure is measurable but ABPI is higher than 1.4 (Abouhamda et al., 2019; V. Aboyans et al., 2012). There are also instances when due to medial arterial calcification (MAC), the ankle pressure is measured but is falsely elevated due to delayed arterial closure by the cuff caused by arterial stiffness leading to pseudo-normal ABPI values in patients with significant disease (C. Formosa et al., 2013). This

occurs because when calcification is present, stenotic disease is not detected by ABPI (V. Aboyans et al., 2008). For this reason, when diagnosing PAD, an ABPI of <0.9 has a sensitivity of 75% and a specificity of 86% but sensitivity has been reported to be as low as 38% in individuals with diabetes and patients with medial calcification (Khan et al., 2008).

In patients with bilateral claudication, ABPI was compared as a diagnostic tool for PAD with Duplex ultrasound, which is considered to be highly accurate (Allen et al., 1996). ABPI was significantly more consistent when the most symptomatic limb was compared. Better sensitivity in detecting disease by ABPI was reported when the lower of the pressures recorded between the two pedal arteries (posterior tibial and dorsalis pedis) was used (Schröder et al., 2006). This method was applied in several epidemiological studies (Kumbhani et al., 2011; Rantner et al., 2017). Although it is argued that for screening the general population for PAD using the higher of the two is more feasible because it yields better specificity resulting in less erroneous referrals (V. Aboyans & Lacroix, 2007), using the lower ankle pressure improves the diagnostic performance of ABPI to detect PAD and is a better tool when assessing risk in symptomatic patients (Schröder et al., 2006).

The significant limitations of ABPI as a measure of PAD in patients with MAC has driven researchers and clinicians to increase the application of TBPI as an additional modality of vascular assessment due to its improved reliability even in patients with arterial stiffness (Chisalita et al., 2020).

2.4.1.2 The Toe-brachial pressure index

The toe-brachial pressure index (TBPI) is the ratio of the toe pressure divided by the systolic brachial pressure and objectively measures blood perfusion up to the toes (P. Tehan et al., 2015). It is conducted by measuring the toe pressure using a small pressure cuff and a photoplethysmographic sensor to detect a pulse at the big toe instead of the pedal pulses used for ABPI tests (Figure 5.2, Chapter 5 section 5.6.2.3).

In the last decade this assessment modality has received increasing attention (Bundo et al., 2013; Martin Borge et al., 2008; Stoekenbroek et al., 2015; P. E. Tehan et al., 2017; P. Tehan et al., 2015) due to its ability to provide more reliable results than ABPI in patients with MAC

since the digital arteries are less prone to calcification (P. E. Tehan et al., 2016). In this regard, TBPI has a sensitivity of 71% compared to 45% in ABPI in patients with confirmed PAD but a lower specificity than ABPI (93% for ABPI and 78% for TBPI). Overall, TBPI is considered to have better efficacy than ABPI in the diagnosis of PAD using receiver operator characteristic analysis (ROC 0.77 and 0.65 respectively) (P. E. Tehan et al., 2017).

Due to its diagnostic accuracy even in patients with calcified ankle arteries, TBPI has been shown to be a significant predictor for major cardiovascular events, irrespective of arterial stiffness (Chisalita et al., 2020) and in predicting major amputation in patients with CLI (Salaun et al., 2019). To date, its predictive properties in patients with IC have not yet been evaluated in published literature.

While TBPI measurement is a relatively simple cost-effective modality for diagnosing PAD, there are considerations such as room temperature (19°C–22°C/66°F–72°F, Høyer et al., 2013), cuff size (recommended size 2.5cm, Påhlsson et al., 2007) and resting time (minimum of 10 minutes, Sadler et al., 2015) that can affect reliability of readings. Additionally, particularly in patients with co-existent MAC and occlusive PAD in distal segments, TBPI accuracy is negatively affected yielding lower sensitivity, therefore it is recommended that for PAD diagnosis, more than one objective assessment should be used concomitantly (P. E. Tehan et al., 2017).

2.4.1.3 Doppler waveform analysis

In view of the challenges associated with each method of haemodynamic test modality available in the clinical setting, a local study (Azzopardi et al., 2019) has determined that the best way to diagnose PAD is by using ABPI and TBPI together with Doppler waveform analysis. In their study, Doppler waveform analysis was found to be the most reliable method in detecting PAD. Interpretation of Doppler waveforms and expertise in the use of the Doppler probe to accurately detect the pulses are important factors (Scissons & Comerota, 2009).

General agreement exists in the interpretation of triphasic waveforms which are defined as waveforms with three components - systole forward flow, reverse flow (early diastole / late systole) and forward flow (late systole, end-systolic notch) with the waves crossing the zero flow line (Kim et al., 2020). Biphasic waveforms are denoted by a systolic forward flow with

diastolic reverse flow. The waves cross the zero flow line without an end-diastolic notch (Scissons, 2008). Monophasic waveforms are waveforms which reflect blood flowing in one direction and do not cross the zero-flow baseline (Kim et al., 2020). Controversies exist in the interpretation of waveforms with a sharp upstroke, a brisk downstroke above the zero flow line but with an end-systolic notch with some authors describing it as biphasic. However, the latest consensus (Kim et al., 2020) denoted that due to the lack of reverse flow it should be classified as a monophasic intermediate resistive waveform or as previously suggested by Scissons (Scissons & Comerota, 2009) and Spronk (Spronk et al., 2005) as 'sharp' monophasic.

2.4.1.4 Imaging techniques

There are multiple imaging techniques that have established reliability in diagnosing PAD which include duplex ultrasound, computed tomography angiography and MRA (V. Aboyans & Jean-BaptisteRicco, 2017). Duplex ultrasound imaging, which enables the practitioner to identify, localise and assess severity of vascular lesions is recommended as first-line imaging modality for patients being considered for revascularisation (Bevan & White Solaru, 2020). It has a sensitivity of 85-90% and a specificity of more than 95% for detection of arterial stenosis. Its reliability is however operator dependant and requires extensive training (Sheehan & Zierler, 2018). This diagnostic modality is not normally found in primary care clinics and are not used for initial diagnosis of PAD in IC patients, but is usually located in outpatient secondary care clinics as is the case in Malta.

Other methods of evaluation of PAD include the Bollinger classification method (Bollinger et al., 1981) which utilizes angiographic imaging to determine grading of stenosis and Graziani's morphologic categorization (Graziani et al., 2007) which is based on the anatomic distribution of the stenosis also defined angiographically. However, these latter two classification systems are also not used clinically for classifying patients with IC in real world scenarios of outpatient clinics, but are more directed for patients with CLI requiring revascularisation (Hardman et al., 2014).

For assessment of PAD, the considerations highlighted in this review were taken into account during the design phase of the data collection and data analysis of this research as explained in further detail in Chapters Five and Seven respectively.

2.4.2 Evaluation of IC symptoms

For patients with IC, once diagnosis of PAD is established, the clinical stage of the disease is commonly determined by the Fontaine classification or the Rutherford classification (Hardman et al., 2014) (Table 2.1). The Fontaine classification (Fontaine, 1954) grades the clinical presentation into 4 stages without any adjunct diagnostic tests. Rutherford later developed another classification system (Rutherford et al., 1986), with the addition of objective noninvasive data including ankle or toe pressures.

Fontaine Classification		**Rutherford Classification for chronic limb ischaemia**		
Grade	**Symptoms**	**Grade**	**Category**	**Description and objective criteria**
Stage I	Asymptomatic, incomplete blood vessel occlusion	0	0	Asymptomatic – no haemodynamically significant occlusive disease - No reactive hyperaemia test
Stage IIa	Mild claudication at >200m	I	1	Mild claudication - AP after exercise >50mmHg but at least 20mmHg lower than resting value
Stage IIb	Moderate claudication at <200m	I	2	Moderate claudication - Between categories 1 and 3
		I	3	Severe claudication - after exercise AP<50mmHg
Stage III	Rest pain	II	4	Ischaemic rest pain - Resting AP<40mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP<30mmHg
Stage IV	Necrosis and / or gangrene in the limb	III	5	Minor tissue loss- non-healing ulcer, focal gangrene with diffuse pedal ischaemia - Resting AP <60mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP<40mmHg
			6	Major tissue loss- extending above TM level, functional foot not salvageable - Same as category 5
TP= toe pressure, AP= Ankle pressure, PVR = pulse volume recording, TM= transmetatarsal				

Table 2.1 The Rutherford and Fontaine classifications

In the clinical context it is important to evaluate the severity of symptoms by determining the distance walked until symptoms occur (M. S. Conte et al., 2015). Although this can be measured objectively through treadmill testing as often described in published research (Nicolaï, Viechtbauer et al., 2009), with regards to the clinical decision on whether to perform revascularisation, patient perception is deemed important (M. S. Conte et al., 2019). Symptom evaluation in clinical settings commonly occurs by patient-reported inability to perform everyday tasks as treadmill tests are often not available or impractical (Gardner et al., 1996).

The modalities available for symptom evaluation in patients with IC are discussed in further detail in sections 2.4.2.1 and 2.4.2.2.

2.4.2.1 Treadmill test

The treadmill test is an objective test used to assess functional impairment in patients with IC. Patients are asked to walk on a treadmill at 3Km/ hour on a 10% slope which is stopped when the patient is unable to walk further due to limb pain, defining maximum walking distance (MWD) (Nicolaï, Viechtbauer et al., 2009). Importantly, due to the possibility of increased cardiac stress, treadmill claudication distance measurement is contra-indicated in populations with severe aortic stenosis, uncontrolled hypertension, congestive heart failure or chronic pulmonary disease (Gibbons et al., 2002). Despite its use in research, it is recognised that distance walked on a treadmill does not reflect severity of PAD or the disability experienced during daily life (Frans et al., 2013). This is because impairment in walking capacity may be due to other existing exercise-limiting co-morbidities such as musculoskeletal pain or breathlessness causing a low correlation of ABPI with treadmill-based claudication assessment and also because reduced walking distance may result in significant life-style limitation for an individual but may have no effect on quality of life in another. Therefore, to evaluate severity of IC symptoms a comprehensive approach which includes patient-focused clinical outcomes such as using validated questionnaires is suggested to be the most accurate method with which to assess patient disability over time (Andreozzi & Martini, 2002). In this context, questionnaires assessing symptoms through the patient's perspective have been developed for the evaluation of IC as a symptom of PAD (Frans et al., 2013).

2.4.2.2 Questionnaires

Over the years several self-reported questionnaires (M. H. Criqui et al., 1985; F. G. Fowkes et al., 1991; Leng & Fowkes, 1992; ROSE, 1962) were developed in attempt to provide an easy and accurate method to diagnose IC due to PAD efficiently while simultaneously aiming to focus on patient centered outcomes by considering perceived disability in this context. Perceived disability is an important aspect of evaluating symptom severity as it guides the clinical decision regarding invasive treatment (M. S. Conte et al., 2015).

The first developed questionnaires, such as the Rose questionnaire and the WHO/ Rose questionnaire (Leng & Fowkes, 1992; ROSE, 1962), were reported to have a low sensitivity when compared with physician diagnosis of PAD (A. B. Newman et al., 2001). In fact, as well described in a structured review by Schorr et al (Schorr & Treat-Jacobson, 2013), the strict definition of classic claudication in the Rose questionnaire resulted in a large variability of reported prevalence of IC among PAD patients. The Edinburgh claudication questionnaire was later developed with improved sensitivity but in their definition, pain had to be present in the calf, therefore its use excluded patients with thigh or buttock claudication and without right or left side discrimination (M. H. Criqui et al., 1985; F. G. Fowkes et al., 1991). Schorr et al (Schorr & Treat-Jacobson, 2013), concluded that the use of questionnaires alone is not sufficient to diagnose PAD and may lead to under-diagnosis since only up to 33% (M. H. Criqui et al., 1996) develop symptoms. On the other hand, the use of questionnaires alone may also lead to mis-diagnosis since there may be alternative causes of IC symptoms, other than PAD (K. Cassar, 2006; Dormandy & Rutherford, 2000).

With the known reliability and increased availability of non-invasive physiologic testing (Doppler waveform analysis, ABI and TBI) to diagnose PAD, for patients with IC, the use of questionnaires shifted to a more adjunct role of evaluating severity of symptoms rather than to diagnose PAD. The San Diego claudication questionnaire (SDCQ) (M. H. Criqui et al., 1996), the Intermittent claudication questionnaire (ICQ) (Chong et al., 2002) and the Walking impairment questionnaire (WIQ) are validated questionnaires (Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008) which inquire about the type of pain and location of pain and perceived walking impairment. The SDCQ and ICQ are generally used for studies investigating health related quality of life while the WIQ (McDermott et al., 1998; Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008) was found to be useful for measuring progression of symptoms over time.

The WIQ, originally designed by Regensteiner, (J. Regensteiner, 1990) has been extensively studied with several versions (Coyne et al., 2003; Mahé et al., 2011; Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008). It is a disease-specific interviewer administered questionnaire, validated for patients with IC which focuses on symptom severity perceived in real life activities such as climbing stairs and perceived walking distance (Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008). The adapted version by Coyne et al (Coyne et al., 2003) achieved good reliability and validity when interviewer completed with Cronbach's

alpha ranging from 0.92 to 0.97 (Ouedraogo et al., 2011). Interviewer-completed questionnaires require more time but have better rates of completion, better reliability (Mahé et al., 2011) and less response errors (Conijn et al., 2015).

With regards to perceived walking distance, the WIQ distance score was strongly correlated with estimated maximum walking distance in metres (r=0.81; 95% CI) and moderately correlated with distance walked in corridor (r=0.59; 95% CI) (Frans et al., 2013; Mahé et al., 2011). When compared to treadmill walking distance, the WIQ estimated distance and speed components demonstrated strong correlations (Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008). The WIQ was reported to be a valid tool to measure functional status (Coyne et al., 2003) and is one of the few questionnaires with assessed reliability and measurement error (Conijn et al., 2015). Importantly, the WIQ was found to be a valid tool to detect symptom deterioration or improvement in patients with IC, making it a useful tool for objective testing of functional walking ability both in the routine clinical context and in research (Nicolaï et al., 2009).

The utility of questionnaires in evaluating symptom severity among patients with IC has been highlighted while also acknowledging that they are not sufficient to diagnose PAD due to the risk of under-diagnosis or mis-diagnosis (M. H. Criqui & Aboyans, 2015; Schorr & Treat-Jacobson, 2013). In this context, haemodynamic analysis is an important element to be used adjunctively with a validated claudication questionnaire to determine symptom severity of IC due to PAD. This concept was adopted in this research where haemodynamic analysis and the WIQ were used concurrently for data collection (Chapter 5).

2.5 The prevalence of IC

In current literature and guidelines related to IC (V. Aboyans et al., 2018; M. S. Conte et al., 2019), the prevalence data of IC is generally derived from large population studies conducted over the last three decades (F. G. Fowkes et al., 1991; W. T. Meijer et al., 1998; J. M. Murabito et al., 2002). However, following a review of the literature, it appears that the reported IC prevalence in published literature is highly variable, ranging from 7.5% to 33% among patients with PAD (Collins et al., 2003; M. H. Criqui et al., 1996; McDermott et al., 1999; J. M. Murabito et al., 2002; Wang et al., 2005) and between 0.4 to 14.4% among the general population (Diehm et al., 2004; HALE et al., 1988; Mohler et al., 2008).

Data from the Framingham offspring study (J. M. Murabito et al., 2002) reports an IC prevalence among an elderly population of 1.9% in men and 0.8% in women while prevalence rates of IC of 4.5% in an unselected population were reported in the Edinburgh study (F. G. Fowkes et al., 1991) using the WHO questionnaire and ankle-brachial pressure index measurement (ABPI) <0.9 for IC diagnosis. Using the same diagnostic criteria, the Rotterdam study (W. T. Meijer et al., 1998) reported a prevalence of IC of 1.6% among an elderly population and 6.3% among patients with PAD. A higher IC prevalence of 14.4% in men and 14.1% in women reported by Hale et al (Hale et al., 1988) was also among a cohort of elderly participants.

Specific patient characteristics within the participant cohort of the studies may correspond to an increase in reported prevalence. Within the recruited participants, higher proportions of male gender (J. M. Murabito et al., 2002), diabetes (Wang et al., 2005), hypertension (F. G. Fowkes et al., 1992; E. Selvin & Erlinger, 2004) and a more severe form of PAD (M. H. Criqui et al., 1996; Wang et al., 2005) may influence the prevalence results. Reported prevalence of IC is also thought to be influenced by location of atherosclerotic lesions among the participants where reports are higher among patients with stenosis in distal arteries such as infrapopliteal branches (van Zitteren et al., 2012).

Prevalence of IC is therefore not clearly defined, possibly due to varying diagnostic methods of IC where some studies used questionnaires (W. Kannel & McGee, 1985; Leng et al., 1996) and others used haemodynamic analysis (F. G. Fowkes et al., 1991) or also due to different population characteristics (W. T. Meijer et al., 2000). Potential confounders of symptom reporting may also impact prevalence results. For example, when questionnaires alone are used to determine the presence of PAD, other conditions which affect mobility (such as arthritis or breathlessness) preclude elderly patients from walking long enough to experience IC, therefore in such populations IC prevalence may be underestimated (Schorr & Treat-Jacobson, 2013). On the other end of the spectrum, when questionnaires alone were used to diagnose IC, without haemodynamic analysis, prevalence could have been overestimated due to inclusion of patients who experienced IC as a result of other conditions such as spinal stenosis (K. Cassar, 2006).

Overall, there is however agreement that prevalence of IC increases with increasing age (Figure 2.2) (V. Aboyans et al., 2018; M. S. Conte et al., 2015; Norgren et al., 2007; E. Selvin & Erlinger, 2004; Song et al., 2019) and is present in approximately 4.5% of the general

population over 40 years of age (Fakhry et al., 2018). There is also agreement that the major risk factors for IC are similar to those for coronary and cerebrovascular vascular disease and include smoking, diabetes, hypertension and dyslipdaemia (Song et al., 2019).

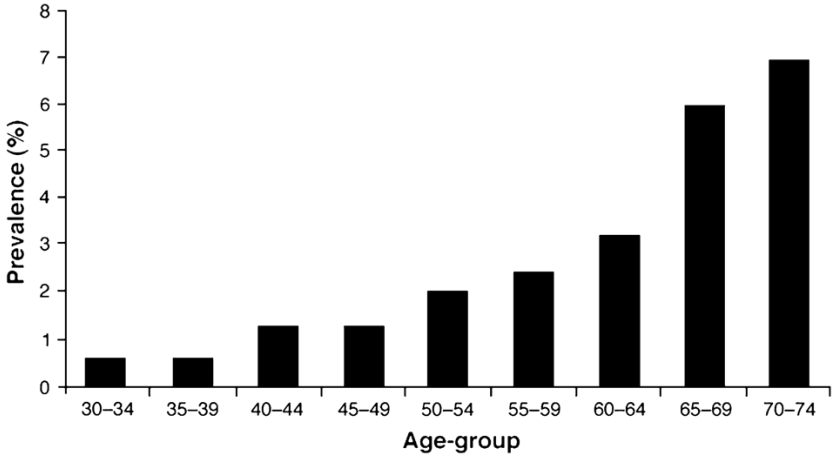


Figure 2.2: Mean prevalence of IC according to age (Norgren et al., 2007)

There is currently no specific data related to the prevalence of PAD or IC in Malta where the current study was conducted. It is also not known whether estimates from published literature demonstrating prevalence in other countries are relevant to the Maltese population. However, of relevance to the Maltese population and to the current work, is that existing epidemiological data demonstrate that Mediterranean countries have a higher prevalence of PAD than other western and northern European counterparts (Cimminiello et al., 2011) which therefore translates to higher prevalence of patients with IC. Furthermore, the prevalence of IC increases further with exposure to atherosclerotic risk factors (American College of Cardiology Foundation et al., 2011) such as diabetes, which is more prevalent in Malta compared to other European countries (Cuschieri, 2020). In view of the ageing population worldwide and the increasing burden of chronic diseases, namely diabetes, hypertension and dyslipidaemia, the prevalence of PAD and consequently IC is likely to increase markedly in the forthcoming decades (Marbach et al., 2020). This will inevitably increase the burden on healthcare systems across the world including Malta, due to the increased risk of morbidity and mortality among patients with IC.

2.6 Progression of PAD in patients with IC

This section explored the literature which investigated PAD progression among patients with IC. This knowledge is required in order to define the lower limb prognosis of patients with this condition because prediction of impending disease progression would help identify those who are at risk of deterioration and guide management plans in terms of timely revascularisation. In published literature, progression of disease in patients with IC has been investigated in terms of symptomatic progression and in terms of development of CLI or amputation rates (Andreozzi & Martini, 2002). In order to provide a better understanding of the risk of progression of IC, the available evidence was synthesised in this review.

2.6.1 Symptomatic progression

An early study (McAllister, 1976) of 100 IC patients followed for 6 years, reported that 78% remained stable or improved in terms of IC symptoms. Similarly, another study (O'Riordain & O'Donnell, 1991) of 112 patients monitored for 8 years stated that 66% of the survivors reported improvement of symptoms or remained stable and only 6.5% required revascularisation due to disabling claudication. Methods of symptom evaluation are however not clear in these early studies. Similar proportions of worsening symptoms, but observed in a shorter time (Martone et al., 1998), were obtained when objective measures of claudication were applied using treadmill exercise in 110 patients with IC, reporting that 74% remained stable while 26% deteriorated after 24.4 months. In their study only 4.7% required revascularisation for worsening claudication symptoms during the course of the study. Similarly, reports of symptom stability and improvement, measured by a validated questionnaire (Edinburgh questionnaire) in the majority of patients (67%) were reported in a larger study of 255 male participants over 7 years (Rantner et al., 2017). Worse outcomes were reported (Cronenwett et al., 1984) in a group of 91 men with mild IC when walking distance was defined using a questionnaire, indicating that after a mean follow-up of 2.5 years, 60% reported worse claudication and 40% stated that their symptoms improved or were stable. Among their cohort, 7.6% required revascularisation within 2 years of diagnosis. A more recent study (Mazari et al., 2017) of 111 patients followed for 5.2 years reported no change in walking distance measured in meters among patients with IC who were treated conservatively. A prospective cohort study (Kumakura et al., 2016) of 1107 patients newly diagnosed with IC,

recruited from a cardiovascular hospital, reported symptomatic deterioration in 14.8% of the participants over 5 years. A larger study (Muluk et al., 2001) of 2777 patients with IC reported that over 10 years, 18% required revascularisation procedures due to symptom deterioration.

Direct comparison of results between the identified studies is difficult due to variations in patient characteristics, where studies included previously revascularised patients (Rantner et al., 2017), only male participants (Muluk et al., 2001) or only patients with mild symptoms (Cronenwett et al., 1984). Overall, the literature reports that revascularisation due to worsening of symptoms ranged from 4.7% to 7.6 % in 2years to 14.8% in 5 years and 18% in 10 years, while the majority of patients remained with stable symptoms. However, due to the heterogeneity of the studies it is difficult to accurately define the prognosis of symptom progression in the individual patient.

In literature investigating symptom deterioration, worsening symptoms are generally reported during the first year after diagnosis, as symptoms seem to stabilise in the subsequent years (Norgren et al., 2007). It has been suggested that symptomatic stabilisation is influenced by the patient's perception of the severity of their symptoms (Spannbauer, Chwała, Ridan, Berwecki, Mika, Kulik, Berwecka, & Szewczyk, 2019b), by development of collaterals or gait alternation to favor non-ischaemic muscle groups (Konik et al., 2016). Nevertheless, despite patient reported symptom stability, functional status measured by 6-minute walking performance decreased and was associated with a decline in ABPI (McDermott et al., 2004), indicating that improving functional ability may not necessarily reflect haemodynamic improvement.

2.6.2 Progression to CLI

Critical limb ischaemia [CLI], is the term used for pain at rest, ulceration, tissue loss or gangrene due to PAD and is the most severe clinical manifestation of PAD (Bevan & White Solaru, 2020). In some recent literature, CLTI (chronic limb threatening ischaemia) is the preferred term over CLI which implies defined values of perfusion rather than a continuous progression (M. S. Conte et al., 2019). In this thesis, because some reviewed literature which pre-dated the development of this term was important and influential in some aspects, CLTI and CLI are used interchangeably, referring to the continuous progression of PAD with clinical manifestation and not defined by values of perfusion.

The clinical course of IC as reported in the TASC document (Norgren et al., 2007), states that deterioration from IC to CLI occurs in 5-10% of IC patients over 5 years, the ACC/AHA report deterioration to CLI in 1-2% every 5 years (A. T. Hirsch, Haskal, Hertzer, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Hunt et al., 2006) while the Society for Vascular surgery quote a rate of 1-3% (M. S. Conte et al., 2015). Overall, across all published guidelines, it is commonly accepted that only 20-25% of patients with IC will deteriorate and out of these only 5%-10% will develop CLI (Norgren et al., 2007). The origin of these estimates is not clear but Hirsch et al (A. T. Hirsch, Haskal, Hertzer, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Hunt et al., 2006) refer to a review by Weitz et al (Weitz et al., 1996) of studies from the 1980s (W. Kannel & McGee, 1985; McDaniel & Cronenwett, 1989). A more recent systematic review and meta-analysis (B. Sigvant et al., 2016) investigating disease progression of different classifications of PAD, reported a deterioration rate (which included deterioration from IC to CLI and also symptom deterioration requiring revascularisation) ranging from 12 to 29% over 5 years. The authors stated that this is significantly higher than what is reported in international guideline documents, indicating that guidelines may be underestimating disease progression among IC patients.

In the review presented in this chapter, studies which have investigated the progression to CLI or CLTI among patients with IC were evaluated to provide further understanding of the prognosis of IC in terms of development of CLI.

The progression of PAD in patients with IC has been a source of investigation in several studies (Cronenwett et al., 1984; Dormandy & Murray, 2011; Giugliano et al., 2010; Jelnes, Gaardsting, Hougaard Jensen, Baekgaard, Tonnesen, & Schroeder, 1986a; Kumakura et al., 2016; McDaniel & Cronenwett, 1989; O'Riordain & O'Donnell, 1991), including large epidemiological surveys (Leng et al., 1996; Rantner et al., 2017) and a systematic review with meta-analysis (B. Sigvant et al., 2016). Despite the extensive research, the specific progression rate from IC to CLI is difficult to establish because the reported risk of deterioration to CLI in this population is varied, ranging from 1.4% per year to 27% within 5 years of diagnosis (Aquino et al., 2001; Jelnes, Gaardsting, Hougaard Jensen, Baekgaard, Tonnesen, & Schroeder, 1986; Jensen et al., 2006; Kumakura et al., 2016; Naschitz et al., 1988; B. Sigvant et al., 2007).

A synthesis of studies reporting progression rates and risk of progression from IC to CLI is presented in this section, highlighting the heterogeneous nature of these investigations.

Large epidemiological studies such as the Edinburgh Artery study (Leng et al., 1996) reported low rates of deterioration. In the Edinburgh study a prospective cohort of 1592 randomly selected individuals from GP practices aged between 55 and 74 years were followed for 5 years. Intermittent claudication was prevalent in 4.5% of their participants, diagnosed by the Edinburgh claudication questionnaire of whom 28.8% continued with IC after 5 years, 8.2% required revascularisation or amputation and 1.4 % developed ischaemic ulcers.

Another study of 1244 male patients (Aquino et al., 2001) diagnosed with IC in a medical centre were followed for a mean of 45 months also reported relatively low rates of deterioration. Serial measures of ABPI were recorded at 6 month intervals and a decline of 0.014 per year was reported. In their study, patients with calcified arteries and abnormally high ABPIs were excluded. Deterioration to CLI in terms of ulceration and rest pain was 23% and 30% respectively over 10 years, equivalent to an annual rate of 5.3% developing CLI per year. Patients with medial arterial calcification are at high risk of deterioration (Ho & Shanahan, 2016), therefore their exclusion from the study may have resulted in an underestimation of the rate of development of CLI. Similarly, patients with abnormally high ABPIs are likely to have calcified atherosclerotic disease and their exclusion from the cohort may have resulted in an underestimate of the true risk of deterioration.

A prospective cohort study (Kumakura et al., 2016) of 1107 patients newly diagnosed with IC, recruited from a cardiovascular hospital, reported that 1.1% developed CLI over 5 years. The authors identified haemodialysis and diabetes as independent risk factors for progression of IC to CLI. Although reporting a low deterioration to CLI, a high proportion of their cohort (63.1%) underwent revascularisation during the study. The authors specified that revascularisation was performed in cases of symptom deterioration, disease progression, ABPI decline by ≥0.1 or stenosis of ≥50% defined angiographically. The low rate of CLI reported in this study excludes participants who experienced progression of the disease and were treated with revascularisation and therefore needs to be interpreted within context. Additionally, as discussed in section 2.4.1 in this chapter, in patients with arterial calcification, ABPI may not detect deterioration (C. Formosa et al., 2013). Since in their study deterioration was defined as a decline in ABPI by

0.1 or more, in patients with calcification deterioration would not be detected hence using this measure to define deterioration may have resulted in an underestimation of the progression of the PAD.

Higher reports of deterioration to CLI were published in another study investigating the progression of PAD in a cohort of 257 consecutive patients referred to a vascular clinic due to IC, where 7.5% demonstrated significant deterioration within the first year of follow-up (Jelnes, Gaardsting, Hougaard Jensen, Baekgaard, Tonnesen, & Schroeder, 1986). The authors stated that PAD progression was approximately 3 times faster in the first year following diagnosis than in subsequent years. This fact was attributed to the possibility that patients seek medical advice during periods of symptom deterioration. An independent association with PAD progression was reported for ankle systolic pressure below 70mmHg, an ABPI <0.5 and a toe systolic pressure below 40mmHg. It should be noted that at follow-up after 6.5 years, 44% of the recruited participants had died, meaning that follow-up data included that retrieved only from survivors, possibly introducing survival selection bias.

A similar study (Naschitz et al., 1988) of 460 patients referred to a surgical centre due to IC reported a deterioration to CLI requiring revascularisation in 9.1% of their cohort per year. In their study, IC was measured using a treadmill and ABPI was recorded at regular intervals for a mean of 4.1 years. The authors reported worse symptoms in 11.9% of the cohort and clinical deterioration to CLI in 44.1% during the whole follow-up period ranging up to 10 years. An ABPI of >0.7 at baseline and lack of decline by >0.15 were reported to be predictors of favourable outcomes. On the other hand, an ABPI <0.5 at initial consultation was associated with an increased risk of deterioration by 3.8 times and a decline >0.15 in ABPI predicted an increased risk of deterioration by 1.9 times. The authors report that a higher rate of revascularisation procedures may be attributed to physician's preferred practice and may be influenced by the interventional policies of the treating hospital.

In a study investigating PAD progression among 397 patients having symptomatic PAD in a vascular clinic, the authors reported that over 5 years, a decline in ABPI of >0.15 was found in 31% of the patients, while 22% suffered clinical progression of PAD based on worsening symptoms or on the requirement of surgical intervention (Nicoloff et al., 2002). Similarly, Bird et al (Bird et al., 1999) demonstrated that in a study of patients with IC referred to a vascular laboratory, 30.2% of limbs deteriorated to a more severe category of PAD during an average

of 4.6 years. In their study IC was independently associated with disease progression (Bird et al., 1999).

The CAVASIC study (Rantner et al., 2017) followed 246 patients with IC recruited from 3 medical centres including a vascular surgery unit. Symptom severity and PAD were assessed and followed using the Edinburgh claudication questionnaire, ABPI measurements, treadmill examination and arterial imaging. The authors reported that 33% of the patients required an intervention during the 5-year follow-up. In their cohort, patients with prior revascularisation procedures were not excluded. This may have resulted in higher proportion of patients deteriorating to CLI since patients who underwent interventional procedures were probably at a more advanced stage of disease and are at higher risk of deterioration (Venermo et al., 2019).

It has been suggested (Bitar & Garcia, 2010) that higher rates of deterioration may be reported in studies investigating disease progression in IC among patients referred to vascular centres (Jelnes et al., 1986; Naschitz et al., 1988; Rantner et al., 2017), when compared to unselected patients (Leng et al., 1996). It is thought that referred patients may have more advanced disease or worse symptoms and such studies yield reports of worse outcomes (Bitar & Garcia, 2010). This notion was taken into consideration in the research presented in this thesis and was addressed in the preliminary phase as discussed in Study 2 (Chapter 4).

Therefore, following the review of the studies investigating the progression from IC to CLTI, the clinical heterogeneous nature of the studies makes it difficult to arrive to clear conclusions, except some agreement that an ABPI of ≤0.5 at diagnosis is associated with development of CLI. For example, some studies (Naschitz et al., 1988; Rantner et al., 2017) defined CLTI as development of chronic ischaemic rest pain, ulcers or gangrene (Becker et al., 2011), others (Kumakura et al., 2016) included ankle pressure below 50-70mmHg and /or toe pressure below 30-50mmHg or transcutaneous oxygen pressure ($TcPO_2$) below 30-50mmHg as defined by Rutherford (Rutherford et al., 1986) and others (Leng et al., 1996) included amputation rates. The use of haemodynamic data to define CLI has been questioned as there is no prospective evidence to validate it (Constans et al., 2018) and amputation rates do not accurately reflect disease progression since several other patients undergo revascularisation procedures for CLI without amputation (Hata et al., 2020). There are also differences in participant characteristics at recruitment, since epidemiological studies (Leng et al., 1996) included participants from the

general population while other studies were based on referrals for vascular clinics (Naschitz et al., 1988; Rantner et al., 2017) It therefore seems that the wide variation of progression reported in the studies may be attributed to differences in risk factor prevalence, population characteristics, definition of CLTI, baseline inclusion criteria and study design used (Bitar & Garcia, 2010).

However, although the evidence is unclear, the main international bodies which formulate guidelines for the management of IC (V. Aboyans et al., 2018; M. S. Conte et al., 2019; Gerhard-Herman et al., 2017; Norgren et al., 2007) [The American college of cardiology / American heart association (ACC/AHA), the TASC group, Global vascular guidelines writing group (GVG) and European society for vascular surgery (ESVS)], state that overall in 5 years, 70-80% of patients with IC will stabilize or improve and among those 20-30% who experience symptom deterioration, less than 5% will develop CLI, as shown in figure 2.3.

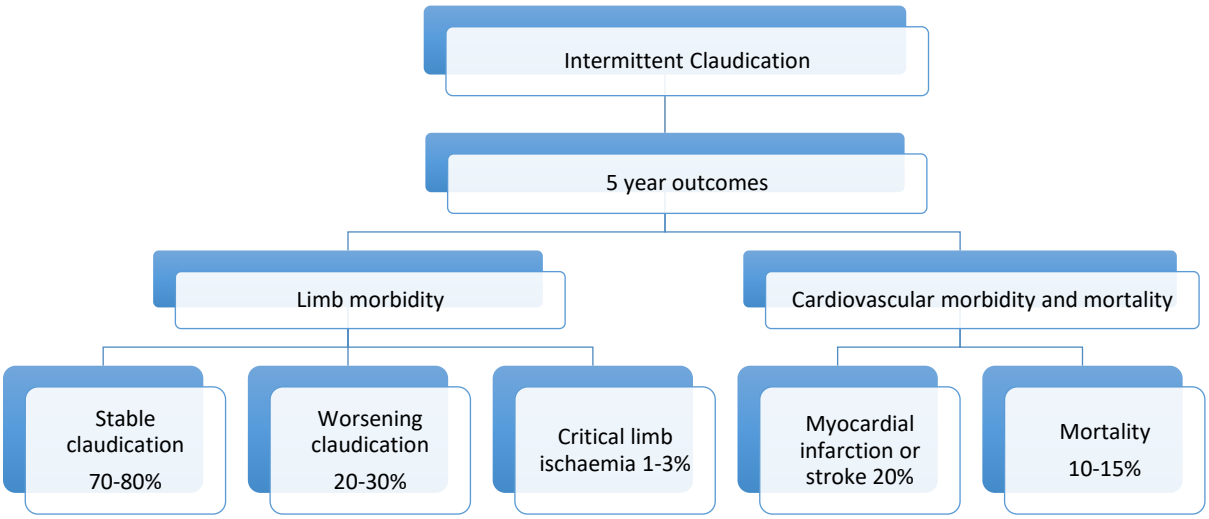


Figure 2.3 Outcomes of patients with IC. Adapted from (M. S. Conte et al., 2015)

It seems that since early studies, which date back to the 1950s (Richards, 1957; Spaulding, 1956), the prognosis of the lower limb among patients with IC is described as being favourable, both in terms of symptom progression as denoted by the quote herein, and in terms of amputation where the authors reported a rate of 10% in five years.

'The present study indicates that the prognosis is relatively good. At the end of the five-year period more than half the survivors were no more disabled by their intermittent claudication than they had been when they first seen, and several were convinced that they were better' (Richards, 1957, p. 1093)

Therefore, over the past 60 years, the assumed benign prognosis remained relatively unchallenged, as stated in the latest published international guidelines by the American Heart Association (Bevan & White Solaru, 2020). They report that although PAD is considered as a progressive disease, its clinical course, as far as the affected limb is concerned, is thought to be stable in most cases. While assuming a benign prognosis for the affected limb, in the latest Global Vascular Guidelines, Conte et al (M. S. Conte et al., 2019) stated that for the patient with IC, reliable data on the epidemiology of CLI are lacking and estimates can be highly misleading (M. S. Conte et al., 2019) since progression is likely underestimated in published reports (B. Sigvant et al., 2016). The possible underestimation of disease progression suggests that the assumption of a benign prognosis may need to be reconsidered (B. Sigvant et al., 2016).

In the literature, the progression of IC is sometimes measured as worsening claudication, with a measured claudication distance or time to claudication (McDermott et al., 2004), or as worsening clinical outcome defined as development of CLI or amputation (Muluk et al., 2001). Very few studies have measured haemodynamic progression in conjunction with clinical progression of symptoms, therefore with the current evidence available it is difficult to predict the risk of deterioration in a patient presenting with IC (V. Aboyans et al., 2018; Norgren et al., 2007). The difficulty in identifying patients at risk of deterioration, coupled with the perceived benign prognosis of the claudicant limb, led to the recommendation of conservative management at initial diagnosis as is discussed in further detail in section 2.7.

An overview of the current recommended management guidelines for the patient with IC is presented in section 2.7, highlighting the clinical implications which have influenced the need of this research.

2.7 Management of the patient with intermittent claudication

Management of the patient presenting with IC is guided by international bodies which include the TASC group, ACC / AHA, GVG writing group and ESVS (V. Aboyans et al., 2018; M. S. Conte et al., 2019; Gerhard-Herman et al., 2017; Norgren et al., 2007). Overall, there is a general consensus that when a patient presents with IC, due to the low risk of limb-threatening ischaemia, the primary focus is management of the systemic impact of atherosclerosis and symptom improvement. As discussed in further detail in section 2.7.1, this is achieved by a conservative medical approach through risk factor management and lifestyle changes, aiming

to reduce risk of possible subsequent cardiovascular events (Bevan & White Solaru, 2020). On the other hand, guidelines for revascularisation in IC are less well defined and intervention is generally not recommended as an initial approach but used in cases of failure of symptom improvement or in case of disabling symptoms (Gerhard-Herman et al., 2017) as discussed in detail in section 2.7.2. However, in individuals whose disease progresses rapidly, this approach may result in delayed revascularisation, leading to deterioration to CLTI with a significant increased risk of morbidity and mortality (Anand et al., 2018).

2.7.1 Conservative management for IC

Evidence of high risk of MACE (major adverse cardiovascular events) and low risk to the lower limb has influenced management guidelines to recommend risk factor management as first line treatment for this group of patients. An abundance of literature (V. Aboyans et al., 2018; Mc Grae McDermott et al., 2002; Rooke et al., 2012; Y. Zhang et al., 2016) has provided evidence identifying modifiable risk factors associated with atherosclerosis and its progression which include diabetes mellitus, smoking, hypertension, obesity and hyperlipidaemia. Each identified risk factor and its impact on PAD is individually discussed in section 2.8. Medical management therefore includes lipid lowering drugs, blood pressure control and antiplatelet agents which have all been shown to decrease the risk of adverse cardiovascular events (Gerhard-Herman et al., 2017; Hess et al., 2017) and improve long-term outcomes (Malgor et al., 2015; Thomas Manapurathe et al., 2017). As an adjunct to medical therapy, conservative management includes lifestyle modifications which have also shown evidence of improving outcomes as discussed in section 2.7.1.1.

2.7.1.1 Life style modifications

Functional status and quality of life are known to be improved by supervised exercise and smoking cessation and are an important component of conservative management for patients with IC (V. Aboyans et al., 2018). Smoking cessation has been reported to significantly improve symptoms (Armstrong et al., 2014; Kalbaugh et al., 2018; Quick & Cotton, 1982) and supervised exercise therapy (Wisloff et al., 2007) has been found to be effective in improving symptoms when combined with medical therapy (Fakhry et al., 2018; Konik et al., 2016).

Smoking cessation

The role of smoking as a risk factor of PAD and IC has been widely recognised and smoking cessation has in fact been shown to significantly reduce the progression and mortality risk in patients with PAD (Greenhalgh, 2008). However, while the benefits related to smoking cessation programs have been emphasized (M. S. Conte et al., 2019), the most recent report on global targets to reduce tobacco use indicates that patient uptake of dedicated cessation programs is very low across several countries, including Malta (World Health Organization, 2019).

In recent years there has been an increase in the use of E-cigarettes to aid smoking cessation but they are still controversial with regards to cardiovascular disease (CVD) risk (Buchanan et al., 2020). Whilst an undoubtedly beneficial reduction in toxic elements within tobacco smoke is demonstrated, animal models of nicotine exposure still display CVD effects with increased atherosclerotic plaques (J. Stewart et al., 2017). Long-term data to determine the effect upon humans is still unavailable (Buchanan et al., 2020).

Exercise Therapy

Supervised exercise therapy [SET] has been shown to significantly improve claudication symptoms when used as an adjunct to medical therapy, compared to patients treated with medical therapy only (Gardner et al., 2011; Lane et al., 2014). Studies comparing SET and revascularisation however, report mixed results. Similar outcomes in terms of improved symptoms were reported in studies comparing SET to endovascular surgery but the benefit lasted less than 6 months and without improvement in perfusion measured by ABPI (J. Perkins et al., 2011; Wilson, 2010). Similar outcomes in terms of QOL between revascularisation and SET were reported in a Cochrane systematic review but better outcomes were reported when the two treatment modalities were combined (Fakhry et al., 2018). Two RCTs, the MIMIC (Greenhalgh, 2008) and the OBACT studies (Nylaende et al., 2007), found that exercise and endovascular revascularisation together were superior to exercise training alone. Notably in these studies, interventions were limited to aortoiliac and femoropopliteal lesions. Another RCT (the CLEVER study) (Murphy et al., 2015) investigating exercise against endoluminal revascularisation showed improved peak walking time in the supervised exercise group but better improvement in quality of life in the interventional group.

The association between haemodynamics and physical limitation is not clear since some undergo surgery but symptoms improve slightly while non-invasive therapies have been shown to improve walking time without significant haemodynamic improvement. Although there may be issues of calcification which may have masked perfusion improvement, it is known that impaired metabolic activity within the muscles plays an important role in impaired exercise capacity but not with local perfusion (J. Perkins et al., 2011). It seems therefore that while they are linked, one is not entirely dependent on the other. Improvement in phosphocreatinine recovery following percutaneous intervention has been suggested but it is still unclear (Norgren et al., 2007).

Overall there is considerable evidence supporting the administration of SET as an adjunct to medical therapy or revascularisation, although evidence related to the efficacy of unsupervised exercise as an effective therapy is insufficient (Bendermacher et al., 2006). The use of monitored home-based exercise has been suggested in a small study (Gardner et al., 2011) but efficacy is less than when SET is administered. The difference in efficacy between supervised and unsupervised exercise has been attributed to presence of co-morbidity in 34% of patients with IC which impedes them from walking while another 30% refuse to walk. The lack of specific advice and supervision also hinders the efficacy of exercise therapy (Bartelink et al., 2004).

Therefore, in clinical practices where supervised exercise programs are not available, such as Malta, patients only receive oral advice to increase their walking activity which has been shown to have limited benefit (Bendermacher et al., 2006; Taylor, 2009). Additionally, a local study investigating content in referral tickets written by GPs demonstrated that only 2% had written that they had advised exercise to the patient (Chetcuti et al., 2009). Under-treatment of patients with IC in Primary care is evidenced not only in Malta, but worldwide (V. Aboyans et al., 2018; Argyriou et al., 2013; Norgren et al., 2007).

Despite optimal conservative management, according to the literature, 25% of the patients fail to improve and up to 3% deteriorate to CLI within 5 years (M. S. Conte et al., 2015). International clinical recommendations state that when patients do not respond to conservative treatment and IC is limiting their lifestyle, revascularisation may be considered (Giannopoulos et al., 2020; Jaff et al., 2015).

2.7.2 Revascularisation for IC

There are multiple strategies for revascularisation techniques for IC, including open surgery (surgical bypass), endovascular techniques (angioplasty with or without stenting) and atherectomy or a combination of endovascular and open strategies often referred to as hybrid procedures (Giannopoulos et al., 2020). Compared with lower limb bypass surgery, endovascular interventions have been associated with lower morbidity (K. Cassar et al., 2003; Sachs et al., 2011) but a higher risk of restenosis (Ramkumar et al., 2019) while bypass surgery has a higher risk of perioperative complications but better patency rates (Alshaikh et al., 2019).

Following review of the clinical guidelines (V. Aboyans et al., 2018; M. S. Conte et al., 2019; Gerhard-Herman et al., 2017; Norgren et al., 2007), indications for revascularization in patients with IC are unclear. The clinical decision on whether to revascularise a patient presenting with IC and the technique of choice, is highly variable and depends on several factors, including patient characteristics, anatomic location and extent of arterial disease, symptom severity as perceived by the patient, requirement for possible repeat revascularisation in the future, availability of conduit and patient and physician preferences (Bevan & White Solaru, 2020; M. S. Conte et al., 2015; Hess et al., 2017). The reason for clinical variability and vague indications in the guidelines is because the evidence related to revascularisation in a patient presenting with IC is unclear (Hess et al., 2017).

There are several randomized controlled trials (Fakhry et al., 2018; H. Lindgren et al., 2017; J. Nordanstig et al., 2016; J. Nordanstig et al., 2014) suggesting that revascularisation in IC patients improves quality of life. A meta analysis of randomized controlled trials (Pandey et al., 2017) further corroborated this evidence while stating that endovascular revascularisation is beneficial provided that exercise is also applied as an adjunct treatment. In contrast, in an observational study of patients with IC referred to vascular specialists, Golledge et al (Golledge et al., 2018) concluded that early revascularisation was associated with amputation when compared to those who had initial conservative management. However, the patients who underwent early intervention in their study had worse PAD at recruitment with significantly lower ABPI, had higher smoking rates and lower eGFR. These factors may have had an impact on their results and need to be taken in consideration. Similarly, a recent study (Gunnarsson et al., 2020) of 8-year follow-up of patients with IC undergoing infrainguinal invasive treatment reported high mortality of >40% within 8 years. However, up to 72.7% of the cohort had an

ABPI <0.5 at recruitment as previously published (H. Lindgren et al., 2014). An ABPI <0.5 is indicative of subsequent high risk of cardiovascular and cerebrovascular events (V. Aboyans et al., 2018; Hajibandeh et al., 2017), it is therefore not clear whether the increased morbidity in their study was due to the infrainguinal intervention. A Cochrane systematic review (Fakhry et al., 2018) investigating endovascular revascularisation versus conservative management for patients with IC concluded that the combination of endovascular management, exercise and medical management yielded better results in functional activity and QOL scores compared to conservative treatment alone.

There therefore appears to be conflicting evidence and clinical uncertainty exists whether optimal conservative management with or without revascularisation are better (Malgor et al., 2015). Even after the clinical decision of revascularisation as a management approach, further uncertainty exists related to the most beneficial type of procedure (Bevan & White Solaru, 2020).

The International symposium in Charing Cross, where experts from a variety of disciplines discussed the latest updated TASC IIb guidelines [https://www.cxsymposium.com] pointed out that evidence related to revascularisation in IC is still lacking in meaningful grade A data and the classification of lesions indicated for surgery does not predict symptoms, does not predict ABPI and does not predict outcome. It was concluded that further evidence related to the treatment of the individual patient with IC, rather than a consensus based on low grade evidence, is required to be able to identify who are those patients who would benefit from revascularisation. The need for further research which assessed haemodynamic analysis and the associated outcomes in this group of patients was highlighted underpinning the study design in the research presented in this thesis.

Non-invasive testing of PAD, such as ABPI and TBPI (Toe-brachial pressure index) has received significant interest within the medical field (Chisalita et al., 2020) and a large body of literature has developed establishing the ability of tests to quantitatively document disease progression that correlates directly with increasing severity in the arterial network being examined (Nicoloff et al., 2002; Salaun et al., 2019). Additionally, a relationship between severity of disease measured by non-invasive tests and subsequent prognosis has been suggested, indicating that quantitative measures of PAD are associated with severity of the systemic atherosclerotic process (V. Aboyans et al., 2018).

Due to the assumed benign course of IC discussed in section 2.6 in this thesis and limited evidence available to predict outcomes and to identify patients who would benefit from revascularisation, to date, recommended initial management of the patient with IC is conservative management (Bevan & White Solaru, 2020). The latest reports by the European Society for Vascular medicine (Wanhainen et al., 2019) state that the available classifications of PAD are incomplete and there is a need to categorise patients with a high risk of significant deterioration to CLI and to identify those whose prognosis would improve with revascularisation. The only available evidence in published guidelines up till now indicate that systolic toe pressure below 30mmHg warrants revascularisation, while the rest (i.e. those who have STP >30mmHg) should be treated conservatively (Constans et al., 2018).

This approach may however lead to delayed revascularisation in patients with IC who are more likely to progress to CLI. The implications in these patients are significant because passage of time during tentative conservative management may result in the loss of opportunity for revascularisation due to deterioration of the patient's clinical condition (B. Sigvant et al., 2016) and consequent increase in surgical risk (Fridh et al., 2017). In addition, rest pain may deteriorate to tissue loss and gangrene with subsequent need for minor amputations which in turn increases the risks of non healing and the need for major amputation with its associated significant mortality risk (Anand et al., 2018). In patients who progress rapidly to CLTI despite optimal conservative management, the opportunity for less invasive interventions may be lost (Fridh et al., 2017; Wolosker et al., 2003) and more extensive and risky invasive interventions may be required to save the limb (M. S. Conte et al., 2019). The involvement of small calibre arteries, longer atherosclerotic occlusions and multilevel disease contribute to the challenges in revascularisation interventions in patients with CLTI compared to those with IC (M. S. Conte et al., 2019; Giannopoulos et al., 2020). Furthermore, once a patient deteriorates from IC to CLTI, their mortality risk increases 3 fold, the chance of successful revascularisation decreases and the risk of amputation increases 200 fold (Anand et al., 2018). These factors highlight the clinical implications of tentative conservative management approach in those patients who deteriorate rapidly to CLTI highlighting the need for further research to identify these patients at initial stages.

On the other hand, due to the current lack of sufficient evidence to identify who is most likely to benefit from intervention, physician decision to treat IC by revascularisation is mostly patient oriented, with quality of life measures being used as treatment outcomes and

management is therefore aimed at relieving symptoms (M. S. Conte et al., 2015). Clinical ambiguity in management approach for patients with IC has been shown to lead to significant variation in the choice of management (Birkmeyer et al., 2013; Soden et al., 2017) since the decision for invasive intervention is highly dependent on the patient's perception of symptom discomfort (Jaff et al., 2015). While patient-centred outcomes have been found to be beneficial to the patient (Lokin et al., 2015), it is thought that they may not always reflect disease severity (Devine et al., 2016) and revascularisation may be the result of the symptom being judged to be *'too severe'* than it really is with the assumption that the procedure *'does not harm the patient'* (Sterpetti, 2012). Decisions about intervention are also dependent on clinician and institutional factors (Malgor et al., 2015). Clinicians with a very heavy workload and limited resources are less likely to offer interventional options to patients with IC. On the other hand, in institutions where the number of vascular clinicians is high in relation to the population, more opportunities may be available to offer IC patients interventional options. The workload of interventional radiologists may also determine timing of treating patients with IC. The vagueness of current guidelines (Bevan & White Solaru, 2020) result in low prioritisation of interventional treatment for IC patients and failure in some institutions to allocate appropriate resources for what is perceived to be a relatively benign condition. Thus it has been recognized that efforts should be directed at providing evidence in areas of clinical uncertainty and where high variation in management exists (Soden et al., 2017).

The definition of '*evidence-based medicine'* by Sackett (Sackett et al., 1996), stating that the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients, highlights the need for further insight in this field. Data on specific individual patient characteristics which can help predict the progress of symptomatic PAD to CLI are currently lacking (B. Sigvant et al., 2016). Further knowledge related to the progression of PAD in relation to the individual patient characteristics is required to help in the identification of those who are more likely to deteriorate to develop CLI and may support physician's decision for early intervention.

For patients with CLI, the clinical decision for revascularisation is supported by the use of available clinical predictive algorithms which help stratify patients according to their predicted cardiovascular (Bertges et al., 2010; Cohn & Giese, 2016) or amputation risk (Huang et al., 2019; Sanz et al., 2016) if they undergo revascularisation. For example, the CART (classification and regression tree) risk stratification model (Huang et al., 2019) was developed

for healthcare professionals to use in an easy way upon admission using readily available data from clinical records to predict risk of amputation in CLI patients following endovascular revascularisation. Another model (Kodama, Meecham & Popplewell et al., 2018), the Global Anatomic Staging System (GLASS) predicts immediate technical failure and clinical outcomes in patients with CLI undergoing infra-inguinal endovascular revascularisation using the angiographic pattern of the disease.

Predictive clinical algorithms identify the combination of known independent predictors such as presence of diabetes, hypertension, ischaemic heart disease and smoking, to determine whether a patient has a low, medium or high risk of morbidity. Clinical predictive algorithms provide clarification of the patient's risk status, allowing for better informed clinical decision making, tailoring management plans for the individual patient and allow for better informed patient consent (Stoia et al., 2018). From a socio-economic point of view, knowledge of the the patient's predicted risk of deterioration reduces the chances of delay in treatment, reduces over testing and over-treatment, reduces treatment costs while improving efficiency of the healthcare system (Stoia et al., 2018). While several clinical algorithms exist to estimate the predicted risk related to revascularisation in patients with CLTI, to date there are none designed for predicting deterioration in patients with IC. The lack of evidence in identifying independent predictors of deterioration in patients with IC makes it difficult to estimate the predicted risk for the individual patient. Knowledge of an IC patient's predictive risk of deterioration may change the current approach of conservative management for all patients at initial diagnosis to a more individualised approach, possibly considering early revascularisation in those identified to be at high risk of developing CLI.

This gap in knowledge identified following review of literature in this thesis justified the need for the research presented in chapters 4, 6 and 7. The paucity of adequate scientific data to identify the best management approach for the individual patient contributes to clinical uncertainty (Beresford, 1991; Sommers & Launer, 2014). Uncertainty in medical practice has been extensively discussed in the literature due to its influence on clinicians' decision to initiate definitive treatment strategy (Beresford, 1991; Djulbegovic et al., 2011; Evans & Trotter, 2009; Sommers & Launer, 2014). Thus, clinical uncertainty can potentially contribute to delay in treatment, over-testing or over-treatment (Green et al., 2008). The uncertainty surrounding management choices for the patient with IC and the clinical implications of possible delayed treatment in those who are at high risk of deterioration justify the need for further insight in the

patient factors associated with disease progression leading to possible identification of those who are more likely to benefit from early revascularisation.

Knowledge of the risk factors and their association with IC is important for a better understanding of the management and progression of this condition. Knowledge gained from this review helped to set the groundwork for the design of the main study within this thesis.

2.8 Risk factors of progression of PAD in IC

Before embarking on the review of literature related to the risk factors of IC, it is important to note that the strongest evidence demonstrating a relationship between recognised risk factors and PAD are derived from epidemiological studies involving measurement of risk factors at baseline (M. H. Criqui & Aboyans, 2015). To define a variable as a risk factor, it needs to show evidence of altering the course of the disease when that variable is altered (Norgren et al., 2007), as for example has been shown with smoking cessation and PAD progression (Greenhalgh, 2008; J. T. Lu & Creager, 2004; I. Smith et al., 1996). Therefore, for most of the risk factors, causation cannot be concluded as it is not known from these studies whether PAD preceded the risk factor or vice versa (M. H. Criqui & Aboyans, 2015). Nevertheless, in concordance with the literature in general, the various factors associated with PAD discussed in this section and the rest of the thesis are referred to as risk factors.

Since the most common cause of PAD is atherosclerosis, the epidemiology and clinical consequences of PAD are closely associated with classic atherosclerosis risk factors identified for other arterial beds (Althouse et al., 2014; F. G. R. Fowkes et al., 2013; Song et al., 2019). An extensive review of the literature by Criqui et al (M. H. Criqui & Aboyans, 2015) and a systematic review by Song et al (Song et al., 2019) identified the important risk factors for IC drawing on data from several studies worldwide, including those published from high and low income countries. The major identified risk factors were previous history of CVD, age, smoking, diabetes, hypertension, hyperlipidaemia and C-reactive protein (figure 2.4). Despite extensive research, data on significant independent predictors associated with PAD progression are relatively sparse (M. H. Criqui & Aboyans, 2015) and are discussed in the following sections.

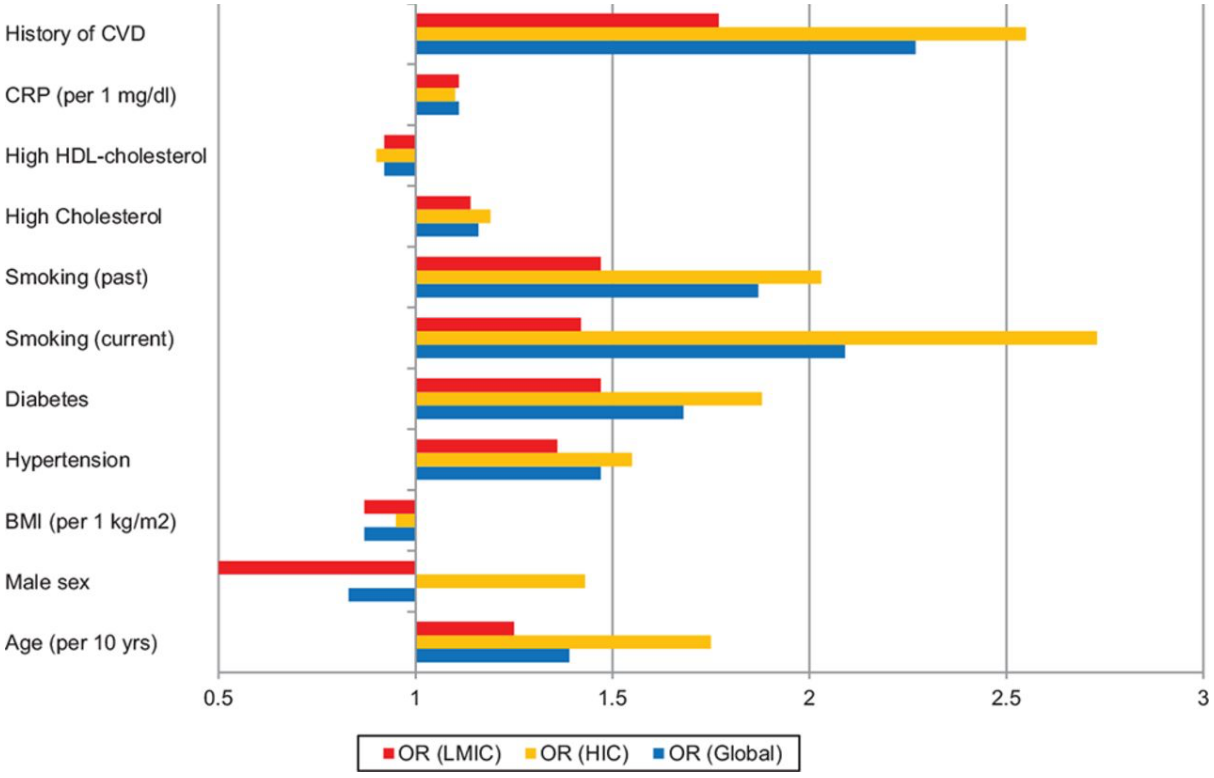


Figure 2.4 Approximate range of odds ratios for risk factors in IC (Criqui & Aboyans, 2015)

2.8.1 Smoking

The association of cigarette smoking with IC has long been recognized and early publications from the Framingham Study have provided significant evidence (W. B. Kannel & Shurtleff, 1973; J. M. Murabito et al., 1997) demonstrating that IC is three times more common among smokers than non smokers (Gordon & Kannel, 1972). Epidemiological studies have suggested that smoking is a strong risk factor for the development of PAD and is 2 to 3 times more likely to cause lower extremity artery disease than coronary artery disease (M. H. Criqui & Aboyans, 2015; Price et al., 1999). Furthermore, epidemiological evidence from large studies (Bowlin et al., 1994; W. Kannel & McGee, 1985; W. T. Meijer et al., 1998; F. Smith et al., 1998; G. D. Smith et al., 1990) suggests that the risk of developing lower extremity PAD is increased 2 to 7 fold by smoking, while the risk of developing IC is 3 to 10 fold. The rate of major amputation in patients with IC was in fact reported to be 6-11% in patients who smoked, compared with no major amputations in non-smoking claudicants (Dormandy & Rutherford, 2000) while those who continue to smoke have a 5-year mortality rate of 40 to 50% (W. Kannel & McGee, 1985). A more recent systematic review (Song et al., 2019) concluded that the odds ratio for current smokers in developing PAD was 2.83, increasing to 3.43 among high income countries.

Previous studies have also shown that the risk of developing PAD increases with increasing number of cigarettes smoked per day and number of years smoked (J. T. Lu & Creager, 2004; Powell et al., 1997). In an early study, Cronenwett et al (1984) have shown that patients with IC who smoked 40 pack-years (20 cigarettes smoked every day for one year) or more required reconstructive vascular surgery more frequently by at least 3 fold than those who smoked less (Cronenwett et al., 1984).

Although studies vary in the measurement of smoking, with some using categorical assessment of current, past, or never while others utilise historical measures such as pack-years, there is an overall agreement that when compared to non-smoking, current smoking has been shown to at least double the risk of developing PAD, with some indicating up to 4 times the risk (Joosten et al., 2012; M. H. Criqui & Aboyans, 2015)

Smoking is highly prevalent among the Maltese population where an estimated 21.5% of the Maltese adult population are smokers, which is among the highest in Europe (WHO, 2012). Smoking is associated with increased risk of development of PAD which is further increased with the concomitant influence of diabetes (V. Aboyans et al., 2006; Kalbaugh et al., 2018; Rooke et al., 2011), also an important risk factor and highly prevalent among the Maltese population (Cuschieri, 2020).

2.8.2 Diabetes Mellitus

Diabetes mellitus is a known major known cardiovascular risk factor and increases the risk of PAD development by 3-4 times (V. Aboyans et al., 2018; S. M. Conte & Vale, 2018; McDermott et al., 2004; E. Selvin et al., 2006; Thiruvoipati et al., 2015). Evidence indicates that for every 1% increase in HbA1c, the risk for developing PAD increases by 26% (E. Selvin et al., 2006). The duration of diabetes mellitus, glycated-haemoglobin levels and use of insulin are significantly associated with worsening PAD (Althouse et al., 2014; Kallio et al., 2003; Tseng, 2003). Additionally, individuals with PAD and diabetes were 5 times more likely to have an amputation when compared with individuals without diabetes (Jude et al., 2001). The characterised increased atherosclerotic burden is due to mechanisms of irregularities within the vessel wall, blood cells and blood rheology. Endothelial cell dysfunction, promotion of vascular inflammation, abnormalities in smooth muscle cells, platelets and haemostatic factors, increase with duration of diabetes and worsening blood glucose control (Kanter & Bornfeldt,

2013; Thiruvoipati et al., 2015). The decreased nitric oxide bioavailability in diabetes results in a cascade of events of vascular smooth muscle cell migration and proliferation with platelet activation. Diabetes also leads to a hypercoagulable state with an elevation in blood viscosity and fibrinogen which have been associated with abnormal ABPI (McDermott et al., 2004).

Despite the dramatic evidence associating diabetes with PAD, there are few studies that have specifically investigated diabetes in relation to IC (Lozano et al., 2014). An investigation of temporal trends of diabetes prevalence among patients with IC in the Framingham study (J. M. Murabito et al., 2005) reported a rise from 2% to 25% between 1969 and 1999. The authors also estimated that symptomatic PAD was twice as common among persons living with diabetes than among individuals without diabetes. Additionally, in a cross-sectional analysis of 3629 patients, diabetes mellitus was found to be an independent risk factor for IC (Wang et al., 2005) following multivariate analysis.

Diabetes is also associated with disease progression among IC patients and earlier reports indicate that people living with diabetes and IC have an overall amputation risk of 20% (Reiber et al., 1992) and risk of mortality is 5 times more than non-diabetic controls (Jude et al., 2001). Diabetes has been shown to affect lower extremity arteries both by promoting atherosclerotic occlusive disease and by causing stiffening of the arterial wall (Edmonds et al., 1982; Everhart et al., 1988). In diabetes, the changes occur predominantly in the distal arteries (Haltmayer et al., 2001), which is associated with a higher risk of amputation and a decreased chance of successful revascularisation (Lauterbach et al., 2005). Since diabetes has a greater effect on smaller vessels, it was not found to be a significant predictor in some studies where progression was measured by ABPI (V. Aboyans et al., 2006; Kennedy et al., 2005). It is not excluded that in some patients arterial stiffening may 'mask' disease progression leading to a normal or elevated ABPI reading (C. Formosa et al., 2013; Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014), emphasizing the importance of using toe-brachial pressure index [TBPI] as a measure of PAD in individuals with diabetes (Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014). This recommendation was acknowledged during the design phase of the research presented in this thesis and TBPI was included as a measure of PAD for all participants.

2.8.3 Gender

The prevalence and incidence of IC is often reported to be higher in men than in women and male gender is often considered as a risk factor for PAD, but the evidence is unclear in the literature. In the Framingham Study, the annual incidence for all ages combined was 7.1 per 1000 in men and 3.6 per 1000 in women, indicating a male to female ratio of 1.97 (W. Kannel & McGee, 1985). A more marked gender difference was demonstrated in a later study (J. M. Murabito et al., 2002) with a ratio of 2.38 in a prevalence of 1.9% in men and 0.8% in women, while in the Rotterdam study which included 7983 participants, prevalence of IC was more common in men with a ratio of 1.83 (W. T. Meijer et al., 1998). In disagreement, an epidemiological investigation of 20,000 unselected individuals concluded that age-adjusted prevalence of IC did not differ between men and women (Jensen et al., 2003). Similar results of no gender difference in prevalence of IC were reported when using ABPI to define symptomatic PAD (Kennedy et al., 2005). Discrepancies in gender ratio between studies could be due to a more frequent presentation of atypical pain in women which influenced results when questionnaires were used as diagnostic tools (V. Aboyans et al., 2018; M. H. Criqui & Aboyans, 2015). Therefore, while it is commonly perceived that patient-reported IC is more common in men than in women, the distinct difference between genders is not yet established.

2.8.4 Age

Age is a known risk factor for PAD and IC (Song et al., 2019) as explained earlier in section 2.5 where figure 2.2 illustrated how the prevalence of IC increases with increasing age (Norgren et al., 2007). In an unselected population, age was independently associated with incident IC with a risk ratio of 1.7 (St-Pierre et al., 2010). An increasing longevity across the world, including Malta, further increases the burden of this condition on the health systems (Podesta et al., 2019), highlighting the need to place research related to PAD and IC in the forefront.

2.8.5 Hypertension

Hypertension has a significant, independent association with PAD, evidenced in several large population-based studies (M. H. Criqui et al., 2005; Dagenais et al., 1991; F. G. Fowkes et al., 1992; Hooi et al., 2001) and is reported to be a highly prevalent risk factor of IC (V. Aboyans

et al., 2018; M. H. Criqui & Aboyans, 2015; Joosten et al., 2012; W. T. Meijer et al., 2000; J. M. Murabito et al., 1997).

A gender difference was also reported in relation to hypertension as a risk factor for IC in the Framingham study where hypertensive men had a 2.5-fold risk of developing IC and women with hypertension had a 3.9-fold risk (J. M. Murabito et al., 1997). While similar evidence was also shown by the Edinburgh study (F. G. Fowkes et al., 1992; Leng et al., 1996), no association between hypertension and IC was found in the Whitehall study which involved 18,388 men aged between 40 and 64 years. In the Rotterdam study, risk factors for symptomatic PAD were investigated in a cohort of elderly patients, reporting an odds ratio for hypertension of 1.32 (W. T. Meijer et al., 2000). In another large prospective cohort study of men, hypertension was found to be strongly and independently associated with risk of developing IC (Joosten et al., 2012) and hypertension severity was associated with severity of PAD. Similarly, Jelnes et al (Jelnes, Gaardsting, Hougaard Jensen, Baekgaard, Tonnesen, & Schroeder, 1986) reported that progression of IC and deterioration was associated with higher systolic pressure, highlighting the need for risk factor control for disease prevention. Improvement of IC symptoms, in terms of walking distance and ABPI have been in fact reported following the administration of blood pressure lowering medications (Thomas Manapurathe et al., 2017).

2.8.6 Dyslipidaemia

Disorders of lipoprotein metabolism has been associated with cardiovascular diseases in several epidemiological studies (S. M. Conte & Vale, 2018; J. Stewart et al., 2017). The most commonly used lipid measure as a risk factor for PAD is total cholesterol (M. H. Criqui & Aboyans, 2015) although the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol has been found to be a better measure of risk (Natarajan et al., 2003; P. M. Ridker et al., 2001). HDL cholesterol was reported to have a protective effect against symptomatic PAD and low levels were significantly associated with increased risk of cardiovascular events and mortality (Martinez-Aguilar et al., 2017). Evidence of low levels of HDL cholesterol was identified in symptomatic PAD patients in a cross-sectional study (Kasko et al., 2014) indicating an inverse relationship between severity of PAD and levels of HDL cholesterol. However, other measures of cholesterol level have been used in different studies which are also included in this review.

A fasting cholesterol level of more than 7mmol/L^{-1} was associated with a two-fold increase in the incidence of IC (J. M. Murabito et al., 1997). Similarly, the Cardiovascular health study (Kennedy et al., 2005) reported an increased risk of developing PAD by 10% with every 10ml/dL^{-1} in total cholesterol. The association between hypertriglyceridemia and the progression of carotid and coronary atherosclerosis is also well established (Amarenco et al., 2004). However, some large population studies (F. G. Fowkes et al., 1991; J. M. Murabito et al., 2002; A. B. Newman et al., 1993) failed to find an independent relationship between triglycerides and PAD when using multivariate models while others (I. Smith et al., 1996) have shown evidence of its association with disease progression. Additionally, a more recent retrospective study on patients requiring revascularisation (Toth et al., 2019) reported that a triglyceride level of more than 150mg/dL was a significant predictor for the need for revascularisation among patients treated with statins. Discrepancies may be due to different methods of defining PAD, where some studies used questionnaires (F. G. Fowkes et al., 1991; A. B. Newman et al., 1993) and others (Toth et al., 2019) used angiographic analysis.

Another study (Bowlin et al., 1994) found a significant association between non-HDL cholesterol (total cholesterol minus HDL cholesterol) and the incidence of IC among Israeli men but no association was reported between PAD and total cholesterol or HDL cholesterol. Among the different measures of cholesterol levels, Ridker et al (P. M. Ridker et al., 2001) concluded that total cholesterol / HDL cholesterol ratio was the strongest lipid measure associated with symptomatic PAD with a 4-fold increased risk of IC among patients within the lowest quartile.

Overall therefore, HDL cholesterol, total cholesterol and triglycerides appear to be associated with PAD but the latter may not be an independent risk factor. There is also consensus that patients with PAD frequently show typical dyslipidaemia with low HDL cholesterol and high triglycerides.

2.8.7 C-reactive protein

Peripheral arterial disease is associated not only with reduced lumen diameter and chronic lower limb ischaemia but also with diffuse atherosclerosis and co-existing cardiovascular risk factors (Montagnana et al., 2007). Epidemiological evidence suggests that atherosclerosis is accompanied by inflammation which plays an important role in both the initiation and the

progression of atherosclerosis of the carotid, coronary and peripheral arteries (P. M. Ridker et al., 1998). Inflammation has a central role in the clinical progression and pathophysiology of atherosclerosis, initiated by the accumulation of T lymphocytes and monocytes in the subendothelium followed by plaque instability and thrombotic formation (Hansson, 2005; Libby, 2012). Activated platelets also participate in the process by promoting inflammation in the vessel wall and forming the thrombus (S. Massberg et al., 2003; S. Massberg et al., 2002).

While several inflammatory markers, namely ESR, interleukin-6 (IL-6) and C-reactive protein (CRP) have been thought to reflect severity of underlying atherosclerotic disease, only CRP demonstrated an association with carotid intima thickness (van der Meer et al., 2002). In their study the authors assessed a random sample of 1317 participants for levels of CRP, interleukin – 6 and soluble cell adhesion molecules. C-reactive protein demonstrated consistent correlations with severity of atherosclerosis at various measured sites while associations with other markers were less consistent. In agreement, in a prospective observational study, serum CRP demonstrated a significant correlation with baseline ABPI and ABPI at 12-month follow-up where a lower ABPI was associated with higher CRP levels ($p<0.01$) (Vainas et al., 2005).

C-reactive protein is an acute phase protein that is mainly regulated by the cytokine IL-6 and is a sensitive marker for inflammation. High levels of CRP have been reported to be able to predict coronary events in patients with stable or unstable angina and in healthy subjects (P. M. Ridker et al., 2000). Moreover, levels of CRP and IL-6 have been positively correlated with peripheral and coronary disease in selected patient populations, although little information exists on the circulating levels of IL-6 in patients with atherosclerosis of the peripheral arteries (Erren et al., 1999). While it is believed that cytokine-stimulated production of CRP by hepatocytes is responsible for the increase in CRP levels in atherosclerosis, the production of CRP by diseased vascular tissue has also been demonstrated, suggesting that CRP is not only a marker but also actively participates in atherogenesis (Erren et al., 1999; Vainas et al., 2005).

In a prospective cohort study of 144 healthy men (P. M. Ridker et al., 1998), baseline levels of CRP >1.34mg/mL were predictive of subsequent development of IC or need for revascularisation within 5 years. In their study, relative risks of developing IC increased significantly with each increasing quartile of baseline concentration of CRP, with a two-fold increased risk in the highest quartile when compared to the lowest quartile of baseline CRP.

Levels of C-reactive protein can indicate low-grade chronic inflammation, prospectively defining the risk of atherosclerotic complications, including the development of IC, adding to the prognostic value provided by traditional risk factors (Libby, 2012).

2.8.8 Body Mass Index

Body mass index (BMI) is a measure of a person's weight in kilograms divided by the square of the height in meters (kg/m^2) (WHO, 2017). Although it does not measure body fat directly, it is correlated to direct measures of body fat (Wohlfahrt-Veje et al., 2014). It is a readily available and inexpensive method to measure obesity (WHO, 2017). Like more direct measures of body fat, BMI has also been suggested to be a risk factor for cardiovascular diseases (Freedman et al., 2009; Willett et al., 2006), however its identification as a risk factor for IC is controversial in the literature (M. H. Criqui & Aboyans, 2015).

In a large epidemiological study (Bowlin et al., 1994) a significant association between BMI and IC was reported with an estimated odds ratio of 1.24 for incident claudication with every $5Kg/m^2$ difference in BMI. Several other large studies (Allison et al., 2006; Hooi et al., 2001; W. T. Meijer et al., 2000; J. M. Murabito et al., 2002) failed to find a relationship between IC or PAD and obesity. Controversial evidence was also reported in the association between BMI levels and CVD risk. A BMI above 25 was found to be a significant risk factor for CVD but an increased risk for all-cause mortality was also reported for levels below 20 in the same study (Khosravi et al., 2012). There is evidence that higher levels of BMI are a good predictor for cardiovascular disease however there is also good evidence that the risk lies with visceral adiposity and liver fat at all levels of BMI (Després, 2012) which may explain the inconsistent evidence (J. Stewart et al., 2017). Indeed, this led to the recommendations of not only weight reduction as a method of risk management but also for a reduction of waist circumference (Ross et al., 2020).

Following review of the literature it can be concluded that the main risk factors for IC and its progression are diabetes, smoking, hypertension, age, dyslipidaemia and CRP. The identification of important risk factors for IC in this chapter provided groundwork for the design of the data collection process for the main study presented in this thesis. While knowledge of the main risk factors has underpinned the conservative management approach for patients presenting with IC, a challenge remains in identifying which of the risk factors are

markers of a greater risk of deterioration to rest pain or ulceration (Martinez-Aguilar et al., 2017).

2.9 Development of research question

Four key aspects have emerged from the review which have contributed to the development of the theoretical framework and focus of the study (Figure 2.5):

- The knowledge related to the prognosis of IC
- Patient factors
- Current management paradigm for patients with IC
- Diagnostic criteria of IC influence study outcome regarding progression

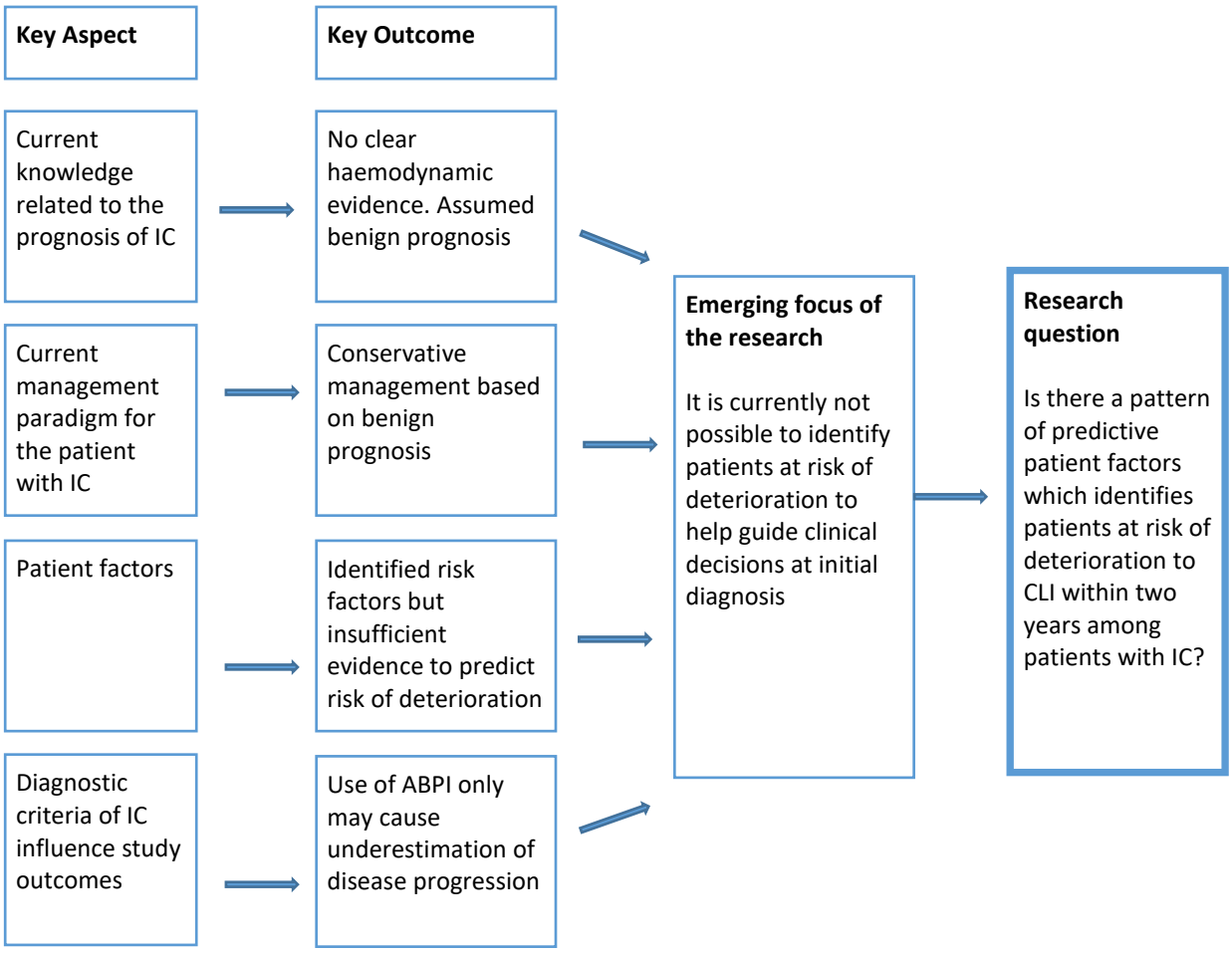


Figure 2.5: Development of the research question

Following review of the literature it is clear that the question of 'who are the patients at risk of deterioration in IC?' cannot be clearly answered. The basic knowledge of the rate of progression and how this may be influenced by specific risk factors in the individual patient is unclear. This has resulted in lack of clear guidance for clinical decision making at early diagnosis.

Therefore, this research aims to identify predictors for the progression of PAD to CLI among patients with IC and use the identified predictive factors to develop a novel patient-specific predictive algorithm to help stratify the predictive risk and define the likely prognosis. Thus, the question remains:

Is there a pattern of predictive patient factors which identifies patients at risk of deterioration to CLI within two years among patients with IC?

In order to reach the aim of this thesis in potentially predicting deterioration to CLI in patients with IC and answering the research question the following objectives were defined:

- *To determine risk factor prevalence and patient characteristics of patients presenting with IC*
- *To determine risk factor prevalence and patient characteristics of patients with IC who deteriorate to CLI within two years*
- *To identify predictive risk factors for deterioration from IC to CLI and the effect of different combinations of risk factors*
- *To develop a novel predictive algorithm for identifying patients at high risk of deteriorating to CLI within two years*

In the context of the planned research, the methodology which underpins the strategy for the study design was explored, described and justified in the chapter 3.

2.10 Summary of evidence

This chapter has highlighted that based on the current available evidence, the progression of PAD among patients with IC is not clear and the assumption of a benign prognosis of the symptomatic lower limb is questionable. Clear evidence to help in the identification of patients who are at a higher risk of progression when they are diagnosed with IC is also lacking, causing a challenge for clinicians to identify patients who would benefit from early revascularisation. Despite the unclear evidence, the current accepted management paradigm at initial diagnosis of IC is conservative management based on the assumed low risk of disease progression, an approach which may result in delayed intervention in those who deteriorate rapidly to develop CLTI. For these individuals, delayed treatment would mean a significant increased risk of morbidity and mortality and poorer prognosis in cases of revascularisation.

The current inability to reliably prospectively identify patients who would have a poor prognosis following conventional medical treatment highlights the need for further research in this field. This knowledge could be used to guide clinical decision making at diagnosis.

The investigation presented in this thesis aimed to fill these gaps in knowledge and was framed within four sequential studies. Firstly, the current knowledge of the progression of PAD among patients with IC in terms of haemodynamic analysis needed to be established since this is still unclear (Study 1). Secondly, the clinical pathway of diagnosis of IC and referral for revascularisation in the local context required investigation to build knowledge in preparation for the main study (Study 2). There was also a need to establish the prognosis of the patient with IC both in terms of symptom severity and in terms of haemodynamic deterioration or improvement since these are still unclear in the literature. Importantly, there was also a need to establish predictive independent risk factors associated with progression to CLI among patients with IC. The established risk factors can be used to develop a predictive algorithm to help stratify the predictive risk and inform clinical decision making regarding early revascularisation at initial diagnosis of IC for the individual patient.

The next chapter presents the philosophical and theoretical framework which provide perspective to the planned research. The specific purpose, aim and objectives of each study are presented in the respective chapters.

CHAPTER THREE

Methodology - Identifying the Philosophical Approach

3.1 Introduction

Following the development of the research question, the approach to the method of investigating it needed to be considered, to ensure that the findings are credible to the field of study. The methodology chosen is concerned with linking the chosen methods to the desired outcomes and hence defines the design of the research. The choice of methodology is justified by the identification of the underlying beliefs of human knowledge and assumptions about reality that the researcher conveys in the research (Crotty, 1998). The chosen methodology describes the procedural framework and underpinning philosophy which guides the research process. This chapter exposes the researcher's philosophical perspective which underpins the methodology applied in the work presented in this thesis.

The theoretical framework of this research relates to the philosophical foundation which guided its development, linking the theoretical context and practical components of the research. The work of this thesis is grounded in the philosophy of Thomas Khun's theory of revolution in science as set out in his seminal book, *The Structure of Scientific Revolutions* (Kuhn, 1962). His philosophy on the growth of science and medical paradigms inspired the development of this research, motivated new ways of thinking, leading to the proposal of new models of treatment approaches to achieve better outcomes in the care of patients with IC. The influence of his ideas is demonstrated by frequent references made to his concepts throughout this chapter which describes the research methodology and philosophical perspective underpinning this work.

3.2 Identifying the methodology and research paradigm

The methodology of a research project describes how the design strategy will proceed and depends on the choice of research paradigm that informs the study (Creswell & Creswell, 2017). A research paradigm is the philosophy, ontology, epistemology and methodology that collectively provide the path of the research. The term 'paradigm' was first used by Thomas Kuhn in his influential monograph 'The structure of Scientific Revolutions (Kuhn, 2012),

where he stated that a paradigm represents the beliefs, values and methods shared by a community of scientists solving problems in their field. In other words, a paradigm is a way of describing the researcher's beliefs about the nature of reality (ontology) and how it is known (epistemology) (Patton, 2002).

Over the years, philosophers have been engaged in a long-standing debate about which is the best paradigm within which to conduct research. The two fundamentally contrasting inquiry paradigms central to this debate are positivism (objectivism), that holds that there is an independent reality and constructionism (phenomenological or interpretive science) that assumes that reality is the product of social processes (Neuman & Kreuger, 2003). These philosophical paradigms have been described as opposites on an epistemological continuum, with varying emerging philosophical positions between them. The contrasting core assumptions between positivism (deduction-objective approach) and constructionism (inductive-subjective approach) and their methodological implications (Burrel & Morgan, 1979) are summarized in figure 3.1. Although it is not universally the case, generally particular paradigms are associated with certain methodologies. Positivist and constructivist ontologies typically underlie quantitative and qualitative methods respectively, bringing fundamentally distinct qualities to the research process.

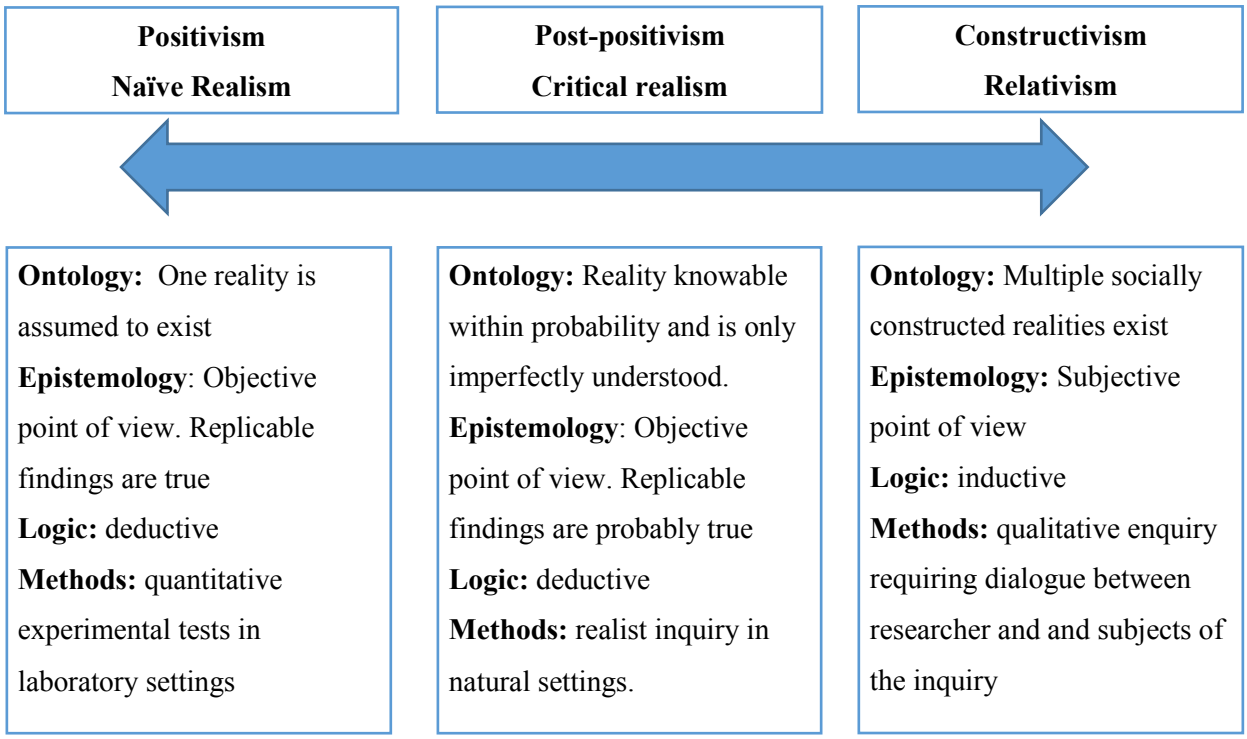


Figure 3.1 Philosophical continuum adapted from Guba and Lincoln (Burrel & Morgan, 1979)

In view of the nature of the research question and the objectives which this investigation aimed to fulfill, this research was framed within the post-positivism philosophical perspective within the critical realist point of view. Further justification and discussion of the core assumptions underlying the critical realist paradigm are presented in the following section.

3.3 The philosophical perspective of the research

In order to be able to identify the paradigm framing a research project, the primary consideration is the research topic, the aims and objectives of the research and the questions posed. This investigation aimed to identify risk factors associated with deterioration to CLI among patients presenting with IC and to apply the findings into developing a predictive model for early identification of these patients. It aimed to test hypotheses for statistical significance, namely the possibility of predicting lower limb prognosis in the individual patient with IC and did not endeavour in generating hypotheses. This work intended to enhance the understanding of patient characteristics in relation to deterioration to CLI, essentially by measuring variables over a period of time, using specific methods and equipment to provide knowledge that has practical implications. Measurement of the variables of interest warranted a quantitative approach to data collection and data analysis while also considering the importance of objectivity. The philosophical underpinnings of this research project is therefore consistent with the core assumptions of the critical realist paradigm which aims to predict results, test a theory, find the strength of associations between variables or investigate a cause and effect relationship within a natural setting. This research aims to provide an understanding of the current theory (of lower limb prognosis) which underpins the management paradigm of the patient with IC, while acknowledging the possibility that theories may be revised.

3.3.1 Positivism, post-positivism and critical realism paradigm

As a paradigm, positivism, also referred to as logical positivism, was established in the Vienna circle between the 1920s and 1930s, and affirms that the only way to establish truth and objective reality is the scientific method (Stadler, 2015). It is based on the belief that the only foundation of true knowledge is science. This approach was criticized by thinkers Karl popper (Popper, 2014) and Thomas Kuhn (Mendie & EJESI, 2014; Reisch, 1991), arguing that human knowledge is unavoidably conjectural and therefore imperfect, and draws from constructionism in forming the understanding and definition of reality (Miller, 2005). Their

criticism led to the emergence of the post-positivism paradigm which, like positivism, is concerned with the objectivity of reality but accepts that not everything is completely knowable (Krauss, 2005) and rejects the purely objective stance adopted by logical positivists. Nevertheless, post-positivism supports the understanding that objectivity can be sought by applying multiple observations and measures. However, while post-positivism also pursues objectivity, it acknowledges that the theories, background knowledge and values of the researcher may influence observations, hence possible effects of biases are recognized (Lindlof & Taylor, 2017).

Post-positivism is largely influenced by the critical realist philosophy (Alvesson & Skoldberg, 2009). Further to the post-positivist point of view, critical realists recognize that observations may involve error and that theories can be adapted. Understanding complex interventions such as medical management paradigms, require a philosophy of science that explains why things work or fail to work (Ellaway et al., 2020). The founder of critical realism, Bhaskar, argues that although researchers may artificially create settings in a laboratory, which he calls 'a closed system', the real world outside the laboratory is open to change and seen by observable events thus called 'an open system' (Cruickshank, 2012). Observations are influenced by the researcher's world view but objectivity can nevertheless be achieved by using multiple measures to gain a clear understanding of what is happening in reality. Indeed, Bhaskar notes that although theories in natural sciences have valid ontological assumptions, they may still be fallible, can be criticized and are open to revision or replacement. This is synonymous with the work presented in this thesis which, as explained in section 3.3, is influenced by the *revolutionary theory* by Thomas Kuhn, and investigates the currently accepted theory of lower limb prognosis in IC, provides evidence indicating the need of a new perspective in the management paradigm of patients with IC, while demonstrating that the previously accepted paradigm needs to be revised.

