University of Manchester

Studies on the prevention of venous insufficiency and ulceration

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by

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Abbreviations

ABPI	Ankle Brachial Pressure Index
AOFAS	American Orthopedic Foot and Ankle Score
ANOVA	Analysis of Covariance
ATM	Advanced Therapeutics Materials Ltd
AVP	Ambulatory Venous Pressure
BMI	Body Mass Index
CEAP	Clinical Etiological Anatomical Pathological
CPF	Calf Pump Failure
CI	Confidence Interval (95%)
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
CVU	Chronic Venous Ulceration
DVT	Deep Venous Thrombosis
ES	Elastic Stockings
ECS	Engineered Compression Stocking
IP	Intellectual Property
LAS	Linear Analogue Scale
LMWH	Low Molecular Weight Heparin
MHRA	Medicines and Healthcare products Regulatory Agency
OMAS	Olerud Molander Ankle Score
OR	Odds Ratio
PE	Pulmonary Embolism
PRI	Pressure Relief Index
PTS	Post Thrombotic Syndrome
QoL	Quality of Life
RCT	Randomized Controlled Trial
Sd	Standard Deviation
VTE	Venous Thrombo-Embolism
VU	Venous Ulcers

The University of Manchester, Abstract submitted by '**Muhammad Junaid Sultan**' for the degree of **MD**; entitled **"Studies on the prevention of venous insufficiency and ulceration", June 2013**

Introduction: Venous disease impairs the quality of life, necessitates time off work and causes venous ulcers. The focus of this thesis is to explore strategies to prevent chronic venous insufficiency (CVI) and venous ulceration.

Aims

1. To identify a population at risk of developing venous ulcers

2. To study the pressure profile required by elastic stockings to halve transit venous time

3. To explore the role of compression following ankle fracture

Methods: Data was collected from 231 patients with venous ulcers and age and sex matched 210 controls to identify risk factors for venous ulceration. Univariate and multivariate analysis of potential risk factors was undertaken to identify those that independently predict this risk. After identifying the population at risk, prophylactic strategies were developed. The effect of Engineered Compression Stockings (ECS) delivering 15mmHg, 25mmHg and 35mmHg pressure at the ankle on the calf venous transit time and volume was measured to determine the ideal pressure profile required to halve transit venous time, which should be appropriate for DVT prophylaxis. A dorsal foot vein was cannulated in 15 healthy volunteers with no venous disease. The transit time (secs) for ultrasound contrast from a foot vein to the popliteal vein was measured using duplex ultrasound. Calf volumes were recorded by water displacement.

ECS delivering 25mmHg of pressure around the ankle were compared with no compression in a randomized controlled trial (RCT) in 90 patients within 72 hours of ankle fracture. Patients were randomised to either i) ECS and air-cast boot or ii) a liner and air-cast boot and were followed at 2, 4, 8, 12 weeks and 6 months. The primary outcome was functional recovery measured using the Olerud Molander Ankle Score (OMAS). Secondary outcomes were i) The American Orthopaedic Foot and Ankle Score (AOFAS), ii) SF12v2 Quality of Life score (QoL), iii) pain, and iv) frequency of DVT.

Results

The risk factors significantly associated with venous ulceration on multivariate analysis included a history of Deep Vein Thrombosis (DVT), phlebitis, hip replacement, poor mobility, weight/kg>100Kg, varicose veins (VV), family history of VV and weight (kg) between 75-100kg. A simple diagnostic scoring system was derived from this regression analysis with scores of ≥ 3 predicting a 6.7% annual risk and of < 1 a 0.6% risk. Mean transit time without compression was 35, 32 and 33 secs while standing, sitting and lying. Transit time was consistently halved by ECS delivering 25mmHg to 14, 13 and 14 secs respectively ($p<0.001$). Mean leg volume whilst standing was reduced significantly from 3447ml with no ECS to 3259ml, 3161ml and 3067ml with ECS applying 15, 25 and 35mmHg respectively ($p<0.001$). ECS in ankle fracture patients reduced ankle swelling at all time points and significantly improved mean OMAS score at six months to 98 compared with 67 for the liner ($p<0.001$). AOFAS and SF12v2 scores were also significantly improved ($p<0.001$, $p= 0.016$). Of 86 patients with duplex imaging at four weeks, only five (12%) of the 43 ECS patients had a DVT compared with 10 (23%) of the 43 controls ($p= 0.26$).

Conclusions: The risk score for venous ulcers will allow us to undertake RCTs on the prevention of leg ulceration. The pressure profile required to halve transit venous time is 25mmHg. The frequency of asymptomatic DVT following ankle fracture is sufficient to justify prophylaxis. Compression has a potential role in the management of ankle fractures by improving functional outcome and QoL. These studies facilitate research into the prevention of venous disease.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Statement of Originality

The work described in this thesis 'Studies on the prevention of venous insufficiency and ulceration' stems from ideas developed jointly by Prof McCollum and myself.

All the research work described in the thesis is original and was undertaken by me, as a member of the research team at the Academic Vascular Unit at University of Manchester/University Hospital of South Manchester between 2009 and 2011. The work was supervised by Professor Charles McCollum and is based entirely on original observations that I carried out myself.

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Dedication

I would like to dedicate this thesis to my mother, Shahida Nasreen and father, Mahmood Sultan, brother, Sohaib Sultan and sister, Humaira Kiran and to Rachael Mellor.

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Limbo Products supplied shower bags; Physio Med Ltd supplied bands to assist in physiotherapy and   DJO Ltd to provide air-cast boots for ankle fracture study. ATM Ltd to provide stockings for ankle fracture and DVT prophylaxis study. Sonosite Ltd to provide portable ultrasound machine for DVT prophylaxis study.

I would like to thank Prof Charles McCollum for the constant guidance and putting up with my incessant questions, and for allowing me access to his previous studies, investigations and patients. I am grateful for his encouragement, which helped to materialise what was initially only an idea and for his help in elucidating many points during the projects regarding the transit venous time measurement. I am especially grateful to him for fighting my case when I made an appeal to the University to allow me to do the PhD for this project on the subsidiary fee.

I would also like to thank my advisor Dr Paul Kingston for taking the trouble to sign innumerable forms; Mr Kurdy for helping me with issues relating to the ankle fracture study and Mrs Julie Morris for guiding on statistical analysis; the Vascular Studies Laboratory for performing duplex ultrasound imaging, the Orthopaedic department, particularly the staff at the fracture clinic, staff at the Venous ulcer clinic, Physiotherapy

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I am grateful to University of Manchester for all the support during this research work but I wish that the University had given me the chance to submit this research work as a PhD on a subsidiary fee as this work was already accepted for PhD at the end of 2nd year transfer report and 30 month progress report.

Most importantly I would like to thank Mum, Dad, Kiran, Soby, Mariam, Iftikhar and Rachael for their never ending faith, support, encouragement and for always being there.

Preface

Qualifications

Royal College of Surgeons (Eng.)	June 2009	MRCS
Royal College of Surgeons (Edinburgh)	June 2008	MRCSEd
Rawalpindi Medical College	1999-2004	MB BS

Awards

Best 'Oral Poster award' at European Foot and Ankle Society meeting at Geneva

Best poster Award at Manchester Academic Health Science Centre (MAHSC)

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'Royal Society of Medicine Bursary' to attend London cardiovascular symposium 2012

Travel fund to attend European Vascular Society meeting

Registration award to attend European Vascular Course

Best oral presentation at National physiology conference in 2nd year of medical college

Grants

Amplify Ext CV185057 trial by Pfizer - £166,091 June 2010

PhD Research Fellowship by 'Manchester Surgical Research Trust' to carry out PhD for

three years - £128,450 Oct 2008

CLAHRC Flexibility and Sustainability Funding for 'Symptoms experienced by women with

pelvic incompetence: an evidence synthesis and characterization study'- £65,911 - Aug

2011

University Hospital of South Manchester Research Endowment fund to support 'Ankle

fracture trial' - £33,087 – April 2010

CLAHRC Flexibility and Sustainability Funding for 'Development and clinical evaluation of Engineered Compression Stockings' - £20,718 – June 2010

Goods supplied by Pyramid for 'Vulval varices' trial worth £55,995 – Aug 2009

SAVE-MED trial – by Sanofi Aventis - £18,000 – March 2009

Equipment supplied by SonoSite to 'identify pressure profile for DVT prophylaxis' - £35,445 - Jan 2010

Goods provided by DJO Ltd for 'ankle fracture trial' - £16,750 – April 2009

Goods supplied by different companies for various studies - £13,270 - 2010

Funding provided by 'Geko' to study nerve stimulator devices- £8,670 – June 2011

Goods provided by ATM for studies on 'Engineered Compression Stockings' - £7,195 - 2010

Original Publications from this Research

Published Abstracts

1. Role of Engineered Compression Stockings in preventing Deep Vein Thrombosis following ankle fractures. **Sultan MJ**, Zheng TT, Kurdy N, McCollum CN. Phlebology 2011; 26:267.

2. What compression is required for Deep Vein Thrombosis (DVT) prophylaxis? **Sultan MJ**, Wajerita A, McCollum CN. Phlebology 2011; 26:267.

3. Role of Compression in the management of ankle fractures. **Sultan MJ**, Zhing TT, Kurdy N, McCollum CN. JBJS 2012

4. Role of Compression in the management of ankle fractures. **Sultan MJ**, Zhing TT, Hodhody G, Kurdy N, McCollum CN. BJS 2011; 98(S2): 41.

5. Asymptomatic deep vein thrombosis is frequent following ankle fractures. **Sultan M J**, Johal K, Zheng T, Kurdy N, McCollum CN. Foot and Ankle Surgery Sep 2010; 16 (3): I-III. (online)

6. Frequency of asymptomatic deep vein thrombosis following ankle fractures. **Sultan M J**, Zheng T, Kurdy N, McCollum CN. Pathophysiol Haemost Thromb 2009-10; 37 (S1): A36.

Papers

1. Ankle injury stockings in ankle fracture: a randomized controlled trial. **Sultan M J,** Zheng T, Almuslam B, Kurdy N, McCollum CN (Submitted to JBJS UK).

2. **Sultan M J**, McKeown A, McLaughlin I, Kurdy N, McCollum CN. Elastic stockings or Tubigrip for ankle sprain: A randomised clinical trial. Injury 2012; 43: 1079–1083.

Section I

INTRODUCTION
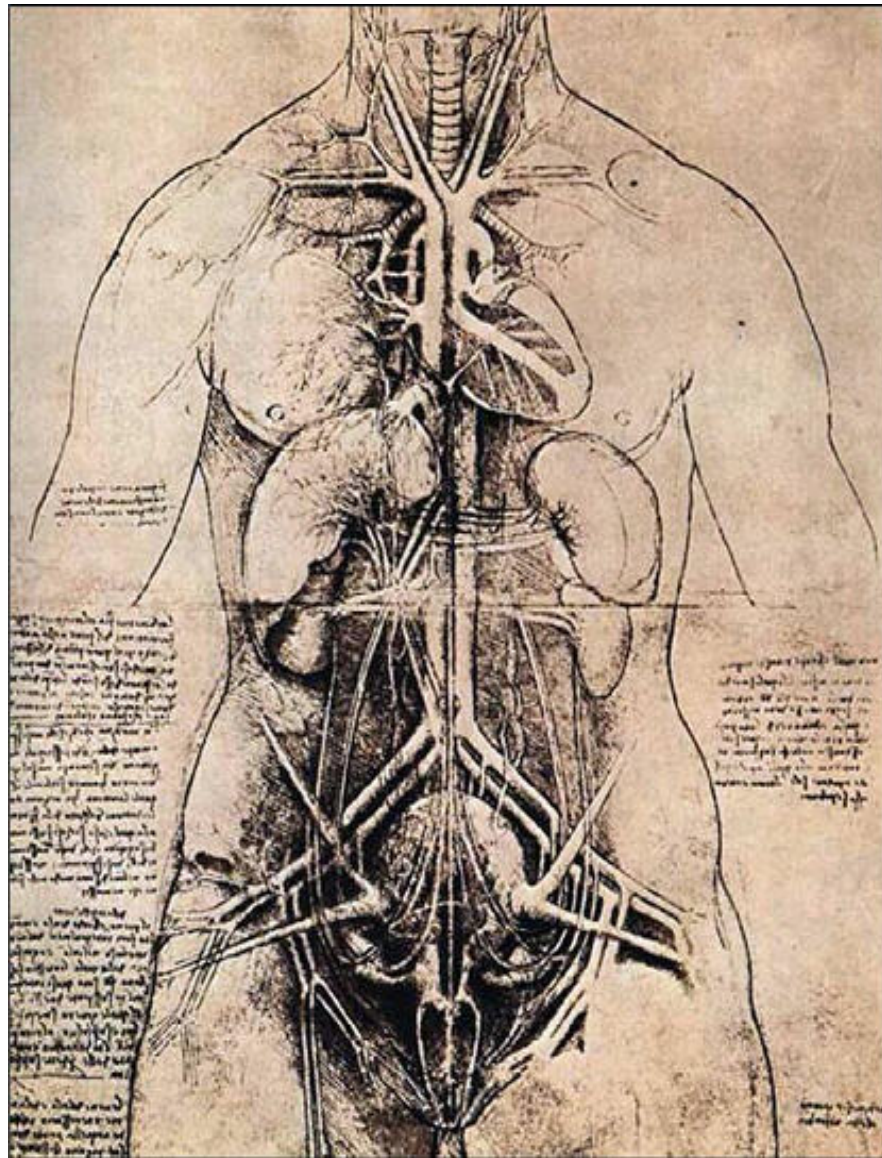
Figure 1: Drawing of the vascular (arterial and venous) and lymphatic system from Leonardo Da Vinci's collection. This figure is a reproduction of one of them provided originally around 1452.

Chapter 1

VENOUS DISEASE

1.1 Earliest references to venous disease

The word vein is derived from the Latin *vena*. The clinical presentation of chronic venous disease (CVD) has been recognized since antiquity. A Greek illustration from Athens dated the fourth century BC shows the medial side of a massive leg with what appears to be a varicose vein [1].

Hippocrates, in *De Ulceribus,* noted the association between varicose veins and ulceration. He recommended that patients with leg ulcers avoid standing and introduced the 'puncturing the ulcer and bandaging' as a treatment of leg ulcers (460-377 BC) [2]. In 200 BC Indians treated ulcers with maggot therapy and bandaging using inelastic Chinese fabric.

During Roman times, Celsus (AD 13-37) advocated the bandaging of ulcers [3]. Following this, from the 10th to 18th Century, various physicians, including Haly, Abbas, Avicenna and Fallopio, linked ulceration of the legs to the accumulation of black bile, bad humors, menstrual blood and faeculent humors, and considered ulceration of the legs a useful portal for getting rid of these vile substances [4]. Maitre Henri de Mondeville believed that compression bandages helped ulcer healing, as did Ambroise Pare' in 1533 [5].

Around 1452, Leonardo Da Vinci provided the first drawings of the vascular (Figure 1) and the venous system (Figure 2). About a hundred years later Vesalius described the anatomy of the veins in detail but did not recognise the presence of valves. It was Salomon Alberti who first described the valves in 1585. In 1628 William Harvey was the first to correctly identify the role of veins in returning blood to the heart, and that valves in the veins allowed unidirectional blood flow [6]. In the 17th Century, Richard Wiseman realised that venous dilatation resulted from valvular incompetence. He concluded that leg ulcers were a direct result of the stagnation of blood, secondary to varicose veins, and coined the term 'varicose ulcer' [7]. He invented a leather lace-up stocking to provide compression and achieve a cure.

During the 18th century, other authors including Bell, Baynton and Whatley rejected the association between leg ulceration and varicose veins, although leg ulcers were treated with paste bandages [8]. In 1850s, Unna described the rigid plaster dressings known as 'Unna Boot' and Virchow described his famous triad for venous thrombosis and the association with lung emboli[9].

Later, in 1868, Gay [10] and Spender [11] noted the role of deep vein thrombosis in the aetiology of leg ulceration, and advocated that the term "varicose ulcer" be dropped in favour of "Venous".

In 1916 Homans clearly established the relationship between previous deep vein thrombosis, recanalization, valve destruction and ulceration of the leg [12].

Cockett hypothesised that transmission of high pressure to the skin through incompetent perforating veins led to skin changes characteristic of venous insufficiency in 1955 [13].
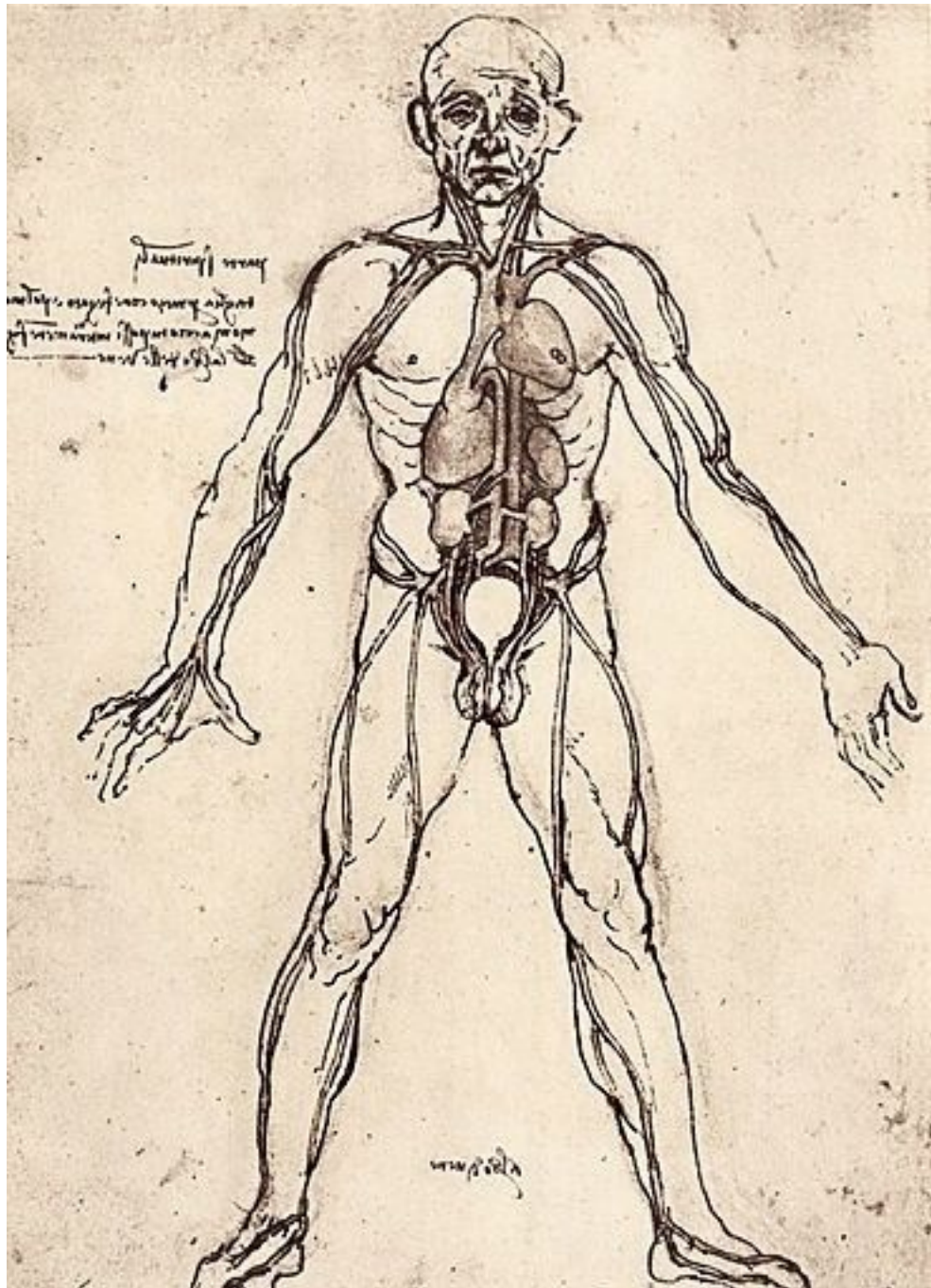
Figure 2: Leonardo Da Vinci provided drawings of the venous system around 1452. This figure is a reproduction of one of them

1.2 The venous system

1.2.1 Anatomy

In the circulatory system, veins are the blood vessels that carry deoxygenated blood towards the heart, against gravity, through the deep and superficial venous system [14] (Figure 3). The perforating veins connect this network of deep and superficial veins. Superficial veins are those whose course is close to the surface of the body, and have no corresponding arteries. Deep veins follow their corresponding arteries and are buried deeper in the body. There are numerous communications between the deep and superficial systems. Lower limb veins, particularly the calf veins, have one-way flaps called venous valves. Unlike arteries, which possess three well-defined layers, most veins are composed of a single tissue layer. Only the largest veins possess internal elastic membranes, and at best this layer is thin and unevenly distributed, providing little buttress against high internal pressures.
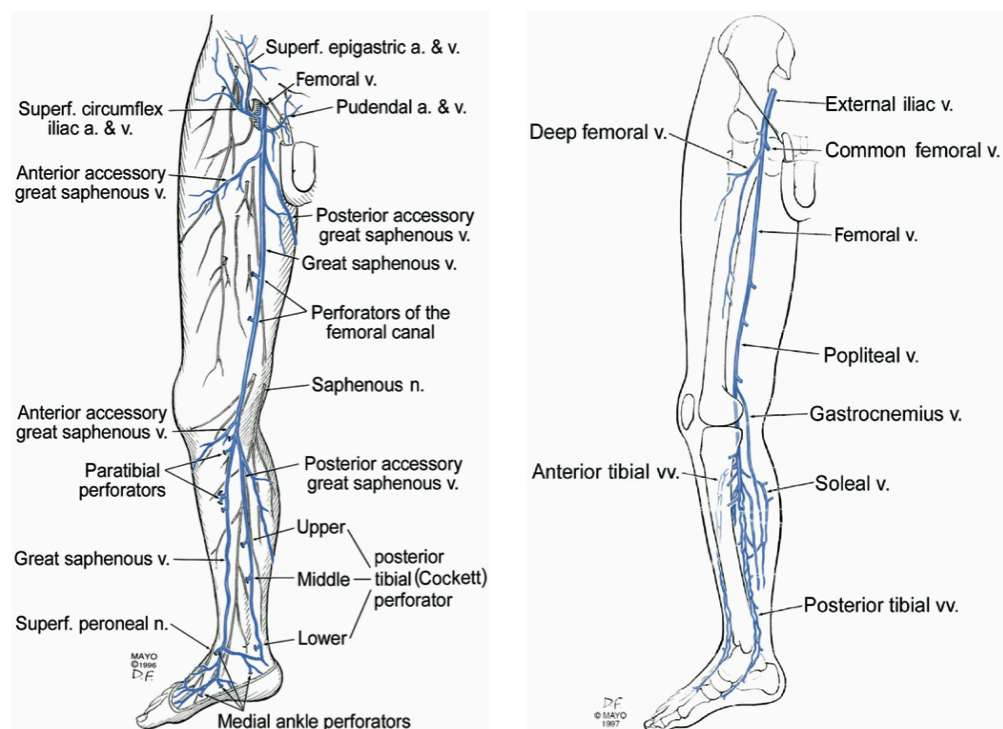
Figure 3: Superficial and deep venous system in lower limbs connecting with perforating veins [14]

1.2.2 Function

The lower limb veins, predominantly the calf veins, have one-way flaps called venous valves, which prevent blood from flowing backwards and pooling in the lower extremities, due to the effects of gravity. Blood is forced back up the leg during leg muscle systole and prevented from flowing back down the leg under the influence of gravity during diastole through the action of muscle pump and closure of venous valves.

The peripheral venous system functions both as a reservoir to hold extra blood and as a conduit to return blood from the periphery to the heart and lungs. Other physiological functions include thermoregulation, the storage of blood (as 70% of blood is stored in venous system), and the regulation of cardiac output [15-18].

1.2.3 Physiology

The primary function of the venous circulation is to return blood to the heart. The enormous capacity of the venous reservoir facilitates cardiovascular homeostasis through volume shifts. Effective venous return requires the interaction of a central pump, a pressure gradient, a peripheral venous pump, and competent venous valves. An appreciation of the relationship between volume and pressure in the venous system is essential to understanding normal and abnormal function. The physiological effects of gravity and hydrostatic pressure oppose return venous flow in the upright position. The forces of gravity are overcome by a system of valves, an efficient peripheral pump mechanism, and a small dynamic pressure gradient[19-24].

1.3 Venous disease

If the venous valves are not working, as they should, it is difficult for blood to circulate upwards, against gravity, to the heart. Prolonged augmented pressure in the veins

overstretches their valves, preventing them from closing properly. Consequently, there is a retrograde flow of blood back in to smaller veins, accumulating in the leg tissues, which causes swelling, or oedema. Another consequence of these ineffective valves is the decreased delivery of oxygen to the leg tissues, leading to cell damage, with inflammation and pain[25].

Venous disease is the most common vascular condition to affect the lower limb. The term 'chronic venous disorders of the leg' covers a wide range of conditions, including deep vein thrombosis, chronic venous insufficiency, asymptomatic incompetence of the venous valves, venous symptoms, telangiectases, varicose veins, oedema, skin changes and leg ulceration. These can be broadly categorised into deep vein thrombosis, chronic venous insufficiency (CVI), varicose veins and venous ulcers. These conditions are interlinked as one can lead to other.

1.4 The Consequences of venous disease

Venous disease is a consequence of sustained venous hypertension. Common causes of sustained venous hypertension include; venous obstruction, superficial and deep venous incompetence, obesity and loss of normal calf muscle pump function.

1.4.1   Varicose veins (VVs)

The most common manifestations of chronic venous disease are dilated cutaneous veins, such as telangiectases and reticular veins, and varicose veins. Varicose veins have incompetent valves with increased venous pressure leading to progressive dilation and tortuosity. VVs are caused by the high flow of turbulent blood refluxing down superficial veins due to incompetence of a proximal valve between the deep and superficial veins of the leg [26]. The superficial veins drain into the deep veins

primarily at the sapheno-femoral and sapheno-popliteal junctions and via perforating veins. Venous valves at these junctions protect superficial veins from the high pressures generated in the deep veins by the calf muscle pump. Varicose veins occur when these valves fail, causing a turbulent reflux of blood down the superficial veins, which results in variable shear stresses on the vein wall and tortuous bulbous varices. These varices are prone to develop bouts of superficial thrombophlebitis. Oedema begins in the perimalleolar (or gaiter) region but ascends up the leg with the dependent accumulation of fluid. The leg pain or discomfort is described as heaviness or aching after prolonged standing and is relieved by elevation of the leg. Oedema presumably causes this pain by increasing intra-compartmental and subcutaneous volume and pressure. There may also be tenderness along varicose veins from venous distension.

1.4.2   Deep Vein Thrombosis (DVT)

Formation of a blood clot in a deep vein results in DVT. Obstruction of the deep venous system may lead to venous claudication, or intense leg cramping with ambulation. Cutaneous changes include skin hyperpigmentation from hemosiderin deposition and eczematous dermatitis. Fibrosis may develop in the dermis and subcutaneous tissue (lipodermatosclerosis). There is an increased risk of cellulitis, leg ulceration, and delayed wound healing. Post-thrombotic syndrome is the signs and symptoms that occur as a result of long-term complications following DVT.

1.4.3   Chronic Venous Insufficiency (CVI)

CVI describes a condition that affects the venous system of the lower extremities with venous hypertension causing various pathologies including pain, swelling, oedema, skin changes, and ulcerations. Itching (pruritus) is sometimes a symptom, along with

hyperpigmentation of the legs. Symptoms of CVI include phlebitic lymphedema and chronic swelling of the legs and ankles. The skin may react with eczema, local inflammation, discolouration, thickening, and an increased risk of ulcers and cellulitis.

1.4.4 Venous Ulcers

The venous ulcers are thought to arise when the venous valves that exist to prevent the backflow of blood do not function properly, causing the pressure in veins to increase. Damage to the venous valvular system results in venous stasis in the lower extremity and, in extreme cases, allows the pressure in the veins to be higher than the pressure in the arteries. This pressure results in transudation of inflammatory mediators into the subcutaneous tissues of the lower extremity and subsequent breakdown of the tissue including the skin. When venous hypertension exists, arteries no longer have significantly higher pressure than veins, meaning that blood is not pumped as effectively in to or out of the area. It is in the gaiter area that the classic venous stasis ulcer occurs.

1.5 Causes

Venous dysfunction occurs when there is a structural or functional abnormality involving any of the mechanisms in place to assist blood flow back to the heart (veins, valves, perforators and the contracting muscles). There are a variety of factors that can lead to venous dysfunction ranging from genetic abnormalities to acquired pathologies [27] (table 1).

Venous dysfunction leads to reduce efficiency in returning blood to the heart. As the column of blood is unable to move against gravity without the support of the valves, retrograde flow and reflux occurs, which lead to venous pooling and dilatation of the veins. This further compromise the valves as the dilatation forces the valve cusps

further apart, meaning that they are unable to meet when required to prevent the backflow of blood [28]. The reflux that subsequently occurs causes an increase in the ambulatory venous pressure [28], which is the foundation of venous disease [27]. These events contribute to a cycle of worsening venous disease (figure 4) and thus the eventual formation of chronic venous hypertension.
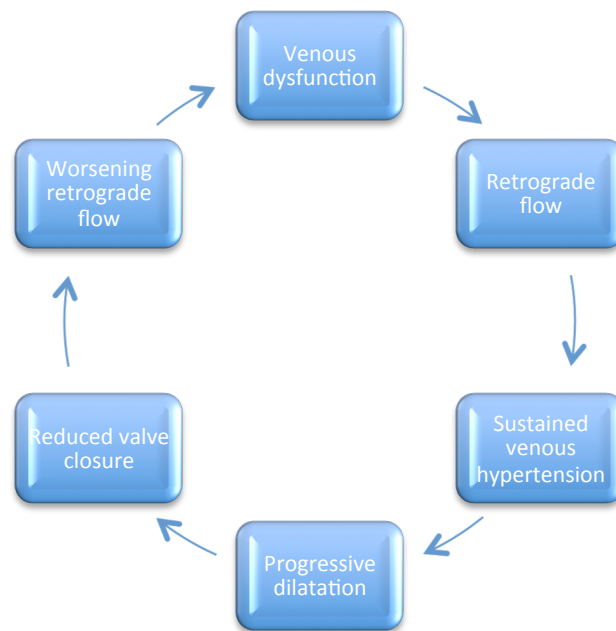
Figure 4: Flow chart to show the progressively worsening events of cyclical venous dysfunction

Table 1: Showing the aetiologies of venous disease

Aetiology of Venous disease	
VALVE DYSFUNCTION	Primary agenesis
	Valve injury (trauma, thrombosis, thrombophlebitis)
	Venous distension
	Hereditary susceptibility
VENOUS OUTFLOW OBSTRUCTION	Deep or superficial vein thrombosis
	Thrombophlebitis
	Tumour obstruction
MUSCLE PUMP FAILURE	Neuromuscular disease
	Muscle wasting / atrophy
	Prolonged standing
PERFORATOR DYSFUNCTION	Thrombosis
	Trauma
	Deep vein reflux or obstruction leading to 'blow out' of the perforator and superficial veins
CONGENITAL VENOUS DISEASE	Klippel - Trenaunacy syndrome
	Parkes Weber syndrome
	Cavernous angiomatosis or angiodysplasia
	Mafucci syndrome

1.6 Epidemiology

The phrase 'venous disease' describes a range of conditions including varicose veins, venous leg ulceration and chronic venous insufficiency. It is one of the most commonly reported chronic medical conditions and a substantial source of morbidity within the Western world [29] but despite this, venous disease is still an undervalued public health problem [30].

