Beyond bandages: Modernising care for patients with venous leg ulcers

Title	Beyond bandages: Modernising care for patients with venous leg ulcers
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Publication Date	2025-10-15
Publisher	University of Galway

Beyond Bandages

Modernising Care for Patients with Venous Leg Ulcers

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June 2024

Acknowledgements

I am deeply indebted to the staff working in Leg Ulcer Centre Ireland for their efforts in supporting this research in what was a difficult time to be working in the health service.

I would like to thank the staff at University Hospital Galway for all of their help and valuable insights. In particular to the co-authors of each of the research papers included in this thesis, thank you!

Finally, to my supervisor Professor Stewart Walsh I extend my unending gratitude for his leadership and mentorship throughout this project and in my broader career. His expertise, encouragement and constructive feedback have been invaluable.

Publications and Presentations

Impact of a One-Stop Rapid Access Venous Ulcer Clinic on Inpatient Admissions

Published in *Phlebology*, 2023 Jun;38(5):341-347

DOI: 10.1177/02683555231174995

Axial Ablation Versus Terminal Interruption of the Reflux Source

Manuscript accepted for publication in *Vascular and Endovascular Surgery,* 16th June 2024

Podium presentation, European Society of Vascular Surgery Annual Scientific Meeting, Belfast, September 2023

Trial Protocol published in *Trials* 2022 Jun 10;23(1):483

DOI: 10.1186/s13063-022-06440-4

Hyperbaric Oxygen as an Adjunct in the Treatment of Venous Ulcers: A Systematic Review

Published in *Vascular and Endovascular Surgery* 2023 Aug;57(6):607-616

DOI: 10.1177/15385744231162924

Abbreviations

AA	Axial Ablation
AAVTIRS	Axial Ablation Versus Terminal Interruption of the Reflux Source
ABI	Ankle-Brachial Index
ASVAL	Ablation Sélective des Varices sous Anesthésie Locale
BMI	Body Mass Index
BWAT	Bates-Jensen Wound Assessment Tool
CCVUQ	Charing Cross Venous Ulcer Questionnaire
CEAP	Clinical, Etiological, Anatomical and Pathological classification
CHIVA	Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
DRG	Diagnosis Related Group
DVT	Deep Venous Thrombosis
ESCHAR	Effect of Surgery and Compression on Healing and Recurrence
EVRA	Early Venous Reflux Ablation
EVLA	Endovenous Laser Ablation
GSV	Great Saphenous Vein
HBOT	Hyperbaric Oxygen Therapy
HSE	Health Service Executive
HIPE	Hospital InPatient Enquiry
IVC	Inferior Vena Cava
IQR	Inter Quartile Range
LUCI	Leg Ulcer Centre Ireland
MMP	Matrix Metalloproteinase
MOCA	Mechanical Occlusion with Chemical Assistance
NIVL	Non-thrombotic Iliac Vein Lesions
OR	Odds Ratio
PHN	Public Health Nurse
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT	Randomised Controlled Trial

RFA	Radiofrequency Ablation
RNS	Reactive Nitrogen Species
RoB-2	Risk of Bias-2 tool
ROBINS-I	Risk of Bias in Non-Randomised Studies of Interventions tool
ROS	Reactive Oxygen Species
SFJ	Sapheno-Femoral Junction
SPJ	Sapheno-Popliteal Junction
SSV	Small Saphenous Vein
SMD	Standardized Mean Difference
SVT	Superficial Venous Thrombosis
TIRS	Terminal Interruption of the Reflux Source
TNF-α	Tumour Necrosis Factor α
UHG	University Hospital Galway
VCSS	Venous Clinical Severity Score
VLU	Venous Leg Ulcer
VTE	Venous Thromboembolism

Contents

Introduction

Venous leg ulcers (VLU) have long been an overlooked and understudied area in the practice of vascular surgery. Until relatively recently they received only token consideration by comparison to arterial disease. There are a number of reasons for this. First, no definitive medical solution was available and so care has been delivered mainly by community and wound care nurses; healing often occurred but was by no means guaranteed and often seen as somewhat of a lottery. Secondly, the chronicity of VLU has meant a lack of urgency. When VLU resolve, recurrence is common. In the past, VLU were therefore viewed as a chronic condition, with active management only required in the event of complications such as infection, pain, or profound exudate. Even then, aside from antibiotics for infection, options for managing complications were sparse, and remain so. Finally, and perhaps the most important reason for overlooking VLU, is a common under-appreciation of their socio-economic impact.

For patients, VLU lead to physical limitation with reduced mobility, pain, and social isolation which often adversely affect patients' quality of life[1]. For health systems, the continued dressings, sporadic hospitalisations and time of nursing, administrative, diagnostic and vascular surgical staff is a formidable economic burden.

Recently, the focus in VLU care has shifted somewhat as it has been recognised that reflux ablation can shorten the time that patients suffer with their VLU, and health systems expend resources treating them. Delivering this requires recalibration of existing services as well as significant research to define future strategies.

Relevant Venous Anatomy

The venous system of the lower limbs consists of deep veins, superficial veins, and perforators. Superficial veins drain the skin and subcutaneous tissue, while deep veins drain the rest of the leg. Perforators join the two, allowing the passage of blood from superficial to deep. Both the deep and superficial systems are aligned to the limb, with a series of valves along their length. There are two main axial veins in the superficial system, the great and small saphenous veins, though there is enormous variation in venous anatomy. The small saphenous vein (SSV) typically drains into the deep system via the popliteal vein at or around the level of the knee joint, at the sapheno-popliteal junction (SPJ), while the great saphenous vein (GSV) drains into the femoral vein at the sapheno-femoral junction (SFJ). A prominent valve is typically found at each of these junctions. These superficial axial veins drain an interconnected plexus of smaller superficial veins. It is typically these smaller superficial veins that become dilated and tortuous to become visible varicose veins. In addition to the SFJ and

SPJ, perforators drain from the superficial veins to the deep system in the calf in particular. In these veins the valves are aligned to permit flow in a superficial to deep direction.

The deep venous anatomy of the leg for the most part mirrors the arterial supply, though often with paired veins, as in the anterior tibial, posterior tibial and peroneal veins in the calf, which join to form the popliteal vein. This becomes the femoral vein in the thigh and is joined in the proximal thigh by the profunda femoris vein, coursing proximally through the groin to the external and common iliac veins in the pelvis. The bilateral common iliac veins join to form the Inferior Vena Cava (IVC).

Classification and Terminology

VLU can reasonably be considered as the end-stage of the broad spectrum of venous disease. This is reflected in the numerical progression in the commonly used Clinical, Etiological, Anatomic and Pathological (CEAP) classification[2]. This system, devised by expert consensus, is used to describe and categorize venous disease, rather than stage severity. However the clinical portion of the classification categorises venous disease in an ordinal manner, from telangiectasia through uncomplicated and complicated varicose veins with oedema or skin changes, to healed and finally active VLU. This system was developed to provide a standardized method for assessing and communicating the severity of venous disease. In particular this classification system aids in treatment planning, assessing disease progression, and comparing outcomes across different patient cohorts and research studies. In the past a whole host of varying terminology, diagnostic criteria and the loose application of these, made it impossible to determine even the scale of the problem of venous disease.

Some of the most basic terminology around venous disease can be misleadingly similar, such as chronic venous disease (CVD) and chronic venous insufficiency (CVI), unhelpfully, these are often used interchangeably. Meanwhile venous hypertension, which helps in the understanding of the disease, is an underutilised term. Classification of reflux in the CEAP system divides superficial and deep reflux, but while attempts have been made to better classify the various types of reflux, this leads to an impractical number of different classifications. The result of this is that there is no uniform terminology for the classification of types of reflux.

Chronic Venous Disease Versus Chronic Venous Insufficiency

Chronic venous disease is a broad term encompassing all forms of lower limb venous pathology, including CVI. Symptoms can occur with CVD, and most commonly include leg pain, fatigue, heaviness and itching[3, 4], though symptoms are not an essential feature. Varicose veins are tortuous dilated superficial veins and are the most frequent manifestation of CVD, though they may remain asymptomatic. In particular smaller reticular veins, commonly referred to as thread or spider veins are

C	**Clinical**	
	C_0	No visible or palpable signs of venous disease
	C_1	Telangiectasia or reticular veins
	C_2	Varicose veins
	C_{2r}	Recurrent varicose veins
	C_3	Oedema
	C_4	Changes in skin and subcutaneous tissue secondary to CVD
	C_{4a}	Pigmentation or eczema
	C_{4b}	Lipodermatosclerosis or atrophie blanche
	C_{4c}	Corona phlebectatica
	C_5	Healed
	C_6	Active venous ulcer
	C_{6r}	Recurrent active venous ulcer
E	**Etiological**	
	E p	Primary
	E s	Secondary
	E si	Secondary – intravenous
	E se	Secondary – extravenous
	E c	Congenital
	E n	No cause identified
A	**Anatomical**	
	A s	Superficial
	A_d	Deep
	Ap	Perforator
	A_n	No venous anatomic location identified
P	**Pathological**	
	P r	Reflux
	P o	Obstruction
	P r,o	Reflux and obstruction
	P n	No pathophysiology identified

Table 1: CEAP Classification

extremely prevalent and usually asymptomatic. Correlations of symptoms with the presence of varicose veins[5] or with patterns of reflux[6] have been shown to be poor.

Chronic venous insufficiency refers to a more advanced stage of venous disease. It is characterized by chronic changes in the skin and subcutaneous tissues of the lower leg, caused by venous hypertension. CVI is typically better correlated with reflux than milder forms of CVD, or can also arise as a result of venous obstruction, such as in post-thrombotic syndrome. Clinical manifestations are more severe, including venous eczema, skin pigmentation or lipodermatosclerosis. Pigmentation occurs as a result of haemosiderin deposition, while lipodermatosclerosis is characterised by thickening of the skin and fibrosis of the subcutaneous fat layer. These changes correspond to CEAP stage C4. VLU occur as a final severe manifestation of CVI. The term CVI predates the CEAP classification. While previously it was applied to a broader range of clinical findings, it is now taken to correspond to clinical grades C4 - C6. VLU are the final and most severe manifestation of CVI, with C5 denoting healed and C6 active ulcers.

There can be some debate as to whether CVD constitutes a true pathology or if it could be considered in a manner analogous to diverticulosis of the colon. Certainly there are similarities in the prevalence of both conditions and their tendency to occur in a latent fashion, without symptoms for the majority of cases. There are pathophysiological features of CVD however that mitigate against such a categorisation. The term venous hypertension is useful in this regard.

Venous Hypertension, Resting Venous Pressure and Ambulatory Venous Pressure

Venous hypertension refers to elevated pressure within the venous system of the lower limbs and can result from a number of different pathologies such as venous reflux and venous obstruction. Importantly, unlike arterial hypertension, venous hypertension does not involve an elevation in the actual pressure within the vein. Ambulatory venous pressure refers to the pressure in the veins of the lower leg on standing and walking. In the standing position the normal pressure in the veins is typically in the region of 90mmHg[7] which we shall refer to throughout as the resting venous pressure. With exercise or, for example, if the foot is elevated, this pressure reduces dramatically, but returns gradually to resting pressure again on return to the standing position[7].

In patients with venous hypertension, this usually gradual return to the normal standing pressure can occur more quickly or, the normal drop in the ambulatory pressure can be lost. Venous insufficiency, ulcers, varicose veins and other venous pathologies such as venous thrombosis are often considered in medical student teaching, and therefore among the broader medical community, as disparate entities. All of these conditions however lead to or result from venous hypertension. It is the common pathway by which a variety of underlying conditions produce the clinical manifestations of CVI and alleviating venous hypertension is therefore the target of all venous interventions. The pathophysiology of venous hypertension, venous reflux and their relation to CVI and VLU are discussed in detail later.

<u>Reflux Terminology</u>

Reflux can affect any site in the venous system either alone, in continuity with other areas, or at multiple non-contiguous sites. Due to the lack of uniform terminology in the literature, for clarity throughout this document; junctional reflux refers to reflux in the SFJ or SPJ, axial reflux is the term applied to full length or functionally full length GSV or SSV reflux, and segmental reflux will refer to any reflux in a limited length of the saphenous veins or any reflux confined to tributaries. Deep segmental reflux will be used to differentiate segmental reflux in the deep system from all other segmental reflux.