3.3.2 Methodology applied in critical realist inquiry

Synonymous with the core objectives of this research, the critical realist investigates an inquiry in its natural setting, observes cause and effect relationships and acknowledges the possibility of a fallible theory (Pawson, 2006). The epistemological assumption of the nature of knowledge is associated with the post-positivistic paradigm which states that facts can be tested empirically, can be verified and can be generalized. For the post-positivist, knowledge typically

comprises of hard data and absolute objectivity is approachable but not entirely achievable (Alvesson & Skoldberg, 2009). Additionally, for the critical realist, research seeks to understand the relationship between the context and study outcome, without controlling for contextual variations, as other paradigms would seek to do (Ellaway et al., 2020). In the case of the inquiry presented in this thesis, the relationship between the patient characteristics and lower limb outcomes is being sought within the natural context, where context refers to the real setting of human actions and clinical organization within a real health care scenario. As reflected in this research, where the management paradigm for patients with IC is driven by the common assumption of low risk to the lower limb, a realist inquiry typically seeks common mechanisms which drive a shared structure (management paradigm) (Alvesson & Skoldberg, 2009).

Beyond the underlying ontological and epistemological foundations underpinning this research, influences from the ideas of the revolutionary theory by Thomas Kuhn (Gutting, 1980; Kuhn, 2012) have guided the conceptual framework of this work. For better understanding of this context, Kuhn's theory is explained in the following section, while also describing how the work of this thesis is grounded within his philosophy of scientific advancement and how it inspired the development of this work.

3.4 The revolutionary theory and its influence on the conceptual framework

3.4.1 The revolutionary theory

There were several scientists and philosophers who investigated the development of science, and different theories were proposed to describe models of medical advancements. Before Kuhn, the philosophy of scientific development was the 'scientific method', underpinned by the logical positivism paradigm together with the philosophy that scientific advancement occurred through the addition of new truths to old ones (Mendie & EJESI, 2014). However, Kuhn's version of scientific development (Kuhn, 2012) differed dramatically from the previously accepted version of cumulative progress.

Instead, according to Kuhn (Kuhn, 2012), advancement in science experiences alternating phases of what he calls normal science and revolutions as illustrated in the figure 3.2. During the phase of *normal science,* the medical community share a common intellectual framework,

or paradigm which encompasses theories, equipment, terminology and empirical methods. During this phase predictions of a disease or a medical condition are defined and accepted by the medical community. The next phase, called the *anomaly phase*, is when problems occur within the current paradigm resulting in unresolved issues. As anomalies increase and observations do not concur with predicted outcomes, then the *model crisis* phase is reached and new research leads to a revolutionary phase. This is called the *model revolution* and indicates the period when a previously accepted model is viewed from a different perspective and new paradigms are explored. This leads to a *paradigm shift* where the new proposed paradigm becomes accepted within the community of practitioners. At this stage the revolution disappears and the new paradigm becomes the accepted paradigm and hence *normal science*, essentially returning to the beginning of the theory.

While Kuhn's philosophy and the term 'paradigm shift' was first known through his book over 50 years ago, his influences are still relevant today and are applied in several medical professions (F. Conte et al., 2019; De Angulo & Losada, 2015; Hays, 2019; Wall & Carraro, 2009). He essentially describes how specialists in particular fields are plunged into periods of uncertainty and are driven to engage in solving discrepancies between what is being predicted and what is revealed by observation or experiment, eventually progressing to a paradigm shift and a revolutionary phase (Kuhn, 2012). The following section describes how his concept of a paradigm shift is embedded in the work presented in this thesis, has guided its development and inspired the inception of this work.

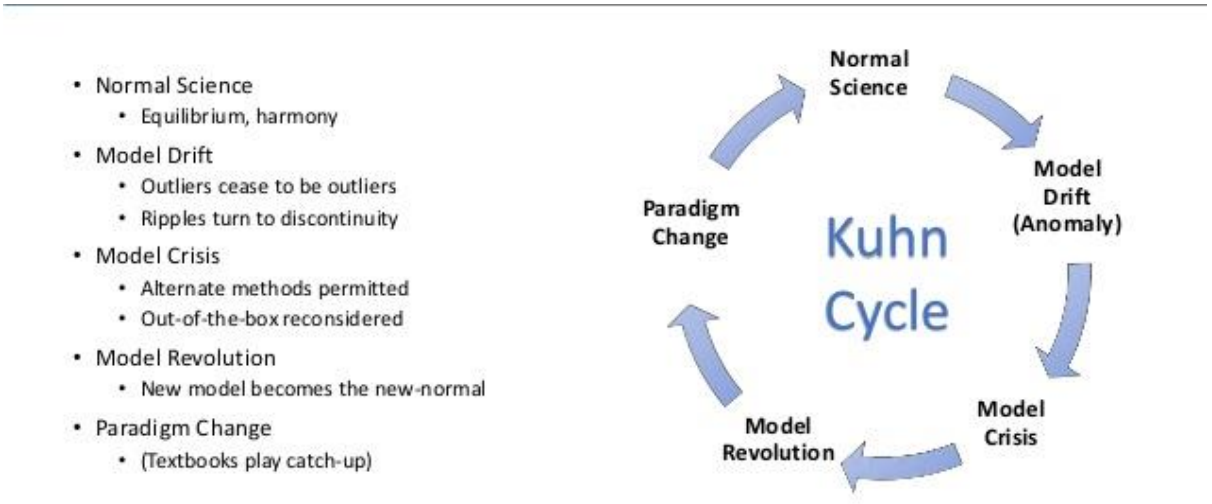


Figure 3.2 The structure of scientific revolutions by Thomas Kuhn (Kuhn, 2012)

3.4.2 The influence of the revolutionary theory on the conceptual framework

While embracing the underpinning of the post-positivism paradigm within a critical realist inquiry in relation to applying objectivity and quantitative measures for data collection, the conceptual framework of this thesis is grounded in the philosophy of Kuhn's concept of advancement in medicine through a paradigm shift. As aptly stated in his seminal book, paradigm shifts arise when the dominant current paradigm under which normal science operates is rendered incompatible with new findings, facilitating the adoption of a new theory or paradigm (Kuhn, 1962).

As described in the review of literature in Chapter two, the currently accepted paradigm (*normal science*) for the patient with IC is the perceived benign prognosis for the lower limb which led to the clinical recommendation of conservative management as first line treatment. However, as described in the first chapter, during the inception of this study, anomalies in this paradigm were perceived during personal clinical experience, where several patients were observed to develop critical limb ischaemia within a short time after initial diagnosis of IC. As described by Kuhn (Kuhn, 2012), while during the *normal science* phase these patients were perceived to be outliers, they were now recognized as a testimony of inconsistency within the accepted paradigm, hence a *model drift* is recognized. According to Kuhn, during this phase practitioners and scientists start to question the fundamental principles and theoretical propositions of the accepted paradigm through research. This guided the design of the first study (Mizzi et al., 2019) (Chapter 4, Study 1 – The progression of PAD in patients with intermittent claudication. A systematic review) which exposed lacunae in knowledge of progression of PAD in these patients, initiating the *model crisis* phase. A discrepancy between the accepted paradigm of a benign prognosis and new observations were further evidenced in the main study which highlighted limb threatening prognosis among patients with IC (studies 3 and 4 presented in Chapters 6 and 7).

The perceived inconsistency of the accepted paradigm motivated new ways of thinking and guided the author into the *model revolution* phase. Based on the findings, Kuhn's philosophy inspired the proposal of new models of treatment approaches to achieve better outcomes in the care of patients with IC, hence proposing a *paradigm shift* in the management of these patients.

3.5 The theoretical framework

The knowledge obtained from the literature review in Chapter Two has influenced the thoughts that the work in this thesis has provoked, providing the theoretical framework of the planned study. The theoretical framework underpins the process defining the specific problem which needs to be investigated and provides the rationale for its focus (Varpio et al., 2020).

In a research framed within a post-positivistic stance, the theoretical framework is constructed before the data collection and typically remains largely unchanged throughout the research process. The theory is turned into a study subject and it unites findings across the research contexts (Varpio et al., 2020). The theoretical framework within the context of an objectivist deductive approach conveys why the current context is a justifiable area of study, shapes the constructs of interest, expresses specific assumptions of the research questions while adapting the approach for analyzing data (Osanloo & Grant, 2016).

Influenced by the works of Thomas Kuhn, the theoretical framework focuses on the investigation of the current management paradigm for patients with IC and the foundations which underpin it, potentially identifying anomalies and hence providing new evidence to support the proposal of a paradigm shift in the management of patients with IC.

Figure 3.3 The theoretical framework

Once the theoretical framework is defined, the methodological approach was identified in order to answer the research question posed in the best possible way.

3.6 Identifying the methodological approach

Different researchers (Rudestam & Newton, 2007) use the terms *quantitative* and *qualitative* in fundamentally different ways, describing quantitative data as including numbers, whereas qualitative data include words, symbols, pictures and other non-numeric data. This is the common understanding of these terms in texts that broadly review research design in the social sciences and in evaluation (Creswell & Creswell, 2017).

This thesis follows the following definitions:

3.6.1 Qualitative approach

The qualitative approach treats the phenomenon in question as a whole system and searches for patterns within it by applying a holistic approach. It reflects an empathic understanding where the researcher sees the structure of the social world through the eyes of the participants (Maltby et al., 2014). Qualitative research tends to focus on exploring, in as much detail as possible, instances or examples which are seen as being interesting or illuminating, and aims to achieve `depth' rather than `breadth' (Maxwell, 2012). Data collected is often non-numeric and it is often collected through focus groups, questionnaires and in-depth interviews aimed at exploring abstract constructs such as attitudes, behaviours, experiences and views. The process of learning knowledge from a qualitative approach is constructive, that is, it generates hypotheses rather than answering them (Merriam & Tisdell, 2015).

3.6.2 Quantitative approach

A quantitative approach to research applies an analytical orientation and while the social phenomena are acknowledged, it reduces facts to simpler models. This approach normally uses deductive logic where researchers start with stating a hypothesis, collect data which requires numeric information in the form of variables and which can be analysed statistically to test the set hypothesis (Creswell & Creswell, 2017).

A study conducted within a post-positivism philosophical stance typically uses quantitative methodology to test a defined hypothesis, applying deduction-objective approach. A critical realist inquiry uses a pragmatic methodological approach which draws on the best methods available to address its problems and questions (Ellaway et al., 2020). In this type of research at the beginning of the investigation, the inquiry statement specifies the variables to be investigated and the relationship between them, defines the theory, leading to hypothesis testing and verification. In this context, data gathering techniques in the investigation presented in this thesis employed a quantitative approach. In this regard techniques used in a quantitative approach are mainly tests, experiments, observations or questionnaires and may include experimental, quasi experimental, causal comparative, correlational and observational designs (Mertens, 2008).

Guiding features of post-positivism that are consistent with this work are the use of research questions and hypotheses to drive method selection, it builds on previous knowledge and seeks answers to inform real world practices while acknowledging the possible effects of bias in the findings (Creswell & Creswell, 2017). In line with the critical realist inquiry, this work aims to provide evidence which helps clinicians predict deterioration in patients with IC in real life scenarios. Therefore, the nature of the research question posed warranted the investigation of the relationship between defined variables of interest by statistical means and to investigate their predictive ability within the clinical setting. These research elements required a quantitative approach to study design and analytic techniques. The knowledge gained within this work was therefore built from objective learning where information was sought by applying quantitative observational methods of inquiry and data collection. The aims and objectives pertaining to each study are presented in the relative chapters.

3.7 Defining the conceptual framework

Following review of the literature pertaining to prognosis of the lower limb in patients with IC, it became clear that further research was required in this field as it underpins the current management paradigm which is hampered by clinical uncertainty. Key aspects which were highlighted and helped in designing the conceptual framework for the planned study were defined in figure 2.5 (Chapter 2). After identifying the philosophical underpinnings of the research, the conceptual framework of the planned research was designed so that the research question could be answered.

In order to achieve the main aim of the study and answer the research question posed, the work of this thesis was developed around a series of four investigations that built sequentially within the critical realist pathway, each with study-specific objectives presented in separate chapters in this thesis. The nature of the research question required quantitative analysis to define relationships between patient characteristics and outcomes after a measured time with the aim of exploring whether patterns of specific variables exist among those who develop CLI.

The first two studies established the groundwork for the main study. Firstly, the current knowledge in the literature related to the progression rate of PAD among patients with IC needed to be explored **(Study 1).** Additionally, the diagnostic methods and referral pathways for the patient with IC in Malta needed to be established **(Study 2)** while also determining the

scale of the problem in the local setting and feasibility for conducting the main investigation. To fulfil the aim of the research in this thesis, the progression of PAD over time among patients diagnosed with IC needed to be established. Patterns of predictive patient factors associated with the development of CLI needed to be investigated to explore the possibility of designing a predictive algorithm of patient factors to identify patients at high risk of deterioration **(Study 3 and study 4)**. The conceptual framework of the planned research was therefore designed and is summarized in figure 3.4

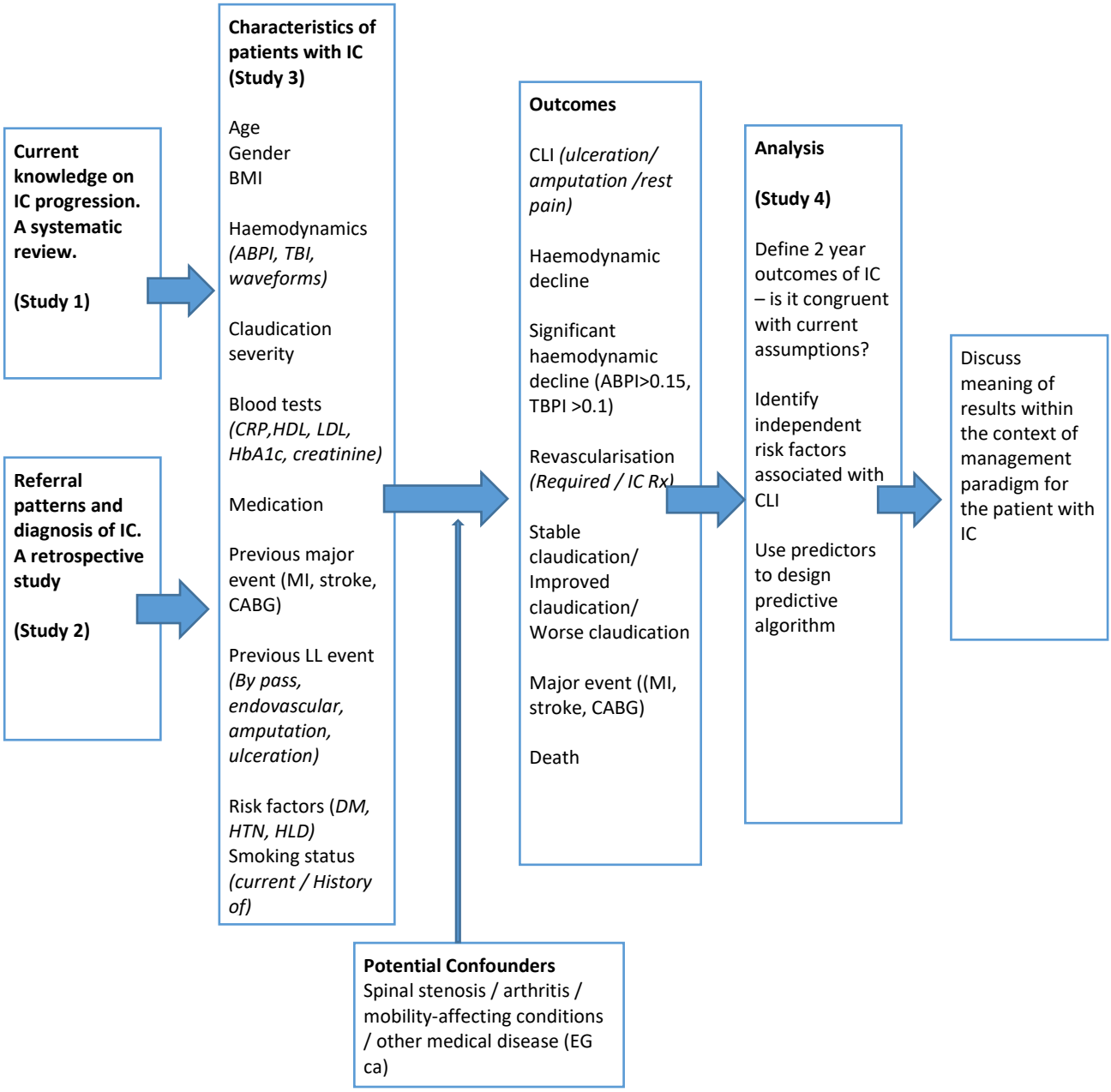


Figure 3.4 The conceptual framework of the planned research

Following identification of the philosophical underpinnings and the conceptual framework of this work, the methodology for data collection was defined.

3.8 Identifying the study design for the main study

The planned research in this thesis aims to identify prognostic factors for deterioration of CLI among patients with IC. As defined by Altman (Altman, 2001), the goals of prognostic studies are:

- To guide clinical decision making, including treatment selection
- To improve understanding of the disease process
- To improve the design and analysis of clinical trials (for example, risk stratification)
- To assist in comparing outcome between treatment groups in non-randomised studies
- To define risk groups based on prognosis
- To predict disease outcome more accurately or parsimoniously

Prognostic research questions are best addressed using cohort study designs (C. Y. Lu, 2009; Blevins & Wallace, 2010). This study design involves identifying a group of patients at the time of their first event or initial diagnosis, collecting baseline data on various patient characteristics which may be associated with the outcome of interest (lower limb event / haemodynamic deterioration or improvement) and following-up the cohort over time to assess which patients develop the outcome (Fineout-Overholt & Melnyk, 2004).

Purpose of the study (Research question)	**Most appropriate study design**
Effectiveness	Controlled trial
Harm	Case control Cohort
Prognosis	Cohort
Aetiology / risk factors	Case control Cohort Cross-sectional survey
Prevalence	Cross-sectional survey
Meaning	Qualitative data collection and analysis

Table 3.1 Identifying the study design. Adapted from (Blevins & Wallace, 2010)

Prognostic studies enhance the understanding of the natural progression of a disease, allow better prediction of disease outcomes and guide the clinical decision making process by facilitating the selection of the treatment options which are most suitable for the patient (Mak & Kum, 2005). Prospective cohort observational longitudinal studies are best suited for investigating the progression of PAD in symptomatic patients because of the facility with which progression of the atherosclerotic lesions can be repeatedly assessed using non-invasive measures, independent of symptoms and without risk or discomfort (Nicoloff et al., 2002). For the main study in this thesis, a prospective cohort observational longitudinal study design was therefore employed and the STROBE statement (Strengthening the reporting of observational studies in epidemiology) was used as a guideline during the study. The STROBE statement (Appendix 2) is a 22-item checklist to enhance reporting of observational studies to facilitate critical appraisal of the study's findings (J. P. Vandenbroucke et al., 2014).

The major challenges of this design include (C. Y. Lu, 2009)

- Selection bias (Eg: systematic differences between study groups when a control group is introduced)
- Inability to control for confounders (Eg: extraneous factors that might be associated with the outcome)
- Bias by differential loss to follow-up (Eg: survival selection bias)

These challenges may have an effect on the validity of the study and are discussed further in section 3.9.

3.8.1 Data analysis

In a realist inquiry, data analysis involves looking for evidence to identify whether any recurring patterns exist which may influence the outcomes of interest. While there are no definitive rules, any post-positivist research process should be open to considerations of alternative explanations such as confounding factors and the method used should be thoroughly documented (Ellaway et al., 2020).

Prognostic variables are often continuous measurements, as in the case of the data collected in this research, such as analysed blood parameters, haemodynamic parameters and patient

characteristics (eg; age, BMI). In cases where such variables are identified as prognostic to the risk of an event then they would be expected to decrease or increase corresponding to the level of risk. According to Altman (Altman & Royston, 2006), categorising participants according to a cut-off point, (that is, converting continuous variables to categorical variables) before analysis would completely discard potentially important information and reduces the ability to detect an association with the outcome of interest. For this reason, for analysis of data in this research, continuous variables were used throughout statistical analysis tests.

Cohort studies can demonstrate causal relationships between variables and outcome and provide the relative risk or probability of developing the outcome of interest in the presence of the identified variable (C. Y. Lu, 2009). In the main study presented in this thesis (Chapters 6 and 7), multinomial logistic regression analysis was applied to evaluate the relative risk of the variables of interest and their relationship with the outcome of patients after two years. Further analysis using the area under receiver operator characteristic (AUROC) was applied to evaluate the predictive value of the proposed predictive model. Further details on the statistical anlysis applied in this work is presented for each study in the respective chapters.

3.9 Validity and reliability

The concept of validity was originally developed within the positivist tradition and abundant literature relating to its complexity has emerged (Heale & Twycross, 2015). Likewise, a concern for validity is held with equal seriousness by practitioners of the interpretive tradition who have claimed their own unique paradigms with corresponding validity criteria (Patton, 2002; Whittemore et al., 2001).

Validity is a construct developed to assess the truth value of inferences made from study findings. The criteria for judging the quality of a research method is derived from the paradigm that drives that method (Mays & Pope, 2000; Morris & Burkett, 2011). Therefore, using quantitative criteria to judge qualitative inquiry has been argued to be inappropriate, resulting in assessments that lack meaning and that are awkward and confusing (Mays & Pope, 2000). In short, the quality of the inferences from a study should be judged by the terms of the paradigm in which the study is situated. For observational studies, both internal and external

validity are important concepts. The important aspects of validity and how they have influenced the design of this research are presented in the next sections.

3.9.1 Internal validity

Internal validity is a term used to describe the strength of the inferences derived from the study (Carlson & Morrison, 2009), i.e. whether the observed outcome is influenced by systematic errors or bias. In observational cohort studies, it is critical to address and minimise the effects of bias and confounding factors as they can be threats to internal validity of the study. Strategies to reduce the risk as defined by (C. Y. Lu, 2009) were applied at the design stage of the main study including following the STROBE statement (J. P. Vandenbroucke et al., 2014) and identification of possible sources of bias.

Selection bias can occur during the recruitment phase of the study since observational cohort studies generally do not employ random selection techniques (J. P. Vandenbroucke, 2004). Since this study aimed to recruit patients with IC referred to the vascular unit in the Maltese national hospital, risks of selection bias were assessed by evaluating referral patterns of patients in a study conducted early in this research (Study 2, Chapter 4). Following results of Study 2, which showed differences in referral patterns between GPs working in primary care, communication was undertaken to encourage and increase referrals of patients who attended primary care clinics complaining of IC by all GPs, reducing effects of differences in GP preference.

Another type of selection bias can occur at recruitment phase when the researcher would have knowledge of the management plan of the patient, influencing selection of participants (J. P. Vandenbroucke, 2004). For example, if patients who are planned to undergo revascularisation would not be recruited, a bias toward selection of healthier patients would occur. To account for this, allocation concealment, where the researcher is blinded of the management of the potential participant should be applied. Allocation concealment was adopted in this research since participants were recruited before they had an appointment with the vascular consultant.

Confounding factors are factors which may be related to the prognostic factor and also have an effect on the outcome (Von Elm et al., 2014). Strategies to reduce confounding at the design phase include primarily to record or measure all potential confounding factors (Hayden et al.,

2013). This was possible because the study was a prospective cohort study and would not have been possible in a retrospective study design. Additionally, no restrictions to a confounder were made in the inclusion criteria (for example some studies restrict gender). In the analytical phase, minimizing confounding bias included avoiding stratifying groups on the basis of characteristics which are potentially confounding. Another strategy which was adopted included applying multinomial logistic model analysis which is a mathematical model that calculates an odds ratio which is controlled for multiple cofounders (Pourhoseingholi et al., 2012). Adequate measurement and recording of important confounding variables and their inclusion in multivariable analysis ensures low risk of bias in a study (Hayden et al., 2013). Important confounding factors for this study included presence of conditions which limited walking (such as arthritic pain, breathlessness), which caused IC other PAD (such as spinal stenos) and which caused mortality (such as malignancy). Residual confounding factors, that is, unmeasured potential confounding variables were acknowledged in the limitation section of each study.

A concept of validity which is key to internal validity in a research study involves the extent to which an instrument measures what it is meant to measure and how accurately (which is a measure of reliability) it can do it (Heale & Twycross, 2015). In this context, validity refers to three categories: Content validity, construct validity and criterion validity which are summarized in table 3.2.

Type of validity	**Description**
Content validity	The extent to which a research instrument accurately measures aspects of a construct.
Construct validity	The extent to which an instrument measures the intended construct
Criterion validity	The extent to which an instrument is related to other instruments that measure the same variables.

Table 3.2 Types of validity adapted from (Heale & Twycross, 2015)

In this thesis, measurement of variables performed by the researcher included haemodynamic analysis (Doppler waveform analysis, ABPI and TBPI) as diagnostic tools of severity of PAD. The validity of these modalities of measurement of blood perfusion to the lower limb were discussed in section 2.4 where following review of the literature it was concluded that for best results, all three measures of perfusion should be used adjunctively. Aspects which may

influence validity of haemodynamic measures included practitioner experience. Being a podiatrist with over 8 years' experience running a vascular assessment clinic minimized the possibility of errors occurring due to inexperience. Additionally, all the recruited participants were also assessed by a vascular surgeon by duplex scanning, therefore confirming diagnosis of PAD. Further to this, a test-re-test reliability test to assess consistency (intra-rater reliability) was also performed on a sample of participants indicating the appropriateness of the haemodynamic measures to be used in the planned research.

Internal validity is a pre-requisite for external validity.

3.9.2 External validity

External validity refers to the degree to which conclusions derived from a study could be sustained for other populations and conditions. Measures to enhance external validity include methods to ensure that the study sample is representative of the study population (Carlson et al., 2009). A method to limit threats to external validity is by avoiding small sample sizes to ensure that the study has adequate power to detect the effects hypothesised in the study. This was calculated and is presented in Chapter 5, section 5.5.1. Another measure to improve external validity included efforts to increase the likelihood of a representative sample by addressing issues of referral patterns identified in Study 2, which encouraged referral of all patients with IC, irrespective of severity, among Primary health care general practitioners. This is explained in further detail in Chapter 4, Study 2.

However, in studies where recruitment was done in a single geographic location, as in the case of the current research where the study was conducted in Malta, external validity could not be verified and would need to be assessed by replicating the study in different populations (Carlson & Morrison, 2009). The STROBE checklist (Appendix 2) was followed to facilitate the assessment of the generalizability of the findings of the study (J. P. Vandenbroucke et al., 2014) if it were to be replicated.

Following the identification of the methodology for the planned research, it was important to ensure that the research protocol employed conformed to the principles of ethical professional practice. Therefore, before embarking on the data collection, ethical approval was sought as

stated by the Declaration of Helsinki (General Assembly of the World Medical Association, 2014) in relation to ethical principles for medical research involving human subjects.

3.10 Ethical Considerations

Although study 1 did not require full ethical approval, this was still sought at the initial stages for the purpose of the planned research. Permissions to access patient databases and medical records were sought and granted by the data protection officer (Health Department, Malta), Head of Surgery (Mater Dei hospital) and Lead consultant vascular surgeon (Vascular unit, Mater Dei hospital). A request (Ethics registration FHS 005/2016) was sent to the University Research Ethics Committee (University of Malta) on 18th January 2016. Approval was granted and received on 21st March, 2016 (Appendix 1). The following topics were taken in consideration.

3.10.1 Initial approach

Patients who were referred to the vascular unit at the national hospital due to IC were given an information sheet (by hand / post or email) providing knowledge about the research prior to being contacted for an appointment for vascular assessment. This gave enough time for the potential participants to read the document and arrive at an informed decision whether they wished to participate. Contact details of the researcher and principal supervisor were provided in case they wished for further information.

3.10.2 Informed consent

For studies 3 and 4, informed consent was obtained from the potential participant who signed a document on the day of the research appointment. Participants were informed once again verbally about the research and any questions were answered at this time. They were informed both in writing and verbally that they could withdraw from the study at any time if they wished.

3.10.3 Confidentiality

For study 2, no personal information was collected and data was anonymized prior to access by the researcher. For studies 3 and 4, all participant identification information was coded and

stored electronically. Hard copies of recorded data and signed consent forms were locked and accessible only to the researcher in accordance with the University of Malta research policy. The processed data will be kept for ten years and destroyed thereafter.

3.11 Conclusion

This chapter has presented the philosophical underpinning and influences on the theoretical and conceptual framework of the planned research. It also provided a justification for the methods employed for data collection and analysis of data which are described in further detail in the relevant sections in each study chapter.

In summary, this research was founded upon four sequential studies which have a post-positivist philosophical underpinning with a critical realist approach. Quantitative methods of data collection and analysis together with a prospective cohort observational longitudinal study design were justified as the best way to answer the research question posed.

The following chapters present the studies employed. Chapter 4 includes the two retrospective studies (Study 1 – Systematic review of progression of PAD in patients with IC and Study 2 – Referral patterns and diagnostic criteria in patients with IC in the local setting). Chapter 5 presents the methods employed for the main studies. Chapter 6 presents Study 3 which provides the cross-sectional data of patients with IC in Malta. The baseline characteristics of the recruited participants were analysed. Chapter 7 presents the 2-year follow-up analysis of data, identification of predictive factors for deterioration to CLI and the development of a predictive algorithm for risk categorisation of patients at initial diagnosis.

CHAPTER FOUR

Retrospective studies: Study 1 and Study 2

This chapter presents two retrospective studies which were conducted at the initial stages of this planned research. Study 1 investigated the current knowledge related to the progression of PAD in patients with IC through a systematic review. Study 2 investigated the referral patterns in patients with IC and assessed the extent of the problem in Malta, providing background knowledge required for the main study.

4.0 Study 1: The progression of symptomatic PAD and the prognosis of patients with IC. A systematic review

This study was published in an international peer reviewed journal (Appendix 3):
Mizzi A, Cassar K, Bowen C and Formosa C. (2019) The progression rate of peripheral arterial disease in patients with intermittent claudication: a systematic review. *J Foot Ankle Res*. 12: 40

4.1 Introduction

The progression of PAD in patients presenting with IC can be diverse, where the majority remain stable, some improve and a small percentage deteriorate to develop CLI (K. Cassar, 2006). As discussed in Chapter Two, the variable progression of the disease makes it difficult to predict the progression risk and rate in individual patients on first presentation, therefore the recommended first-line treatment strategy is conservative treatment since the majority are assumed to have a benign prognosis (Jaff et al., 2015). However, this approach may lead to the possible delay of revascularisation in patients who are more likely to deteriorate to CLI. Knowledge of disease progression rate and identifying those patients with a poor prognosis might help inform a decision for early intervention. In these cases, early intervention may be more favourable since delay may result in the loss of opportunity for less extensive interventional options due to progression of arterial disease and increased surgical risk caused by deterioration of the patient's general condition (Wolosker et al., 2003).

Research related to the prognosis of patients with IC is mainly focused on long-term cardiovascular outcomes, mortality risk and quality of life (Cascini et al., 2020; Hata et al., 2020; Sartipy et al., 2018). As discussed in Chapter Two, prognostic knowledge of the affected limb is limited because the disease progression rate in patients with IC is not clear in the literature and further insight is required. The literature in this area of study has not been evaluated systematically, a systematic review was therefore undertaken to evaluate the current evidence related to the progression rate of PAD in patients with IC.

Systematic reviews identify and synthesise primary research, assess consistency of findings across studies and evaluate the quality of evidence reported (Eden et al., 2011). Within the context of healthcare practices, systematic reviews are encouraged to identify the best available evidence underpinning a treatment strategy. A systematic review supports evidence-based medicine while providing objective criteria to inform decision making in healthcare practice and policy (R. Mallett et al., 2012).

4.2 Aim and objectives of the study

This study aimed to determine the progression rate of PAD in patients with IC by evaluating evidence from identified studies investigating progression of disease.

4.2.1 Objectives

The objectives of the study are:

- To identify and quantify studies that have assessed the temporal progression of PAD in patients presenting with IC reporting haemodynamic measures.

- To evaluate data in relation to study design, participant characteristics and methodology of the studies that report progression of PAD in patients with IC.

4.3 Methodology

A number of methodological components are important when conducting a systematic review, including defining the outcome under review *a priori,* searching for and locating the relevant evidence, applying standardisation in the selection method of included studies and synthesising

the data (Shepperd et al., 2009). In order to ensure consistent, transparent and sound conclusions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Appendix 4) was applied in this study (Moher, Liberati, Tetzlaff, & Altman, 2009).

4.3.1 Eligibility Criteria

As recommended in the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009), explicit declarations of questions being addressed were defined with reference to participants, interventions, comparisons, outcomes and study design (PICOS).

Eligible articles needed to report on the natural history of patients with intermittent claudication as a symptom of PAD, also documenting temporal progression of the disease. Disease progression has been previously suggested to be detectable after 12 months (Walsh et al., 1991), therefore studies were selected if they primarily aimed to investigate the progression of symptomatic arterial disease with at least 1-year follow-up.

Primary endpoints were progression in terms of haemodynamic parameters (expressed as time for defined decrease in ABPI and / or TBPI) and adverse lower limb events (expressed as time to development of ulceration, amputation or gangrene). Secondary endpoints were identification of prognostic factors for the development of adverse lower limb events and for the progression of peripheral arterial disease in patients with IC. In this investigation all study designs were considered, however, prospective cohort studies have the most suitable design to investigate the natural history of events (Tooth et al., 2005).

4.3.2 Data sources and search strategies

A literature search was conducted between 9th and 15th of July, 2018. The search for potentially relevant articles was performed in PubMed and MEDLINE, Cochrane database of systematic reviews, Elsevier (Embase and Sciencedirect), CINAHL, HyDi and Web of Science up to July 2018. Hydi is a one stop search portal provided by the University of Malta that allows the users to perform a single search through all the library's printed and online resources. Reference lists of retrieved full-text articles were also cross-checked and OpenGrey database was searched for any relevant grey literature. The searches were performed without restrictions on

publication date, or publication status. Search results were downloaded into a bibliographic software Refworks (ProQuest LLC).

Limits for the search strategy included studies on humans and English language. The search terms used for this literature search were identified after reading several publications related to the subject area. The keywords and Boolean terms present in the title or abstract, used in this search are presented in the table 4.1. Each search was repeated for each database.

Intermittent Claudication and prognosis
Intermittent Claudication and fate
Intermittent Claudication and natural history
Intermittent claudication and progression
Intermittent claudication and outcome
Symptomatic peripheral arterial disease and Prognosis
Symptomatic peripheral arterial disease and Progression
Symptomatic peripheral arterial disease and natural history
Symptomatic peripheral arterial disease and outcome

Table 4.1 Keywords used for literature search

4.3.4 Study selection and data extraction

Titles and abstracts of studies identified by the search strategy were assessed in terms of relevance and design. The full versions of the articles were retrieved if they fulfilled the inclusion criteria and were reviewed by two investigators independently (SM and CF, both podiatrists and academics). Methodological quality of each trial was assessed systematically with the aid of the Cochrane Vascular guidelines for external referees and The Reporting of Observational Longitudinal Research checklist (Appendix 5). The process was pilot-tested on a selection of studies and refined where required. Disagreement between reviewers was discussed until agreement was reached.

4.3.5 Data items

Data collected included study design, methods, participant characteristics, baseline components reported, PAD and IC diagnostic criteria and trial outcomes defined as decrease in ABPI / TBPI or other haemodynamic parameter. Trial data were extracted and summarised and are presented in table 4.3.

4.3.6 Evaluation of risk of bias and quality of evidence of individual studies

The Reporting of Observational Longitudinal Research checklist was used to evaluate risk of bias in cohort studies (Tooth et al., 2005). Study quality of the studies was evaluated using the Cochrane Collaboration Tool for Assessing Risk of Bias (J. Higgins et al., 2011) and was applied for each important outcome (across domains) within and across studies as summarized in table 4.2.

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias.	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias.	Plausible bias that raises some doubt about the results.	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias.	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

Table 4.2 – Cochrane collaboration interpretation of bias (J. Higgins et al., 2011)

4.4 Results

The initial search yielded a total of 794 potentially relevant papers. After duplicates were removed, 471 records remained of which 404 were excluded based on the content of their titles and abstracts. Fifty-five full text papers were retrieved for review and an additional 12 papers were retrieved from bibliography lists. Following review of the full-text versions by SM and CF, a further 59 papers were excluded while 8 papers fulfilled the inclusion criteria. The reasons were failure to report measurable haemodynamic deterioration, no report on

participants with IC, failure to report temporal progression of PAD and use of same cohort. The PRISMA flow chart and reasons for exclusion are shown in figure 4.1

Due to the heterogeneity of the methods used in reporting haemodynamic deterioration and outcome measures, a narrative synthesis of the 8 included studies was conducted without meta-analysis.

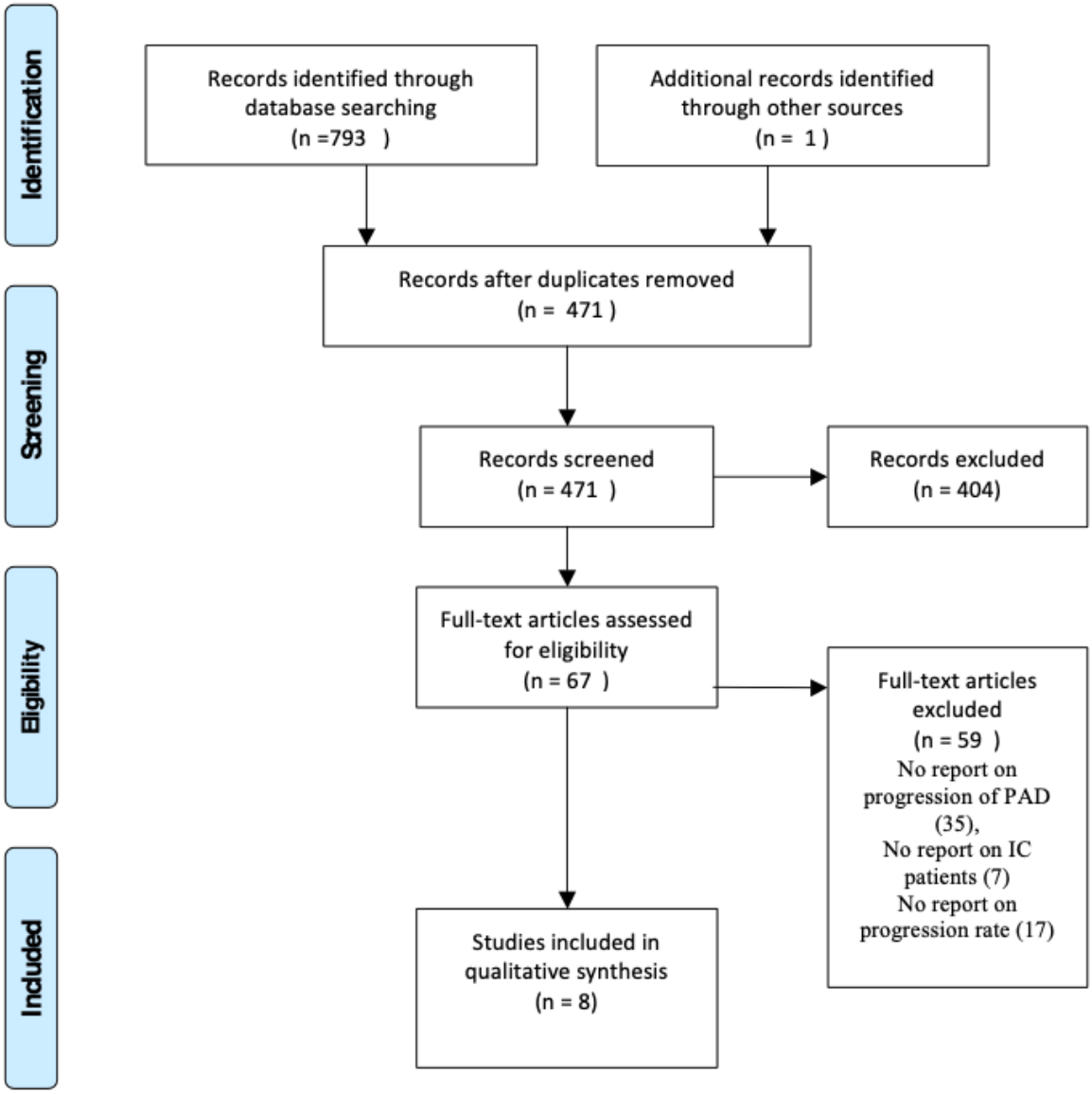


Figure 4.1 PRISMA flow chart

4.4.1 Characteristics of included studies

The characteristics in term of study design, participants included and reported outcomes are discussed in the following sections.

4.4.1.1 Study design and participants

Eight full-text articles met the selection criteria reporting temporal progression of IC (Aquino et al., 2001; Bird et al., 1999; F. Fowkes et al., 1993; Naschitz et al., 1988; F. B. Smith et al., 2003; I. Smith et al., 1996; Walsh et al., 1991; Whyman et al., 1993). Study designs included were 7 prospective cohort studies, and one retrospective cohort study. The number of participants ranged from 38 to 1244, with the largest study recruiting only male participants. All studies included ABPI as a baseline clinical measure of PAD except two studies (Walsh et al., 1991; Whyman et al., 1993) which reported duplex angiography results. Only one study (Bird et al., 1999) included TBPI. Diagnosis of IC as a symptom of PAD, in order to exclude any alternative diagnosis, varied considerably across the studies. Smith et al (F. B. Smith et al., 2003) used the WHO questionnaire, while 5 studies used ABPI <0.9 as a cut-off point and the other studies (Walsh et al., 1991; Whyman et al., 1993) used duplex scan reports. Two studies evaluated walking distance using treadmill tests, one other study included data using the San Diego claudication questionnaire while the rest did not report walking distance. Follow-up period ranged from 1 year to 12 years.

4.4.1.2 Outcome- Haemodynamic deterioration

A decline in ABPI was reported in the prospective cohort study by Smith et al (I. Smith et al., 1996) who investigated the association between smoking and cardiovascular disease in 415 participants with IC for a follow-up period of up to 6 years. The authors reported a decline of 21% of baseline ABPI by >0.14 after 1 year, followed by a decline of 16% and 17% in the second and third years respectively. By the end of the study period 12.5% developed CLI. An ABPI <0.5 and hyper triglyceridaemia were significantly associated with risk of deterioration of ABPI. Diabetes and smoking were not found to be predictive of ABPI deterioration. However, the authors stated that 29% of the participants were lost to follow-up without reporting reasons for this and an additional 26% died during the study and were therefore excluded. This may result in selective survival bias where the authors report data only on the survivors, omitting those who were either lost to follow up or who died and who could have

been more likely to have a more rapid decline in ABPI. Causes of death were also not reported therefore it is not known whether it was due to lower limb deterioration or not. Such a method may underestimate the true deterioration in PAD in patients with IC.

Bird et al (Bird et al., 1999) investigated the natural history of PAD in 423 participants, of whom 177 experienced IC as a symptom. The authors report an overall mean change in ABPI of -0.019 and an overall mean decline in TBPI of -0.013 in their participants but do not report haemodynamic decline in participants with IC. However, a decline of '-1 unit' (one standard deviation derived from z-scores) was associated with having Rose claudication and reflects a change in PAD over time in a given limb. These results however need to be interpreted with caution since in this study those who required revascularisation or who died were excluded from the study. In this way those participants who had more severe disease were possibly excluded resulting in a source of survival selection bias with an underestimation of the quantitative progression of PAD. The authors also acknowledge an element of systematic bias due to arterial calcification which may have masked a decline in ABPI and resulted in underestimation of PAD progression. Additionally, out of the initial number of possible participants, approximately 50% (n=1276) were non-responders. The authors attempted to address possible selective bias by assessing retrospectively obtained baseline data of 77 of the non-responders. They stated that the baseline haemodynamic data was comparable to the study group data.

Smith et al (F. B. Smith et al., 2003) investigated changes in ABPI in 131 participants with IC who were participants in the Edinburgh study with a follow-up of 5 years. The authors reported a decline of 0.04 in ABPI over a period of 5 years in the limb with lower ABPI at baseline and a decline of 0.09 in the limb with higher ABPI at baseline. At baseline the authors used the lower ABPI between the left and right limb as an indication of worse disease in the analysis. The ABPI however may be falsely elevated due to arterial calcification and hence the severity of disease could have been underestimated. Similar to the previous study, participants who did not attend follow-up or who died (approx. 50% of participants) were excluded from the study. The authors acknowledge an element of survival selection bias in their results which may underestimate the deterioration of PAD since the excluded participants were probably those who declined more rapidly. Additionally, the authors did not exclude participants with calcified arteries and an ABPI of 1.5 when calculating the mean, potentially resulting in a false elevation in the mean overall ABPI of the participants.

Walsh et al (Walsh et al., 1991) investigated the progression of PAD in 38 participants with superficial femoral artery (SFA) stenosis, 28 of whom had IC and who were treated conservatively. Patients who were referred for revascularisation were excluded. Diagnosis was based on arteriography and duplex scans and their study cohort was followed up for a mean period of 37 months. In their cohort, 28% demonstrated atherosclerotic progression with worsening of symptoms. This progression was faster in symptomatic patients when compared to those without symptoms (15.6% per year vs 3% per year p=0.006). Additionally, a faster progression rate was observed in patients whose contralateral SFA was occluded (10% per year vs 1.6% per year p=0.04). Furthermore, SFA disease progresses in a way that is synchronous to symptom progression, indicating that worsening of claudication symptoms are indicative of further SFA occlusion. However, this did not necessarily reflect severity of disease across patients. Through multivariate regression analysis, symptom progression and smoking history were found to be predictive factors for SFA stenosis progression. The authors concluded that among those whose SFA stenosis progressed to occlusion, the average progression rate was 12% per year with the highest rate of progression reported as 30% per year. The authors suggested that knowledge of the predicted rate of progression can help in decision making related to follow-up or prophylactic endovascular treatment of SFA stenosis. In this study the authors did not use ABPI or TBPI as a measure of PAD and therefore results cannot be compared to other studies reviewed in this chapter. The authors acknowledge the possibility of type II errors in this study due to the limited number of participants.

Fowkes et al (F. Fowkes et al., 1993) investigated the progression of PAD in a cohort of 617 claudicants with the aim of identifying haemostatic factors as predictors of cardiovascular disease. The ABPI at baseline and after one year was measured. Critical limb ischaemia developed in 4.8% of the study cohort and progression of PAD expressed as a mean decline of -0.01 in ABPI per year was found. At recruitment, participants with severe disease, that is, those who required revascularisation, were excluded, thus creating possible selection bias and recruiting only those with milder disease and who may possibly progress at a slower rate. The authors report an overall mean decline in ABPI of 0.01 after 1 year, while 2.4% developed CLI (rest pain/ ulceration or gangrene) and a further 2.4% required surgical intervention, the reason for which is unspecified. The authors did not provide the mean decline in ABPI of those who deteriorated. There is also no reference made to possible falsely elevated ABPI readings due to calcification when 91% of the participants smoked or had a smoking history which increases the risk of calcification (Tsai et al., 2020).

Naschitz et al (Naschitz et al., 1988) investigated retrospectively, the predictors and outcome in 460 patients with claudication who were referred to a vascular laboratory. The participants included were only those who received conservative treatment. The authors did not report the yearly ABPI decline but they stated that a decline of 0.15 in ABPI in patients who had an ABPI of <0.5 at baseline increased the risk of requiring revascularisation by 1.9 times. In their report there is no reference to attrition rate or to possible arterial calcification altering ABPI readings. An element of selection bias in recruiting only those who were allocated to conservative treatment may have resulted in a selection of participants with milder disease.

Aquino et al (Aquino et al., 2001) investigated the natural history of IC in 1244 male veterans. Serial data of ABPI and walking distance was available in 779 participants who were followed for at least 2 years. Inclusion criteria included an ABPI <0.9 and a report of IC symptoms in the buttock, thigh or calf. Participants with calcified arteries and an ABPI >1.25 were included provided that they had a reduction by more than 50% in amplitude of pulse volume recording when compared to thigh. The authors reported a yearly decrease in ABPI of 0.014 and a yearly decrease in walking distance by 8.41 meters (self-reported distance). The authors acknowledged missing or unreliable data of 465 participants who were therefore excluded from the analysis. In this study there are elements of selective bias since the participants were all male veterans with no representation of the female gender, limiting external validity of the study. It is unclear whether the excluded participants had similar baseline data to the recruited participants. Additionally, there is no reference to the possibility that falsely elevated ABPI readings may have affected the calculation of the mean yearly reduction in ABPI or whether calcification may have occurred during the study period, which may have hidden the true deterioration of PAD.

Whyman et al (Whyman et al., 1993) investigated the progression of atherosclerosis in femoropopliteal lesions in 35 patients with IC. Progression was expressed as velocity ratio (VR) and the Bollinger score. The authors reported that 21% of the participants deteriorated to occlusion of the artery within a median of 13 weeks. Rapid progression of disease was associated with a VR>3 at baseline, which indicates the presence of significant stenosis, while those with a VR<3 did not deteriorate. The authors postulate that a short window of opportunity exists to undertake revascularisation in patients with a VR>3 before rapid progression occurs.

Table 4.3 Studies reporting progression of PAD in IC

Studies	Methodology	Study Population (age & gender)	Baseline Characteristics	Diagnosis of IC	Follow-up period in months	Outcome MACE-CVD morbidity and mortality (CVD death)	Outcome Lower limb	Progression of PAD	Prognostic factors for progression of PAD to CLI
Smith et al 1996 Influence of smoking cessation and HLD on progression of PAD	Prospective study	235 - 151 smokers / 83 stoppers with IC	Triglycerides, HT, ABPI	ABPI <0.9	3 years, f/u every 12 months		21% had a reduction in ABPI by >0.14, 12.5% developed CLI and req revsc.	ABPI decreased by >0.14	High Triglyceride >2.2mmoles associated with 1.77 risk of ABI reduction & 2.31 risk of CLI. ABPI <0.5 associated with 1.8 increased risk of deterioration. Pack yrs >50 and younger age associated with deterioration.
Smith et al 2003 Changes in ABPI – Edinburgh Artery Study	Prospective cohort using subset from Edinburgh study	131 patients who had IC at baseline/ developed during F/u. No report of patients with IC at baseline only.	WHO questionnaire, smoking status, HT, ECG, BMI, ABPI	WHO (grades 1,2 & probable IC)	5yr and 12 yr	Mortality excluded, no report on MACE outcomes	No report of outcome of pts with IC at baseline only	Decrease in ABI by 0.09 over 5 yrs. No report at 12 yrs due to loss to F/U. Decline faster than non-claudicants.	Higher ABI =faster decline but lower ABI = increased risk of Lower Limb events

Walsh et al 1991 Natural history of SFA stenosis	Prospective study	38 patients with IC (45 limbs)		Arteriograms, duplex	37 months interval (3yrs)		72% of SFA stenosis stable, 28% progressed (17% occluded at a rate of stenosis progression of 12% per year). Symptoms progressed in these pts also.	9.1% angiographic evidence of progression. Stenosis progressed more rapidly when contra-lateral SFA is occluded.	Smoking and symptom progression predictive of SFA stenosis progression. SFA occlusion is synchronous with symptom progression.
Bird et al 1999 Quantitative and qualitative progression	Prospective cohort study	423 with PAD- 177 claudicants	ABPI, TBPI, peak PT flow velocity	ABPI, San Diego Claudication questionnaire	4.7 years	No report	No report re claudicants	Rose claudication associated with -1.0 unit progression over 5 years. ABI 0.9 decrease of 0.02 over 4.6yrs	Age, DM, LV PAD, contra-lateral limb LV PAD ass with rapid progression *Comments-limbs not individuals were used. Difficult to predict outcome per pt.*
Aquino et al 2001 Natural history 1244 claudicants	Prospective cohort	1244 males Veterans Admin Hosp-799 LL analysis	ABPI, PVR, BP, DM, Smoking status, HTN, Ho CVD	ABPI <0.9, PVR, Treadmill exercise – induced reduction by 0.29 ABPI	45 months		10 year cumulative frequency of 23% IU, 30% rest pain	ABI at baseline of <0.58 decreased by 0.014/ year, WD -9.2 yards / year	Lower ABI <0.5, high smoking pack years and IDDM increased risk of IRP, Lower ABI and DM increased risk of IU

Naschitz et al 1988 Intermittent Claudication Predictors and Outcome	Retrospective study	460 patients referred for vascular surgical consultation	Age, smoking, medical history	ABI, Doppler waveforms, angiography, IC distance by treadmill, PVR	3.8 years		43.9% imp of symptoms, 11.9% worse symptoms, 9.1% surgery for limb salvage, 44.1% vascular surgery needed	Dec by 0.15 in ABPI in those who deteriorate but no report of timing – no data of review timings	ABI >0.7, no deterioration of ABI predicts good outcome, ABI < 0.5(increased by 3.8 times), ABI decrease by 0.15 increased by 1.9 times need of eventual surgery.
Fowkes et al 1993 Cross-linked fibrin degradation products (XLFDP), progression of PAD and risk of coronary disease	Prospective cohort study	617 patients with IC	Age, smoking status, Cross-linked fibrin, DM	ABPI, pulses	1 year	32 died, 32 MI (15 fatal), 4 angina	4.8% developed CLI	ABPI decrease by --0.01 per year ***expressed as mean***	Age, smoking XLFDP associated with deterioration in ABPI, XLFDP associated with 4.4 Relative risk of coronary events
Whyman et al 1993	Prospective cohort study	43 femoral artery stenosis in 38 IC patients	Bollinger score	Duplex scan (Bollinger score)	median 6 months, max 19 months	76 weeks max	21% progressed to occlusion. No change in VR if occlusion does not occur	Patients with VR >3 progressed to occlusion within 13 weeks	Only stenosis with velocity ratio of >3 progressed to occlusion within 76 weeks

4.4.1.3 Haemodynamic outcomes of identified studies

- Two studies reported yearly haemodynamic decline in ABPI by 0.014 (Aquino et al., 2001) and 0.01 (F. Fowkes et al., 1993)
- Another study reported an overall decline in ABPI of 0.02 or 0.013 in TBPI – not only IC participants (Bird et al., 1999).
- Others reported that ABPI <0.58 at baseline and/or a decline by 0.15 in ABPI is indicative of progression to critical limb ischaemia (CLI), without reporting the temporal element (Naschitz et al., 1988).
- A faster atherosclerotic progression rate was observed in claudicants compared to non-claudicants (Walsh et al., 1991) and a yearly 30% increase in SFA stenosis is indicative of requirement for revascularisation.
- Smith et al (F. B. Smith et al., 2003) reported a decline after 5 years in ABPI by 0.04 in the limb with lower ABPI at baseline and a decline of 0.09 in the limb with higher ABPI.
- Smith et al (I. Smith et al., 1996) reported a decline of 0.14 of ABPI in 21% of the participants after 1 year of diagnosis
- Whyman et al (Whyman et al., 1993) reported that a velocity ratio >3 was predictive of rapid progression of disease in the femoropopliteal segment from stenosis to occlusion.

4.4.2 Appraisal of included studies

The studies were analysed for risks of bias which could occur in observational longitudinal studies following the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). The Cochrane Collaboration's tool for assessing risk of bias in included studies was applied (Higgins et al., 2014). The Collaboration recommended the assessment and presentation of individual domains such as selection bias (allocation concealment) and reporting bias (survival selection) with consideration of the importance of the different domains (empirical evidence bias, likely direction of bias and likely magnitude of bias). The use of scores or scales is discouraged, instead an estimate of high risk, low risk or unclear risk is recommended. The criteria to judge risk of bias according to the Cochrane Collaboration can be found in Appendix 6.

- *Empirical evidence bias* – the association between bias such as allocation concealment or blinding and outcome
- *Likely direction of bias* – failure to meet criteria such as allocation concealment associated with overestimate of effect
- *Likely magnitude of bias* – for example inadequate allocation concealment might result in a large estimate of effect while how incomplete outcome data was addressed might not substantially affect confidence in estimated effect

Table 4.4 Risk of bias in studies included in systematic review

First author	Allocation concealment	Selective recruitment	Incomplete outcome data	Survival selection	Summary risk of bias
Naschitz (1988)	yes	yes	no	yes	high
Walsh (1991)	yes	yes	no	no	high
Fowkes (1993)	yes	yes	no	yes	high
Whyman (1993)	no	no	yes	no	unclear
Bird (1999)	yes	yes	yes	yes	high
Smith (1996)	no	yes	yes	yes	high
Smith (2003)	no	yes	yes	yes	high
Aquino (2005)	no	yes	no	yes	high

The presence or potential presence of a source of bias is indicated as "yes". Summary risk of bias was determined using The Cochrane Collaborationfor assessing risk of bias. Studies were rated as having high risk of bias (i.e., "low-quality" trials) or low risk of bias (i.e., "high-quality" trials) if there was evidence for the presence of ≥3 or <3 sources of bias, respectively.

4.4.2.1 Selection bias among studies

Selection bias because of inadequate allocation concealment at recruitment stage was observed in 4 out of the 8 studies reviewed (Bird et al., 1999; F. Fowkes et al., 1993; Naschitz et al., 1988; Walsh et al., 1991). Inadequate allocation concealment occurs when the researcher is aware of the next treatment allocated for the patient, which may lead to selection bias in observational studies. Participants with IC who were referred for revascularisation or who were

severely ischaemic were excluded from these studies, resulting in the recruitment of only those with milder disease. Subsequently the disease progression reported by a mean or percentage decline in ABPI in these studies, does not include those with more severe PAD and results therefore underestimate the true progression. This underestimation is sometimes exacerbated when survival selection bias is also present, as discussed further in the following sections.

4.4.2.2 Under-reporting

The reporting of methodological detail about aspects that threaten internal validity such as measurement precision of the tools used were often reported. Having reliable and valid instruments is one of the best ways of reducing measurement bias in epidemiologic research. However, reports of measurement quality due to the possibility of arterial calcification and hence reporting were also neglected, with only 1 article (Bird et al., 1999) reporting the possibility of artefactually elevated ABPI. While Walsh et al (Walsh et al., 1991) analysed atherosclerotic progression using angiographic studies, other studies which used the ABPI as a surrogate measure of peripheral perfusion, are susceptible to the hidden dangers associated with this tool (C. Formosa et al., 2013) which were discussed in Chapter two. Individuals with conditions such as Diabetes, smoking and renal disease in whom ABPI measurement may be unreliable, are known to be at a higher risk of deterioration of PAD. Using ABPI in this cohort of patients to determine deterioration in PAD is likely to significantly underestimate their deterioration. (Bundo et al., 2013; S. M. Conte & Vale, 2018). In these patients, the ABPI needs to be interpreted with caution since results may be artefactually elevated due to non-closure or delayed closure of the artery when the cuff is inflated. In such cases the TBPI is recommended since the digital arteries of the foot are less susceptible to arterial calcification (S. M. Conte & Vale, 2018). However, among the studies included in this systematic review, only 1 study (Bird et al., 1999) reported TBPI readings while another 5 studies (Aquino et al., 2001; F. Fowkes et al., 1993; Naschitz et al., 1988; F. B. Smith et al., 2003; I. Smith et al., 1996) did not discuss the possibility of artefactually elevated results potentially resulting in an underestimation of the true decline of ABPI in their results (V. Aboyans et al., 2006).

Aspects of recruitment, particularly the proportion of sampled subjects meeting the eligibility criteria and then consenting to participate, were poorly reported. In addition, the reasons that people did not consent, and comparisons of consenters with non-consenters in terms of baseline demographic or clinical features, were also scarcely reported. Only one study (Bird et al., 1999)

which had approximately 50% non-responders, attempted to address this bias threat by comparing a sample of non-consenters with the recruited participants. None of the other studies included in this review reported details regarding non-consenters or those who dropped out from the study, even though some authors declared between 29% to 64% of attrition rate or non-consenters. These aspects of selection bias are potentially important because if consenters differ from non-consenters, the study findings may be skewed (Dunn et al., 2004). The authors recommend that researchers plan *a priori* their sample sizes to account for potential losses and consider the biases likely to be associated with non-consent and dropout.

Although the numbers of participants at each stage of the studies were reported in all the articles, accounting for loss to follow-up and missing data, items in the analyses were rarely stated. In longitudinal studies, participants can be lost to follow-up over the years, resulting in missing data as shown in Smith et al (Smith et al., 2003) where the data after 12 years was not reported due to a high attrition rate. Data missing not at random can be a source of bias affecting internal validity (Perkins et al., 2017) and may influence estimates of disease progression or incidence of adverse events. In observational studies, missing data can either be accounted for statistically using imputation, weighting or sensitivity analyses or the authors may postulate the likely impact of the missing data on the results (Higgins et al., 2014; Tooth et al., 2005). Although debate exists about the benefits of using complex statistical imputation techniques to treat missing data, it is recommended that at least the pattern or the potential impact that the missing data may have on the final estimates should be determined (Sterne et al., 2009).

4.4.2.3 Survival selection bias

Survival selection bias was evident in 6 studies (Aquino et al., 2001; Bird et al., 1999; F. Fowkes et al., 1993; Naschitz et al., 1988; F. B. Smith et al., 2003; I. Smith et al., 1996) out of the 8 studies reviewed. This occurred when authors excluded participants who required revascularisation during the course of the study or who died by the end of the study. In the context of evaluating the natural history of PAD in IC patients, survival selection bias, sometimes referred to as selective reporting, often results in the underestimation of the true progression of the disease since those who most likely progressed rapidly were excluded from the analysis. Among the reviewed studies, this source of bias was often coupled with selection bias at recruitment stage, as discussed earlier, which may have exacerbated the possibility of underestimation of the progression of PAD in this group of patients.

4.5 Discussion

This systematic review is the first to evaluate the progression rate of PAD in individuals with IC. The studies assessed in this systematic review have shown variable reporting of some of the major threats to the internal and external validity of observational longitudinal studies (Tooth et al., 2005). Selection bias due to inadequate allocation concealment, limited reporting of methodological detail in some studies, incomplete information related to attrition or non-consent and survival selection bias were the most common sources of bias observed in these studies. Therefore, this review has shown that the existing knowledge is limited to a small number of studies providing mostly low-quality evidence related to measurable haemodynamic progression rate in patients with IC. Consequently, there is insufficient evidence to draw conclusions and accurately predict progression and prognosis of the individual patient presenting with IC. Since a reliable definition of the natural history of IC is required to evaluate the need for early or prophylactic revascularisation (Muluk et al., 2001), this is an important finding as it highlights the need for more rigorous trials of patient characteristics and PAD progression rate in this population.

While longitudinal observational studies are considered as the most suitable methodology to evaluate the natural history of a disease, poor design and reporting can introduce bias and reduce the robustness of data (N. J. Perkins et al., 2017; Tooth et al., 2005). Data from the reviewed studies have generally agreed on an overall decline in ABPI by 0.01 to 0.02 over 1 year (Aquino et al., 2001; Bird et al., 1999; F. Fowkes et al., 1993) and a decline of 0.15 in severe cases of PAD (Naschitz et al., 1988). However, these results are probably an underestimation of the true overall deterioration in this population. A faster progression rate was reported in another study, stating a decrease of 0.14 in ABPI in 21% of the cohort within the first year (I. Smith et al., 1996). Similarly, Whyman et al (Whyman et al., 1993) reported rapid deterioration in 21% of their cohort who had more severe disease at baseline.

Despite ongoing efforts in research in this population, the prognosis and progression of arterial disease is still not clear due to the diverse methods of assessment utilised in these studies. There are no well established criteria which allow the clinician to predict outcomes in an individual patient (Muluk et al., 2001; Conte et al., 2019). This finding highlights the need for further insight into the progression rate of PAD in individuals with IC because there is a lack of explicit criteria in decision-making due to a lack of high quality evidence.

4.5.1 Potential limitations

In this review it was not possible to perform meta analysis due to the high degree of heterogeneity in clinical methods, primarily variations in haemodynamic measurement protocol and settings across the studies.

Efforts to reduce the researcher's reporting bias were made by following the PRISMA checklist as a methodological approach, searching grey literature and by including two independent researchers in the reviewing process.

This review offers evidence only of hemodynamic measures and omits other clinical questions such as quality of life or functional improvement. These questions also deserve further investigation.

4.6 Conclusion

This review highlights existing inconsistencies and a paucity of scientific evidence related to the temporal progression of PAD in patients with IC. Despite the assumed benign prognosis of the condition, the progression of PAD in this group of patients is still not clear in published literature. There is a distinct lack of high quality evidence which helps estimate the prognosis of the individual patient, lacking support for clinical decision making in the selecting the best management approach for the patient with IC. More evidence is needed to be able, to not only identify who will deteriorate to CLI, but also to distinguish those who will deteriorate more rapidly than others and possibly predict the time interval until development of CLI. Results from this systematic review have emphasized the need for further investigation into the progression and outcomes of patients with IC in terms of haemodynamics and lower limb events.

These considerations have led to the inception of this research and form the basis of this work. Establishing the lower limb prognosis of patients with intermittent claudication could help in the early identification of those patients who are more likely to deteriorate. This would in turn allow physicians to help patients make a better informed clinical decision on treatment selection, potentially early intervention.

4.7 Study 2 - Referral patterns and diagnostic criteria in patients with IC: a retrospective study

During the initial phase of this research, in order to determine the scale of the problem and feasibility for conducting the main study, the annual incidence rate of patients with IC referred for revascularisation at the national vascular unit and the service pathways employed were explored through a retrospective study of referral pathways in Malta **(Study 2)**. This study draws on retrospective data from electronic databases within the Vascular unit in the general hospital to determine the incidence of the potential participant population for the planned research while also illustrating the clinical referral pathways employed for specialist intervention.

4.8 Introduction

In the initial phase of this research, knowledge of the incidence of patients with IC referred to the vascular clinic and also of the clinical pathways utilized by these patients to access specialist care was important in order to obtain a realistic view of the impact of this condition on the Maltese healthcare system and to help define the potential development and sample size of the main study. There were no published data relating to patients with IC in Malta and there was no published information or register related to the incidence rate of referrals for IC. At this stage of the research it was important to determine the approximate number of patients with IC referred for specialist intervention in Malta and also to further understand the care pathways and diagnostic processes applied during clinical practice. A scoping study, was therefore undertaken at the vascular unit where the main study was planned to be conducted. The vascular unit is located within the only general hospital in Malta which is run by two vascular surgeons and one lead vascular surgeon.

4.9 The aims and objectives of the study

The aim of this scoping study was to determine the annual number of patients with intermittent claudication due to PAD referred for specialist intervention. The second aim was to assess clinical pathways of referral employed for patients with IC who are referred for potential specialist intervention. This included the profession of the referrer, the diagnostic processes

involved prior to referral, location where participants were referred from and approximate waiting time from referral to specialist appointment.

4.9.1 Objectives of Study Two

The objectives of the scoping study were:

- To determine the annual number of patients referred to the vascular unit due to IC, with a diagnosis of PAD as the cause of the symptoms as defined by the vascular surgeon.

- To describe the clinical pathways employed by participants who are referred to the vascular unit by GPs or other medical practitioners.

- To describe the clinical pathways employed by participants who are referred to the vascular unit by podiatrists.

4.10 Location of the study

The study took place in the vascular unit within the national hospital in Malta. This is the only outpatient vascular unit on the island where patients with arterial disease are referred to be seen by a vascular surgeon for further assessment and potential revascularisation. Referrals are sent in the vast majority by general practitioners from all the primary care clinics and also by podiatrists working in primary care. Since the vascular unit is the only vascular clinic in Malta, data gathered incorporated all referrals from the primary care sector referred for potential revascularisation.

4.11 Methodology

This study utilized a service evaluation approach which is designed to describe the current care employed by a specified service without comparing it to a standard (Moule et al., 2016). This method assesses the service delivery by the healthcare professional, practiced according to their professional standards, guidance or preference, providing an evaluation of health practices of interest in real clinical settings. A service evaluation is specifically designed around the context

of interest and data generated cannot be generalized. However, they can be powerful in providing evidence for the need of improvement in specified aspects of the service (Moule et al., 2016). Analysis of existing data is the common approach of a service evaluation study and does not require randomization. Other methods, such as a clinical audit approach, could not be employed for this scoping study since such a study design would require the comparison of the service to a predetermined standard of service (Bowling, 2014) which is not clearly defined for patients with IC.

Therefore, retrospective analysis of existing data was employed by assessing anonymized records in the clinical database of patients attending the vascular unit. All the patients attending the vascular unit at the hospital are registered with a unique registration number in the database which is run and managed by the lead vascular consultant. The reason for referral, clinical diagnosis, source of referral and management are also recorded in this database.

4.12 Methods

The data from 28th March, 2015 to 28th March, 2016 was analysed and participants were divided according to reason for referral and clinical diagnosis. This data was recorded on a separate excel sheet. The main focus of the service evaluation study included: reason for patient referral, referral date and waiting time for specialist appointment, profession of referrer and clinical diagnosis by vascular surgeon. To reflect realistic recruitment rates for the main study, study-specific inclusion criteria for the main study were taken into consideration when recording data for IC as the clinical diagnosis, meaning that, IC due to PAD and IC due to other possible medical problems such as neurological IC, were specified. Other data such as gender and medical status were also recorded.

The study population included all records on the vascular database in the previous year from the time of this scoping study. Previous timelines were not chosen since the clinical picture closest to this research was of interest to the author and also because a third vascular surgeon had been employed with the vascular unit at the end of 2014, therefore records previous to that date may not have reflected the current service practice.

The data was retrieved from an anonymized version of the database available at the vascular unit in the national hospital

4.12.1 Inclusion and exclusion criteria

Inclusion criteria

All anonymized patient records registered in the database were included.

Exclusion criteria

Patient records which were incomplete were excluded.

4.12.2 Data collection

The database used at the vascular unit is kept on an Access sheet and specific codes for different diagnoses are used. For data collection, filters for each code were applied in order to identify the participants for each diagnosis and record the information of interest. This data was in turn recorded on a separate excel sheet by the author to enable data analysis.

4.12.3 Data analysis

The IBM statistical Package for Social Sciences (SPSS) version 26.0 for Mac (SPSS inc, NY, USA) was used for statistical analysis. The data are presented in numbers and percentages. The data was also discussed with the lead vascular surgeon to ensure understanding of the coding process and reduce risk of errors.

4.13 Results

4.13.1 Number of participants with IC per year

Eight hundred and sixty-nine participant records were retrieved from the database as 'all patients seen during 1 year'. Out of these, 3 had 'null' for diagnosis and were therefore excluded, leaving 866 records for analysis.

The majority of the participants referred to the vascular unit were due to venous related problems (n=292), followed by 192 participants who were reported to have 'other' diagnoses, meaning that these patients did not have any vascular problems and were erroneously referred to the vascular unit. Figure 4.2 illustrates the distribution of different patient diagnoses as reported by the vascular surgeon.

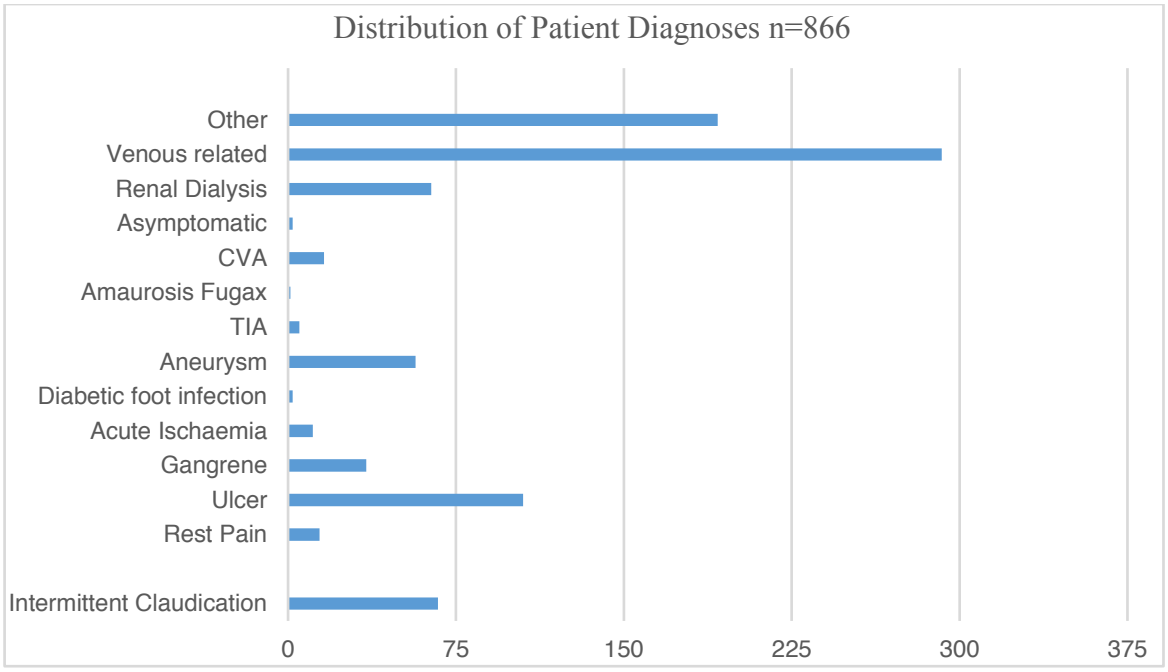


Figure 4.2 Diagnoses of participants referred to the vascular unit in 1 year

In total there were 424 participants who had been referred due to symptoms related to PAD. Out of these, 165 were diagnosed with CLI (rest pain, ulceration or gangrene), 67 were new cases diagnosed with IC due to PAD and 192 (listed as 'other') had been referred due to symptoms of IC but when assessed by the vascular surgeon, the cause of their symptoms was unrelated since they had normal peripheral perfusion. All the incorrectly referred participants had been referred by GPs in primary care.

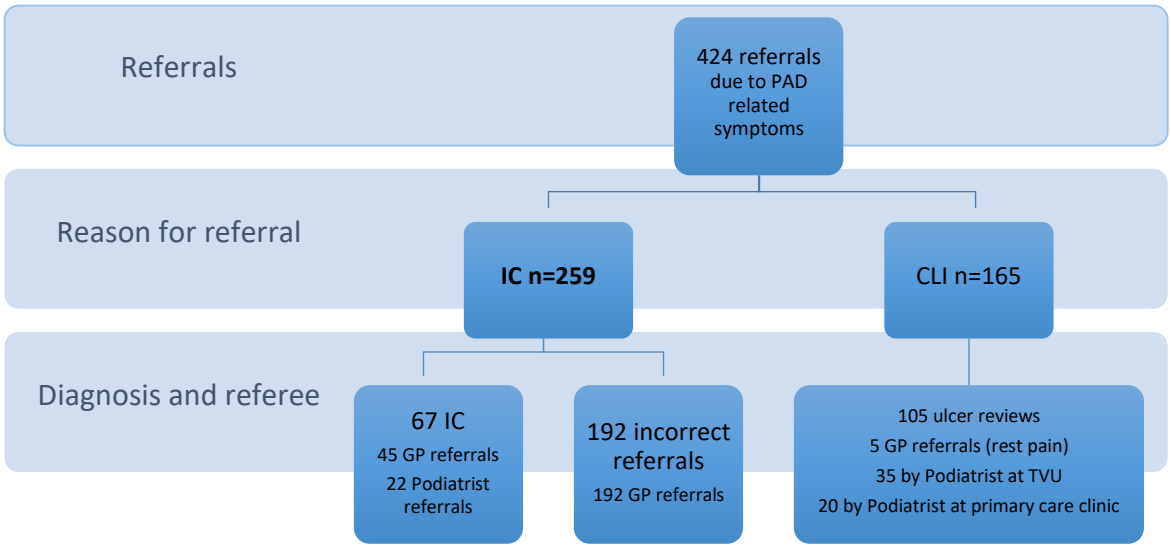


Figure 4.3 Referrals due to peripheral arterial disease (TVU-tissue viability unit)

Among the participants with IC (n=67) 58 were men and 9 were women. The risk factors reported in this database were diabetes, smoking and hypertension. Thirty-seven (55% of the participants with IC) had diabetes out of whom 16 also smoked. The rest were smokers (n=30) without diabetes. A large majority (72%) of the participants with IC had hypertension.

A total of 165 patients were referred due to symptoms of critical limb ischaemia, with ulceration, acute ischaemia, gangrene or rest pain. All these were correctly referred and the majority (n=105) were reviews booked by the staff at the vascular unit themselves (figure 4.3).

4.13.2 Referral pathways for participants with IC

The referrals identified in the service evaluation demonstrate that the participants with IC accessed the vascular surgeon for specialist assessment through two care pathways which are detailed in the following sections. The diagrammatic illustration (Figure 4.4) describes the service pathways used by the participants identified in this study.

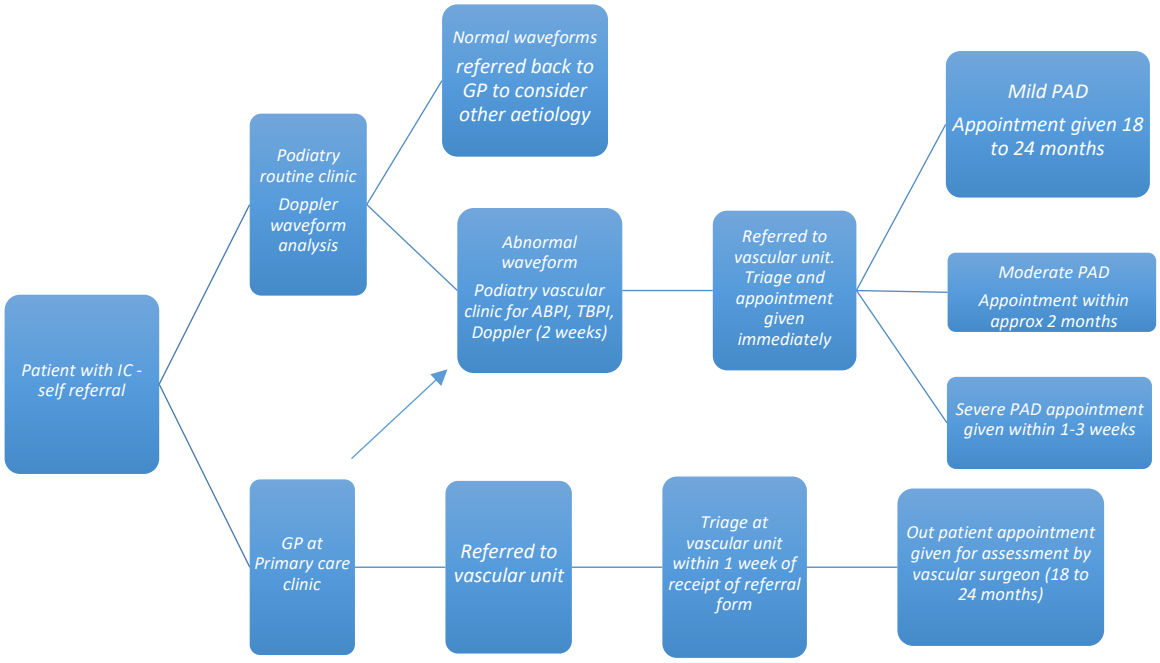


Figure 4.4 Service pathways for patients with IC

When participants sought medical help from the GP, referral routes often varied according to the preference of the GP. Most commonly, the patients were referred directly to the vascular

surgery department (vascular unit) in the local general hospital. Only two participants were referred by the GP to the Podiatry vascular clinic for further assessment.

4.13.2.1 Referral pathway through general practitioner

Participants complaining of IC who attended primary care GP clinics, were in the vast majority referred directly to the vascular surgeon for further assessment and consideration of revascularisation. However, referral by GPs was generally done without haemodynamic analysis (assessment of Doppler waveforms or ankle / toe –brachial pressure indices) except for possibly clinical pulse palpation. This was noted in the surgeon's notes in the database and was also evident in the referral notes sent by GPs as shown in the samples shown in figures 4.5a and 4.5b which have been retrieved during the data collection in study 3, where a lack of haemodynamic information in referrals by GPs sent to the vascular surgery unit is demonstrated. Due to the lack of information and the assumed benign prognosis of IC (as discussed in Chapter 2), those who were referred directly to the hospital were often given the first available free slot which is between 18 to 24 months, unless specified in the referral form as 'urgent'. Cases with tissue loss or rest pain were referred either to the Accident and emergency department in the hospital where they were assessed by the vascular surgeon on call and given an urgent appointment or were noted as urgent on the referral note. Urgent referrals are seen at the vascular clinic within 2 weeks.

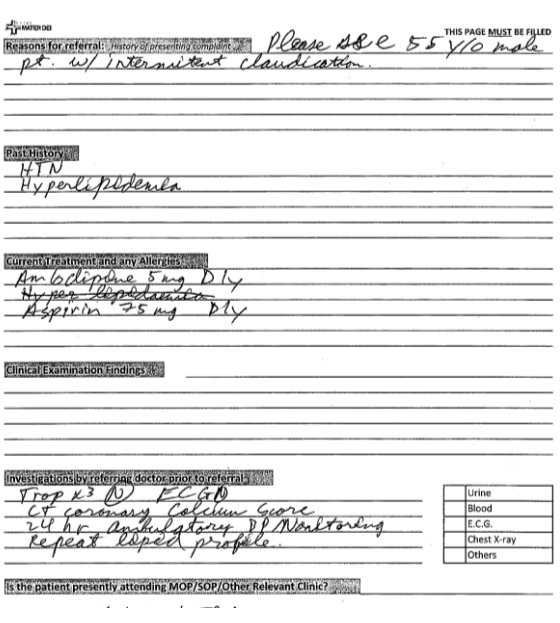


Figure 4.5a GP referral sample 1

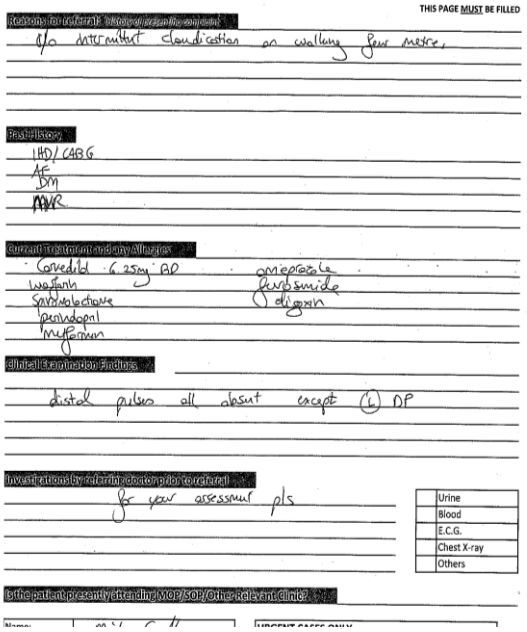


Figure 4.5b GP referral sample 2

4.13.2.2 Referral pathway through the podiatry service in primary care

A different approach to diagnosis and referral pathway was employed by the podiatry service. The author is familiar with this process through personal clinical experience working in this department. The participants with IC who sought help from the podiatrists working at the routine clinics were assessed using Doppler waveform analysis. Participants with abnormal waveforms were referred to the Podiatry vascular assessment clinic within Primary healthcare department where haemodynamic analysis through non-invasive diagnostic tests were employed to confirm diagnosis. Doppler waveform assessment, ankle-brachial pressure index, toe-brachial pressure index and absolute toe pressures were performed to help confirm the diagnosis and differentiate from other causes of IC.

In those patients where PAD was confirmed, direct referral to the vascular surgeon at the general hospital was undertaken including the Doppler and ankle/ toe pressure reports which help the triaging of patients and determine the waiting time to be seen at the local hospital. Referral was made by the podiatrist leading the vascular clinic (the author) through email directly to the leading vascular surgeon in the vascular unit at the hospital. Figure 4.6 is a sample of such referrals. The participants were triaged by the vascular surgeon and a timely appointment was provided. Depending on the severity of PAD as determined in the referral note, these participants were seen by the vascular surgeon within a reasonable time ranging from a week to a few months. In the podiatry vascular clinic, those participants who were found not to be taking risk factor control therapy such as statins, antiplatelet or antihypertensive treatment as recommended in treatment guidelines (Gerhard-Herman et al., 2017), were also referred to the GP for the prescription of the required medication.

Dear Prof.……,
can I please refer the patient below due to mono-continuous waveforms and very low pressures on his Left LL? He also complains of IC in his Left calf after just 5 mins. I also referred him for antiplatelet therapy to his GP.

Name:

ID

PMH- Hypertension, dyslipidaemia

Symptoms - IC L calf after 5 mins of walking

Medication - simvastatin, amlodipine

Doppler waveforms Right Biphasic PT and DP
Left Mono-cont PT and DP

ABPI Right 1.05 Left 0.47

TBPI Right 1.01 Left 0.33

Figure 4.6 Sample of referral by the podiatrist

4.14 Discussion

The management of IC is reported to be challenging for health practitioners due to the diversity of outcomes among patients presenting with this symptom of PAD (Jaff et al., 2015). This scoping study has shown that the first encounter of the patient with IC is generally a GP or a Podiatrist within the primary health sector. However, results demonstrate that the outcome of the referral process greatly depends on the health provider. This study has provided insight into the referral processes employed in the health service in Malta and provided some data related to the annual number of patients referred and diagnosed with IC, revealing possible lacunae in the health system related to this group of patients. A number of concerns have emerged following this study, highlighting areas for clinical recommendations prior to the recruitment for the main study.

4.14.2 Annual number of referred patients with IC

The scoping study showed that over a period of 12 months, the number of patients referred to the vascular surgeon in the national hospital who were diagnosed to have IC due to PAD was

67. This number was distinctly smaller than what was anticipated, clearly exposing several issues which could have been of concern during the recruitment phase of the research.

It was expected that the number of patients referred due to IC would be higher than 67 due to a number of reasons. The literature reports that (Ouriel, 2001) the incidence of IC ranges between 8.8% to 20% among the population aged 65 and over. In Malta there are approximately 80,000 (Podesta et al., 2019) people in this age group, meaning that possibly 7000 (8.8%) to 16,000 (20%) people suffer from IC, numbers which are clearly not reflected in the results of the scoping study. However, this estimation is based on published literature from other countries and not from data on the Maltese population. With an estimated prevalence of >10% of people living with diabetes, high obesity rates and high smoking rates among the Maltese population (Cuschieri, 2020) (total population in Malta is approx. 514,564 (NSO Malta, 2020)), the number of patients presenting with IC who would seek medical advice per year was expected to be much higher than that found in the scoping study, and that the numbers demonstrated may not reflect the yearly incidence of IC amongst the Maltese population. Currently there is no data in Malta documenting the incidence of IC since there are no well-woman or well-man clinics for regular health visits from which such data could be gathered, instead patients seek medical help only when problems arise. Although it cannot be ascertained from this study, the reasons for the low number of referrals could be:
i) The actual incidence/ prevalence of the condition is indeed low but this is highly unlikely considering the prevalence of the risk factors in this population.
ii) there is a proportion of patients living with IC who are not being referred to the vascular unit either because diagnosis is missed or due to patient / practitioner preference
iii) there is a proportion of patients with IC who do not seek medical help

The low number of referrals of patients with IC yielded in the scoping study elicited important issues which needed to be addressed before embarking onto the main study, while the high proportion of incorrect referrals suggested that improvements in the system are required.

4.14.2 Participant demographics

Among the participants referred from primary care clinics with IC due to PAD, the ratio of male: female was approximately 5:1. This is congruent with published reports in the literature, stating that the progression from asymptomatic to symptomatic PAD has a prolonged latent

phase in women and that women are less likely to report physical symptoms than men (Schramm & Rochon, 2018). The previously held view that oestrogen confers a protective effect against atherosclerotic disease (Westendorp et al., 2000) as a reason for the lower number of women reporting IC, has been discredited in large randomized trials which demonstrated that hormone replacement therapy did not demonstrate any benefits in decreasing events related to PAD in post-menopausal women (Grady et al., 2002; Writing Group for the Women's Health Initiative Investigators, 2002).

This scoping study has shown that all the participants with a confirmed diagnosis of IC due to PAD had either diabetes or smoking (or both) as a risk factor. This is also in agreement with published literature where tobacco smoke and diabetes are declared as main risk factors for the development of IC (Criqui & Aboyans, 2015; Kalbaugh et al., 2018) as discussed in detail in Chapter 2.

4.14.3 Incorrect referrals

This service evaluation study has shown that 45.2% of participants referred due to symptoms of PAD were incorrectly referred by GPs in primary care clinics. The samples of referral notes presented in this chapter (but retrieved during data collection in Study 3) give an indication of the reason behind this shortcoming in the system, where no haemodynamic assessments (Doppler waveform analysis, ABPI or TBPI) were performed in order to confirm that the cause of the symptoms is actually PAD. This practice resulted in detrimental consequences for patients, primarily delay in treatment in those who had severe PAD and also inefficient use of the service in those who did not have PAD as a source of their symptoms.

Firstly, this study has highlighted that GPs were limited in their ability to accurately diagnose PAD in patients with IC. Although the reasons were not investigated in this study this could possibly occur due to lack of equipment (Doppler), time constraints, inadequate training, limited exposure to vascular disease in the underguaduate program (AlHamzah et al., 2019) or personal interest (Sommers & Launer, 2014). The poorly completed referrals by GPs to the vascular unit was also identified in a previous study (Chetcuti et al., 2009). Consequently, due to the lack of information regarding the severity of the disease provided in the referral notes, most patients were given the first available appointment within 18 to 24 months at the vascular clinic. While IC is defined as having a generally benign prognosis (Jaff et al., 2015), in some

cases deterioration may occur rapidly and 18 to 24 months may be too long. As witnessed first hand during clinical hours, this delay may result in patients presenting with worse symptoms or CLTI at the primary care clinics even before their appointment with the vascular surgeon. These patients, once they have deteriorated to CLTI, are then generally referred for urgent treatment, with increased risk of morbidity and mortality due to the worse status of the disease (Anand et al., 2018). This practice is reflected in the higher number of participants referred due to CLI (n=165) compared to the number of IC (n=67) demonstrated in this evaluation study. Future investigations of the reason why GPs do not refer the patients to the podiatry vascular clinic may be beneficial in this context.

Secondly, those patients who were incorrectly referred, meaning patients who were found to have normal peripheral perfusion by the vascular surgeon, had waited 18 to 24 months only to be referred back to the GP for consideration of an alternative diagnosis such as spinal stenosis. This practice therefore caused delay in their diagnosis and management of their condition.

Thirdly, outpatient appointments with the vascular surgeon are limited as evidenced by the long wait of 18 to 24 months for the first available appointment in this service evaluation study. Incorrect appointments occupy important slots for those who really need them, leading to delayed treatment for patients who have PAD. Following personal discussion of the results of this service evaluation with the lead vascular surgeon the following comment was reported:

> *'The large proportion of inappropriate referrals to the vascular clinic is itself one of the reasons for the significant delay between referral and allocation of a vascular clinic appointment. The referral of patients to the vascular clinic when no such referral is warranted constitutes an opportunity cost as such patients who do not merit a vascular appointment take up precious time and appointment slots at the single national vascular clinic in the country. In the vast majority of cases referred to the vascular clinic, not only have no physiological tests been performed by the referring doctor but neither has a basic clinical examination of the pulses been performed. In many such cases the peripheral pulses were strong and easily palpable and a cursory clinical examination would have been sufficient to elicit in the clinician's mind the possibility of alternative diagnoses'.*
>
> (Lead vascular surgeon, Mater Dei Hospital, April, 2016)

4.14.4 Recommendations on clinical practice

This scoping study explored the current referral pathways used in the Maltese health system by patients with IC and provided some insight into the characteristics of this population. Results from this study revealed possible issues within the clinical diagnostic and referral processes which may benefit from improvement. Results demonstrate a clear and vital need for an increase in awareness of the burden of IC on the patient and the consequences associated with lack of haemodynamic assessment prior to referral. The results of this service evaluation study were discussed with the lead vascular surgeon and some changes were agreed upon and implemented immediately.

- A personal communication with Primary care GPs was undertaken indicating the importance of referral of patients complaining with claudication symptoms. This was done because of the low number of annual referrals suggesting that many patients were not being referred for assessment.

- **A 'Claudication clinic' was set up within the podiatry vascular clinic.** The scope of this clinic was to receive referrals from GPs and other care providers involved with the management of patients with IC for assessment by haemodynamic analysis (Doppler waveform analysis, ABPI and TBPI). This would ensure the diagnosis of PAD as a cause of the symptoms, enhancing a more efficient approach to treatment and referral pathway. Awareness among primary care GPs and the importance of the diagnosis of PAD in patients with IC was provided via personal communication and later through communication in the biennial Primary Care conference (November 2016, Malta), which is strongly attended by GPs working in the sector. The author was an invited speaker at the conference and the results of this service evaluation study were presented together with the awareness of the new Claudication clinic. General practitioners were informed about the haemodynamic analysis performed at the podiatry vascular clinic to encourage referrals to this clinic. In view of the predicted increase in referrals to the claudication clinic, a team of two other podiatrists was set up. Training was provided via a one year course at the University of Malta (entitled Vascular assessment of the lower extremities) which includes theory and practical sessions taught by the author, the lead vascular surgeon and other experts in the field. This clinic was set up with the

aim to reduce the number of incorrect referrals to the vascular unit at the hospital and improve the efficiency of the service for this population by implementing a fast-track referral pathway for patients who are found to have severe PAD. This was enabled through the full support from the management of the podiatry department, the management of the primary care department (Malta) and the lead vascular surgeon within the general hospital.