Venous disease is chronic in nature and follows a relapsing and remitting course, which puts a heavy burden on health care services, amounting to >£600 million per annum [31] in the United Kingdom. Venous disease consumes 1-2% of the health care budgets of European countries. The socio-economic impact is significant not only in terms of the medical care required for each patient, but also in the ability of the patient to perform their activities of daily living, such as their role within the family and workplace (e.g. time off work due to disability) [30].

Chronic venous insufficiency and chronic leg ulceration affect approximately 5% and 1% of the adult population of developed countries, respectively [33], and up to half of the adult population experience some form of stigmata of venous disease affecting their lower limb (e.g. telangiectasia) [30]. The peak incidence of chronic insufficiency is 40-49 years in women and 70-79 years in men.

1.6.1 Varicose veins

Varicose veins have an estimated prevalence of 5% to 30% in the adult population, with a female to male predominance of 3 to 1, although a more recent study supports a higher male prevalence [34]. The Edinburgh Vein Study screened 1566 subjects with duplex ultrasound for reflux, and found CVI in 9.4% of men and 6.6% of women, after age adjustment, which rose significantly with age (21.2% in men >50 years old, and 12.0% in women >50 years old) [35]. The San Valentino Vascular Screening Project found

that among the 30 000 subjects evaluated by clinical assessment and duplex ultrasound, a prevalence of 7% for varicose veins and 0.86% for "symptomatic" CVI [36]. The rate of varicose vein development may be estimated from the Framingham Heart Study, which found an annual incidence of 2.6% in women and 1.9% in men [37].

Bonn vein study, a cross-sectional study of 3,072 people randomly selected from population registries of Bonn and the surrounding area, found a pathological reflux in 35.3% of subjects with 21.0% showing reflux in at least one superficial vein and 20.0% showing reflux in at least one deep vein. Authors observed significantly higher reflux prevalence for the superficial veins in women while for the deep veins reflux prevalence were significantly higher in men. Reflux prevalence was associated with gender, age and CEAP classification [32].

Approximately 2% of NHS resources in the UK are spent on managing venous disease, with an estimated £20-25 million (excluding non-hospital costs) spent on operations for varicose veins in the year 2001[38].

Varicose veins have a significant impact on healthcare resources, with millions of people seeking medical attention for their cosmetic appearance annually. Although often marginalised, the cosmetic consequences may adversely affect an individual's quality of life and are associated with other manifestations.

1.6.2 Deep Venous Thrombosis (DVT)

Deep vein thrombosis (DVT) is well reported in hospitalised patients [39]. The annual incidence of Venous Thrombo-embolism (VTE) is 1 in 1000 per annum. The number of deaths per year due to venous VTE in the UK varies but the figure ranges from between 24,000 to 32,000 [40].

UK data suggests that in 1993 the total cost of VTE to National Health Service was £235-£257 million [41]. The combined direct and indirect cost estimates are now approximately £640 million [42]. When long-term complications, such as the post-thrombotic syndrome (PTS), are taken in to account, the costs are further increased [43-44].

1.6.3 Chronic venous insufficiency (CVI)

Chronic venous insufficiency affects approximately 5% of the adult population of developed countries [33] and up to half of the adult population will experience some form of stigmata of venous disease affecting their lower limb (e.g. telangiectasia) [30]. The peak incidence of chronic insufficiency is 40-49 years in women and 70-79 years in men.

Jawien et al [45] assessed 40,095 patients aged between 16-97 attending outpatient clinics in Poland. Prevalence of CVI was found to be 49% and of trophic changes 6.1%. However, majority of this study patients were recruited from the gynaecology clinics, which explains the large proportion of this study population being female (86%).

The Vein Consult Program [46] was an international, observational survey conducted worldwide recruiting 91545 subjects with help of 6232 GPs. Worldwide prevalence of CVD was found to be 83.6% with majority (63.9%) ranging C1-C6 and 19.7% as C0. Men were found to be more frequently in the C0 category whereas; women were mainly in the range C1-3 regardless of the geographical zone. Interestingly there was no difference in the prevalence with severe stages (C4-6).

In the 1950s, Coon et al [48] conducted an epidemiologic study of venous disease in the Tecumseh community. The prevalence of "stasis skin changes" in the population aged >10 years was found to be 3.0% for males and 3.7% for females.

Cesarone et al [49] conducted an epidemiological study of 30,000 civilians in the San Valentino region of Italy. The prevalence of CVI was reported as 0.86%, although they failed to include a definition for CVI.

Chiesa et al [50] also conducted a study on the epidemiology of CVI in Italy. The study advertised for volunteers in the national press and in newspapers, and therefore represented a non-random sample. 5,187 patients were clinically assessed and only 22.7% were free from signs of venous disease. 8.6% had skin changes (C4b-C6).

In 1979, Krijnen identified a random sample of 4,530 persons from the city of Tübingen, in Germany, and assessed them for signs of CVI. 59% had mild varicosities, 15% had evident varicosities and 12% were found to have "progressive CVI" [47](data from Krijnen, original article in German).

The Basle II study looked at the prevalence of CVI in 4,422 employees in the chemical industry, aged 20-70 [51]. 22% of subjects had signs of CVI (Widmer I-III). There was a bias towards good health, as subjects were fit to work, and therefore prevalence in the general population may be higher.

Carpentier et al [52] performed a cross-sectional epidemiologic study of adults (>18 years) in 4 geographic regions in France. A random sample of the population was examined for signs of venous disease. There were no significant geographical variations in prevalence of venous insufficiency and the overall prevalence of 'skin trophic changes' was 5.4% in males and 2.8% in females.

1.6.4 Venous ulcers

Venous leg ulcers occur in 1.7% of the elderly population and cost the UK NHS £600 million/year [32, 53]. 58% to 70% of all leg ulcers are venous leg ulcerations [54, 55]. It is estimated that 80% of ulcer patients are cared for solely in the community [56].

There have been immense savings to the health care service by prevention of venous disease and ulceration [59]. A delay in ulcer recurrence by a single month can make a significant difference by saving 8% of the time spent by district nurses on ulcer care and reducing the cost for our health service [60].

In a review article on the prevalence of venous ulceration, Fowkes estimated the prevalence of active ulceration in UK (i.e. point prevalence) to be 0.3% of the adult population. 1% of the population was found to have active or healed ulceration (i.e. overall prevalence). However, the article conceded that these figures are very rough estimates [61]. If we take Fowkes' estimates of a point prevalence of 0.3% and overall prevalence of 1% and apply this to the UK population (total population 58,789,194, census data 2001), then 176,000 are affected at any one time, and 588,000 are at risk.

The Basle II study looked at the prevalence of ulcers in 4,422 employees in the chemical industry, aged 20-70 [51]. Active or healed venous ulceration was noted in 1.1% of males and 1.4% of females. There was a bias towards good health, as subjects were fit to work, and therefore prevalence in the general population may be higher.

Cesarone et al [49] conducted an epidemiological study of 30,000 civilians in the San Valentino region of Italy. Excluding cases whose ulcers were of mixed aetiology, the prevalence of venous ulcers was 0.48%.

In the 1950s, Coon et al [48] conducted an epidemiological study of venous disease in the Tecumseh community. The prevalence of active or healed ulceration was 0.1% in males and 0.3% in females.

Jawien et al [45] assessed 40,095 patients aged between 16-97 attending outpatient clinics in Poland. The prevalence of active or healed ulceration was 1.5% with 0.5% as

active ulcers. However, due to a large proportion of patients being recruited from the gynaecology clinics, 86% of this study population was female.

These studies assume that the population attending outpatient clinics is representative of the population at large, however this is unlikely to be the case and therefore the data will be skewed.

The overall prognosis of venous ulcers is poor, with delayed healing and recurrent ulceration being common [62]. More than 50% of venous ulcers require prolonged therapy lasting >1 year [63]. The socioeconomic impact of venous ulceration is dramatic, resulting in an impaired ability to engage in social and occupational activities, thus reducing the quality of life and imposing financial constraints. Disability related to venous ulcers leads to the loss of productive work hours, estimated at 2 million workdays/year, and may cause early retirement, which occurs in up to 12.5% of workers with venous ulcers [64]. The financial burden of venous ulcer disease on the healthcare system is readily apparent: An estimated $1 billion is spent annually on the treatment of chronic wounds in the United States, or up to 2% of the total healthcare budget in all Western countries, and recent estimates place the cost of venous ulcer care at $3 billion annually [65, 66].

Given the prevalence and socioeconomic impact of chronic venous disease, an understanding of the clinical manifestations, diagnostic modalities, preventive and therapeutic options is warranted. This thesis highlights the importance of a change in the focus of research onto the prevention rather than therapeutic options.

1.7 Venous ulcers

1.7.1 Aetiology

Venous ulceration is the end stage in CVI caused by sustained venous hypertension secondary to

i)   Venous disease - superficial or deep vein incompetence, previous deep vein thrombosis (DVT) [27]

ii)   Impaired calf muscle pump function – venous disease and immobility associated with old age, joint disease or paralysis [27]

1.7.2 The impact of venous ulcers

Leg ulcers are painful and often malodorous sores affecting 1.7% of our elderly population in the UK [32]. They cost the NHS £600 million a year to treat, mainly in skilled nursing time to apply 4-layer compression bandages (4LB) [53]. Much of this expense is the staff time taken by district nurses in dressing and bandaging patients with ulcers, the current gold standard for treating venous ulceration [57]. District nurses spend up to 50% of their working hours caring for patients with ulcers [58].

4LB heal 45-70% of leg ulcers within 12 weeks, but compression varies due to differently shaped legs, and between different nurses and bandaging techniques. Elastic stockings deliver more predictable and sustained compression, but are available currently in four sizes only and rarely fit individual patients precisely.

Leg ulceration carries significant morbidity and a marked reduction in quality of life. Frequent visits to leg ulcer clinics, prescription costs for dressings, poor sleep associated with pain and restrictions to social, leisure and work activities all contribute to the negative impact of this condition on the patient [67-69]. In addition, reduced mobility and a protracted healing course lead to social isolation, loss of independence and emotional despair [70-71].

1.7.3 Pathogenesis

The final pathogenesis is still hotly disputed; venous hypertension stimulates changes in the microcirculation, triggers an inflammatory response resulting in inflammation, swelling and eventually tissue breakdown [30]. As a result of venous hypertension, fluid is transudated into the interstitial space between the capillaries and the cells, which increases the distance over which metabolites must diffuse [72]. With the leg in a dependent posture, the soft tissues around the ankle become ischaemic and are subject to a reperfusion injury on walking or elevation [31]. Due to the repeated low-grade ischemia-reperfusion injury, a chronic inflammatory response is triggered, resulting in ulceration of the skin, mostly in the gaiter area of the ankle [31, 73].

There is often a history of venous thrombosis occurring during an illness or pregnancy, which has resulted in deep and communicating vein damage. Patients often experience the symptoms of chronic venous insufficiency many years prior to ulceration. Oedema and skin changes, including lipodermatosclerosis, white atrophie and ankle flare, are all sequelae of chronic venous insufficiency.

In most cases, venous ulcers are spontaneous but occasionally there may be an initiating event that leads to ulceration; usually some form of blunt trauma, which breaks the surface of the skin. Dry skin that has been scratched by the patient, penetrating trauma, contact dermatitis and cellulitis has also been documented as direct triggers of ulceration [74].

1.7.4 Risk factors

Venous hypertension culminating in chronic venous insufficiency (CVI) is the cause of all venous leg ulcers. Causes of sustained venous hypertension, such as previous deep vein thrombosis (DVT), and superficial and deep venous incompetence are the risk

factors for primary ulceration. Leg injury, osteoarthritis, obesity, heart disease, age and female sex are additional reported risk factors for lower limb ulceration [75, 63].

a) Age

Perhaps the most important risk factor for CVI is age. The studies on prevalence of varicose veins, venous ulceration and CVI clearly demonstrate that prevalence is higher with increasing age. This effect is likely to be due to the presence of an increasing number of risk factors, which are also associated with increasing age, such as immobility, arthritis, DVT and varicose veins. Nelzen et al [76] clearly demonstrated increased prevalence of venous ulceration with advancing age; in fact 92% of the patients with active leg ulceration in this study were over 60 years of age. Similarly Scott et al [63] showed that age is significantly associated with CVI in a case control study.

b) Gender

Several epidemiological studies have shown increased prevalence of varicose veins in the female population [52, 77]. In his comprehensive review of the epidemiology of varicose veins, Callam concludes that there is a clear female preponderance in the prevalence of varicose veins with a ratio of between 1.5:1 and 3.5:1.

The prevalence of venous leg ulcers was higher in women the Tecumseh Community Study of the 1950s, and it also demonstrated an increased prevalence of venous insufficiency in the female population[48]. Maffei also demonstrated an increased prevalence in the female population [78]. However, a more recent study in Scotland demonstrated an increased prevalence in males [35].

Chronic Venous Ulceration (CVU) is frequently stated to be more common in women [29, 46], although epidemiological studies suggest that, once prevalence is corrected for age, men and women are affected almost equally. The excess of women observed in clinical

practice is largely due to their longevity, together with an apparent reluctance on the part of workingmen to seek medical attention.

It has been postulated that the increased frequency of venous ulceration in women may be due to the fact that they may be more likely to present to their doctor for treatment, whereas many males self-treat their ulcer.

c) Obesity

Obesity is defined as a body mass index (BMI) >30. Body mass index is calculated by dividing weight in kilograms by the height in metres squared. Venous ulcers have been noted to be particularly difficult to treat in obese patients, and in a series of 39 limbs in 20 obese patients with CVI, duplex abnormalities were detected in just 44% of cases, suggesting that obesity may cause venous hypertension and ulceration by an alternative mechanism [79]. Several theories exist to explain these findings: obesity may produce venous and lymphatic obstruction, in addition to an increased risk of congestive cardiac failure. Scott et al [63] also demonstrated in a case control study that obesity is significantly associated with CVI.

Danielsson et al concluded that being overweight appears to be a separate risk factor for increased severity of skin changes in patients with venous ulcers [80].

d) Thrombophilia

Thrombophilia can be described as an abnormality of the clotting and/or fibrinolytic cascade resulting in hypercoagulability [81]. Examples of these abnormalities include deficiency of the factors anti-thrombin, protein C and protein S and resistance to activated protein C. Whilst there is a clear link between thrombophilia and DVT, there is less evidence to link thrombophilia with CVI, however a cohort study of 88 patients with venous ulceration found that thrombophilia was up to 30 times more prevalent than in the background population [82].

e) Deep vein thrombosis (DVT)

DVT is considered a major risk factor for CVI and venous ulceration. Studies examining the relationship between symptomatic DVT and Post Thrombotic Syndrome (PTS) have shown a prevalence of 29%-90% of PTS following DVT [83-88]. A severe form, involving venous ulcers, occurs in up to one third of patients with PTS [89, 90].

Fowkes et al [61] found that risk of venous ulceration is increased following DVT. Vlajinac et al [91] also reported DVT as an independent risk factor for venous ulceration.

f) Arthritis

There is very little data on the influence of arthritis on the prevalence of venous disease. An epidemiological study using the United Kingdom General Practice Research Database found there was a significant association between a diagnosis of osteoarthritis and the subsequent development of a venous ulcer [92]. Patients with osteoarthritis have reduced mobility, resulting in impaired calf-muscle pump activity and, therefore, may be at risk of DVT, which subsequently causes venous ulceration.

1.7.5 Management

Patients with leg ulcers should have an initial assessment in a hospital vascular clinic, with patients who are unlikely to benefit from surgery then being cared for in the community.

Management must begin with a comprehensive history and examination to identify the risk factor profile for ulceration. The typical patient with a venous leg ulcer is female and elderly with a longstanding history of venous disease [31]. Many patients will have experienced recurrent ulceration, sometimes prior to seeking medical advice. There is often a history of venous thrombosis during an illness or pregnancy, which has

resulted in deep and communicating vein damage. Mobility and social circumstances must be fully reviewed because without help at home, immobile patients are unlikely to be compliant with treatment [93].

When examining a patient with leg ulceration (Figure 5), the presence of oedema should be noted and any non-venous causes, such as cardiac failure and renal disease excluded. Joint mobility should be assessed, with emphasis placed on the ankle joint, an important contributor to the calf muscle pump [94]. Both legs must be examined for signs of venous disease, in particular for varicose veins, skin changes and previous DVT.

Patients should be advised to try to keep active by walking regularly. Immobility can make venous leg ulcers and the associated symptoms, such as oedema, worse. Whenever these patients are sitting or lying down, they should try to keep their affected leg elevated. Foot care is an important aspect of management and patients should be advised to be careful not to injure their affected leg, and wear only comfortable well-fitting footwear. Skin care is an important aspect of management and patients should be prescribed an emollient for venous eczema to use as often as possible.

The surface area, position, ulcer edge and base of the ulcer should be serially monitored to assess the healing course, which is often frustratingly slow for both the patient and health service professional. It is fundamental that patients are reassessed at regular intervals to monitor ulcer healing. Compression therapy should be maintained following ulcer healing for the purpose of secondary prevention [56, 95]. ABPI monitoring at regular intervals is essential to reassure it is safe to carry on the compression therapy.

Malignancy is a rare complication of chronic ulceration of the lower limb and is known as Marjolins ulcer. The diagnosis should be considered if there is deterioration or

failure to progress after 12 weeks and, in this case, referral for biopsy is indicated [96].

Enlarged inguinal lymph nodes, thickening of the ulcer edge, pain and malodour are also indicative of squamous cell carcinoma.

A venous ulcer can be healed by applying either strong sustained compression with a bandage or a stocking, and by treating the underlying cause of the ulcer. When appropriate, both treatments can be used at the same time.

1.7.6 The role of ischemia and diabetes/neuropathies

Patients with foot ulceration should be referred to hospital for investigation because many will have underlying arterial ischemia that requires prompt intervention. Diabetic patients with signs of infection should have plain radiography of the foot to look for osteomyelitis. Patients with venous ulceration should have their ankle brachial pressure index measured and can be managed either primarily in the community by trained nurses or referred to hospital for further investigation into the underlying venous abnormality.

It is important to assess the arterial circulation and nervous system to exclude an ischaemic or neuropathic cause of the ulcer. It is well documented that one in five patients with a leg ulcer has significant arterial disease [97]. Palpation of the pulses must be combined with measurement of the ankle brachial pressure index (ABPI) in both legs, using Doppler to competently assess arterial insufficiency [98, 99]. An ABPI of less than 0.8 is indicative of significant arterial disease and warrants specialist referral.

The collection of routine bacteriological swabs is unnecessary in the absence of clinical signs of infection [100]. Such signs include cellulitis, purulent exudate, pyrexia and increased pain. Ulcer healing is not thought to be influenced by the presence of bacteria [101, 102].

Leg ulceration can occur as a result of a combination of underlying conditions. In the case of a venous ulcer that is complicated by arterial insufficiency, compression treatment may be hazardous and risks inducing ischemia. Diabetic patients with leg ulcers are at risk of arterial calcification and may also be harmed by compression therapy. Compression should be used cautiously in these situations.

Figure 5: Venous ulcer in characteristic position, proximal to the malleoli[103]

1.7.7 Recurrence

The recurrence of ulceration is common, with rates of 26-69% reported at one year [104]. It is evident that patient compliance to compression treatment is paramount in improving healing times and reducing ulcer recurrence [105, 106]. Several independent risk factors that influence ulcer-healing times have been identified; these include age, ulcer chronicity and venous refill time [107-108]. In the Lothian and Forth Valley Leg Ulcer Study, multiple

recurrences were documented in 67% of ulcerated legs, the remaining 33% never having healed their first ulcer [62].

1.7.8 Prevention of recurrence

Leg ulcers commonly recur after healing [62, 109]. Healing therefore represents an opportunity for secondary prevention, either by conservative measures or venous surgery. It is logical to offer newly healed patients professionally fitted graduated compression stockings, because although it is known that superficial venous surgery reduces the risk of recurrence [110], surgery will not be appropriate for all patients, and a minority will refuse or be unsuitable for surgery [110]. Franks et al [111] found that non-compliance with compression is associated with an increased risk of recurrence.

Compression hosiery is advised after leg ulcer healing, but the optimal grade of compression required to prevent recurrence is not known [112-113]. Preventing recurrence is very important because of the high recurrence rates. In patients with healed ulcers who have not had surgery, the mainstay of preventing recurrence is graduated elastic compression hosiery. However, elderly patients with arthritis of the knee or hip may struggle to apply class II compression hosiery, therefore class I hosiery is a sensible compromise. Such patients may find a hosiery applicator useful.

There may well be a trade-off between compliance, thought to be higher with lower levels of compression, and effectiveness, because higher compression is often recommended. The highest compression hosiery available in the United Kingdom (class 3 compression) may be associated with poor compliance, particularly in the elderly; therefore, any advantage of high compression over moderate compression may be compromised by poor compliance. Nelson concluded that there was no evidence of a significant difference in recurrence rates with grade II and grade III compression, but the lowest recurrence rates were seen in people who wore the highest degree of

compression. Therefore, patients should wear the highest level of compression that is comfortable [114].

1.7.9 Scoring systems for venous ulcers

Previous studies have created scoring systems for the prediction of leg ulcer healing [115-116] but no scoring system is available to predict the annual incidence of primary venous ulcers. Researchers have been focused on evaluating the prognostic factors in uncomplicated venous leg ulcer healing [117]. Much current research is focused on the treatment of active ulcers. However, it has been suggested that information about a family history of venous insufficiency and monitoring of physical activity can be used to predict ulcer risk and can ultimately lead to ulcer prevention [118]. The prevention of ulceration, by identifying at-risk populations, would provide a more cost effective solution and improve the quality of life for patients with sustained venous hypertension at risk of ulceration.

Chapter 2

CHRONIC VENOUS INSUFFICIENCY (CVI)

2.1 Definition

The International Consensus Committee on Chronic Venous Diseases has defined chronic venous insufficiency (CVI) as "an abnormally functioning venous system caused by venous valvular incompetence with or without associated venous outflow obstruction, which may affect the superficial venous system, the deep venous system, or both" [119]. This definition encompasses a wide variety of symptoms and signs, ranging from asymptomatic venous reflux, to varicose veins, to more advanced signs such as lipodermatosclerosis (LDS) and, eventually, venous ulceration. The valvular abnormalities lead to venous hypertension, the hallmark of CVI.

In the clinical setting, CVI is often used to describe the advanced skin changes, which occur as a result of persistent venous hypertension.

2.2 Economic considerations and the size of the problem

Chronic venous insufficiency affects approximately 5% and chronic leg ulcers approximately 1% of the adult population of developed countries. Recent quality of life studies highlight the magnitude of the major disability and social impairment that results from these conditions [30, 33]. Due to their chronic relapsing and remitting nature, they inevitably give rise to massive health care expenditure amounting in the UK to around £400 million per annum [31].

More than half of venous ulcers require prolonged therapy lasting more than a year [63]. The socioeconomic impact of venous ulceration is dramatic, resulting in an impaired ability to engage in social and occupational activities, thus reducing the quality of life and imposing financial constraints. Disability related to venous ulcers leads to the loss of productive work hours, estimated at 2 million workdays/year, and may cause early retirement, which is found in up to 12.5% of workers with venous ulcers [64]. The financial

burden of venous ulcer disease on the healthcare system is readily apparent: An estimated $1 billion is spent annually on the treatment of chronic wounds in the United States, or up to 2% of the total healthcare budget in all Western countries, and recent estimates place the cost of venous ulcer care at $3 billion annually [65-66].

Chronic venous disease is often overlooked by primary and secondary care providers because of an under appreciation of the magnitude and impact of the problem. The importance of chronic venous disease is related to the number of people with the disease and the socioeconomic impact of its more severe manifestations. Unfortunately, the literature concerning the prevalence and incidence of chronic venous disease has varied greatly because of differences in the methods of evaluation, criteria for definition, and the geographic regions analysed. Given the prevalence and socioeconomic impact of chronic venous disease, an understanding of the clinical manifestations, diagnostic modalities, therapeutic options and the prevention of risk factors are warranted.

2.3 Classification

Classification of knowledge is important for progression in any scientific field and venous disease has, for many years, lacked a precise classification system. This has resulted in conflicting reports in studies of prevalence and management of venous disease. A large number of classification systems have been proposed [120]. The most commonly used systems are presented below.

a) Widmer classification

One of the earliest and most commonly quoted classification systems was that used by Widmer et al in the Basle studies on the prevalence of venous disease [121]. The Widmer classification system (Table 2) is a basic way of classifying CVI. It considers only the subjectively measured superficial effects of CVI, such as varicose veins, stasis skin changes

and ulceration [51]. It does not consider any objective measures of the function of the venous system.

Class	Description
Class I	Dilated subcutaneous veins, 'corona phlebectatica'
Class II	Hyper- or de-pigmented areas ± 'corona phlebectatica'
Class III	Open or healed ulcus cruris

Table 2: Widmer classification of CVI

b) CEAP classification

An ad hoc international committee at the American Venous Forum proposed the CEAP system in 1994 as a method of categorising CVI more precisely [122]. The classification grades the severity of CVI on the basis of clinical appearance (C), aetiologic factors, (E), anatomical distribution of abnormalities (A) and underlying pathophysiology (P) (Table 3).

A revision of the classification was published in 2004:

- Definitions of clinical classes were refined

- C4 was divided into two subgroups to stratify the severity of stasis skin changes

- A basic scoring system was proposed, whereby only the highest score in each category is quoted

- The addition of a subscript 'S' or 'A' to the 'C' score indicates whether the patient is symptomatic or asymptomatic

- The addition of a subscript, 'n' was recommended to highlight where no venous abnormality was identified in the 'E', 'A' or 'P' scores.

One omission from the CEAP classification is grading of corona phlebectatica (also known as ankle or malleolar flare), which is often considered a precursor of advanced venous disease. A subgroup of the AVF committee advised collecting data on ankle flare in addition to CEAP data [123].

In the advanced version of the CEAP classification, numbers representing one of 18 named venous segments are listed as a suffix to the pathophysiology score to denote the distribution of venous pathology.

Table 3

CEAP classification				
Clinical Classification		**Segment**		
C_0	no visible or palpable signs of venous disease			
C_1	telangiectasies or reticular veins	1	telangectasia or reticular veins	
C_2	varicose veins	2	above knee LSV	
C_3	Oedema	3	below knee LSV	
C_{4a}	pigmentation or eczema	4	short saphenous vein	
C_{4b}	LDS or atrophie blanche	5	non-saphenous veins	
C_5	healed venous ulcer	6	inferior vena cava	
C_6	active venous ulcer	7	common iliac vein	
S	symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction	8	internal iliac vein	
		9	external iliac vein	
		10	pelvic vein	
		11	common femoral vein	
A	Asymptomatic	12	Deep femoral vein	
Etiologic Classification				
E_c	Congenital	13	femoral vein	
E_p	Primary	14	popliteal vein	
E_s	secondary (post-thrombotic)	15	crural vein: anterior tibial, posterior tibial, peroneal veins (all paired)	
E_n	no venous abnormality identified			
Anatomic Classification				
A_s	Superficial	16	muscular: gastrocnemial, soleal vein	
A_p	Perforator	17	thigh perforating vein	
A_d	Deep	18	calf perforating vein	
A_n	no venous location identified			
Pathophysiology Classification				
P_r	Reflux			
P_o	Obstruction			
$P_{r,o}$	reflux and obstruction			
P_n	no venous pathophysiology identifiable			

2.4 Pathophysiology

It is agreed that the hallmark of CVI and venous ulceration is persistent venous hypertension either due to:

i)   Venous abnormalities: deep or superficial venous incompetence

ii)   Calf pump failure syndrome.

Several theories exist on the causation of venous ulceration [30]:

An early theory by Homans suggested that stasis of blood may occur in the tortuous and dilated veins close to the skin [124]. The term 'stasis' has persisted in clinical practice to this day e.g. stasis skin changes, stasis ulcer. This concept was later refuted when the differences were demonstrated to be due to the dependent posture of the limb at the time of sampling [125].

In 1982, Browse and Burnand suggested that venous hypertension results in increased pressure within the capillary bed[126]. They suggested that this raised pressure increases the size of the capillary bed and the filtration through the pores of the capillary, in particular the amount of fibrin filtrate. A pericapillary fibrin cuff develops which was claimed to be a barrier to oxygen diffusion, leading directly to hypoxia of the skin, cell death and ulceration.

There is actually little evidence to suggest that the fibrin cuff acts as a barrier to oxygen diffusion [127] and the fibrin cuff occurs elsewhere in the body in the absence of venous hypertension [128].

In 1989, Coleridge-Smith et al proposed an alternative mechanism; the 'white cell trap theory' [129]. Increased capillary pressures lead to decreased capillary perfusion, allowing leucocytes to become trapped. The trapped leukocytes release toxic oxygen metabolites

and proteolytic enzymes, causing capillary damage, increased permeability to large molecules and causing additional leucocyte trapping.