Normal Venous Physiology

The venous system's primary function is to return blood to the heart. Venous return to the right atrium must be maintained at a level which matches cardiac output due to the closed nature of the circulatory system. A second vital function is to act as a high capacity blood storage reservoir with an important role in cardiovascular haemostasis, but this aspect of the venous system is largely outside the scope of this thesis.

The pressure in a given vein is largely determined by its position relative to the right atrium. In the supine position, the pressure at the venous end of the capillary is the residual pressure transmitted from the arterial inflow through the capillary bed, and is approximately 12-18mmHg[8]. Pressures in the extremities vary widely however depending on their position relative to the right atrium. In the arm and forearm, venous pressures reflect the vertical distance between the atrium and the first rib when the arm is dependent, but veins collapse when the arm is elevated. Likewise in the lower limb venous pressure is determined at rest by the vertical height below the right atrium, while elevation of the foot decreases the pressure in the

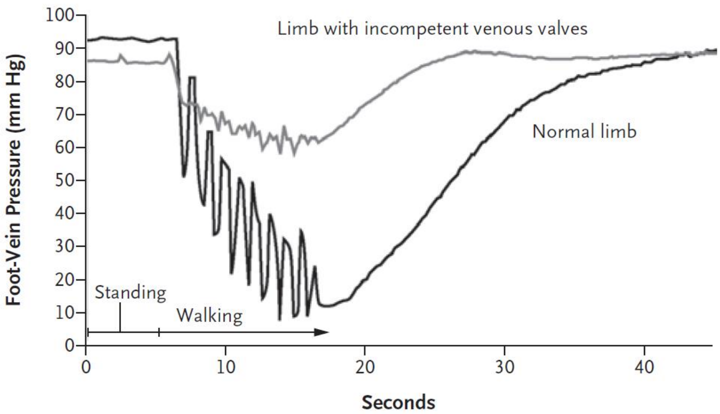

Figure 1 Action of the Musculovenous Pump in Lowering Venous Pressure. Reproduced from Coleridge Smith with the publisher's permission

veins of the foot and lower leg in line with the vertical height of elevation. In the standing position blood in the IVC, iliac and lower limb veins constitute a continuous column of fluid. The weight of this column of fluid leads to a predictable rise in venous pressure as one moves down the leg, at a rate of 0.77mmHg/cm[8]. The normal pressure within the right atrium is around 4mmHg, while the pressure in the veins of the foot may be in the region of 90mmHg, determined largely by the height of the patient, though there is some inspiratory variation and alterations in intra-abdominal pressure as seen for example in pregnancy, ascites or obesity can also affect the value seen. This pressure differential between the lower limb and the right atrium facilitates venous return from the peripheries, though to achieve meaningful flow against gravity another mechanism is required. The soft thin walled nature of veins means than as the muscles of the lower limb around them contract, the veins are compressed, forcing blood out of them. The presence of valves directs the flow from this passive compression[9]. This process is termed the muscle pump of the lower limb[7, 10].

Contraction of the muscles of the thigh has some effect on venous return, but it is much less than that of the calf, where contraction of the soleus and gastrocnemius can produce pressures of up to 200mmHg[11], and lead to 40-60% of the venous volume to be ejected in a single contraction[12]. The foot also acts as a primer-pump, analogous in the 'peripheral-heart' to the atria, generating flow into the calf pump of up to 25ml with each step[13]. The sequential functions of the foot, calf and thigh pump mechanisms create an effect analogous to systole, combined with the prevention of bidirectional or retrograde flow by venous valves. This drives the column of blood toward the heart thus reducing the pressure in the deep veins with each step so that ambulatory venous pressure falls to 30mmHg or less (Figure 1)[14]. In the normal state, during calf relaxation veins refill from capillaries and blood also flows in a superficial to deep direction via perforators. Cessation of exercise abolishes the action of the lower limb muscular pump, and gradual venous filling from capillary beds slowly restores the column of blood from the right atrium to the veins of the foot. This returns the pressure within these veins to the resting venous pressure.

Pathophysiology of Venous Hypertension

As already touched upon, venous hypertension is a quite different entity to hypertension as most clinicians are accustomed to it in the arterial system. Venous hypertension is the prolonged exposure of the venous system to pressures close to the resting venous pressure in the standing position. It occurs when there is a failure of venous pressure to fall adequately in response to exercise, premature return to resting pressure after exercise, or both. It is the common pathway by which multiple causes of venous disease lead to venous insufficiency and in some cases VLU. It can't be overstated that the simplest way in which patients have a prolonged exposure to resting venous pressure is from prolonged standing. This can produce symptoms which are in keeping with venous disease even in the presence of normally functioning veins, and is an unfortunate reality for many people, especially those working in service industries. This is not pathological, though prolonged standing is also a significant risk factor for venous reflux. When venous reflux arises from such environmental factors it is classed as primary CVD. A familial predisposition may also play a role.

Secondary CVD can arise from a number of conditions either affecting the veins themselves or any other part of the process of venous return. When venous hypertension arises as a result of anything other than primary venous reflux it is classed as secondary CVD. Venous obstruction is the main cause of secondary CVD.

Reflux and obstruction are the two main mechanisms by which venous hypertension occurs and are discussed in greater detail in the following sections. It is important to note however that venous hypertension is a multifactorial problem. Reflux is a particular focus of attention because superficial reflux can be treated surgically, but there are many cases when the role of other factors in creating venous hypertension are more relevant. Some of these are modifiable and some not.

<u>Obesity</u>

Excess body weight is associated with increased venous resistance. This is thought to be explained mainly by the obstructive effect of fat mass on pelvic veins, and increased abdominal pressure caused by abdominal wall mass. These effects persist when supine. Obesity is also associated with release of cytokines and other adipose derived hormones which affect vessel walls and microcirculation. These may also increase venous resistance, though their effect has not been fully delineated. Musculovenous pump function actually improves in obesity, though the association with sedentary lifestyle may negate some of this effect. CEAP clinical stage is more advanced in obese patients than non-obese patients with comparable anatomical patterns of venous incompetence[15].

<u>Muscle Weakness</u>

Muscle weakness can occur as part of the normal aging process, or as a result of muscle atrophy either from a pathological process or simply arising from a sedentary lifestyle. If the gastrocnemius and soleus are unable to contract with sufficient force, this will reduce the efficacy of the calf muscle pump. Aside from weakness intrinsic to the muscle, there are a number other conditions that can affect the capacity of the pump by impairing muscle activity.

Conditions affecting the nerves innervating the lower extremities, such as diabetic neuropathy or other causes of peripheral motor neuropathy can also be a cause of muscle weakness. Likewise injury to the spinal cord or peripheral nerves.

Ankle Immobility

Even with an otherwise functioning neuromuscular unit, impairment of ankle movement creates a similar effect. Arthritis or a history of ankle surgery can reduce a patient's plantar flexion ability, which is the principle function of the soleus and gastrocnemius muscles. In the case of ankle fusion surgery this movement is prevented entirely, almost completely abolishing the effect of the calf muscle pump[16, 17]. This has been independently linked with non-healing of VLU[18].

Venous Reflux

Venous reflux was first described in real detail by Trendelenburg. Put simply, it is the retrograde flow of blood in a vein. It occurs in both the deep and superficial veins of the legs and is the most common pathology contributing to venous disease[19], with superficial reflux seen in 88% of patients with VLU[20]. Deep venous reflux is undoubtedly important in the genesis of venous hypertension and CVI, as it is associated with increasing CEAP class[20, 21], especially in the setting of combined superficial and deep reflux[20]. However, reflux in the deep veins is usually not amenable to surgical treatment[22]. Superficial reflux can be treated by numerous modalities and is also a far more common condition with nearly half of VLU demonstrating isolated superficial reflux[20].

By definition, a significant degree of retrograde flow means that the valves in an affected vein segment cannot be functioning adequately. Valve dysfunction is therefore universal to venous reflux. Not all valve dysfunction occurs as a result of an intrinsic valve pathology however. Venous hypertension leads to distension of the vein wall; this can distort the valve leaflets or distend the annulus of the valve affecting the ability to form a seal, thus permitting reflux[23].

Venous reflux can be primary or secondary. Secondary reflux accounts for 25% of all cases[21]. When valves have been injured by some external factor such as the damage caused by DVT in the case of post-thrombotic syndrome, or scarring and other damage due to trauma or surgery, this can lead to valve failure and secondary reflux. Other causes of venous obstruction can also lead to secondary reflux without direct damage to the valves themselves, if obstruction leads to venous hypertension which causes the veins to become distended. Most secondary reflux occurs as a result of venous obstruction with or without recanalization, with reflux and obstruction present together in 65% of post-thrombotic limbs[24] and history of DVT shown in up to 25% of VLU[25].

Diseased or varicose veins demonstrate multiple pathological changes from healthy veins, in particular degradation of the extracellular matrix[26] and damage to the endothelium[27]. Endothelial dysfunction can lead to release of pro-inflammatory mediators, as well as growth factors such as basic fibroblast growth factor and platelet-derived growth factor from endothelial cells[28, 29]. Increase of these pro-inflammatory mediators leads to leukocyte activation[30, 31], which increases inflammatory cell proliferation and fibrosis as well as upregulating proteases in the extracellular matrix such as matrix metalloproteinases (MMP)[28, 29], while growth factors contribute to smooth muscle cell proliferation[32]. Proliferation leads to medial thickening[33], but involves dedifferentiation of smooth muscle cells from contractile subtypes to the proliferative and synthetic phenotypes[29, 32], and is also accompanied by cell atrophy[26, 28, 34]. The net effect of this is disorganised smooth muscle with dampened venous tone[32, 34] and some smooth muscle cell migration into the intima also occurs[34]. The balance between MMP and their inhibitors is essential for extracellular matrix homeostasis[23, 35] and their dysregulation, which is also implicated in aneurysm formation[36], has been observed in varicose veins[35]. The matrix has important roles in cellular activity in the media[36], but also as a structural framework. Degradation of the matrix, with reduced elastin[37, 38] and changes in the balance of collagen subtypes from elastic type-III collagen to less elastic type-I collagen[37, 39], decreases the integrity of the vein wall with increased fibrous tissue and a relative decrease in elastic fibres and smooth muscle function[26]. While inflammation can, as described, increase MMP activity, they can also be upregulated as a result of vessel wall stretch[23], providing a mechanism whereby venous distension can create a vicious cycle of extracellular matrix degradation and further distension.

Slower flow, as seen in venous hypertension and reflux can lead to reduced wall shear stress. Shear stress inhibits leukocyte adhesion molecules and other membrane proteins involved in the maintenance of normal endothelial function[40]. Reduced shear stress therefore contributes to endothelial dysfunction, as can ischaemia as a result of stasis[29]. Thus there is a histopathological basis for distension and stasis to lead to venous dysfunction even if they occur without demonstrable reflux.

Since Trendelenburg's time, primary venous disease has been attributed to primary reflux as a result of valve dysfunction, leading to the prevailing 'descending theory' of venous reflux progression. The frequency of saphenous vein reflux in patients with symptomatic CVD has meant that venous reflux has traditionally been attributed to the failure of the valves at the saphenous junctions, leading to distension and in turn reflux in the superficial axial veins, which propagates distally in a cycle of distension, reflux and venous hypertension, with progressively smaller and more distal veins demonstrating reflux, and superficial tributaries visible in the form of varicose veins[41].

More recently this theory has been called into question, primarily by the dramatic improvement in our ability to assess the anatomy of venous reflux with colour-flow Doppler ultrasound, but also by the histopathological findings discussed above. The descending theory was based on examination of patients and suffices as an explanation for those findings discernible on examination. It is based on the assumption that where reflux is not demonstrated proximally on exam, it is present but undetectable. It was previously impossible to tell on exam whether, for example, an incompetent proximal GSV is due to an incompetent SFJ, or actually arises from the GSV itself with a competent SFJ. Ultrasound however can answer this question. It is now possible to accurately confirm reflux in veins or segments of veins and repeatedly it has been shown that reflux in superficial veins does not necessarily originate in a manner in keeping with the descending theory.

Numerous studies have shown the SFJ, SPJ, GSV and SSV to all be normal in many limbs with distal reflux and CVD[42-44]. Even in limbs with reflux in the proximal GSV or SSV it has been shown that this does not necessarily mean junctional reflux is present[45-49], nor is the converse true; an incompetent SFJ may coexist with a normal GSV[50]. Within the GSV itself it has been reported that most reflux is segmental[42, 51], calling into question the role of axial reflux in the spread of reflux from proximal to distal, or junctional to axial.