- A new system was set up where patients with IC who are managed conservatively were enrolled into a monitoring program and followed at the podiatry vascular clinic. Patients are given follow-up appointments at the podiatry vascular clinic including those referred to the vascular unit at the hospital. A recall system of patients was implemented to reduce the likelihood of patients missing their review appointment since in some cases this was more than 6 months after their previous visit.

The recommendations addressed several issues which were identified through this scoping study. These included:

- Referrals of patients with IC to the vascular unit increased, subsequently potentially improving recruitment rate for the main study of the main study.
- Training and enhanced knowledge was achieved among clinicians involved in the management of patients with IC, leading to an improved clinical pathway for this group of patients.
- Potential reduction of incorrect referrals to the vascular unit within the hospital ensuring a more efficient service.
- Early detection of deterioration among patients who are managed conservatively was achieved through haemodynamic monitoring at the new claudication clinic.

4.15 Conclusions

This scoping study has provided preliminary figures of number of participants with IC referred from primary care to the vascular surgeon within the local general hospital. It has provided insight into the referral pathways employed for the patient with IC and highlighted concerns within this field which promoted beneficial changes in clinical practice. The changes in practice

increased the likelihood that patients with IC attending the primary care sector are referred to the vascular unit in the general hospital or to the podiatry vascular clinic for haemodynamic analysis to confirm the presence of PAD. Apart from improving the care for this group of patients, these changes addressed the potential barriers which may have hindered the recruitment process for this research and facilitated the author's access to the patients with IC attending primary care in Malta.

The results of this service evaluation study have also brought to light that, the current lack of an appropriate registry of patients with IC in Malta makes it difficult to establish the outcomes of these patients. This therefore emphasized the need for a Prospective registry of patients with IC in Malta which would be followed by a prospective follow-up of patients in order to determine firstly, the baseline characteristics of patients with IC and secondly the outcomes of these patients over a defined period of time.

CHAPTER FIVE

Methodological approach for prospective studies (Studies 3 and 4)

5.1 Introduction

This chapter presents the general methodological approach employed for the data collection of Study 3 and Study 4 presented in this thesis. It describes the site, equipment and measurement protocols applied for the variables measured and recorded. Justification and definitions for each variable are also presented in this chapter.

As discussed in detail in Chapter 3, the methodology chosen for the prospective main study entailed a quantitative approach to data collection procedures within a critical realist philosophical perspective. As stated in Chapter 2 (section 2.9) the study explored the possibility of identifying IC patients at risk of deterioration within a clinical setting to be able to adapt management plans accordingly. Therefore, all data collection was employed within a real clinical scenario, avoiding laboratory settings in an attempt to capture data close to what is normally recorded during routine clinical sessions.

5.2 Methods

A strict defined protocol for data collection was used to ensure consistency throughout the process. All measurements were performed by the researcher in the same room and using the same equipment.

5.2.1 Study design

As discussed in detail in Chapter Three, an observational prospective cohort study of patients presenting with IC was employed. The results obtained in study 3 (cross-sectional observational prospective cohort study) comprised the baseline data for the main study (Study 4) which followed. Therefore, the study design for study 4 was a longitudinal prospective cohort observational design.

5.3 Study site

The site where data collection was undertaken was within a primary care podiatry clinic and therefore conformed to an up-to-standard level of patient safety which is periodically verified by the department Health and Safety officer. All the necessary equipment was located within this clinic to minimise the need for transport of patients. The clinic is centrally located on the island and is easily accessible both by public and private transport.

5.4 Ethical considerations

Ethical approval was sought and granted (Ethics registration FHS 005/2016, Appendix 1) by the University Research Ethics Committee (University of Malta) as detailed in Chapter Three, section 3.6. The study conforms to the highest standards of ethics for studies conducted on human subjects as declared by the Helsinki Declaration (General Assembly of the World Medical Association, 2014) in terms of recruitment, consent to participate and safety protocols (Chapter 3, section 3.9).

5.5 Study population

The study population comprised of all new cases referred to the to the vascular surgery unit in the local hospital over a period of 1 year (July 2016 to July 2017) with IC as the reason for referral. Only new cases were considered as potential participants. Patients who had any previous appointment at the vascular unit registered in the hospital appointment system were not included. All referrals both from the private and primary health sector within the Maltese health care system, by GPs and other health care professionals were considered for inclusion.

5.5.1 Sample size

An estimate of an adequate sample size to detect the effects hypothesised in the study was required. This was estimated by a power calculation which determined the minimum number of participants needed to be able to detect the true relationships between variables (Tooth et al., 2005), i.e. statistical power. Such a calculation takes into consideration the pre-determined probability of false positive (type I errors) and false negative (type II errors) associations. The incidence of the studied event (in the case of this research, CLI) occurring in the general

population and in the study population were required to be able to conduct a power calculation. Since no local data was available, these parameters were derived from published literature.

- The incidence of lower limb events 0.18% among the general population (Baser et al., 2013)
- The incidence of lower limb events among patients with IC is 3% (V. Aboyans et al., 2018)

The following power calculation was applied using the identified parameters where

p^0 = proportion (incidence) of population
p^1 = proportion (incidence) of study group
N = sample size for study group
α = probability of type I error (0.05) false positive
β = probability of type II error (0.2) false negative
z = critical Z value for a given α or β

$$N = \frac{p_0 q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

$$N = \frac{0.0018 * 0.9982 \left\{ 1.96 + 0.84 \sqrt{\frac{0.03 * 0.97}{0.0018 * 0.9982}} \right\}^2}{(0.03 - 0.0018)^2}$$

$$N = 65$$

The required number of participants with IC required for adequate statistical power to detect the effects hypothesised in the study was found to be N=65.

5.5.2 Recruitment

When identifying the study location from where the patients could potentially be recruited for the study, efforts were made to increase the likelihood that there was an appropriate population representation from all over the island and all district primary care clinics. Since in Malta there is only one vascular surgery unit, which is located in the national hospital, all referrals of

patients with IC from the district clinics are sent to this unit. Following Study 2, communication with district clinic GPs was implemented to encourage that all patients complaining of IC were referred. Hence permissions were sought to recruit patients from the vascular unit through the referrals received from all the district clinics. Enrolment commenced in July 2016 and was completed in July 2017, inviting all patients referred to the vascular unit with 'intermittent claudication' as the reason for referral, to take part in the study.

All consecutive referral forms received by the officer in charge at the vascular surgery unit, which had 'Intermittent claudication' or 'IC' in the 'reason for referral' section, were forwarded by the intermediary as a scanned copy to the researcher. The potential participants were contacted by phone to inform them verbally about the study and that they will be receiving an information sheet (Appendix 7) which they were invited to read. They were also informed that they will be sent an appointment by post or by phone within 2 weeks to attend for haemodynamic analysis, should they wish to participate. As instructed in the information sheet, they were assured that participation was voluntary and refusal or withdrawal would not interfere with their medical care in any way. Within 2 weeks, the potential participants were given an appointment to attend the health centre where the data collection was taking place, for haemodynamic analysis and the required baseline data. Due to known effects on peripheral vascular assessment results, all potential participants were asked to refrain from exercising, smoking or drinking caffeine for at least one hour prior to their appointment (Jones & Hall, 2004). Only participants who satisfied the inclusion and exclusion criteria were enrolled for the study.

5.5.3 Inclusion and exclusion criteria

Inclusion Criteria

- All patients who were referred for the first time to the vascular surgery unit due to IC and who had PAD.
    - PAD was defined as either abnormal waveforms (not triphasic (Shaalan et al., 2003)), ABPI <0.9 or TBPI <0.7 (Rooke et al., 2012) in the symptomatic limb / limbs (Bevan & White Solaru, 2020; Norgren et al., 2007). PAD was also confirmed following Duplex scan by the vascular surgeon (Bevan & White Solaru, 2020).

    - IC was defined as cramping, discomfort, fatigue or aching occurring in the calves, thighs or buttocks, which is reproducibly produced due to exercise-induced ischaemia and is relieved by rest within ten minutes (Moyer & U.S. Preventive Services Task Force, 2013) as reported by the patient in the Walking Impairment Questionnaire (Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008).
- Patients who had either bilateral or unilateral symptoms according to Fontaine classification IIa and IIb were included, equivalent to Rutherford classification grade I, categories 1-3 (Hardman et al., 2014).

Exclusion Criteria

- Patients who were referred due to symptoms of IC but who did not have PAD.
- Patients who experienced pain or discomfort in the calf / thigh or buttocks which is not elicited by exercise and relieved by rest, for example pain experienced at rest or pain relieved by exercise.
- Patients who have been previously diagnosed with spinal stenosis or arthritis as a cause of their pain as reported in the patient medical notes and /or national database following previous orthopaedic specialist assessment and diagnosis
- Patients who had CLTI defined as rest pain, active ulceration, tissue loss or absolute toe pressure <30mmHg (Constans et al., 2018) or Rutherford Grades 2 to 3 (Hardman et al., 2014).
- Patients who underwent previous lower limb revascularisation.
- Patients who had a previous appointment with a vascular surgeon and have been previously diagnosed with IC due to PAD.
- Patients with contraindications to cuff placement for ankle, toe or brachial pressure measurements including active digital ulcerations, active leg ulceration, lymphedema, history of deep vein thrombosis, patients with arteriovenous fistula in both arms and patients with vasospastic disorders.

Participants who fulfilled the inclusion and exclusion criteria were recruited and the haemodynamic report was sent to the vascular unit. Recruitment prior to the appointment with the vascular surgeon was important to minimize bias by allocation concealment (J. Higgins et al., 2011; Mizzi et al., 2019).

5.6 Data collection procedures

At their appointment, the potential participants were asked to sign the consent form provided (Appendix 8) and the procedure was verbally explained to them while also answering any queries. It was explained that, on consent, they will be enrolled in the study only if they fulfilled the inclusion criteria which were verified after haemodynamic analysis and a detailed medical history. Potential participants were asked to bring the list of medications taken and any medical discharge notes from previous hospital appointments. Following recruitment, the haemodynamic reports were sent to the lead vascular surgeon and the participants were given an appointment for duplex scanning within 4-6 weeks together with an immediate booking for blood tests as indicated in section 5.7.

5.6.1 Participant demographics

Participant demographics collected for the study included those identified as risk factors in Chapter Two.

- Age – determined by date of birth
- BMI – determined by dividing the weight by the square of the height of the participant. Height and weight were measured using a medical digital height and weight scales.

5.6.2 Haemodynamic analysis

Haemodynamic analysis included Doppler waveform analysis, ABPI and TBPI measurement. The measurements were recorded for both limbs even in cases when unilateral symptoms were reported.

5.6.2.1 Doppler waveform analysis

Doppler waveform analysis was performed using an 8MHz Doppler probe which was attached to the Dopplex assist (Huntleigh®) (Figure 5.1). Aquasonic® ultrasound transmission gel (Parker Laboratories, New Jersey) was used during assessment of waveforms. The probe was placed in the area of the pulse at a 45° to 60° angle to the surface of the skin and was moved

around until the clearest waveform signal was heard. The waveforms were recorded as triphasic, biphasic, monophasic/sharp monophasic, monophasic continuous or absent, applying the terminology currently used in the local hospital clinical reports when communicating with vascular surgeons. For interpretation of waveforms this research followed the definitions by (Kim et al., 2020; Scissons & Comerota, 2009; Spronk et al., 2005).

- Triphasic waveforms were defined as waveforms with three components - systole forward flow, reverse flow (early diastole / late systole) and forward flow (late systole, end-systolic notch). The waves cross the zero flow line.

- A biphasic waveform is denoted by a systolic forward flow with diastolic reverse flow. The waves cross the zero flow line without an end-diastolic notch.

- Waveforms with a sharp upstroke, a brisk downstroke above the zero flow line but with an end-systolic notch (rapid deceleration during end systole followed by diastolic acceleration) was noted as 'sharp monophasic' (Kim et al., 2020; Scissons, 2008; Scissons & Comerota, 2009; Spronk et al., 2005).

- Monophasic waveforms are waveforms which reflect blood flowing in one direction and do not cross the zero-flow baseline but are discontinuous with zero flow until the next wave.

- Monophasic continuous waveforms are waveforms which demonstrate a single wave with a continuous flow during diastole above the zero-flow baseline.

- Absent waveforms occur when there is no signal of flow.

5.6.2.2 The ankle-brachial pressure index

The Dopplex assist (Huntleigh®) was used to assess Doppler waveforms and ABPI (Figure 5.1). Following recommendations (V. Aboyans et al., 2012) due its enhanced accuracy compared to automated devices (Benchimol et al., 2009) an 8MHz probe was used to assess

Doppler waveforms at both the dorsalis pedis and posterior tibial artery and the brachial artery pulse for ABPI calculation.

Figure 5.1. Equipment used to measure ABPI

The protocol for conducting the ankle brachial pressure index used in this study was that proposed by Aboyans et al (V. Aboyans et al., 2012) and is summarised in table 5.1.

Table 5.1 Protocol for measuring ABPI adapted from (V. Aboyans et al., 2012)

- The potential participant lay at rest for 10 min in the supine position, relaxed, head and heels supported, in the room with a comfortable temperature (19°C–22°C/66°F–72°F).
- The cuff was chosen adequately according to the limb size with the width contouring at least 40% of the limb circumference.
- Any open lesion posing potential contamination was covered with an impermeable dressing.
- The participant was asked to stay still during the pressure measurement.
- The cuff was placed around the ankle using the straight wrapping method and the lower edge of the cuff was placed 2 cm above the superior aspect of the medial malleolus.
- An 8MHz Doppler probe was used and Doppler gel was applied over the sensor.
- After the Doppler device was turned on, the probe was placed in the area of the pulse (posterior tibial and dorsalis pedis artery) at a 45° to 60° angle to the surface of the skin and was moved around until the clearest waveforms signal was heard.

- The cuff was inflated progressively up to 20 mmHg above the level of flow signal disappearance and then deflated at 2mmHg per second pressing the deflate button on the Dopplex Assist until the flow signal reappeared. The Dopplex Assist stopped automatically indicating the level of pressure at the first signal. This could also be manually adjusted if deemed necessary such as in cases when the signal was too weak to be automatically detected. The maximum inflation was 300mmHg; if the flow was still detected, the cuff was deflated rapidly to avoid pain.
- The detection of the brachial blood flow during the arm pressure measurement was also done by Doppler.
- The same sequence of limb pressure measurements was used, keeping the same sequence for all participants. In this study the counterclockwise sequence was applied, i.e right arm, right PT, right DP, left PT, left DP, left arm.
- During the sequence of measurement, the first measurement was repeated at the end of the sequence and both results averaged to minimise the white coat effect of the first measurement, except if the difference between the 2 measurements of the first arm exceeded 10mmHg. In that case, another measurement was taken and accepted if the difference was less than 10mmHg.
- In case of the requirement of repeat measurement of the 4 limb pressures, the measurements were repeated in the reverse order of the first series i.e the clockwise sequence was used starting and ending with the left arm.
- The ABPI of each leg was calculated by dividing the lowest ankle pressure by the highest brachial pressure (Schröder et al., 2006). To calculate risk of an event as in the case of this research, the lowest ankle pressure is recommended (V. Aboyans & Jean-BaptisteRicco, 2017).

Participants who had an ABPI >1.4 or who had incompressible arteries due to non-closure after inflating cuff >300mmHg were classified as having calcified ankle arteries (Hirsch, et al., 2006).

5.6.2.3 Toe-brachial pressure index

The equipment used to assess toe pressures was the Huntleigh (Huntleigh®) ATP Ankle and toe pressure kit (Figure 5.2). This handheld equipment is specifically designed to assess toe pressures utilising an arterial plethysmography probe which is attached to a Doppler unit. The

toe pressure cuff (2.5cm) is also attached to the unit and an internal pressure sensor in the adaptor provides a direct pressure reading on the display. This equipment was utilised for assessing toe pressures because it automatically increases the sensitivity of photoplethysmography (PPG) probe up to 40 times when required. In this way the toe pressures could be recorded even in participants with very low toe PPG waveforms, otherwise undetectable by other equipment.

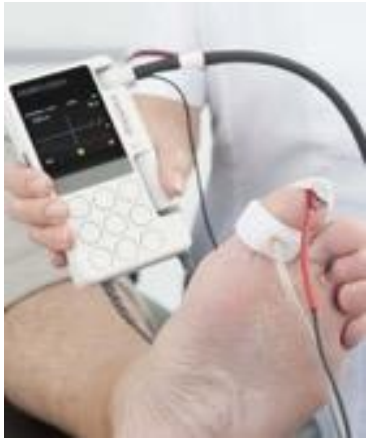


Figure 5.2 Equipment to measure TBPI

A number of potential factors which may influence toe pressure readings identified in the literature (Sonter et al., 2014; P. E. Tehan et al., 2016) were addressed during the procedure. Methodological considerations for TBPI assessment included:

- Toe cuff size – there is some evidence in one study (Påhlsson et al., 2007) which evaluated the influence of cuff size on TBPI indicating that the 2.5cm cuff provides the most accurate measurement while smaller cuffs result in variable pressures. Therefore 2.5cm cuff was applied for all participants.

- Ambient temperature – toe pressure measurements are unreliable when skin temperatures are below 20 degrees Celsius (Cloete et al., 2009; Sonter et al., 2014). Adequate temperature can be achieved by acclimatization for a minimum of 15 minutes in a room temperature kept at 24 to 25 degrees as recommended by (Høyer et al., 2013). This was monitored using a digital room thermometer.

- Positioning – hydrostatic pressure from an elevated torso over the lower limb significantly elevates lower extremity pressures (Gornik et al., 2008). Therefore,

participants were asked to lie in a flat supine position for the duration of ABPI and TBPI assessment.

- Rest time – A systematic review (Sadler et al., 2015) noted a decrease in brachial blood pressure after 10 minutes of rest but no evidence was reported indicating the effect of rest time on ankle or toe pressures. Nevertheless, a rest time in supine position was undertaken in all participants prior to ABPI and TBPI measurements.

- Minimising perturbations – through clinical experience it is known that movement, coughing or talking during TBPI measurement creates perturbations in the PPG waveform, disrupting the reading. Therefore, participants were asked to remain as still and as quiet as possible during the reading. In cases where the TBPI readings were affected, the procedure was repeated until a clear reading was obtained.

The protocol for TBPI measurement is described in table 5.2. TBPI measurements were undertaken immediately after the ABPI readings.

- Following ABPI measurement, the PPG sensor was placed on the distal pulp of the hallux or second digit if this was amputated or ulcerated. The sensor was fixed with tape as in figure 5.2.
- The device automatically increased the sensitivity up to 40 times until a clear signal was obtained. Once this was stable, the 2.5cm toe cuff was placed proximally to the PPG as shown in Figure 5.2.
- The cuff was inflated until a flat lined PPG signal was shown on the display until a maximum of 150mmHg.
- The cuff was then slowly deflated at 2mmHg per second as indicated in the display.
- When a constant PPG wave signal returned, the device automatically indicated the pressure of the first return signal. In cases when the return wave was very low and was undetected by the device, the pressure reading of the first return wave was recorded manually by the researcher.
- The TBPI was calculated by dividing the toe pressure by the highest brachial pressure.

Table 5.2 Protocol for measuring TBPI during the study

Participants who had incompressible arteries due to non-closure after inflating the digital cuff >150mmHg were classified as having calcified digital arteries.

5.7 Blood parameters

Patients who attend the vascular unit and are diagnosed with PAD have blood tests booked as a routine procedure testing for: Renal profile, lipid profile, liver profile, HbA1c, fasting blood glucose, full blood count and erythrocyte sedimentation rate. For the purpose of this research C-reactive protein was added in the analysis since it is a known inflammatory marker of atherosclerotic disease (M. H. Criqui & Aboyans, 2015) as identified in Chapter Two.

5.8 Medication and Medical History

Current medication information was retrieved by reviewing the hospital discharge letters and through information provided by the potential participants. All medications prescribed to the participants were recorded for the purpose of this research.

Relevant previous medical history information was also obtained by reviewing hospital discharge letters together with analyzing the national hospital electronic database where any surgical procedures are recorded. The relevant information recorded were previous lower limb revascularisation, previous cardiac surgery, previous hospitalization due to a major adverse event (Myocardial infarction or stroke), known cardiovascular disease or spinal disease.

Following the literature review in Chapter Two it was important to note the presence of diabetes, hypertension and hyperlipidaemia. The definitions according to Criqui et al (M. H. Criqui et al., 2010) were applied to determine the presence of these risk factors:

- Hypertension - a resting systolic BP >140mmHg or participants with a history of hypertension taking anti-hypertensive drugs.

- Dyslipidaemia – total cholesterol to HDL cholesterol ratio >5mmol/L or medication use.

- Diabetes – Diabetes mellitus was defined according to the criteria of the American Diabetes Association (American Diabetes Association, 2018), that is: fasting glucose >126mg/dl or HbA1c >6.5%, and was assumed to be present in participants with a history of diabetes taking anti-diabetic medication.

5.9 Smoking history

Smoking habits were recorded according to guidelines (M. S. Conte et al., 2019) in routine clinical care, that is, as current smoker, previous smoker or never smoked. Potential participants were asked whether they currently smoke, how many cigarettes they smoke per day and for how long (years). If they were past smokers they were asked how long ago they quit, how many cigarettes they smoked daily and how long they had been smoking for (in years). Packet years were calculated by multiplying the number of cigarettes smoked per day by the number of years.

5.10 Disease location

Defining anatomical location of stenosis was performed following assessment by Duplex scan performed by the vascular surgeon at the vascular unit. This information was retrieved after the participants' appointment at the hospital. The duplex scan reports of the participants were analysed in order to establish the location of the disease, as described by the vascular surgeon. The reports were accessed through the Vascular lab online database. This thesis followed the definitions of anatomical locations as described by the TASC steering committee (Jaff et al., 2015) where authors divided the locations as aortoiliac, femoropopliteal and infragenicular / infrapopliteal as illustrated in figure 5.3. For data collection, duplex scan images of the participants were retrieved and the location of the stenosis indicated in the image was recorded as illustrated in figure 5.4.

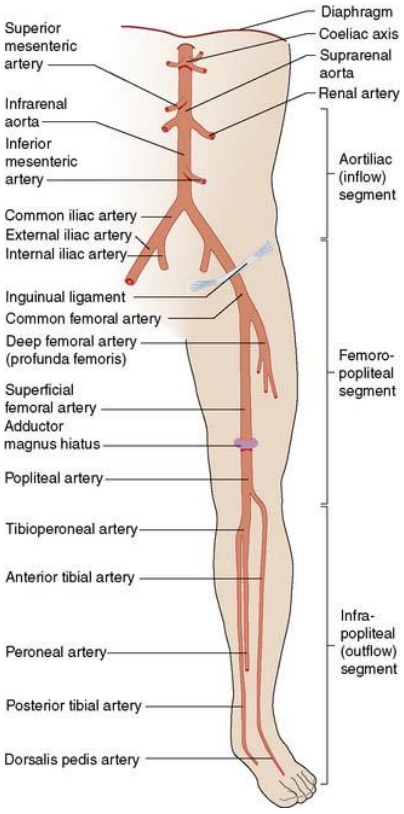


Fig. 5.3 Anatomical arterial segments. Image retrieved from https://basicmedicalkey.com/vascular-and-endovascular-surgery/

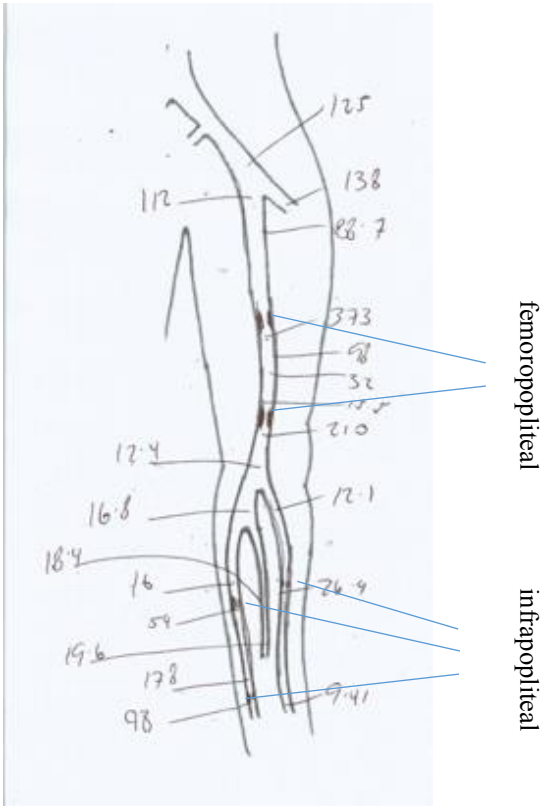


Fig. 5.4. Duplex scan image indicating participant location of stenoses

5.11 Calcified arteries

Following retrieval of Duplex scan reports, each document was assessed for reports of arterial calcification in the aortoiliac, femoropopliteal or infrapopliteal arterial segments as indicated by the vascular surgeon. Those who had calcified arteries were recorded as such on the data collection excel sheet of the study. Haemodynamic parameters were still assessed and recorded in these participants. As stated in sections 5.6.2.2. and 5.6.2.3, participants who had an ABPI>1.4 or non-closure when inflating the cuff were also recorded as having calcified arteries

5.12 Symptom severity

In this thesis symptom severity was measured using the Walking Impairment questionnaire (WIQ). As discussed in Chpater Two, section 2.4.2.2, the WIQ (Conijn et al., 2015; Coyne et al., 2003) is a validated function-specific interviewer administered questionnaire (Appendix 9) which focuses on symptom severity perceived in real life activities. The questionnaire (Coyne

et al., 2003) assesses four subscales – pain, distance, speed and stairs as perceived by the patient in the previous week. It can reliably detect symptom deterioration or improvement as perceived by the patients, making it a useful tool for objective testing of functional walking ability both in the routine clinical context and in research during patient follow-up (Nicolaï et al., 2009).

On the day of their appointment the questionnaire was first described verbally to the participants and then the questions were read to the participants by the researcher since interviewer-administered WIQ was found to be more reliable (Ouedraogo et al., 2011). For the purpose of this study, the questionnaire was translated to Maltese (Appendix 9) using the forward-backward translation method as defined by the WHO (Kalfoss, 2019). An independent Maltese language lecturer performed the forward translation, this was reviewed by the researcher and another bilingual professional to assess for inconsistencies between the translated document and the source language. The translated document was then back translated to English by another independent translator and the back-translated document was reviewed by the researcher for any inconsistencies which were amended accordingly. The preferred language (English or Maltese) was chosen by the participant and the score on the Likert scale was marked by the researcher.

The protocol for scoring the WIQ has been described by Mcdermott (McDermott et al., 1998) and was applied in this research. Of special interest was the WIQ distance score since the estimated walking distance by the patients is the most commonly reported symptom disability observed in the referral forms retrieved in this study. The participant estimated walking distance on the WIQ was reported for every participant as proposed by Frans et al (2013) since this was found to be strongly correlated to the treadmill test (Myers, Johanning, Stergiou, Lynch, Longo, & Pipinos, 2008).

The WIQ distance score (Fig. 5.5) describes the degree of difficulty experienced when walking specified distances ranging from 20 metres to 500 metres, ranked on a Likert scale from 1 to 5 where 1 represents no difficulty to walk the distance and 5 represents inability to walk the distance (McDermott et al., 1998). The distances are weighted from 1 to 5. Each Likert score is multiplied by the weight, summed and divided by the maximum possible score to calculate the score for that domain. The higher the score obtained, the worse are the symptoms experienced. An additional option of ‘didn’t do for other reasons’ was included in a later version (Coyne et al., 2003) (Figure 5.5) of the WIQ for patients who could not walk due to

other reasons such as breathlessness, hip or knee pain etc. In cases when this occurred at baseline, participants were excluded since IC could not be defined, when this occurred during follow-up, the WIQ score was not calculated and excluded from analysis.

During the last week *how difficult was it for you*	**No diffuculty**	**Slight difficulty**	**Some difficulty**	**Much difficulty**	**Unable to do**	**Didn't do for other reasons**
Walk indoors such as around the house	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
1. Walk 20m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. Walk 50m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Walk 100m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Walk 200m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5.Walk 300m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Walk 500m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Figure 5.5 The *walking distance* subscale of the Walking Impairment Questionnaire (Coyne et al., 2003)

5.13 Potential cofounders

Potential cofounders were identified in the literature when assessing IC symptoms (Kalfoss, 2019; Schorr & Treat-Jacobson, 2013). These were recorded at each participant appointment.

- Spinal stenosis – defined by report on national patient information database following diagnosis by an orthopaedic surgeon.
- Neuropathy – was assessed by 10g monofilament following definition by (Feng et al., 2009)
- Arthritis – as reported by the participant following diagnosis by GP or orthopaedic surgeon.
- Depression – defined by anti-depressive medication.
- Malignancy – defined by diagnosis on patient medical records
- Breathlessness which precludes walking – defined by the patient

5.14 Outcome measures

Following recruitment all the participants were provided with a follow-up appointment after 12 months and after 24 months of the first visit. Each participant was reminded by phone about the appointment two weeks before and amendments were made if needed. At the follow-up appointments the following data was recorded:

- ABPI
- TBPI
- Doppler waveforms
- Symptom severity
- Adverse events (explained in further detail the following section 5.14.1)

Outcome of events were extracted from three databases for which ethical approval for access was obtained previously (Chapter 3, section 3.10) – The CPAS (Central patient access system) which is a patient identification and patient care locator system which records patient attendance at any clinic within the Health department in Malta, both in primary and secondary care. Reports of mortality are also recorded in this system. The second database is the iSoft database which reports any intervention, blood results and angiographic reports of the patients. The third database is the Vascular laboratory database where reports of patients' diagnoses by the vascular surgeon, treatment plan (revascularisation, amputation, review or other) and duplex scan reports were retrieved.

Prior to the follow-up, the databases were assessed for any new reports occurring in the past 12 months. This allowed recording of the outcomes of interest defined in section 5.14.1. On the day of the follow-up visit participants were asked about the occurrence of any adverse events to verify the information retrieved from the database and also in case they attended for care in a private hospital. When a possible event was noted, hospital discharge letters were retrieved from the patients' medical files for verification of information and confirmation of the event.

5.14.1 Adverse events

The adverse events of interest recorded in this thesis were:

Development of CLI - The term critical limb ischemia refers to all patients with chronic ischemic rest pain, ulcers / tissue loss or gangrene attributable to objectively proven arterial occlusive disease (M. S. Conte et al., 2019).

Revascularisation – any reported revascularisation procedure including angioplasty, bypass, thrombectomy or hybrid procedures.

Significant haemodynamic deterioration – defined as a decrease in ABPI by ≥0.15 or in TBPI by ≥0.1 (M. S. Conte et al., 2019). The 0.15 cut-off point represents clinically significant change in ABPI (M. H. Criqui et al., 2008).

Significant deterioration - referral for revascularisation due to deterioration of PAD and / or due change in the participants' symptom severity (surgery related to initial referral and any subsequent operation related to a failed primary procedure was not included as an adverse event).

Haemodynamic deterioration – a decrease in ABPI less than 0.15 and / or a decrease in TBPI <0.1 or a change in waveforms

Symptom deterioration –an increase in WIQ distance score

Cerebrovascular event – transient ischaemic attack, stroke, carotid revascularisation

Cardiovascular event – MI, Angina, cardiac revascularisation (CABG, PCI)

Mortality – death reported on the national database

5.14.2 Haemodynamic and symptom improvement

Haemodynamic improvement – an increase in ABPI provided that the participant did not have arterial calcification identified by duplex scan or improvement did not exceed 0.15 without revascularisation (V. Aboyans et al., 2018). An increase in TBPI without

revascularisation and / or a change in waveforms (indicating haemodynamic improvement). Those participants who had improved haemodynamics due to revascularisation were not considered as 'improved' for statistical analysis.

Symptom improvement – a decrease in WIQ distance score

Following data collection, the statistical analysis procedures were defined.

5.15 Statistical analysis

This section provides an overview of the statistical methods employed in this research, which were identified following guidance and advice from a statistician. Further details of each test are provided in the results sections of the respective tests.

As stated in Chapter 3, section 3.7.1, all continuous measures of gathered data were used for analysis which improves the test's ability to detect the outcome of interest (S. Mallett et al., 2012). Continuous data were given as mean and standard deviation or median and interquartile range, depending on the distribution pattern, while discrete data were presented as counts and percentages. The Chi-square test was applied to compare groups of categorical data and to test for trends. Mann – Whitney U tests were applied to compare groups of unpaired continuous data and Wilcoxon paired tests used to analyze repeated measurements.

Regression analysis was used to assess for factors associated with deterioration to CLI, significant haemodynamic deterioration, using respective models. The outcome of interest (Eg: development of CLI) was the dependent variable and the measures of baseline variables were the independent variables. Regression analysis is the most commonly used method for reducing confounding in cohort studies as it uses the data to estimate how confounders are related to the outcome and produces an adjusted estimate of the intervention effect (Hoffman, 2015). Since the estimated association between the baseline variables and outcome adjusts for the effects of all the measured baseline characteristics, the resulting estimate is the adjusted effect (Y. Zhang et al., 2016). The choice of method of regression analysis (linear, logistic, proportional hazards, etc) depends on the type of dependent variable. When the outcome is binary such as occurrence of an event, as in this research, the logistic regression model should be the method of choice (Hoffman, 2015). The main advantage of regression techniques is that data from all the

participants is used. Additionally, most researchers are familiar with the technique and the analysis can be done using readily available software. The results of the regression analysis were expressed as odds ratio (OR) and 95% confidence interval (95% CI).

While logistic regression calculates the OR of the variables of interest, the relative risk (RR) of the variables which were identified as significant independent predictors for the development of CLI was also calculated. The relative risk is defined as the ratio of the probability of the outcome (CLI) occurring in the group. When the incidence or risk of an outcome is very low in the general population, the rare disease assumption is adopted and the odds ratio derived from the regression analysis is assumed to be a good estimation of the relative risk as can be calculated by the formula (Grant, 2014).

Relative risk=odds ratio/(1-p_0 + (p_0 x odds ratio))
p_0 =baseline risk

The prevalence of CLI in the general population reported in the literature is 0.24% (Bitar & Garcia, 2010; Jensen et al., 2006; Nehler et al., 2014). Therefore, since the incidence of CLI in the general population is less than 10% the odds ratio and relative risk are very similar and do not vary and the rare disease assumption is applied where the OR derived from the logistic regression analysis can be expressed as RR (J. Zhang & Kai, 1998).

The ROC (receiver operator characteristic) analysis was applied to assess the performance of the predictive model as a diagnostic test. The ROC curve is a two-dimensional plot where the vertical axis represents the true positive rate and the horizontal axis represents the false-positive rate. Therefore, classifying whether a disease is predicted or not is represented by a single point on the ROC curve. In cases where a continuous variable is being tested, then the binary classification can be specified by a 'cut-off' point or threshold which best determines the prediction (Shapiro, 1999). Statistical analysis was performed using SPSS for MAC (Version 26.0, SPSS Inc., IL, USA). The results following data collection are presented in the succeeding chapters.

CHAPTER SIX

Characteristics of patients with IC. A cross-sectional prospective cohort observational study (study 3)

6.1 Introduction

As highlighted in Chapter Two and confirmed in study 1, evidence reporting the progression of PAD in patients with IC is limited in published literature (Mizzi et al., 2019). This information is required for clinicians to make an informed decision when selecting treatment to reduce the risk of deterioration to CLI which would otherwise increase the risk of morbidity and mortality significantly (Anand et al., 2018). Furthermore, the scoping study presented in Chapter four (Study 2) demonstrated that in Malta (where the study took place), there was a lack of knowledge related to the characteristics of the patient presenting with IC, making it difficult to evaluate the outcomes of these patients in relation to their condition. The aim of this study (Study 3) was therefore to establish the characteristics, medical condition and medication through the development of a prospective registry of patients with IC. Results from this study were used as the baseline data for the prospective longitudinal observational study which is presented in Chapter Seven.

The development of a Prospective registry of patients with IC in Malta would provide insight into patient characteristics and treatment outcomes in Malta. To date, there is no national Prospective Registry of this kind in Malta and its formulation would provide an opportunity to explore the local current prevalence of PAD risk factors among patients with IC.

6.2 Aim and objectives of the study

The aim of this study was to establish the participant characteristics in terms of risk factors, medication, blood profile (detailed in Chapter Five), haemodynamics and symptom severity of patients diagnosed with IC. The data gathered was used to establish the baseline data for the longitudinal observational study which followed (Study 4).

This study aims to answer the question:

What are the characteristics of patients presenting with IC?

6.2.1 Objectives

- To identify baseline patient characteristics in patients with IC
- To identify baseline medication use in patients with IC
- To compare baseline characteristics of the Maltese population with IC with established population characteristics observed in other populations evidenced in published literature.

A discussion and a detailed description of the methods employed for this study have been presented in Chapter Five. As formerly described therefore, this study employed a cross-sectional observational prospective cohort design and included new consecutive referrals to the vascular unit of patients with IC over a period of twelve months. The referrals were received from all primary care clinics as established by the changes implemented following the scoping study (Study 2).

The study protocols for the recruited participants, including obtaining consent, haemodynamic analysis, blood results, medication and medical condition, were followed as explained in Chapter five. Formal ethics approvals were obtained as also described in Chapter Three.

6.3 Results

A total of 246 potential participants were referred with IC as the reason of referral to the vascular unit. Out of these, 3 participants did not respond, 93 were incorrectly referred to this clinic since they were found not to have PAD and 150 participants were eligible for the study. All 150 participants agreed to participate and were recruited to this study.

This section first presents the baseline characteristics of the participants, the baseline haemodynamic data, medical history profile and medication profile. The difference in participant characteristics, medical history and haemodynamic parameters between men and women and also between participants with a history of chronic heart disease (CHD) or diabetes and those without, were also explored. The correlation between the haemodynamic parameters recorded (Doppler waveforms, ABPI, TBPI, absolute toe pressures) was also explored and presented in this chapter.

In order to assess whether any differences exist between IC participants in Malta and those in other countries, the participant characteristics, medical history, medication history and haemodynamic parameters were compared with previously published data from a similar cohort of patients in the UK (Khan et al., 2007). The one-sample t-test was applied in this analysis.

In this chapter, for ease of understanding, only the main results of the statistical tests are presented. The full relevant individual tests can be found in Appendix 10.

6.3.1 Descriptive statistics

6.3.1.1 Participant Characteristics

A total of 150 participants were recruited of whom 31 (20.7%) were women and 119 (79.3%) were men. The recruited participants' age and BMI are presented in the table 6.1 as means and standard deviation.

	Mean	SD	Minimum	Maximum
Age (years) n=150	69.7	9.3	38	88
BMI n=150	27.8	4.27	18.9	47.1

Table 6.1 Mean age and BMI

The mean age of the participants was 69.7 years, ranging from 38 to 88 years. The mean BMI (defined as weight in kg divided by height in m^2) was 27.8 which falls within the 'overweight' range (25 to 29.9Kg/m^2). In this study 119 participants were men while 31 were women, indicating that the majority of the recruited participants were male (79.3%).

6.3.1.2 Smoking status

The smoking status of the participants at recruitment is presented as counts and percentages in the table 6.2. The number of years smoked and pack years smoked, for current smokers and ex-smokers is presented in table 6.4. Pack years is defined as number of packs of cigarettes smoked daily multiplied by number of years smoked (One pack=20 cigarettes).

		Frequency	Percentage
Smoking Status	Current Smoker	55	36.7%
	Ex-smoker	62	41.3%
	Never smoked	33	22%
	Total	150	100%

Table 6.2 Smoking Status of participants

A total of 78% of the participants had a smoking history, that is, were either current smokers or ex-smokers. Fifty-five (36.7%) participants were smoking at recruitment, while 62 (41.3%) were ex-smokers and 33 (22%) participants had never smoked.

		Mean	SD	Minimum	Maximum
Ex-Smokers (n=62)	Smoking duration (years)	40.7	9.91	20	66
	Pack years smoked	72.5	43.62	8	200
Current Smokers (n=55)	Smoking duration (years)	45.3	14.15	15	70
	Pack years smoked	54.8	43.28	6	235

Table 6.3 Smoking duration and pack years smoked

Among the ex-smokers (Table 6.3), mean smoking duration was 40.7 years and mean pack years smoked was 72.5. For current smokers, mean smoking duration was 45.3 years and mean pack years were 54.8.

6.3.1.3 Medical History and medication

The medical history and medication taken by the participants at recruitment are presented in counts and percentages in table 6.4. As described in Chapter 3, section 3.10, the information was retrieved from the medical records, participant medication forms and databases of the national health service, after obtaining the relevant permissions. The definitions used in this investigation for each medical condition are presented in Chapter Five, section 5.8.

		Frequency (n=150)	Percentage
Medical History	Ho of Diabetes	104	69.3%
	Ho of hypertension	129	86%
	Ho of hyperlipidaemia	116	77.3%
	Ho of renal disease	47	31.1%
	Ho cardiac disease	61	40.7%
	Prior cardiac intervention	58	38.7%
	Prior MI	29	19.3%
	Prior CVA	15	10%
Medication	Statins	113	75.3%
	Antiplatelets	112	74.7%
	Anticoagulants	12	8%
	On Antiplatelet / anticoagulant	119	79.3%
	Not on Antiplatelet / Anticoagulant	31	20.7%
	ACE inhibitor	72	48%
	Angiotensin receptor blocker	22	14.7%
	Calcium channel blocker	36	24%
	Beta Blocker	12	8%

Table 6.4 Medical history and medication taken by participants

Results show that the most common medical conditions among the participants were hypertension, hyperlipidaemia and diabetes. Cardiac disease was present in 40.7% of the participants and 38.7% had a prior cardiac intervention (Cardiac bypass or stenting).

Results also show that approximately 75% of the participants were taking statins and anti-platelet therapy and 8% were taking anti-coagulants. A total of 31 (20.7%) participants were not taking any antiplatelet or anti-coagulant therapy. The most common anti-hypertensive drugs prescribed among the participants were Ace inhibitors followed by calcium channel blockers.

6.3.1.4 Blood parameters

The median values of the blood test results collected prospectively at recruitment are presented in table 6.7 as median and interquartile range (IQR) since the data did not have a normal distribution (Shapiro Wilk test, Appendix 11).

Table 6.5 Participant blood results at baseline

Blood parameters	Median	Interquartile range		Normal range
		First	Third	
eGFR (mls/min/1.73m^2) n=150	79.50	54.75	97.00	> 60
Cholesterol (mmol/l) n=150	4.31	3.57	5.10	2.0 - 5.0
Triglyceride (mmol/l) n=150	1.44	1.00	2.03	0.1 - 2.26
HDL Cholesterol (mmol/l) n=150	1.17	.93	1.42	0.9 - 1.45
Non HDL Cholesterol (mmol/l) n=150	3.04	2.36	3.88	0 - 3.36
LDL Cholesterol (mmol/l) n=150	2.27	1.65	2.96	0.1 - 3.88
Total Cholesterol: HDL ratio n=150	3.64	2.82	4.72	-
Fasting Glucose (mmol/l) n=115	**7.55**	5.94	9.90	3.88-6.38
HbA1c (%) n=150	**6.69**	5.80	7.60	4.7 - 6.4
Creatinine (umol/l) n=150	82.5	69.75	113.50	59 - 104
CRP (mg/L) n=139	2.20	1.10	5.40	0 - 5
ESR (mm 1st hr) n=136	15	8.00	29.00	28 - 32

Results show that the median values for fasting glucose (median 7.55mmol/L IQR 5.9,9.9) and HbA1c (median 6.6% IQR 5.8, 7.6) were above the normal range. The rest of the blood parameters were within the normal range.

6.3.1.5 Location of disease and symptoms

The location of symptoms, indicating the location of stenosis identified by Duplex scans is reported in table 6.6. Additionally, the location of symptoms whether unilateral or bilateral, as reported by the participants is presented as counts and percentages. A total of 132 out of 150 participants were scanned by duplex following recruitment. Table 6.6 illustrates the location of disease (defined as stenosis/occlusion and/or calcification) as reported by the vascular surgeon on the duplex scan report.

Table 6.6 Location of disease and symptoms at baseline

		Frequency	Percentage
Disease location n=132	Aortoiliac (artoiliac only)	18 (0)	13.6%
	Femoropopliteal (femoropopliteal only)	101 (39)	76.5%
	Infrapopliteal (infrapopliteal only)	67 (15)	50.8%
Symptom Location	Bilateral calf claudication	86	57.3%
	Unilateral calf claudication	64	42.7%

Table 6.6 illustrates that the most common disease location was the femoropopliteal segment, reported in 76.5% of the scanned participants, followed by the infrapopliteal segment (50.8%) and the aortoiliac segment (13.6%). None of the participants only aortoliliac disease, 39 participants had disease only in the femoropopliteal segment while 15 participants had only IPA artery disease.

Eighty-six participants (57.3%) complained of bilateral calf claudication while 64 (42.7%) experienced the symptom only in one leg. In those who had bilateral IC, the side (left or right) denoting the most symptomatic limb was also recorded to be used for further analysis as recommended by Allen et al (Allen et al., 1996).

6.3.1.6 Brachial systolic blood pressure

The mean systolic blood pressure of the participants recorded during ABPI assessment is presented as mean and SD in the table 6.7.

Table 6.7 Brachial systolic blood pressure at baseline

Systolic BP mean 149.96 mmHg (±22.3)		Frequency n=150	Percentage
Systolic blood pressure	<140mmHg	46	30.7%
	140mmHg to160mmHg	60	40%
	>160mmHg	44	29.3%

The mean brachial systolic blood pressure (Table 6.9) recorded during ABPI measurement was 149.96mmHg (SD 22.3) ranging between 100 and 217mmHg. A total of 104 participants (69.3%) had a systolic pressure exceeding 140mmHg, out of these, in 44 participants, the brachial systolic pressure was above 160mmHg at the time of assessment.

6.3.1.7 Haemodynamic parameters and symptoms

The results of the haemodynamic tests at recruitment, that is, ABPI, TBPI, absolute toe pressures and claudication distance and WIQ score are presented as median and IQR in the table 6.8 since the data did not have a normal distribution (Shapiro-Wilk test, Appendix 11).

Table 6.8 Haemodynamic parameters and symptoms at baseline

Parameter	Median	Interquartile range	
		First	Third
ABPI R n=148	0.81	0.69	0.96
ABPI L n=150	0.82	0.68	0.98
ABPI (symptomatic limb) n=150	0.66	0.55	0.81
ABPI* (excluding calcified arteries) n=125	0.62	0.53	0.74
TBPI n=150	0.38	0.28	0.5
Absolute toe pressures (mmHg) n=150	58	42	80.25
Claudication distance (m) n=150	100	50	200
Walking impairment questionnaire score	65.7	46	74

ABPI includes readings of symptomatic or most symptomatic limbs, excludes ABPI of asymptomatic limbs.
ABPI* excludes results of calcified arteries defined by ABPI >1.4 or calcification reported in duplex scan

The overall median ABPI (including both symptomatic and asymptomatic limbs) in the right was 0.81 and the left was 0.82. The median ABPI of the symptomatic or most symptomatic limbs was 0.66 (IQR 0.55, 0.81). This was calculated by including the ABPI results only of the symptomatic limb in those who had unilateral IC and the most symptomatic limb, in those with bilateral IC as recommended by Allen et al (Allen et al., 1996). Following this, in order to investigate ABPI reading when eliminating artefactually elevated ABPI results occurring due to arterial calcification, the median ABPI excluding those with calcified arteries was also calculated (n=125). Calcification was defined as ABPI >1.4 or calcification reported in the duplex scan. This is denoted as 'ABPI*' and was 0.62 (IQR 0.53, 0.74). The median TBPI (0.38 IQR 0.28, 0.5) and absolute toe pressures (58mmHg IQR 42, 80.25) at recruitment, are those reported in the symptomatic or most symptomatic limbs.

For further analyses shown in the following sections only ABPI readings of the symptomatic or most symptomatic limbs (in cases who had bilateral claudication) and ABPI* (symptomatic limbs excluding calcified arteries) were used since it was the data of interest.

6.3.2 Analysing gender differences

Due to the known increased risk of PAD in men and the delayed presentation of PAD in women (Criqui & Aboyans, 2015), gender differences in the baseline variables were analysed (table 6.9). The chi square test and one-way Anova or Kruskal-Wallis (for variables with a non-normal distribution) were applied. The significance level was set at 0.003 after applying the Bonferroni correction as recommended by Bland and Altmann (1995). The full test results can be found in Appendix 10.

Table 6.9 Gender differences in baseline characteristics

	Female N=31	Male N=119	N=150	p-value	Statistic
Age at enrolment, mean (SD)*	69.4 (8.9)	69.8 (9.5)	150	0.82	F(1,148)=4.64
BMI mean (SD)*	27.5 (5.9)	27.9 (3.8)	150	0.682	F(1,148)=0.17
Ho of Diabetes n (%)**	17 (54.8%)	87 (73.1%)	104 (69.3%)	0.049	**X^2 (1)=3.86**
Ho of hypertension n (%)**	25 (80.6%)	104 (87.4%)	129 (86%)	0.36	X^2 (1)=0.931
Ho of hyperlipidaemia n (%)**	24 (77.4%)	92 (77.3%)	116 (77.3%)	0.99	X^2 (1)=0.001
Ho of renal disease n (%)**	7 (22.6%)	40 (33.6%)	47 (31.3%)	0.24	X^2 (1)=1.39
Prior MI n (%)**	2 (6.5%)	27 (22.7%)	29 (19.3%)	0.041	**X^2 (1)=4.16**
Ho cardiac disease n (%)**	9 (29%)	52 (43.7%)	61 (40.7%)	0.14	X^2 (1)=2.19
Prior Cardiac intervention n(%)**	9 (29%)	49 (41.2%)	58 (38.7%)	0.216	X^2 (1)=1.53
Prior CVA n (%)**	4 (12.9%)	11 (9.2%)	15 (10%)	0.55	X^2 (1)=0.37
Previous major event	12 (38.7)	55 (46.2)	67 (45)	0.46	X^2 (1)=0.56
Statin medication	19 (61.3)	94 (79)	113 (75.3)	0.04	X^2 (1)=4.15
Antiplatelet medication	19 (61.3)	93 (78)	112 (94)	0.06	X^2 (1)=3.67
Smoking history n (%)**	14 (45.2%)	103 (86.5%)	150	**<0.0001**	**X^2 (2)=27.0**
ABPI median (IQR)***	0.62 (0.51, 0.71)	0.68 (0.56, 0.84)	150	0.207	2.997
ABPI* median (IQR)***	0.57 (0.49,0.68)	0.61 (0.52. 0.75)	125	0.083	1.593
TBPI median (IQR)***	0.34 (0.25, 0.42)	0.41 (0.28, 0.51)	150	0.063	3.46
Absolute toe pressures (mmHg)***	54 (41,69)	60 (44, 83)	150	0.15	1.992

*One-way Anova test performed, **Chi square test performed, *** Kruskall-Wallis test performed.

Results (table 6.9) show that there was a significantly higher proportion of men who smoked or had a history of smoking compared to women ($p<0.0001$). There was no significant difference between gender in the rest of the parameters investigated.

6.3.3 Analysis Diabetes

The differences in baseline parameters recorded between participants who had diabetes and participants who did not, were analysed. The One-way Anova, Chi square test and Kruskal-Wallis tests were applied according to the distribution of the data. The results are summarized in table 6.10. The significance level was set at 0.003 after applying the Bonferroni correction as recommended by Bland and Altmann (1995).

Table 6.10 Baseline differences between participants with and without diabetes

	Diabetes n=104	No Diabetes n=46	N=150	Test statistic	p-value
Age at enrolment, mean (SD)*	71.3 (8.4)	65.9 (10.2)	150	**F(1,148)=11.7**	**0.001**
BMI mean (SD)*	27.9 (3.2)	27.4 (6.1)	150	F(1,148)=0.44	0.51
Ho of hypertension n (%)**	97 (93.3)	32 (69.6)	129	**X^2 (1)=14.89**	**<0.0001**
Ho of hyperlipidaemia n (%)**	86 (82.7)	30 (65.2)	116	X^2 (1)=5.56	0.018
Ho of renal disease n (%)**	40 (38.5)	7 (15.2)	47	X^2 (1)=8.00	0.005
Prior MI n (%)**	22 (21.1)	7 (15.2)	29	X^2 (1)=0.72	0.4
Ho cardiac disease n (%)**	49 (47.1)	12 (26.1)	61	X^2 (1)=5.85	0.016
Prior cardiac intervention n(%)	46 (44.2)	12 (26.8)	58	X^2 (1)=4.43	0.035
Prior Major event n (%)**	54 (51.9)	13 (28.3)	67	X^2 (1)=7.23	0.007
Prior CVA n (%)**	13 (12.5)	2 (4.3)	15	X^2 (1)=2.36	0.125
Smokers (Current/past) n (%)**	81 (77.9)	37 (80.4)	118	X^2 (1)=0.12	0.725
Statin medication**	91 (87.5)	22 (47.8)	113	**X^2 (1)=27.0**	**0.001**
Antiplatelet medication**	86 (82.7)	26 (56.5)	112	**X^2 (1)=11.55**	**0.001**
ABPI median (IQR)***	0.69 (0.56,0.91)	0.62 (0.51,0.78)	150	6.377	0.012
ABPI* median (IQR)***	0.63 (0.53, 0.73)	0.56 (0.47,0.68)	125	4.227	0.04
TBPI median (IQR)***	0.4 (0.3,0.53)	0.37 (0.28,0.44)	150	4.453	0.035
Absolute toe pressures (mmHg)***	60.5 (45,83)	54.5 (38,70)	150	3.479	0.05

*One-way Anova test performed, **Chi square test performed, *** Kruskall-Wallis test performed.

Results indicate that group of participants with diabetes was significantly older, had a higher proportion of participants with hypertension ($p<0.003$). A significantly higher proportions of participants with diabetes were on statin and antiplatelet medication ($p<0.003$).

6.3.4 Analysing coronary heart disease

Coronary heart disease (CHD) (defined as prior MI, angina, prior CABG or prior PTCA) was analysed in further detail. Differences in variables of interest were assessed between participants who had known CHD and those who had no prior history of CHD (Table 6.11). The significance level was set at 0.003 after applying the Bonferroni correction as recommended by Bland and Altmann (1995).

Table 6.11 Differences between participants with CHD and without CHD

Characteristic	Prior CHD N=61	No prior CHD N=89	Statistic	p-value
Age at enrolment, mean (SD)*	70.8 (9.4)	68.4 (9.2)	F(1,148)=1.44	0.232
BMI, mean (SD)*	28.3 (4.2)	27.5 (4.3)	F(1,148)=1.28	0.259
Gender Female n (%)**	9 (14.8%)	22 (24.7%)	X^2 (1)=2.19	0.14
Male n (%)**	52 (85.2%)	67 (75.3%)		
Claudication distance m, median (IQR)***	100(50,200)	100 (25,200)	0.054	0.83
Ho of Diabetes n (%)**	49 (80.3%)	55 (61.8%)	X^2 (1)=5.85	0.016
Ho of hypertension n (%)**	59 (96.7%)	70 (78.7%)	**X^2 (1)=9.82**	**0.002**
Ho of hyperlipidaemia n (%)**	58 (95.1%)	58 (65.2%)	**X^2 (1)=18.46**	**<0.0001**
Ho of renal disease n (%)**	23 (37.7%)	24 (27%)	X^2 (1)=1.94	0.164
Prior CVA n (%)**	6 (9.8%)	9 (10.1%)	X^2 (1)=0.003	0.96
Systolic blood pressure (mmHg) mean (SD)*	145.2 (20.2)	153.2 (23.2)	F(1,148)=4.72	0.031
Smokers** Current/ past smokers	48 (78.6%)	70 (78.7%)	X^2(1)=0.00	0.996
Statin therapy	57 (93.4)	56 (63)	**X^2 (1)=18.14**	**<0.0001**
Antiplatelet therapy	53 (86.9)	59 (66.3)	X^2 (1)=8.14	0.004
ABPI* median (IQR)***	0.66 (0.53,0.74)	0.58 (0.50, 0.7)	2.902	0.088
ABPI median (IQR)***	0.70 (0.59,0.95)	0.62 (0.53,0.79)	5.679	0.017
TBPI median (IQR)***	0.39 (0.34,0.53)	0.38 (0.25,0.50)	3.271	0.07
Absolute toe pressures (mmHg)***	58 (50,81)	57 (36,79)	0.362	0.32

*One-way Anova test, **Chi square test, *** Kruskall-Wallis test.

There was a significantly greater proportion of participants with hypertension and hyperlipidaemia and taking statin therapy in those with known CHD compared to those without CHD (Chi squared test p <0.003) but there was no difference in the rest of the parameters between the two groups (p>0.003).

6.3.5 Analysing age

The age-wise distribution of PAD risk factors was assessed in the following sections.

6.3.5.1 Age group and medical history

Differences in medical history according to age group was analysed using the Chi square test and results are presented in table 6.12. Significance for each variable was set at 0.006 according to the Bonferroni correction.

Medical history			≤59 years	60-69 yrs	70-79 yrs	≥80 yrs	Total	X^2	df	P value
Diabetes	Diabetes	Count	12	32	40	20	104	10.11	3	0.021
		Percentage	46.2%	66.7%	80.0%	76.9%	69.3%			
	No Diabetes	Count	14	16	10	6	46			
		Percentage	53.8%	33.3%	20.0%	23.1%	30.7%			
Hyper-tension	Hypertension	Count	23	39	44	23	129	1.33	3	0.723
		Percentage	88.5%	81.3%	88%	88.5%	86%			
	No Hypertension	Count	3	9	6	3	21			
		Percentage	11.5%	18.8%	12.0%	11.5%	14.0%			
Hyper-lipidaemia	Hyperlipidaemia	Count	20	34	42	20	116	2.43	3	0.488
		Percentage	76.9%	70.8%	84%	76.9%	77.3%			
	No hyperlipidaemia	Count	6	14	8	6	34			
		Percentage	23.1%	29.2%	16.0%	23.1%	22.7%			
Cardiac Disease	Cardiac Disease	Count	10	17	21	13	61	1.58	3	0.665
		Percentage	38.5%	35.4%	42%	50%	40.7%			
	No Cardiac disease	Count	16	31	29	13	89			
		Percentage	61.5%	64.6%	58.0%	50.0%	59.3%			
Renal Disease	Renal Disease	Count	1	10	19	17	47	26.63	3	**<0.001**
		Percentage	3.8%	20.8%	38%	65.4%	31.3%			
	No renal disease	Count	25	38	31	9	103			
		Percentage	96.2%	79.2%	62.0%	34.6%	68.7%			
History of MI	History of MI	Count	6	10	9	4	29	0.62	3	0.892
		Percentage	23.1%	20.8%	18.0%	15.4%	19.3%			
	No History of MI	Count	20	38	41	22	121			
		Percentage	76.9%	79.2%	82.0%	84.6%	80.7%			
History of CVA	History of CVA	Count	2	2	9	2	15	5.68	3	0.128
		Percentage	7.7%	4.2%	18.0%	7.7%	10.0%			
	No history of CVA	Count	24	46	41	24	135			
		Percentage	92.3%	95.8%	82.0%	92.3%	90.0%			

Table 6.12 Differences in medical history by age group (X^2 test)

The results show (table 6.12) that as age increases, there is a higher percentage of participants having renal disease, with the highest percentages being 80 or older (Fisher's exact test P<0.0001). Post hoc analysis indicates that the difference lies in the group aged 80 or older (p=0.0007). Post hoc tests, expected values and Fisher's exact test results can be found in Appendix 10, Tables 10.3 to 10.5). There was no significant difference in age-wise distribution in hypertension, hyperlipidaemia, cardiac disease and history of MI or CVA.

6.3.5.2 Age group and smoking status

The chi square test was applied to assess the age-wise distribution of smoking history among the participants (table 6.13).

Table 6.13 Age group vs smoking status

			Age-group				Total
			59 years or less	60-69 years	70-79 years	80 years or more	
Smoking status	Current smoker	Count	22	16	10	7	55
		Percentage	84.6%	33.3%	20.0%	26.9%	36.7%
	Ex-smoker	Count	3	23	26	10	62
		Percentage	11.5%	47.9%	52.0%	38.5%	41.3%
	Never smoked	Count	1	9	14	9	33
		Percentage	3.8%	18.8%	28.0%	34.6%	22.0%
Total		Count	26	48	50	26	150

$X^2(6) = 35.249$, **$p < 0.001$**

The results show that as age increased, the number of current smokers decreased, with the highest number of current smokers being 59 years of age or less. The number of ex-smokers also increased with increasing age. These percentage differences are significant since the p value is less than the 0.05 level of significance.

6.3.5.3 Age group and haemodynamics

The difference in baseline haemodynamics between age groups was assessed using the Kruskal-Wallis test. In section 6.3.7.2 the relationship between age and haemodynamic parameters is also presented.

Variable	≤59 years	60-69 yrs	70-79 yrs	≥80 yrs	Df	p-value
ABPI median (IQR)	0.66 (0.53,0.79)	0.66 (0.55,0.78)	0.7 (0.55,0.86)	0.66 (0.54,1.0)	3	0.72
ABPI* median (IQR)	0.62 (0.53,0.77)	0.61 (0.51,0.68)	0.61 (0.52,0.75)	0.56 (0.43,0.65)	3	0.27
TBPI median (IQR)	0.42 (0.28,0.55)	0.41 (0.32,0.56)	0.37 (0.27,0.46)	0.38 (0.26,0.51)	3	0.28
Absolute toe pressure mmHg median (IQR)	72 (43.5,88.7)	62.5 (44.5,85.8)	56.5 (40.8,67.8)	54 (35.5,63.7)	3	0.08
Claudication distance m median (IQR)	100 (50,225)	100 (50,200)	100 (50,150)	100 (50,150)	3	0.71
WIQ score median (IQR)	65 (42.8,69)	65.2 (46,74)	65.4 (49,74)	65.7 (50,74)	3	0.75

Table 6.14 Difference in haemodynamic parameters between age groups (kruskal-wallis)

Results in table 6.14 show that there was no significant differnce in haemodynamic parameters or symptom severity across age groups.

6.3.6 Analysing haemodynamic parameters

This section presents the results investigating the correlation between the haemodynamic parameters recorded (ABPI, TBPI, ABPI* and absolute toe pressures) and also between the haemodynamic parameters and Doppler waveforms. This is followed by an investigation of the association between haemodynamic parameters and main known risk factors for PAD (section 6.3.6).

6.3.6.1 Correlation between haemodynamic parameters

The correlation between the haemodynamic parameters recorded was investigated using the Spearman correlation test since the variables did not have a normal distribution (Shapiro Wilk test, Appendix 11). The results are presented in table 6.15.

Table 6.15 Correlation between haemodynamic parameters

		Spearman's rho	P value
ABPI (n=150)	**ABPI*** (n=125)	0.796	**<0.0001****
	TBPI	0.379	**<0.0001****
	Absolute toe pressures	0.332	**0.011***
	Claudication distance	0.1	0.08
ABPI* (n=125)	**TBPI**	0.387	**<0.01****
	Absolute toe pressures	0.344	**<0.0001****
	Claudication distance	0.29	**<0.01****
TBPI (n=150)	**Absolute toe pressures**	0.922	**<0.001****
	Claudication distance	0.157	**0.03***
Absolute toe pressures	**Claudication distance**	0.177	**0.03***

*Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed).

Results show that ABPI*, TBPI, absolute toe pressures and claudication distance have a statistically significant positive correlation ($p<0.05$). The ABPI (including calcified arteries) has a significant correlation with ABPI*, TBPI and absolute toe pressures but no significant correlation with claudication distance was found.

6.3.6.1.2 Relationship between Doppler waveforms and other haemodynamic parameters

The association between Doppler waveforms and ABPI, TBPI, absolute toe pressures and claudication distance was assessed according to waveform recorded using the Kruskal-Wallis test. The waveforms ranged from absent to biphasic. No triphasic waveforms were present in the symptomatic or most symptomatic limbs analysed. The DP and PT waveforms were analysed separately (tables 6.16 and 6.17 respectively)

		N	Median	IQR 1	IQR 3	P value
ABPI* N=125	Absent	3	0.52	0.4	0.8	**<.0001**
	Monophasic Continuous	56	0.56	0.47	0.64	
	Monophasic	57	0.66	0.56	0.74	
	Biphasic	9	0.77	0.69	0.83	
ABPI N=150	Absent	4	0.56	0.21	0.87	**0.005**
	Monophasic Continuous	68	0.60	0.51	0.8	
	Monophasic	68	0.69	0.59	0.79	
	Biphasic	10	0.82	0.73	0.92	
TBPI	Absent	4	0.46	0.29	0.65	**<.0001**
	Monophasic Continuous	67	0.34	0.27	0.47	
	Monophasic	68	0.41	0.33	0.51	
	Biphasic	10	0.54	0.46	0.73	
Absolute toe pressure	Absent	4	61	42	88	**0.001**
	Monophasic Continuous	67	55	37	73	
	Monophasic	68	59	44	82	
	Biphasic	10	83	73	92	
Claudication distance	Absent	4	50	50	87	**0.011**
	Monophasic Continuous	68	100	50	100	
	Monophasic	68	100	71.3	200	
	Biphasic	10	200	131.5	325	

Table 6.16 Haemodynamics and DP Doppler waveforms

Results show (Table 6.16) that overall as the waveform deteriorated from biphasic to absent, the haemodynamic results also declined. The overall difference in ABPI, ABPI*, TBPI, absolute toe pressures and claudication distance is significant between the categorized DP

Doppler waveforms. Post hoc analysis (Tukey, Appendix 10) shows that the difference lies between biphasic waveforms and all the other categorized waveforms (p=<0.05).

		N	Median	IQR 1	IQR 3	P value
ABPI* N=125	Absent	4	0.55	0.31	0.61	**<.0001**
	Monophasic Continuous	47	0.56	0.47	0.66	
	Monophasic	65	0.62	0.52	0.72	
	Biphasic	9	0.77	0.71	0.83	
ABPI N=150	Absent	4	0.55	0.22	0.62	**0.003**
	Monophasic Continuous	57	0.61	0.52	0.75	
	Monophasic	77	0.68	0.55	0.83	
	Biphasic	12	0.80	0.76	0.98	
TBPI N=150	Absent	4	0.36	0.18	0.50	**<0.0001**
	Monophasic Continuous	56	0.34	0.2	0.44	
	Monophasic	77	0.41	0.16	0.02	
	Biphasic	12	0.51	0.46	0.65	
Absolute toe pressure mmHg N=150	Absent	4	49	35	63	**0.002**
	Monophasic Continuous	56	52	36	71	
	Monophasic	77	58	44	85	
	Biphasic	12	76	63	98	
Claudication distance	Absent	4	62.5	50	93.7	**0.002**
	Monophasic Continuous	57	100	50	100	
	Monophasic	77	100	60	200	
	Biphasic	12	200	150	375	

Table 6.17 Haemodynamics and PT Doppler waveforms

The results for the PT artery (Table 6.17) were similar to those found for the DP artery indicating that as the waveform deteriorated from biphasic to absent, the haemodynamic results

also deteriorate. The overall difference in ABPI, ABPI*, TBPI, absolute toe pressures and claudication distance is significant between the categorized PT Doppler waveforms (P<0.01) (Kruskall-wallis). Post hoc analysis (Tukey, Appendix 10) showed that the difference in ABPI, ABPI*, TBPI, absolute toe pressures and claudication distance between biphasic waveforms and all the other categorized waveforms is significant (p=<0.05). Additionally, a significant difference in TBPI and absolute toe pressures was also found between monophasic and monophasic continuous waveforms.

6.3.7 Relationship between risk factors and haemodynamic parameters

The association between haemodynamic parameters diabetes, age and smoking were further analysed. The results are presented in the following sections.

6.3.7.1 Diabetes and haemodynamic parameters

The association between diabetes and ABPI, ABPI*, TBPI and absolute toe pressures was investigated by the Kruskal-Wallis test.

		Median	IQR 1	IQR 3	95% CI for Mean		N	P value
					Lower	Upper		
ABPI*	Diabetes	0.63	0.53	0.73	0.59	0.66	82	**0.04**
	No Diabetes	0.56	0.47	0.68	0.50	0.61	43	
ABPI	Diabetes	0.69	0.56	0.91	0.69	0.81	104	**0.012**
	No Diabetes	0.62	0.51	0.78	0.51	0.65	46	
TBPI	Diabetes	0.40	0.30	0.53	0.37	0.44	103	**0.035**
	No Diabetes	0.37	0.28	0.44	0.28	0.38	46	
Absolute toe pressure mmHg	Diabetes	60.5	45	83	55.73	65.15	103	**0.05**
	No Diabetes	54.5	38	70	42.54	58.33	46	

Table 6.18 Differences in haemodynamics between participants with diabetes and without

The results show (table 6.21) that participants with diabetes had significantly higher haemodynamic parameters (ABPI, ABPI*, TBPI and absolute toe pressures) compared to those without diabetes (p=< 0.05).

6.3.7.2 Age and haemodynamic parameters

The correlation between age and haemodynamic parameters at baseline was assessed using the Spearman correlation test (Table 6.19) since ABPI and TBPI data did not have a normal distribution (Shapiro Wilk test, Appendix 11).

		Spearman's rho	P value
Age (n=150)	ABPI	0.072	0.382
	ABPI* (n=125)	-0.153	0.139
	TBPI	-0.174	**0.033**
	Absolute toe pressures	-0.235	**0.004**

Table 6.19 correlation between and haemodynamic parameters and age

The results indicate that age was significantly correlated with TBPI and absolute toe pressures (p=<0.05), where as age increased, the TBPI and absolute toe pressures decreased. No significant correlation was found in ABPI and ABPI* readings.

6.3.7.3 Smoking status and haemodynamic parameters

The haemodynamic parameters of participants having different smoking status were compared (Kruskal-Wallis) and presented in the table 6.20. Further smoking parameters (duration of smoking and pack years smoked) for both smokers and ex-smokers were also assessed in relation to haemodynamic parameters (tables 6.21 and 6.22) using the Spearman correlation test.

Haemodynamics	Smoking status	N	Median	IQR 1	IQR 3	Lower bound	Upper bound	P value
ABPI*	Current Smoker	51	0.59	0.51	0.69	0.54	0.63	0.903
	Ex- Smoker	48	0.63	0.52	0.75	0.55	0.66	
	Never smoked	26	0.64	0.52	0.7	0.52	0.67	
ABPI	Current Smoker	55	0.63	0.54	0.78	0.58	0.72	0.291
	Ex-Smoker	62	0.66	0.30	0.04	0.63	0.79	
	Never smoked	33	0.69	0.56	0.92	0.62	0.88	
TBPI	Current Smoker	55	0.4	0.25	0.51	0.32	0.41	0.06
	Ex-Smoker	62	0.41	0.34	0.52	0.38	0.46	
	Never smoked	33	0.33	0.18	0.45	0.28	0.41	
Absolute toe pressure	Current Smoker	55	54.7	37	85	47.88	61.56	0.341
	Ex-Smoker	62	60.9	48.2	78.5	55.16	66.75	
	Never smoked	33	54	33.5	73	44.43	65.33	

Table 6.20 Differences in haemodynamic parameters by smoking status

Results show that there was no significant difference in haemodynamic parameters between current smokers, ex-smokers and those who never smoked since the p-values exceeded the 0.05 criterion.

Haemodynamics	Ex-smokers N=62	Mean	SD	Correlation coefficient	P value
ABPI*	Duration (years)	40.7	9.9	0.049	0.74
	Pack years	72.5	43.6	-0.201	0.167
ABPI	Duration	40.7	9.9	0.055	0.67
	Pack Years	72.5	43.6	0.014	0.92
TBPI	Duration	40.7	9.9	-0.164	0.20
	Pack Years	72.5	43.6	-0.17	0.187
Absolute toe pressure	Duration	40.7	9.9	-0.151	0.243
	Pack years	72.5	43.6	-0.108	0.40

Table 6.21 Correlation between smoking parameters and haemodynamic parameters in ex-smokers

Table 6.21 shows that among the ex-smokers (n=62), There was no significant correlation between duration of smoking or pack years smoked and haemodynamic parameters.

Haemodynamics	**Current smokers** N=55	Mean	SD	Correlation Coefficient	P value
ABPI*	Duration (years)	45.3	14.1	-0.190	0.181
	Pack years	54.8	43.3	-0.180	0.21
ABPI	Duration	45.3	14.1	-0.029	0.837
	Pack Years	54.8	43.3	-0.269	**0.049**
TBPI	Duration	45.3	14.1	-0.057	0.68
	Pack Years	54.8	43.3	-0.039	0.776
Absolute toe pressure	Duration	45.3	14.1	-0.14	0.31
	Pack years	54.8	43.3	-0.034	0.803

Table 6.22 Correlation between parameters and haemodynamic parameters in current smokers

Results show (table 6.22) that among current smokers (n=55), as smoking duration and pack years increased, ABPI*, ABPI, TBPI and absolute toe pressures decreased, demonstrated by the negative correlation coefficient. This relationship was statistically significant only for ABPI (including calcified arteries) and pack years smoked (p=0.049).

6.3.8 Analysing disease location

In 132 participants, the disease location at recruitment was recorded as reported by the vascular surgeon in the duplex scans. This section presents an analysis of the disease location in relation to haemodynamic parameters, followed by an analysis of the disease location in relation to diabetes.

6.3.8.1 Disease location and haemodynamic parameters

The association between haemodynamic parameters and disease location was assessed using the Kruskal-Wallis (table 6.23).

Haemodynamics	Disease Location	N	Median	IQR 1	IQR 3	95% Conf Int		P Value
						Lower Bound	Upper bound	
ABPI*	Aortoiliac	17	0.56	0.46	0.61	0.42	0.59	0.221
	Femoropopliteal	86	0.57	0.52	0.71	0.55	0.62	
	Infrapopliteal	54	0.61	0.53	0.71	0.53	0.64	
ABPI	**Aortoiliac**	18	**0.56**	0.47	0.61	0.44	0.62	**0.048**
	Femoropopliteal	101	0.63	0.54	0.79	0.61	0.73	
	Infrapopliteal	67	**0.68**	0.56	0.84	0.64	0.82	
TBPI	Aortoiliac	18	0.31	0.13	0.39	0.22	0.36	0.123
	Femoropopliteal	101	0.37	0.27	0.47	0.33	0.39	
	Infrapopliteal	67	0.38	0.28	0.51	0.33	0.41	
Absolute toe pressures	Aortoiliac	18	46.5	38	64	35.06	56.17	0.211
	Femoropopliteal	101	57	38.5	73	49.24	58.52	
	Infrapopliteal	67	57	42	73	49.83	61.54	

Table 6.23 Disease location and haemodynamic parameters

The results (table 6.23) show that the ABPI reading prior to excluding calcified arteries differs significantly according to the location of disease (p=0.048). A post hoc analysis using the Tukey test by pairwise comparison (Appendix 10) demonstrates that the ABPI was significantly higher when there was infrapopliteal disease compared to when disease was present in the aortoiliac segment. There was no significant difference in the other haemodynamic parameters according to disease location.

6.3.8.2 Disease location and diabetes

Since diabetes is associated with a more distal presentation of arterial disease (Jude et al., 2001), the location of arterial disease was analysed in relation to diabetes by performing the Chi square test.

Table 6.24 Disease Location and Diabetes

			Diabetes	No diabetes	Total
Disease Location	Aortoiliac	Count	9	9	18
		% within Diabetes	7%	15.5%	9.7%
	Femoropopliteal	Count	64	37	101
		% within Diabetes	50%	63.8%	54.3%
	Infrapopliteal	Count	55	12	67
		% within Diabetes	43%	20.7%	36%

X^2 (2) =9.868, **p=0.007**

The crosstab shows that there was a higher proportion of participants with disease located in the femoropopliteal and aortoiliac segments in the group without diabetes compared with the group living with diabetes, while a significantly higher proportion of participants with infrapopliteal artery disease was observed in the group living with diabetes compared to those without diabetes (p=0.007).

6.3.9 A comparison of participant characteristics with previously published data

The results obtained in the current study were compared to those published in the PREPARED UK study (Khan et al., 2007). This analysis was of interest since there is a lack of epidemiological data on the Maltese population in relation to PAD associated parameters. Consequently, local health policies are generally based on published data comprising populations from other countries. Therefore, this analysis aimed to assess whether the local IC population differs from the UK IC population. The PREPARED UK study was chosen since the cohort of participants is similar to the present study in terms of recruitment (IC patients referred to the vascular surgery unit) and similar characteristics to those observed in the current study were reported, thus enabling comparison.

The participant characteristics at recruitment of both studies were first compared using the one-sampled t-test, the difference in two population proportions test and the Wilcoxon signed rank test to assess whether significant differences between cohorts exist (table 6.28). The characteristics which were found to have a statistically significant difference between the two populations are highlighted in bold. Significance level was adjusted to 0.003 according to the Bonferroni correction. This is followed by an analysis of medications prescribed to the participants (table 6.29, significance level set at 0.006) together with an analysis of the blood parameters recorded at recruitment (table 6.30, significance level set at 0.007). A summary of the results is presented at the end of this section.

In the previous sections in this chapter, the haemodynamic and blood test data were presented as median and IQR since the data did not have a normal distribution. However, the PREPARED UK study reported means and standard deviations for some of the data therefore these were calculated to enable comparison.

6.3.9.1 Comparing baseline characteristics between cohorts

Table 6.25 Baseline characteristics Current study VS PREPARED UK data

Characteristic	Current study N=150	PREPARED UK (N=478)	Test statistic	p-value
Age at enrolment, mean (SD)*	69.7 (9.3)	68 (9.7)	1.7	0.03
BMI, mean (SD)*	27.8 (4.3)	26.5 (4.4)	1.29	**<0.0001**
Gender Female n (%)***	9 (14.8%)	159 (33.3%)	-6.5	**<0.001**
Male n (%)***	52 (85.2%)	319 (67.7%)	-6.97	**<0.001**
Claudication distance m, mean (SD)*	138.6 (115.5)	150	-13.8	0.13
Ho of Diabetes n (%)***	104 (69.3%)	96 (15%)	18.52	**<0.001**
Ho of hypertension n (%)***	129 (86%)	265 (55%)	7.55	**<0.001**
Ho of hyperlipidaemia n (%)***	116 (77.3%)	206 (43%)	8.41	**<0.001**
Systolic blood pressure mmHg mean (SD)*	149.96 (22.3)	154.7 (23.6)	-4.74	0.01
Ho of renal disease n (%)	47 (31.1%)	**	**	**
Prior MI n (%)***	29 (19.3%)	69 (14%)	1.44	0.15
Ho cardiac disease n (%)***	61 (40.7%)	141 (29%)	2.55	0.011
Prior Cardiac intervention n (%)***	58 (38.7%)	44 (9%)	12.55	**<0.001**
Prior CVA n (%)***	15 (10%)	35 (7%)	1.057	0.29
Smoking Current***	55 (36.7%)	185 (39%)	-0.445	0.65
Ex-smoker***	62 (41.3%)	221 (46%)	-0.215	0.29
Never smoked*	33 (22%)	57 (12%)	3.07	**0.002**
ABPI Overall mean (SD)*	0.81 (0.32)	0.73 (0.17)	0.077	0.004
ABPI* mean (SD)	0.6 (0.14)	**	**	**
ABPI mean (SD)	0.71 (0.32)	**	**	**
TBPI mean (SD)	0.38 (0.17)	**	**	**
Absolute toe pressures (mmHg)	57.4 (24.2)	**	**	**

* one-sample T-test, test statistic: mean difference, ** not investigated in PREPARED UK study, *** Difference in two population proportions test, test statistic: z-score

Results show that in the current study, participants were significantly more obese and more predominantly male than those recruited in the UK study (p=<0.003). There was a significantly larger proportion of participants living with diabetes, hypertension, hyperlipidaemia and prior cardiac intervention in the current study population compared to the PREPARED UK population (p=<0.001).

6.3.9.2 Comparing medication use between cohorts

Table 6.26 Baseline medication Current study VS PREPARED UK data. Difference in two population proportions test

Medication	Current study N=150	PREPARED UK N=478	Z score	p-value
Antiplatelet therapy	112 (74.7%)	335 (70%)	1.15	0.28
Anticoagulant therapy	12 (8%)	17 (4%)	2.26	0.02
Not taking antiplatelet or anticoagulant	31(20.7%)	143 (30%)	-2.21	0.03
Statin	113 (75.3%)	212 (44%)	7.65	**<0.001**
ACE inhibitor	72 (48%)	123 (26%)	6.05	**<0.001**
Beta blocker	12 (8%)	85 (18%)	23.48	**<0.001**
Calcium channel blocker	36 (24%)	108 (23%)	0.357	0.72
Angiotensin II antagonist	22 (14.7%)	32 (7%)	37.44	**0.002**

Results show that in the current study population there was a significantly greater proportion of participants taking, statins, ACE inhibitors and Angiotensin II antagonists but fewer taking beta blockers when compared to the PREPARED UK participants (p=<0.006). There was no significant difference in the proportion of participants taking antiplatelet therapy (p=>0.006).

6.3.9.3 Blood parameters in the current study and PREPARED UK study

Table 6.27 Baseline blood results Current study VS PREPARED UK data

Blood results	**Current study**	**PREPARED UK**	**Test statistic**	**p-value**
eGFR n=150	79 (54.7,97)	**	**	**
Cholesterol n=150 Median (IQR) mmol/L***	4.31 (3.6,5.1)	**	**	**
Triglyceride n=150 Median (IQR) mmol/L***	1.43 (99,2.03)	1.7 (1.25, 2.85) n=266	-1.723	0.086
HDL Cholesterol n=150 Median (IQR) mmol/L***	1.17 (0.93, 1.4)	1.4 (1.1,1.5) n=180	-5.435	**<0.001**
Non HDL Cholesterol n=150 Median (IQR) mmol/L***	3.04 (2.35,3.9)	**	**	**
LDL Cholesterol Median (IQR) mmol/L***	2.27 (1.6, 2.9)	3.2 (2.3, 4) n=112	-7.31	**<0.001**
Total Cholesterol Mean (SD) mmol/L*	3.88 (1.33)	5.4 (1.2) n=351	-1.5	**<0.001**
Fasting Glucose Median (IQR) mmol/L n=115***	7.55 (5.9,9.9)	5.3 (4.8) n=265	3.02	**<0.001**
HbA1c n=150 Median (IQR) %***	6.6 (5.8,7.6)	**	**	**
Creatinine n=150 Median (IQR) mmol/L***	82 (69.5,113.5)	98.9 (27.4) n=323	4.3	0.48
CRP Median (IQR) ***	2.2 (1.1, 5.4) n=139	5 (5, 6.5) n=68	-3.85	**<0.001**
ESR n=136 Median (IQR)	136 (16.46)	**	**	**

* one-sample T-test, test statistic: mean difference, ** not investigated in PREPARED UK study, *** one-sample Wilcoxon signed rank test, test statistic: z-score

Results show that the study population of the current research had significantly lower HDL, LDL and total cholesterol levels and CRP but higher fasting glucose levels compared to the UK study population. There was no significant difference in creatinine and triglyceride levels between the two study populations.

6.4 Summary of main results of Study 3

The characteristics of patients with IC were:

- Predominantly **male (79.3%)**, **obese (BMI 27.8)** with a mean age of **70 years.**
- Over 69% of participants had **main risk factors** for PAD (Diabetes 69.3%, hypertension 86%, hyperlipidaemia 77.3% and smoking history 78%).
- The median haemodynamic parameters of the symptomatic limbs were **ABPI 0.66** (IQR 0.55,0.81) **(ABPI* was 0.62** (IQR 0.53,0.74) **when excluding calcified arteries)**, **TBPI 0.38,** absolute toe pressure 58mmHg and claudication distance of 150m and these were **significantly correlated** with each other and with Doppler waveforms (p=<0.01).
- **More men smoked than women** (p<0.001)
- A significantly **higher proportions** of participants with **diabetes were taking statins and antiplatelet therapy** compared to participants without diabetes (p<0.05).
- Duplex scans showed that the most **common location of disease was the femoropopliteal segment** followed by the infrapopliteal artery segment. Infrapopliteal artery disease was significantly associated with diabetes (p=0.007).

The medication use in patients with intermittent claudication:

- Approximately **75% of the participants** were taking **statins** and **anti-platelet therapy**.
- A total of **20.7%** participants were **not taking any antiplatelet or anti-coagulant therapy**.
- The most common anti-hypertensive drugs prescribed among the participants were Ace inhibitors followed by calcium channel blockers.

A comparison of the Maltese population with IC with UK IC population

- The Maltese participants were significantly **more obese and more predominantly male** than those recruited in the UK study.
- There was a significantly **larger proportion** of participants having **main risk factors** (diabetes, hypertension, hyperlipidaemia) in the current study population compared to the UK population with IC.
- Participants in local study had significantly **lower HDL, LDL** and **total cholesterol levels**, when compared to the UK counterparts (p=<0.001). In this context, there was

significantly **higher proportion** of participants in the current study who are taking **statins** when compared to the UK participants (p=<0.001).

- In both studied populations, approximately 1/3 of the participants were not taking antiplatelet therapy. It should be noted that the PREPARED UK study was conducted over 10 years prior to the current study. It could be that the noted improved medication control could be attributed to improvement of international recommendations over the years.
- **ACE inhibitors and Angiotensin II antagonists** are **more commonly prescribed** in the local studied population as anti-hypertensive medication when compared to the PREPARED UK population. **Mean systolic blood pressure** was >140mmHg in both studies. Beta blockers are more commonly used in the UK study population compared to the population in the current study.

6.5 Discussion

This study sought to develop a prospective registry of patients with IC in Malta and establish the patient characteristics of this population. This study is the first of its kind in Malta since to date, local data on patients with IC was not available. The data also portrays that populations with IC may differ in risk factor prevalence and patient characteristics, highlighting the need of more individual consideration of risk during clinical management, rather than applying international guidelines for all.

6.5.1 Risk factor prevalence

At baseline, the cohort of the current study had, a mean age of 70 years and the prevalence of diabetes, smoking and dyslipidaemia were 69%, 78% and 77% respectively. The prevalence of the main risk factors (diabetes, hypertension, hyperlipidaemia, a history of CHD, older age, BMI) in the cohort of this research was found to be significantly higher than that reported in previously published studies investigating similar cohorts (Safley et al., 2011; Stansby et al., 2011). The reason could be attributed to the high prevalence of diabetes and cardiovascular disease present in the Maltese population, as discussed in Chapter One. The current study was conducted in a southern European country (Malta) where the national prevalence of diabetes is 13.8% and the age adjusted comparative prevalence is 9% (Ogurtsova et al., 2017), distinctly higher than other European countries. Furthermore, according to the latest country health profile conducted by WHO, cardiovascular disease and the associated risk factors is also higher in Malta than in other European countries (OECD., 2018).

The TASC and AHA documents proposing the 5-year prognosis of 5-10% development of CLI in a population of IC, do not present detailed information on the various risk factor prevalence rate of participants at baseline, therefore they cannot be compared to the current data. However, most studies on which the document is based (Fowkes et al., 1992; W. Kannel & McGee, 1985; McDaniel & Cronenwett, 1989; Murabito et al., 1997; Price et al., 1999; Weitz et al., 1996) are derived from northern European countries or the United states, where the rates of diabetes at the time ranged from 2-4% (NCD Risk Factor Collaboration, 2016).

The risk of PAD and disease progression associated with diabetes is well known. The duration of diabetes mellitus, glycated-haemoglobin levels and use of insulin are significantly associated with worsening PAD (Althouse et al., 2014; Kallio et al., 2003; Tseng, 2003). Additionally, individuals with PAD and diabetes were 5 times more likely to have an amputation when compared with individuals without diabetes (Jude et al., 2001). Furthermore, it is well known that the presence of known risk factors is independently associated with the development of CLI, and when combined, the risk is cumulative (Norgren et al., 2007). The cumulative effect of multiple risk factors is thought to have a significant effect on developing PAD. In fact, a large retrospective study on 7,057 PAD subjects concluded that one CV risk factor increased the risk of PAD by a mean of 1.5- fold, whilst the cumulative effect of three or more risk factors increased the risk of PAD by ten-fold (A. Nicoloff et al., 2002).

It may therefore be postulated that the high prevalence of risk factors at baseline, particularly diabetes, in the cohort of the current study, may be higher than the prevalence of risk factors among the participants in the studies included in the TASC and AHA documents, and may contribute to a different deterioration rate in this cohort. These results also highlight the fact that characteristics of IC patients may differ across populations and this notion needs to be acknowledged in international guidelines.

6.5.2 Haemodynamic profile of patients with IC

This cross-sectional observational study demonstrated that patients with IC had low median haemodynamic parameters of the symptomatic limbs - ABPI 0.66 [IQR 0.55, 0.81], TBPI 0.38, absolute toe pressure 58mmHg and claudication distance of 150m, and these were significantly correlated with each other and with Doppler waveforms ($p=<0.01$). There were no studies investigating IC patients which have reported TBPI or waveforms at baseline, therefore comparisons with previous studies can only be made with ABPI readings. In order to compare results with previously published works, who most commonly reported mean data, the mean and standard deviation of the haemodynamic parameters observed in the current study were also calculated and are presented in Appendix 10.

Comparing the baseline ABPI found in the current study with previous published studies is difficult due to the heterogeneity with which ABPI was calculated and reported among studies. The mean baseline ABPI of the current study (0.71 SD ±0.3) is similar to that observed in the

CAVASIC study (B. Rantner et al., 2017) who reported a mean ABPI of 0.72 in a population of patients with IC. In their study the authors reported the lowest ABI value from the 4 calculated ratios (two for each foot using DP artery and PT artery), without defining of whether the limb was symptomatic or not in cases who had unilateral IC. A lower mean ABPI of 0.62 (SD 0.21) was reported in a study conducted in a cardiovascular hospital (Kumakura et al., 2016) but it is not clear how this was calculated. The comparison of the results observed in the current study with the data reported in PREPARED UK study (Stansby et al., 2011) indicated that the authors used the overall ABPI including asymptomatic limbs, yielding an ABPI of 0.73 which was significantly lower than the overall ABPI reported in the current study (0.81, p=0.004). It is however not feasible to use overall ABPI which includes asymptomatic limbs when evaluating IC symptoms.

In this cross-sectional study, the ABPI of the symptomatic limb (or most symptomatic limb reported by the patient) was of interest for baseline evaluation rather than including both limbs.

Of note, the median ABPI of the symptomatic limb was further assessed by excluding readings from known calcified arteries which may falsely increase the ABPI levels (Formosa et al., 2013) as discussed in Chapter 2 in this thesis. This study found that the median ABPI decreased to 0.62 (IQR 0.53,0.74) when calcified arteries were excluded from the analysis. These results cannot be compared with previous data since to the author's knowledge there are no similar studies which have investigated changes in ABPI after excluding calcified arteries. An ABPI of 0.7 or lower has been associated with a 2-fold increased risk of deterioration to CLI (Jaff et al., 2015), indicating that the cohort recruited for this research fall within this category.

While the results of this study confirm previous affirmations (Formosa et al., 2013) of the influence of arterial calcification on ABPI readings, they also highlight the benefits of using TBPI to evaluate PAD since it is affected less by MAC and can be effectively used as a predictor of adverse events (Chisalita et al., 2020). These results also emphasise the risky situation of patients with IC at baseline with regards to lower limb perfusion, justifying the need for further research related to the prognosis of this population.

6.5.3 Gender prevalence

The results show that the cohort with IC in this study is predominantly male with the vast majority of recruited participants being men (79.3%). The proportion of men in this research is higher with that reported in the PREPARED UK study (Stansby et al., 2011) but is in agreement with several previous works investigating PAD who report a higher proportion of men recruited in the respective studies (Kumakura et al., 2016; B. Rantner et al., 2016; B. Rantner et al., 2017). In this context it has been suggested that PAD is commonly identified as a male-dominant disease (Schramm & Rochon, 2018). Although there are theories that suggest that the prevalence of PAD among women is lower than in men because of oestrogen protection (Westendorp et al., 2000), it is also postulated that women have different presentation of symptoms, more commonly asymptomatic which leads to a delayed diagnosis. It has also been suggested that women are less likely to report physical symptoms compared to men (Schramm & Rochon, 2018).