In 1993, Falanga proposed that fibrin and other macromolecules leak into the dermis, by either of the previously proposed mechanisms, and 'trap' growth factors, rendering them unavailable for tissue repair and maintenance [130]. In support of this hypothesis is the observation that wound fluid collected from venous ulcers inhibits cell growth of keratinocytes, fibroblasts and endothelial cells in-vitro, whereas fluid from acute wounds stimulate these cell types [131]. This theory does not however explain the observations of inflammation and cell death.

Powell et al [132] identified increased levels of circulating aggregates of monocytes/platelets in patients with venous insufficiency. It was suggested that these aggregates might damage the venous epithelium and cause valve dysfunction. Activated leucocytes and platelets increase leucocyte adhesion to the endothelium.

Pascarella et al [133] explained the inflammatory process seen in venous ulceration in terms of rheology. Venous hypertension results in low flow through the capillaries, which in turn causes reduced shear forces between the blood cells and the vessel wall. Shear stress is defined as the tangential force per membrane area produced by moving blood while acting on the endothelial surface. It is directly proportional to flow velocity and blood viscosity and inversely proportional to vessel radius. Leucocytes become activated and extend pseudopodia in conditions of low shear stress, allowing margination and migration into the surrounding tissues.

Herouy investigated the role of cellular tight junctions in chronic venous insufficiency [134]. Protein and mRNA levels of specific tight junction molecules were significantly reduced in patients with venous insufficiency when compared to healthy control subjects.

a)   Lipodermatosclerosis

Lipodermatosclerosis is characterised by a 'brawny' thickening of the subcutaneous tissues. It occasionally presents acutely as a panniculitis and is often misdiagnosed as cellulitis.

Histology of lipodermatosclerotic skin reveals thickening of the perivascular area, and an acellular space around the capillaries of the superficial dermis [135]. It has been proposed that the proliferation of capillaries seen in CVI is surrounded by fibroblasts and connective tissue, which become part of a deeper fibrotic layer in a process of scarring. The endothelium and muscle layers of lymphatic's close to ulceration have been noted to be partially destroyed [136].

b)   Atrophie blanche

Atrophie blanche is a skin disorder characterised by smooth, depressed ivory-white plaques and surrounded by a pigmented ring of several millimetres width. It is associated with systemic diseases such as systemic lupus erythematous and scleroderma; however it is most commonly associated with CVI. The histologic findings in atrophie blanche include endovascular inflammation, proliferation and thickening of the deep dermal vessels. The atrophic scar is devoid of capillaries. Figure 6 [137] shows a patient with signs of CVI.

Figure 6: Manifestations of CVI. A, Uncomplicated varicose veins. B, Hyperpigmentation, dermatitis, and severe oedema likely resulting from combined lymphoedema. C, Active and healed venous ulcerations [137]

2.5 CVI and venous ulceration

Chronic venous insufficiency (CVI) is a common cause of leg pain and swelling, and is frequently associated with deep vein thrombosis and varicose veins. It occurs when the valves of the veins do not function properly, meaning the circulation of blood in the leg veins is impaired. Valve dysfunction may be a result of deep-vein thrombosis (DVT), or blood clots in the deep veins of the legs. If a clot forms in the superficial veins, there is a very low risk of DVT occurring. Over time, CVI may result in swelling, itching and discolouration of the legs, and can result in the development of ulcers near the ankles.

The term 'Chronic Venous Insufficiency' (CVI) is generally restricted to patients who have developed irreversible skin damage as the result of sustained ambulatory venous hypertension.

CVU may be defined as a break in the skin, present for more than 6 weeks, between the malleoli and tibial tuberosity, which is presumed to be wholly or partly due to venous disease.

CVI culminating in CVU is the most common vascular disease affecting the lower limb and represents a major health and socio-economic problem for many patients.

2.6 Risk factors for CVI

Venous hypertension culminating in CVI is the cause of all venous leg ulcers. Causes of sustained venous hypertension, such as previous DVT, and superficial and deep venous incompetence are the risk factors for primary ulceration. Leg injury, osteoarthritis, obesity, heart disease, age and female sex are additional reported risk factors for CVI and lower limb ulceration [63, 76].

Scott et al[63] concluded that patients with CVI are older, male, obese, have a history of phlebitis, and have a history of serious leg injury. These results suggest that a prior deep vein thrombosis, either clinical or subclinical, may be a predisposing factor for CVI. He found histories of serious leg injury or phlebitis were important associations resulting in a 2.4-fold and 25.7-fold increase in risk for CVI, respectively.

In another study Capitao et al found factors that are independently correlated with the severity of CVI are body weight, environmental heat, a sedentary lifestyle, double heredity, high-dose oestrogen formulations, osteo-articular disease of the lower limbs, presence of truncular varices, involvement of the internal saphena, lymphedema or history of thrombophlebitis [138].

The risk of ulceration is related to the severity of varicosities and venous insufficiency, and is increased following deep vein thrombosis.

2.6.1 Deep Vein Thrombosis (DVT)

Deep vein thrombosis (DVT) is the formation of a blood clot in a deep vein. Deep vein thrombosis commonly affects the deep veins of the legs or pelvis. A DVT can occur without symptoms, but in many cases the affected extremity will be painful, swollen, red, warm and the superficial veins may be engorged.

DVT is a medical emergency, therefore all limb swellings, however trivial, should be regarded as a DVT until proven otherwise. Untreated lower extremity DVT has a 3% PE-related mortality rate.

Aetiology and Pathophysiology

Virchow's triad is a group of three factors known to affect clot formation [139] (Figure 7):

DVT is most commonly initiated in the valve cusps of the calf veins, which is where the highest incidence of venous stasis occurs. If the DVT is left untreated there is a chance of extension into the proximal veins leading to an increased risk of embolization and permanent scarring of the delicate valve cusps, which can cause chronic venous insufficiency and the subsequent development of venous ulcers.
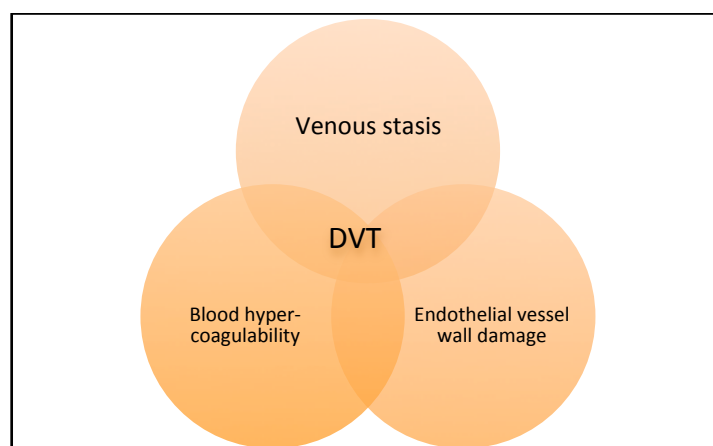
Figure 7: Showing Virchow's triad

Risk factors

There are many factors, which can increase a individual's risk of DVT, including surgery, hospitalisation, immobilization (such as when orthopaedic casts are used, or during long-haul flights, leading to travellers' thrombosis), smoking, obesity, age, certain drugs (such as oestrogen or erythropoietin) and inborn tendencies to form clots known as thrombophilia (for example, in carriers of factor V Leiden) [140-145].

Women have an increased risk during pregnancy and in the postnatal period. Several medical conditions can lead to DVT, such as compression of the veins, physical trauma, cancer, infections, certain inflammatory diseases and specific conditions such as stroke, heart failure or nephrotic syndrome.

Presentation

DVT encompasses a range of clinical presentations. Venous thrombosis is often asymptomatic; less frequently it causes pain and swelling in the leg. Part or all of the thrombus can come free and travel to the lung as a potentially fatal pulmonary embolism. Symptomatic venous thrombosis carries considerable morbidity, which sometimes becomes long term, because of chronic venous insufficiency. This in turn can cause venous ulceration. While DVT itself can be a painful condition, it is the risk of pulmonary embolism that makes early detection of the condition important. It is estimated that 95% of pulmonary emboli occur as a result of DVT [146] with 30% being fatal [147]. As many as 50% of patients with DVT have been shown to experience asymptomatic "silent embolism" on subsequent imaging of the lungs [148].

A late complication of DVT is the post-thrombotic syndrome, which manifests as oedema, pain or discomfort, and skin problems. The post thrombotic syndrome (PTS) is a chronic condition that develops in 20% to 50% of patients after deep venous thrombosis (DVT)

[89,149]. PTS is termed a "syndrome" because it is associated with groupings of symptoms and clinical signs, which may vary from patient to patient. Patients with PTS can experience pain, heaviness, swelling, cramps, itching, or tingling in the affected limb. Symptoms may be present in various combinations and may be persistent or intermittent. Typically, symptoms are aggravated by standing or walking and improve with resting, leg elevation and lying down. Therefore, It is important to take all the precautions to prevent PTS, which begins with the prevention of initial and recurrent DVT.

The Role of DVT in CVI and venous ulceration

Browse et al[150] used the term 'calf pump failure' (CPF), which is the inability of the calf muscle pump to maintain venous return from the lower extremity. CPF is often caused by venous valvular incompetence secondary to a deep venous thrombosis, which has caused post-thrombotic syndrome, but may be due to primary valvular incompetence as well. Venous distension occurs as a result of the accumulation of blood in the deep venous system caused by CPF. Further valve failure increases venous distension and venous hypertension. Pressures created in the deep system are freely transmitted to the superficial system, when the communicator valves are compromised. Superficial venous hypertension is in turn transmitted upstream to the dermal vasculature.

Nicolaides reported some of the most convincing evidence supporting the relationship between calf pump failure and chronic venous ulceration [151]. Christopoulos et al [152] found, using the air plethysmograph, a pneumatic device designed specifically to measure calf pump function, that the probability of ulceration was markedly increased when patients demonstrated either poor pump function (as measured by reduced ejection fraction) or severe valvular incompetence (shortened refill time). When both poor ejection fraction and significant reflux were observed, then patient had a 70 percent

probability of ulceration [153].

Prophylaxis

Prophylaxis usually involves a combination of pharmacological and mechanical agents. Although the pharmacological agents have better results in the prevention of DVT, they are not suitable for all patients and carry a degree of risk e.g. haemorrhage or discomfort. Mechanical prophylaxis in the form of compression stockings provides a versatile means of prophylaxis as they are safe and easy to use, relatively inexpensive, and reusable.

NICE guidelines recommend the use of stockings that provide graduated compression and produce a calf pressure of 14-15mmHg [154]. There is lack of adequate scientific evidence to justify the application of this pressure and its impact on venous return or calf volume.

Management

a) Anticoagulation

Anticoagulation is the usual treatment for DVT. In general, patients are initiated on a brief course (i.e. less than a week) of Low Molecular Weight Heparin (LMWH) treatment while they start on a 3- to 6-month course of warfarin (or related vitamin K inhibitors) [155-159]. In patients who have had recurrent DVTs (two or more), anticoagulation is generally "life-long".

b) Thrombolysis

Thrombolysis is generally reserved for extensive clot, e.g. an iliofemoral thrombosis. Although a meta-analysis of randomised controlled trials by the Cochrane collaboration shows improved outcomes with thrombolysis, there may be an increase in serious bleeding complications [160].

c) Thrombectomy

Thrombus can be removed with a mechanical thrombectomy device. Combination therapy that uses mechanical thrombectomy to deliver localized thrombolytics has recently received considerable attention as a treatment for DVT.

d) Compression stockings

NICE guidelines recommend the use of elastic compression stockings "beginning within 1 month of diagnosis and continuing up to two years after diagnosis" to reduce the risk of post-thrombotic syndrome. Starting within one week may be more effective [155, 161-164].

2.6.2 Ankle Fracture as a cause of DVT and CVI

Ankle fractures are usually a result of either an indirect force or torsion. This type of injury would not be expected to cause direct venous or lymphatic injury, however, leg swelling in the period following an ankle fracture is a significant problem, and can last for months following the injury. The persistence of the swelling long after the injury cannot be attributed to the trauma of the fracture alone. It may be that local venous hypertension or reduced venous pumping, secondary to immobilisation of the leg, may be a factor contributing to this persistent leg swelling [165]. Tierney et al concluded that there is a significant and prolonged impairment in venous pump function following ankle fracture [166].

Lower-limb fractures are associated with a high incidence of leg swelling, when direct venous injury may lead to a significant incidence of venous thrombosis [167, 168] and chronic venous disease [169-171]. Although there have been extensive studies related to the incidence of venous thrombosis in patients with tibial fractures [167, 168], there is a paucity of information with regard to ankle fractures.

Venous return from the leg and foot depends primarily on the emptying of the soleal venous plexus. This usually occurs with contraction of the plantar flexors of the ankle or by activation of the plantar venous pumps by weight bearing, in the presence of an intact valvular system [172].

The persistent swelling, reduced range of ankle movements and associated increased incidence of DVT leads to CVI following ankle fractures in long term.

Epidemiology

Ankle injuries are one of the most common reasons for referral to Accident and Emergency (A&E) departments. Among these injuries, ankle fractures are common. An incidence of 125/100,000/yr of ankle fracture has been reported by Court-Brown et al [173]. They occur equally in both sexes, but are more common amongst young men and older women.

Classification

In 1768, Sir Percivall Pott described ankle fracture as, 'fibular fracture with deltoid disruption' [174].

There are many classifications of ankle fracture, which involve the mechanism of injury, as well as correlation with fracture patterns. The Danis-Weber classification is one the most common classification systems in use [175]. This is based on the level of the lateral/fibular fracture, the level of the tibiofibular syndesmotic disruption and potential talar (ankle) instability [176]. Classification is shown in Table 4 [177].

Type	Description
A	Transverse fibular fracture below the joint line, with the intact syndesmosis
B	Fracture at the level of the ankle joint line, with a partial syndesmotic injury
C	Fibular fracture proximal to the tibiofibular joint with associated disruption of the syndesmosis

Table 4: Weber classification of ankle fractures

Treatment

Ankle fractures can be treated either conservatively or operatively, depending on the fracture type, circulation, skin condition, general health of the patient and the numerous possible complications. The standard management of ankle fracture includes open reduction and internal fixation for displaced fractures, which are unstable, or immobilisation in a cast for undisplaced, stable injuries [177].

Functional outcome and quality of life following ankle fractures

Long-term complications are frequent, with up to three-quarters of patients reporting persistent ankle pain, stiffness and swelling after 14-24 months [178, 179], and half of them reporting persistent pain after five years [180]. Ankle fractures are associated with an impaired long-term functional outcome and health-related quality of life [181-184].

DVT following ankle fractures

Asymptomatic DVT is a common occurrence following surgery for ankle fracture and Achilles tendon repair, affecting 21% and 35% respectively [185, 186]. The incidence of asymptomatic DVT following ankle fractures treated conservatively has not been studied

very much, but we commonly see patients suffering DVT following foot, ankle and calf injuries. Patil et al report a 5% incidence of DVT in conservatively managed ankle fractures [187].

The incidence of DVT after injuries to the lower limb which were treated in a plaster cast has been reported to be between 1.1% and 20% [188-190]. The use of compression stockings in addition to chemical thromboprophylaxis may reduce the incidence of DVT in both surgically and conservatively managed ankle fractures, although the latter do not usually receive any thromboprophylaxis.

Chapter 3

COMPRESSION

3.1 Compression and venous disease

Compression is considered the mainstay of treatment in chronic venous disease (CVD). Different varieties of compression systems are used in the management of chronic venous disorders. It is essential in acute conditions, such as deep vein thrombosis (DVT) and superficial phlebitis, and also very effective in chronic conditions like chronic venous insufficiency (CVI), gravitational dermatitis, lipodermatosclerosis, leg ulcers and lymphedema. Further indications include thromboembolic prevention and the prevention of oedema in pregnancy, long and microgravity flights, or softening of burns scars, amongst others [191-196]. Lower limb compression has been used to treat varicose veins since biblical times [197]. Nowadays, compression stockings are first-line treatment for varicose veins, especially in the primary care [198, 199]. Compression systems improve the healing of venous leg ulcers and should be used routinely in uncomplicated venous ulcers. Underestimated, or even totally ignored by many physicians, compression therapy is often poorly prescribed and demonstrated to the patients, who may then discard the most effective and economical treatment for their condition. There is a lack of reliable evidence to indicate which system is the most effective. More good quality, randomised controlled trials, in association with economic evaluations are needed to ascertain the most cost effective system for treating venous leg ulcers.

Compression, either active or passive, mainly aims to reduce or control venous reflux and peripheral oedema, by applying different modalities of compression therapy. Passive compression is produced by inelastic bandages, which reduce the increase in muscle volume resulting from muscle contraction. The bandage delivers little or no pressure force at rest; therefore it is well tolerated for several days. A pressure force is created because the inelastic bandage restrains the increasing muscle volume, which is produced by muscle contraction. Passive compression is therefore most active during muscle

contraction, as in walking ("working pressure"), and almost totally inactive at rest ("resting pressure"). Active compression is delivered both at rest and during exercise by an elastic orthosis. The powerful recoil forces of the elastic fibres exert a dynamic pressure on the limb, which is augmented by muscle contraction. This means that both "working" and "resting" pressure are raised. Bedridden or immobile patients may not tolerate active compression. Active and passive compression may be combined, in multilayer bandages.

Compression may be achieved by different modalities, such as inelastic bandages (Unna boot), multi-layered wrapped dressings, short, medium, and long stretch bandages, compression stockings, or legging orthoses. External pneumatic compression devices and mercury baths are alternative modalities [192].

a) Bandages

Short stretch bandages exert passive compression. Properly trained staff is required to fit them. They are indicated in the treatment of oedema, deep vein thrombosis, or trophic lesions of CVI. They are very useful in patients who cannot fit their bandage alone because of hand, hip, or knee arthrosis or in the elderly. However, they lose a lot of their pressure within the first hours of wear [200].

Long stretch elastic bandages are easier to use. Their high resting pressure effectively compresses superficial veins after surgery, sclerotherapy, or in thrombophlebitis. However, compared to short stretch bandages, their working pressures may be less effective. Working pressure is improved by superimposition of spirals. These bandages have to be removed during the night as they are poorly tolerated at rest. The comparative studies of short and long stretch bandages are difficult to evaluate [201] as effectiveness depends largely on the skill of the practitioner.

Other bandage materials include the four-layer bandage, adhesive dressing, zinc-coated bandages, and cohesive bandages. Four-layer bandages (Figure 8) are normally used for 5-7 days at a time and consist of four superimposed layers: padding with orthopaedic wool, which absorbs exudates and protects the bony prominences, cotton crepe bandage, which holds the wool in place, long stretch elastic bandage, and cohesive bandage, which strengthens and provides support. Four-layer bandages (4LB) may be more effective for reducing deep vein refluxes or in healing ulcers [203] than elastic bandages [202]. The four-layer bandage provides permanent pressure to the leg in patients with CVI, in particular those with leg ulcers.
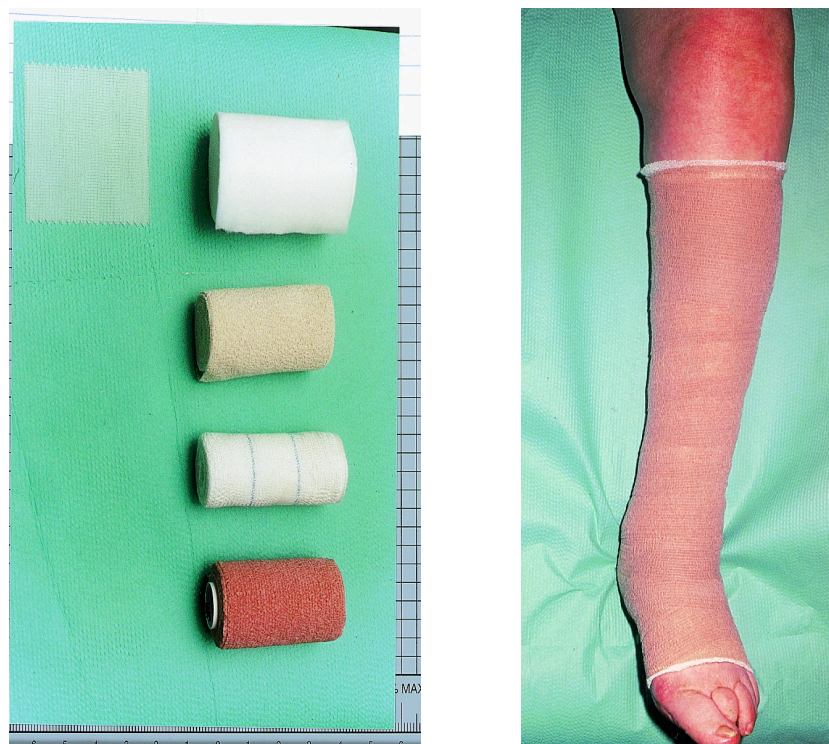
Figure 8: Components of Charing Cross four layer bandaging regimen. The primary wound dressing (left) is a non-adherent dressing, over that are placed (middle; top to bottom in order of use) wool, crêpe, Elset, and Coban bandages. The bandages (right) need replacing once or twice a week [103]

b) Stockings

Stockings offer intermediate support between short and long stretch bandages. The type of stocking is selected depending on the indication and the patient's tolerance and acceptance [192,204]. There are four compression classes, I being the weakest, IV the strongest, depending on the pressure exerted at the ankle.

Compression classes vary from one country to another. The classification system proposed by the European Standardization Commission is [198]:

Class I, 15–21 mmHg: minor varicose veins, functional venous insufficiency

Class II, 23–32 mmHg: slight CVI, or after surgery

Class III, 34–46 mmHg: more advanced CVI, leg ulcers, and lymphedema

Class IV, >49 mmHg: lymphedema, very severe CVI

Various lengths exist in each class [198]:

Socks

Thigh-length stockings: Either simple, requiring a garter or a supporter, or self-maintaining through a silicone band sewn into the upper part of the stocking, adhering to the thigh skin.

Tights: Widely used as they adapt well to a wide range of female anatomic morphologies.

Maternity tights: With an adapted waistband to fit the morphology of pregnant women

A wide range of ready-to-wear stockings is commercially available. In the case of marked anatomical abnormalities, or when the circumferences are very small, stockings can also be made to measure. Ideally, stockings must be put on before getting up or, at the latest, immediately after a morning shower. Devices have been developed to assist in putting on

stockings.

Elderly patients often struggle with putting their stockings on. Mild to intermediate compression stockings are easier to put on than stronger support stockings. Superimposition of two pairs of stockings can easily resolve this difficulty. The wearing of two pairs of superimposed class I stockings is at least equal to wearing one pair of class II stockings (Figure 9). Stockings deteriorate after repeated wearing and washing. Veraart et al concluded pressure progressively diminishes and becomes ineffective over 12 months [205]. Therefore, two to three pairs are necessary per year.

Figure 9: Showing Class II above knee close toe elastic stockings

3.2 The Mechanism of action

External compression works in a variety of ways to interrupt the progression of venous disease [206] as shown in figure 10.
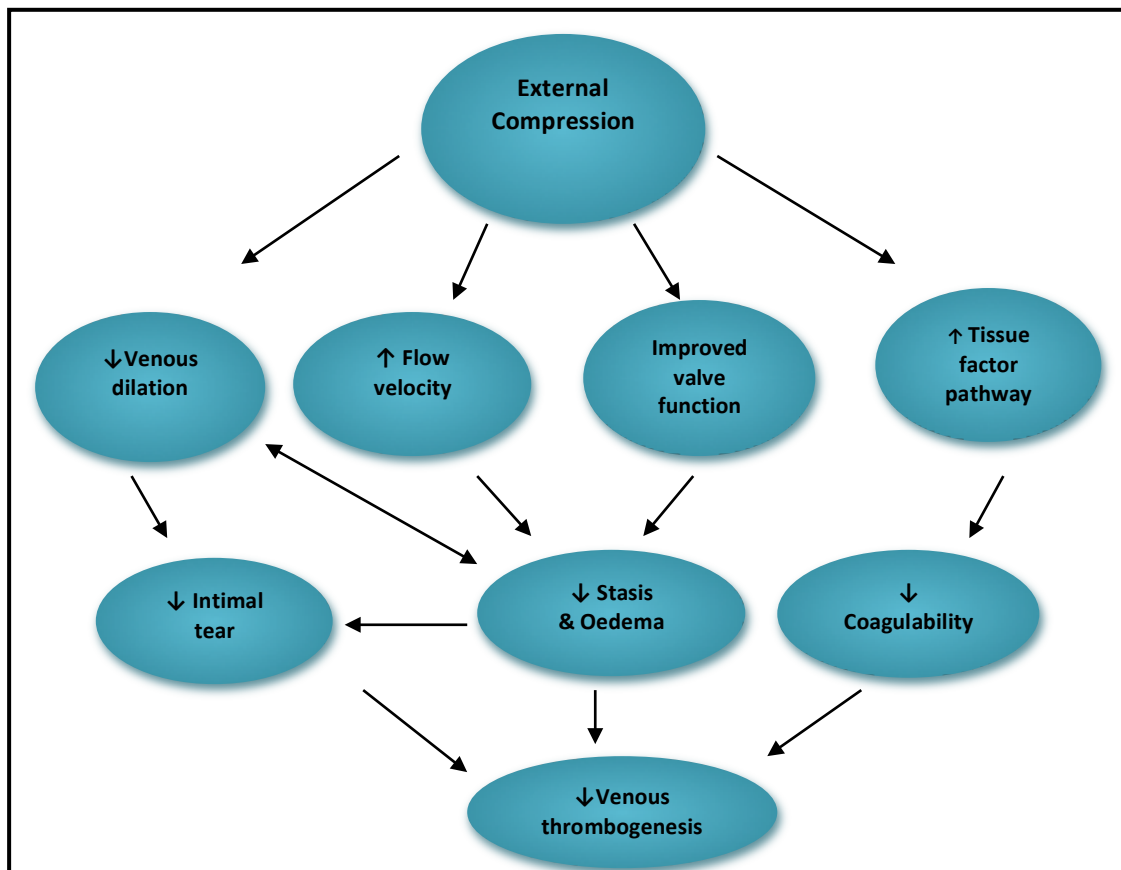
Figure 10: Showing the possible mechanisms of action of graduated compression stockings in prevention of deep vein thrombosis

Compression reduces the cross sectional area of the venous system on which it is being exerted, resulting in an increase in the linear velocity of blood. Increasing the velocity within the venous system reduces stasis, which therefore reduces the opportunity for pooling and thus venous dilatation.

Changes have been observed in the femoral vein, as a result of calf and thigh compression

[207-214], and of foot compression [211-216]. In the popliteal vein changes are seen with calf compression, [210, 212-213] and foot compression; [210, 212-213, 215-216] and in the posterior tibial vein after foot compression [210, 216].

Reducing venous dilatation is important for several reasons. Firstly, the distension caused by venodilatation stretches the intimal endothelium allowing micro tears to develop. This stimulates the clotting cascade with subsequent platelet aggregation and thrombus formation. Secondly, the distension means that the cusps of the valves cannot appose effectively, as the distance between them is too great, rendering this ineffective and further contributing to venous stasis. The area behind the valvular cusps is a common site for blood stasis and so provides the ideal environment for clot formation. External compression reduces the cross sectional area of the blood vessels, which allows the cusps to appose more effectively, clearing the area behind them and thus reducing the chance of clot formation (figure 11). This can be useful in terms of deep vein thrombosis prophylaxis as it reduces the opportunity for damage to venous system, which can result in venous leg ulceration. The loss of pooling and stretching of the intimal epithelium also diminishes the pressure being exerted upon the vessel walls and therefore has the potential to reduce venous hypertension.

Figure 11: Showing the restoration of valvular function by bringing the walls of the veins closer together

Figure 12 shows the reintegration of interstitial liquids into veins, which results in improvement of the venous pump and restoration of the direction of the venous circulation, from the superficial to the deep network, and back towards the heart. It also accelerates the filtration rate in the capillaries, stimulates lymphatic drainage and reduces oedema. Malanin et al [217] investigated the haemodynamic and volumetric effects of intermittent pneumatic compression (IPC) in patients with Venous Leg Ulcers (VLUs) and recorded tibial artery Doppler scan waveforms and skin perfusion with laser Doppler flux. Intermittent pneumatic compression produced a significant reduction in leg volume in patients with VLUs compared to healthy patients (P = .016). The authors suggested that reduction of oedema leads to a redistribution and increase of skin blood flow favouring superficial capillary perfusion.
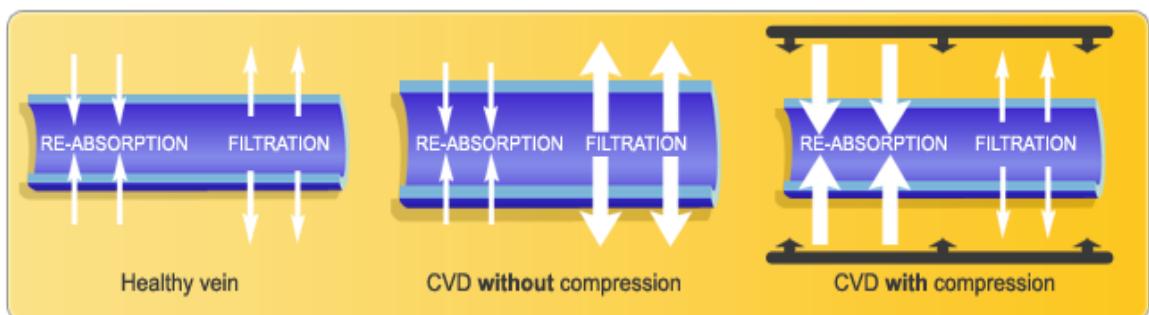
Figure 12: Showing the reintegration of interstitial fluids into veins

3.3 The role of compression in venous ulceration and CVI

The role of compression in healing venous leg ulcers is well-established [218]. Compression hosiery remains the primary treatment for venous leg ulcers [104], and compression therapy in the form of elastic stockings should be maintained following ulcer healing for the purpose of secondary prevention [56, 95]. Currently, the four-layer compression bandaging system (Fig 8) is the gold standard treatment for venous ulcers [219].