In addition, it has been shown that tributary reflux is more common in younger patients, with nearly half of the legs in one study of varicose vein patients demonstrating normal saphenous veins[52]. This earlier onset has been taken as a potential indicator that perforator incompetence is the true site of origin of venous reflux, and that incompetent perforators allow superficial transmission of the force of the calf muscle pump, leading to distension of the axial superficial veins and reflux as a result.

Finally, it has been shown in numerous studies that deep vein reflux is improved in many cases by treatment of reflux in the superficial veins[53, 54]. This cannot be explained by the descending theory.

The 'ascending theory' of venous reflux[19, 55] proposes that reflux originates in superficial tributaries and propagates in a centripetal direction to in turn affect the axial superficial veins, followed by the junctions and then deep veins. While the above evidence queries the validity of the descending theory, others argue clearly in favour of the ascending theory[56, 57] which has led to much debate and multiple studies have attempted to establish the origin of venous reflux[19, 28, 55, 58]. It seems likely that neither of these theories is universal and a pragmatic view is that reflux originates from several sites and may progress in an ascending or descending direction[19, 55, 59]. Which direction, or indeed whether or not it progresses at all, probably depends on myriad individual patient factors. Involvement of the axial veins does increase the haemodynamic significance of reflux however[60], and is associated with more severe grades of CVI[61].

The relative impact of various contributing factors on development of reflux is difficult to quantify. Patients with a positive family history have been shown to be 20 times more likely to develop CVD in one study[62], while amongst patients with varicose veins a family history was three times more likely than in those without varicosities[63]. While there is no coherent genetic explanation that has been implicated in the development of reflux, genetic studies have implicated structural proteins including collagen, elastin, and tropomyosin[64]. Up-regulation of genes associated with fibrosis, coding for proteins such as type 1 collagen, tubulin, actin, and tropomyosin has also been shown in varicose veins[65]. Numerous genetic disorders lead to varicosities, such as in Klippel-Trenaunay Syndrome, but these genetic disorders are so rare compared to chronic venous disease in general that genetics alone cannot be implicated in the vast majority of cases.

The prevalence of chronic venous disease increases with age. Longer lifetime exposure to the effects of gravity no doubt promotes reflux, while other influences such as weakened muscle and reduced mobility[66] degrading the function of the lower limb muscular pump contribute further to venous hypertension. Immobile elderly patients are one of the groups which most often suffer from VLU.

The influence of gender is uncertain. Many studies report the prevalence of varicose veins as being higher in women[67], however the Edinburgh Veins Study reported the opposite in a cross-sectional population[68]. This may be a function of affected women presenting more frequently than men[5] and thus appearing more commonly in datasets derived from varicose vein patients rather than the wider population.

Pregnancy is certainly a factor leading to more reflux in women however. The risk of developing varicose veins increases with parity[69], though this does not necessarily mean axial reflux is increased[70]. Hormones such as relaxin, oestrogen and progesterone are upregulated, and can lead to increases in vein capacitance[28], accommodating the increased circulating volume seen in pregnancy. As with any cause of venous distension, this can contribute to reflux, while a degree of venous obstruction occurs with the effect of the gravid uterus.

Obesity contributes to reflux by increasing venous resistance. This cannot be reliably quantified clinically so there is no standard at which primary reflux occurring in the setting of obesity can be differentiated from secondary reflux due to obesity. This is one of the difficulties in establishing the epidemiology of chronic venous disease, as different populations have different combinations and severity of risk factors.

Venous Obstruction

Venous obstruction is the other major category of venous disease. While less common, it can lead to severe symptoms. Obstruction can be considered in terms of intrinsic and extrinsic processes. Intrinsic venous obstruction most commonly occurs as a result of venous thrombosis. Superficial and Deep Venous Thrombosis (SVT and DVT) can occur at any level. SVT, also known as superficial thrombophlebitis, has relatively insignificant haemodynamic effects compared to DVT. SVT can contribute to impairment of venous return if occurring alongside other causes, but is rarely more than a minor contributing factor though it is a risk factor for DVT. DVT is the most common secondary cause of venous hypertension and CVI[71]. Thrombus can occlude the affected vein, while even non-occlusive thrombus will increase venous resistance and can be flow limiting. Resolution of thrombosis can occur naturally or with clot-removal procedures such as thrombolysis or thrombectomy, but even after resolution venous return can continue to be compromised. Damage caused to the valves at the site of old thrombosis can give rise to secondary venous reflux, while venous resistance can remain increased, thus both reflux and obstruction can contribute to post-thrombotic venous insufficiency.

Congenital obstruction of venous return can take many forms. The process of embryological formation of the IVC is complex, and multiple variants may occur, ranging from a duplex IVC, to IVC atresia or complete absence of the IVC. Such anomalies are a rare cause of venous obstruction, though IVC agenesis may be a contributing factor in up to 5% of DVTs occurring under the age of 30[72].

The normal anatomy of the aortic bifurcation and confluence of the common iliac veins means that some compression is always liable to occur; where the left common iliac vein passes behind the right common iliac artery the vein can be compressed between the solid bone of the lumbar vertebral body posteriorly and the artery anteriorly. May-Thurner Syndrome is the name that has come to be commonly used to refer to iliac vein thrombosis related to compression in this area, though the original definition of May-Thurner Syndrome related to the development of fibrous bands in the iliac vein, sometimes called venous spurs, as a result of repeated compression of the vein in this area[73]. Thus one could argue for May-Thurner syndrome to be classed as a venous pathology, but it certainly arises as a result of extrinsic compression.

Today, with the proliferation of cross-sectional imaging, many more instances of iliac vein compression are found incidentally or on investigation for a cause of venous hypertension. These are broadly termed Non-thrombotic Iliac Vein Lesions (NIVL), though this is a collective term and often it is more useful to consider them not as a heterogenous group but in terms of their underlying cause. Extrinsic compression commonly occurs during pregnancy and while this is obviously not a pathological process it can lead to significant increases in venous hypertension because the effect of the gravid uterus causes compression of the pelvic veins. This is in addition to the changes in venous function during pregnancy mentioned already. Other space occupying lesions such as malignancy of the pelvic organs or non-malignant masses such as fibroids can also lead to obstruction of venous return. Retroperitoneal fibrosis, post-operative scarring, or even endometriosis can also lead to NIVL with or without compression.

The body compensates for chronic obstruction by a number of means, often dependent on the underlying pathology, for example recanalization may occur following a DVT. Probably the most important compensatory mechanism for obstruction at any level and a process common to almost all forms of venous obstruction is the ability to recruit collateral pathways to maintain venous drainage. This is an important factor in determining the effect of any obstructive process on venous hypertension and clinical presentation.

Venous obstruction can severely compromise venous return and the magnitude of this effect is usually determined by the site of obstruction. In general, the more proximal the lesion the greater the impact. Flow through the proximal veins is higher by virtue of the additive effect of multiple veins converging and the increasing calibre of the veins as they course proximally. Rate of flow through any vein or artery obeys Poiseuille's law, in which flow rate is determined by pressure times π, times the fourth power of the radius, divided by 8 times the viscosity of the fluid, times the length of the tube.

$$Q = \frac{P\pi r^4}{8\eta l}$$

Because of this, any reduction in the radius of a vein is magnified to the power of 4. Stenosis or occlusion of a large vein can therefore be particularly difficult to compensate for. As an example, an 8-10mm vein such as an external iliac requires 16 collaterals of 4-5mm to maintain the same flow around an occlusion. The larger calibre of proximal veins means that the more proximal an obstruction or occlusion occurs, the more significant the clinical impact tends to be.

Venous Leg Ulcers

The pathophysiology of VLU is complex and incompletely understood. There remains no doubt over the role of venous hypertension, with a linear relationship between the incidence of ulceration and increases in ambulatory venous pressure above 30 mm Hg. Ulceration is also associated with a 90% venous refill time of <20 seconds[74]. The pathological processes that lead from venous hypertension to VLU have not been described satisfactorily.

There are have been many theories regarding the pathogenesis of venous ulceration, from arteriovenous shunts or tissue hypoxia due to venous stasis, which have not been supported by physiological or pathologic findings, to more recent theories which associate microcirculatory abnormalities caused by venous hypertension with the generation of an inflammatory response.

Browse and Burnand proposed the fibrin cuff hypothesis in 1982[75]. Venous hypertension being transmitted to the superficial veins of the skin and subcutaneous tissue of the gaiter area was thought to lead to distension in capillary beds, with resultant widening of endothelial pores. This would allow larger molecules to escape into the interstitial fluid, of which fibrinogen was thought to be most important as it would lead to the formation of fibrin cuffs which they observed histologically. These were thought to act as a barrier to oxygenation and diffusion of other nutrients. Fibrin cuffs have not been demonstrated to be a real barrier to diffusion however[76], and are not universally present in VLU[77].

Coleridge Smith *et al*. proposed an alternative hypothesis in 1988[78]. Venous hypertension was thought to have the knock-on effect of stasis in capillaries. This was thought to trap leukocytes which then release toxic oxygen metabolites and proteolytic enzymes. These would damage capillaries, increasing their permeability, creating further oedema, promoting additional leukocyte trapping as well as extravasation of fibrinogen and other plasma proteins causing fibrin cuffs as above. Trapped leukocytes would additionally damage perfusion of the affected capillaries, resulting in ischemic areas. The flaw with this theory and its supporting evidence is that it is difficult to determine whether the 'leukocyte trap' is a cause or effect of the local inflammation.

Tumour necrosis factor alpha (TNF-α) may be a contributing factor. It can decrease fibrinolytic activity, and secondarily induces the formation of fibrin cuffs. It is upregulated by both increased permeability and leukocyte activation[79]. Extravasation of macromolecules may also contribute by causing a functional inhibition of endogenous growth factors making them unable to maintain tissue integrity[76].

Finally, activated monocytes and platelet-monocyte aggregates have been found to be elevated in VLU[80], while increased circulating levels of these aggregates have been shown in all classes of CVI[81] and are also linked to valve dysfunction as they can cause endothelial damage. The activated monocytes release many of the macromolecules discussed above and activated platelets can also release TNF-α. Why monocytes become activated in the first instance, or aggregates form remains unexplained however.

None of these theories provides a complete and uncontested explanation of VLU development, and many factors remain unexplained. For instance the role of prothrombotic states; patients with VLU have been found to have a 41% prevalence of micro-thrombi[82]. Is this an effect of stasis leading to both distension and thrombus formation independently?

It may well be the case that multiple disease processes resulting from venous hypertension may each play a role in certain conditions.

Management of Venous Hypertension

Elevation has been a recommended treatment for the management of VLU as far back as Asclepius and Hippocrates, and bandaging therapy for ulcers is mentioned in the Old Testament. These remain the basic tools in the management of venous hypertension and VLU today. Elevation is very effective, and bed rest can reduce the venous pressure at the ankle to about 12-15mmHg but this is not a very practical solution for anyone hoping to continue their normal daily activities, and the associated prolonged inactivity required for effective elevation can contribute to a decline in mobility, in particular among the elderly. Nevertheless, elevation when possible should still be encouraged for patients with venous hypertension, alongside an appropriate degree of exercise, and can reduce oedema, help to reduce exudate from VLU and help skin changes to regress[83]. Even in those undergoing other forms of treatment these general measures remain an important feature of CVI and VLU management. To facilitate patients continuing with their day to day routine, compression has been used to reduce the degree of venous hypertension in the leg. While compression and ablation of reflux are suitable for a broad spectrum of stages of CVD, this thesis is particularly directed toward the management of VLU.

Compression for Venous Leg Ulcers

When general measures are not successful in managing CVI, compression remains the first line intervention for many patients. This can be done using some type of graduated elastic compression hosiery or bandages. In either case, pressure should be highest at the ankle, and gradually decrease proximally.

Hosiery can take the form of stockings or wraps, with the former more commonly used, and the latter generally reserved for those who struggle with putting on stockings. Thigh length stockings seem to confer little if any benefit over knee length[84, 85], and tend to be more difficult to put on. European Class II stockings deliver a pressure at the ankle in the region of 25-35mmHg and are typically the preferred option for patients with CVI or VLU without arterial insufficiency. Even though stockings with a higher degree of compression may provide greater benefit and have been shown to reduce VLU recurrence, compliance is a greater problem and non-compliance is positively correlated with VLU recurrence[86].