However, the prevalence of PAD amongst women increases after menopause and the risk of developing IC is determined by the risk factors present during that period (Daviglus et al., 2004). The main risk factors for the development of PAD are shared between both sexes (Mendis et al., 2011). In this study, more men had diabetes, a prior MI and a history of smoking. However, it has been suggested that women with IC, although generally are fewer in number, have a higher risk than men in progression of disease and have increased functional impairment (Schramm & Rochon, 2018).

6.5.4 Diabetes

Although not statistically significant (significance level was set at 0.003 following the Bonferroni correction), the results in this study demonstrate that the participants with diabetes had higher median ABPI levels compared to participants without diabetes (0.69 and 0.62 respectively, p=0.012). The haemodynamic parameters were also higher in the group with diabetes when calcified arteries were excluded and when TBPI levels were compared (p=0.04 and p=0.035 respectively). It is possible that participants with diabetes are better monitored during their diabetes consultant visits and receive better vascular care than participants without diabetes. On the other hand, participants without diabetes who have PAD may only seek medical help when symptoms arise, possibly later in the course of the disease (Argyriou et al., 2013). Individuals living with diabetes may therefore be referred for specialist vascular care

earlier in the course of the disease than participants without diabetes, which may have contributed to the results observed.

6.5.5 Disease Location

In agreement with previously published works (Greenhalgh, 2008; Mazari et al., 2017; van den Houten et al., 2019), this study demonstrated that the most common location of arterial disease among the cohort of participants with IC was the femoropopliteal segment. This study has also shown that there was a significantly higher proportion of participants with diabetes having infrapopliteal disease compared to those without diabetes. This is also in agreement with published literature where diabetes is associated with a more anatomically distal distribution of the disease, that is, distal to the knee, when compared with people living without diabetes (Haltmayer et al., 2001).

Typically, infrapopliteal artery disease has been associated with worse prognosis and a higher risk of death and major amputation with more challenging revascularisation procedures when compared to above knee disease (Gray et al., 2010; Neupane et al., 2018). The importance of diabetes in this group of individuals is therefore highlighted, indicating an increased risk of worse prognosis.

6.5.6 Medication profile

The cross-sectional data evidenced in the current study has shown that medical management of the cohort was suboptimal. Serum cholesterol levels were above recommended targets (Saratzis et al., 2019), a high proportion had systolic brachial pressure above 140mmHg and recommended best medical therapy was lacking in more than a quarter of the participants. These results are comparable with previously published studies (Khan et al., 2007; Reinecke et al., 2015) which highlight that oral therapy in IC patients does not reach the recommended standards in published guidelines. Poor adherence to recommended guidelines regarding medical optimisation for patients with IC is higher among health practitioners who are not vascular surgeons (Chaar et al., 2020).

In part because of the absence of or atypical symptoms, PAD is poorly understood by the public, underdiagnosed in the primary care setting and patients rarely receive the optimal

treatment (Hirsch et al., 2006). These results therefore emphasize the need for further awareness among health practitioners about the benefits of oral medication and the consequences of poor medical management of risk factors in patients with IC.

6.5.7 Clinical implications

The results of this registry confirm that the main risk factors for PAD are highly prevalent in this population of patients with IC and emphasise the seriousness of IC as a symptom of PAD. As compiled in the TASC document and expounded in the literature review in this thesis (Chapter 2), diabetes increases the risk of deterioration to CLI by 4 times, smoking by 3 times, dyslipidaemia, >65 years of age and an ABPI <0.7 by 2 times. The high proportion of risk factors reported in this registry, together with the low ABPI observed, indicate that patients with IC are at an increased risk of morbidity even at the time of first encounter in a primary health clinic. Therefore, better monitoring of this cohort is warranted in order to detect deterioration at an early stage, enabling immediate treatment modification. Additionally, early identification of those who are at a higher risk of deterioration would help in making informed clinical decisions relating to the management plan.

The higher proportion of risk factors observed in this study, compared to a UK based study (Safley et al., 2011) also highlights the need for a more individualised prediction of disease in patients presenting with IC. While IC is assumed to have a benign prognosis for the affected limb in published literature (S. M. Conte & Vale, 2018), this assumption was based on population studies with lower risk factor prevalence, particularly diabetes. It is possible that disease progression is therefore underestimated in populations where associated medical risk factors are more prevalent, suggesting that a more threatening prognosis may be more relevant in such populations.

Results of this cross-sectional study demonstrate that patients with PAD are not provided optimal medical therapy in primary health. Poor medical management is associated with an increased risk of major adverse cardiovascular events, indicating that better awareness is required among health practitioners working in the primary health sector.

6.5.8 Impact of the study on the local clinical practice

- The results of this registry were presented in a primary healthcare conference (Malta) [*The need for improvement in the diagnosis and management of patients with IC in primary care- Comprehensive Primary care, 9th biennial Primary Care Conference, Malta. October 2017]* and in the Malta Medical school conference [*Intermittent claudication referral patterns in Malta – 10th Malta Medical School conference, Westin Dragonara Hotel, Malta, November 2018, also published in the Malta Medical Journal (30): Suppl December 2018. Pg 119*]. This raised awareness, principally among primary health GPs but also with other care providers. In these presentations, the suboptimal use of medical therapy, namely statins and anti-platelet medication among patients with IC was emphasised and the importance of haemodynamic analysis prior to referral was highlighted.

- Data from the registry indicate that the changes proposed following the scoping study resulted in improvement in terms of an increase in number of referrals of patients with IC in 12 months. Fewer incorrect referrals were also observed since and an increased number of patients were being referred to the new Claudication Clinic within the vascular clinic in the podiatry department which was a new service for patients with IC. The idea to initiate the new Claudication Clinic in primary health emerged from findings of the work presented in this thesis and was developed by the author with the support of the Lead vascular surgeon and management of primary healthcare.

- Since all the referred patients were assessed by haemodynamic analysis for the purpose of this study within two weeks of referral, several benefits were achieved for the patient. Firstly, since a detailed report including vascular assessment of each participant was sent to the vascular surgeon, better triaging could be done using the report rather than the limited information on some of the referrals which were previously sent. This resulted in more timely appointments provided to the patients according to their severity of disease. Those who were assessed as potential participants and were found to have normal peripheral perfusion were immediately contacted by the vascular surgeon and referred back to the GP to consider alternative diagnosis. This way they did not have to wait 18-24 months to be assessed and also did not take important appointments with the vascular surgeon unnecessarily. Secondly, those who were not taking the

recommended medical therapy were referred to the GP by the author immediately instead of having to wait for 18-24 months to be assessed by the vascular surgeon due to the long waiting time for this sole clinic in the island. Thirdly, the author alerted the vascular surgeon about those who were found to be severely ischaemic through an urgent referral and an appointment was provided within a week. These clinical benefits resulted in better patient care for patients with IC and it was therefore agreed upon to adopt this system even after the research was finalised, thus bringing about a change in current clinical practice.

- Excerpts of this study indicating the impact of the misdiagnosis of IC were submitted as an abstract to the College of Podiatry conference (Liverpool) 2017. This abstract obtained the highest number of points among submitted abstracts and was awarded the 'Jewel in the Crown', a prestigious award as best and innovative abstract in the conference. It was presented as an oral presentation in the plenary session of the conference, increasing awareness related to the benefits of comprehensive haemodynamic analysis, including Doppler analysis, ABPI and TBPI measurements prior to referral to the vascular surgeon in patients with IC.

6.5.9 Strengths and potential study limitations

Allocation concealment was applied in this study, meaning that the author did not know the management plan for the participants and this therefore could not influence recruitment.

All eligible participants agreed to participate in the study.

Age distribution, DM prevalence and patient characteristics may vary between countries (Behrendt et al., 2018). However, despite limitations inherent to use of data gathered from one country, the findings of this study are important and indicate that further research is required to improve limb salvage in different demographic settings.

Referral bias may occur when recruitment is done from a referral center, possibly leading to overestimation of disease severity. However, efforts were done to minimize this possibility through communication with the referrers (following the scoping study), encouraging GPs and podiatrists to refer all patients with IC encountered within primary care clinics while also highlighting the detrimental consequences associated with late or no referral. Nonetheless, the

cohort recruited in this study represents typical patients seen by vascular specialists as was intended for this study.

In this study claudication distance was derived from the walking impairment questionnaire where distance was self reported and which was found to correlate well to objective measures of walking distance (Frans et al., 2013). While some authors suggest that measuring claudication distance using a treadmill may be more accurate (van den Houten et al., 2019), the implementation of this technique was not viable for this study for the following reasons:

- this research aims to evaluate prognostic clinical factors for development of CLI which can be identified in a real life clinical setting. The use of treadmill measures is generally employed in research labs and not clinical practice and would therefore be of limited use in this study since it is not a measure commonly employed in a clinical setting. This approach was also employed by previous researchers (Khan et al., 2007) in a similar prospective registry investigating characteristics of patients with PAD referred to vascular clinics in the UK.
- Measure of claudication distance using a treadmill is contra-indicated in patients with cardiac disease unless appropriate cardiac monitoring is undertaken with the instructions of a cardiologist, nurse and physiotherapist. It was not feasible for this study to apply such an approach for the participants with known cardiac disease due to limitation of resources to book the personnel for the purposes of the study.
- Additionally, given that patients with IC are at an increased risk of CV disease, there was the possibility that some patients were living with cardiac disease unknowingly, hence it would have been unsafe to use the treadmill measure on this cohort.

While objective testing of walking distance using standardised methods has less risk of reporting bias, nevertheless, symptoms reported by the patient are considered as the most important stimulus for considering revascularisation in claudication (Amighi et al., 2004). Furthermore, since this study aims to assess factors obtained in a real life clinical setting, self-reported claudication distance using a validated questionnaire was feasible.

Limitations inherent to ABPI due to arterial calcification are well known (Formosa et al., 2013), however this was overcome by using TBPI and Doppler waveform analysis together with ABPI as analysis of PAD severity, a method which demonstrates better reliability as diagnostic measures of PAD (Azzopardi et al., 2019; Chisalita et al., 2020). Additionally, the

presence of PAD was further confirmed following assessment by Duplex scanning by the vascular surgeon.

6.6 Conclusions

This study aimed to develop a prospective registry of patients with IC, whilst evaluating the characteristics of this population. The data from this registry highlight the important role of associated risk factors of PAD as coexisting mechanisms in the disease process of IC. The possible diversity of patient characteristics among different populations of patients with IC is also emphasised indicating the need for further evaluation of the outcomes of IC in relation to the baseline characteristics of the individual patient.

The study presented in next Chapter (Chapter Seven, Study 4) details an extensive two-year follow up of this patient cohort to evaluate the impact of their baseline factors on the progression of PAD and possibly identify prognostic factors in those who develop CLI.

CHAPTER SEVEN

> *'Most physicians are familiar with patients who had intermittent claudication for many years without developing gangrene or any other serious cardiovascular catastrophe, but they also recall others who, within a short time of presenting with claudication, have lost a limb or suffered a myocardial infarction or had a cerebrovascular accident. Such patients are remembered, but it is difficult to obtain accurate data on what happens to the majority of patients who present with intermittent claudication.'*
>
> (Richards, 1957 p.1093)

Study 4 - Identifying prognostic factors for development of CLI in patients with IC. A prospective cohort longitudinal observational study.

7.1 Introduction

For the vascular surgeon to make an informed clinical decision related to management in patients presenting with IC, knowledge of the disease progression and prognosis of the individual patient is crucial (M. S. Conte et al., 2019). As highlighted in the systematic review (Study 1) (Mizzi et al., 2019) presented in Chapter Four, the progression rate of PAD in patients with IC is not clear in published literature. Furthermore, while some factors such as diabetes, an ABPI less than 0.5 and a smoking history have been associated with an increased risk of deterioration, this information is insufficient to accurately identify those who are more likely to deteriorate and hence would benefit from preventive revascularisation. Identification of patients who are at risk of developing CLI would support clinical decision making for early intervention in those who are more likely to deteriorate, subsequently reducing their risk of future morbidity. This study therefore aimed to identify common patterns, if any, among participants who developed CLI within two years.

Study 3 presented in Chapter six provided the foundation for Study 4, a prospective longitudinal study where 150 participants were recruited and followed for two years with a follow-up assessment every 12 months. The methodology and methods for this study are presented in detail in Chapter five. The outcome of the participants was recorded at each visit in terms of major adverse cardiovascular events (MACE), adverse lower limb events (CLI), haemodynamic measures and WIQ questionnaire. In this study baseline data were analysed for

association with outcomes and potential identification of predictive factors for development of CLI within 2 years.

7.2 Aim and objectives of the study

The aim of this study was to identify patterns, if any, of characteristics and risk factors among participants with IC who develop critical limb ischaemia within two years. The information from this study was applied to help determine the possibility of identifying which patients are more likely to benefit from early revascularisation to avoid the development of CLI.

7.2.1 Objectives

The objectives of this study were to:

- Assess outcomes of patients presenting with intermittent claudication over a 2- year period

- To identify factors associated with higher risk of lower limb events including need of revascularisation, minor /major amputation, gangrene and ulceration

- To identify factors associated with significant haemodynamic deterioration

7.2.2 Research question

This study aims to answer the question:

Are there common predictors among patients with intermittent claudication who progress to critical limb ischaemia over a 2-year period?

The research hypothesis is therefore:

H_1: Patients with IC who progress to critical limb ischaemia have a common pattern of predictive factors.

H_0: Patients with IC who progress to critical limb ischaemia do not have a common pattern of predictive factors.

7.3 Methods

A detailed discussion and description of the methods employed for this study have been presented previously in Chapter five. As described therefore, this study employed a prospective observational longitudinal study design where new consecutive referrals of patients with IC to a vascular unit were followed for 2 years with a review every 12 months.

Ethical approval was obtained, together with consent processes and permissions to access patient data, as detailed in Chapter Three. The study protocols employed for haemodynamic analysis (Doppler waveform analysis, ABPI and TBPI) and WIQ are also detailed in Chapter Five.

During follow-up visits, at 12 months and 24 months, haemodynamic analysis (Doppler waveform assessment, ABPI and TBPI) was performed and the WIQ score was also recorded at each visit. Data related to participant outcomes was retrieved both verbally from the participants and verified by accessing the patient database within the vascular unit. Blood results were retrieved from iSoft clinical software which is a system used by the national health service where each participant can be identified using a unique identification number. After recruitment and during the whole study, the researcher had access to the diagnostic notes and duplex scan reports performed by the vascular surgeon in order to confirm treatment plans and outcomes. Reports and dates of any intervention, hospitalisation or clinical visits within the health service were retrieved from the national clinical software and patient records.

7.4 Results

This section presents the findings of the final phase of this research where the prognostic factors of CLI in patients with IC were explored. Details about the participants' demographic and health status variables at baseline were presented in Chapter Six. The first part of this results section explains the data availability following the recruitment and review processes after 1 and 2 years, including non-responder data analysis. This is followed by a description of the haemodynamic and clinical outcomes of all the participants after 2 years. The subsequent section then presents the main of focus of the results chapter with an analysis of data of participants who deteriorated to CLI or experienced significant deterioration after 2 years, together with the identification of predictive factors for deterioration. An analysis of disease progression in terms of haemodynamic data can be found in the next subsections, followed by

analysis of results of participants with improvement as an outcome after 2 years and subsequent assessment of Walking impairment questionnaire scores.

7.4.1 Recruited participants and data availability

The recruitment procedure is described in detail in Chapter five. A diagram (figure 7.1) illustrating the recruitment process and participant follow-up, as recommended by the 'Strengthening the reporting of observational studies in epidemiology (STROBE) (Vandenbroucke et al., 2014) is presented.

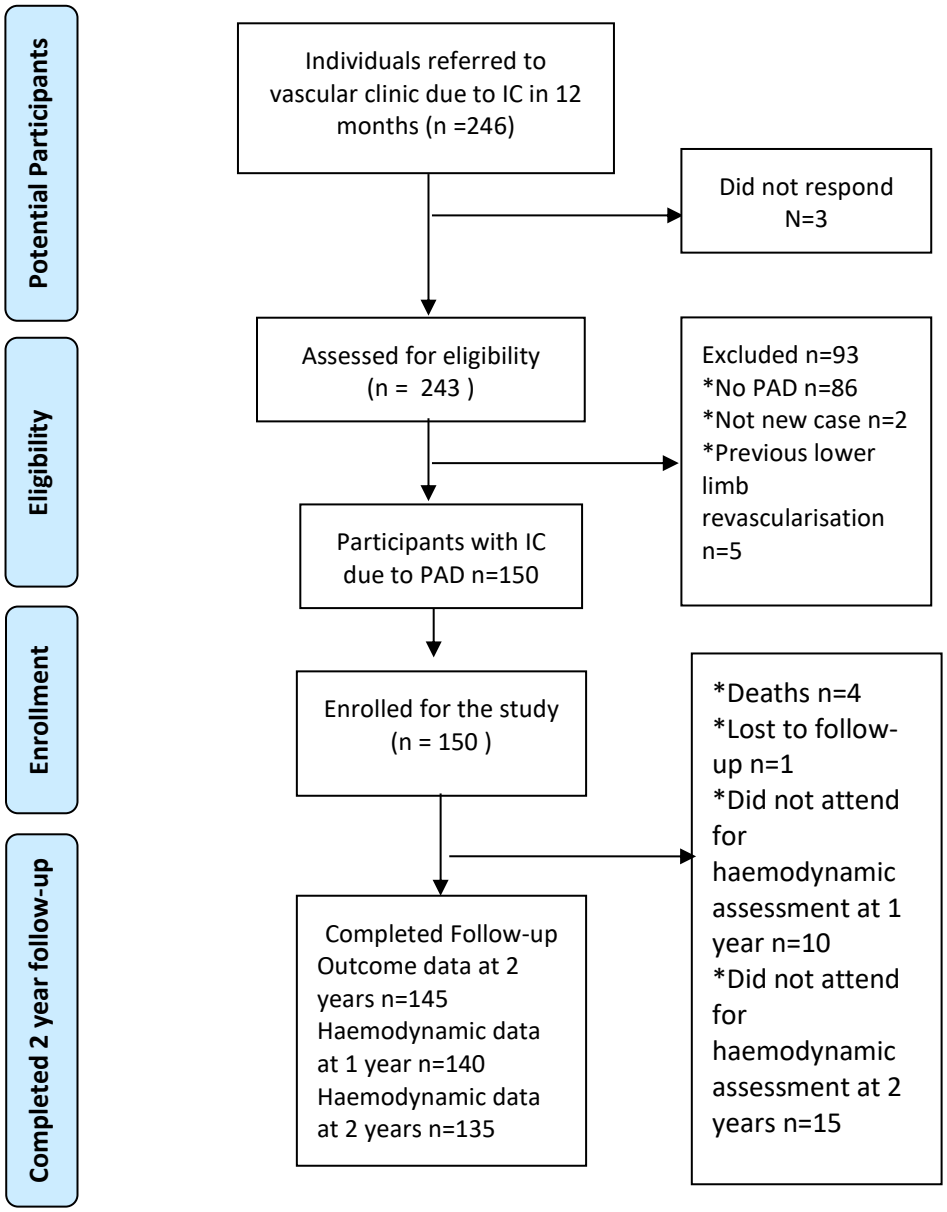


Figure 7.1: STROBE diagram illustrating the recruitment process

Following the initial recruitment process after identifying the eligibility of participants which is described in detail Chapter five, recruited and consenting participants (n=150) were followed for two years with a follow-up assessment every 12 months which included recording of haemodynamic data and IC symptoms using the Walking impairment questionnaire (WIQ). Revascularisation procedures, reports of Duplex scans and lower limb outcomes (i.e CLI, ulceration, amputation, rest pain and hospital admission due to PAD) were retrieved from the database of the vascular unit at the hospital. Reports of mortality were retrieved from the centralised patient access system (CPAS) of the health department (Malta).

7.4.1.1 Availability of haemodynamic and WIQ data

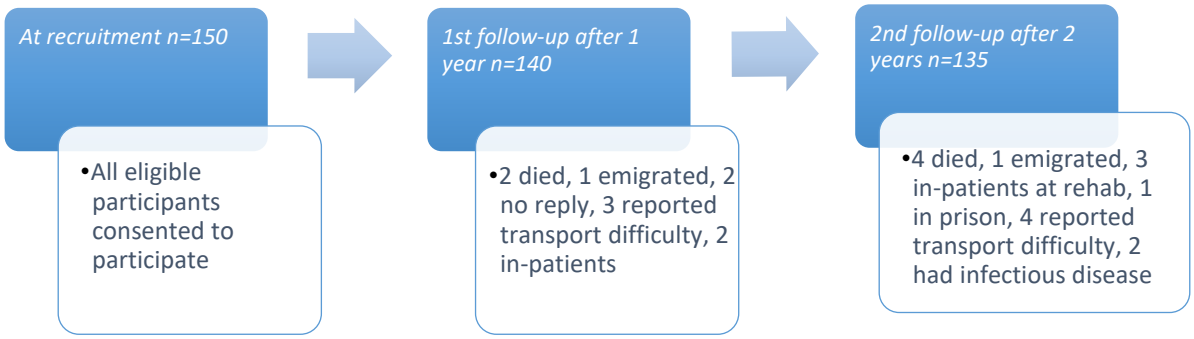


Fig 7.2 Availability of haemodynamic and WIQ data

Figure 7.2 illustrates the recruitment process and participant data availability during the study. At the first follow-up after 1 year, 140 participants attended for review and the haemodynamic and WIQ data were recorded. At the second follow-up after 2 years, 135 participants attended for review and the haemodynamic and WIQ data of 135 participants were recorded. It should be noted that the participants who did not attend for review did not withdraw from the study and reasons for non-responding are illustrated in the diagram. Therefore, other data which could be retrieved from the hospital databases such as lower limb outcomes (development of CLI, ulceration or rest pain), hospital admissions and mortality were still retrieved for these participants. For example, 2 participants who did not attend for review developed CLI (data retrieved from the vascular unit database) and were therefore included in the CLI group and not in the missing data group.

7.4.1.2 Availability of lower limb outcome data

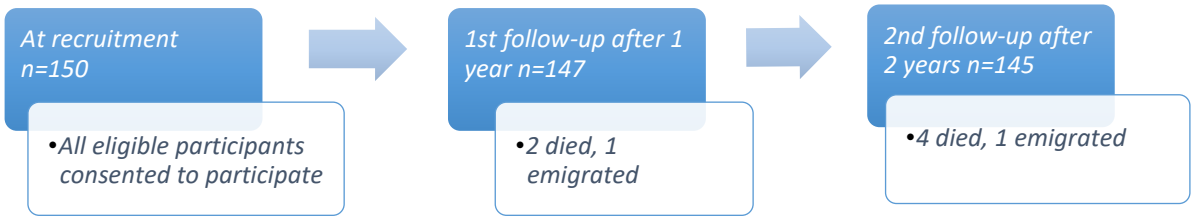


Fig.7.3 Availability of lower limb and major adverse events data

Figure 7.3 illustrates the availability of lower limb and adverse events data during the study. Lower limb outcomes were retrieved from the database of the vascular unit within the hospital which included clinical reports, reports of the duplex scans and treatment plans or revascularisation procedures reported by the vascular surgeon. At first follow-up after 1 year, the lower limb outcome data of 147 participants were recorded as 2 participants had died and 1 participant was lost to follow-up. At the second follow-up after 2 years, lower limb outcome data and adverse events data of 145 participants (out of 150 initially recruited) were recorded because 4 participants had died and 1 participant was lost to follow-up due to emigration.

7.4.1.3 Non-responder analysis

Figure 7.2 illustrates that haemodynamic data of 15 participants was missing at the end of the study. The reasons were: 4 died, 1 participant was lost to follow-up as they emigrated to another country, 4 participants reported difficulty in finding time and transportation to the clinic due to other several hospital appointments, 3 participants were admitted in a rehabilitation hospital recovering from orthopaedic surgery, 1 participant was incarcerated and did not attend for review and 2 participants acquired an infectious disease which precluded the use of the brachial or digital cuffs due to infection control policies. The latter 2 participants also developed CLI and were hence included in the CLI group. Therefore, excluding the non-responder participants who developed CLI (n=2 since their lower limb outcome is known), there were 13 non-responders with missing haemodynamic data after 2 years. As stated earlier, since the participants did not withdraw from the study, lower limb and major adverse events were still retrieved for the non-responders.

The difference in baseline parameters between the participants who attended for follow-up and the non-responders was analysed. Mann-Whitney U tests were applied to compare unpaired continuous data and Chi squared tests were applied to compare categorical data and to test for trends. Non-parametric tests were applied since the parameters did not have a normal distribution as shown by the Shapiro Wilk test (Appendix 11). The results show that non-responders had a higher BMI than responders (32.3 and 27.6 respectively) and this difference was significant ($p<0.05$). There was no significant difference in any of the other parameters measured. The results of these tests are presented in Appendix 12.

During the study, haemodynamic data was recorded for both limbs at baseline, first and second follow-up. However, since the main focus of this study is the deterioration to CLI and progression of PAD, the data of the limb with worse outcome was used for the analysis in cases of bilateral IC. In all cases who had bilateral IC and developed CLI, the affected limb was the most symptomatic limb at baseline. The data of both symptomatic limbs was assessed in section 7.7 when analysing the progression rate of PAD in all symptomatic limbs (n=236).

7.4.2 Participant outcomes after 2-year follow-up

The main outcomes of interest in this study was deterioration to CLI, haemodynamic deterioration and symptom deterioration. As described in chapter five, deterioration to CLI was determined by the clinical presentation of tissue loss (ulceration), rest pain or gangrene. Haemodynamic deterioration was determined by a decline in haemodynamic measures (ABPI, TBPI and Doppler waveform analysis) and symptom deterioration was determined using the Walking impairment questionnaire (WIQ). Due to the varying influence of confounding factors on the different haemodynamic measures (such as calcification or revascularisation) in an individual participant, ABPI, TBPI and waveforms were described and analysed separately. The following sections in this chapter describe the outcomes experienced by the participants after 2 years.

7.4.2.1 Haemodynamic outcomes

The proportion of the various haemodynamic outcomes of the participants at two years after recruitment is illustrated in figure 7.4. The outcomes are explained in detail in chapter 5: CLI is defined as development of ischaemic ulceration or rest pain, while significant haemodynamic

decline is defined as a decrease in ABPI and /or TBPI by ≥0.15 and ≥0.1 respectively, mild haemodynamic decline is defined as a decrease in ABPI and/or TBPI which is less than 0.15 or 0.1 respectively, while improved or stable haemodynamics is defined as no change or an increase in ABPI or TBPI.

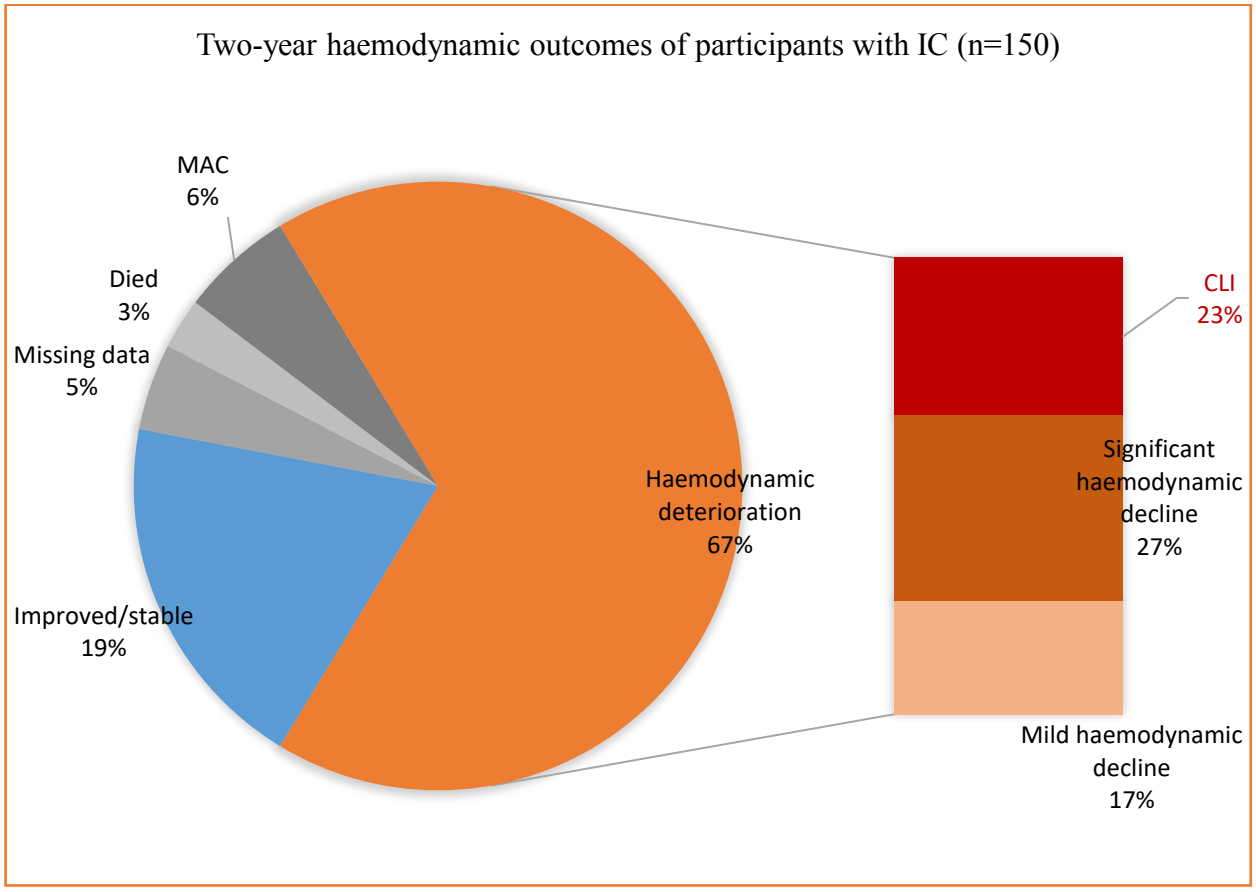


Figure 7.4 Participant outcomes after 2 years

After two years 67.3% (n=101) of the participants experienced haemodynamic deterioration of whom 23.3% (n=35) deteriorated to CLI, 27.3% (n=41) experienced significant haemodynamic deterioration (without developing CLI symptoms) and 17% (n=25) experienced mild haemodynamic decline. During the study 14 participants developed medial arterial calcification (MAC) evident in ABPI and/or TBPI assessments or reported in duplex scans, resulting in falsely elevated haemodynamic readings at the time of the first and/ or second follow-up, therefore haemodynamic deterioration could not be assessed in these participants. However, 7 of these participants developed CLI and are therefore included in the CLI group. Another 15 participants did not attend for the second follow-up at 2 years (as described in section 7.2.1 and 7.2.2) which precluded the assessment of haemodynamic deterioration. It

should be noted that clinical lower limb outcomes (namely CLI development and/or revascularisation) and Doppler waveforms of participants who did not attend for follow-up or who developed MAC were still retrieved from the hospital database of the vascular unit, therefore those who deteriorated to CLI and also developed MAC (n=7) or missed the follow-up appointment (n=2) were included in the CLI group and not in the missing data group when analysing lower limb outcomes. During the study period 29 participants (19.3%) demonstrated stable / improved haemodynamic measures.

As described in detail in Chapter 5, significant haemodynamic decline was calculated by subtracting the haemodynamic measure (ABPI or TBPI) at baseline from that recorded at time 2 (2^{nd} follow-up). For this analysis, participants who had improved readings due to revascularisation for IC or developed calcification during the study period were excluded, since inclusion would not represent the natural progression of the disease in the former group and yield misleading results in the latter. In total 41 participants were found to experience significant haemodynamic decline without developing symptoms of CLI, 12 experiencing both ABPI and TBPI significant decline, 8 participants had a significant decline in ABPI only and 21 participants had a significant decline in TBPI only.

Haemodynamic outcome assessed by Doppler waveforms

At each visit (baseline, time 1 and time 2) the Doppler waveforms of the DP and PT were recorded. After 2 years the haemodynamic outcome of the participants classified according to the Doppler waveforms analysed is presented in fig 7.5. For this analysis, participants who underwent revascularisation during the study period (n=50) were excluded.

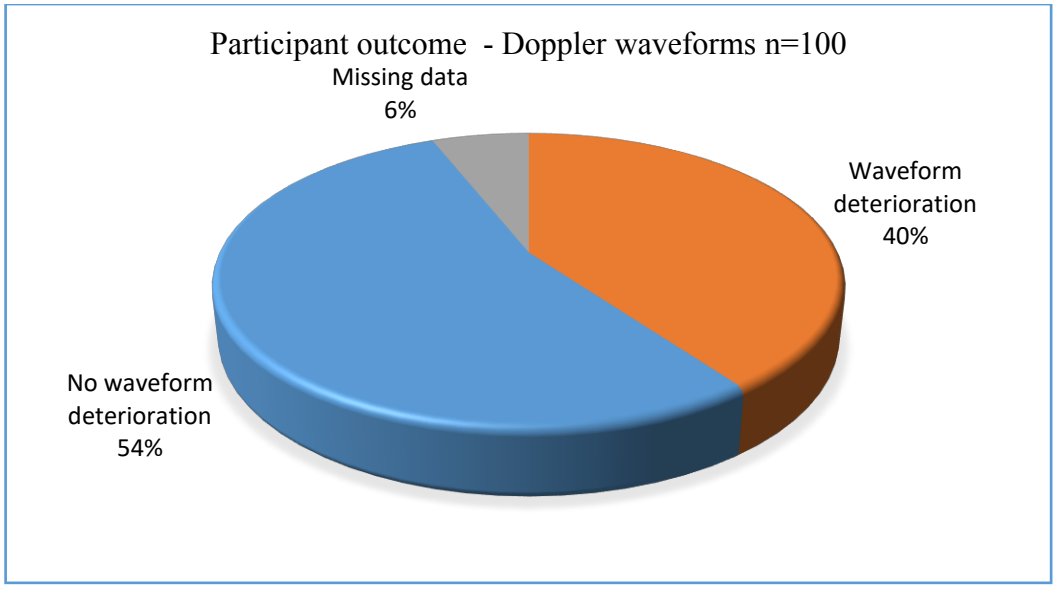


Fig 7.5 Haemodynamic outcome of participants by Doppler waveforms (excluding revascularised participants)

Within two years, 40% of the study population experienced a deterioration in waveforms (DP and / or PT) while 54% did not have a deterioration in waveforms within 2 years. The data of 6 participants was missing (4 died, 1 lost to follow-up and 1 participant did not attend). Participants who did not attend for haemodynamic analysis for the purpose of the study had their waveforms analysed at the vascular unit by the vascular surgeon and the reports were retrieved for data analysis.

Doppler waveforms are further analysed in the sections pertaining to the outcomes presented later in this chapter.

7.4.2.2 Clinical outcomes

Figure 7.6 illustrates the clinical outcomes experienced by the participants after 2 years following recruitment. Clinical outcomes were not defined by haemodynamic measures but by symptoms reported or retrieved from the databases, as detailed in Chapter 5. Three participants developed other medical conditions during the study period which precluded walking (hip fracture, knee pain and breathlessness) therefore Walking impairment questionnaire (WIQ) responses related to IC were excluded for these participants.

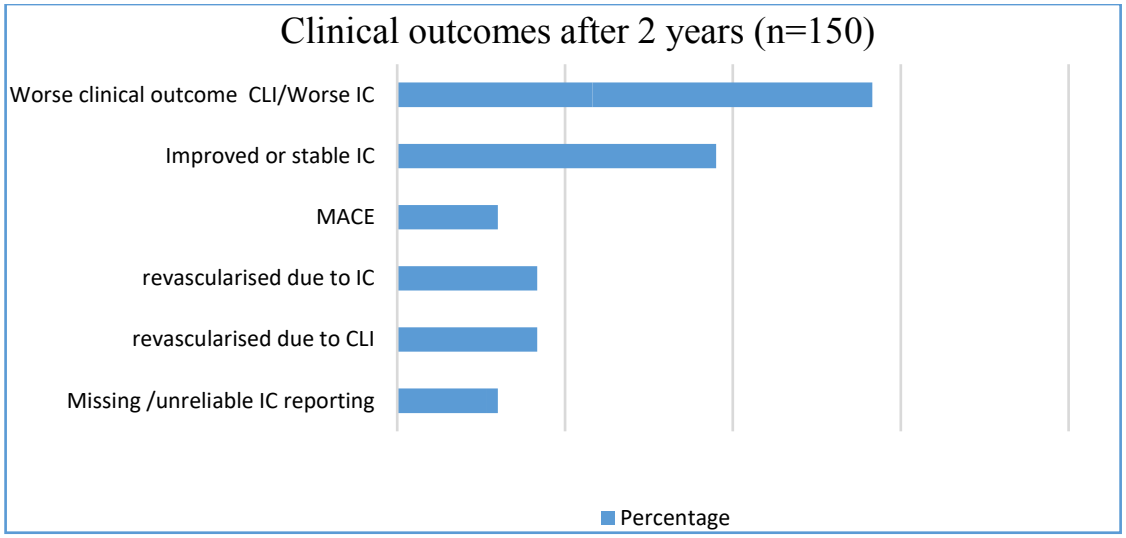


Figure 7.6 Clinical outcomes of participants after 2 years

The results of this study indicate that overall 56.6% (n=84) of the participants experienced worse clinical outcomes within 2 years, of whom 33.3% (n=49) developed worse IC symptoms with shorter claudication distance and higher WIQ scores (indicating worse symptoms) from the time of recruitment while 35 deteriorated to CLI. In total 50 participants underwent revascularisation procedures, 25 (10.7%) due to CLI and 25 (10.7%) due to IC. These results indicate that out of 84 participants who experienced clinical deterioration, 50 participants (59.5%) underwent revascularisation. Improved IC symptoms indicated by WIQ score and longer walking distance were reported in 38% (n=57) of the study cohort. Major adverse cardiovascular and cerebrovascular events were recorded in 12% (n=18) of participants, 3 of which were fatal events, the other mortality during the study was due to malignancy. WIQ responses were missing for 18 participants (4 died, 1 emigrated and 10 could not attend for review appointment and 3 reported inability to walk due to other reasons) however any other clinical outcome such as development of CLI, MACCE or revascularisation was recorded for these participants.

7.4.3 Baseline haemodynamic data of participants with specified outcomes

The baseline data of all the participants have been presented previously in Chapter Six. Table 7.1 presents the baseline haemodynamic data of the participants, categorised according to their outcome two years following recruitment. The baseline haemodynamic parameters of participants who experienced significant deterioration during the 2-year study period, which includes participants who had significant haemodynamic decline and those who developed CLI

were analysed. Participants who experienced significant deterioration but also developed symptoms, that is, developed CLI were also analysed separately.

Due to the inherent concerns associated with interpretation of ABPI and TBPI in the presence of medial arterial calcification (MAC), the table presents the medians of the participants in each category and also the median excluding readings of the known calcified arteries which were present at baseline or developed during the study period. This was done in order to avoid the possibility of presenting falsely elevated haemodynamic measures which do not represent the true measure of PAD, as discussed in detail in Chapter 2 Section 2.4.1.1. It should be noted that in several cases, falsely elevated readings for ABPI and not for TBPI in the same participant were evident, hence the number of participants when excluding calcified arteries for ABPI and TBPI vary. Calcified or falsely elevated readings were identified either by Duplex scan or by an ABPI ≥1.4 or TBPI with absolute toe pressure ≥150mmHg as previously explained in more detail in Chapter 5.

Table 7.1: Baseline haemodynamic parameters according to outcome after 2 years

Category according to outcome in 2 years	**ABPI median (IQR)** N=	**TBPI median (IQR)** N=	**Absolute toe pressure** mmHg median (IQR)
Significant deterioration	0.69 (0.55, 0.89) n=55	0.42 (0.32, 0.53) n= 68	60.5 (46.8, 84.7) n=68
Significant deterioration excluding calcified arteries at baseline	0.60 (0.50, 0.74) n=40	0.41 (0.32, 0.53) n=65	60.5 (46.8, 84.7) n=65
Developed CLI	0.66 (0.51, 0.7) n=35	0.33 (0.2, 0.43) n=35	51.1 (31, 65) n=35
Developed CLI excluding calcified arteries at baseline	0.53 (0.48, 0.69) n=27	0.33 (0.2, 0.43) n=34	51 (31, 65) n=34
Developed MACCE	0.63 (0.56, 0.) n=17	0.43 (0.29, 0.54) n=18	62.8 (20.9) n=18
Developed MACCE excluding calcified arteries	0.56 (0.50, 0.77) n=11	0.43 (0.29, 0.54) n=18	62.8 (20.9) n=18
Improved / stable	0.71 (0.55, 0.85) n=29	0.38 (0.26, 0.53) n=29	57.0 (38, 89) n=29
Improved / stable excluding calcified arteries at baseline	0.64 (0.53, 0.76) n=22	0.38 (0.26, 0.53) n=28	57.0 (38, 89) n=28

The results presented in table 7.1 describe the baseline haemodynamic data of the participants who developed different outcomes within two years. The results demonstrate that the participants who had stable or improved haemodynamics had a baseline median ABPI of 0.64 (0.53, 0.76) and TBPI of 0.38 (0.26, 0.53). Lower readings were evident in the group who experienced significant deterioration in ABPI 0.60 (0.50, 0.74) but these had a higher baseline of TBPI 0.41 (0.32, 0.53), while the lowest baseline readings were recorded in those who eventually deteriorated to CLI within 2 years of recruitment (ABPI 0.53 IQR 0.48, 0.69), TBPI 0.33 (IQR 0.2, 0.43).

Since the main aim of this research was to assess the risk of deterioration to CLI among patients presenting with IC and possibly identify predictors among this sub-group, a focus on the analysis of the data in this group of participants was applied. Therefore, the following section presents the analysis of data pertaining to the participants who deteriorated within 2 years and developed CLI.

7.4.4 Deterioration to critical limb ischaemia

In this study cohort (n=150), 35 participants (23.3%) deteriorated to CLI within 2 years. Nineteen of these participants developed CLI signs (foot ulceration) within 1 year of recruitment before the first follow-up, while 16 participants developed CLI in the 2nd year. The sections below explore the association of baseline data with deterioration to CLI in an attempt to identify baseline parameters which could help predict this deterioration and hence help identify participants who are more likely to deteriorate within 2 years of presenting with IC.

7.4.4.1 Baseline characteristics of participants who developed CLI

The tables 7.2 and 7.3 present the baseline characteristics and measured variables of the participants who deteriorated to CLI. Continuous data are presented as mean and standard deviation or median and interquartile range (depending on the distribution of data) while discrete data are presented as counts and percentages.

Table 7.2 : Baseline characteristics of participants who developed CLI within 2 years

Baseline Variables n=35		Mean / median / Frequency within group	SD	IQR	Percentage within group
ABPI median, IQR		0.66	-	0.51, 0.70	-
ABPI* median, IQR		0.53	-	0.48, 0.69	-
TBPI median, IQR		0.33	-	0.2, 0.42	-
Absolute toe pressure (mmHg) median, IQR		51	-	31, 65	-
PT Doppler waveform n, %	Monophasic	15	-	-	42.9
	Monophasic-continuous	20	-	-	57.1
DP Doppler waveform n, %	Monophasic	11	-	-	31.4
	Monophasic-continuous	24	-	-	68.6
Disease Location n,%	IPA disease present	21	-	-	60
	No IPA disease present	14	-	-	40
Claudication distance (m) median, IQR		100	-	50,100	-
Gender	Male n, %	26	-	-	74.3
	Female n,%	9	-	-	25.7
BMI mean SD		27.25	5.21	-	-
Age (years) mean SD		69.86	7.91	-	-
Smoking status n,%	Current smoker	11	-	-	31.4
	Past smoker	14	-	-	40
	Never smoked	10	-	-	28.6
Diabetes n,%		28	-	-	80
Hypertension n,%		30	-	-	85.7
Hyperlipidaemia n,%		26	-	-	74.3
Cardiac disease n,%		11	-	-	31.4
Renal disease n,%		9	-	-	25.7
Systolic blood pressure (mmHg)		148.94	18.81	-	-

Previous major event (MI/stroke) n,%	14	-	-	40
Taking statins and/or antiplatelet n,%	30	-	-	85.7
Ace inhibitor n,%	19	-	-	54.3
Angiotensin II antagonist n,%	6	-	-	17.1
Calcium channel blocker n,%	7	-	-	20
Beta blocker n,%	1	-	-	2.9

(IPA=infrapopliteal artery disease)

Results (Table 7.2) show that participants who deteriorated to CLI had a mean age of 69.9 years and were predominantly male (n=26, 74.3%). Development of CLI occurred in 22% (n=26) of the whole male cohort and in 29% (n=9) of the whole female cohort. Infrapopliteal artery disease (IPA) was present in 60% of this group and the PT and DP Doppler waveforms were predominantly monophasic continuous (57.1% and 68.6%). A high prevalence of diabetes (80%), hypertension (85.7%), hyperlipidaemia (74.3%) and smoking history (71.4%) was also evident. At baseline, the majority (85.7%) of the participants in this group were on the recommended medical therapy (Norgren et al., 2007) taking anti platelet and statin therapy.

Baseline blood parameters of participants who developed CLI

Baseline Parameters	**Median**	**IQR 1**	**IQR 3**	**Normal range**
eGFR mls/min/1.73m^2	86	64	101	> 60
Cholesterol mmol/l	4.31	3.34	4.97	2.0 - 5.0
Triglyceride mmol/l	1.36	1.0	1.71	0.1 - 2.26
HDL Cholesterol mmol/l	1.18	0.92	1.4	0.9 - 1.45
Non HDL Cholesterol mmol/l	2.98	2.3	3.5	0 - 3.36
LDL Cholesterol mmol/l	2.35	1.52	3.0	0.1-3.88
Total: HDL Cholesterol ratio	3.52	2.61	4.12	-
Fasting blood glucose mmol/l	**7.55**	6.0	11.9	3.88-6.38
HbA1c (%)	**7.0**	5.8	8.6	4.7 - 6.4
Creatinine umol/l	81	68	96	59 - 104
CRP mg/L	2.9	1.1	7.8	0 - 5
ESR mm 1st Hr	**15.5**	7.5	32.5	28 - 32

Table 7.3: Baseline blood parameters of participants who developed CLI within 2 years

Table 7.3 presents the blood parameters measured at baseline of the participants who deteriorated to CLI within the study period. The median fasting blood glucose and HbA1c level were above the normal range at baseline (7.55 mmol/L (IQR 6,11.9) and 7% (IQR 5.8,8.6) respectively) and the ESR level was below the normal range (15.5mm1st Hr (IQR 7.5,32.5)). The cholesterol ratio of 3.52 indicates a high risk of heart disease. The rest of the blood parameters recorded were within the normal ranges.

7.4.4.2 Analysing baseline variables in relation to development of CLI

In the following section the analysis of baseline factors in relation to deterioration to CLI is presented. Following a test for normalcy of distribution of the measured variable scores (Shapiro-Wilk Appendix 11), baseline variables were analysed for significant differences between participants who deteriorated to CLI and participants who did not. This is followed by Multinomial logistic regression models which were used to assess for independent factors associated with deterioration to CLI. Additionally, a receiver operator curve (ROC) analysis was applied to determine the best cut-off values of identified significant factors for predicting deterioration to CLI. A p-value of 0.05 was considered statistically significant.

7.4.4.3 Test for normalcy of data

The Shapiro-Wilk test was performed using the individual data measurements at baseline, first and second follow-up to assess the normality assumption of measured variables of all the participants. The Shapiro-Wilk test is used to determine whether a parameter score distribution is normal or skewed. The null hypothesis specified that the parameter score distribution was normal and was accepted if the p-value exceeded the 0.05 level of significance. The alternative hypothesis specified that the score distribution was skewed and was accepted if the p-value was less than the 0.05 criterion.

Almost all the results obtained from the Shapiro-Wilk normality test (Appendix 11) had a p-value less than 0.05 level of significance indicating that the parameter score distribution does not satisfy the normality assumption. For this reason, non-parametric tests were used for the analysis.

7.4.4.4 Baseline parameter differences in participants who developed CLI

Initial analysis included assessing the difference in baseline parameters between participants who developed CLI within 2 years and participants who did not. Mann-Whitney U tests were applied to compare unpaired continuous data and Chi squared tests were applied to compare categorical data and to test for trends. Non-parametric tests were applied since the parameters did not have a normal distribution as shown by the Shapiro Wilk test (Appendix 11).

Table 7.4: Mann Whitney U test comparing baseline parameters between participants who deteriorated to CLI and participants who did not

Continuous Variables		N	Median	IQR 1	IQR2	Mann Whitney U	P value
ABPI	CLI	35	.60	.51	.70	1519	**0.033**
	No CLI	115	.68	.56	0.84		
ABPI*	CLI	27	0.53	0.48	0.69	805.5	**0.002**
	No CLI	90	0.65	0.55	0.77		
TBPI	CLI	35	.33	.20	.42	1463	**0.015**
	No CLI	115	.41	.31	0.52		
Absolute toe	CLI	35	55	31	65	1566	**0.047**
pressure	No CLI	115	60.00	44.00	84.00		
BMI	CLI	35	26.5	23.4	30	1766.5	0.274
	No CLI	115	27.90	25.60	30.00		
Age	CLI	35	69	64	75	1997	0.945
	No CLI	115	70.00	64.00	77.00		
Claudication	CLI	35	50	100	100	1628	0.082
distance	No CLI	115	100.00	50.00	200.00		
Smoking duration	CLI	13	43	36.5	50	246.50	0.45
Current smokers	No CLI	44	45.50	38.50	55.75		
Pack Years	CLI	13	50	19.8	80	281.50	0.93
Current smokers	No CLI	44	45.00	26.25	69.63		
eGFR	CLI	35	86.00	64.00	101.00	1737	0.22
	No CLI	115	77.00	53.00	97.00		
Cholesterol	CLI	35	4.31	3.34	4.97	1882.50	0.56
	No CLI	115	4.32	3.59	5.25		
Triglyceride	CLI	35	1.36	1.0	1.71	1855.00	0.48
	No CLI	115	1.52	.99	2.13		
HDL Cholesterol	CLI	35	1.18	0.92	1.4	1884.00	0.57
	No CLI	115	1.13	.93	1.43		
	CLI	35	2.98	2.3	3.5	1845.00	0.46

Non HDL Cholesterol	No CLI	115	3.07	2.42	4.04		
LDL Cholesterol	CLI	35	2.35	1.52	3.0	1781.00	0.30
	No CLI	115	2.26	1.71	2.95		
Total Cholesterol	CLI	35	3.52	2.61	4.12	1684.50	0.15
	No CLI	115	3.78	2.89	4.77		
HbA1c	CLI	35	7.0	5.8	8.6	1725.50	0.20
	No CLI	115	6.60	5.80	7.60		
Creatinine	CLI	35	81	68	96	1713.00	0.18
	No CLI	115	86.00	71.00	119.00		
CRP mg/L	CLI	35	2.9	1.1	7.8	1657.00	0.43
	No CLI	104	2.00	1.02	4.75		
ESR	CLI	34	15.5	7.5	32.5	1679.50	0.78
	No CLI	102	15.00	8.00	29.00		
Systolic blood pressure	CLI	35	152	132	158	1975.0	0.87
	No CLI	115	147.00	132.00	166.00		

Results demonstrate that the participants who deteriorated to CLI had significantly lower values of ABPI, ABPI*, TBPI and absolute toe pressures at baseline compared to the participants who did not deteriorate to CLI (p=<0.05). No significant difference was found in the other parameters measured.

The Chi square test was used to compare the baseline categorical data between the participants who developed CLI and those who did not. The results are presented in the table 7.5.

Table 7.5: Chi square tests analysing differences in parameters at baseline between participants who deteriorated to CLI and participants who did not develop CLI

Parameter	Category	Group	N	% within group	X^2	df	P value
PT Doppler waveform	Biphasic	CLI	0	0	9.67	2	**0.008**
		No CLI	15	13			
	Monophasic	CLI	15	42.9			
		No CLI	60	52.2			
	Mono-cont	CLI	20	57.1			
		No CLI	38	33			

DP Doppler waveform	Biphasic	CLI	0	0	9.16	2	**0.01**
		No CLI	10	8.7			
	Monophasic	CLI	11	31.4			
		No CLI	56	48.7			
	Mono-cont	CLI	24	68.6			
		No CLI	48	41.7			
Gender	Male	CLI	26	74.3	0.709	1	0.4
		No CLI	93	81			
	Female	CLI	9	25.7			
		No CLI	22	19			
Smoking status	Current smoker	CLI	11	31.4	1.26	2	0.53
		No CLI	44	38.3			
	Past smoker	CLI	14	40			
		No CLI	48	41.7			
	Never smoked	CLI	10	28.6			
		No CLI	23	20			
Diabetes		CLI	28	80	2.44	1	0.12
		No CLI	76	66.1			
Hypertension		CLI	30	85.7	0.003	1	0.96
		No CLI	99	86.1			
Hyperlipidaemia		CLI	26	74.3	0.24	1	0.62
		No CLI	90	78.3			
Cardiac Disease		CLI	11	31.4	1.61	1	0.2
		No CLI	50	43.5			
Renal Disease		CLI	9	25.7	0.67	1	0.41
		No CLI	38	33			
		CLI	30	85.7	1.13	1	0.29

Taking antiplatelet and/or anticoagulant	No CLI	89	77.4			
Ace inhibitor	CLI	19	54.3	0.72	1	0.4
	No CLI	53	46.1			
Angiotensin II Antagonist	CLI	6	17.1	0.22	1	0.63
	No CLI	16	13.9			
Calcium channel blocker	CLI	7	20	0.4	1	0.53
	No CLI	29	25.2			
Beta blocker	CLI	1	2.9	1.64	1	0.2
	No CLI	11	9.6			
Previous major event	CLI	14	40	0.4	1	0.53
	No CLI	53	46.1			
Infrapopliteal artery disease	CLI	21	60	4.34	1	**0.037**
	No CLI	46	40			

The cross tab clearly shows a significantly larger proportion of participants with monophasic-continuous waveforms at baseline (in both PT and DP) in the group who developed CLI and a larger proportion of participants with biphasic waveforms in the group who did not develop CLI. Additionally, results also demonstrate that a significantly larger percentage of participants had infrapopliteal artery disease in the group who developed CLI within 2 years compared to those who did not develop CLI. These percentage differences are significant since the p-value is less than the 0.05 criterion. There is no significant difference between the 2 groups in the other measured categorical parameters.

7.4.5 Predictors for deterioration to CLI

Binomial logistic regression models were applied to determine factors independently associated with deterioration to CLI. The results of the regression models are given as the odds ratio (OR) and 95% confidence interval (95% CI).

Due to the inherent limitations associated with the interpretation of ABPI in cases of MAC, calcified arteries were excluded from the regression analysis. However, since this process

results in the exclusion of all the data of the affected participants, two separate binomial regression models were applied. The first model (Regression Model 1) included baseline ABPI excluding known falsely elevated readings due to calcified arteries as a haemodynamic measure. Toe brachial pressure indices and absolute toe pressures were not included, while the rest of the factors measured and participants' characteristics recorded at baseline were included. The number of participants in this analysis was 117 (CLI n=27, No CLI n=90). In the second model (Regression Model 2) ABPI was excluded from the analysis and TBPI and absolute toe pressures were included, together with the rest of parameters measured at baseline. The number of participants in this model was 150 (CLI n=35, No CLI n=115).

The results of the initial model of Regression model 1 and Regression model 2 are presented in Appendix 13 'Regression Models results'. All the factors recorded were inserted in the models and the interaction effect was analysed by backward elimination. The tables below present the final models and the significant predictors for deterioration to CLI identified through this analysis.

Parameter Estimates

Deterioration to CLI[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% CI for OR	
								Lower Bound	Upper Bound
Deteriorated to CLI	Intercept	-4.016	1.237	10.54	1	.001			
	IPA disease	.809	.413	3.84	1	**0.049**	2.25	1.0	5.04
	No IPA disease	0[b]	.	.	0	.	.	.	.
	ABPI	-0.4361	1.516	8.280	1	**0.004**	0.647	0.001	0.249
	HbA1c	.274	.144	3.60	1	0.058	1.32	.99	1.74
	ABPI ≤0.5	1.360	.712	3.65	1	**0.046**	3.89	.97	15.72
	ABPI 0.51-0.69	.668	.594	1.26	1	0.261	1.95	.61	6.25
	ABPI 0.7-0.89	-.162	.711	.052	1	0.819	.85	.21	3.43
	ABPI ≥0.9	0[b]	.	.	0	.	.	.	.

a. The reference category is: Did not deteriorate to CLI.

b. This parameter is set to zero because it is redundant.

Table 7.6- Significant predictors for deterioration to CLI for Model 1. Multinomial logistic regression analysis.

Pseudo R-Square	Cox and Snell	Nagelkerke	McFadden
	.0179	.266	.176

Table 7.6b Model 1

The significant independent predictors for deterioration to CLI identified in the first model were baseline ABPI (reciprocal OR 1.5, p=0.004), ABPI ≤0.5 (OR 3.9, p=0.046) and the presence of Infrapopliteal artery disease (OR 2.25, p=0.049).

While logistic regression reports the odds ratio of the variables of interest, in this study the relative risk (RR) of the variables which were identified as significant independent predictors for the development of CLI was also calculated. As described in chapter 3, since the incidence of CLI in the general population is less than 10% (0.24%) (Bitar & Garcia, 2010; Jensen et al., 2006; Nehler et al., 2014), the odds ratio and relative risk do not vary and the rare disease assumption is applied where the OR derived from the logistic regression analysis can be expressed as RR (J. Zhang & Kai, 1998).

Therefore, the results of this study demonstrate that participants with baseline ABPI of ≤0.5 are 3.9 times more likely to develop CLI within 2 years than participants who have higher ABPIs; participants who have infrapopliteal artery disease at baseline are 2.25 more likely to develop CLI within 2 years than participants who do not have infrapopliteal artery disease at baseline and for every 0.1 decrease in ABPI the risk of deterioration to CLI increases by 1.5 times.

Table 7.7- Significant predictors for deterioration to CLI for Model 2. Multinomial logistic regression analysis.

		Parameter Estimates							
Deterioration to CLI[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% Confidence Interval for OR	
								Lower Bound	Upper Bound
Deteriorated to CLI	Intercept	-4.02	1.16	11.96	1.00	.0001			
	TBPI	-0.3266	1.291	6.404	1	**0.011**	0.327	.003	.479
	TBPI ≤0.39	1.28	.56	5.32	1.00	**0.02**	3.60	1.21	10.71
	TBPI 0.4-0.69	.38	.70	.29	1.00	.59	1.46	.37	5.78
	TBPI ≥0.7	.00[b]	.	.	.00	.	.	.	.
	HbA1c	.30	.14	4.67	1.00	**.03**	1.35	1.03	1.78

a. The reference category is: Did not deteriorate to CLI.

b. This parameter is set to zero because it is redundant.

Pseudo R-Square	Cox and Snell	Nagelkerke	McFadden
	.097	.143	.090

Table 7.7b Model 2

The significant predictors for deterioration to CLI identified in the second model were baseline TBPI ([Reciprocal] OR 3.06, p=0.01), baseline TBPI ≤0.39 (OR 3.6, p=0.02) and baseline HbA1c (OR 1.35, p=0.03).

The results demonstrate that participants with baseline TBPI of ≤0.39 are 3.6 times more likely to develop CLI than participants with higher TBPI (RR 3.6, p=0.02); with every 1-unit increase in baseline HbA1c the risk of developing CLI increases by 1.35 times (RR1.35, p=0.03) and with every 0.1-unit decrease in baseline TBPI participants are 3 times more likely to deteriorate to CLI.

Overall, the results of this regression analysis therefore demonstrate that in this study population the significant independent predictors for developing CLI within 2 years were baseline ABPI (excluding calcified arteries), baseline TBPI, infrapopliteal artery disease and HbA1c. None of the other variables measured were found to be significant predictors for the development of CLI among the participants.

7.4.6 Significant haemodynamic deterioration

Since the aim of this study was to identify patients who are more likely to deteriorate, baseline parameters of participants who experienced a significant decline in ABPI ≥0.15 and / or TBPI ≥0.1 within 2 years were assessed. The significant haemodynamic decline defined as ≥0.15 for ABPI and ≥0.1 for TBPI was discussed previously in Chapter Five. The decline in haemodynamic readings was calculated by subtracting the reading at baseline by the reading after 2 years. In order to focus on the natural disease process and limiting threats to validity of the study (discussed in detail in Chapter Three) some participants were excluded from the analysis of ABPI decline (n=21) and TBPI decline (n=3) for the following reasons: Participants who experienced a haemodynamic improvement due to revascularisation for IC, were excluded since the natural history of the disease could not be evaluated. Additionally, in order to limit threats to validity due to inherent issues associated with arterial calcification and the reliability of the haemodynamic change as a measure of PAD (discussed in detail in Chapter 2), participants who developed MAC (defined by duplex scan and /or ABPI>1.4 and/or increase in ABPI >0.15 without revascularisation) during the study period, were also excluded from the analysis.

Since the main focus of this study was the identification of participants who experienced a significant deterioration within 2 years, the baseline parameters of those who deteriorated to CLI (n=35) were included in the group 'significant deterioration analysed ABPI' and 'significant deterioration analysed TBPI' even in cases of revascularisation since their significant deterioration was confirmed by the development of tissue loss.

Since deterioration by ABPI and TBPI were calculated separately, the analysis of haemodynamic deterioration measured by ABPI and TBPI are analysed and presented separately in the following sections where participants identified as having experienced a significant deterioration by a decline in ABPI by ≥0.15 are categorised as 'Significant deterioration- ABPI' and participants who were identified as having experienced a significant deterioration by a decline in TBPI of ≥0.1 were categorised as Significant deterioration- TBPI

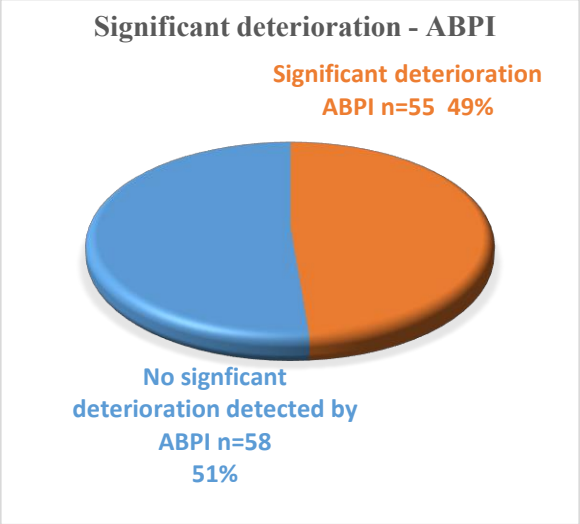


Fig 7.7 Significant deterioration-ABPI

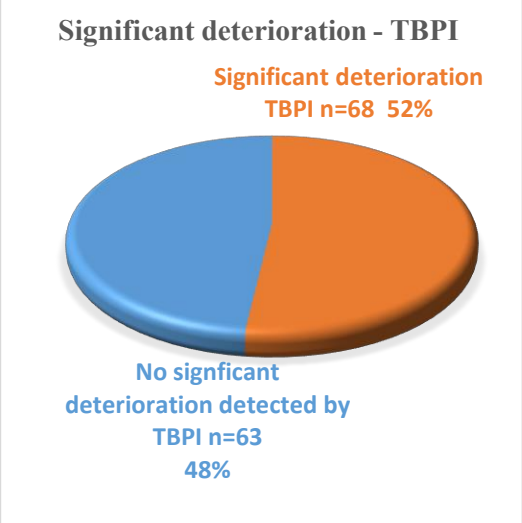


Fig. 7.8 Significant deterioration - TBPI

Figures 7.7 and 7.8 illustrate that when analysing significant deterioration by assessing the change in ABPI over 2 years, 55 participants were shown to have experienced significant deterioration (decline in ABPI by ≥0.15 or development of CLI) and 58 participants did not. When analysing significant deterioration over 2 years detected by a decline in TBPI of ≥0.1 or development of CLI, results indicate that 68 participants experienced significant deterioration while 63 participants did not. Therefore, a larger proportion of participants were detected as experiencing significant deterioration by analysing the decline in TBPI when compared to deterioration detected by ABPI decline because more participants were excluded in the ABPI analysis due to calcification. Further analysis of these groups indicated that 8 participants

experienced significant deterioration detected by ABPI and not TBPI while 16 participants experienced significant deterioration detected by TBPI and not by ABPI. The rest (n=52 of whom n=35 had CLI) were common in both groups. This difference in detection of deterioration was due to the fact that participants who experienced a significant decline in ABPI may have experienced a decline in TBPI but which was less than 0.1. However, in total 76 participants experienced significant deterioration, 41 detected by ankle or toe brachial pressure measurements and 35 developed CLI symptoms.

7.4.6.1 Baseline characteristics of participants with a significant deterioration assessed by decline in ABPI or CLI

The baseline descriptive data of participants who experienced a haemodynamic decline detected by ABPI decline by ≥0.15 or deterioration to CLI are presented in the following tables.

Table 7.8: Baseline characteristics of participants who experienced significant deterioration assessed by decline in ABPI or CLI within 2 years

Baseline Variables		Mean / Median /Frequency within group	SD	IQR	Percentage within group
ABPI baseline n=55 median IQR		0.69	-	0.55, 0.89	-
ABPI * baseline n=40 median IQR		0.60	-	0.5, 0.74	-
TBPI baseline n=55 median IQR		0.37	-	0.27, 0.46	-
TBPI* n=55 median IQR		0.37	-	0.27, 0.46	-
Absolute toe pressure (mmHg) median IQR		57	-	44. 73	-
PT Doppler waveform %	Monophasic	28	-	-	50.9
	Biphasic	5	-	-	9.1
	Monophasic-continuous	22	-	-	40
DP Doppler waveform %	Monophasic	24	-	-	43.6
	Biphasic	3	-	-	5.5
	Monophasic-continuous	28	-	-	50.9
Disease Location n,%	Infrapopliteal artery disease present	35	-	-	46.7
	No Infrapopliteal artery disease present	40	-	-	53.3

Claudication distance (m) median IQR		100	-	50, 150	
Gender n,%	Male	41	-	-	74.5
	Female	14	-	-	25.5
BMI mean SD		27.4	4.5	-	-
Age (years) mean SD		70.9	7.7	-	-
Smoking status n,%	Current smoker	18	-	-	32.7
	Past smoker	22	-	-	40
	Never smoked	15	-	-	27.3
Diabetes n,%		43	-	-	78.2
Hypertension n,%		49	-	-	89.1
Hyperlipidaemia n,%		44	-	-	80
Cardiac disease n,%		22	-	-	40
Renal disease n,%		22	-	-	40
Previous major event (MI/stroke) n,%		26	-	-	47.3
MACCE n,%		8	-	-	14.5
Systolic blood pressure (mmHg) mean SD		148.63	22.13	-	
Statins Antiplatelet and /or anticoagulant n,%		45	-	-	81.8
Ace inhibitor n,%		31	-	-	56.4
Angiotensin II antagonist n,%		7	-	-	12.7
Calcium channel blocker n,%		12	-	-	21.8
Beta blocker n,%		3	-	-	5.5

Results (Table 7.8) indicate that this group had a mean age of 70.9 years and were predominantly male (74.5%) while 25.5% (n=14) of the group were women. It should be noted that the 14 women who experienced significant deterioration constitute 45.2% of the women in the whole study cohort while the men who deteriorated significantly comprised 34.5% of the whole male cohort. The median baseline ABPI was 0.69 (IQR 0.55, 0.89) and 0.6 (IQR 0.5, 0.74) when excluding calcified arteries. Baseline median TBPI was 0.37 (IQR 0.27, 0.46). Infrapopliteal artery disease (IPA) was present in 46.7% of this group. A high prevalence of diabetes (78.2%), hypertension (89.1%), hyperlipidaemia (80%) and smoking history (72.7%) was also evident. The majority (81.8%) of the participants in this group were on best medical therapy at baseline taking anti platelet and statin therapy.

Table 7.9: Baseline blood parameters of participants who experienced significant deterioration - ABPI

Blood parameters n=55	Median	IQR 1	IQR 3	Normal range
eGFR mls/min/1.73m^2	77	51	92	> 60
Cholesterol mmol/l	4.4	3.6	4.9	2.0-5.0
Triglyceride mmol/l	1.45	1.0	2.03	0.1-2.26
HDL Cholesterol mmol/l	1.21	1.02	1.45	0.9-1.45
Non HDL Cholesterol mmol/l	3.31	2.37	3.53	0-3.36
LDL Cholesterol mmol/l	2.47	1.63	2.86	0.1-3.88
Total Cholesterol	3.58	2.66	4.58	_
HbA1c %	**6.6**	5.8	7.6	4.7-6.4
Fasting glucose mmol/l n=42	**7.55**	5.54	9.5	3.88-6.38
Creatinine umol/l	85	72	126	59-104
CRP mg/L n=54	3	1.18	7.8	0-5
ESR mm 1st Hr n=51	**18**	8	34	28-32

Table 7.9 presents the blood parameters measured at baseline of the participants who experienced significant deterioration measured by ABPI within the study period. The median fasting blood glucose and HbA1c level were above the normal range at baseline (7.55mmol/L and 6.6% respectively) and the ESR level was below the normal range (18mm1st Hr). The total cholesterol of 3.58 indicates a high risk of heart disease. The rest of the blood parameters recorded were within the normal ranges.

7.4.6.2 Baseline parameter differences in participants who experienced significant decline assessed by ABPI or CLI

Initial analysis included assessing the difference in baseline parameters between those participants who experienced a significant deterioration (decline in ABPI of ≥0.15 or CLI within 2 years) and those who did not. Continuous variables were assessed statistically using the Mann Whitney U test between the 2 groups. A non-parametric test was applied since the parameters do not have a normal distribution as shown by the Shapiro Wilk test (Appendix 11).

Results of the Mann Whitney test are shown in the table 7.10. Differences in categorical variables between the two groups were assessed statistically using the Chi square test. Results are presented in table 7.11.

The differences between baseline parameters of those who experienced a significant deterioration assessed by ABPI or development of CLI (n=55) and those who did not (n=58) are presented in table 7.10.

Table 7.10 Baseline parameter differences between participant with significant ABI decline and participants without significant ABI decline within 2 years. Mann Whitney U test

Baseline parameters	Groups	N	Median	IQR 1	IQR 3	Mann Whitney U	P value
ABPI* baseline	Sig deterioration ABPI	40	0.61	0.51	0.74	772	0.2
	No sig deterioration	47	0.66	0.56	0.76		
ABPI baseline	Sig deterioration ABPI	55	0.69	0.55	0.89	1568	0.88
	No sig deterioration	58	0.69	0.56	0.84		
TBPI baseline	Sig deterioration ABPI	55	0.37	0.27	0.46	1328	0.13
	No sig deterioration	58	0.42	0.32	0.52		
Absolute toe pressure baseline	Sig deterioration ABPI	55	57	44.00	73.00	1366	0.18
	No sig deterioration	58	61.50	45.50	88.25		
BMI	Sig deterioration ABPI	55	27.50	24.80	29.60	1470	0.47
	No sig deterioration	58	27.90	25.60	29.75		
Age	Sig deterioration ABPI	55	72.00	66.00	77.00	1573.5	0.9
	No sig deterioration	58	70.00	64.50	80.00		
Smoking duration Current smokers	Sig deterioration ABPI	20	45.50	40.00	54.50	195	0.7
	No sig deterioration	21	50.00	40.00	58.50		
Pack Years smoked Current smokers	Sig deterioration ABPI	20	53.00	28.06	77.50	179.5	0.43
	No sig deterioration	21	37.50	23.50	68.25		
eGFR	Sig deterioration ABPI	55	77	51	92	1498.5	0.58
	No sig deterioration	58	77.50	55.75	95.50		
Cholesterol	Sig deterioration ABPI	55	4.4	3.6	4.9	1346.5	0.15
	No sig deterioration	58	4.01	3.42	4.87		

Triglyceride	Sig deterioration ABPI	55	1.45	1.0	2.03	1523.5	0.68
	No sig deterioration	58	1.67	1.00	2.19		
HDL Cholesterol	Sig deterioration ABPI	55	1.21	1.02	1.45	1281	0.07
	No sig deterioration	58	1.09	.90	1.33		
Non HDL Cholesterol	Sig deterioration ABPI	55	3.31	2.37	3.53	1458	0.43
	No sig deterioration	58	2.92	2.22	3.84		
LDL Cholesterol	Sig deterioration ABPI	55	2.4700	1.63	2.86	1435.5	0.36
	No sig deterioration	58	2.18	1.50	2.66		
Total Cholesterol	Sig deterioration ABPI	55	3.58	2.66	4.58	1495	0.57
	No sig deterioration	58	3.57	2.91	4.69		
HbA1c	Sig deterioration ABPI	55	6.6	5.8	7.6	1541.5	0.76
	No sig deterioration	58	7.00	5.90	7.60		
Creatinine	Sig deterioration ABPI	55	85	72	126	1584.5	0.95
	No sig deterioration	58	87.00	72.75	110.50		
CRP	Sig deterioration ABPI	54	3	1.18	7.8	1100	**0.04**
	No sig deterioration	53	1.70	.80	4.15		
ESR	Sig deterioration ABPI	51	18	8	34	1215.5	0.57
	No sig deterioration	51	15.00	9.00	29.00		
Systolic blood pressure	Sig deterioration ABPI	55	149	131.00	161.00	1592.5	0.99
	No sig deterioration	58	146.50	131.25	162.25		

The results indicate that participants who experienced a significant deterioration in ABPI and /or developed CLI had higher CRP values at baseline (p=<0.05). There was no significant difference in other parameters recorded at baseline between participants who experienced a significant deterioration detected by ABPI and participants who did not.

The baseline parameter differences of categorical variables between participants who experienced a significant deterioration measured by ABPI decline and participants who did not, are presented in table 7.11.

Table 7.11: Difference in baseline parameters between participants who had a significant decline in ABPI and participants who did not experience significant decline. Chi square test.

Parameter	Category	Group	N	% within group	X^2	df	P value
PT Doppler waveform	Biphasic	Sig deterioration ABPI	5	9.1	1.67	2	0.43
		No sig deterioration	8	13.8			
	Monophasic	Sig deterioration ABPI	28	50.9			
		No sig deterioration	33	56.9			
	Monophasic -continuous	Sig deterioration ABPI	22	40			
		No sig deterioration	17	29.3			
DP Doppler waveform	Biphasic	Sig deterioration ABPI	3	5.5	3.17	2	0.20
		No sig deterioration	5	8.6			
	Monophasic	Sig deterioration ABPI	24	43.6			
		No sig deterioration	33	56.9			
	Monophasic -continuous	Sig deterioration ABPI	28	50.9			
		No sig deterioration	20	34.5			
Gender	Male	Sig deterioration ABPI	41	74.5	3.43	1	0.06
		No sig deterioration	51	87.9			
	Female	Sig deterioration ABPI	14	25.5			
		No sig deterioration	7	12.1			
Smoking status	Current smoker	Sig deterioration ABPI	18	32.7	2.37	2	0.31
		No sig deterioration	21	36.2			
	Past smoker	Sig deterioration ABPI	22	40			
		No sig deterioration	28	48.3			
	Never smoked	Sig deterioration ABPI	15	27.3			
		No sig deterioration	9	15.5			
Diabetes		Sig deterioration ABPI	43	78.2	0.006	1	0.94
		No sig deterioration	45	77.6			
Hypertension		Sig deterioration ABPI	49	89.1	0.17	1	0.68
		No sig deterioration	53	91.4			
Hyperlipidaemia		Sig deterioration ABPI	44	80	0.55	1	0.46
		No sig deterioration	43	74.1			
Cardiac Disease		Sig deterioration ABPI	22	40	0.11	1	0.74
		No sig deterioration	25	43.1			
Renal Disease		Sig deterioration ABPI	22	40	0.99	1	0.32
		No sig deterioration	18	31			
Taking antiplatelet and/or anticoagulant		Sig deterioration ABPI	45	81.8	0.02	1	0.89
		No sig deterioration	48	72.8			
Statins		Sig deterioration ABPI	42	76.4	0.37	1	0.54
		No sig deterioration	47	81			
Ace inhibitor		Sig deterioration ABPI	31	56.4	0.46	1	0.5

	No sig deterioration	29	50			
Angiotensin II Antagonist	Sig deterioration ABPI	7	12.7	0.45	1	0.5
	No sig deterioration	10	17.2			
Calcium channel blocker	Sig deterioration ABPI	12	21.8	0.83	1	0.36
	No sig deterioration	17	29.3			
Beta blocker	Sig deterioration ABPI	3	5.5	0.92	1	0.38
	No sig deterioration	6	10.3			
Previous major event	Sig deterioration ABPI	26	47.3	0.07	1	0.79
	No sig deterioration	26	44.8			
Infrapopliteal artery disease	Sig deterioration ABPI	29	52.7	1.05	1	0.31
	No sig deterioration	25	43.1			

The results in the cross tab (table 7.11) indicate that there was no significant difference in the baseline categorical parameters recorded between the participants who experienced a significant deterioration detected by ABPI decline and participants who did not (p=>0.05).

7.4.6.3 Baseline characteristics of participants with a significant haemodynamic decline by TBPI

Similar to the participants who experienced deterioration detected by ABPI decline, the baseline descriptive data of participants who experienced a haemodynamic decline detected by TBPI (decline by ≥0.1 and/or deterioration to CLI) are presented below in tables 7.12 and 7.13.

Baseline Variables n=68		Mean / median/ Frequency within group	SD	IQR	Percentage within group
ABPI median IQR		0.68		0.55, 0.86	
ABPI* (n=50) median IQR		0.60		0.51, 0.71	
TBPI median IQR		0.42		0.32, 0.53	
TBPI* (n=68) median IQR		0.42		0.32, 0.53	
Absolute toe pressure (mmHg) median IQR		60.5		46.7, 84.7	
PT Doppler waveform n,%	Biphasic	6			8.8
	Monophasic	36			52.9
	Monophasic-continuous	26			38.2
DP Doppler waveform n,%	Biphasic	4			5.9
	Monophasic	32			47.1

	Monophasic-continuous	32			47.1
Disease Location n,%	IPA disease present	36			52.9
	No IPA disease present	32			47.1
Claudication distance (m) median IQR		100		50, 150	
Gender n,%	Male	51			75
	Female	17			25
BMI mean SD		27.40	4.17		
Age (years) mean SD		71.35	7.96		
Smoking status n,%	Current smoker	25			36.8
	Past smoker	28			41.2
	Never smoked	15			22.1
Diabetes n,%		54			79.4
Hypertension n,%		60			88.2
Hyperlipidaemia n,%		53			77.9
Cardiac disease n,%		27			39.8
Renal disease n %		21			30.9
Systolic blood pressure (mmHg) mean SD		149	20.9		
Previous major event (MI/stroke) n,%		29			42.6
Experienced MACCE n,%		8			11.8
Underwent revascularisation n,%		30			44.1
Deteriorated to CLI n,%		35			51.5
Taking statins and/or antiplatelet n,%		51			75
Ace inhibitor n,%		35			51.5
Angiotensin II antagonist n,%		10			14.7
Calcium channel blocker n,%		17			25
Beta blocker n,%		4			5.9

Table 7.12 : Baseline characteristics of participants who experienced a significant decline in TBPI and/or CLI within 2 years. TBPI* - excluding known calcified reading at baseline.

Table 7.12 describes the baseline characteristics of participants who experienced a significant deterioration measured by TBPI or who developed CLI. This group had a mean age of 71.35 years and were predominantly male (75%, n=51) while 25% (n=17) of the group were women. It should be noted that the 17 women who experienced significant deterioration by TBPI comprised 54.8% of the women in the whole study cohort while the men who deteriorated significantly comprised 42.8% of the whole male cohort. The median ABPI was 0.69 (IQR 0.55, 0.86) and 0.6 (IQR 0.51, 0.71) when excluding calcified arteries. The median TBPI was 0.42 (IQR 0.32, 0.53). Infrapopliteal artery disease (IPA) was present in 52.9% of this group. A high prevalence of diabetes (79.4%), hypertension (88.2%), hyperlipidaemia (77.9%) and smoking history (78%) was also evident. Two thirds (75%) of the participants in this group were on best medical therapy at baseline taking anti platelet and statin therapy.

Table 7.13: Baseline blood parameters of participants who experienced significant deterioration - TBPI

Blood parameter n=68	Median	IQR 1	IQR 3	Normal range
eGFR	78.5	56.5	94.5	> 60
Cholesterol mmol/l	4.46	3.5	5.0	2.0 - 5.0
Triglyceride mmol/l	1.47	1.14	2.06	0.1 - 2.26
HDL Cholesterol mmol/l	1.17	0.9	1.4	0.9 - 1.45
Non HDL Cholesterol mmol/l	3.19	2.4	3.6	0 - 3.36
LDL Cholesterol mmol/l	2.4	1.5	2.97	0.1 - 3.88
Total Cholesterol	3.82	1.10	4.5	-
Fasting Glucose mmol/l n=52	**7.89**	5.8	10.2	3.88-6.38
HbA1c %	**6.8**	5.8	7.9	4.7 - 6.4
Creatinine umol/l	81.5	70.5	107	59 - 104
CRP mg/L n=65	3.1	9.55	0.9	8.0
ESR mm1st Hr n=63	**16**	9.0	35.7	28 - 32

Results (Table 7.13) show that for participants who experienced significant deterioration measured by TBPI, the median fasting blood glucose and, HbA1c level, were above the normal range at baseline (7.89mmol/L and 6.8% respectively) and the ESR level was below the normal

range (16mm1st Hr). The total cholesterol of 3.82 indicates a high risk of heart disease. The rest of the blood parameters recorded were within the normal ranges.

7.4.6.4 Baseline parameter differences in participants with significant haemodynamic decline - TBPI

Initial analysis included assessing the difference in baseline parameters between those participants who experienced a significant haemodynamic decline in TBPI of ≥0.1 or developed CLI within 2 years and those who did not. Continuous variables were assessed statistically by the Mann Whitney U test between the 2 groups. A non-parametric test was applied since the parameters do not have a normal distribution as shown by the Shapiro Wilk test (Appendix 11). Results of the Mann Whitney test are shown in the table 7.14. Differences between the 2 groups in categorical variables were assessed statistically using the Chi square test. Results are presented in table 7.15.

In the analysis, the differences between baseline parameters of those who experienced a significant haemodynamic decline measured by TBPI (n=68) and those who did not (n=63) are presented. A similar process to that used to calculate deterioration by ABPI was applied. Participants whose improvement was attributed to revascularisation for IC were excluded from the analysis since the natural process of the disease could not be calculated. Participants who underwent revascularisation due to CLI were included since the deterioration was determined by the clinical symptoms.

Table 7.14. Differences in baseline parameters between participants who experienced significant Deterioration within 2 years measured by TBPI decline or developed CLI and participants who did not.

Baseline parameters		N	Median	IQR 1	IQR 3	Mann Whitney U	P value
ABPI baseline	Significant deterioration- TBPI	68	0.68	0.55	0.84	2056.5	0.92
	No sig deterioration	63	0.69	0.56	0.82		
TBPI baseline	Significant deterioration- TBPI	68	0.42	0.32	0.53	1830	0.19
	No sig deterioration	63	0.38	0.27	0.47		

Absolute toe pressure	Significant deterioration- TBPI	68	60.50	48.25	84.75	1825	0.18
	No sig deterioration	63	55.00	40.00	71.00		
BMI	Significant deterioration- TBPI	68	27.60	24.85	29.18	1859	0.24
	No sig deterioration	63	28.70	25.50	30.40		
Age	Significant deterioration- TBPI	68	70.50	66.00	77.00	1856.5	0.24
	No sig deterioration	63	70.00	62.00	77.00		
Claudication distance	Significant deterioration- TBPI	68	100	50.00	150.00	1907	0.34
	No sig deterioration	63	100	50.00	200.00		
Smoking duration Current smokers	Significant deterioration- TBPI	26	50.00	42.00	56.00	241	0.35
	No sig deterioration	22	44.50	35.00	57.75		
Pack Years smoked Current smokers	Significant deterioration- TBPI	26	50.00	25.00	80.00	239	0.33
	No sig deterioration	22	42.50	28.00	62.75		
eGFR	Significant deterioration- TBPI	68	78.50	56.50	94.50	2014	0.65
	No sig deterioration	63	73.00	51.00	94.00		
Cholesterol	Significant deterioration- TBPI	68	4.46	3.49	4.97	1957.5	0.48
	No sig deterioration	63	3.94	3.40	4.92		
Triglyceride	Significant deterioration- TBPI	68	1.47	1.15	2.06	1886.5	0.3
	No sig deterioration	63	1.36	0.85	2.19		
HDL Cholesterol	Significant deterioration- TBPI	68	1.17	0.90	1.40	2102	0.97
	No sig deterioration	63	1.11	0.93	1.33		
Non HDL Cholesterol	Significant deterioration- TBPI	68	3.20	2.38	3.61	1876.5	0.28
	No sig deterioration	63	2.87	2.18	3.86		
LDL Cholesterol	Significant deterioration- TBPI	68	2.41	1.53	2.97	2020.5	0.68
	No sig deterioration	63	2.18	1.55	2.65		
Total Cholesterol	Significant deterioration- TBPI	68	3.72	2.91	4.54	1999	0.6
	No sig deterioration	63	3.43	2.82	4.86		
HbA1c	Significant deterioration- TBPI	68	6.80	5.80	7.93	2103.5	0.97

	No sig deterioration	63	6.70	6.00	7.60		
Creatinine	Significant deterioration- TBPI	68	81.50	70.50	107.00	1908.5	0.35
	No sig deterioration	63	90.00	73.00	125.00		
CRP	Significant deterioration- TBPI	65	3.10	0.90	8.00	1453	0.07
	No sig deterioration	56	1.60	1.10	4.18		
ESR	Significant deterioration- TBPI	62	16.00	9.00	35.70	1488.5	0.3
	No sig deterioration	54	14.50	8.00	25.00		

There was no significant difference in the continuous variables measured between participants who experienced a significant deterioration detected by TBPI and participants who did not.

Table 7.15: Differences in parameters at baseline between participants who had a significant decline in TBPI and participants who did not experience significant decline. Chi square test.

Parameter	Category	Group	N	% within group	X^2	df	P value
PT Doppler waveform	Biphasic	Sig deterioration TBPI	6	9	1.47	2	0.48
		No sig deterioration	10	16.1			
	Monophasic	Sig deterioration TBPI	36	54.5			
		No sig deterioration	32	51.6			
	Mono-cont	Sig deterioration TBPI	24	36.4			
		No sig deterioration	20	32.3			
DP Doppler waveform	Biphasic	Sig deterioration TBPI	4	6	1.19	2	0.57
		No sig deterioration	7	11.3			
	Monophasic	Sig deterioration TBPI	32	48.5			
		No sig deterioration	28	45.2			
	Mono-cont	Sig deterioration TBPI	30	45.5			

		No sig deterioration	27	43.5			
Gender	Male	Sig deterioration TBPI	50	74.2	2.5	1	0.114
		No sig deterioration	54	85.7			
	Female	Sig deterioration TBPI	17	25.8			
		No sig deterioration	9	14.3			
Smoking status	Current smoker	Sig deterioration TBPI	24	35.8	0.65	2	0.72
		No sig deterioration	22	34.9			
	Past smoker	Sig deterioration TBPI	28	41.8			
		No sig deterioration	30	47.6			
	Never smoked	Sig deterioration TBPI	15	22.4			
		No sig deterioration	11	17.5			
Diabetes		Sig deterioration TBPI	53	79.1	2.55	1	0.11
		No sig deterioration	42	66.7			
Hypertension		Sig deterioration TBPI	59	88.1	0.017	1	0.89
		No sig deterioration	55	87.3			
Hyperlipidaemia		Sig deterioration TBPI	53	79.1	0.03	1	0.85
		No sig deterioration	49	77.8			
Cardiac Disease		Sig deterioration TBPI	27	40.3	0.71	1	0.4
		No sig deterioration	30	47.6			
Renal Disease		Sig deterioration TBPI	21	31.3	0.39	1	0.53
		No sig deterioration	23	36.5			
Taking antiplatelet and/or anticoagulant		Sig deterioration TBPI	51	76.1	3.64	1	0.06
		No sig deterioration	56	88.9			
Ace inhibitor		Sig deterioration TBPI	35	52.2	0.28	1	0.6
		No sig deterioration	30	47.6			
Angiotensin II Antagonist		Sig deterioration TBPI	10	14.9	0.022	1	0.88
		No sig deterioration	10	15.9			

Calcium channel blocker	Sig deterioration TBPI	17	25.4	0.04	1	0.84
	No sig deterioration	17	27			
Beta blocker	Sig deterioration TBPI	4	6	1.11	1	0.29
	No sig deterioration	7	11.1			
Previous major event	Sig deterioration TBPI	29	43.3	1.07	1	0.3
	No sig deterioration	33	52.4			
Infrapopliteal artery disease	Sig deterioration TBPI	35	52.2	2.62	1	0.11
	No sig deterioration	24	38.1			

Results presented in table 7.15 indicate that there was no significant difference in categorical baseline parameters between participants who experienced significant deterioration measured by TBPI (≥ 0.1) within 2 years and those who did not. Although there were some percentage differences between parameters (Eg: among those who deteriorated 79.1% were diabetic while among those who did not deteriorate 66.7% were diabetic; the presence of infrapopliteal artery disease was higher in the group who deteriorated 52.2% compared to those who dis not 38.1%), these differences were not statistically significant.

7.4.6.5 Association between haemodynamic decline and Doppler waveform analysis

The association between haemodynamic deterioration assessed by Doppler waveforms (n=40) and haemodynamic deterioration confirmed by significant decline in ABPI and TBPI and was analysed using the X^2 test. Participants who had an increase in ABPI / TBPI due to MAC or revascularisation were excluded as illustrated in figures 7.9 and 7.10. Therefore, in this analysis participants who experienced a significant haemodynamic decline in ABPI (by ≥0.15) (n=20) or in TBPI (by ≥0.1) (n=31) were included.

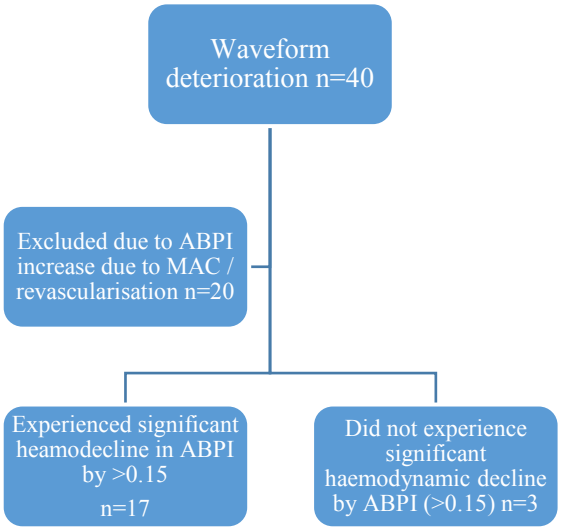


Figure 7.9 Doppler waveform deterioration and ABPI decline

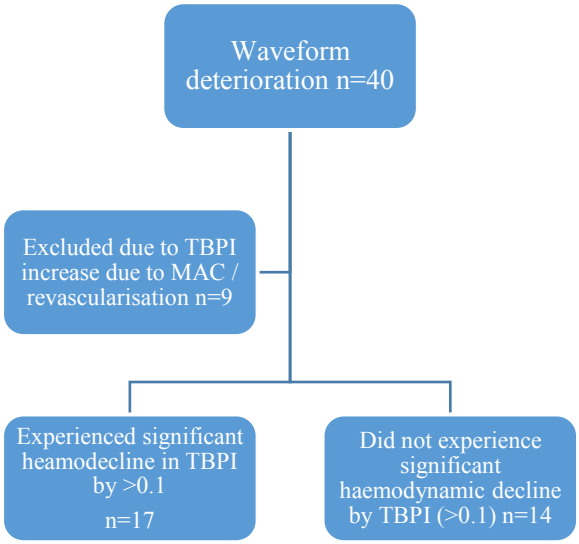


Figure 7.10 Doppler waveform deterioration and TBPI decline

Variables		N (% within group)	Chi Square	df	P value
Deterioration in Doppler waveform	Significant ABPI decline	17 (81%)	14.44	1	**<0.001**
	No Significant decline	3 (19%)			
Deterioration in Doppler waveform	Significant TBPI decline	17 (54.8%)	3.67	1	**0.049**
	No significant decline - TBPI	14 (45.2%)			

Table 7.16 Association between significant decline in ABPI / TBPI and Doppler waveforms. Chi square test.

The results indicate that ABPI and TBPI decline were significantly associated with a decline in Doppler waveforms (p=<0.001 and p=0.05 respectively).

7.4.7 Predictors for significant deterioration

Binomial logistic regression models were applied to determine factors independently associated with deterioration detected both by significant decline in ABPI and/ or TBPI or CLI. The results of the regression models are given as the odds ratio (OR) and 95% confidence interval (95% CI).