The treatment of venous leg ulcers focuses on preventing sustained venous hypertension. Hippocrates referred to compression treatment in his work, *De ulceribus* (c400 BC): "if necessary, cut out the ulcer and then compress it to squeeze out the blood and humours." Although compression hosiery remains the primary treatment for venous leg ulcers [104], the nature of the compression applied has changed since the times of Hippocrates. Multi-layered, high-compression systems have been shown to be more effective than single-layered, low-compression systems [220].

Graduated compression therapy is also beneficial in reducing venous hypertension [117]. Hydrostatic forces within the veins result in progressively decreasing venous pressures proximally, thus the level of compression needed also reduces further up the leg. In terms of dressing materials, there is insufficient evidence to recommend any modern fibres in the treatment of leg ulcers; simple non-adherent dressings are therefore used [221].

Three studies compared elastic high compression 3-layer bandaging with low compression. The results of these studies showed an overall statistically significant relative benefit increase for healing for the high compression bandaging of 54% (95% confidence interval 19% to 100%) [222-225]. Four-layer bandaging was shown to increase the percentage of ulcers healed at 24 and 12 weeks, respectively, in 2 trials, when compared to single layer compression bandaging; Granuflex Adhesive Compression Bandage [226] and Setopress [227].

In the UK and US it is usually nurses who apply compression bandages. There is some evidence that nurses do not know which bandage to choose for a particular clinical application [228] and that inexperienced nurses or those without additional training in compression bandaging apply bandages at inappropriate and widely varying pressures [226, 229, 230].

Compression treatment increases the healing of ulcers compared with no compression. High compression is more effective than low compression. It is not clear which of the high compression systems (3 layer, 4 layer, short stretch, Unna's boot) is the most cost-effective. Therefore, it is sensible to promote the increased use of any correctly applied high compression therapy.

3.4 The role of compression in DVT

Compression is a well-established mechanical prophylactic measure used to prevent DVT [231-234]. Turpie et al [235] reported that graduated compression stockings, either alone, or in combination with IPC are an effective method of preventing DVT in neurosurgical patients. Porteous et al [236] concluded that below-knee stockings are as effective as above-knee in the prevention of post-operative deep vein thrombosis. Above-knee graduated compression stockings are effective in preventing post-operative deep vein thrombosis, but are more expensive and less acceptable than below-knee stockings.

NICE guidelines recommend the use of stockings for DVT prophylaxis that provide graduated compression and produce a calf pressure of 14-15mmHg [154]. However, there is a lack of adequate scientific evidence to justify the application of this level of pressure and its impact on venous return or calf volume. NICE guidelines also recommend the use of compression stockings for up to two years following DVT to prevent post-thrombotic syndrome [154].

3.5 The role of compression in ankle injuries

In my experience, traumatic wounds around the ankle and lower leg heal significantly faster when treated with four-layer bandages, regardless of whether venous disease is present or not. Compression stockings are known to improve venous function and reduce the risk of

arthropathy associated with the persistent venous hypertension that results from calf muscle pump failure [94, 237].

By treating venous hypertension, the healing of cutaneous wounds in the leg is also improved. Theoretically, this could also be important in the healing of injuries around the ankle, as ankle sprain inevitably impairs the range of movement and inactivates the venous calf-muscle pump producing venous hypertension [99, 238].

The role of compression has been recognised in the management of ankle sprains [239]. Type II elastic stockings significantly improved the recovery and quality of life following ankle sprains compared to a Tubigrip bandage.

3.5.1 Traditional modes of compression in ankle injuries

A single or double layer of Tubigrip following ankle sprain has traditionally been used to provide compression. A survey conducted in UK suggests considerable variation exists in the use of Tubigrip following ankle sprain across the country [240]. Tubigrip fails to provide adequate or graduated pressures for a number of reasons:

- It has a fixed diameter and so applies higher pressure proximally as the calf is wider than the ankle

- It is straight, and the functional position of the foot is at 90 degrees to the leg

- The foot and ankle do not have a circular cross section

3.5.2 The role of compression following ankle fracture

Stockings that deliver pressures between 18 and 35mmHg at the ankle are used to reduce oedema [241]. Traumatic swelling can be treated or prevented using compression. The effective treatment of oedema reduces pain, improves the range of movement and may speed up return to normal function following ankle injury [242].

Ankle fracture impairs the ability of the calf muscle pump to expel venous blood. Calf pump inefficiency will lead to the transmission of high pressures directly to the skin of the gaiter area. Compression will help to improve the venous return and prevent persistent venous hypertension. However, compression is not routinely used after ankle fracture, despite the risk of post-traumatic oedema and DVT [186].

Compression has the potential to improve swelling at the ankle joint, which allows surgery to be undertaken at an early stage and speeds up the post-operative recovery by increasing the range of movement and reducing pain and stiffness. This could have a major impact on the health economy by reducing the cost of ankle fracture to the NHS by decreasing hospital admissions, cutting outpatient clinic appointments and reducing complications. Compared to the current best practice, this strategy will also benefit the patients and the economy, as patients will be able to return to work sooner. Compression may also reduce the incidence of DVT, which is one of the most common reasons for chronic venous insufficiency.

3.6 Elastic Compression Stockings

Compression stockings are made of special elastic fabric. Elastic stockings are commonly used to apply compression to prevent DVT [231-234] or the recurrence of venous ulcers [56, 95]. By the law of Laplace, variations in the tension in the elastic can result in either sub-therapeutic compression or a tourniquet effect [307]. The pressure needed to encourage venous emptying, and hence aid the clearance of oedema, can be achieved using class II compression hosiery, as these are fitted and designed to deliver graduated compression. Oedema is reduced as external elastic compression increases the interstitial tissue fluid pressures, favouring resorption of fluid by Starling's equation [308].

The exact mechanism of action of graduated compression stockings is unknown. However, there is evidence to suggest that they exert graded circumferential pressure distally to

proximally and, when combined with muscular activity in the limb, are thought to displace blood from the superficial to the deep venous system via the perforating veins. It is argued that this effectively increases the velocity and volume of flow in the deep system thereby potentially preventing thrombosis [309].

Based on the work of Lawrence [310], Kakkar and Sigel [311] et al, graduated elastic compression stockings have been designed to deliver a gradient of external pressure, which is highest in the ankle region and lowest in the upper thigh region. These pressures are defined as 18mmHg at the ankle, 14mmHg at the calf, 8mmHg at the knee, 10mmHg at the lower thigh and 8mmHg at the upper thigh, although these can vary slightly depending on the hosiery manufacturer [206, 312-313].

There are two main problems that are often encountered with elastic stockings: for the physician, the challenge of prescribing them and for the patient, the difficulty of remaining compliant with them. The prescription must contain five pieces of information: the name of the stocking, the pressure profile, the circumferences, the height and the length. The pressure profile should be noted in mmHg corresponding to the type of disease requiring treatment. It is equally important to take the time to stress to every patient, the value of this type of compression, to review the technical difficulties associated with the putting on and taking off of the stockings and to consider the possibility of superimposition. Compliance with the prescribed treatment is the key to success.

3.6.1 Engineered compression stockings (ECS): A Novel Technology

ECS was developed in a unique collaboration between the Academic Surgery Unit and Textiles Department at The University of Manchester. The Department of Academic Surgery at the University Of Manchester and Advanced Therapeutic Materials Ltd (ATM) formed a collaborative research group to address the problems encountered with

currently available compression therapy by changing the design of compression stockings from a trial and error system to precision engineering. The Academic Surgery Unit and ATM Ltd. refined a 3D laser to scan the leg and linked this to computerised flat-bed knitting machines to produce precisely fitting ECS, delivering the appropriate pressure profiles required by the clinical team for each indication.

The technology is entirely novel: This technology is capable of delivering graduated compression to the leg with ankle pressures in the range 10-60mmHg. They can be knitted to British and European formulated classes I, II or III but are not constrained by these classifications. This scan-to-knit technology manufactures novel, seamless, bespoke stockings, which actually deliver the prescribed pressures (Figure 13).

The designing and engineering processes involved in producing a pair of ECS begins with the capture of a complete leg profile using non-invasive 3D scanning technology, which uses video cameras and white light. The collected data is in the form of Cartesian coordinates and the resultant point cloud is processed in the mathematical engine of the system to generate a 3D surface profile. The colour sensitive 3D leg scanner collects this data with an error margin of $\pm$0.5mm.

Pressure on the leg is a function of the tension in the fabric and the point specific radius of curvature of the leg profile. The software engine can accept a predetermined pressure profile, and, using the radius of curvature profile generated from the point cloud, can output a needle map that is used to generate the control programme of a computerised flat-bed knitting machine for the manufacture of a three dimensionally shaped seamless compression stocking (ECS).
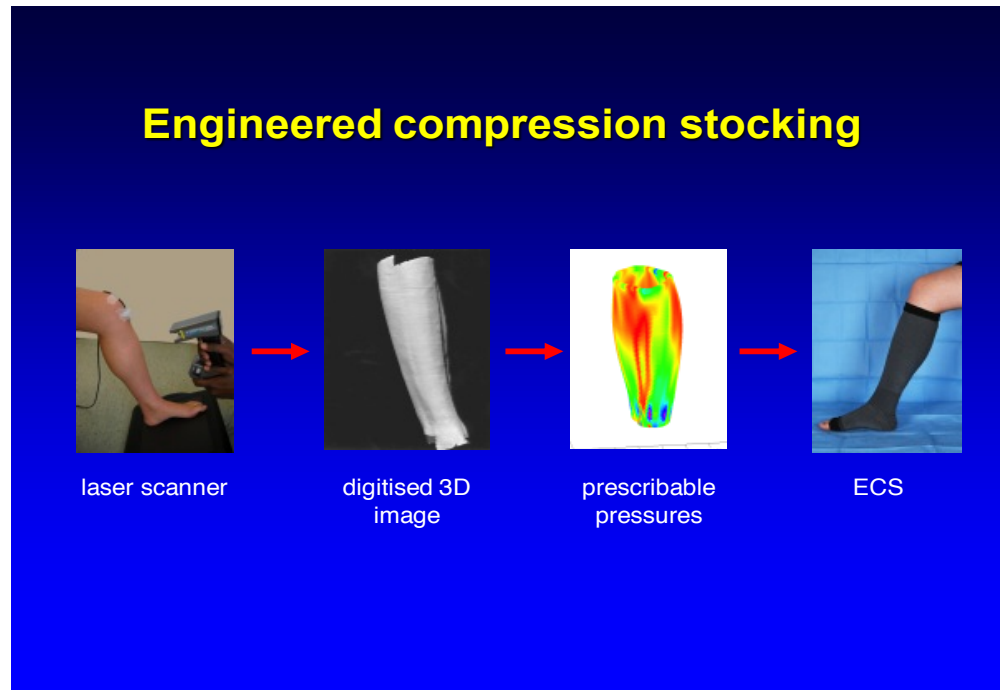
Figure 13: Engineered compression stocking

ECS compared to 'Elastic stockings' on the market

The current technology used circular knitting machines to produce stockings that delivered pressures that were neither uniform nor reproducible. Quality control of the garment was governed by British Standards (BS6612: 1985). These are based on the Hosiery Trade Research Association (HATRA) system, a mechanical testing model for circular knits that measures the pressure profile of stockings. Ten brands of graduated compression stockings were tested using the HATRA model and a range of very different profiles were observed; worryingly some even generated a reversed gradient [314].

Circular knitting machines have a fixed cylinder diameter, which means that shaping the garment is limited to knitting symmetrical heels and toes. This technology does not facilitate accurately knitting shapes to fit legs or any other part of the body.

Engineering circular-knitted seamless garments is imprecise as the radius of curvature of the garment, around the ankle for example, can only be changed symmetrically. This is achieved by varying the yarn run-in tension and/or the stitch cam setting that controls the

stitch size, the main variable in the structure. The current technology will not allow localised variation in the amount of elastomer or even the integration of constant amounts of elastomer into the structure when varying fabric tube diameters. The pressure profiles are, therefore, unpredictable.

Compression stockings are elastomeric knitted structures capable of giving up to 200% strain, and are made from a covered yarn with an elastomeric core yarn, which is stretched and wrapped with one or two continuous-filament inextensible yarns.

ECS are produced from a special yarn that was developed in collaboration with a UK specialist yarn manufacturer. This composite elastomeric yarn was integrated into the knitted structure by being formed into stitches and tuck loops. The stretchiness of the ECS knitted structure is not limited by an inextensible ground structure; a factor which has to be considered seriously in the case of designing products such as medical compression stockings.

One of the issues encountered with commercially available compression stockings is the difficulty of pulling them over the ankle area. This is mainly due to the inextensible ground structure. The reproducibility of the ECS and the accuracy of their performance are ensured by the microprocessor controlled yarn delivery systems (TPF) that deliver precisely controlled quantities of elastomeric yarn.

Elastic stockings fail in some patients for a variety of reasons: they may be ineffective in some despite the patient wearing them with full compliance, but, more commonly patients are unable or unwilling to use them as prescribed. ECS are easier to put on, fitted to the profile of each foot and ankle, with individually prescribed pressures, tailored to each patient. Hence, the comfort, compliance and therapeutic efficacy should all be enhanced. ECS could have a profound effect on the quality of life of millions of people throughout the UK as well as reducing NHS costs.

ECS are manufactured to fit the shape of the leg on an individual basis; this 'made to measure' approach includes the foot, bony high points around the ankle and any deformities of the limb due to arthritis or injury. The result is a prescribed pressure profile that is compliant with current BNF Classes I, II and III, but which can deliver pressures beyond these confines in the range 10-60mmHg, where indicated.

By profiling the ankle, ECS avoid excess pressures over bony highpoints, reducing the risk of pressure sores and improving comfort and, therefore, compliance. The wide elastic range improves 'stretchability', making ECS easier to apply or stretch over a stocking applicator.

Development of ECS

ECS was developed in a unique partnership between the Academic Surgery Unit and Textiles Department at University of Manchester. The ECS intellectual property was licensed to ATM Ltd by Manchester University. ATM refined 3D scanner/knitting machine interfaces to produce ECS that delivered a range of pressure profiles. The Academic Surgery Unit and Advanced Therapeutics Materials Ltd (ATM) carried out the engineering, mathematical modelling, clinical software development and the fabric structure design required to ensure the correct pressure profiles for each garment. Using this new technology to knit seamless garments with an electronic flat-bed knitting machine provided a real opportunity for substantial improvements in compression therapy. Asymmetric shape profiles with 3D shapes mean that seamless garments have been produced; delivering pressure profiles that can be prescribed by the doctor (Figure 14).
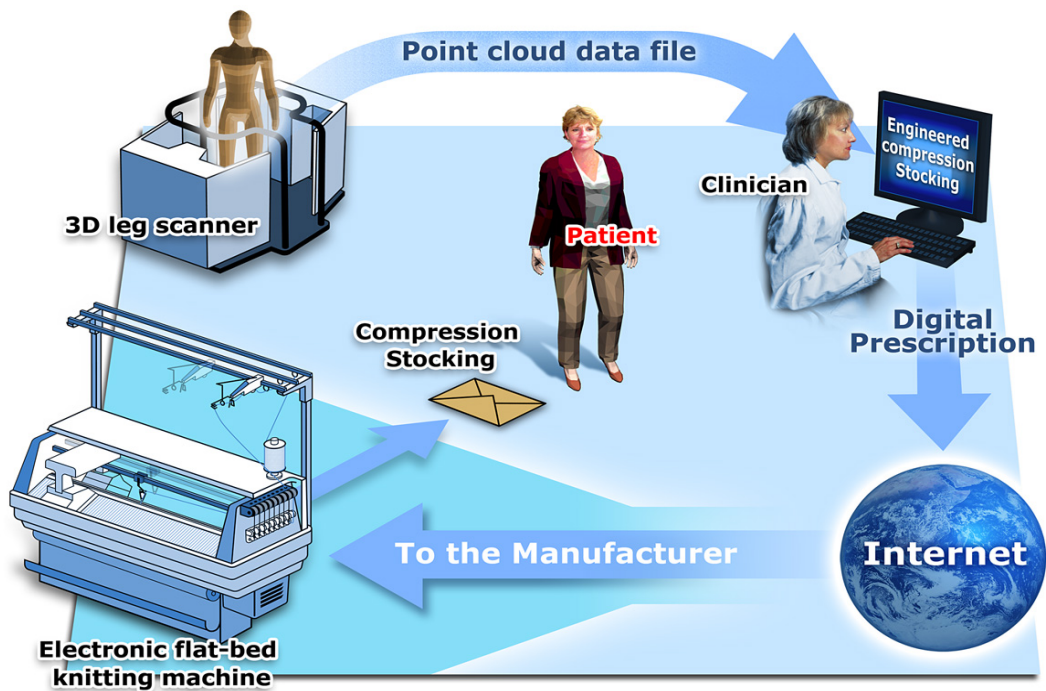
Figure 14: Scan to knit technology

The technology has been registered with the Medicines and Healthcare products Regulatory Agency (MHRA). The manufacture of the stockings conforms to the Essential Requirements set out in annex I of the Medical Device Directive 93/42/EEC dated June 1993, and if any of these requirements are not fully met they are stated in the approved documentation accompanying the stocking.

This ECS technology is entirely novel: 3D digital images of the leg acquired by laser including dimensions, radii of curvature and profile, are combined with the prescribed pressure profile and this data is sent by internet to a computerized flat-bed knitting machine which produces a precisely fitted ECS delivering pressures prescribed individually by the doctor.

Having tested instruments from four manufacturers that digitise the leg profile, we selected a mobile laser scanner (fastSCAN™, Polhemus Ltd), which combines light beams

and video images to calculate the exact three-dimensional measurements of the leg. FastSCAN (Figure 15) can be calibrated by almost anyone, with minimal training and is lightweight and ultra-portable. The 3D laser scanner is also capable of capturing data on leg volumes for research on leg swelling, without the inconvenience of the water displacement method, although this needs validation.

The development of ECS provides a unique opportunity to evaluate the optimal pressures (not confined to Class I, II or III) for each clinical indication, as precise pressure profiles can be evaluated in RCT's for patients suffering from i) VVs ii) CVI iii) lymphoedema and iv) leg ulcers.

ECS are knitted structures made with an elastomeric core yarn, which is stretched and wrapped with one or two continuous-filament inextensible yarns. This unique yarn was developed by a collaborating UK specialist yarn manufacturer (Wykes International). Unlike the compression stockings which are currently available, ECS have no inextensible ground structure and are, therefore, much easier to pull over the ankles and more comfortable to wear.

A microprocessor controlled yarn delivery system (IP protected) delivers the exact amount of elastomeric yarn needed to achieve class I, II and III pressure profiles or beyond if required clinically. CE marking is not currently required, but ATM Ltd. can pursue this when needed. Procedures that comply with ISO13485 are already documented and ATM Ltd. is collecting manufacturing data. For ECS to be prescribed in the NHS, ATM Ltd. would have to apply for FP10 Drug Tariff approval when the necessary clinical trials have been completed.
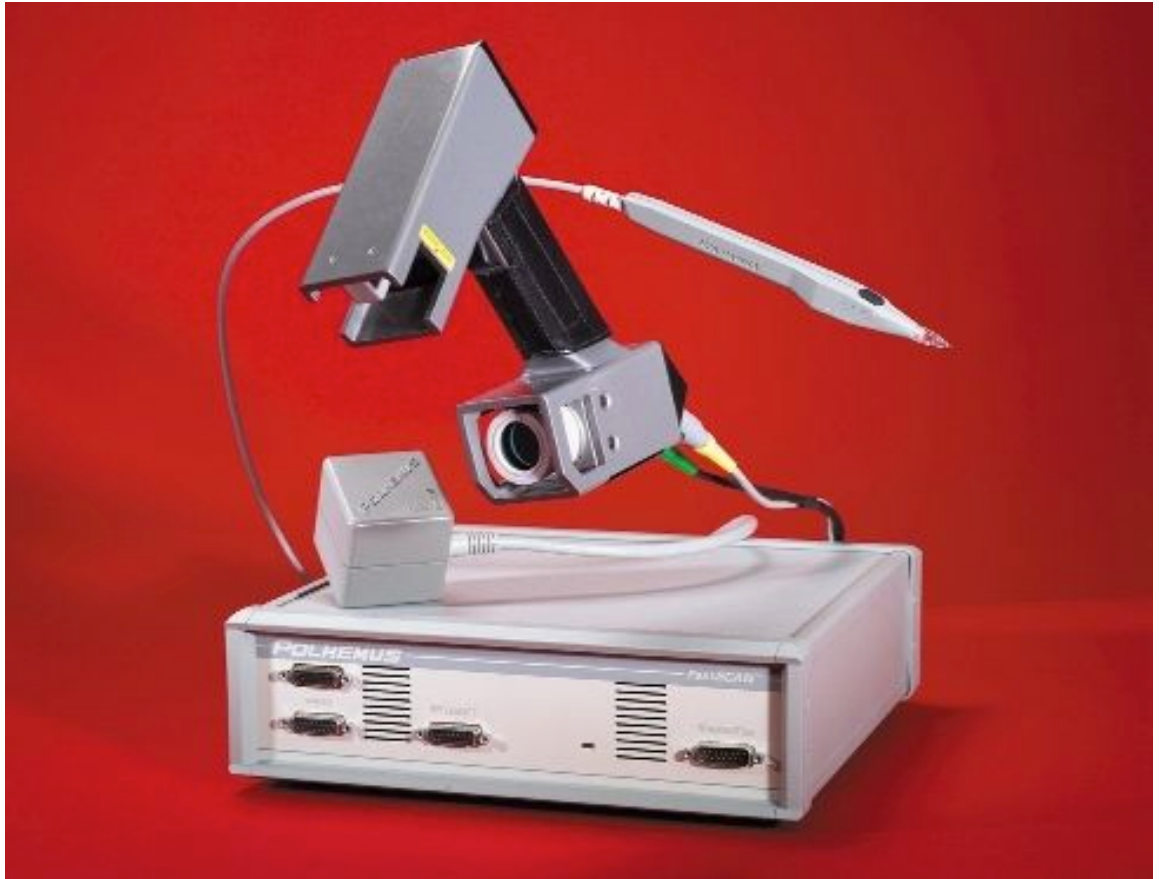
Figure 15: 3D Scanner *(fastSCAN™, Polhemus Ltd)*

Chapter 4

CONCLUSION

4.1 Conclusions from the literature review

4.1.1 No 'at risk' population can be identified currently

Venous ulceration is a chronic debilitating disease, which puts a significant burden on the health care system, but there is no prediction system available to identify patients at risk of developing venous ulcers.

4.1.2 The Pressure profile for DVT prophylaxis is 'unknown'

Compression is recommended to prevent DVT but the ideal pressure profile for DVT prophylaxis remains unknown.

4.1.3 Variability in performance of compression stockings

Despite the widespread use of graduated compression stockings worldwide, little information has been published on the delivery of pressure profiles by different brands.

The published literature shows a wide variation in the performance of the different brands of stockings. Most products deliver statistically lower levels of pressures than marked on the labels, some produce a reverse pressure gradient on the lower leg.

4.1.4 Compression in lower limb injuries

CVI is common after lower limb injuries, especially following ankle fractures. This may be prevented by appropriate prophylactic measures. There is a clear need to establish evidence-based guidelines to prevent DVT and CVI in lower limb injury.

4.2 Research strategy: Prevention rather than treatment

Chronic venous disease is extremely common. Although not restricted to the elderly, the prevalence of chronic venous disease, especially leg ulcers, increases with age [54, 34, 243]. Chronic venous disease affects both sexes, with little difference in prevalence. The high prevalence of CVI means that it has considerable impact on health care resources. In a population study in the UK, the median duration of ulceration was nine months, 20% of ulcers had not healed within two years, and 66% of patients had episodes of ulceration

lasting longer than five years [62]. Venous ulcers cause the loss of approximately 2 million working days and incur treatment costs of approximately $3 billion per year in the United States [244]. Chronic venous disease is associated with a reduced quality of life, due to pain, impaired physical function, and mobility. It is also associated with depression and social isolation [245]. Venous leg ulcers, the most severe manifestation of chronic venous disease, are usually painful [246] and malodourous, impairing quality of life [247].

Venous disease is the most common vascular condition to affect the lower limb. The focus of research over the last three decades has been on the treatment of these conditions. However, considering the scale of this problem and its huge impact on patients and their quality of life, as well as the national financial resources, superimposed on an increasingly elderly UK population; it is essential to implement a change in our research strategy to strive for prevention, rather treatment of venous disease.

This thesis focuses on the identification of patients at risk of developing venous ulceration and on the development of a new technology that can prevent venous ulceration. This will help to improve the quality of life of millions of patients and has the potential to make huge savings for the NHS, which spends more than £650 million each year on treating venous ulcers alone.

4.3 Steps to initiate research on Prevention

4.3.1 Identify an 'at risk' population

CVI is common, with a high prevalence amongst the older population. Among the costly complications of this disease is venous ulceration, which has a particularly adverse effect on quality of life. As the elderly population grows, the prevalence of CVI and its resulting complications will increase proportionately. The prevention of venous ulcers is key to containing health care costs and improving the overall quality of life for these patients.

Armed with an understanding of the pathogenesis of the disease process and its clinical signs, health care professionals must use their skills to identify and educate patients at risk. Prevention programs should be developed and implemented to avoid venous ulceration among patients with or at risk for chronic venous insufficiency.

4.3.2 Potentially preventable/treatable risk factors

After identifying the 'at risk' population, the next step will be to develop appropriate strategies to prevent or treat the risk factors responsible for chronic venous disease. If prophylactic measures are implemented in good time, for these 'at risk' patients, then a reduction in the prevalence of CVI and venous ulceration could be expected.

Chapter 5

AIMS

5.1 AIMS

1. To identify the risk factors associated with venous ulceration in order to identify an 'at risk' population

2. To study the pressure profile required to halve venous transit time and calf venous volume as this should prevent DVT

3. To undertake an RCT evaluating the role of ECS in ankle fractures in order to answer the following research questions:

   a) Do ECS applied shortly after ankle fracture improve functional outcome (Olerud Molander Ankle Score and American Orthopaedic Foot and Ankle Score) and QoL (SF12v2) compared to no ECS at 6 months?

   b) Do ECS reduce ankle swelling and improve the range of ankle movements if applied shortly following ankle fractures?

   c) Do ECS have a role in reducing the frequency of DVT following ankle fractures? The observed frequency of asymptomatic DVT from this trial will inform the development of a definitive RCT on whether ECS prevent DVT; potentially recruiting 400-500 patients.

SECTION II

IDENTIFICATION OF THE 'AT RISK' POPULATION

Chapter 1

DEVELOPMENT AND VALIDATION OF RISK PREDICTION ALGORITHM (MANCHESTER VENOUS ULCER PREDICTING SCORE; MUPS) FOR VENOUS ULCERATION: A PROSPECTIVE CASE-CONTROL STUDY

1.1 Introduction

Venous leg ulceration (VU) is a major problem both for patients and health services. There was little research into the causation and treatment of venous ulceration before the 1990s when several studies were launched demonstrating the importance of venous disease in the causation of leg ulcers [129, 248-250] and investigating potential treatments [251-253]. These studies demonstrated that compression and elevation were central to the treatment of leg ulcers and that the contact dressing material was of little relevance [105, 218, 254-259]. Since establishing these basic principles, progress in the management of VU has stalled and the impact on the overall prevalence of VU has remained limited.

Despite the frequency of this debilitating condition in our population, there has been little research on the prevention of venous ulceration. It is recognised that venous ulceration is caused by sustained venous hypertension and that this may be due to venous disease, such as varicose veins or previous deep vein thrombosis, obesity and immobility precipitated by paralysis or arthritis [27]. These factors are recognised to be risk factors for lower leg ulceration [79, 92] and we know that patients who have suffered a previous VU have annual risk of recurrence of approximately 25% [104]. If we are to explore the use of treatments designed to prevent venous ulceration, we need to identify a population at high risk of developing ulcers.

This case-controlled study was designed to identify risk factors associated with VU and to produce a risk predication score that may, in the future, be used to identify individuals at high risk of developing a VU.

1.2 Materials and Method

This was a case-controlled study in which patients who were treated in a community leg ulcer service in the South Manchester were age and gender matched to controls of a

similar socio-economic status living in the same area. The study received ethical approval from the Stockport Research Ethics Committee.

1.2.1   Cases

Patients with VU were identified from four community VU clinics in South Manchester between April 2008 and April 2010. Potential participants were given invitations and a questionnaire (Appendix 1) by their own leg ulcer nurse, on behalf of the research team. The research staff verified their answers at their next clinic visit or by telephone interview.

1.2.2 Matched healthy controls

Age and gender matched controls were recruited with the help of patients and local GP practices. Each case was asked to identify a friend or colleague with no history of VU who may be willing to participate in the study. Where this was not possible, the patient's general practitioner was asked to write to five sex-matched patients whose birth dates were within two years of the relevant case.

1.2.3 Inclusion and exclusion criteria

Inclusion criteria - cases

•   Patients with active venous leg ulcers receiving compression treatment

•   Age > 16 years

Inclusion criteria - controls

•   Matched for age and sex for patient (+/- 5 years age of case)

•   No history of venous ulceration

Exclusion criteria - cases and controls

•   Known peripheral arterial disease

1.2.4 Outcome

Our clinical outcome was to identify patients at risk of venous ulceration.

1.2.5 Variables

The design and wording of the questionnaire was developed in consultation with patients attending the leg ulcer clinic at UHSM. Confusing terms or layout of the answers was eliminated prior to commencing the study. Patients were given a questionnaire that asked for the following details split into 5 broad categories, as shown in Table 5.

Category	Question
Ulcers	Laterality Time and dates No of times affected
Medical History	Height Weight BMI Previous abdominal surgery Smoking history IHD Hypertension CVA Lung Disease Diabetes Mellitus Pulmonary Embolism/DVT Cancer and treatments Pregnancies Others
Self reported history	General Health Mobility Use of walking aid
Family History	Venous ulcers Varicose veins (VV) Deep Vein Thrombosis (DVT) Pulmonary Embolism
Leg history (both legs)	Current Varicose veins Varicose vein surgery Varicose vein sclerotherapy Thread veins Phlebitis DVT OA of hip, knee, ankle or foot Replacement of hip or knee Previous fracture of bone in leg

Table 5: Categories of questions

The date of each event was recorded along with the side of the leg for leg history. For the leg ulcer patients, the leg affected by ulceration was used as the "index" leg. For patients with bilateral venous ulceration, one leg was selected at random to use as the "index" leg using a code generated from the website RANDOM.ORG (access date: March 2009). The same principle applied to the control participants: one leg was selected at random to use for comparison.