In patients with active VLU, hosiery is generally not the preferred option as issues such as exudate and odour can mean that reusable hosiery is not practical. Some smaller or dry ulcers may be amenable to hosiery, but in general bandages are preferred for active VLU. There are numerous forms of bandage systems. The main differences are the elasticity of the bandages involved and the number of layers involved between the bandages themselves and other component layers such as wool or dressings, as in the Unna boot which uses paste as a primary layer. Compression has been shown to be effective, though the precise mechanism for this is not fully understood. A large Cochrane review examined 48 randomised trials examining various aspects of compression for VLU[87]. It found that compared to no compression, compression is effective in achieving healing of VLU. In addition, multi-component systems are more effective than single-layered, though there was no difference between four-layer and two-layer bandaging systems. A four-layer system is more effective than short-stretch bandaging. The Unna boot is a two or four-layer compression system with a base layer of gauze soaked in zinc-oxide paste, and it has not been shown to be superior to paste-free equivalents. In the Irish setting the two most commonly used commercially available bandage systems are Coban™ (3M, Maplewood, Minnesota, USA) and Profore™ (Smith & Nephew, Watford, UK). The main caution with compression therapy is the potential for mixed arterial and venous insufficiency, though excessively tight application of bandages may cause injury even in the absence of otherwise significant perfusion issues.

There are a wide variety of topical dressings which can be applied as a primary dressing under compression and these have been widely investigated. Another large Cochrane review and network meta-analysis collating the outcomes of 78 randomised trials found no evidence that the dressings or topical treatments applied beneath compression affect ulcer healing[88]. Often in clinical practice the type of dressing used is dictated mostly by trial and error, with patient tolerance the main guiding influence and avoidance of pain or adverse reactions such as allergy.

Small ulcer area, shorter duration, decrease in calf circumference with compression and early signs of improvement are all associated with better outcomes in VLU being treated with compression, while Body Mass Index (BMI) >33, sedentary lifestyle, a history of wound debridement, and deep ulcers at presentation are poor prognostic indicators[18].

Treatment of Reflux for Venous Leg Ulcers

There are two landmark trials which guide the management of reflux in patients with VLU specifically. The Effect of Surgery and Compression on Healing and Recurrence (ESCHAR)[89, 90] study and Early Venous Reflux Ablation (EVRA)[91] trial have very much changed the landscape in recent years.

The ESCHAR trial was a United Kingdom based, multi-centre, randomised trial assessing the impact of surgical treatment of axial reflux, in addition to compression, on healing and recurrence. Patients were randomised to receive compression alone, or SFJ ligation, stripping of the GSV and phlebectomies, or ligation of the SPJ and phlebectomies, depending on the location of reflux, as well as compression. Legs with VLU that were currently active or had healed within the preceding six months were eligible for inclusion, and the trial had 2 primary outcomes; healing and recurrence. 500 legs were randomised, though not all were eligible for analysis for the healing outcome because they had healed prior to enrolment. 341 were eligible for analysis for healing, while all 500 were eligible for the recurrence endpoint. Both arms had achieved a 65% rate of ulcer healing at six months. By the end of the first year of follow up, the recurrence rate was 28% in the compression arm but only 14% in the surgery arm, a 50% relative risk reduction. With follow-up to 5 years, recurrence was up to 56% in the compression arm but 31% in the surgery arm. There was still no significant difference in ulcer healing at 5 years.

The EVRA trial was another United Kingdom-based, multicentre, randomised trial aiming to assess the effect of reflux management on VLU healing, though this time using endovenous ablation rather than surgery. One important aspect of this trial is the focus on early treatment, and VLU were only considered eligible if they were present for less than 6 months. This is often either overlooked, or levelled as a criticism of the trial design, though the principle was there in the title. The aim was to assess the effect of early ablation, not simply ablation of anyone with an ulcer. This has important implications for how services are delivered, which will be discussed further later.

Between 2013 and 2016, 450 patients with active VLU were recruited and randomised to compression alone or compression plus endovenous ablation. Treatment to the lowest point of reflux was a specific requirement for those receiving ablation but pragmatically, the method of ablation was left at the discretion of the treating surgeon. Endovenous foam and thermal techniques such as radiofrequency ablation (RFA) or endovenous laser ablation (EVLA) were employed. The primary outcome was time to ulcer healing, which was significantly shorter with ablation, at 56 days, compared to 82 days in the compression cohort. A remarkable aspect of the EVRA findings is that the significant improvement in ulcer healing with ablation was seen despite the control arm having the best healing rates with compression that have ever been reported in a randomised trial. 76.3% of ulcers healed in compression by 6 months. One interpretation of this is the importance of early high-quality treatment, even if only with compression.

Importantly, though it has elsewhere been reported that foam ablation achieves inferior technical success than thermal ablation[92], no difference was seen in this trial between the rates of ulcer healing in those treated with foam compared to thermal techniques. Other reflux treatment options that utilise non-thermal techniques include Mechanical Occlusion with Chemical Assistance (MOCA) and cyanoacrylate glue, injected via a customised catheter into the GSV to seal it. Mechanochemical ablation involves a device which rapidly rotates a fibre within the vein while injecting sclerosant, as the whole device is slowly withdrawn. The physical trauma to the endothelium combined with the concurrent sclerosant delivery causes the vein to fibrose.

The importance of treating junctional incompetence has been an area for consideration, based on the debate between the ascending and descending theories of reflux progression. For many years some venous specialists have advocated the use of saphenous vein preserving approaches such as CHIVA (Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire or in English; Ambulatory Conservative Haemodynamic Management of Varicose Veins)[93] and ASVAL (Ablation Sélective des Varices sous Anesthésie Locale or in English; Ambulatory Selective Varices Ablation under Local anaesthetic)[94]. One randomised trial has shown that CHIVA is not only comparable to but resulted in almost 50% lower recurrence rates than standard ligation and stripping with phlebectomies[95], while a 2021 systematic review and comprising over 2100 legs found ASVAL to be an effective treatment, but without comparison against axial ablation[96]. Mid-term results are also available for ASVAL, achieving symptomatic relief and non-significant saphenous reflux[97], though this is not comparative data. Recently, a randomised trial has been published which also shows that in patients with varicose veins, outcomes from ASVAL, or a very similar technique, achieved non-inferior short term outcomes compared with thermal ablation plus phlebectomy. While it is maybe no surprise that patients would feel better following removal of their symptomatic varicosities, treating the axial reflux has been perceived to give longer term benefits, with early recurrence expected without management of the underlying reflux. This could prove a more cost effective approach if the results can be shown to be as durable as in other case-series. These techniques have never, to our knowledge, been tested in the setting of VLU.

Terminal Interruption of the Reflux Source (TIRS) aims to directly target veins in the ulcerated area of the leg. There is typically a peri-ulcer plexus of incompetent veins and by only treating these, TIRS aims to reduce venous hypertension locally to facilitate healing. Numerous small studies have reported success in managing VLU with TIRS and healing ranging from 83% to 100% [98, 99]. TIRS has never before been tested in a randomised trial. The encouraging results from CHIVA and ASVAL suggest that axial ablation may not be absolutely necessary to manage reflux effectively, in which case TIRS may have a role.

There are numerous means of achieving TIRS. One method that is commonly used is ultrasound guided foam sclerotherapy. This can be performed using a small needle, often without even a local anaesthetic, and can be delivered as an office-based treatment. This makes it an attractive method in terms of resource use, and it is avoids the necessity for expensive equipment needed for thermal ablation, or in particular cyanoacrylate glue closure. In our experience, it is particularly attractive in more elderly patients, who may be reluctant to have an 'operation' but are happy to receive an injection. Foam sclerotherapy, including perilesional sclerotherapy, has been shown to be safe and effective[98-100].

Other Adjuncts to Compression for Venous Leg Ulcers

In addition to dressings, discussed above, there are many other potential adjuncts to compression in VLU management including complex devices and procedures as well as basic care. Adequate nutrition, for example, is an important element in healing wounds of any type. Protein is especially important as protein loss can occur with high levels of exudate, while hypoalbuminaemia can contribute to oedema in a vicious cycle. Nutritional supplementation may be of value. Vitamins such as A and C are also important in wound healing. Emollients are useful in moisturising and soothing skin, in particular in the case of varicose eczema. Diabetes can impair wound healing and so good glycaemic control is important, especially as infection can interfere with diabetic control, again potentially causing a vicious cycle. Smoking or anaemia can impair tissue oxygenation, so should be avoided or corrected as appropriate.

In Ireland, pharmacological treatments for reflux are very seldom used. As a group, the evidence for these medications has been comprehensively assessed by several Cochrane reviews. Commonly seen 'venotonic' medications include flavonoids, sulodexide and horse chestnut seed extract. Sulodexide, a glycosaminoglycan was found to have only low quality evidence to support its use[101]. Flavonoids are a family of over 10,000 phytochemical compounds present in many plants. Micronized purified flavonoid fragment is a combination of two flavonoid compounds, diosmin and hesperidin. In at least one randomised trial in VLU patients, small VLU had a significantly improved rate of complete ulcer healing at two months with micronized purified flavonoid fraction compared to placebo; 32% (n = 14) Vs 13% (n = 6)[102]. A Cochrane review however has found that while numerous studies suggest a role for venotonics in CVI, only 6 studies looked at VLU, and pooled analysis of these found no benefit[103].

The mechanism of action of venotonic medications seems to be related to their ability to reduce inflammatory response and remodelling in the vein wall arising from hypoxia, stretch and low shear stress[59]. Along similar lines, MMP inhibitors have a theoretical role; marimastat[104], simvastatin[105] and doxycycline[106] have been shown to reduce degradation of the extracellular matrix in arterial wall biopsies and both doxyclcine[107, 108] and simvastatin[109] have shown promising results in managing VLU.

Pentoxifylline is the other medication which has shown potential value. It is not a venotonic as such but a vasodilator and derives its effects from promotion of microcirculatory blood flow and oxygenation though its pharmacological mechanism remains unclear. Pentoxifylline probably has the strongest evidence of any medication to support its use in VLU. A Cochrane meta-analysis of 11 trials in which pentoxifylline was compared with placebo or no treatment, found it to be an effective adjunct to compression bandaging for treating VLU. The relative risk of ulcer healing with pentoxifylline was 1.70 when compared with placebo[110].

Numerous non-pharmacological modalities have also been investigated in the management of VLU. Several theories propose potential effects of pulsed electromagnetic fields on tissue regeneration and cell proliferation in healing wounds; essentially all based on the induction of a charge on the cell membranes of inflammatory cells within wounds. Low level laser has been postulated to enhance healing by encouraging granulation and migration. Therapeutic ultrasound has been suggested as a potential treatment, but its effects are poorly understood, to the point that it is unclear whether increased or decreased blood flow is the aim of treatment. Cochrane reviews have found no evidence to support the use of any of these[111-113].

A Cochrane review did find a potential role for intermittent pneumatic compression. This has long been used to maintain venous return to prevent DVT. The review found that intermittent pneumatic compression may increase healing compared with no compression, but concluded that it was unclear whether it could be used as a substitute for normal compression bandages. Two of five trials assessing it alongside compression bandages found the combination to be superior to compression alone, though the other three trials found no benefit[114].

The Scale of the Problem

The true prevalence of chronic venous disease is difficult to quantify. Some of this difficulty arises from variations in populations with different risk factors. Varicose veins have long been considered a disease of western societies, and there is a complex relationship between CVD and geography and ethnicity. Pacific Islanders in New Zealand were found to be much more likely to have varicose veins than in ethnically similar island societies with a significantly less carbohydrate rich diet[115] and CVD is associated with obesity, sedentary lifestyle, hypertension and smoking, all of which have long been associated with western diets and lifestyle[116]. Compiling global data on the prevalence of C2 veins, the lowest prevalence is found in Africa with just 5.5% compared to 21% in Europe, 22% in South America and 23% in North America[117].