Due to the inherent limitations associated with the interpretation of ABPI in cases of MAC, two separate regression models were applied. The first model (Regression Model 3) included baseline ABPI excluding known falsely elevated readings due to calcified arteries as a haemodynamic measure. Toe brachial pressure indices and absolute toe pressures were not included in this analysis, while the rest of the factors measured and participants' characteristics recorded at baseline were included. The number of participants in this analysis was 87 (Significant deterioration ABPI or CLI n=40, No sig deterioration n=47). In the second model (Regression Model 4) ABPI was excluded from the analysis and TBPI and absolute toe pressures were included. The number of participants in this model was 131 (Significant deterioration TBPI or CLI n=68, No sig deterioration n=63). One participant who had known falsely elevated toe pressures at baseline was excluded.

The results of the initial model of Regression model 3 and Regression model 4 are presented in Appendix 13 'Regression Models results'. All the baseline factors recorded were inserted in the models and the interaction effect was analysed by backward elimination. The tables 7.17 and 7.18 present the final models and the significant predictors for significant haemodynamic deterioration ABPI or CLI (table 7.17) and TBPI or CLI (table 7.18) identified through this analysis.

7.4.7.1 Predictors for deterioration by significant ABPI decline or CLI

The results of the regression model identifying significant predictors for participants who are more likely to deteriorate not only to CLI but also to experience a significant decline in ABPI measures are presented.

Table 7.17. Predictors for significant deterioration by ABPI or CLI

Parameter Estimates

ABPI Sig Decline[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% Confidence Interval for OR	
								Lower Bound	Upper Bound
Significant ABPI decline / CLI	Intercept	1.64	.89	3.44	1.00	0.06			
	Female	1.91	.72	7.05	1.00	**0.01**	6.73	1.65	27.49
	Male	.00[b]	.	.	.00	.	.	.	.
	Calcium channel blocker	-1.61	.64	6.25	1.00	**0.01**	0.20	.06	.71
	No Calcium channel blocker	.00[b]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	-1.45	.70	4.32	1.00	**0.04**	0.24	.06	.92
	No Antiplatelet or anticoagulant	.00[b]	.	.	.00	.	.	.	.
	Infrapopliteal artery disease	1.01	0.50	4.13	1.00	**0.04**	2.75	1.04	7.30
	No Infrapopliteal artery disease	.00[b]	.	.	.00	.	.	.	.

a. The reference category is: No Sig ABI decline exc revasc.

b. This parameter is set to zero because it is redundant.

Pseudo R-Square	Cox and Snell	Nagelkerke	McFadden
	.177	.236	.141

Table 7.17b

This four predictor model indicates that female gender, lack of calcium channel blockers, lack of antiplatelet or anticoagulant therapy and infrapopliteal artery disease are significant predictors of experiencing a significant deterioration in ABPI (≥0.15) or CLI within 2 years.

The results of this regression analysis indicate that female participants were 6.73 times more likely to have a significant deterioration than male participants. Participants presenting with infrapopliteal artery disease are 2.75 times more likely to experience a significant deterioration

than participants who do not present with infrapopliteal artery disease; participants who lack antiplatelet or anticoagulant therapy are 4.17 times more likely to experience significant deterioration and participants who lack calcium channel blockers therapy are 5 times more likely to experience a significant deterioration in ABPI within 2 years.

7.4.7.2 Predictors for deterioration by significant TBPI decline or CLI

The results of the regression model identifying significant predictors for participants who are more likely to deteriorate not only to CLI but also to experience a significant decline in TBPI measures are presented in table 7.18.

Table 7.18 Predictors for significant deterioration TBPI or CLI

Parameter Estimates

Significant deterioration measured by TBPI[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% Conf Int for OR	
								Lower Bound	Upper Bound
Significant deterioration TBPI/CLI	Intercept	-.19	.68	.08	1.00	.78			
	Female	1.38	.63	4.74	1.00	**0.03**	3.97	1.15	13.76
	Male	.00[b]	.	.	.00	.	.	.	.
	Diabetes	2.05	.64	10.25	1.00	**0.0001**	7.73	2.21	27.02
	No Diabetes	.00[b]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	-2.04	.72	8.16	1.00	**0.0001**	0.13	0.03	0.53
	No Antiplatelet or anticoagulant	.00[b]	.	.	.00	.	.	.	.
	Beta blocker	-1.87	1.01	3.43	1.00	0.06	0.15	0.02	1.12
	No Beta blocker	.00[b]	.	.	.00	.	.	.	.
	CRP	.09	0.04	4.64	1.00	**0.03**	1.09	1.01	1.18

a. The reference category is: No significant deterioration measured by TBPI.

b. This parameter is set to zero because it is redundant.

Pseudo R-Square	Cox and Snell	Nagelkerke	McFadden
	.218	.291	.178

Table 7.18b

This four predictor model indicates that female gender, diabetes, lack of antiplatelet or anticoagulant therapy and a high CRP are significant predictors of experiencing a significant deterioration within 2 years.

While logistic regression reports the odds ratio of the variables of interest, in this study the relative risk of the variables which were identified as significant independent predictors for the development of CLI was also calculated. As described in detail in chapter 5, since the incidence of CLI in the general population is less than 10% (0.24% (Jensen et al., 2006; Nehler et al., 2014)), the odds ratio and relative risk are very similar and do not vary and the rare disease assumption is applied where the OR derived from the logistic regression analysis can be expressed as RR (J. Zhang & Kai, 1998).

Therefore, the results of this study indicate that female participants are 4 times more likely to have a significant deterioration than male participants; participants presenting with diabetes are 7.7 times more likely to experience a significant deterioration than participants who do not have diabetes, participants who lack antiplatelet or anticoagulant therapy are 7.7 times more likely to experience significant deterioration and with every 1 unit increase in CRP, the risk of deterioration increases by 1.1 times.

Following the analysis of the several baseline variables recorded, results of this study indicate that baseline ABPI, TBPI and HbA1c were found to be significant predictors for deterioration to CLI. Additionally, female gender, diabetes, no antiplatelet or anticoagulant therapy, no calcium channel blockers, high CRP and the presence of infrapopliteal artery disease were found to be significant predictors for significant haemodynamic decline and clinical deterioration to CLI. Further analysis of these identified predictors was applied in order to analyse the possibility of proposing an algorithm for the early identification of individuals who are more likely to deteriorate within 2 years.

7.4.8 Predicting deterioration to CLI – development of a clinical predictive model

In order to develop a clinical prediction model which can identify those at risk of deterioration and predict the prognosis of the lower limb of the individual patient, further analysis was required. When designing a clinical prediction model, to determine an unbiased estimate of effect, while minimizing conditional associations between variables, which may happen when a large number of variables are entered in the analysis, variable selection was required (Chowdhury & Turin, 2020). In studies where more than 30 independent variables are recorded, variable selection is required in order to design a predictive model which can predict unbiased effect estimates (Heinze, Wallisch and Dunkler, 2018). Variable selection in clinical prediction modeling improves the performance of the model in terms of prediction and offers better data visualisation (Chowdhury & Turin, 2020). The method applied for variable selection in this study was based on significance criteria (Heinze, Wallisch and Dunkler, 2018) where variables which were found to be significant predictors for deterioration, that is, development of CLI, significant decline in TBPI and ABPI, served as a method of systematic selection of variables that provide the best fit for the predictive model. The significant predictors identified in the analysis for significant deterioration including those identified for development of CLI and for significant decline in ABPI and TBPI were applied in a binomial logistic regression model in order to compute a combined log of odds ratio using deterioration to CLI as the dependent variable. This combined predictive variable was used for the receiver operator characteristic curve (ROC) analysis which measures the diagnostic ability of the combined probability variable.

The results of this regression model are presented in table 7.19.

Table 7.19 Significant predictors for deterioration. Regression analysis.

Parameter Estimates

Deterioration to CLI[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% Confidence Interval for OR	
								Lower Bound	Upper Bound
Did not deteriorate to CLI	Intercept	-2.742	2.35	1.36	1.00	.24			
	ABPI baseline	3.90	2.07	3.53	1.00	**.049**	4.41	.02	.30
	TBPI baseline	6.701	2.61	6.61	1.00	**.01**	6.9	.03	.52
	CRP	-.051	.06	.87	1.00	.35	.95	.85	1.06
	HbA1c	-.269	.24	1.22	1.00	.27	.76	.47	1.23
	No IPA disease	1.796	.66	7.31	1.00	**.01**	6.02	1.64	22.14
	IPA disease	0[b]	.	.	.00	.	.	.	.
	Gender Female	.375	.72	.27	1.00	.60	1.45	.36	5.95
	Male	0[b]	.	.	.00	.	.	.	.
	Diabetes	-.182	.88	.04	1.00	.84	.83	.15	4.67
	No Diabetes	0[b]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	-.496	.99	.25	1.00	.62	.61	.09	4.27
	No Antiplatelet or anticoagulant	0[b]	.	.	.00	.	.	.	.
	Calcium channel blocker	1.351	.79	2.90	1.00	.09	3.86	.82	18.27
	No Calcium channel blocker	0[b]	.	.	0	.	.	.	.

a. The reference category is: Deteriorated to CLI.

b. This parameter is set to zero because it is redundant.

Results of the logistic regression model indicate that baseline ABPI and TBPI and the presence of infrapopliteal artery disease were significant predictors (p=<0.05) for deterioration. Therefore, the derived coefficients in the table 7.19 (predictive values) and intercept were used to compute a combined probability variable and plot the ROC presented in figure 7.11.

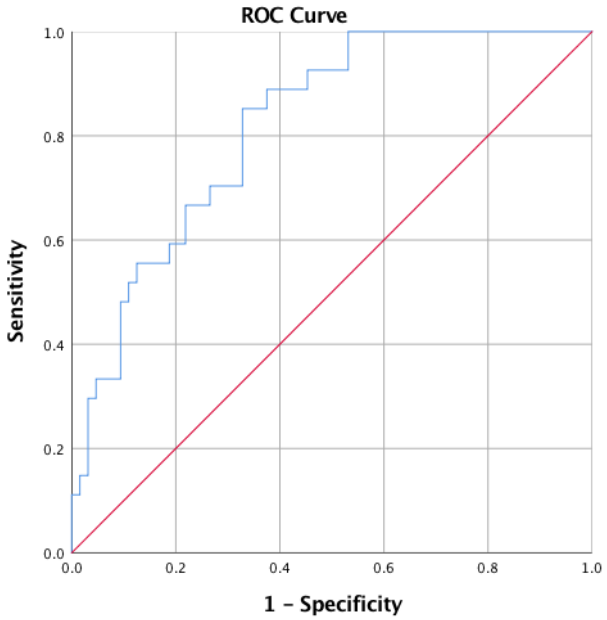


Figure 7.11 ROC of combined predictive values of ABPI, TBPI and IPA disease

An ROC curve is a performance measurement of the diagnostic ability of a model or classification tool (Y. Zhan et al., 2016). It shows the ability of a particular model to predict a specified outcome an individual is more likely to experience. In order to quantify the ability of the model using ABPI, TBPI and IPA disease to predict the outcome (deterioration to CLI), the 'area under receiver operator characteristic' curve (AUROC) was calculated.

Table 7.20 AUROC analysis for combined predictive value of significant predictors for deterioration

Area Under the Curve

Test Result Variable(s): Combined Predictive value ABPI,TBPI + Infrapopliteal artery disease

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.82	.044	.000	0.733	0.905

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

An AUROC analysis was performed in order to assess the suitability and diagnostic ability of this model. Results in table 7.20 demonstrate that this model has significant predictive ability for the development of CLI (p=<0.001) within two years. The strength of the model in predicting CLI is demonstrated by the area under the receiver operator curve and indicates a 'good' level (Unal, 2017) of predictive value (0.82).

Apart from providing the diagnostic accuracy of a test, ROC analysis provides the optimal cut-point values for the test, which requires the simultaneous assessment of sensitivity and specificity (Unal, 2017). Identifying the cut-off points is a trade-off between what is more clinically important- the sensitivity of the tool (i.e the accuracy of the tool in identifying the true positives who are most likely to deteriorate to CLI) and the specificity of the tool (i.e the accuracy of the tool in identifying those who are not likely to deteriorate). Prioritizing sensitivity of an algorithm over specificity or vice versa needs to be adjusted according to the clinical intervention in question. The relative importance of a false positive diagnosis versus a false negative diagnosis (also referred to as relative misclassification) changes according to effect of the test on the patient pathway and who is making the assessment (Mallett et al., 2012). In other words, sensitivity is the primary consideration when the benefits of identifying more true positives outweigh the negative consequences of including more false positives (Chubak et al., 2012). An example of this would be that following identification of patients, the clinical intervention would be increased follow-up frequency and closer haemodynamic monitoring, where false positive participants would not be subjected to any increased risks (McNamara & Martin, 2018). However, specificity should be prioritized over sensitivity in cases when the clinical decision involves interventional risks (Pewsner et al., 2004), such as endovascular treatment or a higher risk of open surgical intervention. In these cases, it is important not to subject false positive participants to undue risk of surgical intervention, therefore the cut-off point identified should have a high specificity value (Sanfilippo et al., 2017). Results of diagnostic accuracy studies which aim to usefully inform clinical practice, should be related to the decision regarding the clinical management of patients (Mallett et al., 2012).

In the case of this study, two different haemodynamic cut-off points were identified to be applied for the identification of participants in two different clinical interventional decisions – i) Increased frequency of haemodynamic monitoring and ii) consideration of revascularisation.

While the strength of the predictive model was obtained from the AUROC of the combined plot, the cut-off points of the haemodynamic predictors (ABPI and TBPI) as a clinical tool to identify participants who are more likely to benefit from a specified clinical intervention (having optimal sensitivity and specificity adapted for a specific clinical interventional decision) are identified from the individual ROC analyses of the predictors (figures 7.12 and 7.13).

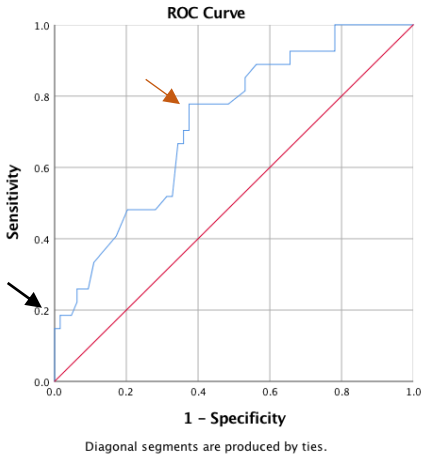


Fig. 7.12 ROC analysis of ABPI

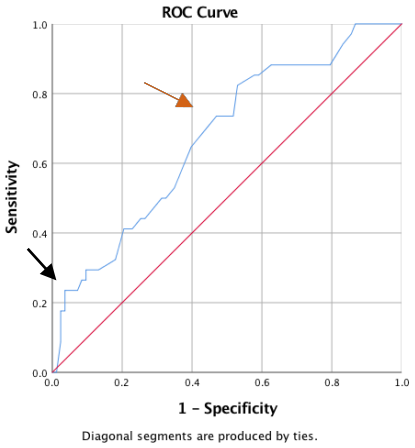


Fig. 7.13 ROC analysis of TBPI

For identifying participants who would benefit from closer haemodynamic monitoring due to the probability of deteriorating to CLI, the 'point closest to 0,1 approach was applied. This approach is in agreement with Youden index approach which is an alternative commonly used approach to determine cut-off values from the ROC curve (Unal, 2017). This approach stipulates that sensitivity is the primary consideration and the benefits of identifying more true positives outweighs the negative consequences of including false positives. The cut-off points for ABPI and TBPI identified are indicated by the red arrows in figures 7.12 and 7.13. The values of the haemodynamic parameters equivalent to the identified points on the individual ROC plots are an ABPI of 0.64 and TBPI of 0.39 (individual sensitivity 77.8% and 73.5% respectively) as defined by the co-ordinates of the plot presented in Appendix 14.

For identifying participants who would benefit from early endovascular or surgical intervention due to the probability of deteriorating to CLI, specificity was optimized over sensitivity by identifying cut-off points with a high specificity (McNamara & Martin, 2018). The strategy of applying more stringent cut-off points in favour of a higher specificity is advised when a lower number of false positives is desirable (Trevethan, 2017). The identified cut-off points are indicated by the black arrows in figures 7.12 and 7.13 with the corresponding ABPI of 0.44 and a TBPI of 0.18 (individual specificity 98% and 96% respectively). The co-ordinates for the individual ROC plots are presented in Appendix 14.

Therefore, results from this study indicate that individuals presenting with IC with an ABPI of ≤0.64 combined with a TBPI of ≤0.39 and in the presence of infrapopliteal artery disease are likely (probability 82%) to deteriorate to CLI within 2 years and would benefit from close

haemodynamic monitoring. Participants presenting with IC in the presence of infrapopliteal artery disease with an ABPI ≤0.44 and a TBPI ≤0.18 are likely to deteriorate to CLI (probability of 82%) and may benefit from early intervention. These models have a 'good' level of predictive value (AUROC 0.82).

7.4.9 Disease Progression

A secondary aim of this study was the assessment of rate of progression of PAD among participants with IC. The progression rate of participants who experienced different outcomes within 2 years was assessed and presented in the following sections.

7.4.9.1 Haemodynamic progression

Table 7.21 and table 7.22 present the progression of PAD in terms of haemodynamic parameters (ABPI and TBPI respectively) experienced by the study population over the 2 years. For each outcome category, in order to also demonstrate the natural progression of PAD, the means of participants excluding those who either developed calcification during the 2 years of follow-up or underwent revascularisation are presented in the tables. The ABPI progression results are presented in table 7.21 followed by TBPI progression results presented in table 7.22. The differences between the values recorded at baseline, time 1 (after 1 year) and time 2 (after 2 years) were analysed using the Friedman test.

Table 7.21: Friedman test comparing ABPI scores over time						
ABPI	**Baseline** Median (IQR)	**1 year** Median (IQR)	**2 years** Median (IQR)	**Test statistic**	**Df**	**P-value**
All Participants n=150	0.66 (0.55,0.81) n=150	0.75 (0.6,0.97) n=136	0.73 (0.57,0.96) n=131	4.88	2	0.08
Excluding revascularised participants and calcified arteries	0.66 (0.56,0.77) n=73	0.68 (0.55,0.81) n=64	0.65 (0.54,0.76) n=61	2.525	2	0.28
Significant deterioration (ABPI decline of ≥0.15 or CLI)	0.69 (0.55,0.89) n=55	0.76 (0.58,0.94) n=53	0.67 (0.53,0.92) n=50	2.33	2	0.31
Significant deterioration including ABPI decline of ≥0.15 only	0.84 (0.71,1.4) n=20	0.61 (0.55,0.81) n=20	0.60 (0.46,0.71) n=20	0.092	2	0.96
Significant deterioration including ABPI decline of ≥0.15 only and excluding calcified arteries	0.73 (0.66,0.85) n=14	0.60 (0.47,0.77) n=14	0.48 (0.39,0.62) n=14	0.043	2	0.98
Developed CLI	0.66 (0.51,0.7) n=35	0.82 (0.58,0.99) n=33	0.85 (0.62,1.26) n=30	2.64	2	0.27
Excluding revascularised participants and calcified arteries	0.64 (0.49,0.71) n=6	0.82 (0.54,0.86) n=5	0.54 (0.48,0.71) n=5	0.86	2	0.65
Improved / stable All	0.71 (0.56,0.85) n=29	0.70 (0.57,0.92) n=24	0.80 (0.64,0.99) n=26	5.42	**2**	0.06
Excluding revascularised participants and calcified arteries	0.65 (0.53,0.77) n=20	0.66 (0.52,0.78) n=16	0.77 (0.56,0.95) n=17	**4.36**	**2**	**0.113**

Deteriorated* =participants who demonstrated a decline in ABPI/TBPI/ waveforms within 2 years

Results in table 7.21 (results excluding revascularised or calcified arteries) show that after the first year, the median ABPI of all the participants increased by 0.02 but after 2 years the median decreased by 0.03, resulting in an overall decrease of 0.01 from baseline. A similar non-statistically significant pattern, was observed in participants who deteriorated to CLI within 2 years where an increase in ABPI by 0.18 is observed after 1 year followed by a decrease of 0.28 after 2 years, leading to an overall decrease of 0.1 in 2 years. Participants who experienced a significant decline in ABPI had a decline of 0.13 after 1 year and a further decline of 0.12 after the 2 years with an overall decline of 0.25 in ABPI over 2 years. Participants who had

improved or stable haemodynamics had a decrease in ABPI by 0.01 after 1 year followed by an increase of 0.1 after 2 years resulting in an overall increase in ABPI of 0.09 from baseline within 2 years.

Table 7.22: Friedman test comparing mean parameter TBPI scores over time

TBPI	**Baseline** Median (IQR)	**1 year** Median (IQR)	**2 years** Median (IQR)	**Test statistic**	**Df**	**P-value**
All Participants n=150	0.38 (0.28,0.5) n=150	0.40 (0.30,0.56) n=136	0.35 (0.23,0.57) n=135	5.79	2	0.06
Excluding revascularised participants and calcified arteries	0.39 (0.31,0.51) n=91	0.37 (0.3,0.54) n=81	0.33 (0.23,0.49) n=78	1.88	2	0.39
Significant deterioration (TBPI decline of ≥0.1 and /or CLI)	0.42 (0.32,0.53) n=68	0.4 (0.29,0.54) n=65	0.29 (0.2,0.41) n=65	4.61	2	0.1
Significant deterioration (including TBPI decline of ≥0.1 only)	0.51 (0.41,0.56) n=33	0.4 (0.35,0.54) n=32	0.26 (0.19,0.34) n=33	2.05	2	0.34
Excluding calcified arteries	0.49 (0.39,0.55) n=31	0.4 (0.35,0.52) n=31	0.25 (0.18,0.33) n=31	3.29	**2**	0.19
Developed CLI	0.33 (0.2,0.43) n=35	0.42 (0.28,0.54) n=34	0.34 (0.23,0.46) n=33	**3.14**	2	0.21
Excluding revascularised participants and calcified arteries	0.36 (0.26,0.45) n=10	0.4 (0.18,0.48) n=9	0.28 (0.19,0.37) n=9	1.2	2	0.55
Improved / stable All	0.38 (0.26,0.53) n=29	0.5 (0.33,0.7) n=23	0.55 (0.35,0.66) n=26	**12.35**	2	**0.002**
Excluding revascularised participants and calcified arteries	0.38 (0.29,0.48) n=21	0.43 (0.33,0.68) n=17	0.55 (0.37,0.68) n=18	8.27	2	**0.01**

**Significant TBPI decline defined as a decline by 0.1 or more in TBPI between baseline and 2 years. Participants who were revascularised due to IC were excluded from analysis related to TBPI decline.

Results in table 7.22 (excluding revascularised or calcified arteries) show that after the first year the median TBPI of all the participants decreased by 0.02 with a further decrease by 0.04 in the second year, resulting in an overall decrease of 0.06 in TBPI from baseline. This decrease was not statistically significant (p=>0.05) and differs in pattern to the ABPI progression in these participants. Participants who deteriorated to CLI had an increase in median TBPI after 1 year by 0.04 followed by a decrease of 0.12 in TBPI after 2 years leading to an overall decrease of 0.08 in 2 years. This decrease was not statistically significant. Participants who experienced a significant decline in TBPI had a decline of 0.09 after 1 year and a further decline of 0.15 after the 2 years with an overall decline of 0.24 in TBPI within 2 years. Participants who had improved or stable haemodynamics had an increase in TBPI of 0.05 after 1 year and a further increase of 0.12 after 2 years resulting in an overall increase in TBPI of 0.17 from baseline within 2 years. This increase was statistically significant (p<0.01).

The natural progression of PAD of participants who deteriorated to CLI and participants who experienced significant haemodynamic decline without CLI symptoms is illustrated in figures 7.14 and 7.15. In order to portray the natural progression of the disease, participants who underwent revascularisation or who developed MAC during the 2 years were excluded from this analysis.

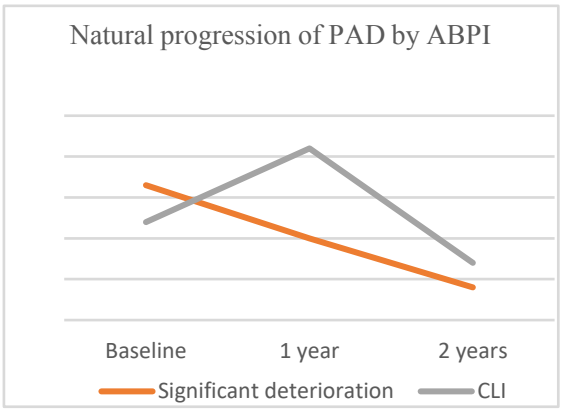


Fig. 7.14 Natural progression of PAD by ABPI

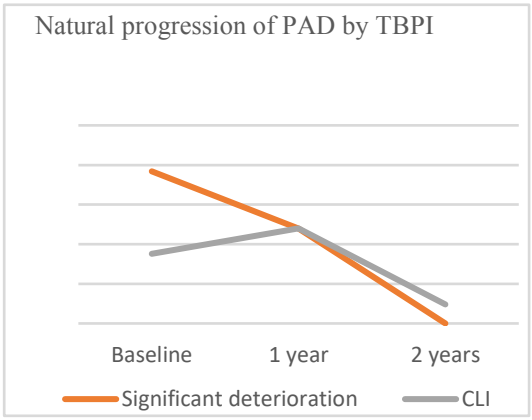


Fig. 7.15 Natural progression of PAD by TBPI

The results illustrate that for participants who developed CLI, ABPI measurement declined by 0.1 while TBPI declined by 0.08 within 2 years. The decline occurred in the 2nd year after initial presentation with IC. This similar pattern is also evident in the participants who experienced significant haemodynamic decline where a higher rate of decline is demonstrated within 2 years of initial presentation with IC when using TBPI as a haemodynamic measure of PAD. Among these 9 participants, 5 deteriorated to CLI within 1 year (2 rest pain, 3 ulceration)

and 4 deteriorated (4 ulceration) to CLI within 2 years. These participants were treated conservatively up to the time of the study since endovascular revascularisation was not possible and by-pass surgery imposed very high risks due to other comorbidities.

Therefore, the results of this study indicate that overall, participants presenting with IC had a decline in ABPI of 0.01 and TBPI of 0.06 within 2 years, with a higher rate of decline in the second year. Participants who eventually deteriorated to CLI had a higher decline in TBPI (0.08) within 2 years, also with a higher rate of decline during the second year and a decline in ABPI by 0.1. Participants with IC who experienced significant haemodynamic decline and eventually deteriorated to very low haemodynamic levels, had a decline in ABPI of 0.25 and TBPI of 0.24 within 2 years of initial presentation with IC.

7.4.9.1 Progression of PAD in all symptomatic limbs

While the sections above analysed the progression of PAD of the limb with worse outcome in each participant since it was the main focus of this study, figures 7.16 and 7.17 illustrate the progression of PAD of all the symptomatic limbs diagnosed with IC at recruitment. In total there were 236 symptomatic limbs in 150 participants since 86 had bilateral IC and 64 had unilateral IC as described in Chapter 6 (results of baseline data).

The following sections illustrate the progression of PAD in the symptomatic limbs (n=236) of 150 recruited participants.

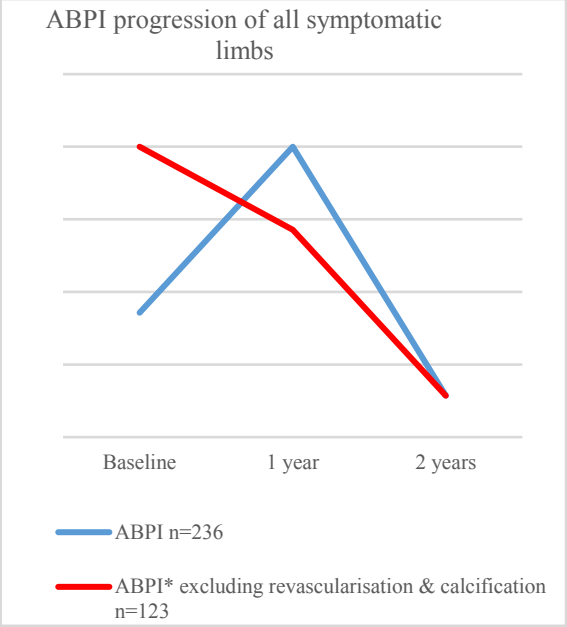


Fig. 7.16 Natural progression of all limbs by ABPI

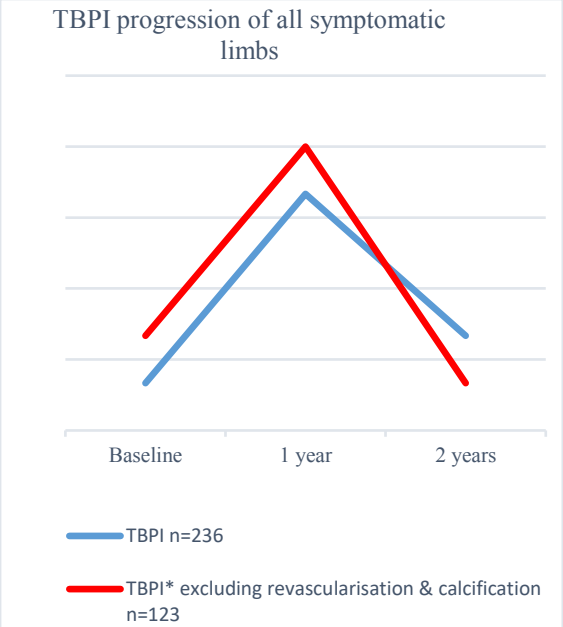


Fig. 7.17 Natural progression of all limbs by TBPI

Figures 7.16 and 7.17 illustrate that the median ABPI of all the symptomatic limbs (excluding calcified and revascularised arteries) decreased by 0.02 after 1 year followed by a decrease of 0.04 during the second year, indicating an overall decrease in ABPI of 0.06 within 2 years. A higher rate of decline is evident during the second year. The median TBPI of all the symptomatic limbs (excluding calcified and revascularised arteries) increased by 0.04 after 1 year followed by a decrease of 0.05 during the second year, indicating an overall decrease in TBPI by 0.01 within 2 years.

7.4.9.3 The progressive pattern of PAD

While it was not the intention of this study to investigate the progressive pattern of PAD in IC, the duplex scan reports of one of the participants, taken as an example, illustrate the atherosclerotic progression in a patient who deteriorated to CLI. The scan in Figure 7.18 was performed at initial presentation, where the patient was complaining of calf IC after 100m. Three months following diagnosis, IC symptoms worsened and a PTA of the superficial femoral, popliteal and posterior tibial artery was performed. The patient returned 9 months later (Figure 7.19) with CLI (5th digit ulceration and ascending erythema), due to now occluded distal SFA and occluded AT. At this stage he was booked for an urgent lower limb by pass.

14.07.2016

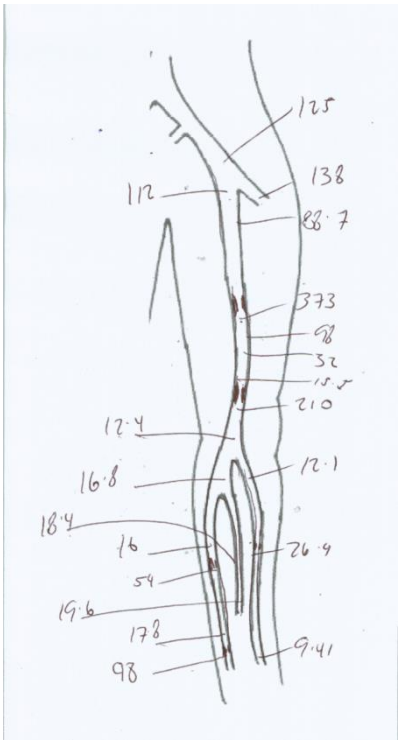


Fig 7.18 Duplex scan of participant at baseline

26.04.2017

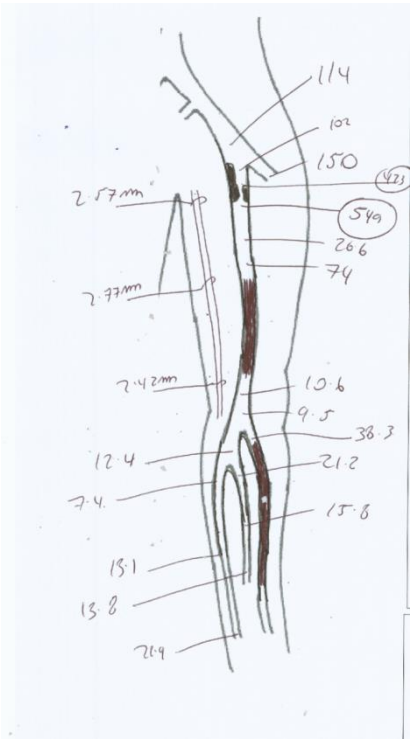


Fig 7.19 Duplex scan 9 months following recruitment

The figures above illustrate the disease progression in a person living with diabetes demonstrating that progression occurred in both the infra-inguinal and infrapopliteal regions. The progression to CLI occurred within 9 months of initial diagnosis, resulting in the need for urgent surgical intervention.

7.4.10 Improved or stable haemodynamics

The participants who demonstrated an improvement or no change in any of the haemodynamic parameters recorded within 2 years were categorized as 'improved or stable'. Baseline haemodynamics (ABPI and TBPI) were subtracted from haemodynamics recorded after 2 years. Participants who did not experience a deterioration in any of the haemodynamic parameters or Doppler waveforms were classified as having improved or having stable haemodynamics. As in previous sections, participants who developed MAC or did not attend for review were excluded from this analysis unless they developed CLI and were therefore included in the 'deteriorated' group. The descriptive data and analysis of this group of participants who had this outcome in 2 years are presented in the following sections.

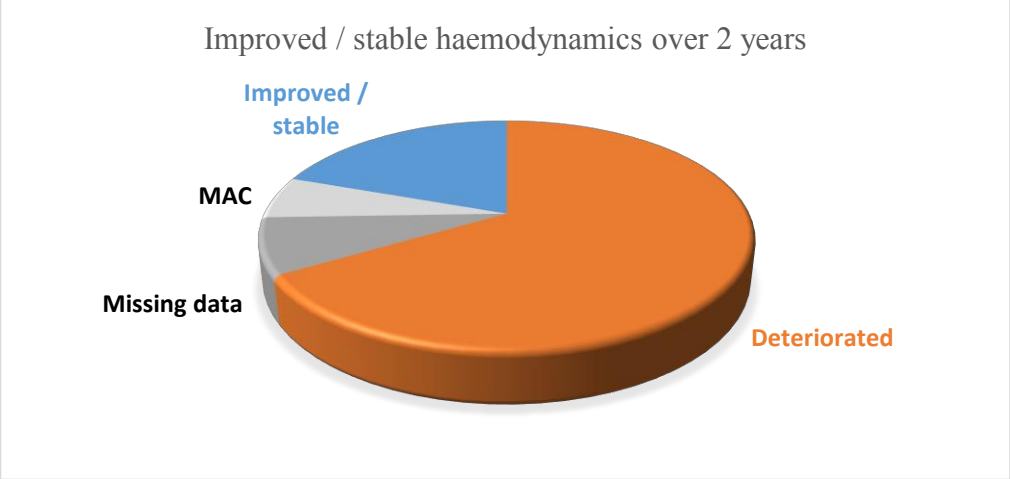


Fig.7.20 Proportion of participants with improved or stable haemodynamics after 2 years

Figure 7.20 illustrates that after 2 years 19.7% of the cohort demonstrated stable or improved haemodynamics (n=29). Out of these participants, 3 underwent revascularisation due to IC, 11 reported that they started walking daily for at least 30 minutes, 8 participants stopped or reduced cigarette smoking and 7 participants did not report any lifestyle change.

7.4.10.1 Descriptive characteristics of participants who had stable or improved haemodynamics after 2 years

This section presents the baseline characteristics of the participants who had stable / improved haemodynamics.

Table 7.23: Baseline characteristics of participants who improved or remained stable after 2 years

	Mean/ median	Min / IQR 1	Max / IQR 3	Std. Deviation
TBPI baseline median , IQR	0.38	0.26	0.53	-
ABPI baseline median, IQR	0.71	0.56	0.85	-
ABPI* baseline n=22 median IQR	0.64	0.53	0.76	-
Absolute toe pressure baseline median	57	38.5	89	31.14
BMI	27.65	20.5	33.6	3.57
Age	68.14	47.0	84.0	9.84
Claudication distance baseline	100	50	200	-
Smoking duration of ex-smokers mean	41.62	30.0	53.0	7.23
Pack years Ex-smokers mean	47.35	9.0	99.0	25.26
Smoking duration Current smokers n=13	45.38	15.0	67.0	14.32
Pack Years smoked Current smokers n=13	43.17	6.7	112.5	33.52
Systolic blood pressure mean	146.10	111.0	198.0	20.73

Table 7.24: Baseline characteristics of participants who improved / remained stable within 2 years

Baseline Variables n=29		Frequency within group	% within group
PT Doppler waveform	Biphasic	5	34.5
	Monophasic	10	17.2
	Monophasic-continuous	14	48.3
DP Doppler waveform	Biphasic	3	31
	Monophasic	9	10.3
	Monophasic-continuous	17	58.6
Disease Location	IPA disease present	13	44.8
	No IPA disease present	16	55.2
Gender	Male	27	93.1
	Female	2	6.9
Smoking status	Current smoker	13	44.8
	Past smoker	13	44.8
	Never smoked	3	10.3
Diabetes		21	72.4
Hypertension		25	86.2
Hyperlipidaemia		18	62.1
Cardiac disease		11	37.9
Renal disease		8	27.6
Previous major event (MI/stroke)		13	44.8
Experienced MACCE		3	10.3
Taking statins, antiplatelet and/ or anticoagulant		24	82.8
Ace inhibitor		12	41.4
Angiotensin II antagonist		4	13.8
Calcium channel blocker		9	31
Beta blocker		1	3.4

Tables 7.23 and 7.24 describe the baseline characteristics of participants who had stable or improved haemodynamics after 2 years. This group had a mean age of 68.4 years and were predominantly male (93.1% n=27) and only 2 female participants were in this group. The median ABPI was 0.71 (IQR 0.56 0.85) and 0.64 (IQR 0.53,0.76) when excluding calcified arteries. The mean TBPI was 0.38 IQR 0.26,0.53) when excluding known falsely elevated readings at baseline. There were more participants without IPA disease (55.2%) in this group than participants who had infrapopliteal artery disease (44.8%). A high prevalence of diabetes (72.4%), hypertension (86.2%), and smoking history (89.6%) was also evident. A high percentage (82.8%) of the participants in this group were on recommended medical therapy at baseline taking anti platelet and statin therapy.

Blood parameter n=29	Median	IQR 1	IQR 3	Normal range
eGFR	89	55.5	101.5	> 60
Cholesterol mmol/l	4.09	3.23	5.18	2.0 - 5.0
Triglyceride mmol/l	1.36	0.78	2.1	0.1 - 2.26
HDL Cholesterol mmol/l	1.12	1.01	1.35	0.9 - 1.45
Non HDL Cholesterol mmol/l	2.79	2.08	4.02	0 - 3.36
LDL Cholesterol mmol/l	2.23	1.52	2.88	0.1 - 3.88
Total Cholesterol	3.31	2.75	4.75	-
Fasting Glucose mmol/l n=22	**7.22**	5.42	9.6	3.88-6.38
HbA1c %	**6.7**	5.7	7.7	4.7 - 6.4
Creatinine umol/l	81	67.5	119.5	59 - 104
CRP mg/L n=23	2.0	1.0	4.3	0 - 5
ESR mm1st Hr n=22	**12.0**	7.8	25.5	28 - 32

Table 7.25: Baseline blood parameters of participants who experienced stable or improved haemodynamics

Table 7.25 presents the blood parameters measured at baseline of the participants who had stable or improved haemodynamics after 2 years. The median fasting blood glucose and, HbA1c level, were above the normal range at baseline (7.22 mmol/l and 6.7% respectively) and the ESR level was below the normal range (12mm1st Hr). The cholesterol of 4.09mmol/l indicates a high risk of heart disease. The rest of the blood parameters recorded were within the normal ranges.

7.4.10.2 Baseline parameter differences in participants who had stable or improved haemodynamics

Initial analysis included assessing the difference in baseline parameters between participants who had stable or improved haemodynamics and participants who had other outcomes. Continuous variables were assessed statistically by the Mann Whitney U test between the 2 groups. A non-parametric test was applied since the parameters do not have a normal distribution as shown by the Shapiro Wilk test (Appendix 11). Results of the Mann Whitney test are shown in the table 7.26. Differences between the 2 groups in categorical variables were assessed statistically by the Chi square test. Results are presented in table 7.27.

The following section presents the analysis of differences between the baseline variables of participants who experienced haemodynamic improvement or were stable (n=29) and participants who experienced haemodynamic deterioration (mild/ significant) (n=89) within 2 years.

Table 7.26: Difference in baseline parameters between participants who had improved or stable haemodynamics and participants who had worse outcomes

		Mean	Std. Deviation	95% Confidence Interval for Mean		Min	Max	Mann Whitney U	P value
				Lower Bound	Upper Bound				
ABPI baseline	Worse outcome	0.73	0.33	0.67	0.79	0.4	1.60	1520	0.42
	Improved or stable	0.80	0.35	0.67	0.93	0.43	1.60		
TBPI baseline	Worse outcome	0.39	0.17	0.36	0.42	0.28	0.94	1657.5	0.9
	Improved or stable	0.43	0.28	0.32	0.54	.21	0.94		
Absolute toe pressure baseline	Worse outcome	59.95	26.15	55.14	64.76	8.00	136	1671	0.96
	Improved or stable	60.41	31.14	48.57	72.26	14.0	145		
BMI	Worse outcome	27.59	4.00	26.86	28.33	18.9	44.8	1585	0.63
	Improved or stable	27.65	3.57	26.29	29.01	20.5	33.6		
Age	Worse outcome	70.34	8.98	68.69	72.00	38.0	88.0	1444	0.24

	Improved or stable	68.14	9.84	64.40	71.88	47.0	84.0		
Claudication distance baseline	Worse outcome	134.96	105.1	115.62	154.29	10.0	400	1594.5	0.66
	Improved or stable	153.45	127.3	105.03	201.87	25.0	400		
Smoking duration of ex-smokers	Worse outcome	40.23	10.72	37.09	43.38	20.0	66.0	278	0.63
	Improved or stable	41.62	7.23	37.25	45.98	30.0	53.0		
Pack years Ex-smokers	Worse outcome (n=47)	76.92	44.69	63.80	90.04	7.50	200	188	**0.03**
	Improved or stable n=13	47.35	25.26	32.08	62.61	9.00	99		
Smoking duration Current smokers	Worse outcome	45.78	13.53	41.51	50.05	15	70	259	0.88
	Improved or stable	45.38	14.32	36.73	54.04	15.0	67.0		
Pack Years smoked Current smokers	Worse outcome	58.81	46.65	44.08	73.53	6.00	234.50	204	0.21
	Improved or stable	43.17	33.52	22.91	63.43	6.70	112.50		
eGFR	Worse outcome	77.10	31.02	71.40	82.81	6.00	164	1479	0.32
	Improved or stable	82.17	31.82	70.07	94.28	25.0	150.0		
Cholesterol	Worse outcome	4.44	1.09	4.23	4.64	2.41	9.00	1545	0.5
	Improved or stable	4.37	1.39	3.85	4.90	2.52	7.74		
Triglyceride	Worse outcome	1.70	1.03	1.51	1.89	0.15	7.96	1544	0.5
	Improved or stable	1.88	1.76	1.21	2.54	0.52	8.80		
HDL Cholesterol	Worse outcome	1.24	0.41	1.16	1.31	0.63	3.11	1640.5	0.84
	Improved or stable	1.20	0.31	1.08	1.31	0.64	2.03		
Non HDL Cholesterol	Worse outcome	3.20	1.05	3.01	3.39	1.32	7.49	1518	0.42
	Improved or stable	3.18	1.37	2.65	3.70	1.38	6.43		
LDL Cholesterol	Worse outcome	2.37	.99	2.19	2.55	0.02	5.85	1632	0.8
	Improved or stable	2.40	1.14	1.96	2.83	0.77	5.62		

Total Cholesterol	Worse outcome	3.83	1.21	3.61	4.05	1.67	7.55	1571	0.58
	Improved or stable	3.85	1.50	3.28	4.42	2.05	7.05		
Fasting Glucose	Worse outcome	8.42	3.17	7.76	9.08	4.56	16.85	918	0.6
	Improved or stable	7.90	2.72	6.70	9.11	4.60	14.06		
HbA1c	Worse outcome	6.95	1.42	6.69	7.21	5.00	10.91	1659	0.91
	Improved or stable	6.79	1.23	6.32	7.26	4.20	8.80		
Creatinine	Worse outcome	104.8	80.77	89.95	119.66	38.00	811.00	1595	0.67
	Improved or stable	99.62	48.42	81.20	118.04	51.00	233.00		
CRP	Worse outcome	5.18	8.40	3.61	6.75	.10	56.00	1193	0.58
	Improved or stable	2.71	1.93	1.88	3.55	.30	6.50		
ESR	Worse outcome	21.21	16.88	18.00	24.41	1.00	74.00	1034	0.31
	Improved or stable	16.05	10.95	11.19	20.90	5.00	46.00		
Systolic blood pressure	Worse outcome	151.36	22.44	147.24	155.49	100.00	217.00	1428	0.21
	Improved or stable	146.10	20.73	138.22	153.99	111.00	198.00		

The results in table 7.26 indicate that ex-smokers among participants who had stable or improved haemodynamics had a lower number of pack-years smoked compared to the participants who had worse outcomes (P=0.03). There were no significant differences in the rest of the parameters assessed.

Table 7.27: Chi square tests analyzing differences in parameters at baseline between participants who had a haemodynamic improvement or remained stable and those who had other outcomes

Parameter	Category	Group	N	% within group	X^2	df	P value
PT Doppler waveform	Biphasic	Improved/stable	5	17.2	5.09	2	0.28
		Worse outcome	9	10.3			
	Monophasic	Improved/stable	10	34.5			

		Worse outcome	48	54.3			
	Mono-cont	Improved/stable	14	48.3			
		Worse outcome	31	35.3			
DP Doppler waveform	Biphasic	Improved/stable	3	10.3	5.3	2	0.26
		Worse outcome	6	6.9			
	Monophasic	Improved/stable	9	31			
		Worse outcome	44	49.1			
	Mono-cont	Improved/stable	17	58.6			
		Worse outcome	39	44			
Gender	Male	Improved/stable	27	93.1	8.29	2	**0.016**
		Worse outcome	69	77.6			
	Female	Improved/stable	2	6.9			
		Worse outcome	20	22.4			
Smoking status	Current smoker	Improved/stable	13	44.8	5.35	4	0.25
		Worse outcome	30	33.6			
	Past smoker	Improved/stable	13	44.8			
		Worse outcome	36	40.5			
	Never smoked	Improved/stable	3	10.3			
		Worse outcome	23	25.9			
Diabetes		Improved/stable	21	72.4	5.95	2	0.05
		Worse outcome	63	70.7			
Hypertension		Improved/stable	25	86.2	2.91	2	0.23
		Worse outcome	78	87.1			
Hyperlipidaemia		Improved/stable	18	62.1	6.09	2	**0.048**
		Worse outcome	73	81.9			
Cardiac Disease		Improved/stable	11	37.9	0.87	2	0.65
		Worse outcome	36	40.5			

Renal Disease	Improved/stable	8	27.6	0.38	2	0.83
	Worse outcome	28	31.9			
Taking antiplatelet and/or anticoagulant	Improved/stable	24	82.8	0.26	2	0.88
	Worse outcome	70	78.4			
Ace inhibitor	Improved/stable	12	41.4	2.46	2	0.29
	Worse outcome	45	50.9			
Angiotensin II Antagonist	Improved/stable	4	13.8	0.13	2	0.94
	Worse outcome	13	14.7			
Calcium channel blocker	Improved/stable	9	31	2.4	2	0.3
	Worse outcome	21	23.3			
Beta blocker	Improved/stable	1	3.4	1.86	2	0.39
	Worse outcome	8	8.6			
Previous major event	Improved/stable	13	44.8	0.5	2	0.78
	Other outcome	39	44			
Infrapopliteal artery disease	Improved/stable	13	44.8	1.28	2	0.53
	Other outcome	41	45.7			

The cross tabs above clearly indicate that there are statistically significant lower percentages of participants with hyperlipidaemia and of female gender in the group who improved or remained stable compared to the group who experienced other outcomes ($p=<0.05$). No other significant differences were identified in the rest of the parameters measured.

7.4.10.3 Predictors for improved or stable haemodynamics

Binomial logistic regression models were applied to determine factors independently associated with improved or stable haemodynamics. The results of the regression models are given as the odds ratio (OR) and 95% confidence interval (95% CI).

The results of the initial model are presented in Appendix 13 'Regression Models results'. All the factors recorded were inserted in the models and the interaction effect was analysed by backward elimination. The tables below present the final models and the significant predictors for improved or stable haemodynamics identified through this analysis.

Table 7.28 Predictors for stable or improved haemodynamics. Binomial regression analysis

Parameter Estimates

Improved or stable haemodynamics[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% Confidence Interval for OR	
								Lower Bound	Upper Bound
Other outcome	Intercept	.11	.60	.03	1.0	.85			
	Hyperlipidaemia	1.47	.60	5.99	1.0	.01	4.35	1.34	14.10
	No Hyperlipidaemia	.00[b]	.	.	.00	.	.	.	.
	CRP	.14	.09	2.22	1.0	.04	1.14	.96	1.37

a. The reference category is: Improved or stable.

b. This parameter is set to zero because it is redundant.

Pseudo R-Square	Cox and Snell	Nagelkerke	McFadden
	.076	.126	.086

Table 7.28b

This two model regression analysis indicates that hyperlipidaemia and CRP are significant predictors for worse outcome, while no factors were found to be independent predictors of improved or stable haemodynamics. The results show that participants with hyperlipidaemia are 4.35 times less likely to have an improved or stable outcome within 2 years and with every 1unit increase in CRP it is 1.14 times less likely to have an improved or stable outcome.

7.4.11 Symptom progression

The scores of the walking impairment questionnaire (WIQ) were recorded at each visit where an increase in score indicated worse symptoms and a decrease in score indicated improved symptoms. The change in WIQ score results and reported claudication distance (within the questionnaire) are presented in Fig 7.21 and 7.22 below.

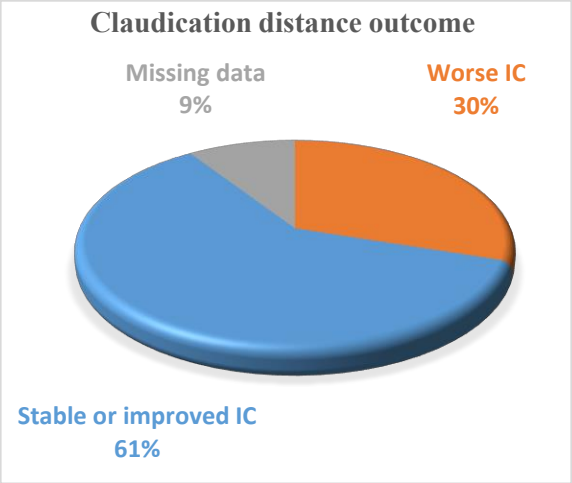


Fig 7.21 Claudication distance outcome

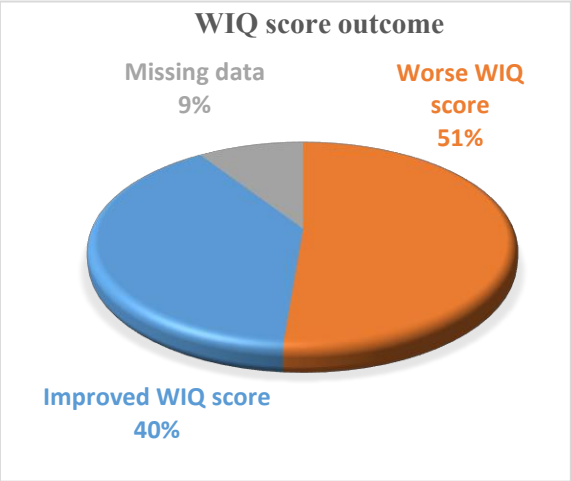


Fig 7.22 WIQ score outcome

The figures indicate that 30% of the study population reported a decrease in claudication distance from baseline while 51% reported worse WIQ scores after two years. The difference in scores was analysed using the Wilcoxon signed ranks test. Results are presented in table 7.29.

Table 7.29 Change in WIQ scores and CD between baseline and 2 years

Variable	Baseline	2 years	Z	P value
WIQ score median (IQR)	65.7 (46, 74)	61.5 (18, 74)	-3.2	0.001
CD distance	100 (50, 200)	125 (50, 400)	-3.78	<0.001

Table 7.29 indicates that after 2 years, although more participants (51%) experienced worse symptoms, there was an overall significant decrease in WIQ score (p=0.001) over two years. Similarly, a significant increase in CD distance reported (<0.001). It should be noted that in this analysis participants who underwent revascularisation were included.

The correlation between the WIQ scores and haemodynamic scores was assessed using the Spearman's correlation test. The relationship between the WIQ was also assessed with the reported CD within the questionnaire. The results are presented in table 7.30.

Table 7.30 Correlation between haemodynamic variables, reported CD and WIQ scores

Variables		Speraman's rho Correlation coefficient	P value
WIQ baseline n=150	TBPI baseline	-0.14	0.08
	ABPI baseline	0.02	0.8
WIQ 2 yrs n=134	**TBPI 2 yrs**	-0.4	**<0.001**
	ABPI 2 yrs	-0.16	0.07
WIQ change n=134	**Change in reported CD**	-0.98	**<0.001**

Table 7.30 indicates that the baseline WIQ scores were not correlated with baseline haemodynamic measures. However, a significant but weak negative correlation (-0.4) was observed between the TBPI results after 2 years and the WIQ results after 2 years indicating that lower TBPI values corresponded to higher WIQ scores (worse symptoms). A strong significant correlation was found between change in WIQ and change in CD (p=<0.001), indicating that as WIQ scores increased (worse symptoms) the CD decreased (shorter walking distance). No significant correlation was found between the ABPI results and the WIQ scores after 2 years.

The correlation between the change in reported WIQ scores and the haemodynamic changes measured by ABPI and TBPI were assessed using the Spearman correlation test. A non-parametric test was applied since the test for normalcy (Shapiro-Wilk) of the data indicated a non-normal distribution (Appendix 11). Scatterplots (Fig 7.23 and 7.24) were plotted to illustrate the results.

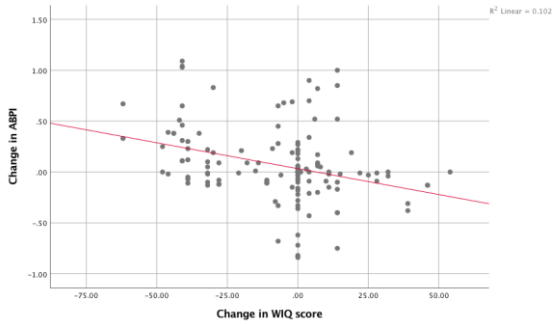


Fig 7.23 ABPI change vs WIQ change

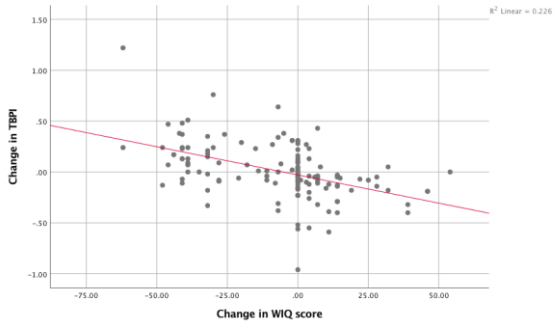


Fig 7.24 TBPI change vs WIQ change

The scatterplots illustrate that the haemodynamic measures are negatively correlated with the haemodynamic changes, where an increase in ABPI or TBPI (haemodynamic improvement) corresponds with a decrease in WIQ (i.e. improvement of symptoms).

Table7.31 Correlation between WIQ and haemodynamic measures

Correlations			
		TBPI change	ABPI change
WIQ change	Spearman's rho Correlation coefficient	-0.52	-0.33
	Sig. (2-tailed)	<0.001	<0.001
	N	134	134

The results in table 7.31 indicate that there was a significant correlation between the change in WIQ scores and change in TBPI and ABPI (<p=0.001 and <0.001 respectively). Results show that as the haemodynamic parameters decreased, the WIQ scores increased, indicating worse IC symptoms. This is also evident in the scatterplots presented in figures 7.23 and 7.24.

7.5 Summary of key findings of Study 4

This section presents the main findings reported in this study. The main study outcome of interest was deterioration rate to CLI in patients with IC, its prevalence, risk factors and characteristics of participants who deteriorated to CLI and the identification of predictive factors for this outcome.

- Within two years, 50.6% of the study cohort experienced significant deterioration, **23.3%** (n=35) of whom deteriorated to **CLI** and 27.3% experienced significant haemodynamic deterioration (decline in ABPI by ≥0.15 and/or decline in TBPI by ≥0.1). Mild haemodynamic deterioration was evident in an additional 17% (n=25) of the study cohort while only 19.3% (n=29) of the sample population had stable or improved haemodynamics. When evaluating clinical symptoms, results indicate that overall 51% (n=76) of the study cohort reported worse IC symptoms according to the WIQ and 33.3% (n=49) reported shorter claudication distance. After two years, overall improvement in IC symptoms was reported in 38% (n=57) of the study cohort.

- Participants who deteriorated to CLI had a median baseline **ABPI** of 0.66 (IQR 0.51,0.7) or **0.53** (IQR 0.48,0.69) when calcified arteries were excluded and a median **TBPI of 0.33** (0.2,0.43) at baseline. These parameters were significantly lower than those observed in participants who did not deteriorate to CLI (p=0.002 and p=0.015 respectively).

- Participants who deteriorated to CLI were more likely to have **infrapopliteal artery disease** (p=0.03) and **monophasic continuous Doppler waveforms** in the pedal arteries (PT and DP) (p=0.04) compared to participants who did not deteriorate to CLI.

- Baseline **ABPI, TBPI, IPA disease** and high **HbA1c** were identified as significant predictors for deterioration to CLI. ($p<0.05$, multinomial logistic regression). While female gender, infrapopliteal artery disease, lack of antiplatelet therapy, high CRP, lack of calcium channel blockers and the presence of diabetes were identified as predictors of significant haemodynamic deterioration (decline in ABPI by ≥0.15 and/or decline in TBPI by ≥0.1) (p=<0.05).

- The combined predictive value of baseline **ABPI, TBPI** and the presence of **infrapopliteal artery disease** was found to be significant for the development of CLI (p=<0.001) within two years (AUROC 0.82 categorized as having a 'good' predictive value).

- A predictive model identified participants with an ABPI ≤0.64 and a TBPI ≤0.39 in the presence of infrapopliteal artery disease and IC are more likely (probability of 82%) to deteriorate to CLI and benefit from close haemodynamic monitoring while participants with ABPI ≤0.44 and a TBPI ≤0.18 and IPA disease may benefit from consideration of preventive revascularisation.

- The rate of progression of PAD among participants who presented with IC overall, and among participants who developed CLI and who experienced significant haemodynamic **deterioration was higher during the second year** of the study after initial presentation with IC. Participants who deteriorated to CLI had a decline in TBPI

of 0.08 and participants who experienced a significant haemodynamic decline had a yearly decline of 0.24 in TBPI.

- Participants with baseline ABPI of 0.5 or less were found to be 3.9 times more likely to develop CLI within 2 years than participants who have higher ABPIs; participants who have infrapopliteal artery disease at baseline were reported to be 2.25 times more likely to develop CLI within 2 years than participants who do not have infrapopliteal artery disease at baseline and for every 0.1 decrease in ABPI the risk of deterioration to CLI increased by 1.5 times. Participants with a baseline TBPI of 0.39 or lower were found to be 3.6 times more likely to develop CLI than participants with higher TBPI (RR 3.6, p=0.02); with every 1 unit increase in baseline HbA1c the risk of developing CLI increased by 1.35 times (RR 1.35, p=0.03) and with every 0.1 unit decrease in baseline TBPI participants were 3 times more likely to deteriorate to CLI.

7.6 Discussion

This prospective longitudinal observational study sought to assess outcomes of patients with IC within two years. It also investigated prognostic factors for the deterioration to critical limb ischaemia (CLI) in patients presenting with intermittent claudication (IC).

Results revealed new knowledge related to the progression of PAD in patients with IC, exposing a more threatening prognosis, than originally thought, of significant haemodynamic deterioration in 51% of the cohort and deterioration to CLI within 2 years in 23.3% of patients presenting with IC. This study also revealed independent predictive risk factors for deterioration to CLI within 2 years. A novel patient-specific algorithm of predictive factors for the early identification of patients who are at risk of deterioration to CLI within two years, has also been developed and is being proposed as a viable tool to support clinical decision making for selection of management approach.

This section presents a discussion of the findings of this study in the light of previous literature. It provides an in-depth evaluation of the results and their significance within the context of clinical decision making for patients presenting with intermittent claudication (IC). An insight into the clinical implications of these results, particularly in relation to the clinical decision of early intervention in patients presenting with IC is also presented.

7.6.1 High rates of deterioration in patients presenting with IC

One of the important findings of this study was the high rate of haemodynamic and clinical deterioration within two years observed in this study cohort. In terms of 'deterioration', this study investigated both development of CLI, (that is development of rest pain and / or ulceration/gangrene) and significant haemodynamic deterioration (decrease in ABPI >0.15 and / or TBPI >0.1) since these are known to be predictive markers of future cardiovascular disease events and CLI (M. S. Conte et al., 2019; M. H. Criqui et al., 2008). The importance of this finding is the fact that it challenges previously held views of a benign lower limb prognosis in patients with IC.

The results of this study contradict currently held views that IC is a benign condition where, according to the literature, approximately only 5-10% deteriorate to CLI within 5 years (Hirsch et al., 2006), as has been discussed previously in Chapter Two. Apart from the high rate of development of CLI in this study, the non-benign lower limb prognosis was also demonstrated by the high rate of haemodynamic deterioration shown in this cohort. Results demonstrate that within 2 years 51% experienced significant deterioration, where 23.3% developed CLI and 27.3% experienced significant haemodynamic decline. As discussed in Chapter two, research into haemodynamic decline in patients with IC is limited. While the proportion of patients experiencing significant haemodynamic decline is consistent with previous research (V. Aboyans et al., 2006; A. Nicoloff et al., 2002) of 28% to 30% in 5years, the decline in the current study was observed in a shorter time period (2 years), further suggesting a more aggressive progression of the disease. This corroborates the proposed revision of the commonly held view that the lower limb prognosis in patients with IC is benign (Mizzi et al., 2019).

It is recognised that the 2 year CLI outcome in the current study (23%) is markedly higher than the predicted 5-year outcome of 5-10% stated in the TASC consensus documents and the 51% significant deterioration is also distinctly higher than the predicted overall 25% deterioration. While the TASC documents were mainly based on large population study findings, comparable proportions were expected in the population with IC having similar atherosclerotic load. If anything, due to the significant improvement in medical treatment in patients with PAD over the years, a lower proportion of deterioration to CLI was expected. The higher rate of deterioration to CLI among IC patients reported in the current study may be due to two possible reasons which will be discussed in depth in this section; firstly, the study design which

addressed sources of bias which may have underestimated disease progression in previous studies and secondly, the high prevalence rate of risk factors in the overall study cohort at baseline.

7.6.2 Influence of study design

This study aimed to evaluate the rate of progression of PAD and risk of CLI development in patients presenting with IC over a 2-year period. Following the systematic review presented in Chapter Four (Mizzi et al., 2019), several sources of bias which may have resulted in the underestimation of the true progression of disease in patients with IC were identified in previous literature. These included selection bias at recruitment with inadequate allocation concealment, survival selection bias, lack of methodological detail with possible use of inexperienced assessors related to haemodynamic analysis, clear definition of outcome measures and incomplete information related to attrition and non-consent. As further detailed in Chapter Five, in this study, the identified sources of bias were addressed and measures to address internal validity of the study were employed to obtain a reliable definition of disease progression and CLI risk in this cohort.

In the recently published guidelines for chronic ischaemia, it was re-iterated that for the patient with IC, reliable data on the epidemiology of CLI are lacking and estimates can be highly misleading (M. S. Conte et al., 2019). The risk of progression to CLI is varied in the literature, ranging from 1.4% per year to 21% within 5 years of diagnosis (Aquino et al., 2001; Jelnes et al., 1986; Jensen et al., 2006; Kumakura et al., 2016; Naschitz et al., 1988; B. Sigvant et al., 2007) and the heterogeneity of the studies makes direct comparison with the results of the current study difficult. The broad variation of risk to CLI among patients with IC indicated in published literature was mainly attributed to difference in risk factor prevalence and population characteristics, definition of CLI as the outcome measure, baseline inclusion criteria and study design (Bitar & Garcia, 2010). While the definition of CLI of the current study is based on the Rutherford classification of Grade II or III (Rutherford et al., 1986) which is also the method supported by international consensus guidelines on PAD (Becker et al., 2011; Dormandy & Rutherford, 2000; Norgren et al., 2007), some early reports used unclear definitions, using either only clinical criteria (Dormandy & Murray, 2011; Murabito et al., 1997), or repeat revascularisation and amputation (Kumakura et al., 2016).

The methodological differences applied in the current study in terms of allocation concealment at recruitment and minimal risk of survival selection bias due to a very low attrition rate may have contributed to the higher proportion of CLI compared to previous published studies.

While the designs of the early studies quoted in the TASC and AHA documents are not comparable with the study design of the current study, the higher proportion of detection of deterioration to CLI within 2 years in the current study is highlighted. These results support the impression that the risk of disease progression in patients with IC had been previously underestimated as demonstrated in the systematic review presented earlier in this thesis (Mizzi et al., 2019) and a meta-analysis which investigated the risk of the limb in symptomatic and asymptomatic PAD (B. Sigvant et al., 2016).

7.6.4 Influence of risk factor prevalence

The TASC and AHA documents propose the 5-year prognosis of 5-10% development of CLI in a population of IC but do not present detailed information on the various risk factor prevalence rate of participants at baseline, and therefore cannot be compared to the current data. However, most studies on which the document is based (Fowkes et al., 1992; W. Kannel & McGee, 1985; McDaniel & Cronenwett, 1989; Murabito et al., 1997; Price et al., 1999; Weitz et al., 1996) are derived from northern European countries or the United States, where the rates of diabetes at the time ranged from 2-4% (NCD Risk Factor Collaboration, 2016).

The current study was conducted in a southern European country (Malta) where the national prevalence of diabetes is 13.8% and the age adjusted comparative prevalence is 9% (Ogurtsova et al., 2017). Additionally, according to the latest country health profile conducted by WHO, cardiovascular disease with the associated risk factors is also higher in Malta than in other European countries (OECD., 2018). It may therefore be postulated that the prevalence of risk factors at baseline in the cohort of the current study, may be higher than the prevalence of risk factors among the participants in the studies included in the TASC and AHA documents, and may have contributed to the higher deterioration in the cohort of the current study. Only one study (CAVASIC study B. Rantner et al., 2017) reported a higher deterioration to CLI than the current study. Rantner et al., (2017) also reported similar baseline proportion of all the risk factors, except for diabetes and age (15% and 59+/-6 years respectively) and a deterioration to CLI of 33% in 7 years was observed. However, their cohort included participants with previous

endovascular interventions, and their high rate of deterioration could be attributed to the fact that the recruited participants had worse disease at baseline.

The risk of PAD and disease progression associated with diabetes is well known. The duration of diabetes mellitus, glycated-haemoglobin levels and use of insulin are significantly associated with worsening PAD (Althouse et al., 2014; Kallio et al., 2003; Tseng, 2003). Additionally, people with PAD and diabetes were 5 times more likely to have an amputation when compared with people without diabetes (Jude et al., 2001). This literature therefore supports the increased rates of deterioration observed in the cohort of this study where a high prevalence of diabetes (69%) was present at baseline. In individuals with diabetes, the characterised increased atherosclerotic burden is due to mechanisms of irregularities within the vessel wall, blood cells and blood rheology. As discussed in section 2.8.2, these mechamnisms are associated with increased duration of diabetes and worsening blood glucose control (Kanter & Bornfeldt, 2013; Thiruvoipati et al., 2015). The decreased nitric oxide bioavailability in diabetes results in a cascade of events of vascular smooth muscle cell migration and proliferation with platelet activation. Diabetes also leads to a hypercoagulable state with an elevation in blood viscosity and fibrinogen which have been associated with abnormal ABPI (McDermott et al., 2004).

Furthermore, diabetes is associated with a more anatomically distal distribution of the disease, that is, distal to the knee, when compared with people without diabetes (Haltmayer et al., 2001). Typically, infrapopliteal artery disease has been associated with worse prognosis and a higher risk of death and major amputation when compared to supra-geniculate artery disease (Gray et al., 2010; Neupane et al., 2018). In the current study, infrapopliteal artery disease was significantly higher in the group of participants who deteriorated to CLI within 2 years compared to those who did not develop CLI (60% vs 40% respectively, p=0.037). The presence of infrapopliteal artery disease at baseline was also found to be a significant independent predictor of deterioration to CLI as discussed in further detail in section 7.6.5. This finding further corroborates the suggestion that the higher proportion of participants with diabetes in the cohort of the current study may have contributed to the higher percentage of CLI within 2 years.

Nevertheless, the diverse risk factor prevalence at baseline compared to previous works, does not diminish the importance of the findings. The demographics of the world populations are constantly changing and with them so are the patient characteristics. This change needs to be

acknowledged and long established notions of disease also require updating to meet the continuous population demographic change. The diversity highlights the need for a more individualised approach to establishing management for the patient with IC. A threatening prognosis for the lower found observed in this study among patients presenting with IC, highlights the need for a review of the benign prediction commonly held with consideration of the influence of risk factors on the progression of the disease.

7.6.5 Predictors of Critical Limb Ischaemia

There is currently limited knowledge to allow for the prediction to CLI in the patient with claudication. It is acknowledged that various risk factors contribute in some way to the progression of PAD and that baseline ABPI of ≤0.5 is currently the best known predictive factor (Norgren et al., 2007). However, alone, this is insufficient to accurately identify individual patients who are more likely to deteriorate (Bitar & Garcia, 2010; Norgren et al., 2007). In a comparative study, Cronenwett et al (Cronenwett et al., 1984) found that a change in ABPI over the study period was significantly different between those whose symptoms progressed and those whose symptoms remained stable. They came to the conclusion that initial ABPI alone is not sufficient to predict outcome but a deteriorating ABPI is an important criterion required to plan a timely operative intervention. Based on this principle, this study focussed on participants who experienced deterioration, rather than only on participants who had a low ABPI at diagnosis, and investigated predictors at baseline which were independently associated with the observed deterioration. The identification of predictive factors for deterioration could help early identification of patients who are at risk and help plan a timely intervention.

This study has identified ABPI, baseline ABPI ≤0.5, TBPI, baseline TBPI ≤0.39, HbA1c and infrapopliteal artery disease as independent predictors for the development of CLI within 2 years in patients with IC. Additionally, female gender, lack of antiplatelet therapy, high CRP, lack of calcium channel blockers and the presence of diabetes were identified as predictors of significant haemodynamic deterioration. In this section each identified predictor will be discussed individually in the light of previous literature.

7.6.5.1 Non-invasive haemodynamic measures

This study has shown that participants with a baseline ABPI of 0.5 or lower are 4 times more likely to develop CLI within 2 years than participants who have higher ABPIs (RR 4, p=<0.05). This is consistent with previous literature investigating ABPI as a predictor of deterioration which showed that an ABPI ≤0.5 was the best predictor for deterioration of PAD in patients with IC (Hazard ratio: >2) (Naschitz et al., 1988; Norgren et al., 2007). The ABPI at initial diagnosis is a known predictor of progression to CLI (Aquino et al., 2001; Kumakura et al., 2016; Naschitz et al., 1988; Rosenbloom et al., 1988), where an ABPI of 0.7 together with a decline of >0.15 in ABPI was associated with a 1.9 fold increased risk of deterioration to CLI (Naschitz et al., 1988). The current study has also shown that with every 0.1 decrease in ABPI, the risk for development of CLI within 2 years increases by 1.5 times (RR 1.5). This is also consistent with previous literature investigating the predictors for CLI where 0.1 decrease in ABPI was associated with an increased risk of development of ischaemic rest pain (RR 2.2) (Aquino et al., 2001).

The usefulness of ABPI as a predictor of PAD progression is widely accepted and is further corroborated in this study. However, in the presence of MAC, ABPI fails to detect disease process and is inaccurate (Aerden et al., 2011; Formosa et al., 2013). This study therefore also assessed the predictive value of TBPI due to its greater likelihood of detecting changes in arterial pressure when stenosis is located below the knee (Chen et al., 2012) and a lower risk of being affected by arterial calcification (Brooks et al., 2001; Sacks et al., 2002; Sahli et al., 2004). This study demonstrated that TBPI is a significant independent predictor of deterioration to CLI within 2 years in patients with IC. Results show that patients with a baseline TBPI of ≤0.39 are 3.6 times more likely to develop CLI within 2 years than participants with higher TBPI (RR 3.6, p=0.02) and with every 0.1unit decrease in TBPI, the risk for deteriorating to CLI increases by 3 times. While the use of TBPI in cases of MAC has been advocated, literature investigating TBPI as a predictor of adverse events is limited to one study investigating TBPI as a predictor of cardiovascular mortality, unrelated to lower limb events (Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014). The authors report that TBPI consistently predicted higher risk of cardiovascular mortality with progressively lower TBPI readings irrespective of diabetes status (Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014). This is therefore the first study to report TBPI as an independent predictor of CLI in

patients with IC. There is a mounting number of studies supporting the use of TBPI for its superior diagnostic potential to ABPI (Bundo et al., 2013; Sahli et al., 2004; Stoekenbroek et al., 2015; Tehan et al., 2016), indicating it is a useful diagnostic modality of haemodynamic status in patients with and without MAC.

The utility of non-invasive measures of PAD has been advocated as predictors not only of lower limb morbidity but also of mortality (V. Aboyans et al., 2012; C. Diehm et al., 2009; Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014; Moyer & U.S. Preventive Services Task Force, 2013; Papa et al., 2013; Velescu et al., 2017). Particularly, the usefulness of TBPI was reported in patents with CLI as it was found to be correlated with diagnostic criteria for limb threatening ischaemia, while ABPI was abnormal in only 58% of patients with CLI (Salaun et al., 2019; Shishehbor et al., 2016). Additionally, TBPI <0.7 was 90% sensitive in the diagnosis of significant stenosis or occlusion of the tibial arteries (Randhawa et al., 2017). The identification of TBPI as an independent predictor of CLI in this study, proposes compelling benefits of non-invasive haemodynamic analysis in patients presenting with IC with the possibility of early identification of those who are at risk of deterioration. The use of haemodynamic measures (ABPI and TBPI) are further discussed in this chapter as part of an algorithm proposed for this purpose.

7.6.5.2 Infrapopliteal artery disease

This study has demonstrated that the presence of infrapopliteal artery disease is an independent predictor for deterioration to CLI within 2 years in patients with IC. Patients with infrapopliteal artery disease at baseline are 2.25 more likely to develop CLI within 2 years than patients who do not have infrapopliteal artery disease at baseline (RR 2.25, p=<0.05). Although no previous studies have investigated IPA disease as a predctor for CLI, this is consistent with previous work where infrapopliteal artery disease was highly prevalent in patients with CLI (Graziani et al., 2007). In agreement, occluded or severely stenosed anterior tibial artery was found in 76% of patients with CLI and calcified arteries and in 83% of patients with CLI and compressible arteries (Randhawa et al., 2017). Individuals with isolated tibial disease are more likely to have worse ischaemia and confounding factors such as diabetes at presentation (Gray et al., 2010). This is in agreement with the findings of the current work where the presence of IPA disease was correlated with diabetes at baseline (Chapter 6, section 6.3.7.2).

Commonly CLI is the result of multilevel arterial occlusive disease or disease involving parallel vascular beds such as the profunda femoris artery and the superficial femoral artery. However, as severity of the disease increases, it frequently involves infrapopliteal arteries (N. Diehm et al., 2006). While there is a general acceptance that for CLI to occur, multilevel disease is required, this is not the case in people living with diabetes or chronic renal disease (M. S. Conte et al., 2019) where diffuse disease of the infrapopliteal and pedal arteries is increasingly being observed in these patients (Ortmann et al., 2012).

The finding of the current study implicating the presence of IPA disease in deterioration to CLI as an independent risk factor is emphasized in the knowledge that isolated tibial disease has a worse prognosis in terms of limb salvage and maintenance of ambulation and independent living status compared to patients with multilevel infrainguinal disease (Gray et al., 2010). This is congruent with worse outcomes in patients with CLI and diabetes, with higher risk of IPA disease, where progression to gangrene was observed in 40% of individuals with diabetes, compared to 9% of individuals without diabetes (W. B. Kannel, 1994).

7.6.5.3 Haemoglobin A1c

In the current study, levels of HbA1c at baseline were independently associated with increased risk of deterioration to CLI. Results indicate that with every 1unit increase in baseline HbA1c, the risk of developing CLI increased by 1.35 times (RR1.35, p=0.03) among patients with IC. This is consistent with findings in the UKPDS trial which demonstrated that for every 1% reduction in HbA1c, the risk for amputation or death following a vascular event decreased by 43% (Stratton et al., 2000).

The ADVANCE collaborative group also showed that with intensive blood glucose control, major macrovascular and microvascular events were lower when compared to the control group after a median 5 year follow up (ADVANCE Collaborative Group, 2008).

These results are also in agreement with recently published Global vascular guidelines, indicating that the severity of PAD is related to the severity and duration of hyperglycaemia (M. S. Conte et al., 2019). This also corresponds to recommended guidelines for the prevention of worsening ischaemia stating that individuals with PAD and diabetes should undergo

aggressive blood glucose level control (Norgren et al., 2007), although the evidence supporting the benefits of this approach is not strong (M. S. Conte et al., 2019).

While there are no studies which have identified HbA1c level *per se* as an independent risk factor for CLI among patients with IC, but have identified diabetes as a main risk factor (V. Aboyans et al., 2018), the findings of this study are important. The lack of identification of diabetes as an independent risk factor for deterioration to CLI may be attributed to the high prevalence of diabetes among the whole cohort of this study (>69%), where a high base rate prevalence of a factor may reduce the impact of the risk factor during analysis (Hinsz et al., 2005). Its relevance however should not be dismissed. It is possible that in the context of the current study, diabetes is a strong modifier and the effect of diabetes is mediated by its influence on the pattern of disease progression into a more distal atherosclerotic distribution evidenced by infrapopliteal artery disease being identified as an independent risk factor for deterioration to CLI. Additionally, the identification of HbA1c as a predictor corroborates this notion. Therefore, the presence of diabetes in the population with IC should not be discounted when determining risk.

7.6.5.4 Diabetes

It should be noted that in the current study diabetes was not found to be a significant predictor in the regression analysis assessing risk factors for CLI but it was found to be an independent predictor for significant haemodynamic deterioration measured by TBPI. Results show that participants with diabetes were 7.7 times more likely to experience significant haemodynamic decline (measured by TBPI) than participants without diabetes. These results are in agreement with an extensive study (V. Aboyans et al., 2006) investigating risk factors for progression of PAD in large (measured by ABPI) and small vessel disease (measured by TBPI). Similar to the current study, diabetes was not found to be an independent predictor of large vessel disease, measured by a decline in ABPI. This was also corroborated in previous studies (Haltmayer et al., 2001; Kennedy et al., 2005). However, consistent with the results in the current study, diabetes was found to be a significant risk factor in disease progression when measured by TBPI (V. Aboyans et al., 2006). Diabetes is associated with disease affecting mostly distal arteries (Haltmayer et al., 2001) with reduced possibilities of revascularisation (Lauterbach et al., 2005) and higher amputation rates. However, it is not excluded that together with the progression of PAD in the small vessels, possible simultaneous calcification conceals

deterioration in the large vessels, resulting in no ABPI decrease in the presence of TBPI decrease.

While the findings of this study highlight HbA1c as an independent risk factor for the deterioration to CLI in patients with IC, the contribution of diabetes is also emphasized, both in the context of significant haemodynamic deterioration and in its association with a more distal atherosclerotic distribution of PAD involving infrapopliteal arterial bed which was in turn also identified as an independent risk factor.

7.6.6 Predictors for significant deterioration

Apart from the identified significant predictors for CLI discussed in the previous sections, female gender, lack of antiplatelet therapy, high CRP and lack of calcium channel blockers were further identified as predictors for significant haemodynamic deterioration.

As discussed in Chaper 2, while IC is commonly regarded as a male disease because of a higher prevalence of men (which was also reported in this study), it is postulated that women are less likely to report symptoms than men or report late when the disease is more advanced (Schramm et al., 2018). Additionally, post menopausal women have a higher risk of PAD progression compared to men (Schramm et al., 2018), which may explain the finding of female gender as an independent predictor for significant deterioration in this study.

The benefits of antiplatelet therapy in limiting disease progression is well known and antiplatelet therapy is in fact the recommended first line treatment for patients with IC (M. S. Conte et al., 2019). The findings in this study, that lack of antiplatelet medication is associated with increased risk of haemodynamic deterioration is therefore, in agreement. Platelets play a significant role in the development of atherosclerosis and medication which causes platelet antiaggregation, such as aspirin and clopidogrel, which are the two most commonly prescribed antiplatelet medication in the current cohort, is important (Moyer et al., 2013). Despite its known significance in decreasing risk of cardiovascular events, there are no previous studies which have identified lack of antiplatelet medication as an independednt predictor for deterioration to CLI among patients with IC (Norgren et al., 2006). This finding is important, particularly in the light that PAD is generally undertreated in primary care and therefore highlights the need for further awareness.

This study also reports high CRP at baseline as an independent predictor for significant haemodynamic deterioration and with every 1-unit increase in CRP, the risk of deterioration increases by 1.1 times. These findings are in agreement with Vainas et al (Vainas et al., 2005) who demonstrated that higher CRP levels were significantly associated with lower ABPI during a 12-month follow-up study. As discussed in Chapter 2, section 2.8.7, CRP is a known predictor for coronary events and is not only a marker of atherosclerosis but has been suggested to actively play a role in atherogenesis (Vainas et al., 2005). Assessing CRP levels in patietns presenting with IC may be of benefit, particularly if other independent predictors are present.

This study has identified lack of calcium channel blockers to be an independent predictor for deterioration to CLI among patients with IC. To the author's knowledge there are no previous studies which have identified lack of calcium channel blockers as predictors of worse lower limb outcomes, however there is evidence of the benefits achieved when it is used to treat PAD. In a systemetaic review, calcium channels blockers were found to be effectiove in preventing PAD in patients with hypertension (Feringa et al., 2009). A meta-analysis study also found that in hypertensive patients treated with calcium channel blockers, the progression of PAD was mitigated (Shetty et al., 2020). Further studies are needed in this regard.

Following the identification of independent predictors for deterioration to CLI in patients with IC, which may help identify patients with a greater risk of deterioration, the diagnostic accuracy using a combined model of risk factors was assessed. An algorithm to guide clinical decision making for patients presenting with intermittent claudication is proposed and detailed in the following section. The predictive algorithm proposes a more individualised treatment approach to patients with IC based on various independent risk factors at baseline.

7.6.7 The clinical prediction model

Current treatment guidelines delineate the need for patient and intervention–specific considerations for the individual patient when revascuarisatin is considered (M. S. Conte et al., 2019). However, the decision whether to intervene or not, often remains arbitrary since definite recommendations detailing specified patient characteristics are not yet available.

This study proposes two clinical models based on the identified independent risk factors for significant deterioration within 2 years in a cohort of patients with IC. An analysis of the

combination of significant risk factors for deterioration to CLI demonstrated that the combined predictive value of baseline ABPI, TBPI and the presence of infrapopliteal artery disease was found to have a significant 'good level' predictive value for the development of CLI within two years (AUROC 0.82 p=<0.001). Cut off points for the clinical models were identified and results showed that individuals presenting with IC with an ABPI of ≤0.64 combined with a TBPI of ≤0.39 and in the presence of infrapopliteal artery disease are likely to deteriorate to CLI within 2 years. Participants presenting with IC in the presence of infrapopliteal artery disease with an ABPI ≤0.44 and a TBPI ≤0.18 are at very high risk of developing CLI and may therefore benefit from early intervention. The models' performance was assessed using the AUROC curve (AUROC 0.82), a method which has been used previously in other prediction models (Y. Zhan et al., 2014; Y. Zhang et al., 2016).

This is the first study to analyse the diagnostic accuracy of combined risk factors for deterioration to CLI among patients with IC, therefore results cannot be compared to previous literature. There are previous studies (Chung et al., 2010; Parameswaran et al., 2005; Tehan et al., 2016; Williams et al., 2005) mostly focusing on the analysis of diagnostic utility of individual haemodynamic tests (TBPI and ABPI) with one study (Tehan et al., 2016) indicating poor diagnostic utility of ABPI (ROC 0.58) and moderate diagnostic utility of TBPI (ROC 0.75) for the detection of PAD among a community based population.

The approach of applying multivariable modelling using routine examination measurements for predicting clinical risk has been used for predicting risk of PAD in communities (Y. Zhang et al., 2016) but not for predicting CLI among IC patients. The several variables applied in the initial regression analysis considered for developing the models, included risk factors identified as independent predictors for risk of haemodynamic deterioration and CLI in this same study. Consistent with previous research (Althouse et al., 2014; M. S. Conte et al., 2019; Selvin & Erlinger, 2004), the included variables (baseline ABPI, baseline TBPI, female gender, infrapopliteal artery disease, lack of antiplatelet therapy, high CRP, lack of calcium channel blockers and diabetes) have been previously identified as risk factors for PAD.

Due to the interventional risks associated with active intervention, two models are being proposed.

i) to identify patients at risk of deterioration to CLI and who would benefit from more frequent haemodynamic monitoring

ii) to identify patients who would benefit from consideration of early revascularisation.

The first model, which indicates that patients with an ABPI of ≤0.64 combined with a TBPI of ≤0.39 and in the presence of infrapopliteal artery disease and IC are likely to deteriorate to CLI within 2 years has a sensitivity of 76% and a specificity of 57% when applying these cut-off points. This model is aimed at identifying patients at risk of deterioration, with the knowledge that having low specificity, false positive identifications are also possible. In this model, specificity was 'sacrificed' for the sake of sensitivity, reflective of the utility of this clinical predictive model which is aimed at identifying patients who would benefit from closer haemodynamic monitoring, with no clinical implications for those who are detected erroneously. Closer haemodynamic monitoring is beneficial in the timely recognition of deterioration, should it occur, deemed to be the best individual predictor since haemodynamic deterioration is likely to continue to occur in the absence of effective treatment (Norgren et al., 2007).

The second clinical predictive model being proposed in this study suggests that patients with an ABPI of ≤0.44 combined with a TBPI of ≤0.18 and in the presence of infrapopliteal artery disease and IC would benefit from early endovascular or surgical intervention due to the high probability of deteriorating to CLI within two years. For this clinical model, specificity (97%) was optimized over sensitivity (McNamara & Martin, 2018) since a lower number of false positives was desirable (Trevethan, 2017) due to the clinical implications for any patients who would be detected erroneously. It is recognized that the haemodynamic parameters in this clinical model are similar to the clinical parameters defining CLI where an absolute toe pressure of 30mmHg is indicative of CLI (Conte et al., 2019). However, this model is aimed at IC patients without rest pain or tissue loss, which are required coexisting features in the definition of CLI (M. S. Conte et al., 2015; M. S. Conte et al., 2019; Norgren et al., 2007). It therefore identifies patients who have low haemodynamic parameters in the presence of IPA and IC as having a high probability of deteriorating to rest pain and/or tissue loss within two years, hence benefitting from early revascularisation. As with any intervention, the life expectancy, general fitness of the patient and other important considerations always need to be evaluated in the clinical decision process (M. S. Conte et al., 2019).

While other predictive classification models have been developed for predicting wound healing in the presence of CLI such as the Wound ischaemia and foot infection (WIFI) and the Global Limb Anatomic Staging System (GLASS) (M. S. Conte et al., 2019), there are currently no clinical models for predicting outcome in patients with IC. The clinical risk prediction model proposed in this study includes a simplified approach which allows clinicians to classify patients according to their disease status at initial presentation. It may help the practitioner identify individuals who will benefit from closer non-invasive haemodynamic monitoring and individuals who are more likely to benefit from early revascularisation. While this proposed clinical prediction model has significant beneficial clinical implications which are discussed in the next section, it is recognized that further validation is required to ensure its satisfactory performance. Further research to improve the sensitivity of the predictive model is also needed. This is discussed in further detail in Chapter 8, section 8.7.

7.7 Strengths and potential limitations of the study

This study not only provides cross-sectional data of a well-defined population of patients with intermittent claudication but presents prospective long-term follow-up data with near complete follow-up information of the whole study population.

This study had a high recruitment of almost 100% and a high follow-up rate. This increased the liklihood that there was a reduced risk of survival selection bias often found in similar studies. Addressing this potential limitation results in a more accurate estimate of the outcomes measured.

One of the strengths in this study is that each recruited participant received a full vascular assessment within 6 weeks following recruitment, ensuring that the diagnosis of PAD was confirmed, and that all participants satisfied the inclusion criteria

7.7.1 Potential influencing factors

There are some important factors requiring consideration which may have contributed to the observed variations in outcomes of IC in the current study when compared to those observed in other countries.

For example, the effect of distribution of specialists may have an influence on referral processes (McPherson, 1989). The dominance of primary care differs from one country to another, as do

the health systems which are free at point of delivery (as in Malta and the UK) or are at a fee such as in the US. In restricted health systems, where specialist care is limited, due to availability of resources, patients are not encouraged to seek advice if a long wait or delay in treatment is suspected. This therefore has an indirect effect of patient's readiness to seek advice and also on the referring practitioner's decision for referral. On the other side of the spectrum, a higher availability of access to specialist care may directly encourage excessive use by patients including those who will achieve marginal benefits. The system in Malta sits in this part of this spectrum, where self-referral to primary care makes accessibility easy for the patient, encouraging them to seek advice even in cases where the ailment is not significant. This was reflected in the wide range of symptom severity, in terms of patient reported claudication distance, recorded in the study cohort as shown in the results of the prospective cross-sectional observational study (Study 3). Of importance, inclusion of all possible ranges of symptom severity within the study denotes better representation of the patient with IC.

However, within the context of the Maltese health system, the exclusive referral system to specialist care, located within the hospital, made access to specialist care, in this case the vascular surgeon, an outcome of several screening processes. This is another factor which needs to be considered when comparing outcomes between countries. Like the UK, in Malta patients need to seek advice from the general practitioners or podiatrists in primary health, who in turn, need to decide to refer the patient. At each point in the process, decisions are constrained by different exogenous influences such as, prevailing medical opinion or patient preferences by long-standing custom or tradition (McPherson, 1989). Inevitably, availability of resources also influences the referrer's decision, where rationing occurs if priorities for worse cases are set (Schieber & Poullier, 1988). On the other hand, in health systems where patients can seek medical advice directly from specialists, admissions to specialist care tend to be higher which may possibly have an effect on the overall reported outcomes in research emerging from those countries. Aspects of culture together with variations in social policy and budgets can result in variations in disease outcomes reported in different countries (McPherson, 1989). These are recognised causes of variation which can provide insights into differences of population outcomes in IC. Understanding and acknowledging such influences is important to identify areas which need to be addressed when conducting and designing research. In this research, to mitigate the effects of external influences pertaining to the referrers in primary care when making decisions for the patient with IC, as highlighted in study 2, actions were undertaken prior to the main study encouraging referral of all patients presenting with IC. This

method increased the likelihood that the population studied was representative of the population with IC in Malta.

When assessing Doppler waveforms, only 40% were found to have a deterioration in waveforms compared to 67% who experienced some form of haemodynamic deterioration (ranging from mild to CLI). This could be due to the fact that a Doppler waveform may change in pulsatility index (which is a measure of flow derived from the maximum, minimum and mean Doppler waveform in three cycles) but not form, in the presence of worsening occlusion. Change in pulsatility index was not investigated in this study and is a limitation. In the initial design stages of this research it was intended to record the pulsatility index (PI) of the waveform in order to account for this limitation. However, following the initial 50 participants this had to be discarded as it was very difficult to obtain reliable information for each participant since to calculate PI, a minimum three consecutive 'clean' waveforms without reflection are required for reliable PI. Despite several attempts in some patients this was difficult and time consuming, making it unacceptable for the patient.