1.2.6 Statistical power

A total of 140 matched case-control pairs was sufficient to detect differences of 15% or more in the prevalence of important risk factors, such as varicose veins, DVT, phlebitis, arthritis, and lower limb surgery with a power level of 80%.

An additional 60 age and sex matched cases were also recruited to allow the construction of a reasonably accurate prognostic scoring system.

A total of 231 cases and 210 controls were recruited. However, only two-thirds of this sample was case-control pairs matched with respect to sex and age within 5 years. Therefore, an unmatched analysis including all 441 subjects, controlling for age and sex, was undertaken.

1.2.7 Analysis

A 70% random sample from the 441 subjects (231 cases and 210 controls) was taken to form the training set, namely the subgroup of subjects on which a diagnostic scoring system was derived. The remaining 30% formed the test set, namely the subgroup of subjects on which the diagnostic scoring system was used to assess its predictive ability. Out of 441 subjects, 312 subjects were in the training set and 129 subjects formed the test set.

Simple univariate analyses (t-tests and chi-square tests as appropriate) were used to identify significant associations with caseness, using a modified significance level of

p<0.10. Multivariate logistic regression was then used to select an optimal set of predictors, which had a significant independent relationship with caseness. This multivariate model was used to derive a diagnostic score, using the regression coefficients from the fitted model.

The scoring system was then applied to the test set and sensitivity and specificity for different cut-off values on the score were calculated. The estimated risk of developing a venous ulcer in the general population was derived for different categories of score, corrected for the prevalence of 1.5% [53] and was then separated in tertiles and the expected risk of venous ulcer for a person with a score in each tertile was calculated using Bayes theorem on the distribution of risk prediction scores in the training set. Data were analysed using SPSS® versions 16 (SPSS, Chicago, Illinois, USA).

1.3 Results

1.3.1 Overall study population

Between April 2008 and April 2010, 305 questionnaire packs were distributed to eligible patients with venous leg ulceration by leg ulcer and tissue viability specialist nurses at participating community and hospital leg ulcer clinics (Table 6).

	Stockport PCT	South Manchester PCT	North Manchester PCT	UHSM Acute
Number distributed	110	30	50	115
Responses	89	10	35	97
Response rate	80.9%	33%	70%	84.3%

Table 6: Response rates of cases by leg ulcer clinic

A total of 231 leg ulcer patients responded, giving an overall response rate of 76%. 210 control participants returned questionnaires. The response rate for the control participants cannot be determined, as the actual number of questionnaires distributed by the leg ulcer participants is not known. Data that was missing on the questionnaire was collected by contacting participants by telephone, interviewing them in the leg ulcer clinic or consulting the ulcer clinic records.

The mean age (range) and the sex ratios of the cases and controls in the overall study population, derivation data set and the validation data set are shown in Table 7.

	All patients n=441		Training set n=312		Test set n=129	
	Cases n=231	Controls n=210	Cases n=167	Controls n=145	Cases n=64	Controls n=65
Age (range) years	72 (31-94)	71 (26-97)	72 (36-94)	71 (41-97)	72 (31-92)	71 (26-94)
Sex ratio (% of Male)	41	39	41	40	41	38

Table 7: Study demographics

1.3.2 Univariate and Multivariate analysis of risk factors

Risk factors significantly associated with venous ulceration were identified by univariate and multivariate analysis as shown in Table 8.

	Cases	Controls	Univariate OR (95% CI)	Multivariate OR (95%CI)
Weight (kg); mean (SD)	82.4 (23.7)	74.6 (17.1)	1.02 (1.01, 1.03); p=0.002	
Weight < 75kg	**42% (67)**	**57% (77)**	**1**	**1**
75-100kg	**36% (58)**	**35% (48)**	**1.39 (0.84,2.30)**	**1.49 (0.80, 2.79)**
> 100 kg	**22% (35)**	**8% (11)**	**3.66 (1.72, 7.76); p=0.003**	**3.45 (1.42, 8.36); p=0.022**
BMI; mean (SD)	29.0 (7.9)	26.6 (5.3)	1.06 (1.02, 1.10); p=0.004	-
Poor/terrible mobility; % (n)	**36% (60)**	**11% (16)**	**4.46 (2.42, 8.20); p<0.001**	**4.00 (1.88,8.50); p<0.001**
Poor health; % (n)	14% (23)	6% (9)	2.46 (1.10, 5.52); p=0.028	-
Requires walking aid; % (n)	44% (73)	21% (30)	2.96 (1.78, 4.90); p<0.001	-
FH varicose veins; % (n)	**50% (82)**	**29% (41)**	**2.52(1.57, 4.05); p<0.001**	**1.89 (1.01, 3.56); p=0.048**
FH DVT; % (n)	13% (21)	6% (8)	2.50 (1.07, 5.82);p=0.035	-
FH Leg ulcer; % (n)	33% (53)	13% (19)	3.17 (1.77,5.69); p<0.001	-
Index side: Current VV; %(n)	42% (67)	18% (26)	3.24 (1.91,5.50); p<0.001	-
Index side: VV surgery; % (n)	22% (36)	9% (13)	2.90 (1.47,5.73); p=0.002	-
Index side: VV sclerotherapy; % (n)	8% (13)	3% (4)	3.09 (0.98,9.72); p=0.053	-
Index side: Phlebitis; % (n)	**20% (32)**	**1% (2)**	**17.38 (4.08,7.40); p<0.001**	**10.28 (2.19, 48.4);p=0.003**
Index side: DVT; % (n)	**16% (25)**	**1% (1)**	**25.9 (3.46,194); p=0.002**	**11.72 (1.43, 95.8);p=0.022**
Index side: Ankle arthritis; % (n)	13% (21)	6% (9)	2.18 (0.97,4.94); p=0.06	-
Index side: Hip replacement; % (n)	9% (15)	3% (4)	3.50 (1.13,10.79); p=0.029	-
Opp side: Current VV; % (n)	**34% (51)**	**14% (20)**	**3.10 (1.73, 5.56); p<0.001**	**2.4942 (1.18, 4.99); p=0.016-**
Opp side: Phlebitis; % (n)	12% (17)	1% (1)	18.05 (2.37, 138); p=0.005	-
Opp side: Hip replacement; % (n)	**9% (13)**	**1% (2)**	**6.55 (1.45,26.6); p=0.015**	**5.28 (1.01, 27.8); p=0.050**

Table 8: Univariate analysis and subsequent multivariate analysis of significantly associated risk factors from the training set

1.3.3 Diagnostic index score

A simple diagnostic scoring system, based on the coefficients from the regression analysis, was devised to provide a quantitative measure of the accuracy of the predictive risk, as shown in Table 9.

Criterion	Component score
Weight 75-100kg	0.40
Family history of varicose veins	0.64
Opposite side varicose veins	0.89
Weight >100kg	1.24
Poor mobility	1.39
Opposite side Total Hip replacement	1.66
Index side phlebitis	2.33
Index side DVT	2.46

Table 9: Diagnostic index score

Sensitivity and specificity values were calculated using different cut-off points of the diagnostic score as shown in Figure 16 and 17 and Table 10.

Predict venous ulcer if score:	Sensitivity	Specificity
> 0	89%	30%
≥ 0.5	83%	42%
≥ 1	78%	55%
≥ 1.5	65%	83%
≥ 2	50%	92%

Table 10: Sensitivity and specificity values for venous ulcer study based on test set data
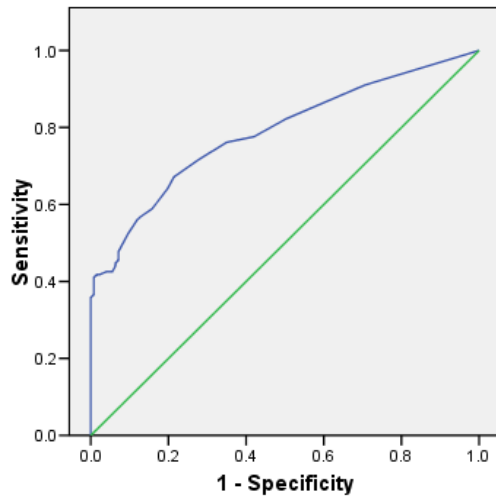
Figure 16: Training set – ROC curve for risk prediction score
Area under ROC curve = 0.79; 95% CI (0.73, 0.84)
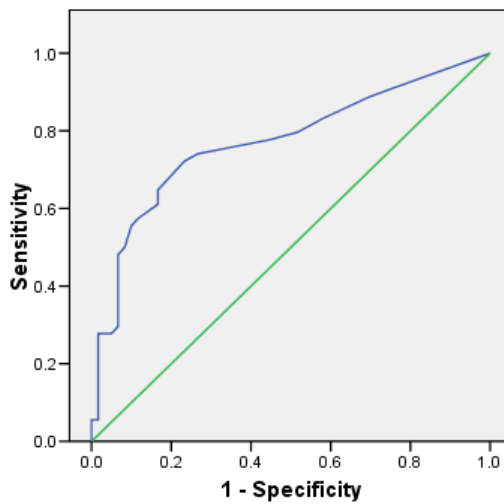
Figure 17: Test set – ROC curve for risk prediction score

Area under ROC curve = 0.77; 95% CI (0.68, 0.86)

The estimated risk of venous ulceration was derived for different categories of score corresponding to the prevalence of venous ulceration of 1.5% [53]. The expected annual risk of a venous ulcer for a person with a risk prediction score in the top tertile is estimated to be 6.7% and in the bottom tertile is 0.6% (using Bayes theorem on the distribution of risk prediction scores in the test set), as shown in Table 11. The area under the curve for the ROC curve was 0.77 (0.68-0.86) demonstrating a promising fit with the data.

Tertile	Percentage of observed venous ulcers		Estimated annual % risk of Venous Ulcer
	Training set	Test set	
1 (score ≤ 0.5)	28%	26%	0.6
2 (score 0.5-1.8)	44%	33%	0.8
3 (score ≥ 1.8)	85%	82%	6.7

Table 11: The observed percentage of venous ulcers in the training and test set cohorts and the estimated risk of venous ulcers in each tertile, based on the test set data and assuming an overall risk prevalence of 1.5%

Example 1

A 40-year-old woman, who is a heavy smoker, has a weight of 80kg and has no significant medical history.

She scores <0.5 within the lowest tertile group. She is at 0.6% risk of venous ulcers.

If the same woman also had a family history of VV, she would now score between 0.5-1.8 and would have a 0.8% risk of venous ulceration.

Example 2

A 70-year-old man, who weighs 110kg, has a poor mobility and previous history of DVT and hip replacement.

He scores >1.8 and is in the top tertile. He has a venous ulceration risk of 6.7%.

1.4 Discussion

This study has developed and validated this scoring tool from the multivariate analysis, which revealed that the variables which had a significant independent relationship with venous ulcer disease were: Weight, poor mobility, a family history of VV, index side phlebitis and DVT, opposite side current varicose veins and a history of total hip replacement. This algorithm has the potential to identify the patients at highest risk of venous ulceration and, therefore, those most likely to benefit from intervention, such as weight loss, elevation and compression therapy.

Leg ulceration carries significant morbidity and a marked reduction in quality of life. Frequent visits to leg ulcer clinics, prescription costs for dressings, poor sleep associated with pain and restrictions to social, leisure and work activities all contribute to the negative impact of this disorder on the patient [67-69]. In addition, reduced mobility and a protracted healing course lead to social isolation, loss of independence and emotional despair [70, 71]. Studies have shown that community leg ulcer clinics improve the quality of care and deliver an improved standard of treatment for leg ulcers based on research, thus improving rates of healing and cost effectiveness [58, 260]. A delay in ulcer recurrence by a single month can make a significant difference, by saving 8% of the time spent by district nurses on ulcer care and reducing cost for the NHS [60].

This algorithm will be useful in several clinical situations, where the algorithm embedded in a clinical risk calculator might be useful. Firstly, it could be used to identify patients at an increased risk of venous ulceration, so that prophylaxis can be considered in a more

systematic way. Secondly, the algorithm could be used to identify high-risk groups of patients suitable for further testing, closer monitoring, or preventative treatment. Pragmatic randomised trials can establish the true benefits of preventative treatment in individuals at high risk of venous ulceration and the exact cut-offs for treatment where the benefits will outweigh the risks.

1.4.1 Comparison with other studies identifying risk factors

While other studies have examined risk factors for venous ulceration, studies specifically designed to develop and validate risk prediction algorithms for venous ulcers are lacking. I could not identify a single case control or cohort study which developed a risk prediction score for venous ulceration and in fact there is even a lack of well designed case control or cross sectional studies to identify risk factors for venous ulceration. Despite the abundance of recent research into the treatment of leg ulceration, there has been limited research on prevention. The first essential step in prevention is to identify the population at risk.

Research by Scott et al [63] investigated risk factors for chronic venous insufficiency (CVI) comparing three groups; 93 patients with venous ulcers, 129 with varicose veins, and 113 patients in the control group. Whilst a case-control design was used, control participants were significantly younger than the CVI population, and were identified from a general surgical outpatient clinic, and hence may not be representative of the general population. Using multivariate analysis, the authors were able to test the frequency of an exposure or characteristic found in each case group compared to a group without the disease. Chronic venous insufficiency was associated with advancing age, male sex, and obesity, and, after adjustment for age, a history of significant leg injury and a history of phlebitis. This study also suggests that a prior DVT may be an important predisposing factor for CVI.

Franks et al [261] used a questionnaire with a case-control design and found patients with venous disease were taller, heavier, and stood for long periods of time, with a strong association with pregnancies and the number of children. They found a weak association with wearing a corset, constipation, and a family history of venous problems.

The study has demonstrated a strong association with some interesting risk factors like opposite side total hip replacement (THR). I believe opposite THR may not be directly responsible for venous ulceration but may have resulted in decrease mobility leading to DVT, which would have been responsible for the venous ulceration. Interestingly ipsilateral hip replacement was significantly associated only on univariate analysis and its not clear why it failed to showed significant association on multivariate analysis.

This is the first prospective, case-control study used to develop a risk assessment tool for the development of venous ulcers. One attempt has been made to develop a risk assessment tool for the development of venous ulcers by Takahashi [262]. Their model identified previous venous ulceration as the major contributor, as well as renal insufficiency, blindness, cataracts and decubitus ulceration. The limits of this study, as identified by the authors, include its retrospective cohort design and the use of medical records entered by coders for the sake of insurance billing, which could pose many inaccuracies and misses patients who do not present to services with ulcers. This scoring system showed a sensitivity of 0.63 and a specificity of 0.88.

1.4.2 Strengths

In summary, the key strengths of this case-controlled study include size, representativeness and lack of selection, recall, and respondent bias. This study has the advantage that it was undertaken in a leg ulcer clinic setting, where most patients in the UK are assessed, treated, and followed up, and that all of the information given by patients was verified, either in clinic or over the phone. The study also includes

established exposures known to increase risk of venous ulceration. It included a long list of predictor variables and establishes which factors remain independent after adjustment and their relative importance. The strength of the association between venous insufficiency and risk of venous ulceration is similar to that reported elsewhere [63, 118, 263].

The size of this study is particularly important since venous ulceration is uncommon in certain population groups. To my knowledge this is the first prospective case control study with sufficient numbers to predict risk factors for venous ulceration.

Furthermore, I developed the algorithm in one cohort and validated it in a separate cohort using training and test sets.

The method of using questionnaires to obtain data from patients is well established, and has been used in an earlier study on the subject of venous ulceration [261]. One of the limitations of this method is the possible misinterpretation of the questions by patients. However, in this study all the patients were contacted by telephone or interviewed in the clinic to verify their answers, reducing this risk.

1.4.3 Limitations

Case-control studies are used to identify factors that may contribute to a medical condition, by comparing subjects who have the condition to those that do not. This type of study is retrospective and non-randomised in nature, and is considered level III evidence.

15% of the cases did not have duplex venous scan but had only hand held Doppler examination to confirm the venous disease. However, none of the controls had Duplex venous scans to rule out the venous disease. Our aim was to keep this study simple. The controls demonstrated general population with no signs and symptoms of venous disease. If we would have investigated them further by duplex scans to rule out the venous disease than we would had a sub-group of general population without

asymptomatic venous disease, not representing true general population. So our controls were actually true reflection of general population.

This is a cross-sectional case-control study, and does not provide information on the temporal order of events, e.g. whether the leg ulcer preceded the varicose veins or vice versa. In order to adjust for this, participants were asked to provide the year that a condition was diagnosed. It soon became apparent that whilst participants could answer whether or not they had a particular condition, they were unable to reliably recall the year it was diagnosed. This brings into question whether weight and poor mobility are actual risk factors, or just associations, for venous ulcers. The timings of the development of ulcers and variables were recorded, but not included in analysis.

A scoring system that has 'previous ulceration' as a major contributor is obviously not of use in predicting first time ulcer development in the population at large. This study does not include previous venous ulceration as a variable and is therefore the only tool of relevance in detection of primary venous ulcer disease.

This study has produced a tool which could be used in both primary and secondary care to calculate the risk of developing venous ulcer disease, which is a common and expensive pathology associated with our ageing population.

Section III

PROPHYLAXIS

Chapter 1

ELASTIC STOCKINGS FOR DVT PROPHYLAXIS: WHAT PRESSURES ARE NEEDED?

1.1 Introduction

Deep vein thrombosis (DVT) is the formation of a blood clot in a deep vein and is a well-documented occurrence in hospitalised patients [39].

The annual incidence of VTE is 1 in 1000 per annum. The number of deaths per year attributed to venous thrombo-embolism in the UK varies, but the figure ranges from 24,000 to 32,000 [40].

UK data suggests that in 1993 the total cost of VTE to National Health Service was £235 - £257 million [41], and the combined direct and indirect cost estimates are now estimated at approximately £640 million [42]. When the long-term complications, such as post-thrombotic syndrome (PTS) are taken in to account, the costs are increased further [43-44].

In the 17th century, Pierre Dionis, who was Surgeon in Ordinary to the Queen of France recommended the use of rigid stockings made from coarse linen or dog skin to apply compression in the treatment of peripheral circulatory disorders [264]. Later, in 1949, Stanton et al used a radiographic technique to demonstrate that externally applied compression could increase the blood flow velocity in the deep veins of the leg [265]. External compression works in a variety of ways to interrupt the progression of venous disease [206]. It reduces the cross sectional area of the venous system on which it is being exerted. This has the resultant effect of increasing the linear velocity of blood, reducing venous stasis, which therefore reduces the opportunity for pooling and thus venous dilatation.

A comprehensive review of the literature on the value of graduated compression stockings in the prevention of DVT shows a significant reduction in rate of DVT with the use of stockings [233, 266-271].

The optimum compression profile required remains uncertain. The NICE guidelines that recommend anti-embolism stockings that provide graduated compression and exert a

pressure of 14-15mmHg upon the calf are based upon insufficient evidence [154]. I believe that a definitive parameter should be used to aim for DVT prophylaxis. In the past blood flow velocity has been commonly used to assess the venous return rate but in this study I used transit venous time for the first time in the literature. I hypothesise that pressure required to halve the transit venous time would be the appropriate pressure profile for DVT prophylaxis.

I utilised the novel technology of ECS, which provided a unique opportunity to carry out research on the optimal pressures required for effective DVT prophylaxis and the treatment of VVs, CVI, lymphedema and leg ulcers.

This study aimed to identify the pressure profile required for engineered compression stockings (ECS) to bring about appropriate physiological changes in the deep venous system for the prevention of DVT and used the micro-bubble technique for the first time in the literature.

1.2 Material and Methods

I carried out a prospective experimental study on 17 healthy volunteers to observe the physiological effects of ECS in the prevention of DVT at University Hospital of South Manchester (UHSM). The study was granted an ethical approval by Stockport research ethics committee.

1.2.1 Participants and setting

Seventeen healthy volunteers (medical students) with no history of venous disease were recruited at UHSM, using an advertising campaign throughout the research and education centre. Volunteers aged over 16 years of age with no history and clinical evidence of venous disease was included. All volunteers had a detailed examination of the lower limbs including hand held Doppler examination to rule out any venous pathology. Any volunteers

with a history of DVT, or of previous surgery on the lower limbs, and those with clinically obvious varicose veins, or with evidence of venous reflux on hand held Doppler examination were excluded.

1.2.2 Venous transit time (VTT)

The venous transit time (VTT) was assessed by measuring the time taken for the micro-bubble emulsion to reach a standardized point in the popliteal vein from the dorsal foot vein at the point of cannula.

The micro-bubble technique was used for the measurement of VTT. Each volunteer had an intravenous cannula sited in a dorsal foot vein, through which the micro-bubble contrast emulsion was injected (Figure 18).

Micro-bubbles are a form of contrast agent commonly used in ultrasound studies to improve the detection and visualisation of blood flow within a target area. Micro-bubbles increase the signal-to-noise ratio which ultrasound utilises [272]. These agents significantly improve the acoustic backscatter from blood when used in conjunction with Doppler scanning. It is a popular technique that is used widely in medicine, for example, trans-cranial Doppler using micro-bubbles as the contrast medium is commonly used for the detection of a patent foramen ovale (PFO) [43].

Doppler scanning was not accurate enough in the detection of micro-bubbles to satisfactorily assess venous transit times. This is because, when scanning the venous system of the lower limb, there is a significant amount of associated artefact present, due to the surrounding tissue mass. In order to avoid this this, we used ultrasound scanning to visualise the micro-bubbles rather than detect them audibly.

Each of the volunteers had their popliteal vein visualised using ultrasound (Sonosite Micromax, M-turbo™). The popliteal vein was accessed by placing the 5-7MHz probe within

the popliteal fossa. The position of the ultrasound probe was then marked at this point to ensure consistent positioning for each of the variables.

Figure 18: Micro-bubble technique for the measurement of venous transit time

Each of the volunteers acted as their own control for the study and the effect of the stockings (Type A, B, C) on the venous transit time was compared with wearing no stockings. Each of the stockings was assessed in the standing, sitting and lying position. For each of these positions, the volunteer was asked to adopt a particular stance:

- Standing - The leg was examined whilst slightly relaxed and the weight supported on the opposite leg, as shown in Figure 19 a & b.

- Sitting - The volunteer sat on an adjustable seat so that the hips, knees and ankles were at 90˚.

- Lying - The volunteer was positioned lying on their side on bed.

The volunteers were fitted with each of their bespoke stockings in turn, remaining in the adopted positions for 2 minutes to allow the veins to reach equilibrium prior to imaging and administration of the micro-bubble emulsion.

Recording of the ultrasound images was commenced at the time of injection of the micro-bubble emulsion. The venous transit time was measured from the time the micro-bubble emulsion was injected to the point where the micro-bubbles became visible in the popliteal vein.

(a)   **(b)**
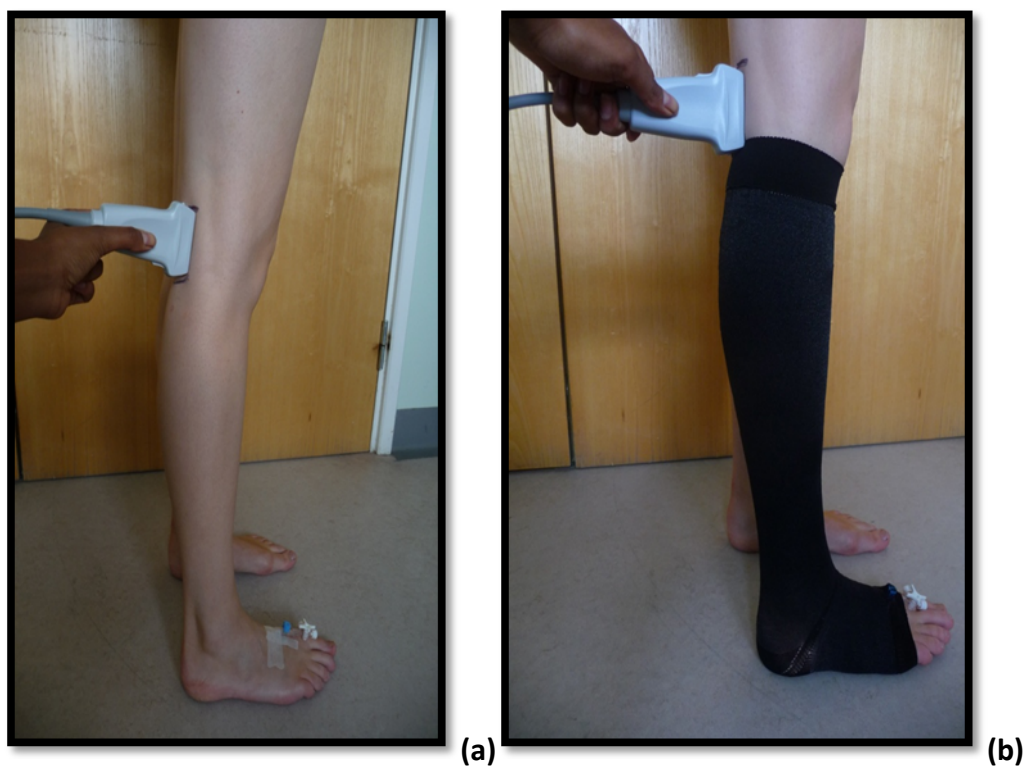
Figure 19: Scanning of the popliteal vein whilst in standing position with no compression stockings (a), and whilst wearing the engineered compression stockings (b) to visualise the micro-bubbles

The ultrasound recordings were read blind, as the status of the compression (no stocking, type A, type B, type C) was not disclosed to the sonographer.

Transit time was measured at three points: at the start of the appearance of contrast, the maximum number of visible bubbles and the tailing off the micro-bubbles. The average of these three timings was taken to report as the transit venous time. Patients were asked

to do 20 toe tip exercises between the injections in each position with each stocking to clear the maximum number of bubbles from previous injections in the veins.

The stockings manufactured for each patient were of the open toe variety, which allowed access to the cannula whilst the volunteer wore each of the stockings. This also enabled the quality of the stockings to be maintained, as they did not need to be altered each time e.g. by inserting a hole, which could have modified the pressure being exerted. A hospital butler was used to carefully apply the stockings over the cannula on the leg.

The cannula was accessed through the open end of the stocking. A 2ml syringe was used for this study, which would not stretch the stocking while connecting to the cannula through the open end.

The venous transit time without stockings was measured first in the standing, sitting and lying positions and then ambulatory venous pressure was measured in the standing position. Later, the same procedure was performed with ECS of 15, 25 and 35mmHg.

1.2.3 Engineered compression stockings (ECS)

After examination of both legs, the leg with the most prominent dorsal veins on the foot was selected and then scanned with a mobile laser scanner (fastSCAN™, Polhemus Ltd) which combines light beams and video images to calculate the exact 3-dimensional measurements of the leg, as shown in Figure 20.

In this novel technology, 3D video images of the leg measuring the dimensions and the profile are digitised and the data is sent, using the internet, to a computerised flat-bed knitting machine which produces a precisely fitting ECS delivering the pressures as prescribed individually by the doctor.
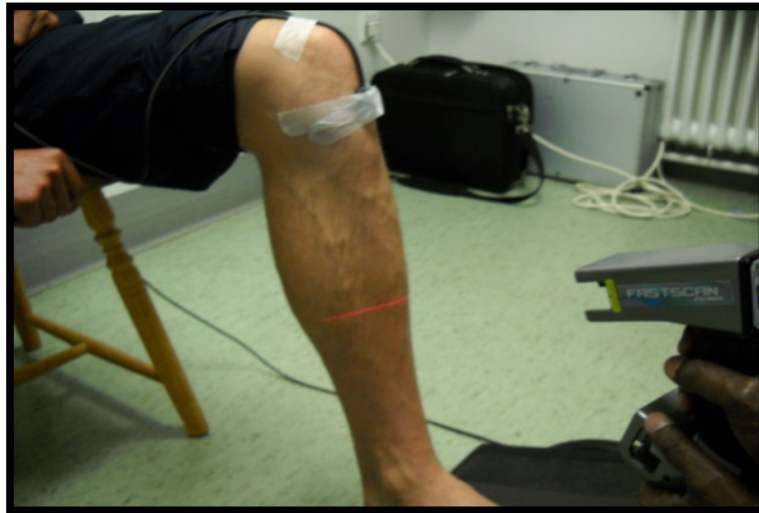
Figure 20: Showing the use of a laser scanner to take measurements to produce the engineered compression stockings

1.2.4 Pressure profiles for ECS

The pressure profile for ECS was graduated along the calf. The pressure should be greatest at the ankle and lowest at the calf. This not only produces the best improvement in venous transit times but also avoids the tourniquet effect produced when a constant pressure is applied to the whole of the lower limb [310].

I evaluated ECS delivering pressures of 15, 25 and 35mmHg in graduated compression profiles, with mid-calf pressures of 11, 18 and 25mmHg respectively and high calf pressures of 6, 10 and 14mmHg. An Oxford pressure manometer was used to confirm that each ECS delivered the specified pressure profile in all of the patients. 16 leads connect to the device and probes are attached to four different points on the leg in the circumferential pattern at the ankle, mid calf and just below the knee.

1.2.5 Micro-bubble technique

The micro-bubble technique is well established and is a standard investigation in cardiology that has been used without any major complications to assess the presence of PFO and venous to arterial circulation shunts [273-276]. This is the first time that the micro-

bubble technique has been used to measure venous transit time. I selected this technique as it is already being used on daily basis in cardiology and is a very simple process, when compared to the complex methodologies adopted in the past to measure the rate of blood flow. I reduced the amount of air used to make micro-bubbles, compared to during cardiology procedures, to avoid any adverse events, which are very rare with this technique.

The micro-bubble emulsion was produced by taking 0.5 ml of the patient's own blood, via the cannula, plus 1.3ml of normal saline and 0.2 ml of air. Using a three way tap connected to the cannula, two 2.5ml syringes were attached. One contained the volunteer's blood, air and saline and the other was empty. The two syringes were briskly pushed back and forth approximately 20 times to produce a fine micro-bubble emulsion that was then quickly injected through the cannula. The same sized syringes were used throughout the trial. The volume of air used overall per patient was 2.4ml, which is much less than the 6ml used to diagnose patent foramen ovale (PFO) in cardiology.