Differences in terminology have also been a significant difficulty in comparing epidemiological studies. While the widespread adoption of the CEAP classification has removed some of this confusion, significant inconsistency and overlap persist, and much of the epidemiological evidence that has been gathered predates CEAP. Also, venous disease frequently goes untreated, undiagnosed or even unnoticed by the patient themselves, and there are several factors which appear to influence symptoms, such as age and gender, as well as whether treatment is sought even when CVD is clinically apparent[5, 118]. Therefore the only way to accurately assess prevalence in the general population is with large and expensive cross-sectional studies.

Large reviews of the literature to date in 2005 and 2006 found such wide ranging results for the prevalence of varicose veins as to be effectively useless in estimating their true prevalence[67, 119]. Results varied from 2% to 56% in men and from < 1% to 73% in women.

A more recent large systematic review comprising 32 studies reporting on the prevalence of clinical manifestations of CVD for a total of 339,505 patients. Estimates of the overall burden of CVD were again very wide, ranging from 38.3% to 90.4%. 19 of the included studies were used to calculate a crude prevalence for each stage of the CEAP classification. The prevalence of varicose veins was found to be 26% for C1 or reticular veins and 19% for C2 veins, or larger varicosities, and the annual incidence of C2 veins was estimated at 0.22-2.3%. C3 veins, i.e. varicose veins with oedema were found to have an 8% prevalence. Skin changes or trophic changes are typically considered to be the first manifestation of CVI and so categories C4-C6 can be considered to have CVI. The Prevalence of C4 veins was found to be 5%, with previous estimates subdividing this and reporting hyperpigmentation in 0.3-8.7% of men and 1.1-9.6% of women, with varicose eczema varying from 0.5-2.5% in men and 1.1-1.8% in women[67].

The principle concern of this work relates to VLU and the prevalence of ulcers was calculated as 1% for inactive VLU, and 0.42% for active VLU. C5 and C6, or active and healed VLU, had a combined incidence of 0.018[120]-0.122[121] per 100 person-years. It is important to note that the VLU are significantly more common with age with increased prevalence among older populations up to 0.4-1.69%[122, 123] and one rural Scandinavian cohort of over 65s were found to have a prevalence as high as 8-12%[124]. While the annual incidence of VLU in the general population is 0.018-0.122%, in the over 65 cohort it may be as high as 0.76 per 100 person-years for men and 1.42 per 100 person-years for women, and this continues to increase with age. The prevalence of VLU in the population below 65 years of age may also be increasing, with one study showing a doubling of prevalence since the 1990s from 0.3% to 0.6% [125], and while the reasons for this have not been shown, one assumes the increase in overweight and obesity likely plays a prominent role.

The most recent data published from Ireland found a prevalence of leg ulcers of 0.12% or 1 per 800 in the general population, rising to 1.2% in the population aged over 70, and the average age of patients with VLU was 75 years[126].

Until recently the use of ultrasound was not common in population-based studies, and so asymptomatic patients with reflux may have been overlooked. The Bonn, Edinburgh and San Diego Vein Studies were large cross-sectional studies which invited random samples of subjects from the general population who were assessed for reflux by duplex scanning alongside a clinical assessment[6, 127, 128]. The Edinburgh Vein Study recruited 1566 participants, the Bonn study 3072, and the San Diego study 2211 in the significantly more mixed-ethnicity population of San Diego. Each study combined clinical and ultrasound findings, though there were some differences in how these were reported.

Overall up to 35.3% of the population had some form of reflux with variation in the different populations, 19-21% had superficial reflux and 9-20% deep[6, 127, 128].

CVI, including C4-C6 was present 4-6% of these populations, in keeping with the large systematic review above. The Bonn study categorised the prevalence of reflux by clinical stage of the CEAP classification and found that from C0 to C3 the prevalence of deep reflux remained relatively constant, but increased markedly in those with CVI, or C4-C6, compared to those without, and continued to increase from C4 to C5 and C6 i.e. with progression from skin changes alone to VLU. In the Edinburgh study 30.8% of subjects with CVI had reflux limited to the superficial veins; 17.3% had deep venous reflux alone, and combined superficial and deep reflux was seen in 26.9%. In San Diego 52.2% of those with CVI had superficial reflux alone, versus 22% with deep reflux of whom 48% had combined reflux (10.5% of the total).

Reflux was demonstrated in over a third of participants for whom complete duplex data was available (219/630) in the Edinburgh study with no clinical signs of CVD[6]. Baseline reflux was associated with a twofold increase in the odds of CVD progression with 57.8% found to have progressed in a follow-up study at thirteen years. The 13-year incidence of reflux was 12.7%, and so approximately 1% of the population developed reflux per annum[129], and the 13 year incidence of CVI was 9.2%[130]. 31.9% of those with varicose veins had developed CVI, and 34.4% with CVI experienced progression of their clinical manifestation[131].

Reflux and CVI both increased dramatically with age in the San Diego study. From the under 50 to over 70 age groups the prevalence of clinical manifestations of CVI more than quadrupled, from 2.3 percent to 10.2 percent while the prevalence of superficial and deep reflux increased with age: from 11.2% to 27.3% in the same age groups and deep reflux increased from 6.9% in under 50s to 11.3% in over 70s.

In the Bonn study however, while the prevalence of reflux in the superficial venous system did increase with age, no change was seen in deep venous reflux and a similar effect was seen with increasing BMI; superficial reflux became more prevalent with increasing BMI, but the prevalence of deep reflux did not change significantly.

Stratification by sex revealed a stronger association between reflux and CVI in men than in women[128], and in the San Diego data more men had CVI (7.8% men and 5.3% women) despite having less reflux overall.

Challenges in Implementing an Evidence Based Service

The real total cost of VLU care is difficult to calculate[132]. Direct costs can be hugely variable and estimates are related to treatment cost of VLU. They do not include the significant indirect financial losses related to factors such as loss of work and disability supports which as far back as the 1970s had been calculated as two million work days lost per annum in the United States[133]. Similar figures were seen in France in the early 1990s, with up to 12% of patients taking early retirement[134]. Nor do estimates account for costs on the patient's side, such as those related to transportation or other out-of-pocket expenses incurred by patients. This is especially important for those of a less affluent socioeconomic background as VLU patients disproportionately tend to be[135].

There is also a significant opportunity cost in VLU management because proper care of VLU is time-intensive. In the community setting this can be exaggerated among elderly populations who may need home visits, and particularly in rural areas. Even in centralised or hospital-based services, the need for regular visits and the extra time taken to remove and re-apply dressings can occupy a disproportionate amount of the available time in outpatient clinics with a knock-on effect on waiting lists, limiting access to specialised care for other patients.

In the United States, among Medicare patients, those with VLU had 77.8% more hospitalization days, 50.0% more emergency department visits, 27.4% more outpatient/physician office visits, and 60.0% more days of home healthcare than case-matched controls[136]. Not all of these episodes are VLU related, and indeed these data cannot discern the influence of VLU from patients' associated comorbidities. It has also been shown however that patients with comorbidities are more likely to end up in the emergency department with their VLU[137], further muddying the waters. Clearly however, VLU are a resource intense cohort compared to non-VLU patients of similar age etc.

Numerous estimates of the total financial cost of ulcer treatment include 1% of the national healthcare budget in industrialized countries[1], 1-2% of United Kingdom's total health expenditure[138, 139], or $14.9 billion annually in the United States. Per-patient cost estimates vary from as little as approximately £500-£1272 in the United Kingdom and €1,332-€2,585 in Sweden in 2002[140], to £4787.70 in the United Kingdom in 2020 or €9,569 per year in Germany at 2010 prices[141], and $30,000 in the United States[1, 125]. These are estimates however. Two retrospective studies have examined actual costs involved in VLU care in detail. One study in 1997 reported median total healthcare cost of $3,036, with median

84 days of follow-up, though the mean cost was much higher, $9,685, demonstrating how variable costs can be. A similar study in 2014 is particularly relevant as the patient cohort was restricted to those in vascular surgeon led services, as is the case in most parts of Ireland. This study found that the mean total cost of treating VLU was $15,732, and required a median 369 days. 60% of patients healed their VLUs without recurrence in a mean time of 122 days with a mean cost of $10,563, less than a third of that incurred managing VLU which did not heal, $33,907[125]. Some of the increase from 1997 to 2014 can of course be attributed to inflation.

Home healthcare accounted for 20-48%[136, 142] of total costs but hospital stays may add enormously to the economic burden on healthcare systems. Though VLU are primarily managed in the outpatient setting, in severe cases or in the event of complications, hospitalization may be required. Costs per bed per night in a public hospital in Ireland were estimated in 2019 at €878[143]. In past cost analyses, the number of patients hospitalised were as high as 12-18%[125, 142]. Reasons for hospitalisation included control of oedema or exudate, infection, complications of surgery, and other medical complications. The most frequent admitting reason is infection necessitating intravenous antibiotics, representing 61%[125]. Costs averaging $10,851 for those managed exclusively in an outpatient setting rose to $33,629 on average for those who needed at least one inpatient admission in the study by Ma et al, while Olin et al found that inpatient expenses accounted for 25% of total costs.

Against these expenses the costs of intervention must be balanced, and these costs can be broken down along similar lines. Reduced time to healing reduces dressing and related costs, but adds costs associated with pre-operative duplex imaging and intervention. Laser or RFA fibres are expensive, and cyanoacrylate glue even more so. Additional staff and labour costs are incurred in theatre or wherever treatment is to be delivered, even in an office-based model, and like any healthcare intervention there is again an associated opportunity cost as theatre space and staff may be diverted from other patients.

A key determinant of the costs of treating VLU is the effectiveness of treatment. The work of Nelzén et al in Sweden has previously shown that a strategy of actively pursuing optimum management of VLU can lead to a detectable change in prevalence in the population as a whole[144]. The key to their outcomes was the recognition that although VLU are challenging to manage, aggressive attempts to heal them can succeed, and that the heterogeneity of the VLU population means that a one-size-fits-all approach is not appropriate. Adapting treatment based on individual patient needs is essential. This however requires that patients be managed in specialist-led services, where this complexity can be properly teased out to ensure treatment is tailored correctly. The offering of endovenous ablation where suitable will be an integral part of this going forward.

In the cost analysis by Ma et al above, the higher proportion of VLU that healed among patients whose superficial veins were treated meant costs were no greater, averaging $11,960, than those treated with, compression and dressings $12,304. Shorter duration of dressings and nursing care offset the initial expense of surgery. Likewise, the cost effectiveness analysis based on the EVRA trial found that after three years of follow up, improvements in ulcer-free time in the endovenous ablation cohort meant that intervention was 91.6% likely to be cost-effective at a willingness to pay ratio of £20,000 per quality-adjusted life year. Unfortunately, cost-effectiveness does not always match with affordability, especially when capital costs to set up a service, or training and staffing issues mean that human rather than financial resources are the limiting factor.

Even if no treatment of reflux or venous obstruction is deemed suitable, the EVRA trial showed in the compression cohort what could be achieved with early access to a dedicated service. The simplest explanation for the high rate of VLU healing see in the compression arm of that trial, higher than in any prior randomised trial, is that these patients were managed in dedicated centres with early institution of high-quality compression.

Leg Ulcer Centre Ireland

The Saolta Hospital Group comprises seven hospitals in the West of Ireland, caring for a total population of approximately 800,000 people. University Hospital Galway (UHG) is the tertiary referral centre for the whole group, where vascular surgical services are centred. Four hospitals provide elective and acute general surgical care, with only complex major elective procedures being referred on to UHG. The remaining two units have no on-call surgical services and are used to provide only elective and day case minor and intermediate general surgery or varicose vein surgery and minor plastic surgery procedures by UHG-based vascular and plastic surgeons.

Roscommon University Hospital is one such unit and in July 2016, a one-stop venous ulcer clinic was introduced, later named the Leg Ulcer Centre Ireland (LUCI). This is run by the vascular surgery team from UHG, operating once weekly for a full day in parallel with a day-case venous surgery operating list. Patients are seen and assessed by a vascular nurse specialist and vascular surgeon, with ultrasound assessment of venous disease and suitability for endovenous intervention. Where necessary, further imaging or investigation of venous obstruction or arterial insufficiency can be carried out, and this is typically done in UHG. For uncomplicated cases, the aim is same day treatment of superficial venous reflux, and/or commencement of compression therapy as appropriate. Suitable patients with great or small saphenous vein reflux are offered axial ablation; typically MOCA using Clarivein™ (Vascular Insights LLC, Quincy, MA, USA), but also RFA. It is performed under local or tumescent anaesthesia.