7.8 Clinical implications of the study findings

The findings of the current study demonstrate that more than half the patients with IC experienced significant haemodynamic deterioration within 2 years, with >23% developing CLI, while only 19% remained haemodynamically stable or improved. This revealed a more aggressive limb threatening prognosis than previously perceived in published literature, suggesting that for the patient with IC the affected limb may not have a benign prognosis and closer monitoring is required if risk of deterioration to CLI is to be avoided. Closer haemodynamic monitoring, better medical management and informed clinical decisions for early revascularisation in patients with identified predictors of deterioration to CLI may mean fewer adverse lower limb events and reduced morbidity in this population.

A more individualised approach to risk categorisation and treatment of these patients is warranted. The importance of developing treatment strategies for the patient with IC based on disease severity, anatomic pattern of the disease and current comorbidities, in particular diabetes and HbA1c is emphasized. The assumption that the affected limb is at minimal risk of morbidity needs to be revised and more attention in terms of research and guideline development should be given to the importance of lower limb outcomes.

Current guidelines suggest that revascularisation should be considered when patients report that IC symptoms interfere with their quality of life. This study has shown that while 19% remained haemodynamically stable, 38% reported stable symptoms. In this study, symptoms were self-reported using a validated questionnaire, rather than using objective claudication distance measured by treadmill, reflecting real-world clinical situations where physician's decision to intervene is partly based on self-reporting of symptoms. Although developing patient-oriented end points is deemed critical when planning treatment strategies for IC (M. S. Conte et al., 2019), the discrepancy between the proportions of those who remained haemodynamically stable (19%) and those who reported stable symptoms (38%) suggests that relying on patient perception of improvement may not be the best measure of disease progression. It is possible that patients make life-style changes to adapt to their decreasing claudication distance, thus perceiving the burden less and reporting this erroneously as improvement. While such an adaptation may not essentially have an impact on the quality of life of the patient and may therefore not necessarily translate into the need for revascularisation, in patients who experience significant haemodynamic deterioration which puts them at high risk of CLI development, this becomes an important issue which may need to be addressed without delay. While further research is required in this field, of importance, this study has shown that symptoms do not always reflect haemodynamic status and for the patient with IC, knowledge of the atherosclerotic severity of the disease is important in order to plan treatment and predict outcome.

7.9 Conclusion

The results of this study provide an insight into the progression rate of PAD in patients presenting with IC and propose a foundation for the early identification of those who are more likely to deteriorate to CLI. The findings and the clinical patient-specific predictive model presented in this chapter have potential value and may help guide the clinical decisions for consideration of early revascularisation in patients with IC who are at an increased risk of deteriorating to CLI.

CHAPTER EIGHT

Proposing a paradigm shift in the management of intermittent claudication: Concluding discussion

8.1 Introduction

This thesis presented the background literature related to the prognosis of patients with IC, the theory and methodological processes employed in a series of quantitative investigations that developed sequentially within a critical realist philosophical approach, leading to the identification of the prognostic factors for the deterioration to CLI. The information gathered from these studies led to the development of a novel patient-specific predictive model for deterioration to CLI among patients with IC, based on prognostic variables identified in this work. The predictive model integrates the pattern of disease and commonly used haemodynamic analysis modalities to quantify the burden of the disease in the patient with IC. The overarching aim of this project was to provide insight into the individual's prognosis of IC in terms of lower limb outcomes, to enable an informed decision when selecting the management strategy at initial diagnosis. The novel findings provide the relative risk of identified predictive variables for development of CLI, while the predictive model is proposed as a viable tool for CLI risk prediction in patients presenting with IC. By applying the proposed predictive model, the prognosis within two years of the individual patient presenting with IC may be predicted with 82% probability, allowing clinicians to make informed clinical decisions, fulfilling the overall research aim of this thesis and accepting the proposed alternative hypothesis.

Through this chapter, the findings from the thesis investigations are collated and presented. Consideration is given to how this research may contribute to advancement in the management of the patient with IC through a paradigm shift inspired by the *revolutionary theory* of Thomas Kuhn (Kuhn, 2012). Potential changes in the current model of treatment that can be adopted in relation to the management of the patient with IC are considered relative to the thesis findings. The potential significance and application of these and translation to clinical practice is also discussed. Finally, the strengths and potential limitations of the thesis are acknowledged and recommendations for future research are also presented.

8.2 The context of the revolutionary theory

Before embarking on the main study of this project, it was important to understand the contextual framework of the research in terms of identifying the need for change in the current management model of the patient with IC while also highlighting the need for new perspectives in treatment, aiming to improve outcomes. As discussed in Chapter 3, the contextual framework of this research is grounded in the ideas of Thomas Kuhn's *revolutionary theory* which describes the philosophy of advancement in medical paradigms (Kuhn, 2012). Kuhn describes how specialists in particular fields are plunged into periods of uncertainty and are driven to engage in solving discrepancies between what is being predicted and what is revealed by observation or experiment, eventually progressing to a revolutionary phase and a paradigm shift (Kuhn, 2012). The process is inherently circular and occurs in cycles of alternating phases (Chapter 3, Figure 3.2) which he identifies as *normal science, model drift, model crisis, model revolution* and *paradigm change (shift).* As discussed in this chapter, this project progressed through these phases, including the identification of the need for a change within the current management paradigm of the patient with IC, exposing discrepancies within the current paradigm, eventually leading to the proposal of a new perspective in management by applying a novel predictive model.

8.2.1 Identifying the need for change within the current management paradigm

Patients with IC are assumed to have low likelihood of significant lower limb deterioration (S. M. Conte & Vale, 2018; Dormandy & Murray, 2011; Kumakura et al., 2016), a notion which led to the recommendation of conservative management with oral medication, smoking cessation and exercise for the vast majority of patients (M. S. Conte et al., 2015). This management paradigm is accepted by the medical community concerned with treating patients with IC (Norgren et al., 2007) and is denoted by Kuhn as a period where the paradigm is considered as *normal science.*

Notably, following review of the literature in Chapter Two, it was concluded that the current management model, could potentially delay treatment in patients who are at high risk of deterioration (Ferrari et al., 2004). Passage of time during a tentative conservative management approach in these patients, may result in a lost opportunity for safer and more effective

revascularisation procedures (Ferrari et al., 2004; Wolosker et al., 2003) apart from significant deterioration in quality of life. The findings in study 4 (Chapter Seven) demonstrate that deterioration to CLI occurred within a relatively short time in a significant proportion of patients (within less than two years of initial diagnosis of IC) highlighting the need for a timely intervention. Furthermore, this work has also demonstrated that haemodynamic decline among those who experienced significant deterioration, a marker for future development of CLI (M. H. Criqui et al., 2008; A. D. Nicoloff et al., 2002), commenced within the first year after diagnosis (Figures 7.14 and 7.15). Timely intervention is therefore critical since deterioration to CLI is denoted by a poor prognosis (Norgren et al., 2007).

> *"The most striking feature of CLI is the dismal prognosis for both life and limb outcomes, no matter what treatment is employed."*
>
> (Norgren et al., 2007, p.S40)

Once a patient with IC deteriorates to CLI, the possibility for successful revascularisation is significantly reduced (M. S. Conte et al., 2019), the risk for amputation increases 200-fold and mortality risk increases 3-fold (Anand et al., 2018). In patients with CLI who undergo lower limb bypass procedures, the risk of graft occlusion is higher than in patients with IC due to worse disease with possibly poor runoff vessels require more complex interventions and greater likelihood of treatment failure (Conte et al., 2019). On the other hand, endovascular or surgical intervention in a patient with IC is associated with significantly lower risk than in a patient with CLI (Dabrh et al., 2016; Hess et al., 2017; Sartipy et al., 2018). The risk of amputation among patients revascularised for CLI is 12% in 6 months compared to 0.4% per year in patients with IC (Fridh et al., 2017). Timely intervention and avoiding development of CLI is therefore of paramount importance in this group of patients and the risk of future deterioration needs to be identified and addressed at an early stage, before development of CLI occurs. The early identification of IC patients at the highest risk of rapid deterioration may therefore be beneficial and early preventive intervention may be justified in selected cases.

Further to identifying the clinical need to change the management paradigm as stated above, this work demonstrated (Chapter 4, study 1), that literature related to the prognosis of the lower limb is unclear (Mizzi et al., 2019) and it is therefore not possible to predict the risk of deterioration of the individual patient at initial diagnosis. Not knowing the patient's risk at initial presentation creates an element of clinical uncertainty (Birkmeyer et al., 2013; Soden et

al., 2017; Sommers & Launer, 2014) making choice of treatment difficult. According to Kuhn's philosophy of advancement in medicine this was equivalent to a *model drift*, indicating uncertainty within the accepted management paradigm (McWHINNEY, 1984).

8.2.2 Exposing discrepancies within the current management paradigm

Following the epistemiological approach of critical realism within which this thesis is grounded where knowledge is partial and therefore progressive (Ellaway et al., 2020), the current management paradigm was questioned, as proposed by *the revolutionary theory* of Thomas Kuhn (Chapter 3, Figure 3.2) (Kuhn, 2012). The work of this thesis therefore sought to explore whether currently accepted views about the benign nature of the natural history of patients with IC was indeed consistent with current observations. Important differences in risk factor prevalence among different populations of patients with IC were highlighted in Study 3, emphasising that prognoses between patient populations are also likely to differ due to the association between risk factors and outcome (V. Aboyans et al., 2018; Kollerits et al., 2008). Anomalies within the current accepted paradigm of predicted low risk to limb among patients with IC were therefore exposed, motivating the author to progress to the next phase within the *revolutionary theory* (Gutting, 1980) by providing further evidence of discrepancies between the accepted notion of a benign prognosis and what is observed through conducted studies.

This new evidence was provided in study 4 (a two-year observational prospective study) where a limb threatening prognosis was exposed among IC patients, highlighting what is described by Thomas Kuhn (Kuhn, 2012) a *model crisis.* This phase within the *revolutionary theory* denotes the exposure of a discrepancy between the accepted current paradigm of a benign prognosis, where 5-10% develop CLI within 5 years (Dormandy & Murray, 2011; Norgren et al., 2007) and the observed evidence (more than 23% developed CLI within 2 years). To the best of the author's knowledge, this is the first study to report such a high rate of deterioration, possibly due to different characteristics of recruited participants between studies (Zieliński et al., 2017) and methodological differences applied in this study to minimise biases which have underestimated progression in previous works (Mizzi et al., 2019; B. Sigvant et al., 2016), as discussed in further detail in Chapter 4. These results have important and meaningful clinical implications which denote the importance to focus not only on reducing cardiovascular risk at initial diagnosis of IC, as currently recommended (Stewart et al., 2017; Velescu et al., 2017), but to also on the high risk of lower limb morbidity documented in this thesis.

Therefore, in line with the theory of Thomas Kuhn's advancement in medicine (Kuhn, 2012) the evidence produced through this thesis indicates the need for a new perspective in the management approach for the patient presenting with IC. The diversity in patient characteristics and high rate of deterioration to CLI demonstrated in this research, indicates that at initial diagnosis, a more individualised approach is warranted, shifting away from the current recommended conservative management approach to the vast majority of patients (M. S. Conte et al., 2019). As explained in further detail below, a novel predictive model proposed in this thesis may make this possible, moving towards a selected individualised approach model based on the estimated prognostic risk estimated at initial diagnosis.

8.3 Proposing a novel patient-specific predictive algorithm

Currently, for the patient with IC, the clinical decision on whether to proceed to an intervention or not remains arbitrary, since definite recommendations detailing specified patient characteristics are not yet available (Norgren et al., 2007). This is because there is no clinical data which may guide the physician to accurately predict risk of deterioration for the individual patient (M. S. Conte et al., 2019). In order to provide this knowledge and support the shift to a more individualised approach, this thesis proposes a clinical patient-specific predictive model based on the prognostic risk factors for significant deterioration identified in study 4 (Chapter 7, section 7.4.8). The novel predictive model, which combines the risk of the identified prognostic factors, was developed for risk stratification at initial diagnosis of IC, with the intention of allowing for an informed clinical decision when choosing the best therapeutic approach in the individual patient. The proposed clinical predictive model incorporates haemodynamic data that can easily be used in an outpatient setting and may allow the clinician to identify the risk category for deterioration to CLI of the patient in a timely manner. Once the risk of progression to CLI is estimated, the clinician can then consider life expectancy and patient preferences in the clinical decision for revascularisation.

As described in Chapter seven, by applying two selected levels of haemodynamic cut-off points, the novel predictive model identifies patients with IC who are at risk of deterioration and enables the categorisation as i] requiring prompt evaluation for revascularisation *or* ii] requiring close haemodynamic monitoring. As shown in Chapter seven, the predictive model demonstrates a 'good' level of discriminating capacity of 0.82 (AUROC statistic) (Unal, 2017), indicating that it may be a viable tool for diagnosing risk among IC patients.

8.3.1 Patients requiring prompt evaluation for revascularisation

The predictive model identifies patients who are at high risk of deteriorating to CLI within 2 years and who may possibly benefit from **prompt evaluation for revascularisation** by applying the combined algorithm of –

ABPI ≤0.44, TBPI of ≤0.18 and IPA disease

While the discriminating capacity of the model is high, determined by the ROC statistic of 0.82, the haemodynamic cut-off points have a high specificity (98% for ABPI ≤0.44 and 96% for TBPI of ≤0.18) but low sensitivity (19% and 24% respectively). Although ideally both sensitivity and specificity should be close to 100%, it is often difficult to achieve in clinical practice (Lutkenhoner & Basel, 2013). Since a positive outcome obtained by a predictive model with high specificity may have significant therapeutic consequences (Trevethan, 2017), as in our case, possibly invasive intervention, it is justified to sacrifice sensitivity for specificity, which is an accepted method applied in diagnostic predictive models (Lutkenhoner & Basel, 2013). A positive outcome of this proposed predictive model corroborates the hypothesis that the investigated patient has a high probability of developing CLI within less than two years with a specificity of >96%, hence potentially providing enough knowledge to support the clinical decision for preventive revascularisation.

It is understood that the low sensitivity of this algorithm within the model may result in a high false-negative rate (Trevethan, 2017). However, it is emphasized that when the sensitivity of a predictive model is low, the test is most useful when applied to a patient population who were selected based on results of previous more unspecific tests (Lutkenhoner & Basel, 2013), a situation which is precisely relevant within the context of the current proposed application. This means that when patients do not fall within this high risk category, it is not a strong enough reason to rule out risk of deterioration. To account for this, an adjunct second level of haemodynamic cut-off points have been identified, this time favouring sensitivity over specificity as described in section 8.3.2.

8.3.2 Patients who would benefit from close haemodynamic monitoring

The risk prediction model for deterioration can be applied to categorise patients who are at risk of deteriorating to CLI and who would benefit from **close haemodynamic monitoring** by applying the following algorithm -

ABPI ≤0.64, TBPI of ≤0.39 and IPA disease.

When identifying the cut-off points for this category, the point closest to 0 method was applied to favour sensitivity over specificity and identify as many patients at risk as possible, while acknowledging the possibility of including false positive patients (McNamara & Martin, 2018). This method is justified since the outcome of applying this algorithm within the predictive model is close haemodynamic monitoring and does not inflict any therapeutic risk (Trevethan, 2017). A positive outcome of this categorised predicted risk corroborates the hypothesis that the investigated patient has a high probability of developing CLI within two years with a sensitivity of 78%. In view of this, it is proposed that patients within this category should be included in a close haemodynamic monitoring program in an outpatient setting so that any minimal deterioration can be detected immediately and a direct referral system for possible intervention can be implemented promptly.

Until now, this is the first predictive model to be developed to predict risk of deterioration to CLI among patients with IC. Other groups (B. L. Bendermacher et al., 2007; B. L. Bendermacher et al., 2006; Grau et al., 2013; Ramos et al., 2011; Y. Zhan et al., 2016) have proposed algorithms to identify patients at risk of developing PAD among the general population, but none have focused on symptomatic PAD and the risk of lower limb morbidity, hence the results of this research cannot be compared. Similar to the method employed in this thesis, these published predictive algorithms were based on predictors identified through regression models and applied AUROC analysis as a method of assessing model performance. In comparison, the proposed predictive model for CLI (AUROC 0.82), yielded better discriminating capacity than previously published models for PAD which have been recommended for clinical use as PAD surveillance models, with AUROC of 0.76 (Ramos et al., 2011) and 0.61 (Duval et al., 2012). This is suggestive that the current proposed predictive model for CLI is a promising tool for risk prediction among patients with IC.

It is acknowledged that further investigations are needed to assess external validation of this proposed predictive model and also to analyse the long-term impact it may have on patient outcomes. Nevertheless, new knowledge gained from this research has provided further insight into the prognosis of the patient with IC. The application of this novel predictive model may potentially assist in risk prediction for CLI development and allow for a timely intervention in those who may potentially deteriorate, reducing the risk of adverse lower limb events and morbidity in this population. Consistent with *the revolutionary theory* for advancement in medicine (Kuhn, 2012), these findings thus provide a foundation for a paradigm shift in the management of IC, applying a new perspective of an individualised approach.

8.4 Shifting towards an individual approach for the management of IC

In view of the evidence presented in this thesis, a paradigm shift in the management of patients with IC, from a conservative approach for the vast majority of patients to a more individualised approach by identifying those who are at higher risk at presentation stage, is being proposed. A new concept of predictive diagnosis, using the clinical predictive model proposed in this work, where the individual predisposition for potentially developing CLI is identified early, thus allowing for targeted prevention strategies, may be a promising approach against limb threatening deterioration in stratified patient groups.

The shift to a more individual approach, also known as personilised medicine, emerges from the field of oncology utilising genetic information (Gil et al., 2018) and has been applied in other medical specialties (Hays, 2019) such as rheumatology (Sirotti et al., 2017), neurology, and cardiovascular disease (Lee et al., 2012). In wound healing, for example, innovative concepts using predictive and personalised medicine have been proposed, by applying knowledge on individual risk factors, functional interrelationships, causality and predictive diagnosis (Avishai et al., 2017).

In personalised medicine, the medical model proposes that clinical decisions, practices and interventions are tailored to the individual patient based on their predicted response or risk of disease, aimed to deliver timely targeted prevention (Vogenberg et al., 2010). While it is argued that medicine has always been personalised, where each clinician tries to find the best possible treatment for the patient at hand (Avishai et al., 2017), the personalised medicine approach proposes the use of prognostic data to aid predictive diagnosis and guide clinical decisions,

possibly allowing for early preventive strategies. It is believed that this approach also provides improved efficiency in healthcare in terms of better and safer therapy for patients, reduced treatment lengths and hence reduced costs (Lee et al., 2012).

The same principle is being proposed here, following the evidence emerging from this thesis, where the concept of a more tailored approach is also applied in the management of the patient with IC. While it is acknowledged that further research may be required to change perspectives in the management of a disease, in view of the findings of this work, it may be plausible to propose a paradigm shift from a conservative approach to the majority of patients into a selected individual approach based on predictive diagnosis. It is hoped the proposed paradigm shift in management of IC, where the patient's individual predisposition to adverse events is addressed, may limit deterioration rates to CLI while still in time to decrease morbidity and mortality rates in patients with IC.

8.4. 1 The impact on the healthcare system

The management of PAD is recognised as an area for potential improvement, both in terms of diagnosis and in terms of medical therapy (Argyriou et al., 2013). In primary care, evidence shows that this condition is undertreated and underdiagnosed (Mohler et al., 2008), while in secondary care, in areas of clinical ambiguity, such as whether to revascularise a patient with IC at initial diagnosis, there is significant variation in choice of management (Birkmeyer et al., 2013; Soden et al., 2017). Despite efforts by treating physicians, variation in management has been associated with inefficient utilization of resources and suboptimal outcomes (Vogel et al., 2009). Currently increasing emphasis is placed within healthcare systems for efficient utilisation of resources while simultaneously improving outcomes (Birkmeyer et al., 2013). This has become more important in current times, as the longevity of the population increases (Podesta et al., 2019) and the healthcare budget continues to consume ever-increasing proportions of the nations' budgets (Azzopardi Muscat et al., 2017). This work and recommendations derived from this thesis, leading to the proposal of a paradigm shift in the management of IC, may not only improve outcomes among patients with IC but may also have a positive impact on current healthcare efficiency.

Furthermore, critical limb ischaemia has a significant socioeconomic impact due to the associated decrease in quality of life, decreased employment ability, possible

institutionalisation and substantial burden on the patient's emotional and social well being (Duff et al., 2019). Improving outcomes and reducing the risk of deterioration to CLI and its clinical consequences may therefore not only have a positive humanistic impact but also improve the socioeconomic and financial challenges.

As discussed in section 8.3, implementing a more individualised approach to management of patients with IC based on predictive diagnosis, may improve focus of secondary care resources on patients who would benefit most from interventional management. Early revascularisation (both endovascular and open surgery/ lower extremity bypass) together with appropriate medical therapy and exercise, has been shown to improve long-term outcomes in patients with IC (Fakhry et al., 2018; Malgor et al., 2015; Pandey et al., 2017). Open surgery, although associated with higher peri-operative risks than endovascular interventions, results in longer patency and a fast improvement of blood flow (Malgor et al., 2015). In patients with IC who have involvement of small caliber arteries, such as infrapopliteal arteries (Lorbeer et al., 2018), lower extremity bypass is the preferred management strategy (M. S. Conte et al., 2015), while endovascular procedures in diabetic patients with infrapopliteal PAD is associated with poor long-term outcomes (Neupane et al., 2018). This is particularly relevant within the context of the current proposed predictive model where it is suggested that early intervention should be considered in patients at risk of CLI based on the haemodynamic parameters and presence of infrapopliteal artery disease. If long-term benefits are to be achieved in these patients, timely intervention is of importance before deterioration of disease and other comorbidities (Ferrari et al., 2004; Wolosker et al., 2003). This approach in selected patients may result in less need of re-intervention (M. S. Conte et al., 2015), improved utilization of hospital resources due to more targeted interventions (Simons et al., 2012), more efficient healthcare systems (Devine et al., 2016), sustained improved physical function and most importantly, better health related quality if life for the affected patient (Malgor et al., 2015).

Although a cost-benefit analysis would be required to ascertain this, the implementation of a haemodynamic monitoring program for patients with IC may also reduce costs in secondary care. Referrals for haemodynamic analysis within a primary care facility, as shown in study 2, may reduce rates of misdiagnosis and associated wrong referrals from primary care for secondary management (Mizzi et al., 2018), while also improving efficiency of timely referrals based on objective haemodynamic reports. The usefulness of ABPI as a marker for both risk of lower limb morbidity (V. Aboyans et al., 2006; M. H. Criqui et al., 2008) and also mortality

(Hyun, Forbang, Allison, Denenberg, Criqui, & Ix, 2014) has been previously reported. However, up till now this has not been translated into the necessity of close haemodynamic monitoring in patients with IC. In this thesis cohort, apart from the participants who deteriorated to CLI, a further 27% experienced significant haemodynamic decline of a median of 0.25 in ABPI and 0.24 in TBPI within two years, both markers of imminent development of CLI (Norgren et al., 2007) and cardiovascular morbidity (M. H. Criqui et al., 2008). The high proportion of significant haemodynamic deterioration during a relatively short time documented in the current research, emphasises the importance of close monitoring of patients who are diagnosed with IC and managed conservatively. Non-invasive haemodynamic assessment by an experienced practitioner such as a podiatrist, may provide an objective measure for IC diagnosis (Mizzi et al., 2018), while also categorising patients within the currently proposed predictive model.

Currently, since the general approach for patients with IC is conservative management, haemodynamic monitoring is not a justified or recommended practice. On the other hand, the current proposal provides clear justification for close haemodynamic monitoring of IC patients so that if deterioration is detected, timely referrals for immediate intervention in patients with a high predisposition for adverse events can be implemented, potentially reducing morbidity rates. By applying the proposal in this thesis, there is potential that health practitioners trained in haemodynamic assessment, working in liaison with vascular consultants may contribute to a highly cost-effective approach, improving health efficiency and reducing health costs associated with morbidity in patients with IC.

Acceptance of new evidence and implementing changes in management guidelines by professional societies is known to be a slow and difficult process and facilitators associated with improved uptake of guidelines may need to be involved (Kastner et al., 2015). The work in this thesis has clearly shown that failure to intervene in the patients identified as being in the high risk of deterioration may result in worse outcomes, both in terms of limb salvage and quality of life (Duff et al., 2019). The next phase of this work, alongside the external validation, is to develop an implementation strategy which would include relevant stakeholders, to facilitate the translation of the findings of this research to be adopted in routine clinical practice and enhance management in this patient cohort.

While the interpretation of this work needs to be considered in relation to the population studied, it has highlighted the fact that the prognosis of IC can be more threatening than previously thought, suggesting that management guidelines for management of this disease may need to be revised and reconsidered. As shown in this research, patients with a higher risk of deterioration may be identified at an early stage, potentially guiding the clinical decision for an invasive approach to treatment in selected cases. Risk categorisation of patients with IC at initial presentation and a more individualised approach to treatment may be beneficial in the patients with high risk of developing CLI. The importance of developing treatment strategies for the patient with IC based on disease severity, defined by haemodynamic analysis and anatomic pattern of the disease is highlighted, aiming to improve outcomes in the population of patients with IC.

8.5 Potential limitations

The limitations pertaining to each study were discussed in the relevant chapters (Chapters 4,6, and 7). However, as with all research studies, some biases related to the overall research need to be acknowledged. Bias is defined as any trend or deviation from the truth in data collection, analysis or interpretation (Simundic, 2013). In order to minimise the deviation from the truth, potential sources of bias need to be identified and the researcher must address them where possible. There are three types of bias- selection bias, information bias and confounding bias which, to some degree, are present in all types of medical research (Grimes & Schulz, 2002).

8.5.1 Selection bias

Selection bias refers to a situation where the sample studied is not representative of the population with the phenomenon of interest (Hren & Lukic, 2006). Often, due to resource and time constraints, the whole population cannot be studied therefore, a sample is recruited, and this sample needs to be representative of the population for acceptable external validity.

In the case of this research, the identified eligible population with IC in Malta who were referred to the vascular clinic was recruited with almost negligible attrition rate or loss to follow-up. This increased the likelihood of better validity of the results representing typical patients seen by vascular specialists. However, it is acknowledged that this study population is a selected group of patients referred to a vascular clinic and findings may differ in a population

of unselected patients with symptomatic PAD. It is possible that patients with IC adapt their lifestyle in such a way that they do not experience debilitating symptoms (Szymczak et al., 2018) and therefore do not feel the need to seek medical help. While efforts were made at the initial stages of this work (Study 2) to encourage that all patients visiting the GP clinic with IC were referred, this group of patients may be under-represented in this study. A larger population study of patients with PAD which includes unselected symptomatic patients could provide a broader insight on the influence of patient characteristics on the progression of PAD.

8.5.2 Information bias (Reporting bias)

During the recruitment process, patients were asked to report the severity of their symptoms and claudication distance through self-reporting. It could be that over-emphasis of their symptoms could occur in order to stress the importance of their ailment to be seen sooner by the vascular specialist. In order to reduce this possibility, a previously validated questionnaire (Walking impairment questionnaire) was used which took into account the perceived walking impairment related to the activity in the past week and was found to effectively reflect walking distances in daily life (Frans et al., 2013).

Potentially under-reporting or non-disclosure of conditions can also occur, particularly in self-reporting health risk behaviours which have unattractive social associations such as alcoholism, drug abuse and smoking (Crutzen & Göritz, 2010). This gives rise to social desirability bias where participants tend to distort self-reports to provide responses that, in their view, are more consistent to social norms (Paulhus et al., 1991). Patients may, as a result, under-report their smoking habits, which would result in a reduced perceived impact of smoking on the outcome. Methods to reduce social desirability bias include the use of indirect questions and re-assuring the patient that no personal judgment will be applied. These methods were therefore adopted in this work with the aim of recording truthful measures.

Improvement of symptoms and haemodynamic parameters could have been due to the development of collateral circulation (Traupe et al., 2013; Yang et al., 2008), metabolic adaptation of ischaemic muscle (Jansson et al., 1988) or gait adaptation by the patient to favour non-symptomatic muscle groups (Szymczak et al., 2018). It was not possible to evaluate these factors in this research due to the invasive nature of some measures and it is therefore not known whether any of these may have contributed to self-reported symptomatic improvement.

Further research related to the development of collateral circulation may help improve the understanding of arteriogenesis and its influence on symptom severity in this group of patients.

8.5.3 Confounding bias

Confounding bias can occur when one or more risk factors can be associated both with the characteristic of interest and with the outcome, but not being necessarily the cause of the adverse event (Ramirez-Santana, 2018).

Confounding factors were identified in the initial stages of the design of the study and these were included in the regression analysis in order to control for their effects. There may have been unmeasured confounding factors or mediating factors such as anxiety (Smolderen et al., 2009) which were not measured in this study. However, all medications were recorded and further investigations to analyse the effect of possible confounding conditions which can be identified through the prescribed medications was employed.

Patients recruited for this study were not precluded from treatment and advice, therefore conventional conservative therapy such as the commencement of aspirin and statins, advice to exercise and to stop smoking were implemented. These factors could have influenced the progression of PAD in the recruited cohort. One way to control confounding effects is by applying multivariate techniques (Grimes & Schulz, 2002). For this reason, to control for such possible confounding factors, any changes in treatment or life-style were recorded during the 12 month and 24-month follow-up and were included in the multinomial analysis. While restriction of these confounding variables would be the best way to avoid them in a study, it was not possible within the context of the patient with IC as this would be unethical. Therefore, the findings of this work do not describe the natural history of PAD progression, since improvement may be attributed to the prescribed treatment. Nevertheless, these findings reflect the progression of PAD in typical patients with IC in the real world and current health systems.

8.6 Implications for clinical practice

The studies within this work have three important outcomes:

i) the provision of evidence of diverse risk factor prevalence at initial diagnosis among different populations with IC

ii) the provision of evidence of a worse limb threatening prognosis among patients with IC than previously assumed

iii) the development of a predictive model that allows for early identification of those who are at a higher risk of developing CLI.

Together, these outcomes have led to potential implications to practice discussed below.

Recommended guidelines for the management of the patient with IC and previous research is generally focussed on addressing cardiovascular risk of major adverse events. Since a benign lower limb prognosis was always assumed, prevention of lower limb morbidity received limited attention. The data obtained from this two-year study shows evidence of significant lower limb deterioration within a relatively short time. The implications are important and clinically meaningful and may change the perspective of IC management in terms of focussing more on improving lower limb perfusion at an early stage in order to limit the risk of developing CLI when the patient is still fit and can safely undergo revascularisation.

The evidence demonstrated in this work, showed that diverse populations have different risk factor profiles and different patient characteristics, which may translate into a limb threatening prognosis when presenting with IC. It is therefore recommended that a more individual and personalised approach to management of the condition should be employed, taking into consideration the independent risk factors identified in this work, namely ABPI and TBPI at initial diagnosis, the presence of infrapopliteal artery disease and HbA1c levels. If patients are identified as high risk for developing CLI, this information can help support alternative clinical decisions for active preventative measures, rather than applying a conservative approach until deterioration occurs.

Early identification of those who are at a higher risk of deterioration, by using the proposed predictive model, would allow better informed clinical decision-making towards an early preventive treatment strategy. Identifying the individual's predisposition to developing CLI would help in formulating a tailored approach to management of the condition, hopefully reducing the risk of future lower limb morbidity which is known to significantly increase mortality risk. This would allow for early preventive intervention in a patient with IC, which is associated with lower morbidity and mortality rates than when the patient potentially deteriorates to CLI. Further research assessing the long-term benefits of applying this approach is however required.

Of note, this research has corroborated the importance of haemodynamic analysis in patients with PAD, but has also shown an increased significance of these parameters as they can be utilised as prognostic tools for early identification of patients at risk of CLI in the future. It is therefore recommended that all patients presenting with IC should be referred for haemodynamic analysis for diagnosis and risk categorisation. Once a patient is diagnosed with IC due to PAD, frequent haemodynamic monitoring is recommended as any deterioration may be detected promptly, allowing for immediate referral and avoidance of delay. An increase in haemodynamic monitoring may mean an increased requirement in education among health professionals in haemodynamic assessment training since accuracy in the use of Doppler ultrasound is skill-dependent (Kim et al., 2020; Tehan & Chuter, 2015). It is thought that this approach would minimise health costs as it works towards a more targeted and efficient referral system to vascular surgery for those who are at a higher risk of deterioration. Haemodynamic assessment results should be available to primary care GPs to assist in diagnosis and to the vascular surgeon for easier triaging of referrals and risk assessment. This would also help in a more objective diagnostic method for IC among primary health GPs which will potentially improve referral patterns and medical management of the patient with IC.

8.7 Recommendations for future research

The application of the predictive model as a tool to identify patients with IC who are at risk of developing CLI requires further investigation. Sensitivity and specificity trials on other cohorts are required to further validate the application of this model. Further research on with regards to inclusion of other variables may be implemented to improve the sensitivity of the model. If data is available, preliminary retrospective studies on cohorts from other countries and different

health systems could be performed in the initial phase, which could be extended to prospective cohort studies in different populations with differing risk factor prevalence at baseline in the subsequent phase. This would determine the external validity of the predictive model in varying populations.

Once this is established, following the '*model revolution'* phase, the new paradigm requires agreement from key experts to initiate the shift in management of patients towards becoming '*normal science'*. Expert consensus to gain agreement on recommendations could be sought through a Delphi process (Humphrey-Murto et al., 2017), engaging key representatives of international and national vascular associations and organizations involved in the development of practice guidelines related to the management of intermittent claudication. The Delphi technique would be ideal as it is a structured process using 'rounds' of questionnaires sent to selected experts or stakeholders in the field, until consensus to adopt an individualised approach using the proposed predictive model is reached. It allows participation of individuals from geographically diverse locations, avoids domination of consensus by one or a few experts and synthesises the knowledge of the whole group (Boulkedid et al., 2011).

The implementation of a paradigm shift in the management of patients with IC to a more individual approach, would require further investigation to determine its feasibility and effectiveness. By identifying patients who are at a higher risk of deterioration, the findings from this thesis provide a foundation for future studies to investigate how best to manage such patients so that their outcomes are improved. It is not yet known whether such patients would benefit from closer follow-up or earlier revascularisation. However, close haemodynamic monitoring, which is a main recommendation from this thesis, is important for identifying those who fail to respond to conservative management. Comparative effectiveness trials investigating different approaches to management of the patient with IC are required. A randomised controlled trial would ideally be designed where a group of patients would be managed according to current guidelines while the second group would be managed by applying the patient-specific predictive models for risk categorisation, employing an individual approach to treatment, depending on the presence or absence of the independent risk factors identified in this thesis. The impact of implementing an individual approach to management of IC on patient outcomes could therefore be compared and its effectiveness could be established by assessing long-term outcomes.

Following the unexpected findings in Study 2 related to the referral pathways employed by primary care GPs, in Malta, it would be interesting to assess whether the implementation of the new claudication clinic had an impact on the service pathways for the patient with IC. This could be assessed through a prospective analysis of patients referred to the vascular specialist clinic at least two years from the inception of the claudication clinic in order to keep to a minimum any patients who had been referred prior to this date. Outcomes of interest such as time from referral to appointment, diagnostic processes employed and number of inappropriate referrals could be assessed and compared to results obtained in study 2. This would allow for the analysis of the impact of such a clinic on specialist vascular care units located within the hospital, helping to establish better protocols for patients with PAD within primary care.

8.8 Conclusion

This research sought to identify risk factors of deterioration to CLI and to explore the prognosis of the patient with IC in terms of lower limb outcomes and haemodynamic progression of PAD. The findings challenge currently held views of the benign prognosis of IC and expose a two-year limb threatening prognosis in more than half of the study participants, indicating the potential need for a paradigm shift in the current management approach. Important predictors for deterioration to CLI were identified and a novel patient-specific model was proposed for risk stratification to support clinical decision making when selecting the optimal treatment approach for the individual patient at initial presentation.

This work was completed through the design of four sequential studies, founded in critical realist epistemological approach. Initial work involved two retrospective studies which questioned current knowledge related to the haemodynamic progression of PAD in patients with IC and the current local diagnostic and referral processes employed in this group of patients. The findings highlighted the current clinical uncertainty associated with lower limb prognosis in IC and laid the groundwork for the main study. The third and fourth studies provided evidence that lower limb prognosis is not as benign as previously assumed and that a shift from a generally conservative management approach to a more individualised approach at initial diagnosis may be appropriate. Potentially useful predictive risk factors for deterioration to CLI were identified and a clinical prediction model which helps identify patients at very high risk of developing CLI is proposed.

The clinical prediction model may potentially be utilised to guide the clinical decision for selection of treatment strategy at initial diagnosis of IC. This model may help the clinician categorise the patient into high risk of CLI, possibly requiring evaluation for preventive intervention, or moderate risk, requiring close haemodynamic monitoring. To date, no prediction model for assessing risk of deterioration in patients with IC has been developed therefore this work is novel and provides a foundation for further studies to evaluate how to best manage these categories of patients to improve their outcomes. As such, close haemodynamic monitoring is an important recommendation from this thesis as it is important for timely identification of those who fail to respond to conservative management. Results from this study may support a radical change in the management of this patient group, potentially allowing prompt intervention in selected patients in order to reduce morbidity rates in this population.

References

2011 WRITING GROUP MEMBERS, 2005 WRITING COMMITTEE MEMBERS, & ACCF/AHA TASK FORCE MEMBERS. (2011). 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): A report of the american college of cardiology Foundation/American heart association task force on practice guidelines. *Circulation, 124*(18), 2020-2045. https://doi.org/10.1161/CIR.0b013e31822e80c3 [doi]

Abouhamda, A., Alturkstani, M., & Jan, Y. (2019). Lower sensitivity of ankle-brachial index measurements among people suffering with diabetes-associated vascular disorders: A systematic review. *SAGE Open Medicine, 7*, 2050312119835038.

Aboyans, V., & Jean-BaptisteRicco, M. E. (2017). Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the european society for vascular surgery (ESVS). *Rev Esp Cardiol (Engl Ed),*

Aboyans, V., Criqui, M. H., Abraham, P., Allison, M. A., Creager, M. A., Diehm, C., Fowkes, F. G. R., Hiatt, W. R., Jönsson, B., & Lacroix, P. (2012). Measurement and interpretation of the ankle-brachial index: A scientific statement from the american heart association. *Circulation, 126*(24), 2890-2909.

Aboyans, V., Ho, E., Denenberg, J. O., Ho, L. A., Natarajan, L., & Criqui, M. H. (2008). The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. *Journal of Vascular Surgery, 48*(5), 1197-1203.

Aboyans, V., & Lacroix, P. (2007). Regarding:"A modified calculation of ankle-brachial pressure index is far more sensitive in the detection of peripheral arterial disease". *Journal of Vascular Surgery, 46*(3), 617-618.

Aboyans, V., Ricco, J., Bartelink, M. E., Björck, M., Brodmann, M., Cohnert, T., Collet, J., Czerny, M., De Carlo, M., & Debus, S. (2018). 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the european society for vascular surgery (E. *European Heart Journal, 39*(9), 763-816.

Aboyans, V., Criqui, M. H., Denenberg, J. O., Knoke, J. D., Ridker, P. M., & Fronek, A. (2006). Risk factors for progression of peripheral arterial disease in large and small vessels. *Circulation, 113*(22), 2623-2629. https://doi.org/CIRCULATIONAHA.105.608679 [pii]

Aboyans, V., Sevestre, M. A., Desormais, I., Lacroix, P., Fowkes, G., & Criqui, M. H. (2018). Epidemiology of lower extremity artery disease. [Epidemiologie de l'arteriopathie des membres inferieurs] *Presse Medicale (Paris, France : 1983), 47*(1), 38-46. https://doi.org/S0755-4982(18)30013-7 [pii]

ADVANCE Collaborative Group. (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine, 358*(24), 2560-2572.

Aerden, D., Massaad, D., von Kemp, K., van Tussenbroek, F., Debing, E., Keymeulen, B., & Van den Brande, P. (2011). The ankle–brachial index and the diabetic foot: A troublesome marriage. *Annals of Vascular Surgery, 25*(6), 770-777.

AlHamzah, M., Eikelboom, R., Hussain, M. A., Syed, M. H., Salata, K., Wheatcroft, M., Verma, S., & Al-Omran, M. (2019). Knowledge gap of peripheral artery disease starts in medical school. *Journal of Vascular Surgery, 70*(1), 241-245. e2.

Allen, J., Oates, C. P., Henderson, J., Jago, J., Whittingham, T. A., Chamberlain, J., Jones, N. A., & Murray, A. (1996). Comparison of lower limb arterial assessments using color-duplex ultrasound and ankle/brachial pressure index measurements. *Angiology, 47*(3), 225-232.

Allison, M. A., Criqui, M. H., McClelland, R. L., Scott, J. M., McDermott, M. M., Liu, K., Folsom, A. R., Bertoni, A. G., Sharrett, A. R., & Homma, S. (2006). The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the multi-ethnic study of atherosclerosis (MESA). *Journal of the American College of Cardiology, 48*(6), 1190-1197.

Alshaikh, H. N., Hicks, C. W., DiBrito, S. R., Zarkowsky, D. S., Siracuse, J. J., & Malas, M. B. (2019). Elective infrainguinal lower extremity bypass for claudication is associated with high postoperative intensive care utilization. *Journal of Vascular Surgery, 69*(6), 1863-1873. e1.

Althouse, A. D., Abbott, J. D., Forker, A. D., Bertolet, M., Barinas-Mitchell, E., Thurston, R. C., Mulukutla, S., Aboyans, V., Brooks, M. M., & BARI 2D Study Group. (2014). Risk factors for incident peripheral arterial disease in type 2 diabetes: Results from the bypass angioplasty revascularization investigation in type 2 diabetes (BARI 2D) trial. *Diabetes Care, 37*(5), 1346-1352. https://doi.org/10.2337/dc13-2303 [doi]

Altman, D. G. (2001). Systematic reviews of evaluations of prognostic variables. *BMJ (Clinical Research Ed.) - 8900488, 323*(7306), 224-228. https://doi.org/10.1136/bmj.323.7306.224 [doi]

Altman, D. G., & Royston, P. (2006). The cost of dichotomising continuous variables. *BMJ (Clinical Research Ed.), 332*(7549), 1080. https://doi.org/332/7549/1080 [pii]

Alvesson, M., & Skoldberg, K. (2009). Positivism, social constructionism, critical realism: Three reference points in the philosophy of science. *Reflexive Methodology: New Vistas for Qualitative Research,* , 15-52.

Amarenco, P., Labreuche, J., Lavallee, P., & Touboul, P. J. (2004). Statins in stroke prevention and carotid atherosclerosis: Systematic review and up-to-date meta-analysis. *Stroke, 35*(12), 2902-2909. https://doi.org/01.STR.0000147965.52712.fa [pii]

American College of Cardiology Foundation, American Heart Association Task Force on Performance Measures, American College of Radiology, Society for Cardiac Angiography and Interventions, Society for Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, Olin, J. W., Allie, D. E., Belkin, M., Bonow, R. O., Casey, D. E.,Jr, Creager, M. A., Gerber, T. C., Hirsch, A. T., Jaff, M. R., Kaufman, J. A., Lewis, C. A., . . . Zheng, Z. J. (2010). ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease. A report of the american college of cardiology Foundation/American heart association task force on performance measures, the american college of radiology, the society for cardiac angiography and interventions, the society for interventional radiology, the society for vascular medicine, the society for vascular nursing, and the society for vascular surgery (writing committee to develop clinical performance measures for peripheral artery disease). developed in collaboration with the american association of cardiovascular and pulmonary rehabilitation; the american diabetes association; the society for atherosclerosis imaging and prevention; the society for cardiovascular magnetic resonance; the society of cardiovascular computed tomography; and the PAD coalition. endorsed by the american academy of podiatric practice management. *Journal of Vascular Surgery, 52*(6), 1616-1652. https://doi.org/10.1016/j.jvs.2010.10.065 [doi]

American College of Cardiology Foundation, American Heart Association Task Force, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Surgery, Rooke, T. W., Hirsch, A. T., Misra, S., Sidawy, A. N., Beckman, J. A., Findeiss, L. K., Golzarian, J., Gornik, H. L., Halperin, J. L., Jaff, M. R., Moneta, G. L., Olin, J. W., Stanley, J. C., . . . Zierler, R. E. (2011). 2011 ACCF/AHA focused update of the guideline for the

management of patients with peripheral artery disease (updating the 2005 guideline). *Vascular Medicine (London, England), 16*(6), 452-476. https://doi.org/10.1177/1358863X11424312 [doi]

American Diabetes Association. (2018). 2. classification and diagnosis of diabetes: Standards of medical care in diabetes—2018. *Diabetes Care, 41*(Supplement 1), S13-S27.

Amighi, J., Sabeti, S., Schlager, O., Francesconi, M., Ahmadi, R., Minar, E., & Schillinger, M. (2004). Outcome of conservative therapy of patients with severe intermittent claudication. *European Journal of Vascular and Endovascular Surgery, 27*(3), 254-258.

Anand, S. S., Caron, F., Eikelboom, J. W., Bosch, J., Dyal, L., Aboyans, V., Abola, M. T., Branch, K. R., Keltai, K., & Bhatt, D. L. (2018). Major adverse limb events and mortality in patients with peripheral artery disease: The COMPASS trial. *Journal of the American College of Cardiology, 71*(20), 2306-2315.

Andreozzi, G., & Martini, R. (2002). The fate of the claudicant limb. *European Heart Journal Supplements, 4*(suppl B), B41-B45.

Aquino, R., Johnnides, C., Makaroun, M., Whittle, J. C., Muluk, V. S., Kelley, M. E., & Muluk, S. C. (2001). Natural history of claudication: Long-term serial follow-up study of 1244 claudicants. *Journal of Vascular Surgery, 34*(6), 962-970.

Arboix, A., Tarruella, M., Garcia-Eroles, L., Oliveres, M., Miquel, C., Balcells, M., & Targa, C. (2004). Ischemic stroke in patients with intermittent claudication: A clinical study of 142 cases. *Vascular Medicine (London, England), 9*(1), 13-17.

Argyriou, C., Saleptsis, V., Koutsias, S., & Giannoukas, A. D. (2013). Peripheral arterial disease is prevalent but underdiagnosed and undertreated in the primary care setting in central greece. *Angiology, 64*(2), 119-124.

Armstrong, E. J., Wu, J., Singh, G. D., Dawson, D. L., Pevec, W. C., Amsterdam, E. A., & Laird, J. R. (2014). Smoking cessation is associated with decreased mortality and

improved amputation-free survival among patients with symptomatic peripheral artery disease. *Journal of Vascular Surgery, 60*(6), 1565-1571.

Avishai, E., Yeghiazaryan, K., & Golubnitschaja, O. (2017). Impaired wound healing: Facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine. *EPMA Journal, 8*(1), 23-33.

Azzopardi Muscat, N., Calleja, N., Buttigieg, S., & Merkur, S. (2017). Malta: Health system review. *Health Systems in Transition, 19*(1), 1-137.

Azzopardi, Y. M., Gatt, A., Chockalingam, N., & Formosa, C. (2019). Agreement of clinical tests for the diagnosis of peripheral arterial disease. *Primary Care Diabetes, 13*(1), 82-86.

Bartelink, M. L., Stoffers, H. E., Biesheuvel, C. J., & Hoes, A. W. (2004). Walking exercise in patients with intermittent claudication. experience in routine clinical practice. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners, 54*(500), 196-200.

Baser, O., Verpillat, P., Gabriel, S., & Wang, L. (2013). Prevalence, incidence, and outcomes of critical limb ischemia in the US medicare population. *Vasc Dis Manag, 10*(2), E26-E36.

Becker, F., Robert-Ebadi, H., Ricco, J., Setacci, C., Cao, P., De Donato, G., Eckstein, H., De Rango, P., Diehm, N., & Schmidli, J. (2011). Chapter I: Definitions, epidemiology, clinical presentation and prognosis. *European Journal of Vascular and Endovascular Surgery, 42*, S4-S12.

Behrendt, C., Sigvant, B., Szeberin, Z., Beiles, B., Eldrup, N., Thomson, I. A., Venermo, M., Altreuther, M., Menyhei, G., & Nordanstig, J. (2018). International variations in amputation practice: A VASCUNET report. *European Journal of Vascular and Endovascular Surgery, 56*(3), 391-399.

Benchimol, D., Pillois, X., Benchimol, A., Houitte, A., Sagardiluz, P., Tortelier, L., & Bonnet, J. (2009). Accuracy of ankle-brachial index using an automatic blood pressure device to detect peripheral artery disease in preventive medicine. *Archives of Cardiovascular Diseases, 102*(6-7), 519-524.

Bendermacher, B. L., Willigendael, E. M., Teijink, J. A., & Prins, M. H. (2006). Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *The Cochrane Library,*

Beresford, E. B. (1991). Uncertainty and the shaping of medical decisions. *Hastings Center Report, 21*(4), 6-11.

Bertges, D. J., Goodney, P. P., Zhao, Y., Schanzer, A., Nolan, B. W., Likosky, D. S., Eldrup-Jorgensen, J., Cronenwett, J. L., & Vascular Study Group of New England. (2010). The vascular study group of new england cardiac risk index (VSG-CRI) predicts cardiac complications more accurately than the revised cardiac risk index in vascular surgery patients. *Journal of Vascular Surgery, 52*(3), 674-683. e3.

Bevan, G. H., & White Solaru, K. T. (2020). Evidence-based medical management of peripheral artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology, 40*(3), 541-553.

Bianchi, C., Montalvo, V., Ou, H. W., Bishop, V., & Abou-Zamzam, A. M.,Jr. (2007). Pharmacologic risk factor treatment of peripheral arterial disease is lacking and requires vascular surgeon participation. *Annals of Vascular Surgery, 21*(2), 163-166. https://doi.org/S0890-5096(07)00110-0 [pii]

Bird, C. E., Criqui, M. H., Fronek, A., Denenberg, J. O., Klauber, M. R., & Langer, R. D. (1999). Quantitative and qualitative progression of peripheral arterial disease by non-invasive testing. *Vascular Medicine (London, England), 4*(1), 15-21.

Birkmeyer, J. D., Reames, B. N., McCulloch, P., Carr, A. J., Campbell, W. B., & Wennberg, J. E. (2013). Understanding of regional variation in the use of surgery. *The Lancet, 382*(9898), 1121-1129.

Bitar, F. G., & Garcia, L. A. (2010). Critical limb ischemia: An overview of the epidemiologic and clinical implications. *Vasc Dis Manag, 7*(9), 182-184.

Bland, J. M., & Altman, D. G. (1995). Multiple significance tests: The bonferroni method. *BMJ (Clinical Research Ed.), 310*(6973), 170. https://doi.org/10.1136/bmj.310.6973.170 [doi]

Blevins, A., & Wallace, S. (2010). LibGuides. evidence based practice. critical appraisal.

Bollinger, A., Breddin, K., Hess, H., Heystraten, F., Kollath, J., Konttila, A., Pouliadis, G., Marshall, M., Mey, T., & Mietaschk, A. (1981). Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. *Atherosclerosis, 38*(3-4), 339-346.

Bonaca, M. P., Scirica, B. M., Creager, M. A., Olin, J., Bounameaux, H., Dellborg, M., Lamp, J. M., Murphy, S. A., Braunwald, E., & Morrow, D. A. (2013). Vorapaxar in patients with peripheral artery disease: Results from TRA2° P-TIMI 50. *Circulation, 127*(14), 1522-1529.

Bouley, J. (1831). Claudication intermittente des membres postÃ©rieurs, dÃ©terminÃ©e par lâ€™oblitÃ©ration des artÃ¨res fÃ©morales. *Recueil MÃ©d VÃ©t, 8*, 517-527.

Boulkedid, R., Abdoul, H., Loustau, M., Sibony, O., & Alberti, C. (2011). Using and reporting the delphi method for selecting healthcare quality indicators: A systematic review. *PloS One, 6*(6), e20476.

Bowlin, S. J., Medalie, J. H., Flocke, S. A., Zyzanski, S. J., & Goldbourt, U. (1994). Epidemiology of intermittent claudication in middle-aged men. *American Journal of Epidemiology, 140*(5), 418-430.

Bowling, A. (2014). *Research methods in health: Investigating health and health services*. McGraw-hill education (UK).

Brass, E. P., & Hiatt, W. R. (2006). Review of mortality and cardiovascular event rates in patients enrolled in clinical trials for claudication therapies. *Vascular Medicine (London, England), 11*(3), 141-145.

Brodie, S. B. (1846). Lectures illustrative of various subjects in pathology and surgery.

Brooks, B., Dean, R., Patel, S., Wu, B., Molyneaux, L., & Yue, D. (2001). TBI or not TBI: That is the question. is it better to measure toe pressure than ankle pressure in diabetic patients? *Diabetic Medicine, 18*(7), 528-532.

Buchanan, N. D., Grimmer, J. A., Tanwar, V., Schwieterman, N., Mohler, P. J., & Wold, L. E. (2020). Cardiovascular risk of electronic cigarettes: A review of preclinical and clinical studies. *Cardiovascular Research, 116*(1), 40-50.

Bundo, M., Urrea, M., Munoz, L., Llussa, J., Fores, R., & Toran, P. (2013). Correlation between toe-brachial index and ankle-brachial index in patients with diabetes mellitus type 2. [Correlacion entre los indices dedo-brazo y tobillo-brazo en pacientes con diabetes mellitus tipo 2] *Medicina Clinica, 140*(9), 390-394. https://doi.org/10.1016/j.medcli.2012.03.012 [doi]

Burrel, G., & Morgan, G. (1979). Paradigms in organizational studies. *New Directions in,*

Carlson, M. D., & Morrison, R. S. (2009). Study design, precision, and validity in observational studies. *Journal of Palliative Medicine, 12*(1), 77-82.

Carman, T. L., & Fernandez, B. B.,Jr. (2000). A primary care approach to the patient with claudication. *American Family Physician, 61*(4), 1027-32, 1034.

Cascini, S., Agabiti, N., Davoli, M., Uccioli, L., Meloni, M., Giurato, L., Marino, C., & Bargagli, A. M. (2020). Survival and factors predicting mortality after major and minor lower-extremity amputations among patients with diabetes: A population-based study

using health information systems. *BMJ Open Diabetes Research & Care, 8*(1), 10.1136/bmjdrc-2020-001355. https://doi.org/e001355 [pii]

Cassar, K. (2006). Intermittent claudication. *British Medical Journal, 7576*, 1002.

Cassar, K., Bachoo, P., & Brittenden, J. (2003). The effect of peripheral percutaneous transluminal angioplasty on quality of life in patients with intermittent claudication. *European Journal of Vascular and Endovascular Surgery, 26*(2), 130-136. https://doi.org/http://dx.doi.org/10.1053/ejvs.2002.1929

Chaar, C. I. O., Gholitabar, N., Detrani, M., Jorshery, S. D., Kim, T. I., Zhuo, H., Zhang, Y., & Dardik, A. (2020). Variations in the management of claudication in a tertiary care center. *Annals of Vascular Surgery,*

Charcot, J. (1858). Sur la claudication intermittente observÃ©e dans un cas dâ€™oblitÃ©ration complÃ¨te de lâ€™une des artÃ¨res iliaques primitives. *CR Soc Biol (Paris),* 5, 225-228.

Chen, P. Y., Lawford, K. M., Shah, N., Pham, J., & Bower, V. M. (2012). Perceptions of the ankle brachial index amongst podiatrists registered in western australia. *Journal of Foot and Ankle Research, 5*(1), 19.

Chetcuti, K., Farrugia, R., & Cassar, K. (2009). GP referral letters: Time for a template. *Malta Medical Journal, 2*1(2), 26-29.

Chisalita, S. I., Wijkman, M., Davidson, L. T., Spångeus, A., Nyström, F., & Östgren, C. J. (2020). Toe brachial index predicts major acute cardiovascular events in patients with type 2 diabetes independently of arterial stiffness. *Diabetes Research and Clinical Practice, 16*1, 108040.

Chong, P. F., Garratt, A. M., Golledge, J., Greenhalgh, R. M., & Davies, A. H. (2002). The intermittent claudication questionnaire: A patient-assessed condition-specific health outcome measure. *Journal of Vascular Surgery, 3*6(4), 764-IN5.

Chowdhury, M. Z. I., & Turin, T. C. (2020). Variable selection strategies and its importance in clinical prediction modelling. *Family Medicine and Community Health, 8*(1)

Chubak, J., Pocobelli, G., & Weiss, N. S. (2012). Tradeoffs between accuracy measures for electronic health care data algorithms. *Journal of Clinical Epidemiology, 65*(3), 343-349. e2.

Chung, N. S., Han, S. H., Lim, S. H., Hong, Y. S., Won, J. H., Bae, J. I., & Jo, J. (2010). Factors affecting the validity of ankle-brachial index in the diagnosis of peripheral arterial obstructive disease. *Angiology, 61*(4), 392-396.

Cimminiello, C., Kownator, S., Wautrecht, J., Carvounis, C. P., Kranendonk, S. E., Kindler, B., Mangrella, M., Borghi, C., & PANDORA Study Investigators. (2011). The PANDORA study: Peripheral arterial disease in patients with non-high cardiovascular risk. *Internal and Emergency Medicine,* 6(6), 509-519.

Cloete, N., Kiely, C., Colgan, M. P., Haider, N., O'Neill, S., Madhavan, P., & Moore, D. (2009). Reproducibility of toe pressure measurements. *Journal for Vascular Ultrasound, 3*3(3), 129-132.

Cohn, S. L., & Giese, G. E. (2016). Perioperative cardiac risk assessment and management for noncardiac surgery. *Hospital Medicine Clinics,*

Collins, T. C., Petersen, N. J., Suarez-Almazor, M., & Ashton, C. M. (2003). The prevalence of peripheral arterial disease in a racially diverse population. *Archives of Internal Medicine, 16*3(12), 1469-1474.

Conijn, A. P., Jens, S., Terwee, C. B., Breek, J., & Koelemay, M. J. (2015). Assessing the quality of available patient reported outcome measures for intermittent claudication: A systematic review using the COSMIN checklist. *European Journal of Vascular and Endovascular Surgery, 4*9(3), 316-334.

Constans, J., Bura-Riviere, A., Visona, A., Brodmann, M., Abraham, P., Olinic, D., Madaric, J., Steiner, S., Quere, I., & Mazzolai, L. (2018). Urgent need to clarify the definition of chronic critical limb ischemia–a position paper from the european society for vascular medicine. *Vasa,*

Conte, F., Fiscon, G., Licursi, V., Bizzarri, D., D'Antò, T., Farina, L., & Paci, P. (2019). A paradigm shift in medicine: A comprehensive review of network-based approaches. *Biochimica Et Biophysica Acta (BBA)-Gene Regulatory Mechanisms,* , 194416.

Conte, M. S., Bradbury, A. W., Kolh, P., White, J. V., Dick, F., Fitridge, R., Mills, J. L., Ricco, J., Suresh, K. R., & Murad, M. H. (2019). Global vascular guidelines on the management of chronic limb-threatening ischemia. *European Journal of Vascular and Endovascular Surgery,*

Conte, M. S., Pomposelli, F. B., Clair, D. G., Geraghty, P. J., McKinsey, J. F., Mills, J. L., Moneta, G. L., Murad, M. H., Powell, R. J., & Reed, A. B. (2015). Society for vascular surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication. *Journal of Vascular Surgery, 6*1(3), 2S-41S. e1.

Conte, S. M., & Vale, P. R. (2018). Peripheral arterial disease. *Heart, Lung and Circulation, 2*7(4), 427-432.

Coyne, K. S., Margolis, M. K., Gilchrist, K. A., Grandy, S. P., Hiatt, W. R., Ratchford, A., Revicki, D. A., Weintraub, W. S., & Regensteiner, J. G. (2003). Evaluating effects of method of administration on walking impairment questionnaire. *Journal of Vascular Surgery, 3*8(2), 296-304.

Creswell, J. W., & Creswell, J. D. (2017). *Research design: Qualitative, quantitative, and mixed methods approache*s. Sage publications.

Criqui, M. H., Ho, L. A., Denenberg, J. O., Ridker, P. M., Wassel, C. L., & McDermott, M. M. (2010). Biomarkers in peripheral arterial disease patients and near-and longer-term mortality. *Journal of Vascular Surgery, 5*2(1), 85-90.

Criqui, M. H., Langer, R. D., Fronek, A., Feigelson, H. S., Klauber, M. R., McCann, T. J., & Browner, D. (1992). Mortality over a period of 10 years in patients with peripheral arterial disease. *New England Journal of Medicine, 32*6(6), 381-386.

Criqui, M. H., Ninomiya, J. K., Wingard, D. L., Ji, M., & Fronek, A. (2008). Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. *Journal of the American College of Cardiology, 5*2(21), 1736-1742.

Criqui, M. H., & Aboyans, V. (2015). Epidemiology of peripheral artery disease. *Circulation Research, 11*6(9), 1509-1526. https://doi.org/10.1161/CIRCRESAHA.116.303849 [doi]

Criqui, M. H., Denenberg, J. O., Bird, C. E., Fronek, A., Klauber, M. R., & Langer, R. D. (1996). The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vascular Medicine (London, England), 1*(1), 65-71.

Criqui, M. H., Fronek, A., Klauber, M. R., Barrett-Connor, E., & Gabriel, S. (1985). The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: Results from noninvasive testing in a defined population. *Circulation, 71*(3), 516-522.

Criqui, M. H., Vargas, V., Denenberg, J. O., Ho, E., Allison, M., Langer, R. D., Gamst, A., Bundens, W. P., & Fronek, A. (2005). Ethnicity and peripheral arterial disease: The san diego population study. *Circulation, 112*(17), 2703-2707. https://doi.org/112/17/2703 [pii]

Cronenwett, J. L., Warner, K. G., Zelenock, G. B., Whitehouse, W. M., Graham, L. M., Lindenauer, S. M., & Stanley, J. C. (1984). Intermittent claudication: Current results of nonoperative management. *Archives of Surgery, 119*(4), 430-436.

Crotty, M. (1998). *The foundations of social research: Meaning and perspective in the research process*. Sage.

Cruickshank, J. (2012). Positioning positivism, critical realism and social constructionism in the health sciences: A philosophical orientation. *Nursing Inquiry, 19*(1), 71-82.

Cuschieri, S. (2020). The diabetes epidemic in malta. *South Eastern European Journal of Public Health (SEEJPH),*

Cuschieri, S., Vassallo, J., Calleja, N., Camilleri, R., Borg, A., Bonnici, G., Zhang, Y., Pace, N., & Mamo, J. (2016). Prevalence of obesity in malta. *Obesity Science & Practice,*

Crutzen, R., & Göritz, A. S. (2010). Social desirability and self-reported health risk behaviors in web-based research: Three longitudinal studies. *BMC Public Health, 10*(1), 720.

Dabrh, A. M. A., Steffen, M. W., Asi, N., Undavalli, C., Wang, Z., Elamin, M. B., Conte, M. S., & Murad, M. H. (2016). Bypass surgery versus endovascular interventions in severe or critical limb ischemia. *Journal of Vascular Surgery, 63*(1), 244-253. e11.

Dagenais, G. R., Maurice, S., Robitaille, N. M., Gingras, S., & Lupien, P. J. (1991). Intermittent claudication in quebec men from 1974-1986: The quebec cardiovascular study. *Clinical and Investigative Medicine.Medecine Clinique Et Experimentale, 14*(2), 93-100.

Davies, J. H., Richards, J., Conway, K., Kenkre, J. E., Lewis, J. E., & Mark Williams, E. (2017). Primary care screening for peripheral arterial disease: A cross-sectional observational study. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners, 67*(655), e103-e110. https://doi.org/10.3399/bjgp17X689137 [doi]

Daviglus, M. L., Stamler, J., Pirzada, A., Yan, L. L., Garside, D. B., Liu, K., Wang, R., Dyer, A. R., Lloyd-Jones, D. M., & Greenland, P. (2004). Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *Jama, 292*(13), 1588-1592.

De Angulo, J. M., & Losada, L. S. (2015). Health paradigms shifts in the 20th century. *Christian Journal for Global Health, 2*(1)

Després, J. (2012). Body fat distribution and risk of cardiovascular disease: An update. *Circulation, 126*(10), 1301-1313.

Devine, E. B., Alfonso-Cristancho, R., Yanez, N. D., Edwards, T. C., Patrick, D. L., Armstrong, C. A., Devlin, A., Symons, R. G., Meissner, M. H., & Derrick, E. L. (2016). Effectiveness of a medical vs revascularization intervention for intermittent leg claudication based on patient-reported outcomes. *JAMA Surgery, 151*(10), e162024-e162024.

Diehm, C., Allenberg, J. R., Pittrow, D., Mahn, M., Tepohl, G., Haberl, R. L., Darius, H., Burghaus, I., Trampisch, H. J., & German Epidemiological Trial on Ankle Brachial Index Study Group. (2009). Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation, 120*(21), 2053-2061. https://doi.org/10.1161/CIRCULATIONAHA.109.865600 [doi]

Diehm, N., Shang, A., Silvestro, A., Do, D., Dick, F., Schmidli, J., Mahler, F., & Baumgartner, I. (2006). Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. *European Journal of Vascular and Endovascular Surgery, 31*(1), 59-63.

Diehm, Kareem, & Lawall. (2004). Epidemiology of peripheral arterial disease. *Vasa, 33*(4), 183-189.

Djulbegovic, B., Hozo, I., & Greenland, S. (2011). Uncertainty in clinical medicine. *Philosophy of medicine* (pp. 299-356). Elsevier.

Dormandy, J., & Murray, G. (2011). Reprinted article "The fate of the Claudicant—A prospective study of 1969 claudicants". *European Journal of Vascular and Endovascular Surgery, 42*, S4-S6.

Dormandy, J., & Rutherford, R. (2000). TransAtlantic inter-society consensus (TASC). management of peripheral arterial disease (PAD). *J Vasc Surg, 31*(1 Pt 2), S1-S296.

Duff, S., Mafilios, M. S., Bhounsule, P., & Hasegawa, J. T. (2019). The burden of critical limb ischemia: A review of recent literature. *Vascular Health and Risk Management, 15*, 187

Dumville, J. C., Lee, A. J., Smith, F. B., & Fowkes, F. G. (2004). The health-related quality of life of people with peripheral arterial disease in the community: The edinburgh artery study. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners, 54*(508), 826-831.

Dunn, K. M., Jordan, K., Lacey, R. J., Shapley, M., & Jinks, C. (2004). Patterns of consent in epidemiologic research: Evidence from over 25,000 responders. *American Journal of Epidemiology, 159*(11), 1087-1094.

Duval, S., Massaro, J. M., Jaff, M. R., Boden, W. E., Alberts, M. J., Califf, R. M., Eagle, K. A., Dâ€™Agostino Sr, R. B., Pedley, A., & Fonarow, G. C. (2012). An evidence-based score to detect prevalent peripheral artery disease (PAD). *Vascular Medicine, 17*(5), 342-351.

Eden, J., Levit, L., Berg, A., & Morton, S. (2011). Standards for synthesizing the body of evidence.

Edmonds, M. E., Morrison, N., Laws, J. W., & Watkins, P. J. (1982). Medial arterial calcification and diabetic neuropathy. *British Medical Journal (Clinical Research Ed.), 284*(6320), 928-930. https://doi.org/10.1136/bmj.284.6320.928 [doi]

Ellaway, R. H., Kehoe, A., & Illing, J. (2020). Critical realism and realist inquiry in medical education. *Academic Medicine : Journal of the Association of American Medical Colleges, 95*(7), 984-988. https://doi.org/10.1097/ACM.0000000000003232 [doi]

Erren, M., Reinecke, H., Junker, R., Fobker, M., Schulte, H., Schurek, J. O., Kropf, J., Kerber, S., Breithardt, G., & Assmann, G. (1999). Systemic inflammatory parameters in patients with atherosclerosis of the coronary and peripheral arteries. *Arteriosclerosis, Thrombosis, and Vascular Biology, 19*(10), 2355-2363.

European Stroke Organisation, Tendera, M., Aboyans, V., Bartelink, M. L., Baumgartner, I., Clement, D., Collet, J. P., Cremonesi, A., De Carlo, M., Erbel, R., Fowkes, F. G., Heras, M., Kownator, S., Minar, E., Ostergren, J., Poldermans, D., Riambau, V., Roffi, M., Rother, J., . . . ESC Committee for Practice Guidelines. (2011). ESC guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: The task force on the diagnosis and treatment of peripheral artery diseases of the european society of cardiology (ESC). *European Heart Journal, 32*(22), 2851-2906. https://doi.org/10.1093/eurheartj/ehr211 [doi]

Evans, L., & Trotter, D. R. (2009). Epistemology and uncertainty in primary care: An exploratory study. *Family Medicine, 41*(5), 319-326.

Everhart, J., Pettitt, D., Knowler, W., Rose, F., & Bennett, P. (1988). Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia, 31*(1), 16-23.

Fakhry, F., Fokkenrood, H. J., Rouwet, E. V., Teijink, J. A., Spronk, S., & Hunink, M. (2018). Endovascular revascularisation versus conservative management for intermittent claudication. *The Cochrane Library,*

Feng, Y., Schlösser, F. J., & Sumpio, B. E. (2009). The semmes weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. *Journal of Vascular Surgery, 50*(3), 675-682. e1.

Feringa, H. H., Emani, U. R., Ardestani, A., Shetty, S., & Pearson, W. N. (2009). Prevention of Peripheral Arterial Disease with Calcium Channel Blockers in Patients with Hypertension: A Meta-Analysis of Randomized Trials. *Circulation.*120:S1148

Ferrari, F. B., Wolosker, N., Rosoky, R. A., D'Ippolito, G., Wolosker, A. M. B., & Puech-Leão, P. (2004). Natural history of stenosis in the iliac arteries in patients with intermittent claudication undergoing clinical treatment. *Revista do Hospital Das Clínicas, 59*(6), 341-348.

Fineout-Overholt, E., & Melnyk, B. M. (2004). Evaluation of studies of prognosis. *Evid Based.Nurs., 7*(1), 4-8. https://doi.org/10.1136/ebn.7.1.4 [doi]

Fontaine, R. (1954). Surgical treatment of peripheral circulation disorders. *Helv.Chir.Acta., 21*, 499-533.

Formosa, C., Mandy, A., & Lucas, K. (2011). Identifying changes in diabetes care. *Practical Diabetes International, 28*(1), 31-34.

Formosa, C., Gatt, A., & Chockalingam, N. (2012). Diabetic foot complications in Malta: Prevalence of risk factors. *The Foot, 22*(4), 294-297.

Formosa, C., Cassar, K., Gatt, A., Mizzi, A., Mizzi, S., Camileri, K. P., Azzopardi, C., DeRaffaele, C., Falzon, O., Cristina, S., & Chockalingam, N. (2013). Hidden dangers revealed by misdiagnosed peripheral arterial disease using ABPI measurement. *Diabetes*

Research and Clinical Practice, 102(2), 112-116. https://doi.org/10.1016/j.diabres.2013.10.006 [doi]

Fowkes, F. G. R., Rudan, D., Rudan, I., Aboyans, V., Denenberg, J. O., McDermott, M. M., Norman, P. E., Sampson, U. K., Williams, L. J., & Mensah, G. A. (2013). Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. *The Lancet, 382*(9901), 1329-1340.

Fowkes, F., Housley, E., Rattray, A., Lowe, G., Rumley, A., Elton, R., MacGregor, I., & Dawes, J. (1993). Cross-linked fibrin degradation products, progression of peripheral arterial disease, and risk of coronary heart disease. *The Lancet, 342*(8863), 84-86.

Fowkes, F. G., Housley, E., Cawood, E. H., Macintyre, C. C., Ruckley, C. V., & Prescott, R. J. (1991). Edinburgh artery study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *International Journal of Epidemiology, 20*(2), 384-392.

Fowkes, F. G., Housley, E., Riemersma, R. A., Macintyre, C. C., Cawood, E. H., Prescott, R. J., & Ruckley, C. V. (1992). Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh artery study. *American Journal of Epidemiology, 135*(4), 331-340.

Frans, F. A., Zagers, M. B., Jens, S., Bipat, S., Reekers, J. A., & Koelemay, M. J. (2013). The relationship of walking distances estimated by the patient, on the corridor and on a treadmill, and the walking impairment questionnaire in intermittent claudication. *Journal of Vascular Surgery, 57*(3), 720-727. e1.

Freedman, D. S., Katzmarzyk, P. T., Dietz, W. H., Srinivasan, S. R., & Berenson, G. S. (2009). Relation of body mass index and skinfold thicknesses to cardiovascular disease risk factors in children: The bogalusa heart study. *The American Journal of Clinical Nutrition, 90*(1), 210-216.

Fridh, E. B., Andersson, M., Thuresson, M., Sigvant, B., Kragsterman, B., Johansson, S., Hasvold, P., Falkenberg, M., & Nordanstig, J. (2017). Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: A population based study. *European Journal of Vascular and Endovascular Surgery, 54*(4), 480-486.

Gardner, A. W., Montgomery, P. S., & Parker, D. E. (2008). Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *Journal of Vascular Surgery, 47*(1), 117-122.

Gardner, A. W., Parker, D. E., Montgomery, P. S., Scott, K. J., & Blevins, S. M. (2011). Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: A randomized controlled trial. *Circulation, 123*(5), 491-498.

Gardner, A. W., Ricci, M. A., Case, T. D., & Pilcher, D. B. (1996). Practical equations to predict claudication pain distances from a graded treadmill test. *Vascular Medicine, 1*(2), 91-96.

General Assembly of the World Medical Association. (2014). World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *The Journal of the American College of Dentists, 81*(3), 14-18.

Gerhard-Herman, M. D., Gornik, H. L., Barrett, C., Barshes, N. R., Corriere, M. A., Drachman, D. E., Fleisher, L. A., Fowkes, F. G. R., Hamburg, N. M., & Kinlay, S. (2017). 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: A report of the american college of Cardiology/American heart association task force on clinical practice guidelines. *Journal of the American College of Cardiology, 69*(11), e71-e126.

Giannopoulos, S., Lyden, S. P., Bisdas, T., Micari, A., Parikh, S. A., Jaff, M. R., Schneider, P. A., & Armstrong, E. J. (2020). Endovascular intervention for the treatment of trans-

atlantic inter-society consensus (TASC) D femoropopliteal lesions: A systematic review and meta-analysis. *Cardiovascular Revascularization Medicine,*

Gibbons, R. J., Balady, G. J., Bricker, J. T., Chaitman, B. R., Fletcher, G. F., Froelicher, V. F., Mark, D. B., McCallister, B. D., Mooss, A. N., & O'reilly, M. G. (2002). ACC/AHA 2002 guideline update for exercise testing: Summary article: A report of the american college of Cardiology/American heart association task force on practice guidelines (committee to update the 1997 exercise testing guidelines). *Journal of the American College of Cardiology, 40*(8), 1531-1540.

Gil, J., Laczmanska, I., Pesz, K. A., & Sasiadek, M. M. (2018). Personalized medicine in oncology. new perspectives in management of gliomas. *Contemporary Oncology (Poznan, Poland), 22*(1A), 1-2. https://doi.org/10.5114/wo.2018.73872 [doi]

Giugliano, G., Brevetti, G., Laurenzano, E., Brevetti, L., Luciano, R., & Chiariello, M. (2010). The prognostic impact of general and abdominal obesity in peripheral arterial disease. *International Journal of Obesity, 34*(2), 280-286.

Golledge, J., Moxon, J., Rowbotham, S., Pinchbeck, J., Yip, L., Velu, R., Quigley, F., Jenkins, J., & Morris, D. (2018). Risk of major amputation in patients with intermittent claudication undergoing early revascularization. *British Journal of Surgery, 105*(6), 699-708.

Gordon, T., & Kannel, W. B. (1972). Predisposition to atherosclerosis in the head, heart, and legs: The framingham study. *Jama, 221*(7), 661-666.

Gornik, H. L., Garcia, B., Wolski, K., Jones, D. C., Macdonald, K. A., & Fronek, A. (2008). Validation of a method for determination of the ankle-brachial index in the seated position. *Journal of Vascular Surgery, 48*(5), 1204-1210.

Grady, D., Herrington, D., Bittner, V., Blumenthal, R., Davidson, M., Hlatky, M., Hsia, J., Hulley, S., Herd, A., & Khan, S. (2002). Cardiovascular disease outcomes during 6.8

years of hormone therapy: Heart and Estrogen/progestin replacement study follow-up (HERS II). *Jama, 288*(1), 49-57.

Grant, R. L. (2014). Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ (Clinical Research Ed.), 348*, f7450. https://doi.org/10.1136/bmj.f7450 [doi]

Grau, M., Baena-Diez, J., Felix-Redondo, F., Fernández-Berges, D., Comas-Cufi, M., Fores, R., Marrugat, J., & Ramos, R. (2013). Estimating the risk of peripheral artery disease using different population strategies. *Preventive Medicine, 57*(4), 328-333.

Gray, B. H., Grant, A. A., Kalbaugh, C. A., Blackhurst, D. W., Langan III, E. M., Taylor, S. A., & Cull, D. L. (2010). The impact of isolated tibial disease on outcomes in the critical limb ischemic population. *Annals of Vascular Surgery, 24*(3), 349-359.

Graziani, L., Silvestro, A., Bertone, V., Manara, E., Andreini, R., Sigala, A., Mingardi, R., & De Giglio, R. (2007). Vascular involvement in diabetic subjects with ischemic foot ulcer: A new morphologic categorization of disease severity. *European Journal of Vascular and Endovascular Surgery, 33*(4), 453-460.

Green, S. M., Martinez-Rumayor, A., Gregory, S. A., Baggish, A. L., O'Donoghue, M. L., Green, J. A., Lewandrowski, K. B., & Januzzi, J. L. (2008). Clinical uncertainty, diagnostic accuracy, and outcomes in emergency department patients presenting with dyspnea. *Archives of Internal Medicine, 168*(7), 741-748.

Greenhalgh, R. (2008). The adjuvant benefit of angioplasty in patients with mild-to-moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: Results from two randomised trials for occlusive femoropopliteal and aortoiliac occlusive arterial disease. *European Journal of Vascular & Endovascular Surgery,*

Grimes, D. A., & Schulz, K. F. (2002). Bias and causal associations in observational research. *The Lancet, 359*(9302), 248-252.

Guest, F., Marshall, C., & Stansby, G. (2019). Amputation and rehabilitation. *Surgery (Oxford), 37*(2), 102-105.

Gunnarsson, T., Gottsäter, A., Bergman, S., Troëng, T., & Lindgren, H. (2020). Eight-year outcome after invasive treatment of infrainguinal intermittent claudication: A population-based analysis from the swedish vascular register (swedvasc). *SAGE Open Medicine, 8*, 2050312120926782.

Gutting, G. (1980). Paradigms and revolutions: Applications and appraisals of thomas kuhn's philosophy of science. *Notre Dame,*

Hajibandeh, S., Hajibandeh, S., Shah, S., Child, E., Antoniou, G. A., & Torella, F. (2017). Prognostic significance of ankle brachial pressure index: A systematic review and meta-analysis. *Vascular, 25*(2), 208-224.

Hale, W. E., Marks, R. G., May, F. E., Moore, M. T., & Stewart, R. B. (1988). Epidemiology of intermittent claudication: Evaluation of risk factors. *Age and Ageing, 17*(1), 57-60.

Haltmayer, M., Mueller, T., Horvath, W., & Luft, C. (2001). Impact of atherosclerotic risk factors on the anatomical distribution of peripheral arterial disease. *International Angiology, 20*(3), 200.

Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine, 352*(16), 1685-1695.

Hardman, R. L., Jazaeri, O., Yi, J., Smith, M., & Gupta, R. (2014). Overview of classification systems in peripheral artery disease. *Seminars in Interventional Radiology, 31*(4), 378-388. https://doi.org/10.1055/s-0034-1393976 [doi]

Hata, Y., Iida, O., Asai, M., Masuda, M., Okamoto, S., Ishihara, T., Nanto, K., Kanda, T., Tsujumura, T., & Okuno, S. (2020). Risk stratification for 2-year mortality in patients

with chronic limb-threatening ischemia undergoing endovascular therapy. *Journal of Atherosclerosis and Thrombosis,* , 57711.

Hayden, J. A., van der Windt, Danielle A, Cartwright, J. L., Côté, P., & Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Annals of Internal Medicine, 158*(4), 280-286.

Hays, P. (2019). Personalized medicine: Paradigm shift or revolution. *Genetics in Medicine, 21*(7), 1662-1662.

Heale, R., & Twycross, A. (2015). Validity and reliability in quantitative studies. *Evidence-Based Nursing, 18*(3), 66-67. https://doi.org/10.1136/eb-2015-102129 [doi]

Heinze, G., Wallisch, C., & Dunkler, D. (2018). Variable selection–a review and recommendations for the practicing statistician. *Biometrical Journal, 60*(3), 431-449.

Hess, C. N., Norgren, L., Ansel, G. M., Capell, W. H., Fletcher, J. P., Fowkes, F. G. R., Gottsater, A., Hitos, K., Jaff, M. R., Nordanstig, J., & Hiatt, W. R. (2017). A structured review of antithrombotic therapy in peripheral artery disease with a focus on revascularization: A TASC (InterSociety consensus for the management of peripheral artery disease) initiative. *Circulation, 135*(25), 2534-2555. https://doi.org/10.1161/CIRCULATIONAHA.117.024469 [doi]

Hiatt, W. R., Goldstone, J., Smith, S. C.,Jr, McDermott, M., Moneta, G., Oka, R., Newman, A. B., Pearce, W. H., & American Heart Association Writing Group 1. (2008). Atherosclerotic peripheral vascular disease symposium II: Nomenclature for vascular diseases. *Circulation, 118*(25), 2826-2829. https://doi.org/10.1161/CIRCULATIONAHA.108.191171 [doi]

Higgins, J., Altman, D., & Sterne, J. (2011). Table 8.5. a the cochrane Collaboration's tool for assessing risk of bias. chapter 8: Assessing risk of bias in included studies. *Cochrane Handbook for Systematic Reviews of Interventions Version, 510*

Higgins, Julian PT, Douglas G. Altman, Peter C. Gøtzsche, Peter Jüni, David Moher, Andrew D. Oxman, Jelena Savović, Kenneth F. Schulz, Laura Weeks, and Jonathan AC Sterne. (2014). *Https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm.* https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm

Hinsz, V. B., Heimerdinger, S. R., Henkel, J. M., & Spieker, C. J. (2005). Test-accuracy and base-rate information in the prediction of medical disease occurrence. *Current Psychology, 24*(2), 80-90.

Hirsch, A. T., Criqui, M. H., Treat-Jacobson, D., Regensteiner, J. G., Creager, M. A., Olin, J. W., Krook, S. H., Hunninghake, D. B., Comerota, A. J., & Walsh, M. E. (2001). Peripheral arterial disease detection, awareness, and treatment in primary care. *Jama, 286*(11), 1317-1324.

Hirsch, A. T., Murphy, T. P., Lovell, M. B., Twillman, G., Treat-Jacobson, D., Harwood, E. M., Mohler III, E. R., Creager, M. A., Hobson, R. W., & Robertson, R. M. (2007). Gaps in public knowledge of peripheral arterial disease: The first national PAD public awareness survey. *Circulation, 116*(18), 2086-2094.

Hirsch, A. T., Haskal, Z. J., Hertzer, N. R., Bakal, C. W., Creager, M. A., Halperin, J. L., Hiratzka, L. F., Murphy, W. R., Olin, J. W., Puschett, J. B., Rosenfield, K. A., Sacks, D., Stanley, J. C., Taylor, L. M.,Jr, White, C. J., White, J., White, R. A., Antman, E. M., Smith, S. C.,Jr, . . . Vascular Disease Foundation. (2006). ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): Executive summary a collaborative report from the american association for vascular Surgery/Society for vascular surgery, society for cardiovascular angiography and interventions, society for vascular medicine and biology,

society of interventional radiology, and the ACC/AHA task force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease) endorsed by the american association of cardiovascular and pulmonary rehabilitation; national heart, lung, and blood institute; society for vascular nursing; TransAtlantic inter-society consensus; and vascular disease foundation. *Journal of the American College of Cardiology, 47*(6), 1239-1312. https://doi.org/S0735-1097(05)02362-4 [pii]

Hirsch, A. T., Haskal, Z. J., Hertzer, N. R., Bakal, C. W., Creager, M. A., Halperin, J. L., Hiratzka, L. F., Murphy, W. R., Olin, J. W., Puschett, J. B., Rosenfield, K. A., Sacks, D., Stanley, J. C., Taylor, L. M.,Jr, White, C. J., White, J., White, R. A., Antman, E. M., Smith, S. C.,Jr, . . . ACC/AHA Task Force on Practice Guidelines. (2006). ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the american associations for vascular Surgery/Society for vascular surgery, society for cardiovascular angiography and interventions, society for vascular medicine and biology, society of interventional radiology, and the ACC/AHA task force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)--summary of recommendations. *Journal of Vascular and Interventional Radiology : JVIR, 17*(9), 1383-97; quiz 1398. https://doi.org/17/9/1383 [pii]

Ho, C. Y., & Shanahan, C. M. (2016). Medial arterial calcification: An overlooked player in peripheral arterial disease. *Arteriosclerosis, Thrombosis, and Vascular Biology, 36*(8), 1475-1482. https://doi.org/10.1161/ATVBAHA.116.306717 [doi]

Hoeks, S. E., Scholte op Reimer, W. J., Lenzen, M. J., van Urk, H., Jorning, P. J., Boersma, E., Simoons, M. L., Bax, J. J., & Poldermans, D. (2007). Guidelines for cardiac management in noncardiac surgery are poorly implemented in clinical practice: Results

from a peripheral vascular survey in the netherlands. *Anesthesiology, 107*(4), 537-544. https://doi.org/10.1097/01.anes.0000281892.15637.fb [doi]

Hoffman, J. I. (2015). *Biostatistics for medical and biomedical practitioners*. Academic press.

Hooi, J. D., Kester, A. D., Stoffers, H. E., Overdijk, M. M., van Ree, J. W., & Knottnerus, J. A. (2001). Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: A longitudinal study. *American Journal of Epidemiology, 153*(7), 666-672.

Høyer, C., Sandermann, J., & Petersen, L. J. (2013). Randomised diagnostic accuracy study of a fully automated portable device for diagnosing peripheral arterial disease by measuring the toe–brachial index. *European Journal of Vascular and Endovascular Surgery, 45*(1), 57-64.

Hren, D., & Lukic, K. I. (2006). Types of studies, power of study and choice of test. [Vrste istrazivanja, snaga istrazivanja i odabir odgovarajuceg statistickog postupka] *Acta Medica Croatica : Casopis Hravatske Akademije Medicinskih Znanosti, 60 Suppl 1*, 47-62.

Huang, H. L., Juang, J. J., Hsieh, C. A., Chou, H. H., Jang, S. J., & Ko, Y. L. (2019). Risk stratification for low extremity amputation in critical limb ischemia patients who have undergone endovascular revascularization: A survival tree analysis. *Medicine, 98*(33), e16809. https://doi.org/10.1097/MD.0000000000016809 [doi]

Humphrey-Murto, S., Varpio, L., Wood, T. J., Gonsalves, C., Ufholz, L., Mascioli, K., Wang, C., & Foth, T. (2017). The use of the delphi and other consensus group methods in medical education research: A review. *Academic Medicine, 92*(10), 1491-1498.

Hyun, S., Forbang, N. I., Allison, M. A., Denenberg, J. O., Criqui, M. H., & Ix, J. H. (2014). Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus. *Journal of Vascular Surgery, 60*(2), 390-395.

Iso, Y., & Suzuki, H. (2015). Exercise therapy for intermittent claudication in peripheral artery disease. *E-Journal Cardiol Pract, 13*

Jaff, M. R., White, C. J., Hiatt, W. R., Fowkes, G. R., Dormandy, J., Razavi, M., Reekers, J., & Norgren, L. (2015). An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: A supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II): The TASC steering committee. *Catheterization and Cardiovascular Interventions, 86*(4), 611-625.

Jansson, E., Johansson, J., Sylven, C., & Kaijser, L. (1988). Calf muscle adaptation in intermittent claudication. Side-differences in muscle metabolic characteristics in patients with unilateral arterial disease. *Clinical Physiology, 8*(1), 17-29.

Jelnes, R., Gaardsting, O., Hougaard Jensen, K., Baekgaard, N., Tonnesen, K. H., & Schroeder, T. (1986). Fate in intermittent claudication: Outcome and risk factors. *British Medical Journal (Clinical Research Ed.), 293*(6555), 1137-1140.

Jensen, S., Vatten, L., & Myhre, H. (2006). The prevalence of chronic critical lower limb ischaemia in a population of 20,000 subjects 40–69 years of age. *European Journal of Vascular and Endovascular Surgery, 32*(1), 60-65.

Jensen, S., Vatten, L., Romundstad, P., & Myhre, H. (2003). The prevalence of intermittent claudication. sex-related differences have been eliminated. *European Journal of Vascular and Endovascular Surgery, 25*(3), 209-212.

Jiang, S., Lu, W., Zong, X., Ruan, H., & Liu, Y. (2016). Obesity and hypertension. *Experimental and Therapeutic Medicine, 12*(4), 2395-2399.

Jones, D. W., & Hall, J. E. (2004). *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and Evidence from New Hypertension Trials,*

Joosten, M. M., Pai, J. K., Bertoia, M. L., Rimm, E. B., Spiegelman, D., Mittleman, M. A., & Mukamal, K. J. (2012). Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *Jama, 308*(16), 1660-1667.

Jude, E. B., Oyibo, S. O., Chalmers, N., & Boulton, A. J. (2001). Peripheral arterial disease in diabetic and nondiabetic patients: A comparison of severity and outcome. *Diabetes Care, 24*(8), 1433-1437.

Kalbaugh, C. A., Gonzalez, N. J., Luckett, D. J., Fine, J., Brothers, T. E., Farber, M. A., Beck, A. W., Hallett Jr, J. W., Marston, W. A., & Vallabhaneni, R. (2018). The impact of current smoking on outcomes after infrainguinal bypass for claudication. *Journal of Vascular Surgery,*

Kalfoss, M. (2019). Translation and adaption of questionnaires: A nursing challenge. *SAGE Open Nursing, 5*, 2377960818816810.

Kallio, M., Forsblom, C., Groop, P. H., Groop, L., & Lepantalo, M. (2003). Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. *Diabetes Care, 26*(4), 1241-1245. https://doi.org/10.2337/diacare.26.4.1241 [doi]

Kannel, W., & McGee, D. (1985). Update on some epidemiologic features of intermittent claudication: The framingham study. *Journal of the American Geriatrics Society, 33*(1), 13-18.

Kannel, W. B., & Shurtleff, D. (1973). The framingham study. cigarettes and the development of intermittent claudication. *Geriatrics, 28*(2), 61-68.

Kanter, J. E., & Bornfeldt, K. E. (2013). Inflammation and diabetes-accelerated atherosclerosis: Myeloid cell mediators. *Trends in Endocrinology & Metabolism, 24*(3), 137-144.

Kasko, M., Gaspar, L., Dukat, A., Gavornik, P., & Oravec, S. (2014). High-density lipoprotein profile in newly-diagnosed lower extremity artery disease in slovak population without diabetes mellitus. *Neuroendocrinol Lett, 35*(6), 531-535.

Kastner, M., Bhattacharyya, O., Hayden, L., Makarski, J., Estey, E., Durocher, L., Chatterjee, A., Perrier, L., Graham, I. D., & Straus, S. E. (2015). Guideline uptake is influenced by six implementability domains for creating and communicating guidelines: A realist review. *Journal of Clinical Epidemiology, 68*(5), 498-509.

Kennedy, M., Solomon, C., Manolio, T. A., Criqui, M. H., Newman, A. B., Polak, J. F., Burke, G. L., Enright, P., & Cushman, M. (2005). Risk factors for declining ankle-brachial index in men and women 65 years or older: The cardiovascular health study. *Archives of Internal Medicine, 165*(16), 1896-1902.

Khan, T. H., Farooqui, F. A., & Niazi, K. (2008). Critical review of the ankle brachial index. *Current Cardiology Reviews, 4*(2), 101-106.

Khawaja, F. J., & Kullo, I. J. (2009). Novel markers of peripheral arterial disease. *Vascular Medicine (London, England), 14*(4), 381-392. https://doi.org/10.1177/1358863X09106869 [doi]

Khosravi, A., Akhavan Tabib, A., Golshadi, I., Dana Siadat, Z., Bahonar, A., Zarfeshani, S., Alikhasi, H., Rezaee, S., Noori, F., Hashemi Jazi, M., & Khosravi, Z. (2012). The relationship between weight and CVD risk factors in a sample population from central iran (based on IHHP). *ARYA Atherosclerosis, 8*(2), 82-89.

Kim, E. S., Sharma, A. M., Scissons, R., Dawson, D., Eberhardt, R. T., Gerhard-Herman, M., Hughes, J. P., Knight, S., Marie Kupinski, A., & Mahe, G. (2020). Interpretation of peripheral arterial and venous doppler waveforms: A consensus statement from the society for vascular medicine and society for vascular ultrasound. *Vascular Medicine,* , 1358863X20937665.