1.2.6 Ambulatory venous pressure (AVP)

The assessment of venous hypertension is ambulatory venous pressure (AVP). The AVP is considered the 'gold standard' of hemodynamic measurement of venous circulation of the lower limbs [315].

AVP was measured with and without each of the stockings. This was used to assess how increased pressure upon the veins of the lower limb affects the venous recovery time, AVP and pressure relief index (PRI).

The intravenous cannula was connected to a pressure transducer at foot level and an amplifier feeding into a potentiometric pen recorder (Lectromed II, Hertfordshire, UK). The volunteer was then asked to stand supporting him or herself upon a frame. In this static position the *'resting pressure'* was recorded as shown in Fig 21a. The frame was

used to prevent the calf muscle from contracting, which can cause artefacts on the recordings during rest periods. The volunteer then performed 10 'tip toe' exercises at the rate of 1 per second and then returned to the resting position until the pressure had returned to the baseline level (Figure 21b). Resting pressure (AVPr), minimum pressure (AVPmin), fall in pressure following exercise (AVPf = AVPr – AVPmin) and recovery time to 90% of normal resting pressure (RT90) were recorded. Pressure relief index (PRI) was calculated as the product of fall in pressure following exercise and recovery time (PRI = AVPf x RT90) as an overall measure of venous function. From these recordings, an AVP and PRI was calculated, which allowed me to view the changes that occurred in response to the varying pressures exerted by each of the stockings used.

Calculations were made from the graph obtained from the Lectromed II machine and entered on the specific software on computer to calculate these values. Numbers of small squares were counted from the baseline (2 squares away from the central blank) to the resting pressure level and multiply by 3.33 to give the resting pressure (AVPr) in mmHg. Post-exercise pressure (AVPmin) was calculated in mmHg by counting small number of squares from the baseline to the minimum reading post exercise and multiply by 3.33. Subtract AVPr-AVPmin to give the AVP fall in mmHg and multiply by 0.90 to give the 90% (AVP90%) recovery pressure. Number of large squares was counted from the AVPmin along the recover curve until the AVP90% is reached, giving 90% recovery time (RT90) in seconds. PRI was calculated by multiplying AVP with RT90.

In a normal subject the venous pressure should fall around 30mmHg from the resting pressure and after exercise this should only raise slowly over half a minute or so back to the standing pressure [315].
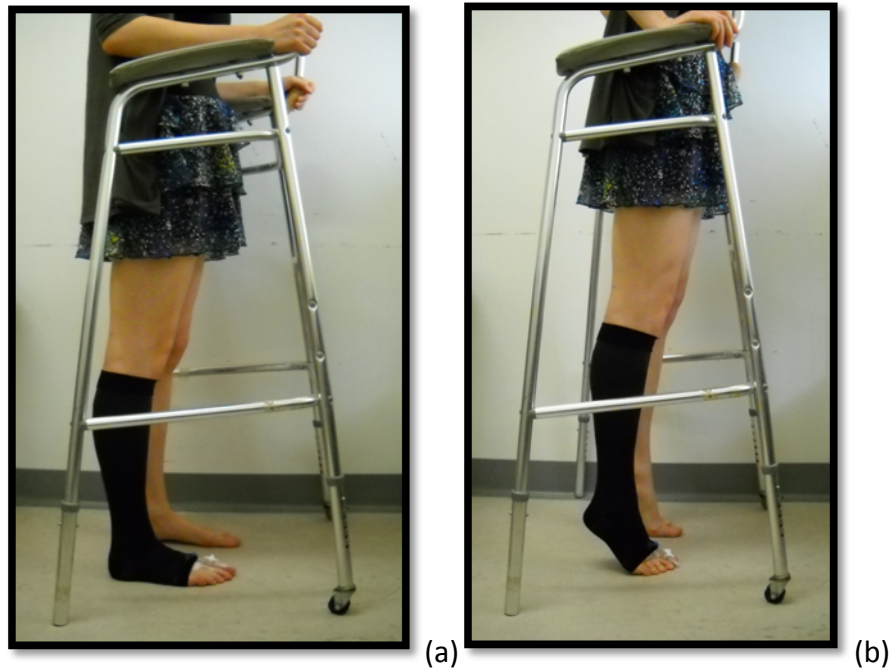
Figure 21 (a) Volunteer is in the resting position to measure the baseline pressure and (b) Volunteer is doing the 'tip toe' exercise holding the frame as a support

1.2.7 Volumetry

A Plexiglas boot, similar to that described by Vayssairat and co-workers was used [277]. In contrast to the original method, the height of the container was taller (43 cm), in order to measure the entire volume of the foot and lower leg extending to below the knee. A water temperature of 30 $^{\circ}$C was used, rather than 24 $^{\circ}$C, as proposed by Thulesius et al [278]. This higher temperature was used to better exclude cutaneous venomotor responses. After filling the device with warm water, the standing subject introduced one leg with extreme care into the volumeter (Figure 22). The displaced water volume was carefully collected and weighed using a precision scale. One gram of displaced water was assumed to correspond to 1mL of volume. The procedure was repeated with and without ECS, delivering 15, 25 and 35 mmHg at the ankle.

Figure 22: Measurement of leg volume

1.2.8 Follow up

All the patients were contacted via telephone 24 hours following the study to establish if there were any adverse events.

1.2.9 Statistical power

In order to have 80% power to detect differences in transit time of 1 second or more between stocking types (using an adjusted significance level of 0.005 to account for multiple comparisons, and assuming a standard deviation of differences between stockings of 1 second), the intention was to recruit a total of 18 subjects.

1.2.10 Statistical Analysis

A repeated measures analysis of variance was used to compare transit time, volume and AVP between stocking types, followed by a pairwise comparison of specific stocking types with Bonferroni's correction to adjust for multiple comparisons.

A generalised estimating equation regression modelling was used to fit regression lines to the pressure and transit time data and identify the pressure required to halve transit time.

 The conventional 5% significance level was used for the main analyses of variance. Data were analysed using SPSS® versions 15 (SPSS®, Chicago, Illinois, USA).

1.3 Results

In April 2010, 19 patients were assessed for eligibility, 17 met the inclusion criteria and were included in the study. None of the patients withdrew during the study. The initial personal and prognostic characteristics of the participants are given in Table 12.

	(n=17)
Age (years)	22 (21-24)
F:M ratio	9:8
Height (cm)	172 (150-186)
Weight (kg)	69 (42-110)
BMI (kg/cm$^{2)}$)	23 (17-33)
Length of leg (cm)	44 (38-51)
Calf circumference (cm)	36 (31-42)
Ankle circumference (cm)	22 (18-27)
Foot circumference (cm)	25 (21-28)
Anthropometric measurements from mid-point of sternum to symphysis pubis (cm)	42 (32-50)
Anthropometric measurements from mid-point of sternum to medial joint line of knee (cm)	86 (66-95)
Anthropometric measurements from mid-point of sternum to tip of medial malleolus (cm)	123 (106-135)

Table 12: Demographic data: mean (range)

1.3.1 Venous transit time

The mean (95%) transit time without compression was 35 (28-43), 32 (25-40) and 33 (27-41) seconds in standing, sitting and lying positions respectively. The mean (95%) transit time with no stockings was the longest at 35 (28-43) seconds whilst standing and was

reduced to 23 (18-29), 14 (11-19) and 7 (6-9) seconds with ECS delivering 15, 25 and 35mmHg respectively (p<0.001).

The ECS delivering 15mmHg of pressure reduced the transit times from 32 (25- 40) to 23 (18-28) seconds whilst sitting, and from 33 (27-41) to 22 (18-27) seconds whilst lying (p<0.001). The transit time was consistently halved by the ECS delivering 25mmHg: from 35 (28-43) to 14 (11- 19) seconds whilst standing, from 32 (25- 40) to 13 (11- 16) seconds whilst sitting and from 33 (27-41) to 14 (12-15) seconds whilst lying (p<0.001), as shown in Figure 23, 24 and 25.
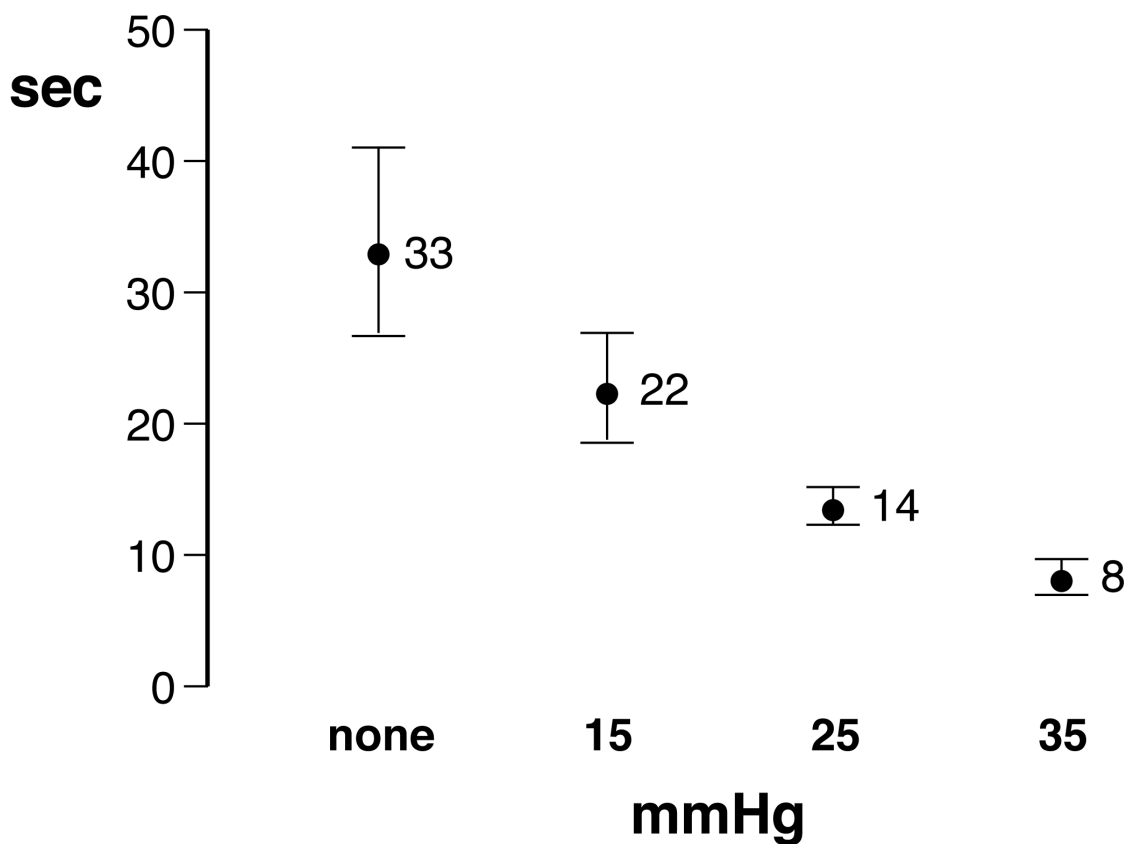
Figure 23: The mean (95% CI) transit venous time was significantly (<0.001) reduced with increasing pressure at ankle in lying position
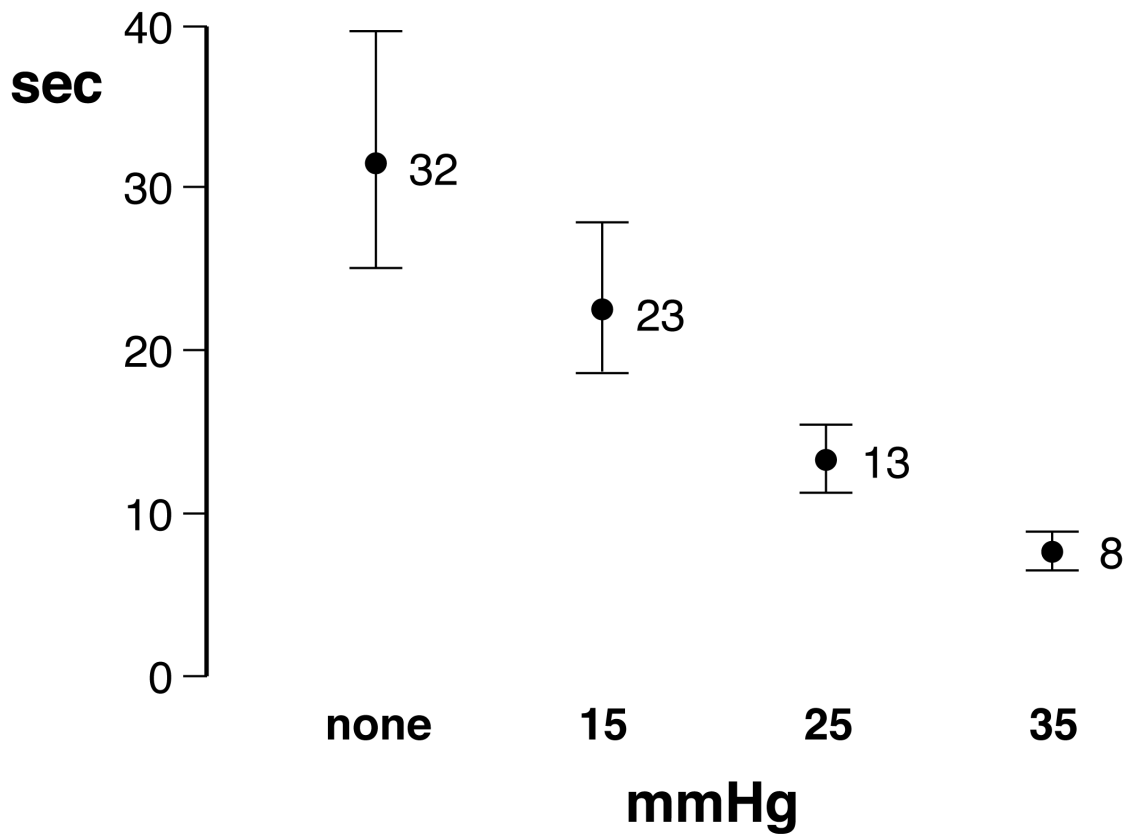
Figure 24: The mean (95% CI) transit venous time was significantly (<0.001) reduced with progressively increased pressure at ankle in sitting position
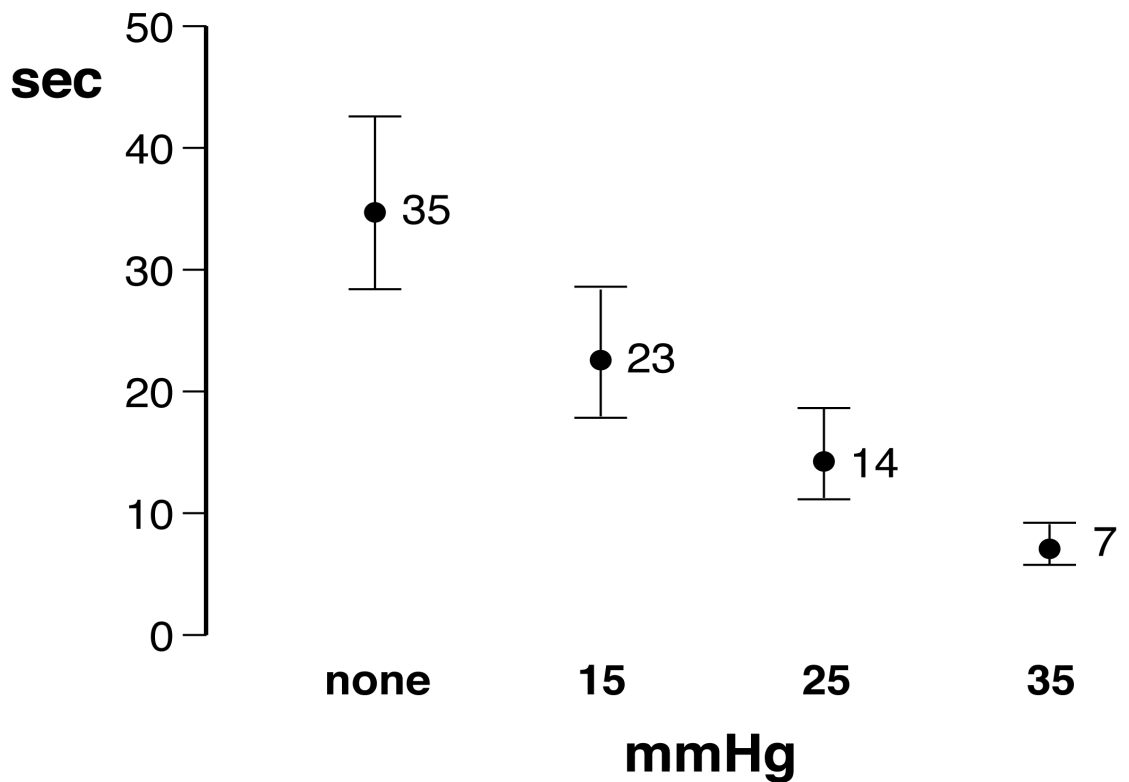
Figure 25: Increasing the pressure at the ankle significantly (<0.001) reduced the mean (95% CI) transit venous time in standing position

Transit venous time was also calculated for % reduction with each stocking. Results showed a significant % reduction in transit time with increase in pressure (table 13).

Type	% Reduction from using no stocking (95% CI)		
	Lying	Sitting	Standing
Stocking A	31.2% (24.4%, 37.9%)	27.0% (21.3%, 32.8%)	34.1% (28.2%, 40.1%)
Stocking B	56.8% (50.1%, 63.5%)	56.4% (50.0%, 62.8%)	57.0% (49.8%, 64.3%)
Stocking C	73.0% (66.3%, 79.6%)	73.8% (68.4%, 79.3%)	78.2% (74.2%, 82.2%)
p value	P<0.0001	P<0.0001	P<0.0001

Table 13: Significant % reduction in transit time with increase in pressure

1.3.2 Ambulatory Venous Pressure (AVP)

No significant difference was observed between the different stockings for the pressure at rest (p=0.24). However, post-exercise (p<0.001), absolute pressure (p<0.001) and recovery time (p=0.017) were reduced, as shown in Table 13.

Sub-analysis by Bonferroni-corrected multiple comparison tests showed significant differences in the pressure post-exercise between no stockings and stockings providing 15mmHg, 25mmHg and 35mmHg. In terms of AVP, there were significant differences between no stockings and all of the ECS, and between stockings providing 35mmHg and 15mmHg and 25mmHg ECS, but no significant difference between the 15mmHg and 25mmHg ECS. There were significant differences between the 35mmHg ECS and all of the other stockings in terms of recovery time.

Type	Mean (95% CI)				
	At Rest (AVPr, mmHg)	Post Exercise (AVPmin, mmHg)	AVP (mmHg)	Recovery time (RT90, sec)	PRI
No stocking	42 (40, 44)	25 (21, 29)	20 (14, 27)	42 (26, 59)	725 (403, 1045)
Stocking A (15mmHg)	41 (37, 43)	28 (26, 31)	15 (11, 19)	39 (25, 53)	520 (305, 735)
Stocking B (25mmHg)	42 (40, 44)	29 (26, 33)	13 (10, 16)	38 (25, 50)	450 (306, 695)
Stocking C (35mmHg)	39.5 (37, 42)	32 (28, 36)	8 (5, 11)	25 (17, 33)	263 (111, 416)
p value	p=0.24	p<0.001	p<0.001	p=0.017	p=0.011

Table 13: Comparing the effect of no pressure versus different graduated compression profiles on ambulatory venous pressure

1.3.3 Pressure Relief index (PRI)

The mean (95% CI) pressure relief index showed a significant stepwise reduction from 725 (403-1045) with no ECS, to 520 (305-735), 450 (306-695) and 263 (111-416) with ECS applying 15, 25 and 35 mmHg respectively (p=0.011), as shown in Table 13.

1.3.4 Volumetry

The mean (95% CI) leg volume whilst standing was significantly reduced from 3447 (3107-3787) ml with no ECS to 3259 (2936-3582) ml, 3161 (2846-3477) ml and 3067 (2753-3380) ml with ECS applying 15, 25 and 35mmHg respectively (p<0.001), as shown in Figure 26. The mean change in venous leg volume compared to not wearing stockings whilst standing was improved significantly by 188ml(5%), 286ml(8%) and 380ml(11%) with ECS applying 15, 25 and 35mmHg respectively (p<0.01).
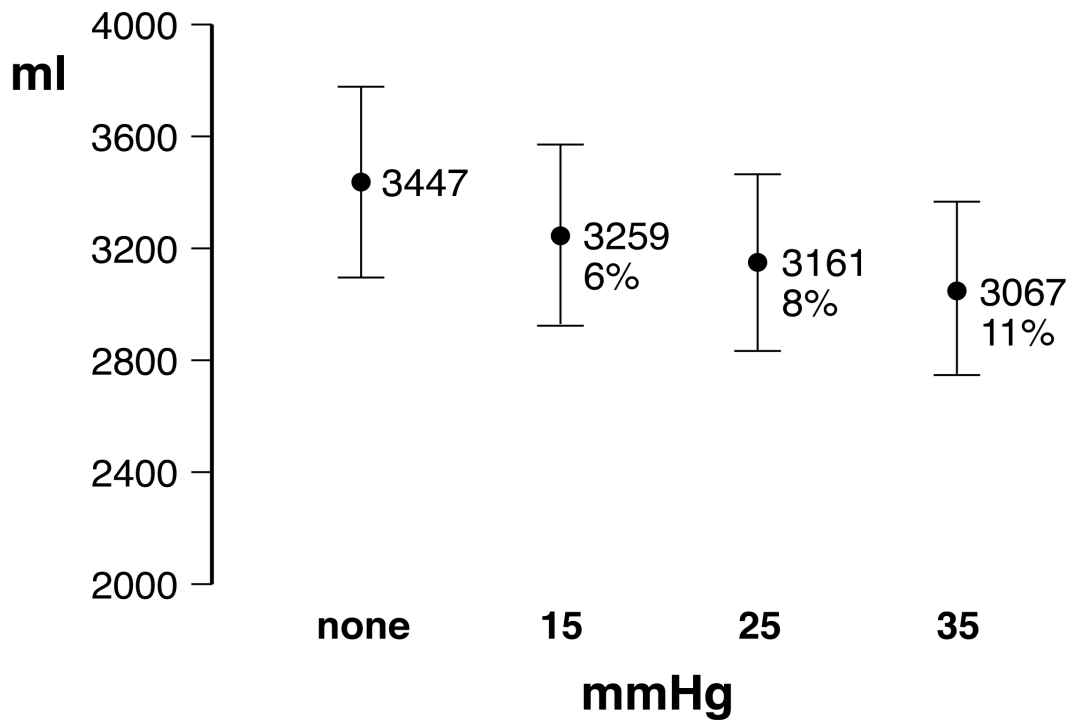
Figure 26: Increasing the pressure at the ankle significantly (<0.001) reduces the mean (95% CI) calf venous volume in standing position

1.3.5 Accuracy and reproducibility

The venous transit time and leg volume measurements were both repeated three times at ten-minute intervals in five patients to observe the consistency of the results. The results were significantly (p<0.001) similar with a difference variability ranging from 1-2 seconds in transit time and 2-4ml in volumetry. This shows that the values remain quite constant.

Oxford pressure manometer was used to measure the pressure delivered by the stockings in all the patients. All the ECS delivered the same pressures written on the label. These pressures were measured at the level of ankle, mid calf and just below the knee. ECS achieved the target in all the cases with 100% efficacy delivering prescribed pressures.

1.3.6 Adverse events

One volunteer dropped their blood pressure during the study from a baseline of systolic 110 mmHg to 99 mmHg systolic for 15 minutes. One volunteer had mild headache that started two hours following the study, which resolved without the need for analgesia and

lasted for 90 minutes. No other adverse events were seen during or 24 hours after the study.

1.4 Discussion

I conclude that ECS delivering 25mmHg at the ankle consistently reduce leg volumes and venous transit times to less than half. Delivering 25 mmHg of compression at the ankle with graduated pressure in rest of the limb is effective prevention against DVT.

This experimental study is novel in demonstrating that the micro-bubble technique can be used to measure venous transit time. It has also demonstrated the effects of a range of pressures on the venous transit time in different postures and, surprisingly, found that there was no evidence that lower pressures can be used for patients who are lying rather than sitting or standing.

Stanton et al [265] injected Evans blue dye into a dorsal foot vein and measured its transport to the femoral vein. They showed that applying a local pressure of 20 mmHg in a supine subject increased the blood flow velocity by 45.5% (range 22-75%). In 1960, Meyerowitz and Crook et al [279] used human albumin labelled with I^{132} to demonstrate that external compression of 10mmHg increased the rate of blood flow by an average of 160%. Many studies conducted later concur with previous results in demonstrating improved blood flow velocity via external compression [280-281, 311]. Lawrence and Kakkar et al confirmed the findings of Sigel that graduated external compression significantly improves the rate of blood flow, compared to uniform pressure [310].

My experimental study is unique because, unlike previous studies, I examined the effect of external compression on the venous transit time in different positions and used the micro-bubble technique for this purpose.

1.4.1 The effects of external compression on blood flow

Sigel et al reported an average increase in blood velocity of 38%, with a pressure gradient of 18 mmHg at the ankle to 8 mmHg at the thigh [311]. Lawrence and Kakkar et al found that the 18-14-8-10-8 mmHg profile produced a mean increase in the deep venous velocity of 75% and that higher levels of compression produced a further increase in the mean velocity [310]. Lewis et al [282], and later Arnoldi et al [283], provided further evidence for the value of the compression profile identified by Sigel and Kakkar. Lewis et al showed that whole leg clearance times were approximately halved in the presence of stockings, and calf clearance times were reduced by approximately 60% [282]. Arnoldi et al observed the highest velocity at pressure levels between 20-30 mmHg. Above this value, a gradual decrease in the flow rate was observed [283].

The literature suggests there is an increase in blood flow velocity with increased external compression, but there is no consistency in the pattern of the increase in the flow with particular pressures. One of the reasons for this was that each author has used a stocking manufactured by a different brand. None of the studies have measured the actual pressures delivered by the stockings compared to what is written on the packaging. It is, therefore, not clear if the stockings were actually delivering the graduated pressures or not. Thomas et al [284] compared six brands of stockings and found that all stockings within the same range were delivering pressures different to each other and only one brand of stocking was delivering pressures that were within the range written on the label.

In this experimental study I used the novel technology of ECS, which reliably and accurately deliver the prescribed pressures. During the study I confirmed that each stocking was delivering the intended pressures, using an Oxford pressure manometer. In contrast to previous studies, I measured the venous transit time rather than the blood flow velocity. The transit time can be measured more easily compared to the flow velocity

and a change in transit time, in effect, is a measurement of flow velocity. I hypothesised that the pressure required to halve the transit venous time will be appropriate for DVT prophylaxis. Based on the observations in this study 25mmHg will be ideal pressure profile for DVT prophylaxis responsible for halving the transit venous time. This pressure profile is much higher than the pressure profile currently used in clinical practice for the DVT prophylaxis recommended by the NICE guidelines, which is 14mmHg around the calf.

1.4.2 The effects of external compression on venous pressure

The prescription of elastic stockings is the most common treatment for deep venous insufficiency, yet some patients refuse to wear them because the stockings fail to relieve their symptoms or even make them worse. Elastic stockings that provide a graduated compression have been shown to reduce the ambulatory venous pressure and are therefore the stockings of choice [285].

In 1980, Horner et al showed that in 22 limbs, the greater the degree of graduated compression between ankle and calf exerted by the stocking, the greater the fall in ambulatory venous pressure [286]. Veraart et al [287] demonstrated that only strong, compression class III stockings (>40 mmHg at the ankle) increased the pressure in the deep venous system in 8 limbs with chronic venous insufficiency and recurrent venous ulceration.

This experimental study used healthy subjects and concurs with Horner's findings. This shows that, in healthy subjects, stockings of around 25 mmHg might be sufficient for DVT prophylaxis. However, in subjects with known chronic venous insufficiency who are at risk of recurrent DVT, a higher pressure may be required. Taking this fact into consideration that ECS are the only technology to allow stockings to have the positive effect on the pathologic deep venous system; ECS is the most appropriate therapeutic measure and should be prescribed in patients with deep venous insufficiency.

1.4.3 The effects of external compression on volume

The normal limb has a calf volume ranging from 1500 to 3000 ml, a venous volume of 100 to 150ml and ejects over 40-60% of the venous volume with a single contraction [19-20, 288].

Ibegbuna et al [289] showed a reduction in the residual volume fraction (RVF) in limbs with chronic venous insufficiency with elastic compression stockings during walking. In their study, stockings delivering 21 mmHg at ankle improved venous hemodynamic by decreasing RVF, from a median of 50.5% without stockings to 40.5% with stockings at 1.0 km/h (19.8% decrease).

Similarly, Pierson et al concluded that graded elastic stockings with 24 mm Hg of pressure at the ankle are effective in decreasing volume, circumference, and symptoms in the lower leg in patients with minimal adverse effects during a one-week period [197].

Partschet al [290] found that calf-length compression stockings with a pressure range of between 11 and 21mmHg are capable of reducing or totally preventing evening oedema and may therefore be recommended for people with a profession connected with long periods of sitting or standing. He also used the water displacement technique. The average volume of the lower limb was 3359 ± 577. The amount of evening oedema ranged between 10.2 and 220.3 ml.

Stockings with a pressure at ankle level of above 10mmHg were able to reduce the leg volume to values that, on average, were even smaller in the evening than in the morning (p<0.0001).

This experimental study also found a progressive reduction in the venous volume with increasing external pressure. The limb volume and reduction in venous volume measurements with 25 mmHg were identical to Partsch. I also observed that higher-pressure stockings of more than 25 mmHg could displace a significant volume from the

limbs, which is even more than the total venous volume. This shows that stockings have a significant effect on the venous physiology and haemodynamic of the lower limbs.