Foam sclerotherapy using Fibrovein™ (STD Pharmaceutical Products Ltd., Hereford, UK) may be used alongside axial ablation if prominent varicose veins are an issue, or to treat to the lowest possible point of reflux in anatomy unsuitable for catheter-based ablation. TIRS is also offered and some, particularly more elderly patients, elect for this alone as it is perceived to be less invasive, while many elect to continue with compression alone. Compression bandaging is offered to all patients with a VLU and superficial or deep venous reflux with no contraindications.

Running the clinic in parallel with a day case operating list allows clinic patients who wish to undergo intervention on the same day to be added onto the end of the operating list. This is particularly attractive for patients having to travel long distances to attend.

On average 2-3 patients are assessed per week. Some patients assessed are unsuitable, such as if further investigation is warranted, while others may wish to take time to consider. Typically half of all attendees get same-day intervention.

Another advantage of running the clinic concurrent with the operating list is that it allows the clinic to be run with only one additional staff member: the clinical nurse specialist. Theatre nurses, administrative and other personnel do so in addition to their normal duties, minimising extra costs.

Patients are referred to the vascular surgery team in UHG from their general practitioner or local community wound care service, or occasionally, the general surgical team in any of the hospitals within the Saolta group if they have come to their attention as commonly occurs if they have been admitted for management of an infected VLU. Appropriate referrals are seen in LUCI. Patients without VLU are not diverted to the rapid access clinic. Following their initial assessment, and intervention if performed, patients are reviewed every four weeks until their VLU has healed. Where this is not practical for other reasons, most commonly if patients have travelled long distances for assessment and treatment, some patients may be followed up locally. If issues arise during follow up, Public Health Nurses (PHN) are able to contact the clinic nurse directly to arrange rapid reassessment, and indeed patients themselves can make contact directly if necessary.

The simple aim of LUCI has been to improve the delivery of care to patients with VLU by offering streamlined care pathways, offering treatment based on up to date evidence, and with a view to engaging in ongoing research to further advance the management of VLU. This thesis comprises some of that research.

Research Goals

The aim of this thesis has been to investigate strategies to improve the delivery of care to patients with VLU in the West of Ireland.

To achieve this aim, three research questions were posed

1. Does a dedicated service like the LUCI clinic make a difference to patients with VLU?
2. Is the use of TIRS a viable alternative to formal endovenous ablation of axial reflux?
3. Are there any other adjuncts to the currently provided treatments, or alternatives for those not suited to available treatment options that could be provided in the West of Ireland?

To determine whether the LUCI clinic has made a difference to VLU patients we set out to establish whether there had been a reduction in the number of patients being admitted to hospitals across the Saolta Hospital Group following the commencement of the clinic.

TIRS has to date never been assessed in a randomised trial. The evidence to support its use is weak though the results are encouraging. To properly evaluate its efficacy, we conducted the Axial Ablation Versus Terminal Interruption of the Reflux Source (AAVTIRS) trial. An assessor blinded randomised trial.

Finally, a brief review of the literature indicated that numerous recent systematic reviews, meta-analyses and Cochrane collaboration reviews had looked at various wound healing adjuncts and techniques. A summary of these findings are presented above. One area where a synthesis of the existing evidence had not been performed, and where several studies had shown promising results, was the use of hyperbaric oxygen. A systematic-review of this evidence was considered worthwhile because Ireland's National Hyperbaric Medicine Unit is located in University Hospital Galway, within the Saolta Hospital Group, and where the LUCI research team are based. This presented the opportunity for a further clinical trial if the existing literature suggested a role for hyperbaric oxygen in VLU management.

Impact of a One-Stop Rapid Access Venous Ulcer Clinic on Inpatient Admissions

Introduction

Venous ulceration poses a massive economic burden on health services [145-148]. Compression therapy has been shown to aid the healing of venous ulcers[149, 150]. It is time consuming for patients and practitioners however and requires significant community support. Traditionally compression was the only treatment offered and VLU have generally been managed in the community alone. It has been shown however in a large Swedish population that a strategy of active diagnosis of the underlying aetiology, appropriate referral pathways and multidisciplinary specialty backup for management of VLU an help VLU to heal and thus reduce the overall prevalence[144].

Superficial venous reflux (varicose veins) is frequently present in patients with VLU[151], and surgical treatment of varicose veins, in combination with compression, has been shown to improve the rate of ulcer recurrence. However, the ESCHAR trial did not show any benefit in ulcer healing from surgery[89, 90]. Therefore, some guidelines only recommend surgery to reduce recurrence[152] and commonly patients have surgical intervention after their ulcers are healed. Numerous observational studies[153-156] and the EVRA trial[91] have shown that early endovenous treatment of reflux in the saphenous veins reduces the time to ulcer healing compared with deferred intervention, and so in recent years guidelines have begun to reflect this[157, 158].

In specialist practice it is uncommon for patients to be admitted for management of VLU, and it is typically dealt with in an outpatient setting unless there is superimposed infection. It is not unusual however for patients to be referred for admission and inpatient management by their primary care doctor with VLU that are proving difficult to manage, even when infection is not necessarily the issue, such as when exudate is excessive. This often leads to prolonged admission in non-specialist centres as this is a frail and comorbid population. These patients, who could otherwise be managed effectively at home, may benefit from an alternative pathway, avoiding emergency department referrals by providing rapid access to specialist care, reducing these admissions.

We introduced a ‘one-stop see and treat’ clinic for venous leg ulcer (VLU) patients in 2016. We aimed to determine how this service impacted upon unplanned hospital admissions for venous ulceration.

Aims

Our primary aim was to determine whether unplanned inpatient admissions due to venous ulceration were reduced following the introduction of a one-stop see and treat clinic offering early reflux ablation for VLU patients.

Secondary outcomes included median hospital bed-day usage, length of stay, mean cost of hospital stay per admission, and annual cost.

Materials and Methods

Study Setting

The Saolta Hospital Group comprises seven hospitals in the West of Ireland, caring for a total population of approximately 800,000 people. University Hospital Galway (UHG) is the tertiary referral centre for the whole group, where vascular surgical services and other surgical specialties are based. Four hospitals provide elective and acute general surgical care, with only complex major elective procedures being referred on to UHG. The remaining two units have no on-call surgical services. They are used to provide only elective and day case surgical services provided by general surgeons based in those units, performing minor and intermediate elective procedures such as hernia repair or laparoscopic cholecystectomy, or by UHG-based specialty surgeons performing varicose vein surgery or minor plastic surgery procedures.

Roscommon University Hospital is one such unit and in July 2016, a one-stop venous ulcer clinic was introduced, run by the UHG vascular surgery team, operating once weekly for a full day in parallel with a day-case venous surgery operating list. . Patients are seen and assessed by a vascular clinical nurse specialist and vascular surgeon from UHG, with ultrasound assessment of venous disease and suitability for endovenous intervention. Where necessary, further imaging or investigation can be arranged but for the majority, the aim is same day treatment of superficial venous reflux, and/or commencement of compression therapy as appropriate. Suitable patients are offered axial ablation (typically mechanochemical ablation using Clarivein™ (Vascular Insights LLC, Quincy, MA, USA)), or foam sclerotherapy (using Fibrovein™ (STD Pharmaceutical Products Ltd., Hereford, UK)) into the sub-ulcer plexus of veins, as appropriate. Axial ablation is offered to patients with great or small saphenous vein reflux and is performed under local or tumescent anaesthesia. Foam is offered along with axial ablation if prominent varicose veins between the ulcer and the ablated segment are an issue, in an effort to treat to the lowest possible point of reflux. Treatment with foam alone is offered for perforator reflux, or reflux without discernible superficial venous disease. All of this is done in consultation with the patient, and some, particularly more elderly patients, elect for foam alone as the, perceived, least invasive procedure, while many elect to continue with compression alone. Compression bandaging is offered to all patients with a VLU and superficial or deep venous reflux with no contraindications.

Running the clinic in parallel with a day case operating list allows clinic patients who wish to undergo intervention on the same day to be added onto the end of the operating list. This is particularly attractive for patients having to travel long distances to attend.

On average 2-3 patients are assessed per week. Some patients assessed are unsuitable, such as if further investigation is required, while others may wish to take time to consider. Typically half of all attendees get same-day intervention. Young fit patients are typically more likely to proceed. One case can always be accommodated, and usually a second, as cases on the operating list are completed without using all of their allotted time. The number of patients attending for assessment is known before finalising the operating list. If there are multiple patients for assessment likely to proceed such as young patients, or others pre-identified from their referral, a blank slot can be allocated on the list. Rarely, more of the assessed patients are candidates to proceed than can be accommodated on the same day, in which case priority is given to those for whom re-attending will be most difficult, based on frailty and/or distance to travel.

Another advantage of running the clinic concurrent with the operating list is that it allows the clinic to be run with only one additional staff member: the clinical nurse specialist. Theatre nurses, secretaries and other personnel do so in addition to their normal duties, reducing costs.

Patients are referred to the vascular surgery team in UHG from their general practitioner or local community wound care service, or occasionally, the general surgical team in any of the hospitals within the Saolta group if they have come to their attention as commonly occurs if they have been admitted for management of an infected VLU. Appropriate referrals are seen in the VLU clinic. Patients with venous reflux of any type, without ulceration, were not diverted to the rapid access clinic. Following their initial assessment, and intervention if performed, patients are reviewed every four weeks until their VLU has healed. Where this is not practical for other reasons, most commonly if patients have travelled long distances for assessment and treatment, some patients were followed up locally. If issues arose during follow up, Public Health Nurses (PHN) were able to contact the clinic nurse directly to arrange rapid reassessment, and indeed patients themselves could make contact directly if necessary.

Data Collection

The Hospital Inpatient Enquiry (HIPE) collects demographic, clinical and administrative data on discharges from acute public hospitals in Ireland. Data are extracted from medical charts or records and coded according to ICD-10 by trained clinical coders.

Patients were deemed to have an unplanned VLU related admission if they had any non-elective admission, to any hospital within the Saolta group, with an appropriate primary diagnosis code over the period July 2014-July 2018. The codes for venous ulcer include “Varicose veins of lower extremities with ulcer”, and “Varicose veins of lower extremities with both ulcer and inflammation”.

Phlebitis alone without ulceration, and varicose veins without ulceration, are both coded elsewhere in the ICD-10 and were excluded. The two years immediately prior to the introduction of the one-stop see and treat clinic (July 2014 to June 2016) served as the control period.

Data on the clinic’s activity was gathered by a combination of prospective documentation as well as retrospective chart review for earlier patients.

Statistical Analysis

Continuous variables were described using means (±standard deviation) for normally distributed data and medians (±interquartile range) for non-parametric data. Categorical variables were described as absolute numbers and percentage frequencies. As length of stay data, and therefore also bed day usage across groups, was non-normally distributed, all analyses relating to these were treated as non-parametric and tested using a Mann-Whitney U. Categorical variables were tested using the Fisher Exact test.

Data was analysed using the StatsDirect™ software package version 3.

Cost Analysis

The Irish Health Service Executive (HSE) periodically publishes an inpatient ready reckoner of acute hospital inpatient and daycase activity costs summarised by diagnosis related group (DRG). The most recent edition was published in 2013 using total costs per DRG from 2011 data broken down into costs per average case. Admissions are further stratified by whether a catastrophic or severe complication occurred during their inpatient stay, but as HIPE data does not provide this information, a total average cost per case was calculated. This was then used to calculate cost per bed-day, which was then applied to bed-day usage data for the current study, to calculate monthly costs.

Results

Over the four-year study period there were 218 VLU-related unplanned, inpatient hospital admissions throughout the Saolta Group. Of these, 122 were coded “Varicose veins of lower extremities with both ulcer and inflammation”, while 96 were coded “Varicose veins of lower extremities with ulcer”. Overall 131 (59%) were female and (41%) male, and the median age was 78.9 (IQR, 69.1-84.9). There was no significant difference in likelihood of inflammation being present based on sex (p=0.09) or age (p=0.15).

In total, VLU patients accounted for a total of 2,529 inpatient bed-days, with 4.5 (IQR, 2-6) admissions per month, and a median hospital stay of 7 (IQR, 4-13) days per month throughout this period. Each month, a median 40.5 (IQR, 21-71) bed-days were devoted to patients with venous ulceration.