Kodama, A., Meecham, L., Popplewell, M., Bate, G., & Bradbury, A. (2018). Validation of the global anatomic staging system (GLASS) using the BASIL-1 best endovascular therapy cohort. *European Journal of Vascular and Endovascular Surgery, 56*(6), e27.

Kollerits, B., Heinrich, J., Pichler, M., Rantner, B., Klein-Weigel, P., Wölke, G., Brasche, S., Strube, G., & Kronenberg, F. (2008). Intermittent claudication in the erfurt male cohort (ERFORT) study: Its determinants and the impact on mortality: A population-based prospective cohort study with 30 years of follow-up. *Atherosclerosis, 198*(1), 214-222. https://doi.org/http://dx.doi.org/10.1016/j.atherosclerosis.2007.09.012

Konik, A., Kuklewicz, S., Rosłoniec, E., Zając, M., Spannbauer, A., Nowobilski, R., & Mika, P. (2016). Effects of 12-week supervised treadmill training on spatio-temporal gait parameters in patients with claudication. *Disability and Rehabilitation, 3*8(12), 1157-1162.

Krauss, S. E. (2005). Research paradigms and meaning making: A primer. *The Qualitative Report, 1*0(4), 758-770.

Kristensen, M. T., Holm, G., Kirketerp-Møller, K., Krasheninnikoff, M., & Gebuhr, P. (2012). Very low survival rates after non-traumatic lower limb amputation in a consecutive series: What to do*? Interactive Cardiovascular and Thoracic Surgery, 1*4(5), 543-547.

Kuhn, T. S. (1962). The structure of scientific revolutions.

Kuhn, T. S. (2012). *The structure of scientific revolution*s. University of Chicago press.

Kumakura, H., Kanai, H., Hojo, Y., Iwasaki, T., & Ichikawa, S. (2016). Long-term survival and fate of the leg in de novo intermittent claudication. *European Heart Journal-Quality of Care and Clinical Outcomes,* , qcw057.

Kumbhani, D. J., Hirsch, A. T., Han, C. H., Ren, F., Goto, S., Steg, P. G., Bhatt, D. L., & REACH Registry Investigators. (2011). Predictors of incident symptomatic peripheral

arterial disease in stable outpatients: The international REduction of atherothrombosis for continued health (REACH) registry. *Circulation, 12*4(Suppl 21), A14117-A14117.

Lane, R., Ellis, B., Watson, L., & Leng, G. C. (2014). Exercise for intermittent claudication. *The Cochrane Database of Systematic Reviews, (7):CD000990. do*i(7), CD000990. https://doi.org/10.1002/14651858.CD000990.pub3 [doi]

Lauterbach, S. R., Torres, G. A., Andros, G., & Oblath, R. W. (2005). Infragenicular polytetrafluoroethylene bypass with distal vein cuffs for limb salvage: A contemporary series. *Archives of Surgery, 14*0(5), 487-494.

Lee, M., Flammer, A. J., Lerman, L. O., & Lerman, A. (2012). Personalized medicine in cardiovascular diseases. *Korean Circulation Journal, 4*2(9), 583-591.

Leng, G. C., & Fowkes, F. G. (1992). The edinburgh claudication questionnaire: An improved version of the WHO/Rose questionnaire for use in epidemiological surveys. *Journal of Clinical Epidemiology, 4*5(10), 1101-1109. https://doi.org/0895-4356(92)90150-L [pii]

Leng, G. C., Lee, A. J., Fowkes, F. G., Whiteman, M., Dunbar, J., Housley, E., & Ruckley, C. V. (1996). Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *International Journal of Epidemiology, 25*(6), 1172-1181.

Levey, A. S., Coresh, J., Balk, E., Kausz, A. T., Levin, A., Steffes, M. W., Hogg, R. J., Perrone, R. D., Lau, J., Eknoyan, G., & National Kidney Foundation. (2003). National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Annals of Internal Medicine, 139*(2), 137-147. https://doi.org/200307150-00013 [pii]

Libby, P. (2012). Inflammation in atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 32*(9), 2045-2051. https://doi.org/10.1161/ATVBAHA.108.179705 [doi]

Lindgren, H., Qvarfordt, P., Åkesson, M., Bergman, S., Gottsäter, A., Jansson, I., Litterfeldt, E., Fransson, T., Öjersjö, A., & Hilbertson, A. (2017). Primary stenting of the superficial femoral artery in intermittent claudication improves health related quality of life, ABI and walking distance: 12 month results of a controlled randomised multicentre trial. *European Journal of Vascular and Endovascular Surgery, 53*(5), 686-694.

Lindgren, H., Gottsäter, A., Qvarfordt, P., Bergman, S., & Troëng, T. (2014). Invasive treatment for infrainguinal claudication has satisfactory 1 year outcome in three out of four patients: A population-based analysis from swedvasc. *European Journal of Vascular and Endovascular Surgery, 47*(6), 615-620.

Lindlof, T. R., & Taylor, B. C. (2017). *Qualitative communication research methods*. Sage publications.

Lindqvist, T. (1945). Intermittent claudication and vascular spasm. I. is vascular spasm a contributory cause of intermittent claudication in patients with structural disease of the arteries? *Acta Medica Scandinavica, 121*(1), 32-48.

Lokin, J. L. C., Hengeveld, P. J., Conijn, A. P., Nieuwkerk, P. T., & Koelemay, M. J. W. (2015). Disease understanding in patients with intermittent claudication: A qualitative study. *Journal of Vascular Nursing, 33*(3), 112-118. https://doi.org/http://dx.doi.org/10.1016/j.jvn.2015.02.002

Lorbeer, R., Grotz, A., Dorr, M., Volzke, H., Lieb, W., Kuhn, J. P., & Mensel, B. (2018). Reference values of vessel diameters, stenosis prevalence, and arterial variations of the lower limb arteries in a male population sample using contrast-enhanced MR

angiography. *PloS One, 1*3(6), e0197559. https://doi.org/10.1371/journal.pone.0197559 [doi]

Lozano, F. S., González-Porras, J. R., March, J. R., Lobos, J. M., Carrasco, E., & Ros, E. (2014). Diabetes mellitus and intermittent claudication: A cross-sectional study of 920 claudicants. *Diabetology & Metabolic Syndrome,* 6(1), 21.

Lu, C. Y. (2009). Observational studies: A review of study designs, challenges and strategies to reduce confounding. *International Journal of Clinical Practice, 6*3(5), 691-697.

Lu, J. T., & Creager, M. A. (2004). The relationship of cigarette smoking to peripheral arterial disease. *Reviews in Cardiovascular Medicine,* 5(4), 189-193.

Lutkenhoner, B., & Basel, T. (2013). Predictive modeling for diagnostic tests with high specificity, but low sensitivity: A study of the glycerol test in patients with suspected meniere's disease. *PloS One,* 8(11), e79315. https://doi.org/10.1371/journal.pone.0079315 [doi]

Mahé, G., Kaladji, A., Le Faucheur, A., & Jaquinandi, V. (2015). Internal iliac artery stenosis: Diagnosis and how to manage it in 2015. *Frontiers in Cardiovascular Medicine, 2*

Mahé, G., Ouedraogo, N., Vasseur, M., Faligant, C., Saidi, K., Leftheriotis, G., & Abraham, P. (2011). Limitations of self-reported estimates of functional capacity using the walking impairment questionnaire. *European Journal of Vascular and Endovascular Surgery, 4*1(1), 104-109.

Mak, K., & Kum, C. K. (2005). How to appraise a prognostic study. *World Journal of Surgery, 29*(5), 567-569.

Malgor, R. D., Alahdab, F., Elraiyah, T. A., Rizvi, A. Z., Lane, M. A., Prokop, L. J., Phung, O. J., Farah, W., Montori, V. M., Conte, M. S., & Murad, M. H. (2015). A systematic

review of treatment of intermittent claudication in the lower extremities. *Journal of Vascular Surgery, 6*1(3 Suppl), 54S-73S. https://doi.org/10.1016/j.jvs.2014.12.007 [doi]

Mallett, R., Hagen-Zanker, J., Slater, R., & Duvendack, M. (2012). The benefits and challenges of using systematic reviews in international development research. *Journal of Development Effectiveness,* 4(3), 445-455.

Mallett, S., Halligan, S., Thompson, M., Collins, G. S., & Altman, D. G. (2012). Interpreting diagnostic accuracy studies for patient care. *BMJ (Clinical Research Ed.), 345*, e3999. https://doi.org/10.1136/bmj.e3999 [doi]

Maltby, J., Williams, G., McGarry, J., & Day, L. (2014). *Research methods for nursing and healthcar*e. Routledge.

Marbach, J. A., Almufleh, A. S., So, D., & Chong, A. (2020). Peripheral artery disease: Current diagnosis and management. *British Journal of Cardiology, 2*7(Supplement 1), S9–S14. https://doi.org/10.5837/bjc2020.s03

Martin Borge, V., Herranz de la Morena, L., Castro Dufourny, I., & Pallardo Sanchez, L. F. (2008). Peripheral arterial disease in diabetic patients: Utility of the toe-brachial index. [Arteriopatia periferica en el paciente diabetico: utilidad del indice dedo-brazo] *Medicina Clinica, 13*0(16), 611-612. https://doi.org/S0025-7753(08)71523-9 [pii]

Martinez-Aguilar, E., Orbe, J., Fernández-Montero, A., Fernández-Alonso, S., Rodríguez, J. A., Fernández-Alonso, L., Páramo, J. A., & Roncal, C. (2017). Reduced high-density lipoprotein cholesterol: A valuable, independent prognostic marker in peripheral arterial disease. *Journal of Vascular Surgery, 6*6(5), 1527-1533. e1.

Martone, V. D., Perna, S., Cacciatore, F., Corrado, S., Di Donato, A., Di Iorio, A., & Brevetti, G. (1998). Intermittent claudication and risk of cardiovascular events. *Angiology, 4*9(9), 843-848.

Massberg, S., Vogt, F., Dickfeld, T., Brand, K., Page, S., & Gawaz, M. (2003). Activated platelets trigger an inflammatory response and enhance migration of aortic smooth muscle cells. *Thrombosis Research, 110*(4), 187-194.

Massberg, S., Brand, K., Gruner, S., Page, S., Muller, E., Muller, I., Bergmeier, W., Richter, T., Lorenz, M., Konrad, I., Nieswandt, B., & Gawaz, M. (2002). A critical role of platelet adhesion in the initiation of atherosclerotic lesion formation. *The Journal of Experimental Medicine, 196*(7), 887-896.

Maxwell, J. A. (2012). *Qualitative research design: An interactive approac*h. Sage publications.

Mays, N., & Pope, C. (2000). Assessing quality in qualitative research. *Bmj, 320*(7226), 50-52.

Mazari, F., Khan, J., Samuel, N., Smith, G., Carradice, D., McCollum, P., & Chetter, I. (2017). Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. *British Journal of Surgery, 104*(1), 76-83.

Mc Grae McDermott, M., Hahn, E. A., Greenland, P., Cella, D., Ockene, J. K., Brogan, D., Pearce, W. H., Hirsch, A. T., Hanley, K., & Odom, L. (2002). Atherosclerotic risk factor reduction in peripheral arterial disease: Results of a national physician survey. *Journal of General Internal Medicine, 17*(12), 895-904.

McAllister, F. F. (1976). The fate of patients with intermittent claudication managed nonoperatively. *The American Journal of Surgery, 132*(5), 593-595.

McDaniel, M. D., & Cronenwett, J. L. (1989). Basic data related to the natural history of intermittent claudication. *Annals of Vascular Surgery,* 3(3), 273-277.

McDermott, M. M., Greenland, P., Liu, K., Guralnik, J. M., Criqui, M. H., Dolan, N. C., Chan, C., Celic, L., Pearce, W. H., & Schneider, J. R. (2001). Leg symptoms in peripheral arterial disease: Associated clinical characteristics and functional impairment. *Jama, 28*6(13), 1599-1606.

McDermott, M. M., Liu, K., Greenland, P., Guralnik, J. M., Criqui, M. H., Chan, C., Pearce, W. H., Schneider, J. R., Ferrucci, L., & Celic, L. (2004). Functional decline in peripheral arterial disease: Associations with the ankle brachial index and leg symptoms. *Jama, 292*(4), 453-461.

McDermott, M. M., Liu, K., Guralnik, J. M., Martin, G. J., Criqui, M. H., & Greenland, P. (1998). Measurement of walking endurance and walking velocity with questionnaire: Validation of the walking impairment questionnaire in men and women with peripheral arterial disease. *Journal of Vascular Surgery, 2*8(6), 1072-1081.

McDermott, M. M., Mehta, S., Liu, K., Guralnik, J. M., Martin, G. J., Criqui, M. H., & Greenland, P. (1999). Leg symptoms, the ankle-brachial index, and walking ability in patients with peripheral arterial disease. *Journal of General Internal Medicine, 1*4(3), 173-181.

McNamara, L. A., & Martin, S. W. (2018). Principles of epidemiology and public health. *Principles and practice of pediatric infectious disease*s (pp. 1-9. e1). Elsevier.

McPherson, K. (1989). International differences in medical care practices. *Health Care Financing Review, Spec N*o, 9-20.

McWhinney, I. R. (1984). Changing models: The impact of kuhn's theory on medicine. *Family Practice,* 1(1), 3-8.

Meijer, W. T., Grobbee, D. E., Hunink, M. M., Hofman, A., & Hoes, A. W. (2000). Determinants of peripheral arterial disease in the elderly: The rotterdam study. *Archives of Internal Medicine, 16*0(19), 2934-2938.

Meijer, W. T., Hoes, A. W., Rutgers, D., Bots, M. L., Hofman, A., & Grobbee, D. E. (1998). Peripheral arterial disease in the elderly: The rotterdam study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 1*8(2), 185-192.

Mendie, P. J., & EJESI, E. (2014). Logical positivism versus thomas kuhn. *THE LEAJON: An Academic Journal of Interdisciplinary Studies,* 6(1), 197-216.

Mendis, S., Puska, P., Norrving, B., & World Health Organization. (2011). *Global atlas on cardiovascular disease prevention and contro*l. World Health Organization.

Merriam, S. B., & Tisdell, E. J. (2015). *Qualitative research: A guide to design and implementatio*n. John Wiley & Sons.

Mertens, D. M. (2008). *Transformative research and evaluatio*n. Guilford press.

Meru, A. V., Mittra, S., Thyagarajan, B., & Chugh, A. (2006). Intermittent claudication: An overview. *Atherosclerosis, 18*7(2), 221-237.

Meshkin, D. H., Zolper, E. G., Chang, K., Bryant, M., Bekeny, J. C., Evans, K. K., Attinger, C. E., & Fan, K. L. (2020). Long term mortality after nontraumatic major lower extremity amputation: A systematic review and meta-analysis. *The Journal of Foot and Ankle Surgery,*

Miller, K. (2005). Communication theories. *USA: Macgraw-Hill,*

Miura, T., Soga, Y., Miyashita, Y., Iida, O., Kawasaki, D., Hirano, K., Suzuki, K., & Ikeda, U. (2014). Five-year prognosis after endovascular therapy in claudicant patients with iliofemoral artery disease. *Journal of Endovascular Therapy : An Official Journal of the International Society of Endovascular Specialists, 2*1(3), 381-388. https://doi.org/10.1583/13-4618R.1 [doi]

Mizzi, A., Cassar, K., Bowen, C., & Formosa, C. (2018). MEETING ABSTRACTS open access. *Journal of Foot and Ankle Research, 1*1(1), O01.

Mizzi, A., Cassar, K., Bowen, C., & Formosa, C. (2019). The progression rate of peripheral arterial disease in patients with intermittent claudication: A systematic review. *Journal of Foot and Ankle Research, 1*2(1), 40.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). RESEARCH METHODS & REPORTING-preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement-david moher and colleagues introduce PRISMA, an update of the QUOROM guidelines for reporting systematic reviews and meta-analyses. *BMJ (CR)-Print, 338*(7716), 332.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine, 6*(7), e1000097.

Mohler, E.,3rd, Giri, J., ACC, & AHA. (2008). Management of peripheral arterial disease patients: Comparing the ACC/AHA and TASC-II guidelines. *Current Medical Research and Opinion, 24*(9), 2509-2522. https://doi.org/10.1185/03007990802274379 [doi]

Montagnana, M., Fava, C., Arosio, E., Degan, M., Tommasoli, R. M., De Marchi, S., Delva, P., Spadaro, R., Guidi, G. C., & Lechi, A. (2007). Inflammation and platelet activation in peripheral arterial occlusive disease. *International Journal of Angiology, 16*(03), 84-88.

Morris, E., & Burkett, K. (2011). Mixed methodologies: A new research paradigm or enhanced quantitative paradigm. *Online Journal of Cultural Competence in Nursing and Healthcare, 1*(1), 27-36.

Motawea[1], M., Kyrillos[1], F., Hanafy, A., Albehairy, A., State, O., & Tarshoby, M. (2015). Impact of big toe amputation on foot biomechanics. *International Journal, 3*(12), 1224-1228.

Moule, P., Armoogum, J., Dodd, E., Donskoy, A., Douglass, E., Taylor, J., & Turton, P. (2016). Practical guidance on undertaking a service evaluation. *Nursing Standard, 30*(45)

Moyer, V. A., & U.S. Preventive Services Task Force. (2013). Screening for peripheral artery disease and cardiovascular disease risk assessment with the ankle-brachial index in adults: U.S. preventive services task force recommendation statement. *Annals of Internal Medicine, 159*(5), 342-348. https://doi.org/10.7326/0003-4819-159-5-201309030-00008 [doi]

Muluk, S. C., Muluk, V. S., Kelley, M. E., Whittle, J. C., Tierney, J. A., Webster, M. W., & Makaroun, M. S. (2001). Outcome events in patients with claudication: A 15-year study in 2777 patients. *Journal of Vascular Surgery, 33*(2), 251-258.

Murabito, J. M., Evans, J. C., D'Agostino Sr, R. B., Wilson, P. W., & Kannel, W. B. (2005). Temporal trends in the incidence of intermittent claudication from 1950 to 1999. *American Journal of Epidemiology, 162*(5), 430-437.

Murabito, J. M., Evans, J. C., Nieto, K., Larson, M. G., Levy, D., & Wilson, P. W. (2002). Prevalence and clinical correlates of peripheral arterial disease in the framingham offspring study. *American Heart Journal, 143*(6), 961-965.

Murabito, J. M., D'Agostino, R. B., Silbershatz, H., & Wilson, W. F. (1997). Intermittent claudication. A risk profile from the framingham heart study. *Circulation, 96*(1), 44-49.

Murphy, T. P., Cutlip, D. E., Regensteiner, J. G., Mohler, E. R., Cohen, D. J., Reynolds, M. R., Massaro, J. M., Lewis, B. A., Cerezo, J., & Oldenburg, N. C. (2015). Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: The CLEVER study. *Journal of the American College of Cardiology, 65*(10), 999-1009.

Myers, S. A., Johanning, J. M., Stergiou, N., Lynch, T. G., Longo, G. M., & Pipinos, I. I. (2008). Claudication distances and the walking impairment questionnaire best describe the ambulatory limitations in patients with symptomatic peripheral arterial disease. *Journal of Vascular Surgery, 47*(3), 550-555. e1.

Naschitz, J. E., Ambrosio, D. A., & Chang, J. B. (1988). Intermittent claudication: Predictors and outcome. *Angiology, 39*(1 Pt 1), 16-22. https://doi.org/10.1177/000331978803900103 [doi]

Natarajan, S., Glick, H., Criqui, M., Horowitz, D., Lipsitz, S. R., & Kinosian, B. (2003). Cholesterol measures to identify and treat individuals at risk for coronary heart disease. *American Journal of Preventive Medicine, 25*(1), 50-57.

NCD Risk Factor Collaboration. (2016). Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4· 4 million participants. *The Lancet, 387*(10027), 1513-1530.

Nehler, M. R., Duval, S., Diao, L., Annex, B. H., Hiatt, W. R., Rogers, K., Zakharyan, A., & Hirsch, A. T. (2014). Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *Journal of Vascular Surgery, 60*(3), 686-695. e2.

Neuman, W. L., & Kreuger, L. (2003). *Social work research methods: Qualitative and quantitative approaches*. Allyn and Bacon.

Neupane, S., Edla, S., Maidona, E., Sweet, M. C., Szpunar, S., Davis, T., LaLonde, T. A., Mehta, R. H., Rosman, H. S., & Yamasaki, H. (2018). Long-term outcomes of patients with diabetes mellitus undergoing percutaneous intervention for popliteal and infrapopliteal peripheral arterial disease. *Catheterization and Cardiovascular Interventions, 92*(1), 117-123.

Newman, A. B., Naydeck, B. L., Sutton-Tyrrell, K., Polak, J. F., Kuller, L. H., & Cardiovascular Health Study Research Group. (2001). The role of comorbidity in the assessment of intermittent claudication in older adults. *Journal of Clinical Epidemiology, 54*(3), 294-300.

Newman, A. B., Siscovick, D. S., Manolio, T. A., Polak, J., Fried, L. P., Borhani, N. O., & Wolfson, S. K. (1993). Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study. cardiovascular heart study (CHS) collaborative research group. *Circulation, 88*(3), 837-845. https://doi.org/10.1161/01.cir.88.3.837 [doi]

Nicolaï, S. P., Kruidenier, L. M., Rouwet, E. V., Graffius, K., Prins, M. H., & Teijink, J. A. (2009). The walking impairment questionnaire: An effective tool to assess the effect of treatment in patients with intermittent claudication. *Journal of Vascular Surgery, 50*(1), 89-94.

Nicolaï, S. P., Viechtbauer, W., Kruidenier, L. M., Candel, M. J., Prins, M. H., & Teijink, J. A. (2009). Reliability of treadmill testing in peripheral arterial disease: A meta-regression analysis. *Journal of Vascular Surgery, 50*(2), 322-329.

Nicoloff, A., Taylor Jr, L., Sexton, G., Schuff, R., Edwards, J., Yeager, R., Landry, G., Moneta, G., & Porter, J. (2002). Homocysteine and progression of atherosclerosis study investigators: Relationship between site of initial symptoms and subsequent progression of disease in a prospective study of atherosclerosis progression in patients receiving long-term treatment for symptomatic peripheral arterial disease. *J Vasc Surg, 35*, 38-46.

Nordanstig, J., Taft, C., Hensäter, M., Perlander, A., Österberg, K., & Jivegård, L. (2016). Two-year results from a randomized clinical trial of revascularization in patients with intermittent claudication. *British Journal of Surgery, 103*(10), 1290-1299.

Nordanstig, J., Taft, C., Hensäter, M., Perlander, A., Österberg, K., & Jivegård, L. (2014). Improved quality of life after 1 year with an invasive versus a noninvasive treatment

strategy in claudicants: One-year results of the invasive revascularization or not in intermittent claudication (IRONIC) trial. *Circulation, 130*(12), 939-947.

Norgren, L., Hiatt, W. R., Dormandy, J. A., Nehler, M. R., Harris, K. A., Fowkes, F. G. R., & Tasc II Working Group. (2007). Inter-society consensus for the management of peripheral arterial disease (TASC II). *European Journal of Vascular and Endovascular Surgery, 33*(1), S1-S75.

NSO Malta. (2020). *National statistics office - malta; news release.* https://nso.gov.mt/en/News_Releases/Documents/2020/07/News2020_114.pdf

Nylaende, M., Abdelnoor, M., Stranden, E., Morken, B., Sandbaek, G., Risum, Ø., Jørgensen, J., Lindahl, A., Arnesen, H., & Seljeflot, I. (2007). The oslo balloon angioplasty versus conservative treatment study (OBACT)—the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. *European Journal of Vascular and Endovascular Surgery, 33*(1), 3-12.

OECD. (2018). *Health at a Glance: Europe 2018*. Organisation For Economic Cooperation and Development.

Ogurtsova, K., da Rocha Fernandes, J., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., Cavan, D., Shaw, J., & Makaroff, L. (2017). IDF diabetes atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Research and Clinical Practice, 12*8, 40-50.

O'Riordain, D., & O'Donnell, J. (1991). Realistic expectations for the patient with intermittent claudication. *British Journal of Surgery, 78*(7), 861-863.

Ortmann, J., Nüesch, E., Traupe, T., Diehm, N., & Baumgartner, I. (2012). Gender is an independent risk factor for distribution pattern and lesion morphology in chronic critical limb ischemia. *Journal of Vascular Surgery, 55*(1), 98-104.

Osanloo, A., & Grant, C. (2016). Understanding, selecting, and integrating a theoretical framework in dissertation research: Creating the blueprint for your "house". *Administrative Issues Journal: Connecting Education, Practice, and Research, 4*(2), 7.

Ouedraogo, N., Mahe, G., Marchand, J., Saïdi, K., Leftheriotis, G., & Abraham, P. (2011). Validation of a new simple questionnaire to "estimate ambulation capacity by history"(EACH) in patients with claudication. *Journal of Vascular Surgery, 54*(1), 133-138.

Ouriel, K. (2001). Peripheral arterial disease. *The Lancet, 358*(9289), 1257-1264.

Påhlsson, H., Laskar, C., Stark, K., Andersson, A., Jogestrand, T., & Wahlberg, E. (2007). The optimal cuff width for measuring toe blood pressure. *Angiology, 58*(4), 472-476.

Pandey, A., Banerjee, S., Ngo, C., Mody, P., Marso, S. P., Brilakis, E. S., Armstrong, E. J., Giri, J., Bonaca, M. P., & Pradhan, A. (2017). Comparative efficacy of endovascular revascularization versus supervised exercise training in patients with intermittent claudication: Meta-analysis of randomized controlled trials. *JACC: Cardiovascular Interventions, 10*(7), 712-724.

Papa, E. D., Helber, I., Ehrlichmann, M. R., Alves, C. M. R., Makdisse, M., Matos, L. N., Borges, J. L., Lopes, R. D., Stefanini, E., & Carvalho, A. C. (2013). Ankle-brachial index as a predictor of coronary disease events in elderly patients submitted to coronary angiography. *Clinics, 6*8(12), 1481-1487.

Parameswaran, G. I., Brand, K., & Dolan, J. (2005). Pulse oximetry as a potential screening tool for lower extremity arterial disease in asymptomatic patients with diabetes mellitus. *Archives of Internal Medicine, 165*(4), 442-446.

Patton, M. Q. (2002). Qualitative research and evaluation methods. thousand oaks. *Cal.: Sage Publications,*

Paulhus, D. L., Robinson, J. P., Shaver, P. R., & Wrightsman, L. S. (1991). Measures of personality and social psychological attitudes. *Measures of Social Psychological Attitudes Series, 1*, 17-59.

Pawson, R. (2006). *Evidence-based policy: A realist perspective*. sage.

Perkins, J., Collin, J., Creasy, T., Fletcher, E., & Morris, P. (2011). Reprinted article "Exercise training versus angioplasty for stable claudication. long and medium term results of a prospective, randomised trial". *European Journal of Vascular and Endovascular Surgery, 42*, S41-S45.

Perkins, N. J., Cole, S. R., Harel, O., Tchetgen Tchetgen, E. J., Sun, B., Mitchell, E. M., & Schisterman, E. F. (2017). Principled approaches to missing data in epidemiologic studies. *American Journal of Epidemiology, 187*(3), 568-575.

Pewsner, D., Battaglia, M., Minder, C., Marx, A., Bucher, H. C., & Egger, M. (2004). Ruling a diagnosis in or out with "SpPIn" and "SnNOut": A note of caution. *BMJ (Clinical Research Ed.), 329*(7459), 209-213. https://doi.org/10.1136/bmj.329.7459.209 [doi]

Podesta, M., Galea, N., & Calleja, N. (2019). Malta's changing demographics: Projecting Malta's future health system demands to 2030.

Popper, K. (2014). *Conjectures and refutations: The growth of scientific knowledge*. routledge.

Pourhoseingholi, M. A., Baghestani, A. R., & Vahedi, M. (2012). How to control confounding effects by statistical analysis. *Gastroenterology and Hepatology from Bed to Bench, 5*(2), 79.

Powell, J. T., Edwards, R. J., Worrell, P. C., Franks, P. J., Greenhalgh, R. M., & Poulter, N. R. (1997). Risk factors associated with the development of peripheral arterial disease in smokers: A case-control study. *Atherosclerosis, 129*(1), 41-48.

Price, J. F., Mowbray, P. I., Lee, A. J., Rumley, A., Lowe, G. D., & Fowkes, F. G. (1999). Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh artery study. *European Heart Journal, 20*(5), 344-353. https://doi.org/S0195668X98911940 [pii]

Quick, C., & Cotton, L. (1982). The measured effect of stopping smoking on intermittent claudication. *British Journal of Surgery, 69*(S6), S24-S26.

Ramirez-Santana, M. (2018). Limitations and biases in cohort studies. *Cohort Studies in Health Sciences,* , 29.

Ramkumar, N., Martinez-Camblor, P., Columbo, J. A., Osborne, N. H., Goodney, P. P., & O'Malley, A. J. (2019). Adverse events after atherectomy: Analyzing Long-Term outcomes of endovascular lower extremity revascularization techniques. *Journal of the American Heart Association, 8*(12), e012081.

Ramos, R., Baena-Díez, J. M., Quesada, M., Solanas, P., Subirana, I., Sala, J., Alzamora, M., Forès, R., Masiá, R., & Elosua, R. (2011). Derivation and validation of REASON: A risk score identifying candidates to screen for peripheral arterial disease using ankle brachial index. *Atherosclerosis, 214*(2), 474-479.

Randhawa, M. S., Reed, G. W., Grafmiller, K., Gornik, H. L., & Shishehbor, M. H. (2017). Prevalence of tibial artery and pedal arch patency by angiography in patients with critical limb ischemia and noncompressible ankle brachial index. *Circulation: Cardiovascular Interventions, 10*(5), e004605.

Rantner, B., Kollerits, B., Pohlhammer, J., Stadler, M., Lamina, C., Peric, S., Klein-Weigel, P., Mühlthaler, H., Fraedrich, G., & Kronenberg, F. (2016). The fate of patients with intermittent claudication in the 21st century Revisited–Results from the CAVASIC study. *European Journal of Vascular and Endovascular Surgery, 52*(3), 416-417.

Rantner, B., Kollerits, B., Pohlhammer, J., Stadler, M., Lamina, C., Peric, S., Klein-Weigel, P., Mühlthaler, H., Fraedrich, G., & Kronenberg, F. (2017). The fate of patients with intermittent claudication in the 21st century revisited–results from the CAVASIC study. *Scientific Reports, 7*, 45833.

Regensteiner, J. (1990). Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol, 2*, 142-152.

Regensteiner, J. G., Hiatt, W. R., Coll, J. R., Criqui, M. H., Treat-Jacobson, D., McDermott, M. M., & Hirsch, A. T. (2008). The impact of peripheral arterial disease on health-related quality of life in the peripheral arterial disease awareness, risk, and treatment: New resources for survival (PARTNERS) program. *Vascular Medicine (London, England), 13*(1), 15-24. https://doi.org/10.1177/1358863X07084911 [doi]

Reiber, G. E., Pecoraro, R. E., & Koepsell, T. D. (1992). Risk factors for amputation in patients with diabetes mellitus: A case-control study. *Annals of Internal Medicine, 117*(2), 97-105.

Reinecke, H., Unrath, M., Freisinger, E., Bunzemeier, H., Meyborg, M., Lüders, F., Gebauer, K., Roeder, N., Berger, K., & Malyar, N. M. (2015). Peripheral arterial disease and critical limb ischaemia: Still poor outcomes and lack of guideline adherence. *European Heart Journal, 36*(15), 932-938.

Reisch, G. A. (1991). Did kuhn kill logical empiricism? *Philosophy of Science, 58*(2), 264-277.

Richards, R. L. (1957). Prognosis of intermittent claudication. *British Medical Journal, 2*(5053), 1091-1093.

Ridker, P. M., Stampfer, M. J., & Rifai, N. (2001). Novel risk factors for systemic atherosclerosis: A comparison of C-reactive protein, fibrinogen, homocysteine,

lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *Jama, 285*(19), 2481-2485.

Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P., & Hennekens, C. H. (1998). Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation, 97*(5), 425-428.

Ridker, P. M., Rifai, N., Stampfer, M. J., & Hennekens, C. H. (2000). Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation, 101*(15), 1767-1772.

Rooke, T. W., Hirsch, A. T., Misra, S., Sidawy, A. N., Beckman, J. A., Findeiss, L. K., Golzarian, J., Gornik, H. L., Halperin, J. L., Jaff, M. R., Moneta, G. L., Olin, J. W., Stanley, J. C., White, C. J., White, J. V., Zierler, R. E., American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, . . . Society for Vascular Surgery. (2011). 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): A report of the american college of cardiology Foundation/American heart association task force on practice guidelines: Developed in collaboration with the society for cardiovascular angiography and interventions, society of interventional radiology, society for vascular medicine, and society for vascular surgery. *Journal of Vascular Surgery, 54*(5), e32-58. https://doi.org/10.1016/j.jvs.2011.09.001 [doi]

Rooke, T. W., Hirsch, A. T., Misra, S., Sidawy, A. N., Beckman, J. A., Findeiss, L. K., Golzarian, J., Gornik, H. L., Halperin, J. L., Jaff, M. R., Moneta, G. L., Olin, J. W., Stanley, J. C., White, C. J., White, J. V., Zierler, R. E., American College of Cardiology Foundation, American Heart Association, Society for Cardiovascular Angiography and Interventions, . . . Society for Vascular Surgery. (2012). 2011 ACCF/AHA focused

update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): A report of the american college of cardiology Foundation/American heart association task force on practice guidelines: Developed in collaboration with the society for cardiovascular angiography and interventions, society of interventional radiology, society for vascular medicine, and society for vascular surgery. *Catheterization and Cardiovascular Interventions : Official Journal of the Society for Cardiac Angiography & Interventions, 79*(4), 501-531. https://doi.org/10.1002/ccd.23373 [doi]

Rose, G. A. (1962). The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bulletin of the World Health Organization, 27*, 645-658.

Rosenbloom, M. S., Flanigan, D. P., Schuler, J. J., Meyer, J. P., Durham, J. R., Eldrup-Jorgensen, J., & Schwarcz, T. H. (1988). Risk factors affecting the natural history of intermittent claudication. *Archives of Surgery, 123*(7), 867-870.

Ross, R., Neeland, I. J., Yamashita, S., Shai, I., Seidell, J., Magni, P., Santos, R. D., Arsenault, B., Cuevas, A., & Hu, F. B. (2020). Waist circumference as a vital sign in clinical practice: A consensus statement from the IAS and ICCR working group on visceral obesity. *Nature Reviews Endocrinology,* , 1-13.

Rudestam, K., & Newton, R. (2007). Methods of inquiry: Quantitative and qualitative approaches. *Surviving Your Dissertation: A Comprehensive Guide to Content and Process,* , 23-58.

Rutherford, R. B., Flanigan, D. P., Gupta, S. K., Johnston, K. W., Karmody, A., Whittemore, A. D., Baker, J. D., Ernst, C. B., Jamieson, C., & Mehta, S. (1986). Suggested standards for reports dealing with lower extremity ischemia. *Journal of Vascular Surgery, 4*(1), 80-94.

Sachs, T., Pomposelli, F., Hamdan, A., Wyers, M., & Schermerhorn, M. (2011). Trends in the national outcomes and costs for claudication and limb threatening ischemia: Angioplasty vs bypass graft. *Journal of Vascular Surgery, 54*(4), 1021-1031. e1.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: What it is and what it isn't. *BMJ (Clinical Research Ed.), 312*(7023), 71-72.

Sacks, D., Bakal, C. W., Beatty, P. T., Becker, G. J., Cardella, J. F., Raabe, R. D., Wiener, H. M., & Lewis, C. A. (2002). Position statement on the use of the ankle-brachial index in the evaluation of patients with peripheral vascular disease: A consensus statement developed by the standards division of the society of cardiovascular & interventional radiology. *Journal of Vascular and Interventional Radiology : JVIR, 13*(4), 353-0443(07)61735-7. https://doi.org/10.1016/s1051-0443(07)61735-7 [doi]

Sadler, S. G., Hawke, F. E., & Chuter, V. H. (2015). The effect of pretest rest time on automated measures of toe systolic blood pressure and the toe brachial index. *Blood Pressure Monitoring, 20*(5), 245-248.

Safley, D. M., Kennedy, K. F., Stansby, G., Flather, M., Cohen, D. J., & Spertus, J. A. (2011). Prevalence and predictors of persistent health status impairment in patients referred to a vascular clinic with intermittent claudication. *European Journal of Vascular and Endovascular Surgery, 42*(3), 355-362. https://doi.org/http://dx.doi.org/10.1016/j.ejvs.2011.02.012

Sahli, D., Eliasson, B., Svensson, M., Blohmé, G., Eliasson, M., Samuelsson, P., Öjbrandt, K., & Eriksson, J. W. (2004). Assessment of toe blood pressure is an effective screening method to identify diabetes patients with lower extremity arterial disease. *Angiology, 55*(6), 641-651.

Salas, C., Adam, D., Papavassiliou, V., & London, N. (2004). Percutaneous transluminal angioplasty for critical limb ischaemia in octogenarians and nonagenarians. *European Journal of Vascular and Endovascular Surgery, 28*(2), 142-145.

Salaun, P., Desormais, I., Lapébie, F., Rivière, A. B., Aboyans, V., Lacroix, P., Bataille, V., Constans, J., & Boulon, C. (2019). Comparison of ankle pressure, systolic toe pressure, and transcutaneous oxygen pressure to predict major amputation after 1 year in the COPART cohort. *Angiology, 70*(3), 229-236.

Sanfilippo, P. G., Hewitt, A. W., & Mackey, D. A. (2017). The importance of conditional probability in diagnostic reasoning and clinical decision making: A primer for the eye care practitioner. *Ophthalmic Epidemiology, 2*4(2), 81-89.

Sanz, J. B., Fajardo, J. G., Taylor, J., Solá, L. R., Moreno, M. M., & Puerta, C. V. (2016). Design of a new risk score in critical limb ischaemia: The ERICVA model. *European Journal of Vascular and Endovascular Surgery, 51*(1), 90-99.

Saratzis, A., Jaspers, N., Gwilym, B., Thomas, O., Tsui, A., Lefroy, R., Parks, M., Htun, V., Mera, Z., & Thatcher, A. (2019). Observational study of the medical management of patients with peripheral artery disease. *British Journal of Surgery, 10*6(9), 1168-1177.

Sartipy, F., Sigvant, B., Lundin, F., & Wahlberg, E. (2018). Ten year mortality in different peripheral arterial disease stages: A population based observational study on outcome. *European Journal of Vascular and Endovascular Surgery, 55*(4), 529-536.

Schieber, G. J., & Poullier, J. (1988). International health spending and utilization trends. *Health Affairs,* 7(4), 105-112.

Schorr, E. N., & Treat-Jacobson, D. (2013). Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: A review. *Vascular Medicine, 18*(2), 95-111.

Schramm, K., & Rochon, P. J. (2018). Gender differences in peripheral vascular disease. Paper presented at the *Seminars in Interventional Radiology, , 35*(01) 009-016.

Schröder, F., Diehm, N., Kareem, S., Ames, M., Pira, A., Zwettler, U., Lawall, H., & Diehm, C. (2006). A modified calculation of ankle-brachial pressure index is far more sensitive in the detection of peripheral arterial disease. *Journal of Vascular Surgery, 44*(3), 531-536.

Scissons, R. (2008). Characterizing triphasic, biphasic, and monophasic doppler waveforms: Should a simple task be so difficult? *Journal of Diagnostic Medical Sonography, 24*(5), 269-276.

Scissons, R., & Comerota, A. (2009). Confusion of peripheral arterial doppler waveform terminology. *Journal of Diagnostic Medical Sonography, 25*(4), 185-194.

Selvin, E., Wattanakit, K., Steffes, M. W., Coresh, J., & Sharrett, A. R. (2006). HbA1c and peripheral arterial disease in diabetes: The atherosclerosis risk in communities study. *Diabetes Care, 29*(4), 877-882. https://doi.org/29/4/877 [pii]

Selvin, E., & Erlinger, T. P. (2004). Prevalence of and risk factors for peripheral arterial disease in the united states: Results from the national health and nutrition examination survey, 1999–2000. *Circulation, 110*(6), 738-743. https://doi.org/10.1161/01.CIR.0000137913.26087.F0

Shaalan, W. E., French-Sherry, E., Castilla, M., Lozanski, L., & Bassiouny, H. S. (2003). Reliability of common femoral artery hemodynamics in assessing the severity of aortoiliac inflow disease. *Journal of Vascular Surgery, 37*(5), 960-969.

Shapiro, D. E. (1999). The interpretation of diagnostic tests. *Statistical Methods in Medical Research, 8*(2), 113-134.

Sheehan, F. H., & Zierler, R. E. (2018). Simulation for competency assessment in vascular and cardiac ultrasound. *Vascular Medicine, 23*(2), 172-180.

Shepperd, S., Lewin, S., Straus, S., Clarke, M., Eccles, M. P., Fitzpatrick, R., Wong, G., & Sheikh, A. (2009). Can we systematically review studies that evaluate complex interventions? *PLoS Medicine, 6*(8), e1000086.

Shetty, S., Malik, A. H., Feringa, H., El Accaoui, R., & Girotra, S. (2020). Meta-analysis evaluating calcium channel blockers and the risk of peripheral arterial disease in patients with hypertension. *The American Journal of Cardiology, 125*(6), 907-915.

Shishehbor, M. H., Hammad, T. A., Zeller, T., Baumgartner, I., Scheinert, D., & Rocha-Singh, K. J. (2016). An analysis of IN. PACT DEEP randomized trial on the limitations of the societal guidelines-recommended hemodynamic parameters to diagnose critical limb ischemia. *Journal of Vascular Surgery, 63*(5), 1311-1317.

Sigvant, B., Lundin, F., & Wahlberg, E. (2016). The risk of disease progression in peripheral arterial disease is higher than expected: A meta-analysis of mortality and disease progression in peripheral arterial disease. *European Journal of Vascular and Endovascular Surgery, 51*(3), 395-403.

Sigvant, B., Wiberg-Hedman, K., Bergqvist, D., Rolandsson, O., Andersson, B., Persson, E., & Wahlberg, E. (2007). A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *Journal of Vascular Surgery, 45*(6), 1185-1191. https://doi.org/http://dx.doi.org/10.1016/j.jvs.2007.02.004

Simons, J. P., Schanzer, A., Nolan, B. W., Stone, D. H., Kalish, J. A., Cronenwett, J. L., Goodney, P. P., & Vascular Study Group of New England. (2012). Outcomes and practice patterns in patients undergoing lower extremity bypass. *Journal of Vascular Surgery, 55*(6), 1629-1636.

Simundic, A. (2013). Bias in research. *Biochemia Medica: Biochemia Medica, 23*(1), 12-15.

Siracuse, J. J., Huang, Z. S., Gill, H. L., Parrack, I., Schneider, D. B., Connolly, P. H., & Meltzer, A. J. (2014). Defining risks and predicting adverse events after lower extremity bypass for critical limb ischemia. *Vascular Health and Risk Management, 1*0, 367-374. https://doi.org/10.2147/VHRM.S54350 [doi]

Sirotti, S., Generali, E., Ceribelli, A., Isailovic, N., De Santis, M., & Selmi, C. (2017). Personalized medicine in rheumatology: The paradigm of serum autoantibodies. *Autoimmunity Highlights,* 8(1), 10.

Smith, F., Lowe, G., Lee, A., Rumley, A., Leng, G., & Fowkes, F. (1998). Smoking, hemorheologic factors, and progression of peripheral arterial disease in patients with claudication. *Journal of Vascular Surgery, 2*8(1), 129-135.

Smith, F. B., Lee, A. J., Price, J. F., van Wijk, M. C., & Fowkes, F. G. R. (2003). Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population. *Journal of Vascular Surgery, 3*8(6), 1323-1330.

Smith, I., Franks, P., Greenhalgh, R., Poulter, N., & Powell, J. (1996). The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. *European Journal of Vascular and Endovascular Surgery, 1*1(4), 402-408.

Smith, G. D., Shipley, M. J., & Rose, G. (1990). Intermittent claudication, heart disease risk factors, and mortality. the whitehall study. *Circulation, 8*2(6), 1925-1931.

Smolderen, K. G., van Zitteren, M., Jones, P. G., Spertus, J. A., Heyligers, J. M., Nooren, M. J., Vriens, P. W., & Denollet, J. (2015). Long-Term prognostic risk in lower extremity peripheral arterial disease as a function of the number of peripheral arterial lesions. *Journal of the American Heart Association,* 4(10), e001823.

Soden, P. A., Zettervall, S. L., Curran, T., Vouyouka, A. G., Goodney, P. P., Mills, J. L., Hallett Jr, J. W., Schermerhorn, M. L., & Society for Vascular Surgery Vascular Quality

Initiative. (2017). Regional variation in patient selection and treatment for lower extremity vascular disease in the vascular quality initiative. *Journal of Vascular Surgery, 65*(1), 108-118.

Sommers, L. S., & Launer, J. (2014). *Clinical uncertainty in primary car*e. Springer.

Song, P., Rudan, D., Zhu, Y., Fowkes, F. J., Rahimi, K., Fowkes, F. G. R., & Rudan, I. (2019). Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: An updated systematic review and analysis. *The Lancet Global Health,* 7(8), e1020-e1030.

Sonter, J. A., Ho, A., & Chuter, V. H. (2014). The predictive capacity of toe blood pressure and the toe brachial index for foot wound healing and amputation: A systematic review and meta-analysis. *Wound Practice & Research: Journal of the Australian Wound Management Association, 22*(4), 208.

Spannbauer, A., Chwała, M., Ridan, T., Berwecki, A., Mika, P., Kulik, A., Berwecka, M., & Szewczyk, M. T. (2019a). Intermittent claudication in physiotherapists' practice. *BioMed Research International, 2019*

Spannbauer, A., Chwała, M., Ridan, T., Berwecki, A., Mika, P., Kulik, A., Berwecka, M., & Szewczyk, M. T. (2019b). Intermittent claudication in physiotherapists' practice. *BioMed Research International, 2019*

Spaulding, W. B. (1956). The prognosis of patients with intermittent claudication. *Canadian Medical Association Journal, 75*(2), 105-111.

Spronk, S., den Hoed, P. T., de Jonge, L. C., van Dijk, L. C., & Pattynama, P. M. (2005). Value of the duplex waveform at the common femoral artery for diagnosing obstructive aortoiliac disease. *Journal of Vascular Surgery, 42*(2), 236-242.

Stadler, F. (2015). *The vienna circle: Studies in the origins, development, and influence of logical empiricis*m. springer.

Stansby, G., Mister, R., Fowkes, G., Roughton, M., Nugara, F., Brittenden, J., Bradbury, A., Ashley, S., Shearman, C., & Hannon, R. (2011). High risk of peripheral arterial disease in the United Kingdom: 2-year results of a prospective registry. *Angiology, 62*(2), 111-118.

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., Wood, A. M., & Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ (Clinical Research Ed.), 338*, b2393. https://doi.org/10.1136/bmj.b2393 [doi]

Sterpetti, A. V. (2012). Regarding "Trends in the national outcomes and costs for claudication and limb threatening ischemia: Angioplasty vs bypass graft". *Journal of Vascular Surgery, 55*(5), 1545.

Stewart, J., Manmathan, G., & Wilkinson, P. (2017). Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. *JRSM Cardiovascular Disease,* 6, 2048004016687211.

Stewart, K. J., Hiatt, W. R., Regensteiner, J. G., & Hirsch, A. T. (2002). Exercise training for claudication. *New England Journal of Medicine, 347*(24), 1941-1951.

Stoekenbroek, R., Ubbink, D., Reekers, J., & Koelemay, M. (2015). Hide and seek: Does the toe-brachial index allow for earlier recognition of peripheral arterial disease in diabetic patients*? European Journal of Vascular and Endovascular Surgery, 49*(2), 192-198.

Stoia, M., Mocan, M., Goidescu, C. M., Mocan, D. L. H., & Chiorescu, R. (2018). Cardiovascular risk evaluation in patients with critical leg ischemia before vascular surgery. *Peripheral Arterial Disease: A Practical Approach,* , 49.

Stone, P. A., Schlarb, H., Campbell, J. E., Williams, D., Thompson, S. N., John, M., Campbell, J. R., & AbuRahma, A. F. (2014). C-reactive protein and brain natriuretic

peptide as predictors of adverse events after lower extremity endovascular revascularization. *Journal of Vascular Surgery, 6*0(3), 652-660.

St-Pierre, A. C., Cantin, B., Lamarche, B., Auger, D., Després, J., & Dagenais, G. R. (2010). Intermittent claudication: From its risk factors to its long-term prognosis in men. the quebec cardiovascular study. *Canadian Journal of Cardiology, 2*6(1), 17-21.

Stratton, I. M., Adler, A. I., Neil, H. A., Matthews, D. R., Manley, S. E., Cull, C. A., Hadden, D., Turner, R. C., & Holman, R. R. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ (Clinical Research Ed.), 32*1(7258), 405-412. https://doi.org/10.1136/bmj.321.7258.405 [doi]

Szymczak, M., Krupa, P., Oszkinis, G., & Majchrzycki, M. (2018). Gait pattern in patients with peripheral artery disease. *BMC Geriatrics, 1*8(1), 52.

Taft, C., Sullivan, M., Lundholm, K., Karlsson, J., Gelin, J., & Jivegård, L. (2004). Predictors of treatment outcome in intermittent claudication. *European Journal of Vascular and Endovascular Surgery, 2*7(1), 24-32.

Taylor, S. M. (2009). Is intermittent vasculogenic claudication still a nonsurgical disease*?* *Advances in Surgery, 4*3(1), 53-72.

Tehan, P. E., Barwick, A. L., Sebastian, M., & Chuter, V. H. (2017). Diagnostic accuracy of resting systolic toe pressure for diagnosis of peripheral arterial disease in people with and without diabetes: A cross-sectional retrospective case-control study. *Journal of Foot and Ankle Research, 1*0(1), 58.

Tehan, P. E., Bray, A., & Chuter, V. H. (2016). Non-invasive vascular assessment in the foot with diabetes: Sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave doppler for detecting peripheral arterial disease. *Journal of Diabetes and its Complications, 3*0(1), 155-160.

Tehan, P. E., & Chuter, V. H. (2015). Use of hand-held doppler ultrasound examination by podiatrists: A reliability study. *Journal of Foot and Ankle Research,* 8(1), 36.

Tehan, P. E., Santos, D., & Chuter, V. H. (2016). A systematic review of the sensitivity and specificity of the toe–brachial index for detecting peripheral artery disease. *Vascular Medicine, 2*1(4), 382-389.

Tehan, P., Bray, A., Keech, R., Rounsley, R., Carruthers, A., & Chuter, V. H. (2015). Sensitivity and specificity of the Toe-Brachial index for detecting peripheral arterial disease: Initial findings. *Journal of Ultrasound in Medicine, 3*4(10), 1737-1743.

Thiruvoipati, T., Kielhorn, C. E., & Armstrong, E. J. (2015). Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. *World Journal of Diabetes,* 6(7), 961-969. https://doi.org/10.4239/wjd.v6.i7.961 [doi]

Thomas Manapurathe, D., Krishna, S. M., Dewdney, B., Moxon, J. V., Biros, E., & Golledge, J. (2017). Effect of blood pressure lowering medications on leg ischemia in peripheral artery disease patients: A meta-analysis of randomised controlled trials. *PloS One, 1*2(6), e0178713. https://doi.org/10.1371/journal.pone.0178713 [doi]

Tooth, L., Ware, R., Bain, C., Purdie, D. M., & Dobson, A. (2005). Quality of reporting of observational longitudinal research. *American Journal of Epidemiology, 16*1(3), 280-288.

Toth, P. P., Philip, S., Hull, M., & Granowitz, C. (2019). Hypertriglyceridemia is associated with an increased risk of peripheral arterial revascularization in high-risk statin-treated patients: A large administrative retrospective analysis. *Clinical Cardiology, 4*2(10), 908-913.

Traupe, T., Ortmann, J., Stoller, M., Baumgartner, I., de Marchi, S. F., & Seiler, C. (2013). Direct quantitative assessment of the peripheral artery collateral circulation in patients undergoing angiography. *Circulation, 128*(7), 737-744.

Tripathi, R. K., & Verma, H. (2014). Endovascular therapy for intermittent claudication: Is it time for re-evaluation*? Journal of Endovascular Therapy, 2*1(3), 389-391.

Trevethan, R. (2017). Sensitivity, specificity, and predictive values: Foundations, pliabilities, and pitfalls in research and practice. *Frontiers in Public Health, 5*, 307.

Tsai, J., Jan, Y., Yun, C., Sung, K., Liu, C., Kuo, J., Hung, C., Wu, T., Lin, J., & Hou, C. J. (2020). Associations of cigarette smoking and burden of thoracic aortic calcification in asymptomatic individuals: A dose-response relationship. *PloS One, 15*(1), e0227680.

Tseng, C. (2003). Prevalence and risk factors of peripheral arterial obstructive disease in taiwanese type 2 diabetic patients. *Angiology, 5*4(3), 331-338.

Unal, I. (2017). Defining an optimal cut-point value in ROC analysis: An alternative approach. *Computational and Mathematical Methods in Medicine, 2017*

Vainas, T., Stassen, F. R., de Graaf, R., Twiss, E. L., Herngreen, S. B., Rob, J. T. J., van den Akker, Luc HJM, van Dieijen-Visser, M. P., Bruggeman, C. A., & Kitslaar, P. J. (2005). C-reactive protein in peripheral arterial disease: Relation to severity of the disease and to future cardiovascular events. *Journal of Vascular Surgery, 42*(2), 243-251.

van den Houten, M. M., Jansen, S. C., Sinnige, A., van der Laan, L., Vriens, P. W., Willigendael, E. M., Lardenoije, J. H., Elshof, J. M., van Hattum, E. S., Lijkwan, M. A., Nyklicek, I., Rouwet, E. V., Koelemay, M. J., Scheltinga, M. R., & Teijink, J. A. (2019). Protocol for a prospective, longitudinal cohort study on the effect of arterial disease level on the outcomes of supervised exercise in intermittent claudication: The ELECT registry. *BMJ Open, 9*(2), e025419-2018-025419. https://doi.org/10.1136/bmjopen-2018-025419 [doi]

van der Meer, I. M., de Maat, M. P., Bots, M. L., Breteler, M. M., Meijer, J., Kiliaan, A. J., Hofman, A., & Witteman, J. C. (2002). Inflammatory mediators and cell adhesion molecules as indicators of severity of atherosclerosis: The rotterdam study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 22*(5), 838-842.

van Zitteren, M., Vriens, P. W., Heyligers, J. M., Burger, D. H., Nooren, M. J., de Fijter, W. M., Denollet, J., & Smolderen, K. G. (2012). Self-reported symptoms on questionnaires and anatomic lesions on duplex ultrasound examinations in patients with peripheral arterial disease. *Journal of Vascular Surgery, 55*(4), 1025-1034. e2.

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gøtzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., Egger, M., & STROBE Initiative. (2014). Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *International Journal of Surgery, 12*(12), 1500-1524.

Vandenbroucke, J. P. (2004). When are observational studies as credible as randomised trials? *Lancet (London, England), 363*(9422), 1728-1731. https://doi.org/10.1016/S0140-6736(04)16261-2 [doi]

Varpio, L., Paradis, E., Uijtdehaage, S., & Young, M. (2020). The distinctions between theory, theoretical framework, and conceptual framework [published online ahead of print november 12, 2019]. *Acad Med, 95*(7), 985-994. https://doi.org/10.1097/ACM.0000000000003075

Velescu, A., Clara, A., Martí, R., Ramos, R., Perez-Fernandez, S., Marcos, L., Grau, M., Degano, I., Marrugat, J., & Elosua, R. (2017). Abnormally high Ankle–Brachial index is associated with all-cause and cardiovascular mortality: The REGICOR study. *European Journal of Vascular and Endovascular Surgery, 54*(3), 370-377.

Venermo, M., Sprynger, M., Desormais, I., Björck, M., Brodmann, M., Cohnert, T., De Carlo, M., Espinola-Klein, C., Kownator, S., & Mazzolai, L. (2019). Follow-up of patients after revascularisation for peripheral arterial diseases: A consensus document from the european society of cardiology working group on aorta and peripheral vascular diseases and the european society for vascular surgery. *European Journal of Preventive Cardiology, 26*(18), 1971-1984.

Vogel, T. R., Dombrovskiy, V. Y., Carson, J. L., Haser, P. B., & Graham, A. M. (2009). Lower extremity angioplasty: Impact of practitioner specialty and volume on practice patterns and healthcare resource utilization. *Journal of Vascular Surgery, 50*(6), 1320-1325.

Vogenberg, F. R., Isaacson Barash, C., & Pursel, M. (2010). Personalized medicine: Part 1: Evolution and development into theranostics. *P & T : A Peer-Reviewed Journal for Formulary Manent, 35*(10), 560-576.

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & Strobe Initiative. (2014). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *International Journal of Surgery, 12*(12), 1495-1499.

Wall, M. L., & Carraro, T. E. (2009). Kuhn's revolutionary theory and its influence on the construction of nursing knowledge. *Revista Latino-Americana De Enfermagem, 17*(3), 417-422.

Walsh, D. B., Gilbertson, J. J., Zwolak, R. M., Besso, S., Edelman, G. C., Schneider, J. R., & Cronenwett, J. L. (1991). The natural history of superficial femoral artery stenoses. *Journal of Vascular Surgery, 14*(3), 299-304.

Wang, J. C., Criqui, M. H., Denenberg, J. O., McDermott, M. M., Golomb, B. A., & Fronek, A. (2005). Exertional leg pain in patients with and without peripheral arterial disease. *Circulation, 112*(22), 3501-3508. https://doi.org/112/22/3501 [pii]

Wanhainen, A., Verzini, F., Van Herzeele, I., Allaire, E., Bown, M., Cohnert, T., Dick, F., van Herwaarden, J., Karkos, C., Koelemay, M., Kolbel, T., Loftus, I., Mani, K., Melissano, G., Powell, J., Szeberin, Z., Esvs Guidelines, C., de Borst, G. J., Chakfe, N., . . . Verhagen, H. (2019). Editor's choice - european society for vascular surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. *European Journal of Vascular and Endovascular Surgery : The Official Journal of the European Society for Vascular Surgery, 57*(1), 8-93. https://doi.org/S1078-5884(18)30698-1 [pii]

Weitz, J. I., Byrne, J., Clagett, G. P., Farkouh, M. E., Porter, J. M., Sackett, D. L., Strandness, D. E., & Taylor, L. M. (1996). Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: A critical review. *Circulation, 94*(11), 3026-3049.

West, A. M., Anderson, J. D., Epstein, F. H., Meyer, C. H., Hagspiel, K. D., Berr, S. S., Harthun, N. L., Weltman, A. L., Annex, B. H., & Kramer, C. M. (2012). Percutaneous intervention in peripheral artery disease improves calf muscle phosphocreatine recovery kinetics: A pilot study. *Vascular Medicine, 17*(1), 3-9.

Westendorp, I. C., Grobbee, D. E., Pols, H. A., Meijer, W. T., Hofman, A., & Witteman, J. C. (2000). Hormone replacement therapy and peripheral arterial disease: The rotterdam study. *Archives of Internal Medicine, 160*(16), 2498-2502.

Whittemore, R., Chase, S. K., & Mandle, C. L. (2001). Validity in qualitative research. *Qualitative Health Research, 11*(4), 522-537.

WHO. (2017). *Body mass index–BMI.* https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

Whyman, M., Ruckley, C., & Fowkes, F. (1993). A prospective study of the natural history of femoropopliteal artery stenosis using duplex ultrasound. *European Journal of Vascular Surgery, 7*(4), 444-447.

Willett, K., Jiang, R., Lenart, E., Spiegelman, D., & Willett, W. (2006). Comparison of bioelectrical impedance and BMI in predicting obesity-related medical conditions. *Obesity, 14*(3), 480-490.

Williams, D. T., Harding, K. G., & Price, P. (2005). An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. *Diabetes Care, 28*(9), 2206-2210. https://doi.org/28/9/2206 [pii]

Wilson, S. E. (2010). Trials of endovascular treatment for superficial femoral artery occlusive lesions: A call for medically managed control patients. *Annals of Vascular Surgery, 24*(4), 498-502.

Wisloff, U., Stoylen, A., Loennechen, J. P., Bruvold, M., Rognmo, O., Haram, P. M., Tjonna, A. E., Helgerud, J., Slordahl, S. A., Lee, S. J., Videm, V., Bye, A., Smith, G. L., Najjar, S. M., Ellingsen, O., & Skjaerpe, T. (2007). Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation, 115*(24), 3086-3094. https://doi.org/CIRCULATIONAHA.106.675041 [pii]

Wohlfahrt-Veje, C., Tinggaard, J., Winther, K., Mouritsen, A., Hagen, C., Mieritz, M. G., de Renzy-Martin, K. T., Boas, M., Petersen, J. H., & Main, K. (2014). Body fat throughout childhood in 2647 healthy danish children: Agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. *European Journal of Clinical Nutrition, 68*(6), 664-670.

Wolosker, N., Nakano, L., Rosoky, R. A., & Puech-Leão, P. (2003). Evaluation of walking capacity over time in 500 patients with intermittent claudication who underwent clinical treatment. *Archives of Internal Medicine, 163*(19), 2296-2300.

World Health Organization. (2016). Growing up unequal: Gender and socioeconomic differences in young people's health and well-being. *Health Policy for Children and Adolescents,* (7)

World Health Organization. (2019). WHO report on the global tobacco epidemic 2019: Offer help to quit tobacco use.

Writing Group for the Women's Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. *Jama, 288*(3), 321-333.

WÜ, E. (1898). Das intermittierende hinken und andere nervöse störungen in folge i. *Von Gefässerkrankungen Z Nervenk, 13*, 1.

Yonclas, P. P., & O'donnell, C. J. (2005). Prosthetic management of the partial foot amputee. *Clinics in Podiatric Medicine and Surgery, 22*(3), 485-502. https://doi.org/S0891-8422(05)00010-8 [pii]

Yang, H. T., Prior, B. M., Lloyd, P. G., Taylor, J. C., Li, Z., Laughlin, M. H., & Terjung, R. L. (2008). Training-induced vascular adaptations to ischemic muscle. *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society, 59 Suppl 7*, 57-70.

Zhan, Y., Holtfreter, B., Meisel, P., Hoffmann, T., Micheelis, W., Dietrich, T., & Kocher, T. (2014). Prediction of periodontal disease: Modelling and validation in different general german populations. *Journal of Clinical Periodontology, 41*(3), 224-231.

Zhan, Y., Zhuang, J., Dong, Y., Xu, H., Hu, D., & Yu, J. (2016). Predicting the prevalence of peripheral arterial diseases: Modelling and validation in different cohorts.

VASA.Zeitschrift Fur Gefasskrankheiten, 45(1), 31-36. https://doi.org/10.1024/0301-1526/a000492 [doi]

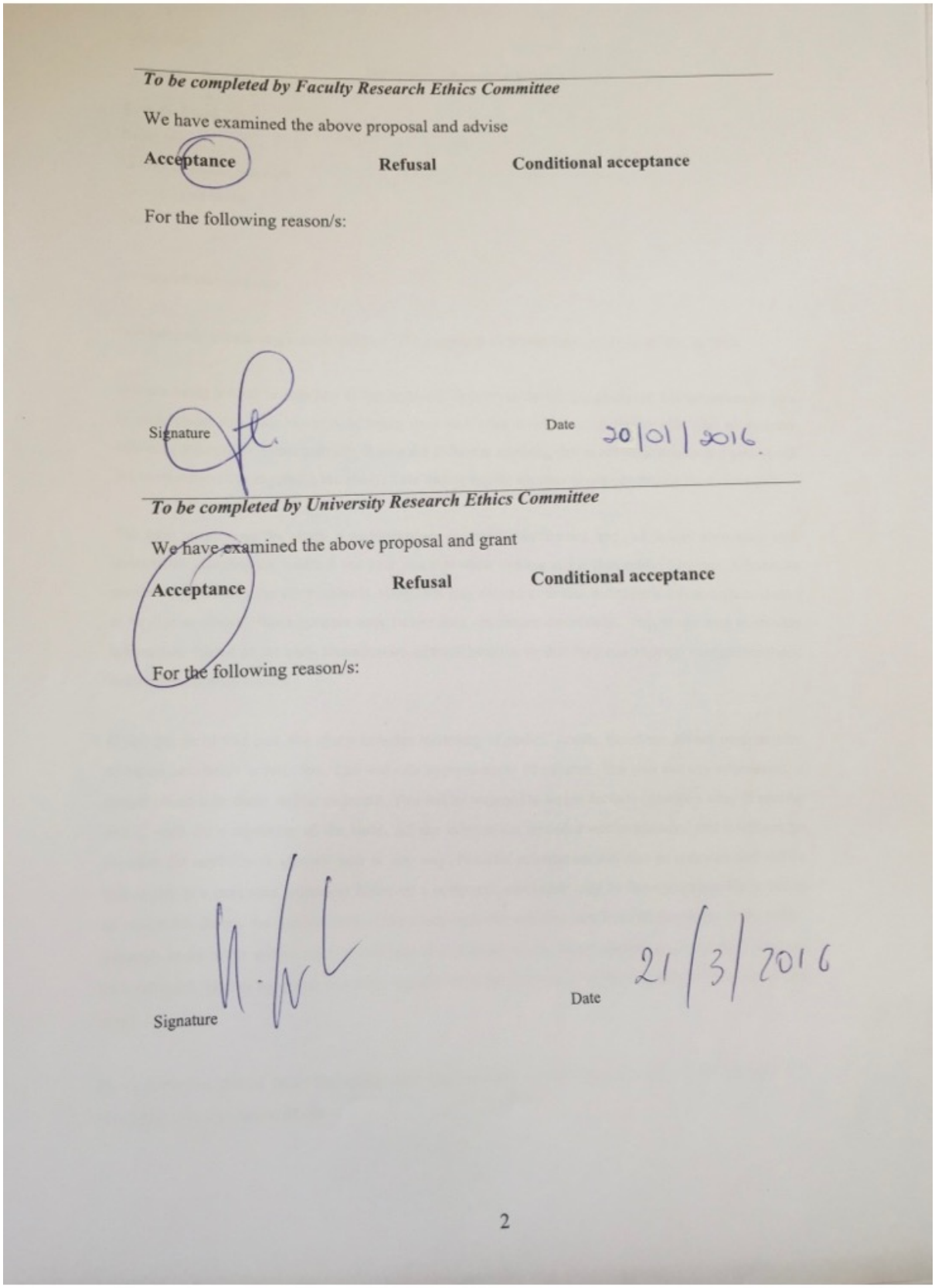
Zhang, J., & Kai, F. Y. (1998). What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. *Jama, 280*(19), 1690-1691.

Zhang, Y., Huang, J., & Wang, P. (2016). A prediction model for the peripheral arterial disease using NHANES data. *Medicine, 95*(16), e3454. https://doi.org/10.1097/MD.0000000000003454 [doi]

Zieliński, L. P., Chowdhury, M. M., Carter, M., Worsfold, B. P., & Coughlin, P. A. (2017). Variability in atherosclerotic disease progression within the infrainguinal arterial circulation is dependent on both patient and anatomical factors. *Annals of Vascular Surgery, 44*, 289-298.

APPENDIX 1

Research ethics application approval



To be completed by Faculty Research Ethics Committee

We have examined the above proposal and advise

Acceptance **Refusal** **Conditional acceptance**

For the following reason/s:

Signature

Date 20/01/2016.

To be completed by University Research Ethics Committee

We have examined the above proposal and grant

Acceptance **Refusal** **Conditional acceptance**

For the following reason/s:

Signature

Date 21/3/2016

2

APPENDIX 2

STROBE statement

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

APPENDIX 3

Mizzi *et al. Journal of Foot and Ankle Research* (2019) 12:40
https://doi.org/10.1186/s13047-019-0351-0

Journal of
Foot and Ankle Research

REVIEW Open Access

The progression rate of peripheral arterial disease in patients with intermittent claudication: a systematic review

A. Mizzi[1*], K. Cassar[2], C. Bowen[3] and C. Formosa[1]

Abstract

Background: Intermittent claudication (IC) is the most common symptom of peripheral arterial disease and is generally treated conservatively due to limited prognostic evidence to support early revascularisation in the individual patient. This approach may lead to the possible loss of opportunity of early revascularisation in patients who are more likely to deteriorate to critical limb ischaemia. The aim of this review is to evaluate the available literature related to the progression rate of symptomatic peripheral arterial disease.

Methods: We conducted a systematic review of the literature in PubMed and MEDLINE, Cochrane library, Elsevier, Web of Science, CINAHL and Opengrey using relevant search terms to identify the progression rate of peripheral arterial disease in patients with claudication. Outcomes of interest were progression rate in terms of haemodynamic measurement and time to development of adverse outcomes. Two independent reviewers determined study eligibility and extracted descriptive, methodologic, and outcome data. Quality of evidence was evaluated using the Cochrane recommendations for assessing risk of bias and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: Seven prospective cohort studies and one retrospective cohort study were identified and included in this review with the number of participants in each study ranging from 38 to 1244. Progression rate reports varied from a yearly decrease of 0.01 in ankle-brachial pressure index (ABPI) to a yearly decrease ABPI of 0.014 in 21% of participants. Quality of evidence ranged from low to moderate mostly due to limited allocation concealment at recruitment and survival selection bias.

Conclusions: Progression of PAD in IC patients is probably underestimated in the literature due to study design issues. Predicting which patients with claudication are likely to deteriorate to critical limb ischaemia is difficult since there is a lack of evidence related to lower limb prognosis. Further research is required to enable early identification of patients at high risk of progressing to critical ischaemia and appropriate early revascularisation to reduce lower limb morbidity.

Keywords: Intermittent claudication, Peripheral arterial disease, Haemodynamic deterioration, Prognosis, Progression

* Correspondence: anabellemizzi@gmail.com
[1]Faculty of Health Sciences, University of Malta, Msida, Malta
Full list of author information is available at the end of the article

Background

Intermittent claudication (IC) is the first symptom of peripheral arterial disease (PAD) and is associated with significant functional impairment [1, 2]. Patients with IC are at significant risk of atherosclerotic morbidity such as stroke and coronary artery disease [3]. The mortality risk of patients presenting with IC is double that of patients with PAD who are asymptomatic [4]. On the other hand, the prognosis and progression of PAD of the affected limbs is known to be less relevant with the majority remaining stable, some improving, while approximately 20–25% requiring revascularisation and 5% eventually deteriorating to critical limb ischaemia (CLI) [5].

Since it is expected that the majority of patients with IC will have a relatively benign lower limb prognosis, the recommended first-line treatment strategy is conservative treatment [6]. This includes lifestyle modification (smoking cessation and exercise [7, 8], and medical therapy [9–11] (antiplatelets, lipid lowering drugs and blood pressure management). The primary objective of this treatment strategy is to reduce the risk of major adverse cardiovascular events in this patient cohort rather than to control lower limb symptoms or delay progression of peripheral arterial disease. Unfortunately, this approach ignores the fact that a proportion of patients with claudication will deteriorate to critical limb ischaemia and will require lower limb interventions. Patients who develop a major adverse limb event (MALE) have more than a threefold increase in mortality and an almost two hundred fold increased risk of limb loss [12].

If those patients with claudication at high risk for deterioration to critical limb ischaemia could be identified before the onset of gangrene and tissue loss, early revascularisation could possibly reduce the risk of minor amputations, major amputations, local and systemic sepsis from ulcers and wet gangrene and mortality [13]. Intervening early when the patient is younger and possibly fitter and without concomitant ulceration or gangrene would more likely lead to better surgical outcomes, lower mortality and less septic complications. There is clear evidence that revascularisation surgery conducted on an urgent or emergency basis and in the presence of gangrene and tissue loss is associated with significantly higher surgical mortality and morbidity [13]. In addition, intervening earlier would often require less invasive and less extensive procedures [14]. Endovascular, open or hybrid procedures involve the treatment of underperfused segments in the lower limb by improving blood flow to increase pain free walking distance. While revascularisation, together with exercise, is superior in treating IC compared to medical therapy alone [15–17], the choice of treatment should rely on patients' values and preferences, clinical context and expertise [18] since well-defined clinical practice guidelines for choice of treatment in patients with IC are still lacking.

Currently there are no predictive formulae that allow the clinician to estimate the level of risk of an individual patient with intermittent claudication to progress to critical limb ischaemia or the time scale in which this is likely to occur [6]. For effective patient specific decisions to be made, tools to predict the risk per year of the patient deteriorating to critical ischaemia are required. This risk could then be balanced against the life expectancy of the particular patient, as well as the risks of the particular intervention/s required to optimise perfusion to the limb. Availability of this information would also enable informed decisions as to which treatment option would be best suited for a particular patient where more than one treatment option is available. Thus for example a lower risk but less effective revascularisation option may be selected in a high risk patient, while for a low risk patient a higher risk but more durable procedure may be indicated.

In order to develop predictive formulae for patient specific lower limb management for IC, detailed PAD progression data is crucial, however this is scarce, since the main focus of research has been coronary disease and stroke with less attention paid to the lower limb [3, 5].

This paper evaluated the current evidence related to the progression rate of PAD in patients with IC which is essential for informed clinical decision making.

Methods

This systematic review was conducted following recommendations from the Cochrane Collaboration [19]. The study design, population selection and follow-up time frame were summarised following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. The search was conducted between 9th July and 25th July 2018.

Literature search

The search for potentially relevant articles was performed in PubMed and MEDLINE, Cochrane database of systematic reviews, Elsevier (Embase and Sciencedirect), Web of Science and CINAHL. Reference lists of retrieved full-text articles were also cross-checked and OpenGrey database was searched for any relevant grey literature. The searches were performed without restrictions on publication date, or publication status. Search results were downloaded into a bibliographic software Refworks (ProQuest LLC).

The inclusion criteria for the search strategy consisted of studies on humans and written in the English language. The search terms used for this literature search were identified after reading several publications related to the subject area and through conducting scoping searches. The terms were formulated by three experienced reviewers who have an interest in the subject area.

Choice of terms was done independently and was finalised by the main researcher who eliminated duplicates but retained all the identified key words. The literature search sought to identify studies reporting the progression of PAD in patients with IC. Search terms included free text terms and Medical Subject Heading (MeSH) terms related to [1] intermittent claudication; [2] PAD; [3] peripheral vascular disease. The keywords and MeSH headings for searching MEDLINE used are presented in Table 1. Search strategies were adapted for searching within different databases. The terms needed to present in the title or abstract.

Study eligibility criteria

As recommended in the PRISMA statement [20], before starting the literature search explicit declarations of questions being addressed were defined with reference to participants, interventions, comparisons, outcomes and study design (PICOS).

Eligible articles needed to report on the natural history of patients with IC as a symptom of PAD, also documenting progression rate of the disease. Disease progression has been previously suggested to be detectable after twelve months [21], therefore studies were selected if they primarily aimed to investigate the progression of symptomatic arterial disease with at least one-year follow-up.

Primary endpoints were progression rate in terms of haemodynamic parameters (expressed as time for change in ankle and / or toe pressures) and adverse lower limb events (expressed as time to development of ulceration, amputation or gangrene). Secondary endpoints were identification of prognostic factors for the development of adverse lower limb events and for the progression of PAD in patients with IC.

While prospective observational longitudinal cohort studies have the most suitable design to investigate the natural history of events [22], in this review all study designs and sample sizes were considered.

Table 1 Keywords and MeSH headings used for literature search

Search 1: MeSH headings – intermittent claudication
Intermittent claudication AND Prognosis
Intermittent claudication AND fate
Intermittent claudication AND natural history
Intermittent claudication AND progression
Intermittent claudication AND outcome
Search 2: MeSH headings - peripheral arterial disease, peripheral vascular disease
Peripheral arterial disease/ peripheral vascular disease AND Prognosis
Peripheral arterial disease/ peripheral vascular disease AND Progression
Peripheral arterial disease/ peripheral vascular disease AND natural history
Peripheral arterial disease/ peripheral vascular disease AND outcome

Study selection

Titles and abstracts of studies identified by the search strategy were assessed in terms of relevance to the study topic. Additional relevant references identified from the bibliography of the reviewed articles and those retrieved from the grey literature search, were also assessed. Full texts of selected articles were retrieved if they fulfilled the inclusion criteria and were reviewed by two investigators independently (SM and CF, both experienced researchers). A meta-analysis was planned if clinical homogeneity was observed. The process was pilot-tested on a selection of studies and refined where required. Disagreement between reviewers regarding the article relevance, inclusion or quality was discussed until agreement was reached.

Quality assessment

Methodological quality of each trial was evaluated systematically with the aid of the Cochrane handbook [19] and reported following the PRISMA checklist [20]. The Cochrane recommended approach for interpretation of the risk of bias for each important outcome (across domains) within and across studies was applied as summarized in Table 2 below [23].

Results

The initial database search yielded a total of 793 potentially relevant papers and an additional paper was retrieved from grey literature search. These were processed as illustrated in Fig. 1 and following the independent review of the full-text versions by SM and CF, a further 59 articles were excluded while 8 studies fulfilled the inclusion criteria and were included. The reasons for exclusion were failure to report haemodynamic deterioration, failure to report outcomes of participants with IC, failure to report temporal progression of PAD and use of same cohort. The PRISMA flow chart and reasons for exclusion are shown in Fig. 1. Due to the heterogeneity of the methods used in reporting haemodynamic deterioration and outcome measures, a narrative synthesis of the 8 included studies was conducted without meta-analysis.

Eight full-text articles met the selection criteria reporting temporal progression of PAD in patients with IC [21, 24–30]. Study designs included were seven prospective cohort studies and one retrospective cohort study. The number of participants ranged from 38 to 1244, with the largest study recruiting only male participants. Six studies [24–29] included ABPI as a baseline clinical measure of PAD and two studies [21, 30] reported degrees of stenosis using duplex ultrasonography. Only one study [26] included TBPI. Diagnosis of IC as a symptom of PAD, in order to exclude any alternative diagnosis, varied considerably across the studies. One study used the WHO questionnaire, while 5 studies used ABPI < 0.9 as a cut-off point and another two studies used duplex ultrasound scan reports to diagnose PAD at

Table 2 Interpretation of bias risk [23]

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias.	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias.	Plausible bias that raises some doubt about the results.	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias.
High risk of bias.	Plausible bias that seriously weakens confidence in the results.	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

baseline and exclude alternative non-atherosclerotic causes of IC. Two studies evaluated walking distance using treadmill tests, one other study included data using the San Diego claudication questionnaire while the rest did not report walking distance. Follow-up period ranged from one year to twelve years. The characteristics of the included studies are described in Table 3.

Progression of PAD

We identified 8 studies which evaluated the progression of PAD in patients with IC. Only two studies [24, 25] reported yearly haemodynamic decline in ABPI by 0.014 and 0.01 respectively. Others reported varied results which are summarized below. The different measures of PAD progression, differing follow-up and outcome data used in the included literature makes inferences difficult as to defining the progression rate of PAD in patients with IC.

Summary of results

In summary, the results of this study demonstrate that yearly haemodynamic decline in ABPI was reported in two study by 0.014 [24] and 0.01 [25]. Another study reported an overall decline in ABPI of 0.02 or 0.013 in TBPI, but included both IC participants and participants

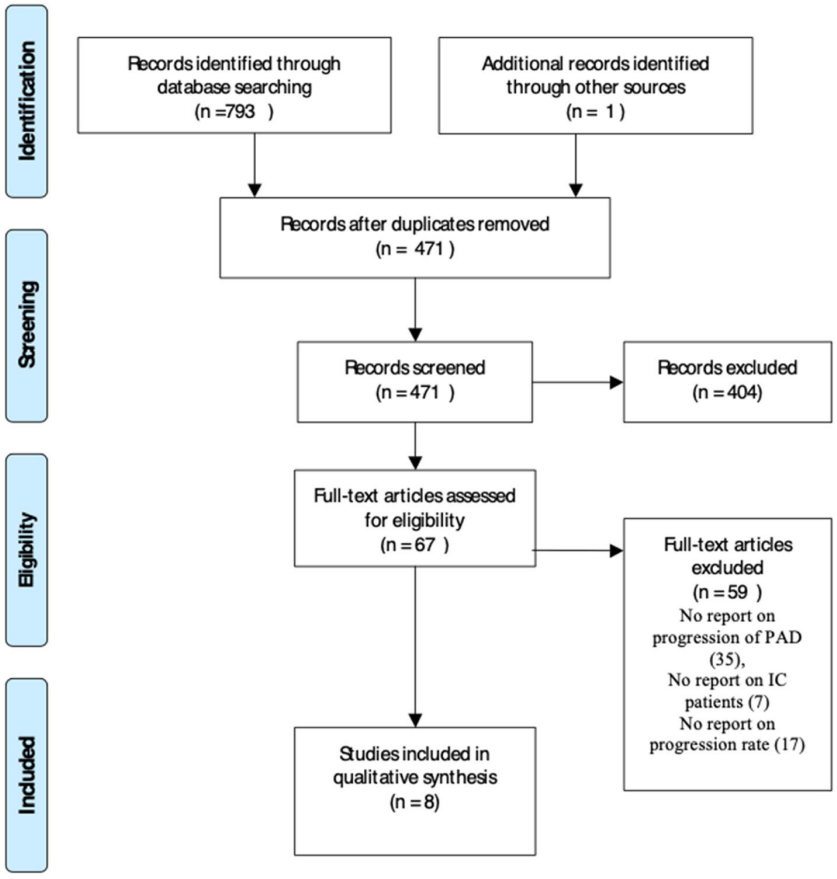


Fig. 1 PRISMA flow chart for study selection

Table 3 Characteristics of included trials

Publications	Trial characteristics	Haemodynamic measure	Progression of PAD	Prognostic factors for progression of PAD
Smith et al. 1998 [29]	Prospective observational cohort study 235 participants with IC 3 year follow-up	ABPI	ABPI decreased by > 0.14 after 1 year in 21% of participants, 12.5% developed CLI after 3 years	Hypertriglycerideamia, ABPI < 0.5 at baseline is associated with increased risk of deterioration
Smith et al. 2003 [28]	Prospective observational cohort study 131 participants with IC 5 and 12 year follow-up	ABPI	Overall decrease in ABI by 0.09 over 5 yrs. in higher ABPI limb. Decrease in ABPI by 0.04 in lower ABPI limb	Higher ABI associated with faster deterioration Lower ABI associated with increased risk of lower limb events
Walsh et al. 1991 [21]	Prospective observational cohort study 38 participants (45 limbs) with IC and SFA stenosis 3 year follow-up	Arteriograms, and duplex scans	15.6% of participants developed a 30% increase in stenosis after 1 year.	Smoking and symptom progression predictive of SFA stenosis progression. SFA occlusion is synchronous with symptom progression. Contralateral SFA occlusion increases risk of faster stenosis
Bird et al. 1999 [26]	Prospective observational cohort study 177 participants with IC 4.7 year follow-up	ABPI, San Diego Claudication questionnaire	Overall ABI decrease of 0.02 over 4.6 yrs. and TBPI decrease by 0.013 in 4.7 years	Age, DM are associated with rapid progression
Aquino et al. 2001 [24]	Prospective observational cohort study 1244 male veterans with IC 3.7 year follow-up	ABPI	Overall yearly decline in ABPI by 0.014	ABPI < 0.5, high smoking pack years and DM increase risk CLI
Naschitz et al. 1988 [27]	Retrospective cohort study 460 participants with IC referred for vascular surgical consultation 3.8 year follow-up	ABPI, Doppler waveforms, angiography	Decrease by 0.15 in ABPI in those who deteriorate (53.2% of participants)	ABI > 0.7, no deterioration of ABI predicts good outcome ABI < 0.5 at baseline increases risk of deterioration by 3.8 times ABI decrease by 0.15 increases risk by 1.9 times for need eventual surgery
Fowkes et al. 1993 [25]	Prospective observational cohort study 617 participants with IC 1 year follow-up	ABPI	Overall ABPI decrease by − 0.01 per year 4.8% developed CLI, no haemodynamic report	Age, smoking associated with deterioration in ABPI
Whyman et al. 1993 [30]	Prospective observational cohort study 38 participants with IC with femoropopliteal artery stenosis 19 months	Duplex scan (Bollinger score)	Patients with velocity ratio > 3 progressed to occlusion within 13 weeks	Velocity ratio of > 3 associated with occlusion within 76 weeks.

with PAD but with no symptoms [26]. Others reported that ABPI < 0.58 at baseline and/or a decline by 0.15 in ABPI is indicative of progression to critical limb ischaemia (CLI), without reporting the temporal element [27]. However, a faster atherosclerotic progression rate was observed in claudicants compared to non-claudicants [21] and a yearly 30% increase in SFA stenosis is indicative of requirement for revascularisation. Smith et al. [28] reported a decline after 5 years in ABPI by 0.04 in the limb with lower ABPI at baseline and a decline of 0.09 in the limb with higher ABPI. While in an earlier study, Smith et al. [29] reported a decline of 0.14 of ABPI in 21% of the participants after 1 year of diagnosis. Using velocity ratio measured by duplex, Whyman et al. [30] reported that a velocity ratio > 3 at baseline is associated with deterioration to occlusion of SFA within thirteen weeks.

The prognostic value of the reports presented in the selected studies is limited due to the quality of evidence of each trial. Overall the reviewers rated the quality of evidence for progression rate of PAD in patients with IC as low mainly owing to the possibility of serious risk of bias in these studies (Table 4). For evidence related to the identification of specific patient characteristics associated with poor prognosis and risk of developing adverse events, reviewers generally rated the evidence as moderate, mainly due to the substantial differences between the studies. A narrative with the rationale for these results is presented below.

Selection bias, because of inadequate allocation concealment at recruitment stage was observed in four out of the seven studies reviewed [21, 25–27]. Inadequate allocation concealment occurs when the researcher is aware of the next treatment allocated for the patient, which often leads to selection bias in observational studies. Participants with IC who were referred for revascularisation or who were severely ischaemic were excluded from these studies, resulting in the recruitment of only those with milder disease. Subsequently the disease progression reported by a mean or percentage decline in ABPI in these studies, does not include those with more severe PAD and results therefore underestimate the true progression.

Survival selection bias was evident in 6 [24–29] out of the seven studies reviewed. This occurred when authors excluded participants who required revascularisation during the course of the study or who died by the end of the study. In the context of evaluating the natural history of PAD in IC patients, survival selection bias, sometimes referred to as selective reporting, often results in the underestimation of the true progression of the disease since those who most likely progressed rapidly were excluded from the analysis. Among the reviewed studies, this source of bias was often coupled with selection bias at recruitment stage, as discussed earlier, which may have exacerbated the possibility of underestimation of the progression of PAD in this group of patients.

The reporting of methodological detail about aspects that threaten internal validity such as measurement precision of the tools used were often reported. Having reliable and valid instruments is one of the best ways of reducing measurement bias in epidemiologic research. However, reports of measurement quality due to the possibility of arterial calcification and hence reporting, were also neglected, with only one article [26] reporting the possibility of artefactually elevated ABPI. While Walsh et al. [21] analysed atherosclerotic progression using sonographic studies, other studies which used the ABPI as a surrogate measure of peripheral perfusion, are susceptible to the hidden risks associated with this tool [31]. Patients with diabetes, smoking, renal disease or aged over seventy five are at a higher risk of medial arterial calcification [32, 33]. In these patients, the ABPI needs to be interpreted with caution since results may be artefactually elevated due to non-closure or delayed closure of the artery when the cuff is inflated. In such cases the TBPI is recommended since the digital arteries of the foot are less susceptible to arterial calcification [34, 35]. However, since most of these studies were published before issues with calcification and ABPI readings were recognized, the possibility of having artefactually

Table 4 Risk of bias of included trials

Source of bias					
First author	Allocation concealment	Selective recruitment	Incomplete outcome data	Survival selection	Summary risk of bias
Naschitz 1988 [27]	yes	yes	no	yes	high
Walsh (1991) [21]	yes	yes	no	no	moderate
Fowkes (1993) [25]	yes	yes	no	yes	high
Whyman (1993) [30]	No	No	yes	No	low
Bird (1999) [26]	yes	yes	yes	yes	High
Smith (1998) [29]	No	yes	yes	yes	high
Smith (2003) [28]	No	yes	yes	yes	high
Aquino (2005) [24]	no	yes	no	yes	moderate

elevated ABPI readings was not addressed. Among the studies included in this systematic review, only one study [26] reported TBPI readings while another six [24, 25, 27–30] did not discuss the possibility of falsely elevated results possibly resulting in an underestimation of the true decline of ABPI in their results [36].

Discussion

This systematic review is the first to evaluate the progression rate of PAD in individuals with IC in terms of haemodynamic assessments of the lower limb, since previous reviews largely focused on mortality or amputation risks [37]. Data from the reviewed studies have generally agreed on an overall decline in ABPI by 0.01 to 0.02 over 1 year [24, 26, 28]. A decline of 0.15 was reported in severe cases of PAD [27] which has been previously associated with a 2.5 increased risk of surgical intervention [38] and is independently associated with increased risk of cardiovascular disease [39]. However, these results are probably an underestimation of the true overall deterioration in this population. The issues with selection bias at recruitment stage and the use of ABPI as a measure of peripheral perfusion with its inherent difficulties in the presence of medial arterial calcification [31, 40] probably resulted in a falsely conservative measure of PAD progression reported in most studies. Indeed, a faster progression rate was reported in only one study, stating an overall decrease of 0.14 in ABPI in 21% of patients within the first year [29].

The underestimated risk to the limb in PAD patients has also been reported in a systematic review investigating the progression of PAD in both asymptomatic and symptomatic patients within the context of amputation and mortality risk [37, 41]. The authors report that while the TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) state an amputation rate of 1–3% after five years [6] in IC patients, results from their review indicate a more aggressive progression of PAD resulting in an amputation rate of 27% in those with IC.

Current level of knowledge precludes the development of robust predictive formulae to identify the risk of haemodynamic deterioration in an individual patient. It is extremely likely that accurate prediction of patient specific risk of deterioration would lead to a paradigm shift in the management of patients with intermittent claudication. Delaying intervention until the patient has already developed critical ischaemia almost invariably means that more extensive occlusive disease has developed. The more complex and the more extensive the disease the more difficult and the riskier the intervention is and the lower the likelihood of success and long-term patency [30]. Furthermore, the incidence of MALE is associated with a very significantly increased risk of limb loss and death [12]. In a systematic review of treatment in IC [18], authors concluded that data related to the identification of the best suited intervention for each individual patient to achieve the most favourable outcome are still lacking. As a result of this uncertainly The Society for Vascular Surgery recommends that patients' values and preferences should guide the clinical decision on intervention in patients with intermittent claudication [42]. Ideally however those preferences should be based on more robust evidence.

The poor design and reporting in the selected studies may have introduced bias and reduced the robustness of data [22, 43]. The studies evaluated in this systematic review have shown variable reporting of some of the major threats to the internal and external validity of observational longitudinal studies [22]. Selection bias due to inadequate allocation concealment, limited reporting of methodological detail, incomplete information related to attrition or non-consent and survival selection bias were the most common sources of bias observed in these studies. Despite ongoing efforts in research in this population, it is common in the literature for the main focus to be mortality and cardiovascular risk rather than the affected limb [37]. This trend has resulted in a limited understanding of the prognosis and progression rate of PAD in IC with no established criteria which allow the clinician to predict outcomes in an individual patient [44].

Limitations of this review

The limitations of this review are mainly related to the significant heterogeneity of data among the studies due to different outcome measures and study cohorts. Therefore, meta-analyses of the data could not be performed and only descriptive analysis of the studies was presented. Methodological quality of the included studies was rigorously assessed.

Although efforts were made to carry out a thorough search of the literature, some studies may have been overlooked during the process.

Future studies

This paper highlights the need for further research to evaluate the progression rate of PAD in patients with IC. Data from registries which include complete consecutive patient cohorts and are protected from selection bias, are important to support such knowledge. Future studies should conceal allocation and pursue a high rate of follow-up, with a maximum of twelve-month interval between reviews in order to capture any haemodynamic change and reduce the risk of survival selection bias observed in studies with long interval periods and high attrition rates. Due to the calcification risk and possibility of artefactually elevated ABPIs, future studies need to include Doppler waveform and toe-brachial pressure analysis since these assessment modalities are less susceptible to arterial calcification and more likely to provide reliable haemodynamic data.

Conclusions

This review has shown that the existing knowledge on the natural progression of intermittent claudication is limited to a small number of studies providing mostly low-quality evidence related to measurable haemodynamic progression rate. The inherent difficulties associated with ABPI as a surrogate measure of peripheral perfusion in patients with medial arterial calcification and the probable underestimated rate of reported progression of PAD have been highlighted. Consequently, international guidelines on the management of PAD are necessarily generic. Further research into the natural progression of the disease is required to enable the development of predictive formulae to guide patient specific management of the condition.