1.4.4 Prevention of deep venous thrombosis

A comprehensive review of the literature on the value of graduated compression stockings in the prevention of DVT shows a significant reduction in rate of DVT with the use of stockings [233, 266-271]. NICE guidelines recommend the use of anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15mmHg [154]. There is no clear description for the basis of the recommendation of the above pressure and its relation to blood flow, transit time or volume in the prevention of DVT.

The aim of this experimental study was to identify the pressure at which the calf venous transit time and venous volume are halved. I hypothesised that reducing the transit time and volume by half should be sufficient for DVT prophylaxis, but that a higher pressure may be required in patients with known chronic venous insufficiency, to prevent recurrent DVT. I found that 25mmHg around the ankle reduces the calf transit venous time and volume by 60% in healthy subjects, and should be considered for DVT prophylaxis.

1.4.5 Strengths

This study is novel in demonstrating that the micro-bubble technique can be used to measure transit venous time. This is the first time, to my knowledge, that this technique of measuring transit venous time has been described and its significance has been correlated with DVT prophylaxis. The procedure was repeated three times in five patients to confirm the reproducibility.

I used the technology of ECS, which are designed to ensure that the prescribed pressures are the pressures delivered. Contrary to previous studies, I measured the pressures delivered by each stocking with an Oxford pressure manometer in all the subjects, in

order to confirm that all the stockings were actually delivering the desired pressure profile. I used stockings with three different pressure profiles and measured the transit time in three different positions.

The trend of change in venous volume was measured with three pressure profile stockings and compared with no stockings rather than only with one pressure profile stocking, as in previous studies. A telephone follow up was also conducted after 24 hours to record any adverse events from the technique, compared to previous studies where no follow up was recorded.

1.4.6 Limitations

I could have measured the changes with 20 mmHg at ankle, but it would have made the study quite lengthy and may have become inconvenient for the subjects, hence a 20mmHg pressure profile was not included.

This study showed that the pressure profile required to halve the transit venous time is 25mmHg. I believe 25mmHg around the ankle would be the appropriate pressure profile to be used for DVT prophylaxis, which is higher than the currently used in the clinical practice. Surprisingly, there was no evidence that lower pressure profiles can be used for patients who are lying rather than sitting or standing.

Chapter 2

COMPRESSION STOCKINGS IN ANKLE FRACTURE: A RANDOMISED CONTROLLED TRIAL

2.1 Introduction

Ankle fractures are common; over 60,000 occur annually in the UK [173]. The standard treatment includes immobilisation in a cast for undisplaced or stable injuries (Weber types A and some type B) or open reduction and internal fixation for displaced, unstable fractures [177]. Swelling occurs within hours, impairing mobilisation and delaying surgery in those with unstable ankles. Early surgery reduces the hospital stay and the rate of post-operative complications [291]. Long-term outcomes are often poor with over 70% of patients reporting persistent ankle pain, stiffness and swelling over two years [178-180]. Functional outcome and health-related quality of life are also impaired [46, 79, 81-82].

Compression is not used routinely in ankle fracture, despite the inevitable swelling and the risk of deep vein thrombosis (DVT) [85, 87]. Effective treatment of oedema reduces pain, improves the range of movement and may accelerate the return to normal function following ankle injury. Pressures between 18 and 35mmHg at the ankle are needed to reduce oedema in other conditions [292, 95]. Compression is well established in the treatment of venous leg ulcers and may well be effective for all leg wounds [218]. There may be a similar benefit in healing bony injuries and the soft tissues around the ankle. Ankle injuries also inevitably damage surrounding tissues and inactivate the calf-muscle pump increasing the risk of DVT [94, 238]. Compression stockings are known to improve venous function and reduce the risk of DVT [231, 270].

ECS were designed with a wide elastic range so that they can be applied using a 'hospital butler' (a metal framed stocking applicator) without compromising the pressure profile. As the pressure prophylaxis study showed that 25mmHg can halve the transit venous time and volume, this was the pressure profile that was used for the specifically designed ECS to evaluate their clinical efficacy in reducing DVT and oedema. This study was

designed to evaluate the influence of ECS on recovery following ankle fracture. As most surgeons use Tubigrip as a simple liner under plaster casts this was used as the control.

2.2 Materials and Method

This was a pragmatic, single-centre, prospective, randomised, stratified, single-blinded, parallel group, two arm clinical trial (RCT) to compare i) ECS plus air-cast boot with ii) a liner plus air-cast boot in 90 patients with ankle fractures. Ethical approval was from the West Midlands Research Ethics Committee.

2.2.1 Participants and setting

Patients within 72 hours of ankle fracture were identified in the A&E or fracture clinic at the University Hospital of South Manchester (UHSM) and were provided with a study information leaflet. After a detailed explanation of the study and fully informed consent in writing, both ankle arteries were insonated by handheld Doppler to ensure bi- or tri-phasic Doppler waveforms and no risk of pressure damage to the skin before randomisation.

2.2.2 Patient eligibility

Eligible participants were aged 16-90 years within 72 hours of a Weber type A, B or C ankle fracture. Participants were excluded if they had had a previous fracture or surgery on the relevant ankle, a complex ankle fracture (pilon fracture), any other injury or a condition sufficient to impair mobility, known peripheral arterial disease or an abnormal Doppler waveform in either of the ankle arteries, were unable to give fully informed consent or if the treating orthopaedic team felt that the patient was inappropriate for any reason.

2.2.3 Randomisation

All consenting and eligible patients were randomised to either 1) compression using ECS and an Air-cast boot or 2) a liner and Air-cast boot using a bespoke laptop based

minimisation procedure stratified for i) surgical or conservative treatment and ii) age < 60 or ≥ 60 years.

2.2.4 Interventions

ECS or Liner plus air-cast boot

ECS or a liner was fitted as soon as possible following presentation in the A&E department or fracture clinic. The contra-lateral (non-injured) leg was measured (Figure 27) to fit the appropriate size ECS or liner from ten size and shape options manufactured for this study. The ECS was fitted using a 'hospital butler' (a purpose designed frame over which the stocking was stretched) using Entonox as necessary for analgesia. ECS or the liner remained in place until the air-cast boot was removed, typically at six weeks. ECS stockings or liner were removed just before surgery in patients undergoing open reduction and refitted immediately after.
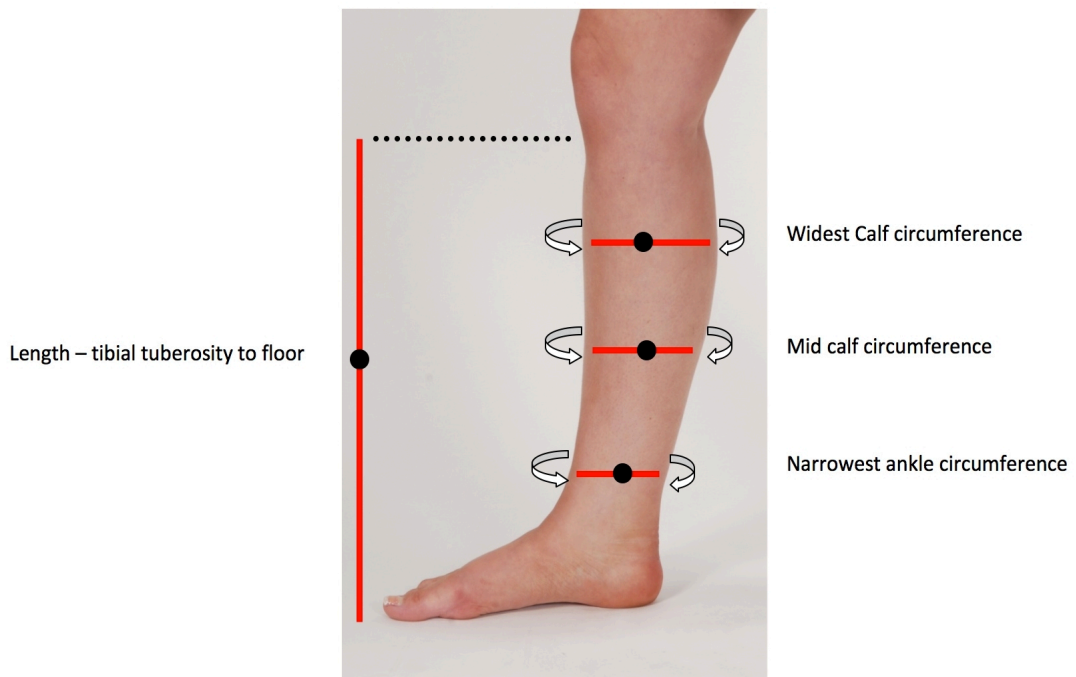
Figure 27: Measurements to fit modified ECS taken from the contralateral normal leg

Air cast boots

A below knee plaster of Paris cast is part of standard treatment for ankle fractures. Studies have shown better results with pneumatic air stirrups versus plaster of Paris casts when compared for comfort at 24 hours, swelling, time to union, arc of movement at union and symptoms at 3 months [293, 294].

The air-cast boot system (Figure 28) offers equivalent stability compared to a plaster cast. In contrast to the plaster of Paris cast, the boot can be removed for body care, ultrasound examination for DVT assessment and physical therapy. Additionally, the range of motion for dorsal flexion/extension in the upper ankle joint can be adjusted [295].

Figure 28: Air-cast boot

2.2.5 Fitting the ECS

As patients following ankle fracture cannot stand for the acquisition of a laser profile of the leg, we profiled 500 legs in healthy volunteers to produce ten size profiles fitting most legs. The pressures applied in this study were 25mmHg at the ankle, 17mmHg mid-calf and 10mmHg in the upper calf. Patients were provided with two ECS that were changed alternately every two weeks for hygienic reasons.

The liner was fitted as a simple liner delivering no compression in control patients.

Stable undisplaced fractures

Applying either the ECS or liner and immobilisation in an air-cast boot treated undisplaced, lateral malleolar fractures of the ankle. Patients were provided with crutches and did not bear weight until advised by the treating orthopaedic surgeon who also assessed bony union clinically. All patients were seen at six weeks when standard antero-posterior and lateral X-rays of the fractured ankle were taken.

Unstable or displaced fractures

Most of the unstable or displaced fractures underwent open reduction and internal fixation. Immediately after fixation, Tubigrip or an ECS was reapplied and the ankle was immobilised in a below knee air-cast boot until bony union.

2.2.6 Follow-up

Patients were followed at 2, 4, 8, 12 weeks and 6 months with assessments conducted independently by a research nurse 'blind' to treatment allocation. Foot, ankle and calf circumferences were recorded on the injured and non-injured leg and the injured leg circumferences calculated as a ratio to the normal leg. Patients were provided with an "injury diary" (Appendix 5) to document analgesia requirements and time to i) walking unaided, ii) climbing stairs without support and iii) return to work. Functional outcome (OMAS) and Quality of Life (QoL) questionnaires were sent in the post with each follow-up appointment letter, to be completed on the appropriate date and returned at the clinic appointment.

For patients requiring open reduction, an objective and validated wound-healing assessment score (Appendix 6) was used at two weeks following surgery [296]. All ankle fractures were X-rayed at two and six weeks with these x-rays reported for bony union by the relevant orthopaedic consultant. The American objective functional outcome score

(AOFAS), range of ankle movement and calf and ankle circumferences were recorded at each visit.

2.2.7 Duplex Doppler ultrasound

An experienced vascular technologist undertook duplex Doppler ultrasound imaging of all the deep veins for DVT at four weeks. With the patient standing with their weight on the contralateral leg, a 4-5MHz duplex ultrasound transducer was used to image the common femoral vein in cross-section; pressure was applied by the probe over the vein with counter-pressure by hand on the opposite side of the leg. This procedure was repeated at 2-3cm intervals along the length of the common and superficial femoral, popliteal and all three-calf veins. Failure to fully compress the vein indicated a clot, with a fresh thrombus having a similar echogenicity to blood, and an old thrombus to the surrounding muscle.

2.2.8 Physiotherapy

All patients underwent a standard physiotherapy protocol starting one week following removal of the air-cast boot and continued for 16 weeks. This included a home exercise programme to encourage weight bearing, proprioception and ankle movement.

2.2.9 Blinding

The treating surgeon and research fellow could not be blinded to the randomised treatment. However, SF-12v2 and OMAS scores were designed to be completed independently by the patient. All other outcome measures, including the range of movement, as assessed by goniometry, the ankle and calf circumferences, the AOFAS and wound assessments were performed by a research nurse who was 'blinded' to treatment allocation. The fracture clinic staff removed the air-cast boot and ECS or liner before the same research nurse, trained in the measurement of these outcomes, performed all the measurements using the same standard techniques throughout the study.

An experienced vascular technician who was also 'blind' to treatment allocation performed duplex imaging for DVT. The x-rays at six weeks were reported twice by i) a consultant orthopaedic surgeon and ii) a consultant musculoskeletal radiologist, both blind to treatment allocation.

2.2.10 Outcome measures

1. The primary outcome measure was the patient's own assessment of recovery using the Olerud-Molander Ankle Score (OMAS) (Appendix 2), a validated patient questionnaire [46, 79, 81, 178-180]. The scale is a functional rating scale from 0 (totally impaired) to 100 (completely unimpaired) and is based on nine different items: pain, stiffness, swelling, stair climbing, running, jumping, squatting, use of walking aides and activities of daily living. The score has been validated against (a) linear analogue scale measurement of subjective recovery, (b) range of motion in loaded dorsal extension, (c) presence of osteoarthritis and (d) presence of dislocation on radiographs, and correlates well with these [297].

2. Secondary outcome measures included an objective functional outcome by the ankle-specific American Orthopaedic Ankle and Foot Society (AOFAS) score (Appendix 3), another well-validated clinical score for outcomes in foot and ankle injury [298, 299].

3. SF12v2 (Appendix 4) is a validated clinical score for quality of life [300].

In patients undergoing open surgical reduction, wound healing at two weeks was assessed by an objective wound assessment score [296] (Appendix 6) based on clinical signs of infection: erythema, warmth, tenderness, discharge, systematic symptoms and use of antibiotics. High scores are associated with poor healing or wound infection. Frequency of DVT and injury diary was also secondary outcomes.

As it was the first trial to evaluate ECS so I decided to use OMAS as primary outcome for two reasons. Firstly, OMAS has sub-components to measure for swelling, pain, stiffness

and subsequent impact on range of movements. Any improvement in these factors will suggest a good functional capability of ECS. Secondly, to evaluate the significant difference in DVT normally a high number of patients are required so it was appropriate to conduct a pilot study first and this study will provide the data to conduct a future definite trial for this purpose.

2.2.11 Sample size calculation and statistical analysis

In similar previous studies, the mean (±sd) OMAS score was 70±15 at six months [137, 39, 218]. With 37 subjects in each group (74 in all), this study had 80% power to detect a clinically relevant difference of 10 in the OMAS score between the groups (i.e. 80 vs 70) at six months using a simple two-sample t-test with the conventional 5% significance level. Sample size was inflated by 10% to adjust for stratifying factors and an additional 10% to compensate for loss to follow up. A total of 90 patients (45 in each arm) were recruited.

Longitudinal regression modelling (using Generalized Estimating Equations with a first-order autoregressive correlation structure), based on intention to treat, was used to compare OMAS, AFOAS, SF-12v2 scores, range of ankle movements and ankle, foot and calf circumferences over the duration of the study. This technique is an efficient method of assessing repeated measurements over time and enables all patients (including those with missing data at any time point) to be included in the analysis [301].

Wound healing, pain, use of crutches and stairs, and return to work were compared by the Mann-Whitney U test. The Chi-square test was used to compare individual components of the OMAS. This study was not planned to be sufficient to detect a statistically significant reduction in the frequency of DVT, but DVT was included to guide power calculations for a subsequent definitive RCT. All data were analysed using SPSS® versions 15 and 16 (SPSS®, Chicago, Illinois, USA).

2.3 Results

Between September 2009 and April 2010, 110 patients were assessed for eligibility, 90 met the inclusion criteria and were randomised to either ECS with an air-cast boot (n=44) or a liner with an air-cast boot (n=46). Figure 30 summarises recruitment, randomisation, and follow-up [302]. The initial demographic characteristics of the two randomised groups were similar (Table 14). Seven patients were lost to follow up; four immediately after recruitment and three before follow-up at four weeks (Figure 29).

All patients were recruited within 24 hours of presentation to the hospital and interventions were applied immediately.

	ECS (n=44)	Liner (n=46)
Age (years)	46.4 (16–79)	47.0 (16–77)
F:M ratio	25:19	29:17
Height (m)	1.69 (1.44–1.94)	1.70 (1.25–1.98)
Weight (kg)	81.4 (58–128)	80.6 (49–127)
BMI	29 (19–43)	28 (17–40)
Lifestyle: Inactive	25 (57%)	22 (48%)
Fractured leg: Left	23 (52%)	15 (33%)
Weber classification A	19 (43%)	17 (37%)
B	20 (46%)	22 (48%)
C	5 (11%)	7 (15%)
Open reduction	13 (30%)	17 (37%)

All values are mean (range) with no important differences between the two treatment groups

Table 14: Demographic data: mean (range)

Ankle fracture trial flow diagram

Enrollment

Assessed for eligibility **110**

Excluded **20**
  - failed inclusion criteria 17
  - declined 3

Randomized **90**

Allocation

Liner + air-cast boot **46**
  - received allocated intervention 46

ECS + air-cast boot **44**
  - received allocated intervention 44

Follow-up

 4 week **45**, 1 withdrew
 8 week **45**
12 week **45**
 6 month **43**, 2 failed to attend
discontinued intervention **none**

 4 week **41**, 3 withdrew
 8 week **41**
12 week **41**
 6 month **40**, 1 failed to attend
discontinued intervention **none**

Analysis

analysed **46**

analysis by longitudinal regression modelling, based on intention to treat

analysed **44**

analysis by longitudinal regression modelling, based on intention to treat

Figure 29: Ankle fracture trial flow diagram

2.3.1 Ankle circumference and range of movement

Injured ankle and calf circumferences were expressed as a ratio of the circumference in the normal contralateral limb with 1.00 indicating no swelling. The mean (95% CI) circumferences in ECS and liner patients were similar before treatment with ratios of 1.10 (1.07, 1.12) for the ankle and 1.03 (1.02, 1.04) for the calf in both groups (Figure 30).
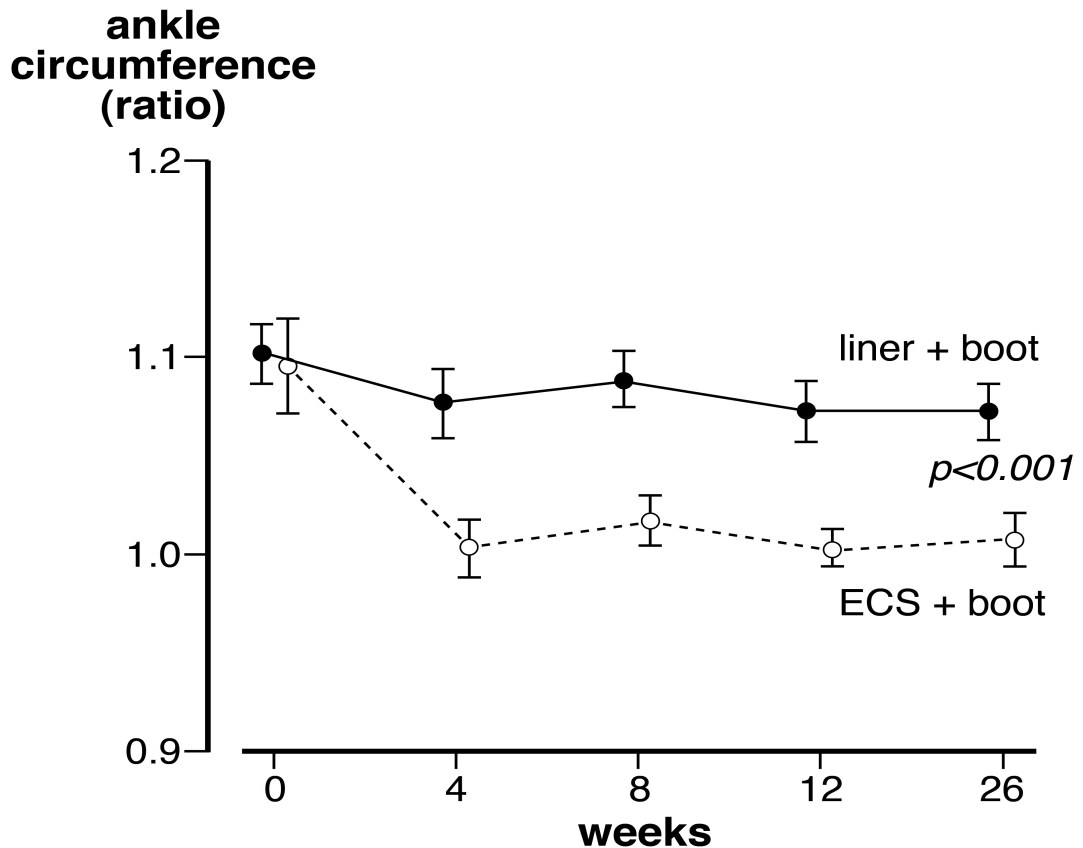
Figure 30: **The mean (95% CI) circumference for the injured ankle expressed as a ratio to the normal contralateral ankle was similar shortly following injury but ECS subsequently achieved near normal ankle circumference at all-time points, a significant (<0.001) reduction compared with a liner**

I observed that ECS markedly reduced swelling within hours of application such that surgery could be performed earlier in ECS patients. By four weeks, the mean (95% CI) ankle circumference ratio with ECS was only 1.00 (0.99, 1.02) compared with 1.08 (1.06, 1.09) for the liner (p<0.001, Figure 31). Calf circumference had recovered to normal at

1.00 (0.99, 1.03) by four weeks in patients treated with a liner, but was significantly smaller at 0.96 (0.95, 0.97) with ECS (P<0.001) and remained smaller at all follow-up intervals. This reduction in swelling was associated with a marked improvement in the range of ankle movements in patients treated using ECS (p<0.001, Table 15).

Ankle range movement				
	Inversion/eversion		Flexion/extension	
	ECS	Liner	ECS	Liner
4 weeks	55% (49%, 61%)	30% (24%, 35%)	$24^{\circ *}$ (23°, 26°)	17° (15°, 19°)
8 weeks	$73\%^{*}$ (68%, 79%)	52% (47%, 57%)	$32^{\circ *}$ (31°, 34°)	25° (23°, 27°)
12 weeks	$91\%^{*}$ (88°, 94°)	68% (64°, 72°)	$37^{\circ *}$ (35°, 38°)	27° (25°, 29°)
6 months	$96\%^{*}$ (94%, 98%)	78% (73%, 83%)	$40^{\circ *}$ (38°, 42°)	31° (29°, 33°)

*p<0.001 comparing ECS with the liner treated patients (GEE analysis)
Table 15: Range of ankle movements (mean, 95% CI)

2.3.2 Olerud Molander Ankle Score (OMAS)

The OMAS score improved progressively over time in both study groups (p<0.001, Figure 31a, Table 16) but OMAS scores at each time point were significantly better for patients randomised to ECS when compared with the liner (p<0.001). By four weeks the mean (95% CI) OMAS score for ECS was 43 (38, 49) rising to 88 (83, 93) at 12 weeks compared with 24 (18, 31) and 58 (52, 64) respectively for the liner (p<0.01). By six months, there was still a marked difference in OMAS score with ECS achieving 98 (96, 99) and liner only 67 (62, 73) (p<0.001). Significant difference was seen among the components of the OMAS score between the two groups as shown in table 17. Pain, stiffness, swelling, running, jumping, squatting, ability to walk stairs and to return back to normal work were all significantly (p<0.001) improved with ECS compared to no compression.

	OMAS		AOFAS		SF12v2	
	ECS	Liner	ECS	Liner	ECS	Liner
4 weeks	43[*] (38,49)	24 (18,31)	78[*] (73,83)	60 (55,65)	83[*] (79, 87)	74 (70,79)
8 weeks	74[*] (68.80)	44 (38,50)	95[*] (92,98)	80 (76,83)	100[*] (96,103)	84 (80,88)
12 weeks	88[*] (83,93)	58 (52,64)	101[*] (98,104)	87 (83,91)	108[*] (104,112)	92 (88,96)
6 months	98[*] (96,99)	67 (62,73)	105[*] (104,105)	90 (86,94)	116[*] (114,117)	99 (94,103)

[*]p<0.001 comparing ECS with the liner treated patients (GEE analysis)

Table 16: Ankle recovery and quality of life scores (mean, 95% CI)

2.3.3 American Orthopedic Foot and Ankle Score (AOFAS)

The mean (95% CI) AOFAS scores were also significantly better with ECS at all follow-up intervals to six months (p<0.001, Figure 31b, Table 16). The different sub-components of AOFAS score were also significantly higher with ECS: at six months, 97% of patients with ECS complained of no pain compared with 33% with the liner (p<0.001), 95% of patients with ECS had no limitations of daily activities comparing to 63% with the liner (p<0.001) as shown in table 18. All of the ECS group, but only 81% of liner patients were able to walk >6 blocks (p=0.005). The range of ankle movement was also significantly improved in ECS patients (p<0.001) (Table 15).

2.3.4 SF12v2: Quality of Life Score

This score had improved by four weeks to 83 (79, 87) with ECS and to just 74 (70, 78.5) with the liner ((p<0.001), Figure 31c, Table 16). By 12 weeks and six months, the SF12v2 scores continued to improve significantly more with ECS to 108 (104, 112) and 116 (114, 117) respectively for ECS compared with 92 (88, 96) and 99 (94, 103) for the liner

(p<0.001). Physical and mental health components of SF12v2 were both significantly improved with use of ECS compared to tubigrip (p<0.001, p<0.001, table 19).

OMAS score

Figure 31 (a)

AOFAS score
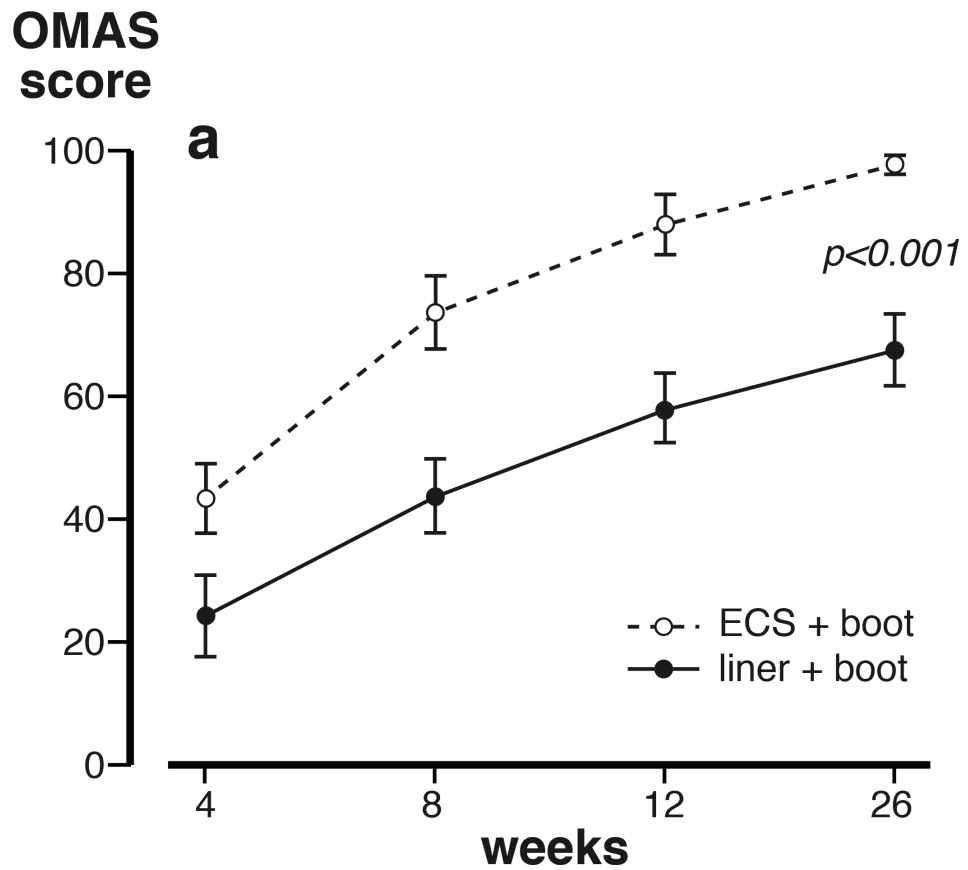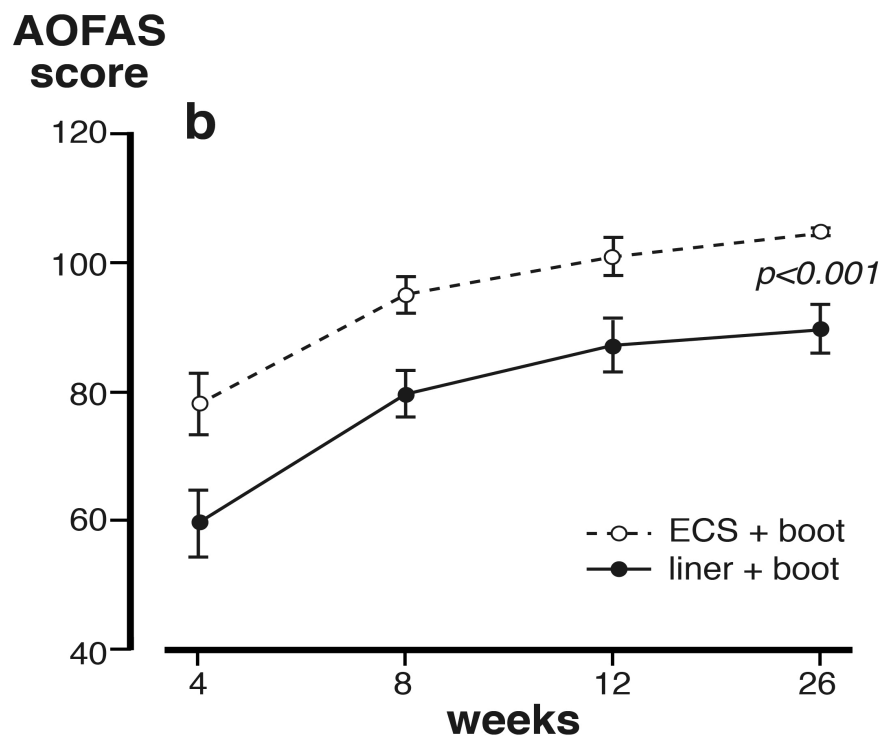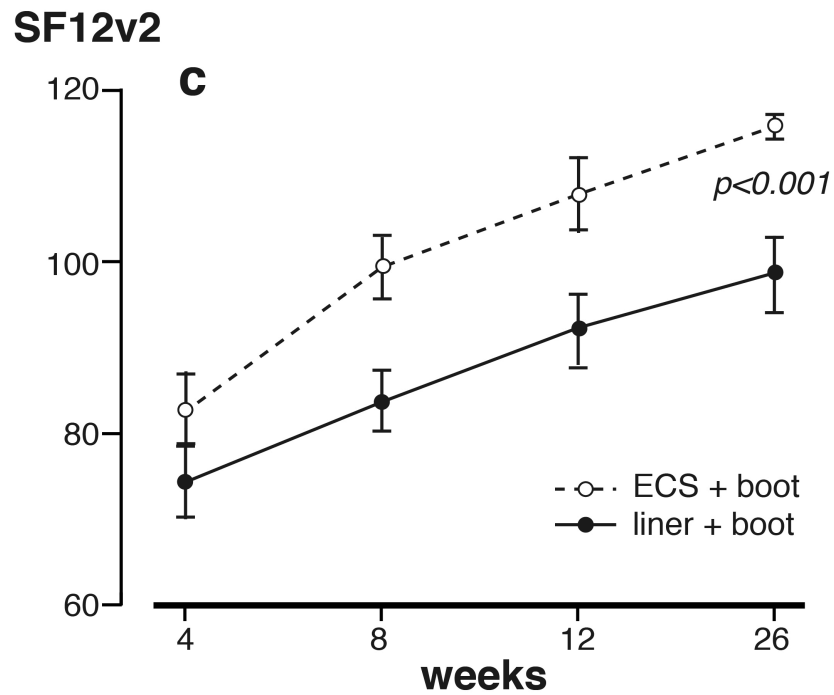
Figure 31 (b)

SF12v2

Figure 31 (c)

Figure 31: Mean (95% CI) symptom and quality of life scores a) OMAS b) AOFAS and C) SF12v2 were all significantly improved in patients treated with ECS at all-time intervals from four weeks out to six months compared with patients treated by the liner (p<0.00)

2.3.5 Wound healing

The wound inspection score, in which a higher score indicates poor healing or signs of infection, was recorded in 28 of the 31 patients undergoing open surgical reduction and fixation: healing appeared better with a mean (95% CI) score of 1.55 (1.19, 1.90) in the 12 patients treated with ECS compared with 3.27 (2.19, 4.34) for the 16 patients using the liner (p=0.009).