Those with ulcers with inflammation or infection accounted for 1,454days (57.5%), with a median 8 (IQR, 4-14) days per unplanned admission, while those without accounted for 1,075 days (42.5%), median 7 (IQR, 3-13) per unplanned admission. There was no significant difference in median length of stay between these groups (p=0.28).

Baseline characteristic	N
Female	88 (54.6%)
Median Age-years	73 (63-79)
Median duration of Ulcer at presentation-months	9 (5-24)
Concurrent PVD	20 (12.4%)
Diabetes	17 (10.5%)
Current Smoker	10 (6.2%
Previous Venous surgery	27 (16.8%)
Previous DVT	13 (8%)
Obese	16 (9.9%)

Table 2 Demographic Data (PVD= peripheral vascular disease DVT=deep vein thrombosis

Since commencement of the rapid access clinic, 161 patients were seen with 183 ulcers assessed. 53 of these ulcers were recurrent, and 8 of these recurrences occurred in legs previously treated in the clinic. Demographic data is presented in table 2, and available retrospective follow-up data in table 3.

	% (no. healed/no. followed)
Healed ulcer at 6 months	50.7% (34/67)
Healed in compression alone	54.5% (12/22)
Healed with any intervention	48.9%(22/45)
Healed with axial ablation	66% (12/18)
Healed with foam	66% (9/15)
Healed with ablation and foam	8.3%(1/12)

Table 3 Ulcer healing rates by treatment modality among those followed for 6 months or until ulcer healed

In this time, 108/183 (59%) have received endovenous treatment for reflux. Of those, both axial ablation and sclerosant foam were performed for 21 (11.5%) of VLU, 42 (22.9%) received foam only, and 55 (30%) underwent axial ablation. 46 (25.1%) VLU were managed with compression alone. The remainder received no treatment of reflux during the study period.

Admissions

The primary outcome measure was number of unplanned admissions per month. Over the four-year period and this showed a significant reduction. Median number of unplanned admissions per month decreased from 6 (IQR, 2.5-8.5) in the control period, to 3.5 (IQR, 2-5); p=0.04 after introduction of the clinic. In particular, there was a significant difference between the numbers admitted without inflammation or infection before and after commencement of the service. In the two years prior to the clinic commencing there were 68 admissions without inflammation, and 63 with inflammation. While the numbers admitted with inflammation remained relatively stable at 59, the number admitted without inflammation reduced to 28 (p=0.005). Point biserial correlation showed a moderate negative correlation between monthly admission rates and whether the month fell before or after the commencement of the clinic r=-0.329 (p=0.022). In the period since the commencement of the clinic there is a moderate negative correlation between monthly admissions and time since commencement r=-0.35 (two sided p=0.039)

Secondary Endpoints

Length of inpatient stay did not change significantly during the study period (p=0.57), regardless of sex (p=0.514), or age (p=0.85).

Bed-day usage was significantly reduced from median 62.5 (IQR, 27-92.5), to 36.5 (IQR, 21-44); p=0.035, bed-days per month.

In 2011, 291 unplanned admissions due to VLU cost the state €2,214,057 in inpatient costs which amounted to a cost per inpatient stay of €7,608 or €533.38 per bed-day. The results of applying these costs to the 2014-2018 Saolta data are shown in table 4 and figure 2. Figure 2 shows the median monthly cost borne by the health service for the inpatient care of patients admitted primarily for management of VLU in the two-year period immediately before and the two-year period since commencement of the VLU clinic.

Year of study	Annual Cost €	Median monthly cost €
Year 1	600 052.50	47 470.82
Year 2	268 823.52	21 601.89
Year 3	289 825.62	21 168.65
Year 4	187 216.38	16 268.09

Table 4 Annual and Monthly Costs (€) of inpatient admissions per year of study

The cost of management of varicose veins on a surgical daycase basis amounts to €2,211 per case. The current data show a median cost per inpatient stay throughout the study period of €3,733.66, which did not change significantly, as length of stay was not significantly reduced. There was however a significant reduction in costs per month from median €33,336.25 (IQR, €14,401.26-€49,337.65) to €19,468.37 (IQR, €11,200.98-€22,401.96); p=0.03 due to the reduced admission rate.

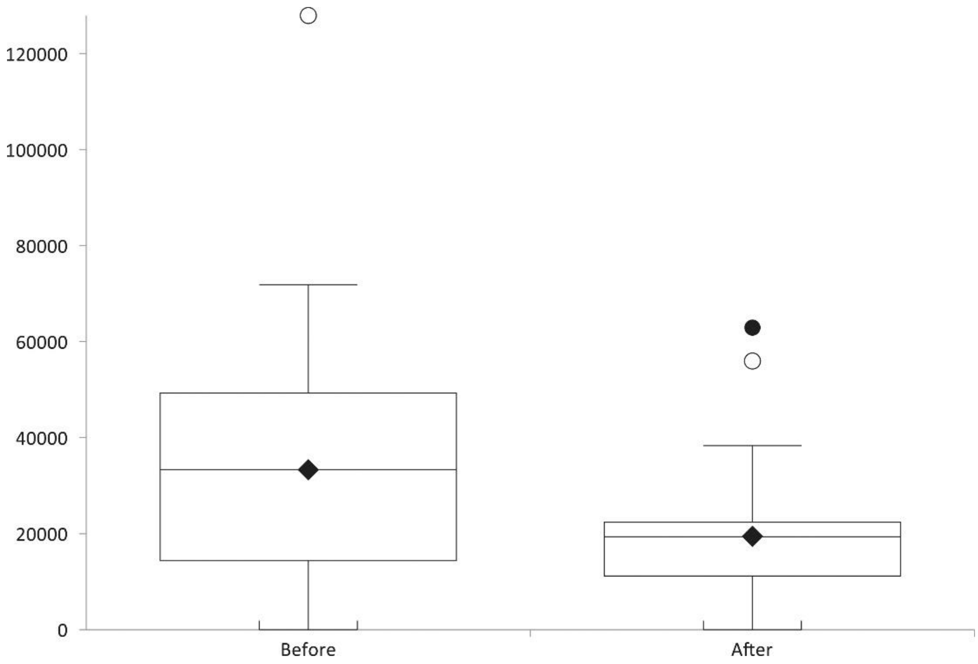

Figure 2 Median monthly cost of inpatient admissions for VLUs in the 2 years before and 2 year after introduction of the rapid access clinic rapid access service. X-axis monthly cost (€).

Discussion

To our knowledge this study represents the first time that a dedicated see-and-treat service for VLU has been assessed in terms of its potential to reduce the burden on inpatient services, and therefore costs.

We have shown that ulcer admission rates have fallen after beginning a rapid access clinic providing aggressive treatment of VLU with surgical intervention. It remains unclear whether rapid access to the actual interventions is wholly responsible for the reduced admissions and observed healing rates do not support this, though it is likely one important factor. We believe that the reduction of inpatient admissions is a result of a combination of factors. These include reduced time from referral to specialist assessment and treatment, greater availability of an alternative referral pathway for primary care physicians, and the safety net effect of frequent follow up and easy access in the event of a setback. The observed saving in bed-days alone suggests there is value providing such a service for management of VLUs, even before financial costs are considered. Cost per admission remained static during the study period, as length of stay per case did not significantly change. The number of admissions however was reduced, leading to significant cost savings as well as freeing up beds. The cost of surgical daycase interventions for varicose veins to the HSE amounts to €2,211 per case. While the addition of 108 of these cases into the system since the commencement of the clinic would offset savings made in admission costs, since current guidelines already advocate surgery in these patients for prevention of recurrence, the majority should undergo a daycase treatment of their varicose veins

An analysis of the breakdown of costs in VLU management, albeit performed in the US where the funding model is markedly different to the Irish or most European systems, found that just 22% of the costs relating to venous leg ulcer management were incurred in the inpatient setting. The rest of the costs incurred were split between outpatient management (42%) and community care (35%) costs[159].

In these areas the one-stop clinic can also have secondary benefits, and from its inception one of the main goals of the clinic was to streamline the process by which patients with VLU are managed. A one-stop clinic reduces the number of hospital visits and removes the need for separate waiting lists for assessment and intervention. Reducing the number of visits required (from one for assessment, one for the procedure at a later date, and perhaps another for ultrasound assessment in between) into a single visit reduces the total number of outpatient visits.

Prompt treatment, while not removing the need for community follow up, should also reduce the number of healthcare interactions required by these patients in the community. Improving the ulcer healing time can eliminate at least one PHN visit for every extra ulcer-free week, and in some cases 2-3 visits. In addition, as the same-day service removes the usual waiting period between assessment and treatment, PHN visits to patients while they are on the surgical waiting list are also saved. The work of Nelzén et al in Sweden has previously shown that a strategy of actively pursuing optimum management of VLU can lead to a detectable change in prevalence in the population as a whole. Long before the EVRA trial, their unit advocated early endovenous intervention[144]. Accepting the evidence of EVRA, treatment of reflux was offered to all patients in whom it was felt to be appropriate. Rolling audit of the service's healing rates shows that about 70% of VLU are healed at six months, less than the 90% healing achieved in the EVRA trial. Our lower figure may reflect greater wound chronicity.

Early and easy access for these patients, also streamlines wound care in the community. More and more of these interactions amount to a simple dressing change, as a full assessment has been carried out already. If an ulcer is thought to be making poor progress, the PHNs know the patient will be seen within a month and in the event of a problem, they have a definite referral pathway, to have patients about whom there is a concern seen at the next weekly clinic. This removes the dilemma, over whether to send a non-acute patient to the emergency department if the patient cannot wait on a normal outpatient waiting list while an ulcer continues to deteriorate. This may be reflected in the evidence presented. Admission rates with inflamed or infected ulcers remained relatively unchanged while there was a marked reduction in admissions of ulcers without inflammation. It is difficult to tease out fully from coding-based data, and so very little can be concluded, but one interpretation of this may be that providing a different referral pathway for the non-infected but difficult to manage cases allows them to remain in the community, contributing to the reduction in admission rates observed.

There were no other significant changes made in service provision in the geographical area in question which account for the significant reduction in inpatient admissions over the course of the study period. We therefore suggest that in light of clinical guidance recommending the surgical management of venous reflux to encourage ulcer healing[157, 158] that this be undertaken in a one-stop clinic to maximise efficiency.

Limitations

The lack of complete prospective data for all patients seen in the clinic, in particular incomplete data in relation to healing rates within the cohort, limits understanding of the precise mechanism by which the reduction in admissions has occurred.

The data source for this study, HIPE, is collected prospectively, by chart review, by trained clinical coders at the time of discharge. The coders review patient notes, radiology and lab data, as well as discharge summaries, to code each admission. The coders receive clinical training, but the focus of the coding is intended towards finance rather than research. There is the potential for some patients to be incorrectly coded, so HIPE data can be limited in its accuracy for each individual case. However, over the course of hundreds of admissions, as in the National Surgical Quality Improvement Program database run by the American College of Surgeons or Hospital Episode Statistics database in the NHS, these inaccuracies are expected to be evenly distributed.

Perforators were treated with foam sclerotherapy and were not singled out as a separate modality in data collection.

Axial Ablation Versus Terminal Interruption of the Reflux Source (AAVTIRS): A Randomised Controlled Trial

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Background

Venous leg ulcers (VLU) are a massive burden on health services internationally[140, 145-147]. In Ireland, prevalence of leg ulcers is 1 per 800 people in the general population, rising to 1 per 100 over the age of 70 years[145]. Compression therapy has been shown to expedite healing of VLU[149, 150]. However, it is time consuming for patients and practitioners and requires significant community support.

Surgical treatment of varicose veins, in combination with compression, has been shown to improve the rate of ulcer recurrence[90] but the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study didn't show any benefit in ulcer healing from surgery[89, 90]. Numerous observational studies[153-156] and in particular the EVRA (Early Venous Reflux Ablation) trial have since demonstrated that after endovenous treatment of reflux, the time to ulcer healing is reduced[91]. This has important implications for the patient, their quality of life[160], and for the economic burden on community and hospital services of ongoing ulcer management.