Abbreviations

CLI: Critical limb ischaemia; IC: Intermittent claudication; MALE: Major adverse limb event; PAD: Peripheral arterial disease,; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Acknowledgements

We would like to thank Dr. Stephen Mizzi for contributing to the reviewing process of the papers during data collection.

Authors' contributions

AM, CB, CF conceived the study, AM, CB designed the study protocol, AM performed data collection and interpretation, CF reviewed the data, AM drafted the manuscript. CF, CB and KC critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Funding

Prof Catherine Bowen is currently being supported to undertake Fellowship from The National Institute for Health Research, UK. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of National Institute for Health Research, NHS or the Department of Health.

Availability of data and materials

The datasets used and / or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Prof Catherine Bowen is the Editor in Chief (UK) of the Journal of Foot and Ankle Research. It is journal policy that editors are removed from the peer review and editorial decision-making processes for papers they have co-authored. The remaining authors declare no conflicts of interest in relation to this work.

Author details

[1]Faculty of Health Sciences, University of Malta, Msida, Malta. [2]Mater Dei hospital, Faculty of Medicine and Surgery, University of Malta, Msida, Malta. [3]School of Health Sciences, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK.

Received: 24 April 2019 Accepted: 29 July 2019
Published online: 06 August 2019

References

1. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA. 2004;292(4):453–61.
2. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, et al. The impact of peripheral arterial disease on health-related quality of life in the peripheral arterial disease awareness, risk, and treatment: new resources for survival (PARTNERS) program. Vasc Med. 2008 Feb;13(1):15–24.
3. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382(9901):1329–40.
4. Sartipy F, Sigvant B, Lundin F, Wahlberg E. Ten year mortality in different peripheral arterial disease stages: a population based observational study on outcome. Eur J Vasc Endovasc Surg. 2018;55(4):529–36.
5. Cassar K. Intermittent claudication. Br Med J. 2006;7576:1002.
6. Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, Razavi M, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II): the TASC steering committee. Catheter Cardiovasc Interv. 2015;86(4):611–25.
7. Greenhalgh R. The adjuvant benefit of angioplasty in patients with mild-to-moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for occlusive femoropopliteal and aortoiliac occlusive arterial disease. Eur J Vasc Endovasc Surg. 2008.
8. Kalbaugh CA, Gonzalez NJ, Luckett DJ, Fine J, Brothers TE, Farber MA, et al. The impact of current smoking on outcomes after infrainguinal bypass for claudication. J Vasc Surg. 2018.
9. Cassar K. Peripheral arterial disease. BMJ Clin Evid. 2007;2007:0211.
10. Bianchi C, Montalvo V, Ou HW, Bishop V, Abou-Zamzam AM Jr. Pharmacologic risk factor treatment of peripheral arterial disease is lacking and requires vascular surgeon participation. Ann Vasc Surg. 2007;21(2):163–6.
11. Fiotti N, Altamura N, Cappelli C, Schillan M, Guarnieri G, Giansante C. Long term prognosis in patients with peripheral arterial disease treated with antiplatelet agents. Eur J Vasc Endovasc Surg. 2003;26(4):374–80.
12. Anand S, Caron F, Eikelboom J, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. J Am Coll Cardiol. 2018;71(20):2306–15.
13. Waton S, Johal A, Heikkila K, Cromwell D Loftus I. National Vascular Registry: 2017 annual report. The Royal College of Surgeons of England.
14. Wolosker N, Nakano L, Rosoky RA, Puech-Leão P. Evaluation of walking capacity over time in 500 patients with intermittent claudication who underwent clinical treatment. Arch Intern Med. 2003;163(19):2296–300.
15. Fakhry F, Fokkenrood HJ, Rouwet EV, Teijink JA, Spronk S, Hunink M. Endovascular revascularisation versus conservative management for intermittent claudication. Cochrane Database Syst Rev. 2018;3:CD010512. https://doi.org/10.1002/14651858.CD010512.pub2.
16. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MM. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training—randomized controlled trial 1. Radiology. 2009;250(2):586–95.
17. Whyman M, Fowkes F, Kerracher E, Gillespie I, Lee A, Housley E, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. Eur J Vasc Endovasc Surg. 1996;12(2):167–72.
18. Malgor RD, Alalahdab F, Elraiyah TA, Rizvi AZ, Lane MA, Prokop LJ, et al. A systematic review of treatment of intermittent claudication in the lower extremities. J Vasc Surg. 2015;61(3):54S–73S.
19. Cochrane Collaboration: https://methods.cochrane.org [accessed 20th December 2018].
20. Moher D, Liberati A, Tetzlaff J, Altman DG. RESEARCH METHODS & REPORTING-preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement-David Moher and colleagues introduce PRISMA, an update of the QUOROM guidelines for reporting systematic reviews and meta-analyses. BMJ (CR)-print. 2009;338(7716):332.
21. Walsh DB, Gilbertson JJ, Zwolak RM, Besso S, Edelman GC, Schneider JR, et al. The natural history of superficial femoral artery stenoses. J Vasc Surg. 1991;14(3):299–304.
22. Tooth L, Ware R, Bain C, Purdie DM, Dobson A. Quality of reporting of observational longitudinal research. Am J Epidemiol. 2005;161(3):280–8.
23. Cochrane collaboration: https://methods.cochrane.org/bias/.
24. Aquino R, Johnnides C, Makaroun M, Whittle JC, Muluk VS, Kelley ME, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. J Vasc Surg. 2001;34(6):962–70.

25. Fowkes F, Housley E, Rattray A, Lowe G, Rumley A, Elton R, et al. Cross-linked fibrin degradation products, progression of peripheral arterial disease, and risk of coronary heart disease. Lancet. 1993;342(8863):84–6.
26. Bird CE, Criqui MH, Fronek A, Denenberg JO, Klauber MR, Langer RD. Quantitative and qualitative progression of peripheral arterial disease by non-invasive testing. Vasc Med. 1999;4(1):15–21.
27. Naschitz JE, Ambrosio DA, Chang JB. Intermittent claudication: predictors and outcome. Angiology 1988 Jan;39(1 Pt 1):16–22.
28. Smith FB, Lee AJ, Price JF, van Wijk MC, Fowkes FGR. Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population. J Vasc Surg. 2003;38(6):1323–30.
29. Smith F, Lowe G, Lee A, Rumley A, Leng G, Fowkes F. Smoking, hemorheologic factors, and progression of peripheral arterial disease in patients with claudication. J Vasc Surg. 1998;28(1):129–35.
30. Whyman M, Ruckley C, Fowkes F. A prospective study of the natural history of femoropopliteal artery stenosis using duplex ultrasound. Eur J Vasc Surg. 1993;7(4):444–7.
31. Formosa C, Cassar K, Gatt A, Mizzi A, Mizzi S, Camileri KP, et al. Hidden dangers revealed by misdiagnosed peripheral arterial disease using ABPI measurement. Diabetes Res Clin Pract. 2013 Nov;102(2):112–6.
32. Azpiazu D, Gonzalo S, González-Parra E, Egido J, Villa-Bellosta R. Role of pyrophosphate in vascular calcification in chronic kidney disease. Nefrologia. 2018;38(3):250–7.
33. Ho CY, Shanahan CM. Medial arterial calcification: an overlooked player in peripheral arterial disease. Arterioscler Thromb Vasc Biol. 2016 Aug;36(8):1475–82.
34. Hyun S, Forbang NI, Allison MA, Denenberg JO, Criqui MH, Ix JH. Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus. J Vasc Surg. 2014;60(2):390–5.
35. Martin Borge V, Herranz de la Morena L, Castro Dufourny I, Pallardo Sanchez LF. Peripheral arterial disease in diabetic patients: utility of the toe-brachial index. Med Clin (Barc). 2008 May 3;130(16):611–2.
36. Aboyans V, Criqui MH, Denenberg JO, Knoke JD, Ridker PM, Fronek A. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation. 2006 Jun 6;113(22):2623–9.
37. Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. Eur J Vasc Endovasc Surg. 2016;51(3):395–403.
38. Cronenwett JL, Warner KG, Zelenock GB, Whitehouse WM, Graham LM, Lindenauer SM, et al. Intermittent claudication: current results of nonoperative management. Arch Surg. 1984;119(4):430–6.
39. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. J Am Coll Cardiol. 2008;52(21):1736–42.
40. Tehan PE, Bray A, Chuter VH. Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. J Diabetes Complicat. 2016;30(1):155–60.
41. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh artery study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1991 Jun;20(2):384–92.
42. Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, Mills JL, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg. 2015;61(3):2S–41S. e1.
43. Perkins NJ, Cole SR, Harel O, Tchetgen Tchetgen EJ, Sun B, Mitchell EM, et al. Principled approaches to missing data in epidemiologic studies. Am J Epidemiol. 2017;187(3):568–75.
44. Muluk SC, Muluk VS, Kelley ME, Whittle JC, Tierney JA, Webster MW, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. J Vasc Surg. 2001;33(2):251–8.

Publisher's Note

APPENDIX 4 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

APPENDIX 5

TABLE 1. The checklist criteria, and their definitions, used to rate the articles included in the study*

Criterion	Definition
1. Are the objectives or hypotheses of the study stated?	Self-explanatory.
2. Is the target population defined?	The group of persons toward whom inferences are directed. Sometimes the population from which a study group is drawn.
3. Is the sampling frame defined?	The list of units from which the study population will be drawn. Ideally, the sampling frame would be identical to the target population, but it is not always possible.
4. Is the study population defined?	The group selected for investigation.
5. Are the study setting (venues) and/or geographic location stated?	Comment required about location of research. Could include name of center, town, or district.
6. Are the dates between which the study was conducted stated or implicit?	Self-explanatory.
7. Are eligibility criteria stated?	The words "eligibility criteria" or equivalent are needed, unless the entire population is the study population.
8. Are issues of "selection in" to the study mentioned?†	Any aspect of recruitment or setting that results in the selective choice of participants (e.g., gender or health status influenced recruitment).
9. Is the number of participants justified?	Justification of number of subjects needed to detect anticipated effects. Evidence that power calculations were considered and/or conducted.
10. Are numbers meeting and not meeting the eligibility criteria stated?	Quantitative statement of numbers.
11. For those not eligible, are the reasons why stated?	Broad mention of the major reasons.
12. Are the numbers of people who did/did not consent to participate stated?	Quantitative statement of numbers.
13. Are the reasons that people refused to consent stated?	Broad mention of the major reasons.
14. Were consenters compared with nonconsenters?	Quantitative comparison of the different groups.
15. Was the number of participants at the beginning of the study stated?	Total number of participants (after screening for eligibility and consent) included in the first stage of data collection.
16. Were methods of data collection stated?	Descriptions of tools (e.g., surveys, physical examinations) and processes (e.g., face-to-face, telephone).
17. Was the reliability (repeatability) of measurement methods mentioned?	Evidence of reproducibility of the tools used.
18. Was the validity (against a "gold standard") of measurement methods mentioned?	Evidence that the validity was examined against, or discussed in relation to, a gold standard.
19. Were any confounders mentioned?	Confounders were defined as a variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factors under investigation.
20. Was the number of participants at each stage/wave specified?	Quantitative statement of numbers at each follow-up point.
21. Were reasons for loss to follow-up quantified?	Broad mention and quantification of the major reasons.
22. Was the missingness of data items at each wave mentioned?	Differences in numbers of data points (indicating missing data items) explained.
23. Was the type of analyses conducted stated?	Specific statistical methods mentioned by name.
24. Were "longitudinal" analysis methods stated?	Longitudinal analyses were defined as those assessing change in outcome over two or more time points and that take into account the fact that the observations are likely to be correlated.
25. Were absolute effect sizes reported?	Absolute effect was defined as the outcome of an exposure expressed, for example, as the difference between rates, proportions, or means, as opposed to the ratios of these measures.
26. Were relative effect sizes reported?	Relative effects were defined as a ratio of rates, proportions, or other measures of an effect.
27. Was loss to follow-up taken into account in the analysis?	Specific mention of adjusting for, or stratifying by, loss to follow-up.
28. Were confounders accounted for in analyses?	Specific mention of adjusting for, or stratifying by, confounders.
29. Were missing data accounted for in the analyses?	Specific mention of adjusting for, or stratifying by, or imputation of missing data items.
30. Was the impact of biases assessed qualitatively?	Specific mention of bias affecting results, but magnitude not quantified.
31. Was the impact of biases estimated quantitatively?	Specific mention of numerical magnitude of bias.
32. Did authors relate results back to a target population?	A study is generalizable if it can produce unbiased inferences regarding a target population (beyond the subjects in the study). Discussion could include that generalizability is not possible.
33. Was there any other discussion of generalizability?	Discussion of generalizability beyond the target population.

* Sources for definitions: Rothman and Greenland (35), Last (37), Twisk (41).
† Represents selection bias at the beginning of a study. Other selection biases (i.e., loss to follow-up, missing data items) are dealt with by other checklist criteria.

APPENDIX 6

Tool to Assess Risk of Bias in Cohort Studies

1. **Was selection of exposed and non-exposed cohorts drawn from the same population?**

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Exposed and unexposed drawn for same administrative data base of patients presenting at same points of care over the same time frame

Examples of high risk of bias: exposed and unexposed presenting to different points of care or over a different time frame

2. Can we be confident in the assessment of exposure?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Secure record [e.g. surgical records, pharmacy records]; Repeated interview or other ascertainment asking about current use/exposure

Examples of higher risk of bias: Structured interview at a single point in time; Written self report; Individuals who are asked to retrospectively confirm their exposure status may be subject to recall bias – less likely to recall an exposure if they have not developed an adverse outcome, and more likely to recall an exposure (whether an exposure occurred or not) if they have developed an adverse outcome.

Examples of high risk of bias: uncertain how exposure information obtained

3. Can we be confident that the outcome of interest was not present at start of study

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?

Definitely yes (low risk of bias)	Mostly yes	Mostly no	Definitely no (high risk of bias)

Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables

Examples of higher risk of bias: matching or adjustment for most plausible prognostic variables

Examples of high risk of bias: matching or adjustment for a minority of plausible prognostic variables, or no matching or adjustment at all. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

5. **Can we be confident in the assessment of the presence or absence of prognostic factors?**

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from data base with documentation of accuracy of abstraction of prognostic data

Examples of higher risk of bias: Chart review without demonstration of reproducibility; data base with uncertain quality of abstraction of prognostic information

Examples of high risk of bias: Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables

6. Can we be confident in the assessment of outcome?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Independent blind assessment; Record linkage; For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture.

Examples of higher risk of bias: Independent assessment unblinded; self-report; For some outcomes (e.g. vertebral fracture where reference to x-rays would be required) reference to the medical record would not be adequate outcomes.

Examples of high risk of bias: uncertain (no description)

7. Was the follow up of cohorts adequate?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a important impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not large enough to have an important impact on the observed effect size; Missing data have been imputed using appropriate methods.

Examples of high risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce important bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is large enough to induce clinically relevant bias in the observed effect size.

8. Were co-Interventions similar between groups?

Definitely yes (low risk of bias)	Probably yes	Probably no	Definitely no (high risk of bias)

Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

Examples of high risk of bias: Few or no relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

APPENDIX 7

Participant Information Sheet

Anabelle Mizzi
Room 56
Faculty of Health Sciences
University of Malta
Date:

To whom it may concern

I am currently conducting a study entitled 'The prognosis of intermittent claudication' for my PhD.

You are being invited to take part in this research. Before you decide to participate, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information sheet carefully. Please ask if there is anything that is not clear to you or if you would like more information regarding the study. Take time to decide whether or not you would like to take part.

The main purpose of the study is to investigate patient characteristics and risk factors associated with intermittent claudication, which is the pain you feel when walking and is then relieved by rest. A literature search has shown that in some patients, symptoms may worsen over time but there is not enough evidence to be able to identify these patients early before their circulation deteriorates. This study aims to provide information related to the early identification of these patients so that they can undergo surgical treatment before deterioration occurs.

If you decide to take part, the study includes recording of medical details, blood results and measurement of blood circulation in your feet. This will take approximately 30 minutes. You may ask any information or details about how these will be collected. You will be required to return for data collection after 12 months and 2 years for a repetition of the tests. All the information recorded will be encoded and it will not be possible for anybody to identify you in any way. Personal information will also be encoded and will be kept safely in a password protected folder on a computer, accessible only by the researcher. There will be no restriction during the participation of the study and if at any time you feel distressed due to the study, although every effort will be made to minimise the chances of this from happening, your participation will be terminated. Ethical approval has been sought from the University of Malta before conduction of the study.

The information gained from this study may help develop new treatment protocols for patients with intermittent claudication in Malta.

It is up to you whether you wish or not to take part. If you decide to take part, you are still free to withdraw from the study at any time, without giving any reason. A decision to withdraw or not to take part will not affect you in any way. If you require any more information about this research, please feel free to contact me or my supervisor on the contact emails below. If you decide to take part, you can contact me on any of contact details below or you can leave your name with the staff at the Vascular Clinic (MDH) so that I can contact

you myself. You will be given this information sheet to keep and will be asked to sign a consent form.

Thank you in advance for taking the time to read this.

Regards

Anabelle Mizzi Researcher
Email:

Dr Cynthia Formosa Supervisor
Email:

APPENDIX 8

Consent Form

Title of Project: The Prognosis of Intermittent Claudication
Researcher: Anabelle Mizzi MSc
Supervisors: Dr Cynthia Formosa
Prof Kevin Cassar

I am a Maltese citizen and am over eighteen (18) years of age.

I have been asked to participate in a research study entitled 'Prognosis of intermittent claudication' conducted Anabelle Mizzi.

The purpose and details of this research have been clearly explained to me by the researcher, Anabelle Mizzi, and all difficulties have been clarified. The tests and procedure for gathering information have also been clearly explained to me.

I understand that the result of this study may be used for medical or scientific purposes and that results achieved from this research which I am participating in may be reported or published, however, I shall not be personally identified in any way, either individually or collectively without my written permission. I was informed that all data will be destroyed after successful completion of this research and all identification numbers of participants will be destroyed as well.

I understand that I may ask for more information about the study now, or at any time as the study progresses.

I am under no obligation to participate in this study and am doing so voluntarily. I may withdraw from the study at any time, without giving any reason. This will not influence in any way the care, attention and treatment normally given to me.

I am not receiving any remuneration for participation in this research.

In case of queries during my participation I may contact Anabelle Mizzi on [redacted].

Signature of Participant:
Name of Participant:
Telephone Number:

Signature of Researcher:
Name of Researcher: Anabelle Mizzi
Telephone Number:

Signature of Supervisor:
Name of Supervisor: Dr Cynthia Formosa
Telephone Number:

APPENDIX 9

The Walking impairment questionnaire

1. ***Please place a √ in the box that best describes how much difficulty you have had walking due to pain, aches or cramps during the last week. The response options range from 'No Difficulty' to 'Great Difficulty.'***

During the last week, *how much difficulty have you had walking due to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Great Difficulty**
a. Pain, aching, or cramps in your calves?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5
b. Pain, aching, or cramps in your buttocks?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5

For the following questions, the response options range from 'No Difficulty' to 'Unable to Do.' If you cannot physically perform a specified activity, for example walk 2 blocks without stopping to rest because of symptoms such as leg pain or discomfort, please place a √ in the box labeled 'Unable to Do.'

However, if you do not perform an activity for reasons unrelated to your circulation problems, such as climbing a flight of stairs because your home is one level or your apartment has an elevator, please place a √ in the box labeled 'Don't Do For Other Reasons.'

2. ***Please place a √ in the box that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:***

During the last week *how difficult was it for you*	**No difficulty**	**Slight difficulty**	**Some difficulty**	**Much difficulty**	**Unable to do**	**Didn't do for other reasons**
Walk indoors such as around the house	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
1. Walk 20m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. Walk 50m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Walk 100m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Walk 200m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Walk 300m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Walk 500m	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

3. *Please place a √ in the box that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week. Please note 1 block is roughly equivalent to 300 feet.*

***During the last week**, how difficult was it for you to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Unable to Do**	**Didn't Do for Other Reasons**
a. Walk 1 block slowly?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
b. Walk 1 block at average speed?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
c. Walk 1 block quickly?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
d. Run or jog 1 block?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

4. *Please place a √ in the box that best describes how hard it was for you to climb stairs without stopping to rest during the last week. Please note 1 flight of stairs is roughly equal to 14 steps.*

***During the last week**, how difficult was it for you to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Unable to Do**	**Didn't Do for Other Reasons**
a. Climb 1 flight of stairs?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
b. Climb 2 flights of stairs?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
c. Climb 3 flights of stairs?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Walking Impairment questionnaire – Maltese version

1. *Jekk jogħġbok immarka √ fil-kaxxa li tiddeskrivi bl-aħjar mod id-diffikulta li jkollok meta timxi minħabba l-uġigħ jew bukgħawwieġ, f'din l-aħħar ġimgħa. Ir-risposta tista tvarja minn 'l-ebda diffikulta' sa 'diffiċli immens'*

F'din l-aħħar ġimgħa, *kemm ħassejt diffikulta biex:*	**l-ebda diffikulta**	**Ftit diffikulta**	**Kemmxejn diffiċli**	**Diffiċli ħafna**	**Ma stajtx**	**Ma stajtx għal raġunijiet oħra**
a. Timxi ġewwa, bħal fid-dar tiegħek	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Timxi 15-il metru	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Timxi 50 metru	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Timxi 100 metru	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e. Timxi 200 metru	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f. Timxi 300 metru	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g. Timxi 500 metru	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

2. *Jekk jogħġbok immarka √ fil-kaxxa li tiddeskrivi bl-aħjar mod id-diffikulta li jkollok meta timxi minħabba l-uġigħ jew bukgħawwieġ, f'din l-aħħar ġimgħa. Ir-risposta tista tvarja minn 'l-ebda diffikulta' sa 'diffiċli immens'*

***F'din l-aħħar ġimgħa**, kemm ħassejt diffikulta biex timxi minħabba:*	**l-ebda diffikulta**	**Ftit diffikulta**	**Kemmxejn diffiċli**	**Diffiċli ħafna**	**Diffiċli immens**
a. Uġigħ, bukgħawwieġ fil-pxiexen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Uġigħ, bukgħawwieġ fil-muskolu tal-patata	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. *Jekk jogħgbok immarka √ fil-kaxxa li tiddeskrivi bl-aħjar mod id-diffikulta li kellek fl-aħħar ġimgħa meta mxejt tul ta' blokk fil-wita' mingħjar ma tieqaf, bil-veloċitajiet differenti ndikati hawn taħt.*

***F'din l-aħħar ġimgħa**, kemm ħassejt diffikulta biex:*	**l-ebda diffikulta**	**Ftit diffikulta**	**Kemmxejn diffiċli**	**Diffiċli ħafna**	**Ma stajtx**	**Ma stajtx għal raġunijiet oħra**
a. Timxi blokk wieħed bil-mod	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Timxi blokk wieħed b'mixja normali	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Timxi blokk wieħed tgħaġġel	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Timxi blokk wieħed tiġri jew jogging	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

3. *Jekk jogħġbok immarka √ fil-kaxxa li tiddeskrivi bl-aħjar mod id-diffikulta li kellek fl-aħħar ġimgħa biex titla t-taraġ mingħjar ma tieqaf. Kul sular fih bejn wieħed u iehor 14-il tarġa.*

F'din l-aħħar ġimħha, *kemm ħassejt diffikulta biex:*	**l-ebda diffikulta**	**Ftit diffikulta**	**Kemmxejn diffiċli**	**Diffiċli ħafna**	**Ma stajtx**	**Ma stajtx għal raġunijiet oħra**
a. Titla sular taraġ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Titla żewġ sulari taraġ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Titla tett sulari taraġ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

APPENDIX 10

Statistical results

Baseline Parameters mean and SD

Variable	Mean	SD	Minimum	Maximum
eGFR (mls/min/1.73m^2) n=150	78.18	31.30	6.0	164.0
Cholesterol (mmol/l) n=150	4.45	1.20	2.41	9.0
Triglyceride (mmol/l) n=150	1.75	1.2	0.15	8.8
HDL Cholesterol (mmol/l) n=150	1.23	0.39	0.63	3.11
Non HDL Cholesterol (mmol/l) n=150	3.23	1.17	1.32	7.49
LDL Cholesterol (mmol/l) n=150	2.41	13.81	0.02	5.85
Total Cholesterol: HDL ratio n=150	3.88	1.33	1.67	7.99
Fasting Glucose (mmol/l) n=115	**8.32**	3.06	4.56	16.85
HbA1c (%) n=150	**6.93**	1.39	4.20	10.91
Creatinine (umol/l) n=150	103.23	74.3	38.0	811
CRP (mg/L) n=139	4.85	7.75	0.10	56.0
ESR (mm 1st hr) n=136	136	16.46	1.00	74.0

	Mean	SD	Minimum	Maximum
ABPI R n=148	0.81	0.32	0.4	1.67
ABPI L n=150	0.82	0.34	0.4	1.6
ABPI (symptomatic limb) n=150	0.71	0.3	0.4	1.60
ABPI* (excluding calcified arteries) n=125	0.60	0.17	0.4	0.86
TBPI n=150	0.38	0.2	0.21	0.94
Absolute toe pressures (mmHg) n=150	57.4	25.3	38	136
Claudication distance (m) n=150	136.2	111.3	50	400
WIQ score n=150	44.9	15.9	28.2	78.8

Waveforms at baseline

PT Doppler waveform

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	4	2.3	2.7	2.7
	Continuous	1	.6	.7	3.3
	Monophasic Continuous	57	32.9	38.0	41.3
	Monophasic	76	43.9	50.7	92.0
	Biphasic	11	6.4	7.3	99.3
	Triphasic	1	.6	.7	100.0
	Total	150	86.7	100.0	
Missing	System	23	13.3		
Total		173	100.0		

DP Doppler waveform

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	4	2.3	2.7	2.7
	Monophasic Continuous	68	39.3	45.3	48.0
	Monophasic	68	39.3	45.3	93.3
	Biphasic	10	5.8	6.7	100.0
	Total	150	86.7	100.0	
Missing	System	23	13.3		
Total		173	100.0		

Analysing Gender

Difference in demographics between men and women

Gender * Age and BMI

		N	Mean	Std. Deviation	P value	95% Conf Int for Mean Lower Bound	95% Conf Int for Mean Upper Bound
Age	Female	31	69.4	8.94	0.818	66.07	72.64
	Male	119	69.8	9.46		68.07	71.51
	Total	150	69.7	9.33		68.19	71.21

Descriptives

BMI

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Female	31	27.516	5.93268	1.0655	25.3400	29.6923	19.20	47.10
Male	119	27.871	3.76019	.34470	27.1888	28.5540	18.90	44.80
Total	150	27.798	4.27841	.34933	27.1077	28.4883	18.90	47.10

Difference in risk factors between men and women

Smoking status* Gender

			Gender		
			Female	Male	Total
Smoking status	Current smoker	Count	10	45	55
		Percentage	32.3%	37.8%	36.7%
	Ex-smoker	Count	4	58	62
		Percentage	12.9%	48.7%	41.3%
	Never smoked	Count	17	16	33
		Percentage	54.8%	13.4%	22.0%
Total		Count	31	119	150
		Percentage	100.0%	100.0%	100.0%

$X^2(2) = 27.002$, **$p < 0.001$**

Cardiac disease * Gender

			Gender		
			Female	Male	Total
Cardiac disease	Cardiac disease	Count	9	52	61
		Percentage	29.0%	43.7%	40.7%
	No cardiac disease	Count	22	67	89
		Percentage	71.0%	56.3%	59.3%
Total		Count	31	119	150
		Percentage	100.0%	100.0%	100.0%

$X^2(1) = 2.12$, $p = 0.139$

Diabetes*Gender

			Gender		
			Female	Male	Total
Diabetes	Diabetes	Count	17	87	104
		Percentage	54.8%	73.1%	69.3%
	No Diabetes	Count	14	32	46
		Percentage	45.2%	26.9%	30.7%
Total		Count	31	119	150
		Percentage	100.0%	100.0%	100.0%

$X^2(1) = 3.861$, **p =0.0**

Gender *MACE

			Gender			P value
			Female	Male	Total	
History of MI	History of MI	Count	2	27	29	**0.041**
		Percentage	6.5%	22.7%	19.3%	
	No History of MI	Count	29	92	121	
		Percentage	93.5%	77.3%	80.7%	
Prior cardiac intervention	Prior cardiac intervention	Count	9	49	58	0.216
		Percentage	29.0%	41.2%	38.7%	
	No prior cardiac intervention	Count	22	70	92	
		Percentage	71.0%	58.8%	61.3%	
History of CVA	History of CVA	Count	4	11	15	0.55
		Percentage	12.9%	9.2%	10%	
	No history of CVA	Count	27	108	135	
		Percentage	87.1%	90.8%	90%	

$X^2(1) = 4.158$, **p =0.041**

Difference in waveforms between men and women

			Gender		
			Female	Male	Total
PT Doppler waveform	Absent	Count	2	2	4
		Percentage	6.5%	1.7%	2.7%
	Continuous	Count	0	1	1
		Percentage	0.0%	0.8%	0.7%
	Monophasic Continuous	Count	12	45	57
		Percentage	38.7%	37.8%	38.0%
	Monophasic	Count	16	60	76
		Percentage	51.6%	50.4%	50.7%

	Biphasic	Count	1	10	11
		Percentage	3.2%	8.4%	7.3%
	Triphasic	Count	0	1	1
		Percentage	0.0%	0.8%	0.7%
Total		Count	31	119	150
		Percentage	100.0%	100.0%	100.0%

$X^2(5) = 3.531$, p =0.

DP waveform * Gender

			Gender		
			Female	Male	Total
DP Doppler waveform	Absent	Count	2	2	4
		Percentage	6.5%	1.7%	2.7%
	Monophasic Continuous	Count	16	52	68
		Percentage	51.6%	43.7%	45.3%
	Monophasic	Count	11	57	68
		Percentage	35.5%	47.9%	45.3%
	Biphasic	Count	2	8	10
		Percentage	6.5%	6.7%	6.7%
Total		Count	31	119	150
		Percentage	100.0%	100.0%	100.0%

$X^2(3) = 3.278$, p =0.351

Descriptive statistics analyzing CHD

						95% C I for Mean			
		N	Mean	SD	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
Absolute toe pressure	Cardiac Disease	61	60.38	24.19	3.10	54.18	66.57	15.00	136.00
	No Cardiac disease	88	55.25	25.87	2.76	49.77	60.73	8.00	130.00
	Total	150	57.35	25.24	2.07	53.26	61.43	8.00	136.00
Claudication distance	Cardiac Disease	61	138.61	115.51	14.79	109.02	168.19	10.00	400.00
	No Cardiac disease	89	134.49	109.01	11.56	111.53	157.46	10.00	400.00
	Total	150	136.17	111.34	9.09	118.20	154.13	10.00	400.00
ABPI	Cardiac Disease	45	.63	.14	.02	.59	.67	.38	.86
	No Cardiac disease	81	.58	.18	.02	.54	.62	.39	.93
	Total	126	.60	.17	.01	.57	.63	.38	.93
ABPIall	Cardiac Disease	61	.77	.32	.04	.69	.85	.38	1.60
	No Cardiac disease	89	.65	.29	.03	.59	.71	.39	1.60
	Total	150	.70	.31	.02	.65	.75	.38	1.60

TBPI	Cardiac Disease	61	.42	.17	.02	.38	.46	.18	.94
	No Cardiac disease	88	.36	.17	.02	.32	.39	.21	.84
	Total	150	.38	.17	.01	.36	.41	.21	.94
Age	Cardiac Disease	61	70.80	9.39	1.20	68.40	73.21	46.00	88.00
	No Cardiac disease	89	68.94	9.26	.98	66.99	70.89	38.00	85.00
	Total	150	69.70	9.33	.76	68.19	71.21	38.00	88.00
BMI	Cardiac Disease	61	46.85	6.43	.82	45.20	48.49	31.30	73.90
	No Cardiac disease	89	44.68	6.91	.73	43.23	46.14	31.30	72.70
	Total	150	45.56	6.78	.55	44.47	46.66	31.30	73.90

Smoking status and cardiac disease

			Cardiac Disease	No Cardiac disease	Total
Smoking Status	Current Smoker	Count	12	43	55
		% within CardiacDisease	19.7%	48.3%	36.7%
	Past Smoker	Count	35	27	62
		% within CardiacDisease	57.4%	30.3%	41.3%
	Never smoked	Count	14	19	33
		% within CardiacDisease	23.0%	21.3%	22.0%
Total		Count	61	89	150
		% within CardiacDisease	100.0%	100.0%	100.0%

X^2 (2)=14.543, **p=0.001**

Systolic blood pressure group * CardiacDisease

			CardiacDisease		Total
			Cardiac Disease	No Cardiac disease	
Systolic blood pressure group	<140mmHg	Count	20	26	46
		% within Cardiac Disease	32.8%	29.2%	30.7%
	140mmHg to 160mmHg	Count	26	34	60
		% within Cardiac Disease	42.6%	38.2%	40.0%
	>160mmHg	Count	15	29	44
		% within Cardiac Disease	24.6%	32.6%	29.3%
Total		Count	61	89	150
		% within Cardiac Disease	100.0%	100.0%	100.0%

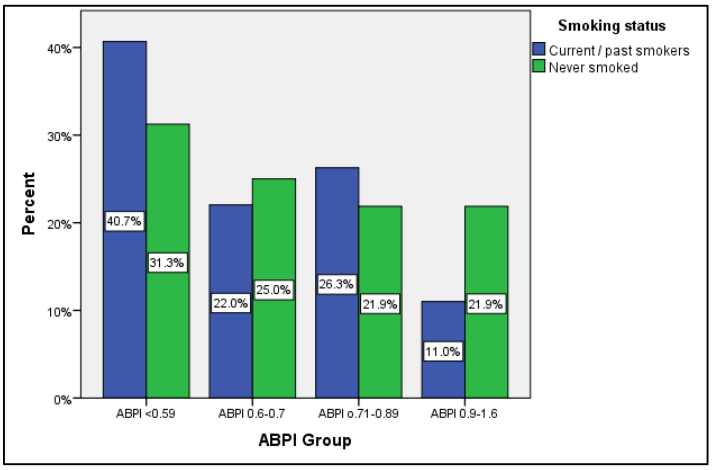
X^2 (2)= 1.116, p=0.572

Analysing Haemodynamics differences between smokers

Difference between current or past smokers and those who never smoked in ABPI

			Smoking status		
			Current / past smokers	Never smoked	Total
ABPI Group	ABPI <0.59	Count	48	10	58
		Percentage	40.7%	31.3%	38.7%
	ABPI 0.6-0.7	Count	26	8	34
		Percentage	22.0%	25.0%	22.7%
	ABPI 0.71-0.89	Count	31	7	38
		Percentage	26.3%	21.9%	25.3%
	ABPI 0.9-1.6	Count	13	7	20
		Percentage	11.0%	21.9%	13.3%
Total		Count	118	32	150
		Percentage	100.0%	100.0%	100.0%

$X^2(3) = 3.094$, $p = 0.377$



cardiac disease *systolic BP

Systolic blood pressure

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
Cardiac disease	61	145.24	20.20945	2.58	140.0700	150.4218	100.00	187.00
No cardiac disease	89	153.191	23.15799	2.45	148.3127	158.0693	111.00	217.00
Total	150	149.960	22.28307	1.8194	146.3648	153.5552	100.00	217.00

ANOVA cardiac disease *systolic BP

Systolic blood pressure

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2284.696	1	2284.696	4.716	.031
Within Groups	71699.064	148	484.453		
Total	73983.760	149			

ABPI Group * Age-group Crosstabulation

			Age-group				Total
			59 years or less	60-69 years	70-79 years	80 years or more	
ABPI Group	ABPI <0.59	Count	12	17	18	11	58
		% within Age-group	46.2%	35.4%	36.0%	42.3%	38.7%
	ABPI 0.6-0.7	Count	5	17	7	5	34
		% within Age-group	19.2%	35.4%	14.0%	19.2%	22.7%
	ABPI 0.71-0.89	Count	9	8	18	3	38
		% within Age-group	34.6%	16.7%	36.0%	11.5%	25.3%
	ABPI 0.9-1.6	Count	0	6	7	7	20
		% within Age-group	0.0%	12.5%	14.0%	26.9%	13.3%
Total		Count	26	48	50	26	150

Age group*ABPI groups

			Age-group				Total
			59 years or less	60-69 years	70-79 yrs	≥80 years	
ABPI Group	ABPI <0.59	Count	12	17	18	11	58
		Percentage	46.2%	35.4%	36%	42.3%	38.7%
	ABPI 0.6-0.7	Count	5	17	7	5	34
		Percentage	19.2%	35.4%	14%	19.2%	22.7%
	ABPI 0.71-0.89	Count	9	8	18	3	38
		Percentage	34.6%	16.7%	36%	11.5%	25.3%
	ABPI 0.9-1.6	Count	0	6	7	7	20
		Percentage	0%	12.5%	14%	26.9%	13.3%
Total		Count	26	48	50	26	150
		Percentage	100%	100%	100%	100%	100%

X^2 (9) =19.675, **p=0.02**

The crosstab clearly shows that the highest proportion of participants was in the ABPI group <0.59, indicating severe PAD. The percentage difference is significant since the p value is lower than the 0.05 criterion.

Reported calcification * Diabetes

			Diabetes		Total
			Diabetes	No Diabetes	
Reported calcification	Reported calcification	Count	28	4	32
		% within Diabetes	26.9%	8.7%	21.3%
	No reported calcification	Count	76	42	118
		% within Diabetes	73.1%	91.3%	78.7%
Total		Count	104	46	150
		% within Diabetes	100.0%	100.0%	100.0%

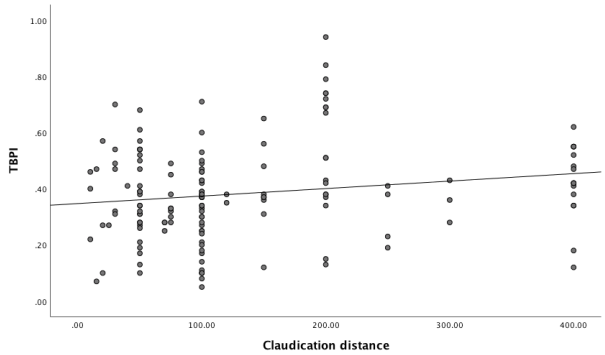
X^2 (1) = 6.314, p=0.012

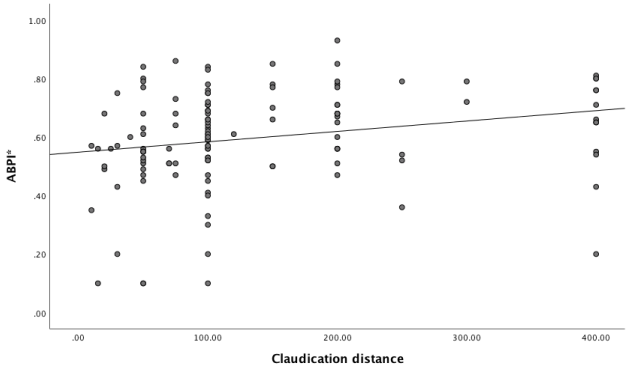
Disease Location * Calcification

			Calcification		
			Reported calcification	No reported calcification	Total
Disease Location	Abdomen	Count	4	14	18
		% within Calcification	7.8%	10.4%	9.7%
	Thigh	Count	27	74	101
		% within Calcification	52.9%	54.8%	54.3%
	Calf	Count	20	47	67
		% within Calcification	39.2%	34.8%	36.0%
Total		Count	51	135	186
		% within Calcification	100.0%	100.0%	100.0%

X^2 (2) = 0.467, p=0.792

TBPI and ABPI vs Claudication distance





Spearman's Correlation test Haemodynamic parameters

Correlations

			ABPI baseline	TBPI baseline	Absolute toe pressure baseline	Claudication distance baseline	ABPI excluding calcified arteries
Spearman's rho	ABPI baseline	Correlation Coefficient	1.000	.379**	.332**	.100	.796**
		Sig. (2-tailed)	.	.000	.000	.224	.000
		N	149	149	149	149	125
	TBPI baseline	Correlation Coefficient	.379**	1.000	.922**	.157	.387**
		Sig. (2-tailed)	.000	.	.000	.054	.000
		N	149	150	150	150	126
	Absolute toe pressure baseline	Correlation Coefficient	.332**	.922**	1.000	.177*	.344**
		Sig. (2-tailed)	.000	.000	.	.031	.000
		N	149	150	150	150	126
	Claudication distance baseline	Correlation Coefficient	.100	.157	.177*	1.000	.290**
		Sig. (2-tailed)	.224	.054	.031	.	.001
		N	149	150	150	150	126
	ABPI excluding calcified arteries	Correlation Coefficient	.796**	.387**	.344**	.290**	1.000
		Sig. (2-tailed)	.000	.000	.000	.001	.
		N	125	126	126	126	126

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Post Hoc Haemodynamics *DP waveforms

Tukey HSD

Dependent Variable	(I) DP Doppler waveform	(J) DP Doppler waveform	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
ABPI	Absent	Monophasic Continuous	-.12	.09	.52	-.36	.11
		Monophasic	-.23*	.09	.05	-.47	.00
		Biphasic	-.32*	.10	.01	-.58	-.06
	Monophasic Continuous	Absent	.12	.09	.52	-.11	.36
		Monophasic	-.11*	.03	.00	-.19	-.04
		Biphasic	-.20*	.05	.00	-.34	-.06
	Monophasic	Absent	.23*	.09	.05	.00	.47
		Monophasic Continuous	.11*	.03	.00	.04	.19
		Biphasic	-.09	.05	.40	-.23	.06
	Biphasic	Absent	.32*	.10	.01	.06	.58
		Monophasic Continuous	.20*	.05	.00	.06	.34
		Monophasic	.09	.05	.40	-.06	.23
ABPIall	Absent	Monophasic Continuous	-.12	.16	.88	-.53	.29
		Monophasic	-.19	.16	.62	-.60	.22
		Biphasic	-.19	.18	.71	-.66	.28
	Monophasic Continuous	Absent	.12	.16	.88	-.29	.53
		Monophasic	-.07	.05	.51	-.21	.06
		Biphasic	-.07	.10	.89	-.34	.19
	Monophasic	Absent	.19	.16	.62	-.22	.60
		Monophasic Continuous	.07	.05	.51	-.06	.21
		Biphasic	.00	.10	1.00	-.27	.27
	Biphasic	Absent	.19	.18	.71	-.28	.66
		Monophasic Continuous	.07	.10	.89	-.19	.34
		Monophasic	.00	.10	1.00	-.27	.27
TBPI	Absent	Monophasic Continuous	.12	.08	.50	-.10	.33
		Monophasic	.06	.08	.89	-.15	.27
		Biphasic	-.12	.09	.59	-.36	.13
		Absent	-.12	.08	.50	-.33	.10

	Monophasic Continuous	Monophasic	-.06	.03	.18	-.13	.02
		Biphasic	-.23*	.05	.00	-.38	-.09
	Monophasic	Absent	-.06	.08	.89	-.27	.15
		Monophasic Continuous	.06	.03	.18	-.02	.13
		Biphasic	-.18*	.05	.01	-.32	-.04
	Biphasic	Absent	.12	.09	.59	-.13	.36
		Monophasic Continuous	.23*	.05	.00	.09	.38
		Monophasic	.18*	.05	.01	.04	.32
Absolute toe pressure	Absent	Monophasic Continuous	10.90	12.42	.82	-21.38	43.19
		Monophasic	3.78	12.42	.99	-28.49	36.05
		Biphasic	-22.00	14.28	.42	-59.11	15.11
	Monophasic Continuous	Absent	-10.90	12.42	.82	-43.19	21.38
		Monophasic	-7.12	4.15	.32	-17.92	3.67
		Biphasic	-32.90*	8.18	.00	-54.17	-11.64
	Monophasic	Absent	-3.78	12.42	.99	-36.05	28.49
		Monophasic Continuous	7.12	4.15	.32	-3.67	17.92
		Biphasic	-25.78*	8.17	.01	-47.02	-4.54
	Biphasic	Absent	22.00	14.28	.42	-15.11	59.11
		Monophasic Continuous	32.90*	8.18	.00	11.64	54.17
		Monophasic	25.78*	8.17	.01	4.54	47.02
Claudication distance	Absent	Monophasic Continuous	-57.21	55.70	.73	-201.96	87.54
		Monophasic	-80.29	55.70	.48	-225.04	64.46
		Biphasic	-170.00*	64.05	.04	-336.45	-3.55
	Monophasic Continuous	Absent	57.21	55.70	.73	-87.54	201.96
		Monophasic	-23.09	18.57	.60	-71.34	25.16
		Biphasic	-112.79*	36.66	.01	-208.08	-17.51
	Monophasic	Absent	80.29	55.70	.48	-64.46	225.04
		Monophasic Continuous	23.09	18.57	.60	-25.16	71.34
		Biphasic	-89.71	36.66	.07	-184.99	5.58
	Biphasic	Absent	170.00*	64.05	.04	3.55	336.45
		Monophasic Continuous	112.79*	36.66	.01	17.51	208.08
		Monophasic	89.71	36.66	.07	-5.58	184.99

*. The mean difference is significant at the 0.05 level.

Post Hoc Haemodynamics * PT waveforms

Tukey HSD

Dependent Variable	(I) PT Doppler waveform	(J) PT Doppler waveform	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
ABPI	Absent	Monophasic Continuous	-.08	.08	.729	-.29	.13
		Monophasic	-.16	.08	.206	-.36	.05
		Biphasic	-.31*	.09	.007	-.55	-.06
	Monophasic Continuous	Absent	.08	.08	.729	-.13	.29
		Monophasic	-.07	.03	.069	-.15	.00
		Biphasic	-.22*	.06	.001	-.37	-.08
	Monophasic	Absent	.16	.08	.206	-.05	.36
		Monophasic Continuous	.07	.03	.069	.00	.15
		Biphasic	-.15*	.06	.039	-.29	-.01
	Biphasic	Absent	.31*	.09	.007	.06	.55
		Monophasic Continuous	.22*	.06	.001	.08	.37
		Monophasic	.15*	.06	.039	.01	.29
ABPIall	Absent	Monophasic Continuous	-.21	.16	.531	-.62	.19
		Monophasic	-.24	.15	.396	-.65	.16
		Biphasic	-.40	.17	.102	-.85	.05
	Monophasic Continuous	Absent	.21	.16	.531	-.19	.62
		Monophasic	-.03	.05	.926	-.17	.10
		Biphasic	-.19	.10	.198	-.44	.06
	Monophasic	Absent	.24	.15	.396	-.16	.65
		Monophasic Continuous	.03	.05	.926	-.10	.17
		Biphasic	-.16	.09	.336	-.40	.09
	Biphasic	Absent	.40	.17	.102	-.05	.85
		Monophasic Continuous	.19	.10	.198	-.06	.44
		Monophasic	.16	.09	.336	-.09	.40
TBPI	Absent	Monophasic Continuous	.01	.08	1.000	-.20	.22
		Monophasic	-.08	.08	.744	-.29	.13
		Biphasic	-.24*	.09	.036	-.48	-.01

	Monophasic Continuous	Absent	-.01	.08	1.000	-.22	.20
		Monophasic	-.09*	.03	.009	-.16	-.02
		Biphasic	-.25*	.05	.000	-.38	-.12
	Monophasic	Absent	.08	.08	.744	-.13	.29
		Monophasic Continuous	.09*	.03	.009	.02	.16
		Biphasic	-.16*	.05	.005	-.29	-.04
	Biphasic	Absent	.24*	.09	.036	.01	.48
		Monophasic Continuous	.25*	.05	.000	.12	.38
		Monophasic	.16*	.05	.005	.04	.29
Absolute toe pressure	Absent	Monophasic Continuous	-6.71	12.11	.945	-38.20	24.77
		Monophasic	-18.68	12.00	.407	-49.88	12.52
		Biphasic	-42.50*	13.51	.011	-77.63	-7.37
	Monophasic Continuous	Absent	6.71	12.11	.945	-24.77	38.20
		Monophasic	-11.96*	4.11	.022	-22.65	-1.28
		Biphasic	-35.79*	7.45	.000	-55.14	-16.43
	Monophasic	Absent	18.68	12.00	.407	-12.52	49.88
		Monophasic Continuous	11.96*	4.11	.022	1.28	22.65
		Biphasic	-23.82*	7.26	.007	-42.70	-4.94
	Biphasic	Absent	42.50*	13.51	.011	7.37	77.63
		Monophasic Continuous	35.79*	7.45	.000	16.43	55.14
		Monophasic	23.82*	7.26	.007	4.94	42.70
Claudication distance	Absent	Monophasic Continuous	-57.74	55.03	.721	-200.76	85.28
		Monophasic	-88.78	54.56	.367	-230.58	53.01
		Biphasic	-186.25*	61.43	.015	-345.89	-26.61
	Monophasic Continuous	Absent	57.74	55.03	.721	-85.28	200.76
		Monophasic	-31.04	18.59	.343	-79.35	17.27
		Biphasic	-128.51*	33.79	.001	-216.33	-40.69
	Monophasic	Absent	88.78	54.56	.367	-53.01	230.58
		Monophasic Continuous	31.04	18.59	.343	-17.27	79.35
		Biphasic	-97.47*	33.02	.019	-183.28	-11.66
	Biphasic	Absent	186.25*	61.43	.015	26.61	345.89
		Monophasic Continuous	128.51*	33.79	.001	40.69	216.33
		Monophasic	97.47*	33.02	.019	11.66	183.28

Age group and ABPI

The participants were stratified by age and also by ABPI result. The distribution of ABPI groups by age is shown in table 5.14 below and was analysed using the Chi-square test.

Table 5.14 Age group vs ABPI groups

			Age-group				Total
			59 years or less	60-69 years	70-79 yrs	≥80 years	
ABPI Group	ABPI <0.59	Count	12	17	18	11	58
		Percentage	46.2%	35.4%	36%	42.3%	38.7%
	ABPI 0.6-0.7	Count	5	17	7	5	34
		Percentage	19.2%	35.4%	14%	19.2%	22.7%
	ABPI 0.71-0.89	Count	9	8	18	3	38
		Percentage	34.6%	16.7%	36%	11.5%	25.3%
	ABPI 0.9-1.6	Count	0	6	7	7	20
		Percentage	0%	12.5%	14%	26.9%	13.3%
Total		Count	26	48	50	26	150
		Percentage	100%	100%	100%	100%	100%

X^2 (9) =19.675, **p=0.02**

The crosstab shows that the highest proportion of participants (38.7%) was in the ABPI group <0.59, indicating severe PAD. The table also indicates that the largest proportion of participants with low ABPI is in the youngest and oldest groups. The percentage difference is significant since the p value is lower than the 0.05 criterion.

Test re-test analysis ABPI and TBPI

			ABPI baseline 2
Kendall's tau_b	ABPI baseline 1	Correlation Coefficient	0.918**
		Sig. (2-tailed)	.
		N	25
Spearman's rho	ABPI baseline 1	Correlation Coefficient	0.946**
		Sig. (2-tailed)	.
		N	25

			TBPI baseline 2
Kendall's tau_b	TBPI baseline 1	Correlation Coefficient	0.912**
		Sig. (2-tailed)	.
		N	25
Spearman's rho	TBPI baseline 1	Correlation Coefficient	0.908**
		Sig. (2-tailed)	.
		N	25

- 1 : perfect reliability,
- ≥ 0.9: excellent reliability,
- ≥ 0.8 < 0.9: good reliability,
- ≥ 0.7 < 0.8: acceptable reliability,
- ≥ 0.6 < 0.7: questionable reliability,
- ≥ 0.5 < 0.6: poor reliability,
- < 0.5: unacceptable reliability,
- 0: no reliability

APPENDIX 11

Shapiro-Wilk test of normality of variables measured

H_1 the alternative hypothesis states that there is a statistically significant difference between the distribution of the test variables and a non-normal distribution.

H_0 – the null hypothesis states that there is no statistically significant difference between the distribution of the test variables and a normal distribution.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
ABPI baseline	.198	100	.000	.807	100	.000
TBPI baseline	.117	100	.002	.854	100	.000
Absolute toe pressure baseline	.081	100	.104	.971	100	.026
BMI	.057	100	.200*	.987	100	.427
Age	.077	100	.151	.981	100	.165
Claudication distance baseline	.300	100	.000	.802	100	.000
eGFR	.070	100	.200*	.980	100	.135
Cholesterol	.088	100	.056	.933	100	.000
Triglyceride	.189	100	.000	.685	100	.000
HDL Cholesterol	.109	100	.005	.950	100	.001
Non HDL Cholesterol	.101	100	.014	.914	100	.000
LDL Cholesterol	.089	100	.047	.931	100	.000
Total Cholesterol	.131	100	.000	.924	100	.000
Fasting Glucose	.141	100	.000	.890	100	.000
HbA1c	.105	100	.009	.912	100	.000
Creatinine	.185	100	.000	.817	100	.000
CRP	.299	100	.000	.468	100	.000
ESR	.141	100	.000	.875	100	.000
Systolic blood pressure	.070	100	.200*	.988	100	.475

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

APPENDIX 12

Non-responder Analysis

Differences in baseline parameters between responders and non-responders. Mann Whitney U Test										
		N	Mean	Std. Deviation	95% CI for Mean		Min	Max	Mann Whitney U	P Value
					Lower Bound	Upper Bound				
ABPI baseline	Non Responder	13	.64	.21	.48	.80	.35	1.05	491	0.33
	Responder	135	.75	.33	.70	.81	.35	1.60		
TBPI baseline	Non Responder	13	.42	.23	.24	.60	.28	.98	580	0.82
	Responder	135	.40	.19	.37	.43	.18	1.60		
Absolute toe pressure baseline	Non Responder	13	60.56	30.68	36.97	84.14	40.00	132.00	571.5	0.77
	Responder	135	60.13	27.12	55.52	64.75	38.00	145.00		
BMI	Non Responder	13	32.33	7.19	26.80	37.86	23.70	47.10	322	**0.02**
	Responder	135	27.55	3.82	26.90	28.20	18.90	44.80		
Age	Non Responder	13	65.22	8.71	58.52	71.92	50.00	77.00	433.5	0.15
	Responder	135	69.71	9.29	68.13	71.29	38.00	86.00		
Claudication distance baseline	Non Responder	13	81.11	57.11	37.22	125.01	10.00	200.00	406.5	0.09
	Responder	135	143.1	111.48	124.10	162.05	10.00	400.00		
Smoking duration of ex-smokers	Non Responder	5	44.80	7.05	36.05	53.55	35.00	52.00	106	0.39
	Responder	55	40.65	9.88	37.98	43.33	20.00	66.00		
Pack years Ex-smokers	Non Responder	5	69.60	45.11	13.58	125.62	35.00	144.00	128.5	0.81
	Responder	55	72.85	43.64	61.05	84.65	7.50	200.00		
Smoking duration Current smokers	Non Responder	4	39.25	19.64	8.00	70.50	15.00	62.00	81.5	0.47
	Responder	52	45.38	13.66	41.58	49.19	15.00	70.00		
Pack Years Current smokers	Non Responder	4	48.25	24.65	9.03	87.47	15.00	71.00	99	0.87
	Responder	52	55.10	44.89	42.60	67.60	6.00	234.50		
eGFR	Non Responder	13	88.89	38.05	59.64	118.14	29.00	149.00	511	0.43
	Responder	135	77.96	30.98	72.68	83.23	6.00	164.00		
Cholesterol	Non Responder	13	4.94	1.51	3.77	6.10	3.38	7.59	505	0.39
	Responder	135	4.44	1.16	4.24	4.64	2.41	9.00		
Triglyceride	Non Responder	13	1.96	1.62	.72	3.21	.66	5.77	596.5	0.93
	Responder	135	1.74	1.19	1.54	1.94	.15	8.80		
HDL Cholesterol	Non Responder	13	1.35	.70	.81	1.90	.79	3.11	606.5	0.99
	Responder	135	1.22	.36	1.16	1.28	.63	2.27		

Non HDL Cholesterol	Non Responder	13	3.58	1.65	2.31	4.85	1.84	6.64	577.5	0.80
	Responder	135	3.22	1.13	3.03	3.42	1.32	7.49		
LDL Cholesterol	Non Responder	13	2.80	1.30	1.79	3.80	1.54	5.50	529	0.52
	Responder	135	2.39	1.04	2.21	2.57	.02	5.85		
Total Cholesterol	Non Responder	13	4.29	2.20	2.59	5.98	1.85	7.99	598.5	0.94
	Responder	135	3.86	1.26	3.65	4.08	1.67	7.55		
Fasting Glucose	Non Responder	6	9.97	3.02	6.80	13.13	5.74	12.73	211	0.17
	Responder	106	8.23	3.08	7.64	8.82	4.56	16.85		
HbA1c	Non Responder	13	7.48	1.33	6.46	8.50	5.70	9.70	428	0.14
	Responder	135	6.86	1.34	6.63	7.09	4.20	10.91		
Creatinine	Non Responder	13	89.56	50.73	50.56	128.55	41.00	212.00	462.5	0.23
	Responder	135	103.7	76.22	90.76	116.71	38.00	811.00		
CRP	Non Responder	6	2.08	1.81	.18	3.99	.20	4.60	299	0.37
	Responder	127	4.86	7.95	3.46	6.25	.10	56.00		
ESR	Non Responder	7	10.43	7.30	3.68	17.18	2.00	21.00	267	0.91
	Responder	123	20.53	16.24	17.63	23.43	1.00	74.00		
Systolic blood pressure	Non Responder	13	145.2	17.75	131.58	158.87	124.0	171.00	514	0.44
	Responder	135	151.0	22.33	147.21	154.82	100.0	217.00		
WIQ1	Non Responder	13	62.00	10.55	53.89	70.11	46.00	78.00	425	0.13
	Responder	135	51.90	15.99	49.18	54.63	16.00	78.00		

Chi square tests analyzing differences in parameters at baseline between responders and non responders

Parameter	Category	Group	N	% within group	X^2	df	P value
PT Doppler waveform	Biphasic	Non Responders	1	11.1	1.05	2	0.49
		Responders	16	11.9			
	Monophasic	Non Responders	3	33.3			
		Responders	70	51.9			
	Mono-cont	Non Responders	5	55.6			
		Responders	49	36.3			
DP Doppler waveform	Biphasic	Non Responders	1	11.1	0.71	2	0.70
		Responders	10	7.4			
	Monophasic	Non Responders	3	33.3			
		Responders	64	47.4			
	Mono-cont	Non Responders	24	68.6			
		Responders	48	41.7			
Gender	Male	Non Responders	6	66.7	1.04	1	0.31
		Responders	109	80.7			
	Female	Non Responders	3	33.3			
		Responders	26	19.3			

Smoking status	Current smoker	Non Responders	4	44.4	2.57	2	0.28
		Responders	50	37			
	Past smoker	Non Responders	5	55.6			
		Responders	55	40.7			
	Never smoked	Non Responders	0	0			
		Responders	30	22.2			
Diabetes		Non Responders	5	55.6	0.87	1	0.35
		Responders	95	70.4			
Hypertension		Non Responders	6	66.7	3.4	1	0.07
		Responders	119	88.1			
Hyperlipidaemia		Non Responders	7	77.8	0	1	1
		Responders	105	77.8			
Cardiac Disease		Non Responders	5	55.6	0.84	1	0.36
		Responders	54	40			
Renal Disease		Non Responders	2	22.2	0.31	1	0.58
		Responders	42	31.1			
Taking statins ,antiplatelet and/or anticoagulant		Non Responders	8	88.9	0.55	1	0.46
		Responders	106	78.5			
Ace inhibitor		Non Responders	3	33.3	0.98	1	0.32
		Responders	68	50.4			
Angiotensin II Antagonist		Non Responders	0	0	1.63	1	0.2
		Responders	21	15.6			
Calcium channel blocker		Non Responders	2	22.2	0.01	1	0.92
		Responders	32	23.7			
Beta blocker		Non Responders	1	11.1	0.1	1	0.76
		Responders	11	8.1			
Previous major event		Non Responders	5	55.6	0.48	1	0.49
		Responders	59	43.7			
Infrapopliteal artery disease		Non Responders	1	11.1	3.99	1	0.06
		Responders	61	45.2			

APPENDIX 13

Initial regression models results

Initial result for Model 1 – including ABPI

Parameter Estimates

Deterioration to CLI[a]		B	Std. Error	Wald	df	Sig.	Odds Ratio	95% Conf Interval	
								Lower Bound	Upper Bound
Deteriorated to CLI	Intercept	371.05	250.22	2.20	1.00	.14			
	PT Doppler waveform monophasic	68.38	45.96	2.21	1.00	.14	50002590	.00	6.57E+68
	PT Doppler waveform biphasic	-25.65	.00	.	1.00	.	.00	.00	.00
	PT Doppler waveform mono-continuous	.00[b]	.	.	.00	.	.	.	.
	DP Doppler waveform monophasic	-50.20	34.81	2.08	1.00	.15	.00	.00	68129445.13
	DP Doppler waveform biphasic	13.35	.00	.	1.00	.	630469.80	630469.80	630469.80
	DP Doppler waveform mono-continuous	.00[b]	.	.	.00	.	.	.	.
	Female	76.67	52.75	2.11	1.00	.15	1986835.0	.00	1.57E+78
	Male	.00[b]	.	.	.00	.	.	.	.
	Diabetes	-6.01	5.47	1.21	1.00	.27	.00	.00	111.11
	No Diabetes	.00[b]	.	.	.00	.	.	.	.
	Hypertension	80.80	58.08	1.94	1.00	.16	122992.00	.00	3.38E+84
	No Hypertension	.00[b]	.	.	.00	.	.	.	.
	Hyperlipidaemia	-95.58	63.79	2.25	1.00	.13	.00	.00	6081.91
	No Hyperlipidaemia	.00[b]	.	.	.00	.	.	.	.
	Cardiac Disease	-75.89	52.91	2.06	1.00	.15	.00	.00	11912.69
	No Cardiac Disease	.00[b]	.	.	.00	.	.	.	.
	Renal Disease	61.14	42.14	2.11	1.00	.15	3568070.0	.00	2.62E+62
	No Renal Disease	.00[b]	.	.	.00	.	.	.	.

	Smoking history	2.74	2.84	.93	1.00	.34	15.41	.06	4008.92
	Never smoked	.00[b]	.	.	.00	.	.	.	.
	Arthritis	63.14	52.14	2.31	1.00	.15	3598070.0	.00	2.63E+74
	No Arthritis	.00[b]	.	.	.00	.	.	.	.
	Malignancy	74.80	88.08	3.94	1.00	.16	122762.00	.00	3.38E+94
	No malignancy	.00[b]	.	.	.00	.	.	.	.
	Statin therapy	-8.00	10.17	.62	1.00	.43	.00	.00	152715.88
	No Statin therapy	.00[b]	.	.	.00	.	.	.	.
	Taking Antiplatelet or anticoagulant	12.72	7.76	2.68	1.00	.10	333295.34	.08	135062.96
	Not Taking Antiplatelet or anticoagulant	.00[b]	.	.	.00	.	.	.	.
	ACE Inhibitor	9.19	7.10	1.68	1.00	.20	9838.86	.01	10855.06
	No ACE Inhibitor	.00[b]	.	.	.00	.	.	.	.
	Angiotensin II antagonist	4.08	6.54	.39	1.00	.53	59.28	.00	218513.29
	No Angiotensin II antagonist	.00[b]	.	.	.00	.	.	.	.
	Calcium channel blocker	-49.54	32.69	2.30	1.00	.13	.00	.00	201865.03
	No Calcium channel blocker	.00[b]	.	.	.00	.	.	.	.
	Beta blocker	-39.74	28.17	1.99	1.00	.16	.00	.00	526569.74
	No Beta blocker	.00[b]	.	.	.00	.	.	.	.
	Previous major event	44.35	31.39	2.00	1.00	.16	182170.00	.00	9.55E+45
	No Previous major event	.00[b]	.	.	.00	.	.	.	.
	Infrapopliteal artery disease	30.70	20.27	2.29	1.00	.13	215237.36	.00	3854831.0
	No Infrapopliteal artery disease	.00[b]	.	.	.00	.	.	.	.
	ABPI baseline	-62.62	42.07	2.22	1.00	.14	.00	.00	401213.99
	BMI	-2.54	1.75	2.09	1.00	.15	.08	.00	2.46
	Age	-1.10	.71	2.41	1.00	.12	.33	.08	1.33
	Claudication distance baseline	.27	.19	2.04	1.00	.15	1.31	.90	1.89
	eGFR	.38	.32	1.45	1.00	.23	1.47	.79	2.73
	Cholesterol	-7.77	566.15	.00	1.00	.99	.00	.00	.[c]
	Triglyceride	-10.42	6.78	2.36	1.00	.12	.00	.00	17.78

	HDL Cholesterol	.02	566.03	.00	1.00	1.00	1.02	.00	.[c]
	Non HDL Cholesterol	-29.05	566.89	.00	1.00	.96	.00	.00	.[c]
	LDL Cholesterol	-56.49	38.54	2.15	1.00	.14	.00	.00	187897.84
	Total Cholesterol	56.58	39.35	2.07	1.00	.15	37303170	.00	1.17E+58
	HbA1c	1.15	1.48	.60	1.00	.44	3.15	.17	56.92
	Creatinine	-.02	.03	.62	1.00	.43	.98	.92	1.04
	CRP	.75	.56	1.79	1.00	.18	2.12	.71	6.34
	ESR	-.60	.48	1.53	1.00	.22	.55	.21	1.42
	Systolic blood pressure	-1.71	1.18	2.10	1.00	.15	.18	.02	1.83

a. The reference category is: Did not deteriorate to CLI.

b. This parameter is set to zero because it is redundant.

c. Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

Initial result for Model 2- including TBPI

Parameter Estimates

Deterioration to CLI[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Deteriorated to CLI	Intercept	-7.11	7.42	.92	1.00	.34			
	PT Doppler waveform Monophasic	-.32	.74	.19	1.00	.67	.73	.17	3.09
	PT Doppler waveform Biphasic	-18.39	1870.23	.00	1.00	.99	.00	.00	.[b]
	PT Doppler waveform Mono-continuous	.00[c]	.	.	.00	.	.	.	.
	DP Doppler waveform Monophasic	-.61	.81	.57	1.00	.45	.54	.11	2.64
	DP Doppler waveform Biphasic	-18.51	2379.58	.00	1.00	.99	.00	.00	.[b]

	DP Doppler waveform Mono-continuous	.00[c]	.	.	.00	.	.	.	.
	Gender Female	-.17	.88	.04	1.00	.84	.84	.15	4.71
	Male	.00[c]	.	.	.00	.	.	.	.
	Current smoker	.63	.99	.40	1.00	.53	1.87	.27	13.04
	Past smoker	-.10	.86	.01	1.00	.91	.90	.17	4.86
	Never smoked	.00[c]	.	.	.00	.	.	.	.
	Diabetes	.47	1.08	.19	1.00	.66	1.61	.19	13.27
	No Diabetes	.00[c]	.	.	.00	.	.	.	.
	Hypertension	-.23	1.24	.03	1.00	.85	.79	.07	9.10
	No Hypertension	.00[c]	.	.	.00	.	.	.	.
	Hyperlipidaemia	-.98	1.12	.77	1.00	.38	.37	.04	3.35
	No Hyperlipidaemia	.00[c]	.	.	.00	.	.	.	.
	Cardiac Disease	-1.31	1.18	1.23	1.00	.27	.27	.03	2.72
	No Cardiac Disease	.00[c]	.	.	.00	.	.	.	.
	Renal Disease	-.96	1.21	.64	1.00	.43	.38	.04	4.08
	No Renal Disease	.00[c]	.	.	.00	.	.	.	.
	Arthritis	63.14	2.14	2.31	1.00	.15	3.5	.00	5.63
	No Arthritis	.00[b]	.	.	.00	.	.	.	.
	Malignancy	74.80	9.08	3.94	1.00	.16	12.2	.00	4.38
	No malignancy	.00[b]	.	.	.00	.	.	.	.
	Statin therapy	.59	1.21	.24	1.00	.62	1.80	.17	19.15
	No Statin therapy	.00[c]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	-.17	1.00	.03	1.00	.86	.84	.12	5.97
	No Antiplatelet or anticoagulant	.00[c]	.	.	.00	.	.	.	.
	ACE Inhibitor	1.56	1.00	2.45	1.00	.12	4.77	.67	33.68
	No ACE Inhibitor	.00[c]	.	.	.00	.	.	.	.
	Angiotensin II antagonist	.64	1.16	.30	1.00	.58	1.89	.19	18.51
	No Angiotensin II antagonist	.00[c]	.	.	.00	.	.	.	.

	Calcium channel blocker	-1.51	.81	3.46	1.00	.06	.22	.05	1.08
	No Calcium channel blocker	.00[c]	.	.	.00	.	.	.	.
	Beta blocker	-1.86	1.84	1.02	1.00	.31	.16	.00	5.70
	No Beta blocker	.00[c]	.	.	.00	.	.	.	.
	Previous major event	1.91	1.20	2.53	1.00	.11	6.74	.64	70.71
	No Previous major event	.00[c]	.	.	.00	.	.	.	.
	Infrapopliteal artery disease	.45	.65	.49	1.00	.49	1.57	.44	5.61
	No IPA	.00[c]	.	.	.00	.	.	.	.
	TBPI baseline	-6.15	10.29	.36	1.00	.55	.00	.00	12348.07
	Absolute toe pressure baseline	.04	.07	.40	1.00	.53	1.04	.92	1.19
	BMI	-.05	.09	.27	1.00	.60	.96	.81	1.13
	Age	.00	.05	.00	1.00	.99	1.00	.91	1.11
	Claudication distance baseline	.00	.00	.11	1.00	.74	1.00	.99	1.01
	eGFR	.05	.02	4.85	1.00	.03	1.05	1.01	1.10
	Cholesterol	45.41	1.08	173.6	1.00	.00	525793.0	6315700	437727.0
	Triglyceride	-.15	.50	.09	1.00	.76	.86	.32	2.29
	HDL Cholesterol	-43.32	1.47	874.24	1.00	.00	.00	.00	.00
	Non HDL Cholesterol	-44.60	.00	.	1.00	.	.00	.00	.00
	LDL Cholesterol	-1.24	1.08	1.33	1.00	.25	.29	.04	2.39
	HbA1c	.30	.25	1.54	1.00	.22	1.36	.84	2.19
	Creatinine	.03	.02	3.91	1.00	.05	1.03	1.00	1.07
	CRP	-.02	.05	.20	1.00	.65	.98	.89	1.07
	ESR	.02	.02	.79	1.00	.37	1.02	.98	1.07
	Systolic blood pressure	-.03	.03	1.40	1.00	.24	.97	.92	1.02

a. The reference category is: Did not deteriorate to CLI.

b. Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

c. This parameter is set to zero because it is redundant.

Initial result for Model 3 – Significant deterioration- ABPI

Parameter Estimates									
ABPISigDecline[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
1.00	Intercept	13.48	12.58	1.15	1.00	.28			
	PT Doppler waveform Monophasic	-.79	1.23	.41	1.00	.52	.45	.04	5.03
	PT Doppler waveform biphasic	-6.92	3.61	3.69	1.00	.05	.00	.00	1.16
	PT Doppler waveform Mono-continuous	.00[b]	.	.	.00	.	.	.	.
	DP Doppler waveform Monophasic	.02	1.08	.00	1.00	.99	1.02	.12	8.51
	DP Doppler waveform biphasic	7.45	3.68	4.10	1.00	.04	1711.50	1.27	2301227.86
	[DP Doppler waveform Mono-continuous	.00[b]	.	.	.00	.	.	.	.
	Female	1.02	1.13	.81	1.00	.37	2.78	.30	25.71
	Male	.00[b]	.	.	.00	.	.	.	.
	Diabetes	-.84	1.37	.38	1.00	.54	.43	.03	6.30
	No Diabetes	.00[b]	.	.	.00	.	.	.	.
	Hypertension	6.47	2.67	5.86	1.00	.02	645.22	3.43	121363.47
	No Hypertension	.00[b]	.	.	.00	.	.	.	.
	Hyperlipidaemia	1.68	1.41	1.43	1.00	.23	5.37	.34	84.80
	No Hyperlipidaemia	.00[b]	.	.	.00	.	.	.	.
	Statin	-1.00	1.54	.42	1.00	.52	.37	.02	7.56
	No Statin	.00[b]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	-4.15	1.74	5.67	1.00	.02	.02	.00	.48
	No Antiplatelet or anticoagulant	.00[b]	.	.	.00	.	.	.	.
	ACE Inhibitor	-.92	1.56	.35	1.00	.55	.40	.02	8.40
	No ACE Inhibitor	.00[b]	.	.	.00	.	.	.	.
	Angiotensin II antagonist	-2.00	1.65	1.47	1.00	.23	.14	.01	3.43

	No Angiotensin II antagonist	.00[b]	.	.	.00	.	.	.	.
	Calcium channel blocker	-3.82	1.48	6.63	1.00	.01	.02	.00	.40
	No Calcium channel blocker	.00[b]	.	.	.00	.	.	.	.
	Beta blocker	-3.71	2.19	2.86	1.00	.09	.02	.00	1.81
	No Beta blocker	.00[b]	.	.	.00	.	.	.	.
	Previous major event	-1.19	.89	1.81	1.00	.18	.30	.05	1.73
	No Previous major event	.00[b]	.	.	.00	.	.	.	.
	Arthritis	3.14	5.14	2.31	1.00	.16	8070.0	.00	2.38
	No Arthritis	.00[b]	.	.	.00	.	.	.	.
	Malignancy	4.20	7.08	3.94	1.00	.19	62.00	.00	4.38
	No malignancy	.00[b]	.	.	.00	.	.	.	.
	Infrapopliteal artery disease	.53	.80	.45	1.00	.50	1.70	.36	8.16
	No Infrapopliteal artery disease	.00[b]	.	.	.00	.	.	.	.
	ABPI baseline	.38	2.98	.02	1.00	.90	1.47	.00	503.55
	TBPI baseline	-30.63	27.29	1.26	1.00	.26	.00	.00	854006.71
	Absolute toe pressure baseline	.17	.18	.84	1.00	.36	1.18	.83	1.70
	eGFR	-.03	.02	2.13	1.00	.14	.97	.94	1.01
	Cholesterol	3.48	1.53	5.16	1.00	.02	32.59	1.61	658.61
	Triglyceride	-1.43	.89	2.58	1.00	.11	.24	.04	1.37
	HDL Cholesterol	-.25	4.67	.00	1.00	.96	.78	.00	7422.81
	Non HDL Cholesterol	-6.92	.00	.	1.00	.	.00	.00	.00
	LDL Cholesterol	.04	.07	.37	1.00	.55	1.04	.91	1.20
	Total Cholesterol	3.03	1.55	3.81	1.00	.05	20.73	.99	435.18
	HbA1c	-.10	.38	.08	1.00	.78	.90	.43	1.90
	CRP	.01	.04	.02	1.00	.90	1.01	.92	1.10
	Systolic blood pressure	-.07	.07	1.02	1.00	.31	.93	.80	1.07

a. The reference category is: 2.00.

b. This parameter is set to zero because it is redundant.

Initial result for Model 4 – Significant deterioration- TBPI

Parameter Estimates

Significant TBPI decline[a]		B	Std. Error	Wald	df	Sig.	Odds ratio	95% Confidence Interval for OR	
								Lower Bound	Upper Bound
Significant TBPI decline	Intercept	-21.89	8.50	6.64	1.00	0.01			
	PT Doppler waveform monophasic	-.88	0.88	1.01	1.00	0.31	0.41	.07	2.31
	PT Doppler waveform Biphasic	-6.22	2.36	6.97	1.00	.01	.00	.00	.20
	PT Doppler waveform Mono-continuous	.00[b]	.	.	.00	.	.	.	.
	DP Doppler waveform Monophasic	.10	.80	.02	1.00	.90	1.10	.23	5.29
	DP Doppler waveform biphasic	-1.08	2.00	.29	1.00	.59	.34	.01	17.07
	DP Doppler waveform mono-continuous	.00[b]	.	.	.00	.	.	.	.
	Gender Female	2.68	1.06	6.39	1.00	.01	14.65	1.83	117.47
	Male	.00[b]	.	.	.00	.	.	.	.
	Smoking Status current smoker	1.42	1.08	1.72	1.00	.19	4.15	.49	34.76
	Past smoker	.60	.94	.41	1.00	.52	1.82	.29	11.39
	Never Smoked	.00[b]	.	.	.00	.	.	.	.
	Diabetes	2.74	1.21	5.12	1.00	.02	15.47	1.44	165.79
	No Diabetes	.00[b]	.	.	.00	.	.	.	.
	Hypertension	3.57	1.83	3.81	1.00	.05	35.35	.99	1266.87
	No Hypertension	.00[b]	.	.	.00	.	.	.	.
	Hyperlipidaemia	.49	.91	.29	1.00	.59	1.64	.27	9.79
	No Hyperlipidaemia	.00[b]	.	.	.00	.	.	.	.
	Cardiac Disease	.75	1.25	.36	1.00	.55	2.11	.18	24.32
	No Cardiac Disease	.00[b]	.	.	.00	.	.	.	.
	Renal Disease	-2.00	1.31	2.33	1.00	.13	.14	.01	1.76

	No Renal Disease	.00[b]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	-5.77	1.61	12.89	1.00	.00	.00	.00	.07
	No Antiplatelet or anticoagulant	.00[b]	.	.	.00	.	.	.	.
	ACE Inhibitor	-.03	1.17	.00	1.00	.98	.97	.10	9.67
	No ACE Inhibitor	.00[b]	.	.	.00	.	.	.	.
	Angiotensin II antagonist	-.57	1.24	.21	1.00	.65	.57	.05	6.49
	No Angiotensin II antagonist	.00[b]	.	.	.00	.	.	.	.
	Calcium channel blocker	-1.31	.74	3.12	1.00	.08	.27	.06	1.15
	No Calcium channel blocker	.00[b]	.	.	.00	.	.	.	.
	Beta blocker	-2.24	1.49	2.26	1.00	.13	.11	.01	1.97
	No Beta blocker	.00[b]	.	.	.00	.	.	.	.
	Previous major event	-.33	1.22	.07	1.00	.79	.72	.07	7.95
	No Previous major event	.00[b]	.	.	.00	.	.	.	.
	Malignancy	-.13	1.16	.10	1.00	.78	.97	.10	9.77
	No malignancy	.00[b]	.	.	.00	.	.	.	.
	Arthritis	3.67	1.54	3.31	1.00	.07	3.35	.79	6.17
	No arthritis	.00[b]	.	.	.00	.	.	.	.
	Infrapopliteal artery disease	-.12	.70	.03	1.00	.86	.89	.23	3.49
	No Infrapopliteal artery disease	.00[b]	.	.	.00	.	.	.	.
	TBPI baseline	1.54	4.56	.11	1.00	.74	4.67	.00	35493.9
	Absolute toe pressure	-.03	.04	.59	1.00	.44	.97	.89	1.05
	BMI	.00	.09	.00	1.00	.96	1.00	.85	1.19
	Age	.12	.06	3.82	1.00	.05	1.12	1.00	1.26
	Claudication distance baseline	.00	.00	.16	1.00	.69	1.00	.99	1.01
	eGFR	.02	.03	.87	1.00	.35	1.02	.97	1.08
	Cholesterol	37.07	1.11	119.3	1.00	.00	126115.0	143731.8	11065.0
	Triglyceride	-.28	.43	.44	1.00	.51	.75	.33	1.74
	HDL Cholesterol	-30.60	3.50	76.62	1.00	.00	.00	.00	.00

	Non HDL Cholesterol	-40.08	.00	.	1.00	.	.00	.00	.00
	LDL Cholesterol	.07	.05	2.09	1.00	.15	1.08	.97	1.19
	Total Cholesterol	3.01	1.13	7.07	1.00	.01	20.33	2.21	187.33
	HbA1c	-.10	.29	.12	1.00	.73	.90	.52	1.58
	Creatinine	.02	.02	.97	1.00	.32	1.02	.98	1.05
	CRP	.18	.09	3.83	1.00	.05	1.19	1.00	1.43
	ESR	.00	.03	.00	1.00	.97	1.00	.95	1.05
	Systolic blood pressure	.02	.02	.47	1.00	.49	1.02	.97	1.06

a. The reference category is: No significant TBPI decline or CLI or revascularisation.

b. This parameter is set to zero because it is redundant.

Initial model for computing a combined coefficient of all significant predictors of significant deterioration

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.642	.420		1.529	.132
	ABPI baseline	.670	.289	.277	2.320	.024
	TBPI baseline	.612	.338	.214	1.809	.076
	Disease Location	.273	.113	.279	2.423	.019
	Gender	.001	.130	.001	.006	.995
	Diabetes	.012	.143	.010	.082	.935
	CRP	-.005	.009	-.063	-.512	.610
	Taking Antiplatelet or anticoagulant	.089	.143	.072	.625	.534
	Calcium channel blocker	-.123	.126	-.110	-.975	.333

a. Dependent Variable: Deterioration to CLI

Initial model for Improved or stable haemodynamics

Parameter Estimates

Improved or stable haemodynamics[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Improved or stable	Intercept	16.65	11.26	2.19	1.00	.14			
	PT Doppler waveform monophasic	-.04	1.03	.00	1.00	.97	.96	.13	7.23

	PT Doppler waveform biphasic	3.47	2.09	2.75	1.00	.10	32.10	.53	1937.40
	PT Doppler waveform mono-cont	.00[b]	.	.	.00	.	.	.	.
	DP Doppler waveform monophasic	-1.98	1.00	3.94	1.00	.05	.14	.02	.97
	DP Doppler waveform biphasic	-2.43	2.06	1.39	1.00	.24	.09	.00	4.98
	DP Doppler waveform mono-cont	.00[b]	.	.	.00	.	.	.	.
	Female	-1.74	1.50	1.35	1.00	.25	.17	.01	3.32
	Male	.00[b]	.	.	.00	.	.	.	.
	Smoking Status current smoker	1.21	1.36	.79	1.00	.37	3.35	.23	47.91
	Past smoker	-.26	1.15	.05	1.00	.82	.77	.08	7.35
	Never Smoked	.00[b]	.	.	.00	.	.	.	.
	Diabetes	.04	1.44	.00	1.00	.98	1.04	.06	17.59
	No Diabetes	.00[b]	.	.	.00	.	.	.	.
	Hypertension	-.29	1.32	.05	1.00	.82	.75	.06	9.91
	No Hypertension	.00[b]	.	.	.00	.	.	.	.
	Hyperlipidaemia	-3.59	1.30	7.66	1.00	.01	.03	.00	.35
	No Hyperlipidaemia	.00[b]	.	.	.00	.	.	.	.
	Cardiac Disease	-2.37	1.46	2.66	1.00	.10	.09	.01	1.62
	No Cardiac Disease	.00[b]	.	.	.00	.	.	.	.
	Renal Disease	.24	1.81	.02	1.00	.89	1.27	.04	43.92
	No Renal Disease	.00[b]	.	.	.00	.	.	.	.
	Malignancy	-.03	1.46	.60	1.00	.78	.57	.10	19.57
	No malignancy	.00[b]	.	.	.00	.	.	.	.
	Arthritis	3.96	1.94	3.52	1.00	.07	3.95	.91	9.18
	No arthritis	.00[b]	.	.	.00	.	.	.	.
	Antiplatelet or anticoagulant	2.37	1.50	2.49	1.00	.11	10.70	.56	203.29
	No Antiplatelet or anticoagulant	.00[b]	.	.	.00	.	.	.	.
	ACE Inhibitor	.33	1.11	.09	1.00	.77	1.39	.16	12.30

	No ACE Inhibitor	.00[b]	.	.	.00	.	.	.	.
	Angiotensin II antagonist	-.48	1.44	.11	1.00	.74	.62	.04	10.44
	No Angiotensin II antagonist	.00[b]	.	.	.00	.	.	.	.
	Calcium channel blocker	1.01	.91	1.24	1.00	.26	2.75	.47	16.23
	No Calcium channel blocker	.00[b]	.	.	.00	.	.	.	.
	Beta blocker	-4.43	3.78	1.37	1.00	.24	.01	.00	19.85
	No Beta blocker	.00[b]	.	.	.00	.	.	.	.
	Previous major event	3.40	1.55	4.80	1.00	.03	29.96	1.43	627.46
	No Previous major event	.00[b]	.	.	.00	.	.	.	.
	Infrapopliteal artery disease	1.28	.94	1.83	1.00	.18	3.58	.56	22.75
	No Infrapopliteal artery disease	.00[b]	.	.	.00	.	.	.	.
	TBPI baseline	2.10	8.58	.06	1.00	.81	8.19	.00	16309.76
	Absolute toe pressure baseline	-.01	.06	.05	1.00	.83	.99	.88	1.11
	BMI	.02	.13	.03	1.00	.87	1.02	.79	1.32
	Age	-.04	.06	.48	1.00	.49	.96	.85	1.08
	Claudication distance baseline	.00	.00	.63	1.00	.43	1.00	1.00	1.01
	eGFR	.01	.03	.11	1.00	.74	1.01	.95	1.07
	Cholesterol	33.17	1.45	523.1	1.00	.00	25374.28	14792.87	43546.50
	Triglyceride	1.08	.71	2.30	1.00	.13	2.94	.73	11.82
	HDL Cholesterol	-37.51	3.94	90.61	1.00	.00	.00	.00	.00
	Non HDL Cholesterol	-32.42	.00	.	1.00	.	.00	.00	.00
	LDL Cholesterol	.45	1.14	.15	1.00	.70	1.56	.17	14.62
	Total Cholesterol	-1.62	1.51	1.15	1.00	.28	.20	.01	3.82
	HbA1c	-.71	.49	2.16	1.00	.14	.49	.19	1.27
	Creatinine	.00	.02	.00	1.00	.99	1.00	.96	1.04
	CRP	-.17	.14	1.53	1.00	.22	.84	.64	1.11
	ESR	.00	.03	.02	1.00	.89	1.00	.94	1.07
	Systolic blood pressure	-.04	.03	1.54	1.00	.21	.96	.90	1.02

a. The reference category is: worse outcome.

b. This parameter is set to zero because it is redundant.

Initial model for computing coefficient of all significant predictors of significant deterioration.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.642	.420		1.529	.132
	ABPI baseline	.670	.289	.277	2.320	.024
	TBPI baseline	.612	.338	.214	1.809	.076
	Disease Location	.273	.113	.279	2.423	.019
	Gender	.001	.130	.001	.006	.995
	Diabetes	.012	.143	.010	.082	.935
	CRP	-.005	.009	-.063	-.512	.610
	Taking Antiplatelet or anticoagulant	.089	.143	.072	.625	.534
	Calcium channel blocker	-.123	.126	-.110	-.975	.333

a. Dependent Variable: Deterioration to CLI

Model summary of significant predictors

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.549[a]	.302	.270	.41718	.302	9.367	3	65	.000

a. Predictors: (Constant), Disease Location, ABPI baseline , TBPI baseline

b. Dependent Variable: Deterioration to CLI

APPENDIX 14

ROC curve coordinates

Table A14.1: Coordinates for ROC curve analysing cut-off point for TBPI vs CLI

Area Under the Curve

Test Result Variable(s): TBPI baseline

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.673	.054	.003	.567	.778

The test result variable(s): TBPI baseline has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Coordinates of the Curve

Test Result Variable(s): TBPI baseline

Positive if Less Than or Equal To[a]	Sensitivity	1 - Specificity
.0000	.000	.000
.0900	.000	.012
.1100	.088	.024
.1250	.118	.024
.1350	.147	.024
.1450	.176	.024
.1600	.176	.036
.1750	**.235**	**.036**
.1850	.235	.048
.1950	.235	.072
.2150	.265	.084
.2350	.265	.096
.2450	.294	.096
.2600	.294	.133
.2750	.324	.181
.2950	.412	.205
.3150	.412	.229
.3250	.441	.253
.3350	.441	.265
.3450	.500	.313

.3550	.500	.325
.3650	.529	.349
.3750	.647	.398
.3850	.706	.446
.3950	**.735**	**.470**
.4050	.735	.482
.4150	.735	.518
.4250	.824	.530
.4400	.853	.578
.4550	.853	.590
.4650	.882	.627
.4750	.882	.663
.4850	.882	.687
.4950	.882	.723
.5050	.882	.735
.5200	.882	.771
.5350	.882	.795
.5450	.941	.831
.5550	.971	.855
.5800	1.000	.867
.6100	1.000	.880
.6350	1.000	.904
.6550	1.000	.916
.6700	1.000	.928
.6850	1.000	.940
.7050	1.000	.964
.7800	1.000	.976
.9100	1.000	.988
1.0000	1.000	1.000

The test result variable(s): TBPI baseline has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Table A14.2: Coordinates for ROC curve analysing cut-off point for ABPI vs CLI

Area Under the Curve

Test Result Variable(s): ABPI baseline

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.720	.056	.001	.610	.831

The test result variable(s): ABPI baseline has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Coordinates of the Curve

Test Result Variable(s): ABPI baseline

Positive if Less Than or Equal To[a]	Sensitivity	1 - Specificity
-.9000	.000	.000
.1500	.111	.000
.2750	.148	.000
.3750	.148	.016
.4150	.185	.016
.4400	.185	.031
.4600	.185	.047
.4800	.222	.063
.4950	.259	.063
.5050	.259	.094
.5150	.333	.109
.5250	.370	.141
.5400	.407	.172
.5550	.481	.203
.5650	.481	.281
.5800	.519	.313
.5950	.519	.328
.6050	.667	.344
.6150	.667	.359
.6250	.704	.359
.6350	.704	.375
.6450	.778	.375
.6550	.778	.422
.6650	.778	.469

.6750	.778	.484
.6850	.815	.531
.6950	.852	.531
.7050	.889	.563
.7150	.889	.625
.7350	.889	.656
.7550	.926	.656
.7650	.926	.703
.7750	.926	.734
.7850	.926	.750
.7950	.926	.781
.8050	1.000	.781
.8200	1.000	.797
.8350	1.000	.813
.8450	1.000	.859
.8600	1.000	.875
.8900	1.000	.891
.9250	1.000	.906
.9550	1.000	.922
.9750	1.000	.938
.9900	1.000	.953
1.0250	1.000	.969
1.2150	1.000	.984
2.3800	1.000	1.000

The test result variable(s): ABPI baseline has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Table A14.3 Co-ordinates of ROC curve – significant predictors applied to CLI model

Coordinates of the Curve		
Test Result Variable(s): Combined Predictive value ABPI,TBPI + Infrapopliteal artery disease		
Positive if Less Than or Equal To[a]	Sensitivity	1 - Specificity
-.8859	.000	.000
.3761	.037	.000
1.0951	.074	.000
1.7106	.111	.000
1.9666	.111	.016
2.3797	.148	.016
2.7897	.148	.031
2.9017	.185	.031
2.9909	.222	.031
3.0714	.259	.031
3.1338	.296	.031
3.3707	.296	.047
3.5773	.333	.047
3.6528	.333	.063
3.7113	.333	.078
3.7184	.333	.094
3.7324	.370	.094
3.7509	.407	.094
3.8082	.444	.094
3.9222	.481	.094
4.0069	.481	.109
4.0343	.519	.109
4.0477	.519	.125
4.1543	.556	.125
4.2658	.556	.141
4.3146	.556	.156
4.3542	.556	.172
4.3613	.556	.188
4.3893	.593	.188
4.4168	.593	.203
4.4723	.593	.219
4.5478	.630	.219
4.5873	.667	.219

4.6299	.667	.234
4.6824	.667	.250
4.7123	.667	.266
4.7574	.704	.266
4.8474	.704	.281
4.8998	.704	.297
4.9244	.704	.313
4.9664	.704	.328
5.0005	.778	.328
5.0174	.815	.328
5.0729	.852	.328
5.1265	.852	.344
5.1510	.852	.359
5.2229	.852	.375
5.2739	.889	.375
5.2770	.889	.391
5.3044	.889	.422
5.4318	.889	.438
5.5354	.889	.453
5.5390	.926	.453
5.6024	.926	.469
5.7724	.926	.484
5.8894	.926	.500
5.9174	.926	.516
5.9594	.926	.531
6.0264	.963	.531
6.1275	1.000	.531
6.2144	1.000	.547
6.2753	1.000	.563
6.3164	1.000	.578
6.3390	1.000	.594
6.3535	1.000	.609
6.3930	1.000	.625
6.4340	1.000	.641
6.4425	1.000	.656
6.4565	1.000	.672
6.5474	1.000	.688
6.6534	1.000	.703
6.7070	1.000	.719
6.7410	1.000	.734
6.7795	1.000	.750

6.9289	1.000	.766
7.0574	1.000	.781
7.1799	1.000	.797
7.3950	1.000	.813
7.5391	1.000	.828
7.6616	1.000	.844
7.7591	1.000	.859
7.7975	1.000	.875
7.9085	1.000	.891
8.1191	1.000	.906
8.3817	1.000	.922
8.8467	1.000	.938
9.2567	1.000	.953
9.6843	1.000	.969
10.3019	1.000	.984
11.5760	1.000	1.000

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.