2.3.6 Injury diary

We used the injury diary to record the time in days from injury until the patient no longer required the following support:

i) Pain killers: Discontinued in a median (range) of 40 (3-182) days for ECS and 52 (7-182) using the liner (p=0.44).

ii) Use of crutches: No longer required at median of 40 (21-130) days for ECS compared with 52 (7-182) using liner (p=0.21).

iii) Support using the stairs: No longer required at a median of 52 (3-110) and 61 (3-182) days for ECS and the liner respectively (p=0.058).

The time to return to work and to normal activities was 40 (3-182) and 52 (0-182) days for ECS compared with 52 (3-182) and 70 (3-182) days of the liner (p=0.27 and p=0.01 respectively).

Recovery was slowest for Weber C fractures, which required surgical reduction.

2.3.7 DVT at four weeks

Of the 86 patients who attended for duplex imaging at four weeks, 15 (18%) had DVTs; five (12%) of 43 ECS patients compared with 10 (23%) of 43 using the liner (p= 0.26). Only patients undergoing open surgical reduction were prescribed low molecular weight heparin prophylaxis and five (17%) of 29 patients treated by open reduction and fixation suffered a DVT, which was similar to 10 (18%) of 57 treated conservatively. The peroneal vein was involved in nine patients; the posterior tibial vein in six, the gastrocnemius vein in five, and the superficial femoral, popliteal and soleal veins each in one patient only (Figure 32). Power calculations based on this frequency of DVT in ECS and the liner patients indicate that a total of 408 patients with ankle fracture (204 in each group) need to be randomised to achieve an 80% power to detect a reduction in the frequency of DVT at the conventional 5% statistical significance.

Figure 32: Distribution of DVTs in injured legs

2.3.8 Adverse events

One patient with the liner suffered a superficial wound infection, which was treated by antibiotics and subsequently healed. One patient fitted with an ECS required removal of a screw and one with the liner underwent revision surgery. Nine (10.4%) of 86 patients had maceration of the skin around the heel (4 ECS, 5 liner), which recovered without intervention. There was skin redness due to pressure from the ECS in three (7%) patients; this improved when a thin layer of orthopaedic wool was applied under the ECS. None of the patients suffered ulceration or skin damage.

OMAS component variables	OMAS component scores					
	4 week			6 month		
	Boot alone	ECS + boot	p value	Boot alone	ECS + boot	p value
No pain	19%	52%	p<0.001	40%	98%	p<0.001
No stiffness	5%	40%	p<0.001	14%	100%	p<0.001
No swelling	5%	78%	p<0.001	12%	95%	p<0.001
Can climb Stairs				74%	95%	P=0.01
Can run				60%	92%	P=0.001
Can Jump				54%	85%	P=0.002
Can Squat				63%	100%	p<0.001
Back to normal daily life activities				65%	92%	P=0.002

Table 17

AOFAS component variables	AOFAS component scores					
	4 week			6 month		
	Boot alone	ECS + boot	p value	Boot alone	ECS + boot	p value
No pain	19%	52%	p<0.001	33%	97%	p<0.001
No limitation of daily activities	58%	88%	p=0.004	63%	95%	p<0.001
Can do maximum walking distance of > 6 blocks				81%	100%	p=0.005
Can walk on all type of surfaces				65%	97%	p<0.001
Sagittal motion – had normal/ mild restriction	0%	28%	p<0.001	60%	100%	p<0.001
Hind foot motion – had normal/ mild restriction	2%	28%	p<0.001	54%	100%	p<0.001

Table 18

Time	Mental component score		Physical component score	
	Liner + boot	ECS + boot	Liner + boot	ECS + boot
4 week	41.5 (37.9,45.1)	46.0 (42.6,49.3)	32.8 (30.6,35.0)	36.8 (34.0,39.7)
8 week	43.7 (40.5,46.8)	53.5 (50.9,56.1)	40.2 (38.5,41.9)	46.0 (43.8,48.2)
12 week	47.3 (43.9,50.7)	56.3 (53.2,59.4)	44.5 (42.5,46.5)	51.8 (50.2,53.3)
6 months	51.1 (48.1,54.0)	61.3 (60.1,62.5)	47.4 (45.1,50.0)	54.3 (53.2,55.3)
p-value (GEE analysis)	Treatment p<0.001 Time p<0.001 Treatment x time p=0.13		Treatment p<0.001 Time p<0.001 Treatment x time p=0.45	

Table 19: Components of SF12v2

2.4 Discussion

ECS applied as soon as possible following ankle fracture significantly improved all measures of recovery. Swelling was rapidly reduced allowing earlier surgery in those requiring open reduction. Ankle movement, pain and both OMAS and AOFAS scores recovered more rapidly at all time points from four weeks to six months. This study was insufficiently powered to address whether ECS may reduce the frequency of DVT following ankle fracture.

Long-term symptoms are frequent following ankle fracture: up to three-quarters of patients report persistent ankle pain, stiffness more than a year following injury and swelling after 14-24 months [178, 179] and half report persistent pain at five years [180]. Ankle fractures have been reported to impair functional outcome and health-related quality of life indefinitely [79, 81-82]. Leg swelling is frequent and may follow DVT in some patients or merely be a consequence of impaired calf pump function due to a stiff ankle [166]. There is also evidence that ankle fracture is a cause of chronic venous insufficiency and even venous ulcers [303-305]. Whether some of these late complications of ankle fracture were due to DVT remains uncertain, but duplex imaging in our study identified a higher than expected frequency of DVT at 18%.

2.4.1 Use of Air cast boot

An air-cast boot was used to immobilise the ankle fracture rather than a plaster cast, as there have been several studies suggesting that patient recovery following ankle fracture is improved using the air-cast boot [293-295]. For this study, the air-cast boot was the only realistic option in patients where ECS were delivering pressures of 25mmHg at the ankle: there would clearly be a risk of pressure damage if a plaster cast, fitted too tight, exerted additional pressure. Air-cast boots could more easily be removed to allow the measurements and duplex imaging in our protocol.

2.4.2 Use of compression

Elastic stockings delivering pressures between 18 and 35mmHg at the ankle have been used to reduce oedema [292, 306]. Effective treatment of oedema has previously been reported to reduce pain, improve the range of movement and restore function earlier following ankle injury [95, 292]. The pressure needed to prevent oedema can be achieved using British National Formulary (BNF) class II compression stockings, but as there are

only five sizes with limited elastic ranges, these fail to fit 20% of the normal population and would be difficult to apply over a fractured ankle.

Compression has not been routine in the treatment of ankle fractures, although the only previous RCT on elastic stockings in ankle fracture randomised only 20 patients [306]. The author used elastic stockings delivering around 18mmHg at the ankle and 8mmHg below the knee or standard immobilization in plaster for six weeks. Compression stockings failed to improve calf ejection or residual venous volumes but significantly reduced swelling. However, this was a small study with inadequate sample size and poor methodology. In comparison, our study was adequately powered with patient led outcomes and indicates the role of compression in the management of ankle fractures by enhanced recovery and improved QoL.

The role of compression in healing venous leg ulcers is well-established [218, 219]. Theoretically, this same principle may apply to all injuries at the ankle or involving the lower leg. In my experience, traumatic skin wounds around the ankle and lower leg also heal significantly faster when treated with compression, regardless of whether or not there is venous disease. The wounds in patients requiring open surgery in this study achieved significantly better scores at two weeks with ECS.

2.4.3 Deep Vein Thrombosis

Asymptomatic DVT is known to occur in over 20% of patients following surgery for ankle fracture and 35% of those undergoing Achilles tendon repair [85, 186]. The frequency of DVT following conservative treatment for ankle fracture is poorly studied but appears to be in the range 5-20% [87, 188-190]. In this study, DVT occurred in 18% of patients treated conservatively and 17% of patients treated surgically, presumably as only the patients undergoing open repair were given low-molecular-weight heparin prophylaxis. ECS

appeared to halve the frequency of DVT, but this difference predictably failed to achieve statistical significance in this number of patients. Assuming that ECS achieved a similar influence on DVT in a larger study, a definitive randomised controlled trial would require a total of 408 patients. In any event, orthopaedic surgeons need to consider whether, in the absence of a contraindication, low-molecular-weight heparin DVT prophylaxis should be prescribed for all ankle fracture patients.

2.4.4 Strengths

This is the first RCT with an adequate sample size to evaluate the role of compression in the management of ankle fracture. Only seven patients dropped out. It was also unique in assessing the functional outcome by subjective (OMAS), objective (AOFAS), and quality of life (SF12v2) scores.

2.4.5 Limitations

The choice of air-cast boots in this study may be considered a limitation, as immobilisation by plaster cast is still standard practice. As compression stockings delivering 25mmHg at the ankle may carry a risk of pressure ulceration under a plaster cast, we used air-cast boots, which could easily be removed to inspect for pressure damage. In reality, air-cast boots are increasingly being adopted, as patient recovery following ankle injury is at least as good as with a plaster cast [293-295].

Patients were followed up for six months only as most patients with ankle fracture are either young males or old females, meaning follow-up beyond eight weeks tends to be difficult. The plan is to approach these patients again by sending out OMAS and SF12v2 questionnaires at two years.

ECS applied early following ankle fracture reduced swelling, enabled earlier surgery where indicated and improved functional outcome. There were no significant complications

associated with ECS use, but a larger definitive study is required to determine whether

ECS reduced the frequency of DVT.

Section IV
DISCUSSION AND CONCLUSIONS

Discussion

Care for patients with venous ulcers has improved in the past two decades as research based approaches have been adopted, but venous ulcers are still a big problem for both patients and health service resources. The aim of my thesis was to develop the research to facilitate the prevention of venous disease.

My case control study identified significant risk factors associated with venous ulceration, which are potentially either preventable or treatable. This means that targeting these risk factors by adopting appropriate prophylactic strategies in a timely manner could substantially prevent venous ulcers.

This case control study presents a tool, which could be used in both primary and secondary care to calculate an individual's risk of developing venous ulcer disease, a common and expensive pathology of our ageing population. Intervention could then be aimed at the modifiable risk factors of weight and mobility in order to reduce the risk of developing ulceration. It may even be possible that prophylactic treatment for ulcers in the form of elevation and compression stockings may decrease the incidence of ulcer formation in high-risk individuals for primary ulcers. This could potentially save the NHS several millions of pounds but obviously would require further investigation. This risk prediction score identifies patients with a >5% annual risk of developing a leg ulcer. This level of risk is sufficient to justify clinical trials on treatments to prevent venous leg ulcers. This case control study showed that incorporating significant risk factors in to a scoring system successfully predicts the risk of venous ulceration. It provides the first validated risk assessment tool for the identification of patients at risk of developing venous ulcer disease. The next natural step is to trial targeted interventions within this population in

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order to discover if it is possible to decrease the risk to these patients in a way that is also cost effective for the health service.

After identifying the 'at risk' population, the next step was to develop the appropriate prophylactic measures to prevent venous ulceration by treating or preventing the risk factors.

Most ulcers are caused by sustained chronic venous insufficiency (CVI) or lymphedema, which affect 1.5 million and 1 million people respectively in the UK, causing leg swelling, aching and skin changes. CVI is often caused by a previous DVT and prevention of DVT is therefore important.

Most people will require DVT prophylaxis at some time in their lives either when undertaking long journeys (flight socks) or when admitted to hospital. Meta-analyses of RCT's on compression stockings for the prevention of DVT confirmed efficacy for long haul flights and for hospital inpatients. NICE and SIGN guidelines also recommend the use of compression stockings for the prophylaxis of DVT.

Interestingly, the experimental study for the first time successfully used the micro-bubble technique to measure the transit venous time, which can be easily measured in the vascular laboratories with good duplex facilities. Technique is reliable as has shown reproducibility and precision. Surprisingly, there was no evidence that lower pressures can be used for patients who are lying rather than sitting/standing. This study highlights the significant need for further research in the area of venous disease.

ECS delivering 25mmHg at the ankle consistently reduce leg volumes and transit times by over 50%, with no difference in standing or lying position. These results may be useful in deriving the optimal compression profile for the maximum benefit in improving the prophylaxis and management of Deep Vein Thrombosis. I anticipate that 25mmHg of pressure should be used for DVT prophylaxis as it halved the transit venous time. This

25mmHg is much higher than the 14mmHg of pressure at calf recommended by NICE for DVT prophylaxis but further research is required to clarify this important issue.

The pressure profiles identified in the experimental study were further evaluated in an RCT. This RCT showed that ECS applied early following ankle fracture reduced swelling and improved validated measures of functional outcome. There were no significant complications associated with ECS use, but a larger definitive study is required to determine whether ECS reduced the frequency of DVT.

This reduction in the swelling shows that if ECS are applied as soon as possible following ankle fractures, which require surgical reduction, it will reduce the swelling and will enable earlier surgery. This can be evaluated further in larger sample size studies, as it will have an impact on the costs as well.

ECS applied early following ankle fracture improved both functional outcome and subsequent quality of life up to six months. DVT occurred in 18% of ankle fracture patients suggesting that DVT prophylaxis should be considered, even in patients treated conservatively.

ECS improved the range of movements, decreased stiffness and pain, and expedited recovery with better wound healing. It appears that the reduction in swelling reduced the pain and stiffness and subsequently improved the range of movements, which resulted in a quicker recovery. This enhanced recovery implies there may be a smaller risk of complications, such as DVT and damage to the venous system, which would be the cause of CVI culminating in venous ulceration in long term. This preventive measure at the early stage could present a huge saving for the NHS budget in the long term.

Elastic compression has an important role in the prevention of deep vein thrombosis (DVT, an important cause of CVI) and in the treatment of varicose veins (VVs), CVI,

lymphedema and leg ulcers. The compression required for each indication remains uncertain, as the pressures delivered by current treatments are highly variable.

ECS can be utilised to determine the pressure prophylaxis required to conservatively treat varicose veins, treat and prevent venous ulcers, lymphedema and to prevent post-thrombotic syndrome. These pressures need to be determined more closely in patients with these pathologies. Well-designed clinical studies with large numbers are needed to conclude the appropriate pressures.

ECS may prove revolutionary in the management of venous disease and save the NHS resources in terms of expenditure, time and manpower. If successful, ECS will definitely have a place globally in the management of venous disease.

To conclude, in spite of the presence of many techniques, diversity of evolving technologies and lots of money spent on research in venous diseases, failings are evident, recurrences are common and patient satisfaction is minimal. Management strategies based on the current pathophysiological concepts are far from perfect.

Are we going in the wrong direction? Don't we need a change of focus, concept and strategy in order to find a more robust solution? We have to face the fact that we are going in the wrong direction and we need to revise our strategy to focus on prevention of venous disease. A venous ulcer is like the iceberg of venous disease. Although it is important to be prepared for collision with the iceberg, it is more appropriate to take all possible precautions to avoid that incidence in the first place.

This thesis sets a new direction for the management of venous disease. Identifying a population at risk of CVI and venous ulceration allows clinical trials on treatments designed to prevent these common pathologies affecting the elderly. My research shows, that pressures of 25mmHg are required to influence physiology sufficiently to ensure a significant impact on the frequency of DVT in patients who are immobilised by illness or

injury. Finally, the augmentation of venous function by compression appears to enhance the healing process in ankle fracture with improved functional outcomes. A definitive trial is required to determine whether engineered compression stockings (ECS) delivering this range of compression might also significantly impact the frequency of DVT and hopefully the subsequent frequency of CVI in patients suffering ankle injury.

Conclusion

1) The Manchester Venous Ulcer Prediction Score (MUPS) identifies patients at risk of developing venous ulcers.

2) The pressure profile required for DVT prophylaxis is higher than anticipated with pressures of 25mmHg at the ankle needed to halve venous transit time.

3) The frequency of asymptomatic DVT following ankle fracture is higher than widely believed.

4) In ankle fracture compression improved functional recovery and may reduce the frequency of DVT and subsequent CVI.

These studies have validated the potential role of the novel technology used to produce ECS in the prevention of venous disease.

Future research

Our focus has now moved from treating active ulcers to the prevention of ulceration by identifying at risk populations. Prevention would undoubtedly be cheaper than cure and would also improve quality of life for patients with CVI at risk of ulceration. We are planning the following research:

1) A definitive RCT to evaluate whether ECS significantly reduce the frequency of DVT following ankle fracture

2) Studies to evaluate the ideal pressure profile required for ECS to prevent and treat varicose veins, lymphedema and leg ulcers

3) RCTs to compare the efficacy of ECS against compression stockings and the bandages in the prevention and treatment of varicose veins, CVI, lymphedema and leg ulcers.

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Appendix

Appendix 1: Questionnaire to identify risk factors for venous leg ulcers

YOUR PERSONAL DETAILS (used for correspondence purposes only)

Title (Mr/Mrs/Miss etc)……………….

First name(s)…………………….   Surname…………………………….

Address……………………………………………………………………………

………………………………………………………Postcode………………………

Telephone no …………………………. (we may contact you to go through your answers)

Date of Birth…………………………..   Age…………………..

Sex (tick) ☐ male   ☐ female

GP Name and Address ……………………………………………………………………..

YOUR GENERAL HEALTH

► **What is you height and weight**? (if unsure, make your best guess)

Height: Weight:

►**How would you describe your previous health?**

☐ excellent   ☐ good   ☐ poor

► **How would you describe your mobility?**

☐ excellent   ☐ good   ☐ reasonable   ☐ poor   ☐ terrible

► **Do you use a walking aid?**

☐ none   ☐ one stick/   ☐ two sticks/   ☐ zimmer   ☐ can't walk
                    crutch   crutches

► **Have you had any serious illnesses?**   ☐ yes   ☐ no

If yes   Year…………   Illness…………………………………………..

          Year…………   Illness……………………………………..

          Year…………   Illness……………………………………..

          Year…………   Illness…………………………………..

► **Have you ever had an operation?**   ☐ yes   ☐ no

If yes   Year…………   Operation…………………………………….

          Year…………   Operation…………………………………….

► **Do you smoke?**   ☐ yes   ☐ no

If yes   What do you smoke?☐cigarettes   ☐cigars   ☐pipe
          How many?   _____ / day   At what age did you start smoking? _____

► **Have you smoked in the past?**   ☐ yes   ☐ no

If yes   What age did you start? _____   What age did you give up? _____
          How many did you smoke? _____ / day

YOUR MEDICAL BACKGROUND

Have you had any of the conditions listed in the left column? Additional information should be given in the next column

Condition	Additional information
► Heart disease ☐ Yes ☐ No	*If yes, please tick all that apply and give year it started* ☐ Heart attack year _____ ☐ Angina year _____ ☐ Valve disease year _____ ☐ Irregular heartbeat (AF) year _____ ☐ Other _____ year _____
► High blood pressure ☐ Yes ☐ No	*If yes, please give year it started*
► Stroke ☐ Yes ☐ No	*If yes, please give year it occurred* *What was affected and how long did the symptoms last?*
► Chest / lung disease ☐ Yes ☐ No	*If yes, please tick all that apply and give year it started* ☐ Chronic bronchitis (COPD) year _____ ☐ Adult asthma year _____ ☐ Other _____ year _____
► Diabetes ☐ Yes ☐ No	*If yes, please give year it started*
► Pulmonary embolism (blood clot on the <u>lung</u>) ☐ Yes ☐ No	*If yes, please give year it occurred*
► Anticoagulants (blood thinners, such as warfarin, NOT aspirin) ☐ Yes ☐ No	*If yes, please say why you were given blood-thinners and year(s) you used them*
► Cancer ☐ Yes ☐ No	*If yes, what type of cancer was it and when did you have it?* *How was it treated?* ☐ an operation ☐ chemotherapy ☐ radiotherapy ☐ hormone therapy ☐ other _____
► Pregnancy ☐ Yes ☐ No ☐ Not applicable	*If yes, how many times have you been pregnant?*

YOUR LEGS

Have any of the following problems affected your legs? *Give answers for both legs!*

	LEFT LEG ▼	RIGHT LEG ▼	
Current varicose veins (these are large, prominent, <u>bulging</u> veins on your legs)	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please state when these first started*
Surgery for varicose veins in the past	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please specify year of treatment*
Injection treatment for varicose veins (not thread veins)	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please state year of treatment*
Thread veins (these are thin, <u>flat</u> veins that do not bulge)	☐ Yes ☐ No	☐ Yes ☐ No	
Phlebitis (this is inflammation of a vein)	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please state year this occurred*
Deep vein thrombosis (known as "DVT", this is a blood clot in the <u>leg</u> causing leg swelling and pain and treated with blood-thinners)	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please state year this occurred*
Hip arthritis	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, since what year?*
Knee arthritis	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, since what year?*
Ankle arthritis	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, since what year?*
Total hip replacement surgery	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please state year surgery took place*
Total knee replacement surgery	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, please state year surgery took place*
A broken bone in your leg	☐ Yes ☐ No	☐ Yes ☐ No	*If yes, what was injured and when?* ☐ hip year _____ ☐ thigh year _____ ☐ shin year _____ ☐ ankle year _____ ☐ foot year _____

To your knowledge, have any of the following problems affected members of your immediate family (parents, siblings or children)?   ▼

Varicose veins (these are prominent, bulging veins on the legs)	☐ Yes ☐ No	*If yes, was it your* ☐ mother/father ☐ brother/sister ☐ son/daughter
Deep vein thrombosis (known as a "DVT", this is a blood clot in the **leg** causing leg swelling and pain and treated with blood-thinners)	☐ Yes ☐ No	*If yes, was it your* ☐ mother/father ☐ brother/sister ☐ son/daughter
Pulmonary embolism (a blood clot on the **lung**. It is treated with blood thinners)	☐ Yes ☐ No	*If yes, was it your* ☐ mother/father ☐ brother/sister ☐ son/daughter
A leg ulcer	☐ Yes ☐ No	*If yes, was it your* ☐ mother/father ☐ brother/sister ☐ son/daughter

YOUR FRIEND/COLLEAGUE

Please give the name of the person who gave you this questionnaire:

………
………………………………………………………………………………………………………

FINALLY

Please go through the questionnaire once more, ensuring that you have filled in all the answers. Try to ensure that dates have been completed. If you are unsure of the exact year, please give your best guess.

Thank you for taking the time to complete this questionnaire. Please return it to us in the postage paid envelope. We may be in contact in the near future to go over your answers with you.

The Leg Ulcer Research Team

OPTIONAL

We would like to contact your GP to request a copy of your medical summary to provide additional information and verify the answers provided. This is entirely voluntary.

Please complete this slip of paper to confirm that you are happy for your GP to release this information:

I, _____ (PRINT NAME), am happy for a summary of my medical details to be released to the Leg Ulcer Research Team, Academic Surgery Unit, University Hospital of South Manchester, Southmoor Road, Wythenshawe, Manchester M23 9LT.

SIGNED _____   Date_____

Pain

None		25
While walking on uneven surface		20
While walking on even surface outdoors		10
While walking indoors		5
Constant and sever		0

Stiffness

None		10
Stiffness		0

Swelling

None		10
Only evenings		5
Constant		0

Stair climbing

No problems		10
Impaired		5
Impossible		0

Running

Possible		5
Impossible		0

Jumping

Possible		5
Impossible		0

Squatting

No problems		5
Problems		0

Supports

None		10
Taping, wrapping		5
Stick or crutch		0

Work activities of daily life

Same as before injury		20
Loss of tempo		15
Change to a simple job/ part time work		10
Severely impaired work capacity		0

Appendix 2: Olerud Molander Ankle Score (OMAS)

Pain (40 points)

- None   40
- Mild, occasional   30
- Moderate, daily   20

Severe, almost always present   0

Function (50 points)

- Activity limitations, support requirement
  - No limitations, no support   10
  - No limitation of daily activities, limitation of recreational activities, no support   7
  - Limited daily and recreational activities, cane   4
  - Severe limitation of daily and recreational activities, walker, crutches, wheelchair, brace   0
- Maximum walking distance, blocks
  - Greater than 6   5
  - 4-6   4
  - 1-3   2
  - Less than 1   0
- Walking surfaces

  No difficulty on any surface   5

  Some difficulty on uneven terrain, stairs, inclines, ladders   3

  Severe difficulty on uneven terrain, stairs, inclines, ladders   0
- Gait abnormality
  - None, slight   8
  - Obvious   4
  - Marked   0
- Sagittal motion (flexion plus extension)
  - Normal or mild restriction ($30°$ or more)   8
  - Moderate restriction ($15°-29°$)   4
  - Severe restriction (less than $15°$)   0
- Hindfoot motion (inversion plus eversion)
  - Normal or mild restriction (75%-100% normal)   6
  - Moderate restriction (25%-74% normal)   3
  - Severe restriction (less than 25% normal)   0
- Ankle-hindfoot stability (anteroposterior,varus-valgus)
  - Stable   8
  - Definitely unstable   0

Alignment (10 points)

Good, plantigrade foot, midfoot well aligned   15

- Fair, plantigrade foot, some degree of midfoot malalignment observed, no symptoms   8

Poor, non plantigrade foot, severe malalignment, symptoms   0

Appendix 3: American Orthopaedic Foot and Ankle Score (AOFAS)

Appendix 4: SF-12v2™ Health Survey Scoring Demonstration

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

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

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

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b Climbing <u>several</u> flights of stairs	○	○	○

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	○	○	○	○	○
b Were limited in the <u>kind</u> of work or other activities	○	○	○	○	○

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	○	○	○	○	○
b Did work or activities less carefully than usual	○	○	○	○	○

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

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

   How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	○	○	○	○	○
b Did you have a lot of energy?	○	○	○	○	○
c Have you felt downhearted and depressed?	○	○	○	○	○

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

Thank you for completing these questions!

Name: _____

Crutches:

    I did not use crutches   ☐

    I last used crutches on

Painkillers:

    I did not use painkillers at   ☐
all

    I last used regular
painkillers on

    I last used any painkiller
on

Stairs:

    I do not have any stairs   ☐

    I was able to walk up stairs
without a handrail on

Work:

    I do not work / I am   ☐
retired

    I returned to work on

Day-to-day activities (around the home/shopping etc):

    I was able to go about my   ☐
usual activities
immediately after my
injury

    I considered myself able
to return to my usual
activities on

Use of stocking:

    I was allocated to wear a   ☐
stocking

        If you discontinued using the stocking early, please give the reason and
date you last used it

Appendix 5: Injury Diary

Appendix 6: Modified wound healing assessment score

Follow-up data collection instrument.

_____

Patient name_____   Medical record no._____
Age_____   Sex ___M ___F
Date of follow–up _____
Days since suturing _____

Purpose of this visit
___ Wound check   ___ Suture removal

ANTIBIOTICS PRESCRIBED?   WOUND KEPT CLEAN?
___ No (0)   ___ No (0)
___ Yes (1)   ___ Yes (1)

Wound description

ERYTHEMA   WARMTH   TENDERNESS   DRAINAGE
___ No (0)   ___ No (0)   ___ No (0)   ___ No (0)
___ Yes (1)   ___ Yes (1)   ___ Yes (1)   ___ Yes
___ mm   ___ mm   ___ mm   ___ Purulent (1)
                                            ___ Serosanguineous(2)

Wound infection grade   **Infection treatment**
___ No infection (0)   ___ Local care only (compresses) (1)
___ Simple stitch abscess (1)   ___ Oral antibiotics (2)
___ Surrounding cellulitis greater   ___ IV/IM antibiotics (3)
       than 1 cm (2)   ___ Admission (4)
___ Accompanying lymphangitis or
       lymphadenitis (3)
___ Systemic symptoms (4)

Sutures removed for infection treatment?   ___ No (0) ___ Yes (1)