Endovenous treatment of reflux can be achieved by ablation of the main superficial veins of the leg, or Axial Ablation (AA), but there is also a growing body of evidence in favour of strategies which aim to preserve these axial veins, such as CHIVA (French Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire)[161] and Ambulatory Selective Variceal Ablation under Local anaesthetic (ASVAL)[96]. Terminal Interruption of the Reflux Source (TIRS) aims to directly target those veins in the peri-ulcer plexus in the leg which should normally drain the ulcerated area, and by only treating these specific veins, treat reflux locally. Numerous small studies have reported success in managing VLU with TIRS and healing ranging from 83% to 100%[98, 99]. TIRS has never before, to our knowledge, been tested in a randomised trial.

There are numerous means of achieving TIRS. One method that is commonly used is foam sclerotherapy, which can be ultrasound guided or directed by other means such as near infrared LASER vein viewer[162]. This can be performed using a small needle, often without even local anaesthetic and can be delivered as an office-based treatment. This makes it an attractive method in terms of resource use and acceptability to patients especially, in our experience, the elderly. Foam sclerotherapy has been shown to be safe and effective, including perilesional sclerotherapy[98-100].

We conducted the AAVTIRS trial to assess whether, in patients with VLU, TIRS is a viable alternative to axial ablation in achieving complete VLU healing.

Methods

Trial Design and Oversight

AAVTIRS was a prospective, single centre, parallel group, assessor-blinded randomised controlled trial. No funding was received and ethical approval was obtained from Galway University Hospitals Clinical Research Ethics Committee. All data was collected by the trial coordinator, under oversight from the department of vascular surgery at University Hospital Galway. Details of the trial design and implementation are provided in the protocol, which has been published previously[163]. The trial was registered at clinicaltrials.gov, reference number NCT04484168.

Setting and Participants

Participants were recruited at the Leg Ulcer Centre Ireland, operating out of Roscommon University Hospital. Patients were considered for enrolment if they had a primary or recurrent VLU, with great or small saphenous vein reflux confirmed on ultrasound assessment, and were suitable for compression therapy.

Reflux was defined as retrograde flow lasting for >0.5 seconds as measured on duplex in the standing position. Suitability for compression was defined as having palpable pedal pulses, or Ankle-Brachial pressure Index (ABI) ≥ 0.8, or Toe-Brachial Index (TBI) ≥ 0.5 and no history of hypersensitivity or other intolerance to compression bandages.

Patients were excluded if clinical assessment suggested a non-venous aetiology, if they had active or recent (within 2 weeks) infection of their ulcer, could not receive sotradecol (e.g. pregnancy or breastfeeding, hypersensitivity to sotradecol), were unable to provide informed consent, had isolated perforator vein reflux only or had evidence of deep venous occlusion.

Patients already attending the leg ulcer clinic were excluded from enrolment with the same VLU but were eligible to enrol with a contralateral VLU.

Sample Size

A prospective calculation of sample size[164] was informed by existing evidence relating to AA[91, 154-156], predominantly the EVRA trial[91], which showed an unadjusted rate of ulcer healing at 24 weeks of 85.6%. A more modest success rate was expected because exclusion criteria did not limit participants to new ulcers. 80% was felt to be reasonable. TIRS has very limited existing evidence, with reported healing rates ranging from 83% to 100%[98, 99]. While this suggested comparable outcomes, the evidence for TIRS to date consists of small case series and this was felt to be somewhat unreliable to inform a sufficiently robust power calculation. We elected to utilise an adaptive approach and commence recruitment with initial enrolment targets calculated for non-inferiority based on the available lower quality data but with a planned interim analysis after 50 patients had completed follow up to allow revision of recruitment targets to reflect a better informed power calculation. The trial would cease recruitment if one arm demonstrated statistically significant superiority at the interim analysis stage. In light of the acknowledged weaknesses in the initial non-inferiority power calculation, the trial could switch to a recruitment target based on a power calculation for superiority if the interim analysis revealed a trend in favour of one arm that wasn't statistically significant but the interim power calculation indicated a revised recruitment target for non-inferiority that was not feasible.

A non-inferiority trial with an 80% success rate in both arms would necessitate a cohort of 308 patients to ensure adequate power at the 5% significance level. By the time of the interim analysis in August 2021 there was a notable trend in favour of one arm, which was not statistically significant but a non-inferiority trial was no longer feasible. A sample size calculation, based on superiority and the trend in the results to date indicated that 98 participants would be required to give 80% power to detect difference in the primary outcome at the 5% significance level in a superiority trial.

Randomisation and Blinding

Once enrolled, patients were randomised on a 1:1 basis to axial ablation or TIRS with stratification by ulcer size (<5cm^2, 5.1 to 10cm^2, 10.1 to 25cm^2, >25cm^2). The randomization sequence was a computer generated random number sequence generated by the trial coordinator (CRK) with allocation concealment using sequentially marked sealed opaque envelopes. The surgical team performing the interventions were necessarily not blinded to allocation, nor were participants, due to the need to provide informed consent. Patients were first enrolled by a member of the trial team, who remained blind to allocation, and gave their consent to participate in the trial. The same trial team member then provided the next numbered envelope unopened to the surgical team. Once opened the allocated intervention was explained to the patient for them to consent to the intervention.

All members of the trial team not involved in the procedure remained blind to allocation, including trial assessors and the trial coordinator. No member of the surgical team who was unblinded had any interaction with the participants after their intervention until their VLU was fully healed, or they completed six months of follow up.

Interventions

TIRS was performed by first assessing the peri-ulcer plexus of veins to identify suitable injection sites to maximise treatment area with the fewest feasible punctures. A sclerosant foam was then created using Sotradecol (Sodium-Tetradecyl-Sulphate) agitated with air. A 1:4 sotradecol:air ratio was used, in two 5ml syringes in a modified Tessari method[165], creating 5ml foam. This method was used for all patients receiving TIRS, with up to an additional 5ml foam allowable to ensure satisfactory spread of foam throughout the target veins.

For those undergoing AA the choice of the method for endovenous ablation was at the discretion of the treating surgeon. Mechanical Occlusion with Chemical Assistance (MOCA) was the preferred method as it is a non-thermal technique, and so could be used in more superficial veins than thermal techniques and this was expected to facilitate use in a wider range of anatomies. Clarivein™ (Vascular Insights LLC, Quincy, USA) uses a catheter to inject sclerosant alongside a rapidly rotating wire. The wire scores the endothelium of the vein as well as spreading the sclerosant around the full circumference of the vein, augmenting the inflammatory response.

For both arms of the study compression with Coban™ (3M, Minnesota, USA) was commenced immediately upon completion of the procedure. A pragmatic approach was used regarding frequency of dressing changes and choice of primary dressings. Choice of initial primary dressing was at the discretion of the trial nurses. Dressing changes were recommended twice weekly initially and at least once weekly for the duration of follow up. Outside of trial follow-up visits, dressing changes were done locally by patients' public health or general practice nurse. Consultation with the trial nurses was encouraged, to try to maintain a degree of homogeneity, but ultimately these local services were not given a prescribed plan beyond their own experience and training.

Outcomes and Assessment

The primary outcome measure was the number of VLU which healed within six months of randomisation, with healing defined as complete re-epithelialisation of the index limb.

Secondary outcomes included time to ulcer healing; wound regeneration as measured using the Bates-Jensen Wound Assessment Tool (BWAT)[166] at each monthly follow up visit; change in VLU area, estimated with a grid and categorised using the same scale as the BWAT (<4cm^2, 4-16cm^2, 16.1-36cm^2, 36.1-80cm^2, >80cm^2); venous disease severity using the Venous Clinical Severity Score[167] at monthly follow up, and ulcer-related quality of life as assessed using the Charing Cross Venous Ulcer Questionnaire at enrolment and upon exiting the trial by healing or reaching six months of follow-up.[168]

Trial assessors were qualified tissue viability nurses who screened all leg ulcers attending the clinic for suitability. On enrolment, baseline VCSS and CCVUQ were completed by the patient and the trial assessors documented baseline BWAT score.

Participants were invited to monthly follow-up visits, at which BWAT and VCSS were documented. Trial assessors determined when a wound was healed. Upon healing, or having completed 6 months of follow up, the participant exited the trial, and a final CCVUQ was again documented.

Statistical analysis

Statistical analysis was performed using StatsDirect™ Statistical Package version 3 (StatsDirect Ltd., Cambridge, UK.). All analyses were performed on an intention to treat basis.

Continuous variables are presented as mean ± standard deviation or median ±interquartile range (IQR) based on parametric or non-parametric distribution. Categorical and ordinal variables are described in absolute numbers with percentage frequencies. For the primary outcome, Fisher's exact test was used to test for significance due to the overall small sample size. Logistic regression was used to evaluate the impact of potential confounding variables on this dichotomous outcome. Kaplan-Meier time to event analysis with log-rank test were used to evaluate time to ulcer healing. The Mann-Wittney U and Wilcoxon Signed-Rank tests were used to assess paired and unpaired non-parametric data such as quality of life outcomes, BWAT scores and ulcer area.

Results

Patients were enrolled from July 2020 through April 2022, during which time 585 consecutive patients with leg ulcers were screened, and 99 eligible VLU consented to participate. The main reasons for non-enrolment were peripheral vascular disease leading to exclusion, or refused consent. One patient healed between enrolment and randomisation so was not randomised. Baseline characteristics of the 98 randomised participants are shown in table 5.

There were no significant differences in the demographic makeup of the two arms in the trial. There were no significant differences in any documented baseline risk factors for impaired wound healing such as smoking, diabetes and immunosuppression between the AA and TIRS groups. More VLU specific factors such as duration, size, and history of DVT were also not significantly different. Median age in the AA group was higher but this was not statistically significant ($p=0.17$). Patients were followed up until their ulcer healed, or they had completed six months of follow up post-intervention with the last patient randomised in April 2022 and follow up completed in October 2022.

Characteristic		Axial Ablation	TIRS
Age		73 (60-79)	67 (60-78)
BMI		30.36 (27.78-32.93)	31.77 (29.1-34.47)
		N (%)	N (%)
Gender			
	Female	36 (65.5)	19 (65.5)
	Male	19 (34.5)	10 (34.5)
Smoking			
	Current	4 (7.5)	2 (5.4)
	Former	17 (32.1)	10 (27.03)
	Never	32 (60.4)	25 (67.57)
	Not recorded	2	2
Obesity			
	Normal	6 (10.9)	5 (12.82)
	Overweight	17 (30.9)	8 (20.51)
	Obese	15 (27.27)	15 (38.46)
	Morbidly Obese	4 (7.27)	2 (5.13)
	No Data	13 (23.64)	9 (23.08)
Diabetes		12 (22.64)	7 (18.92)
Immunosuppression		4(7.5)	4(10.5)
History of Ipsilateral DVT		1 (1.89)	0
History of Ipsilateral Ulcer		21 (42.86)	17 (47.22)
Ulcer Duration (months)		6 (2-12)	5 (2-9)
Ulcer Size			
	<5cm^2	19 (34.54)	17 (43.59)
	5-10cm^2	14 (25.45)	10 (25.64)
	10-25cm^2	7 (12.72)	4 (10.25)
	>25cm^2	15 (27.27)	8 (20.51)
		Median (IQR)	Median (IQR)
Ulcer size		8.04 (3.6-39.58)	5.96 (2.87-12.84)
BWAT at enrolment		28.55 (26.85-30.24)	27.23 (25.04-29.43)
VCSS at enrolment		13 (11-15)	12 (10-15)
CCVUQ at Enrolment		51(36-60)	55 (39-62)

Table 5: Baseline Characteristics Age and Ulcer size are represented in Median (IQR) BMI as Mean (95%CI), all others as Frequency (%)
TIRS= Terminal Interruption of the Reflux Source, BMI= Body Mass Index, DVT= Deep vein thrombosis, BWAT= Bates-Jensen Wound Assessment, VCSS= Venous Clinical Severity Score, CCVUQ= Charing Cross Venous Ulcer Questionnaire

During follow up, Covid-19 restrictions interfered significantly with attendance at the clinic. Enforced reductions in the number of 'non-urgent' patients allowed to attend clinics and the need to balance the competing interests of trial follow up with prioritisation of clinically urgent cases meant that some patients did not attend for assessment by the designated trial assessors. This primarily affected assessment of secondary outcomes and quality of life outcomes in particular, while the primary outcome in some cases was confirmed by phone call to the patient's primary care doctor or primary care nurse. Reduced clinic visits and staffing did not allow an opportunity to re-scan after intervention to document whether ablation had been successful. Four patients withdrew consent or were considered lost to follow up as the primary outcome could not be confirmed.

95 (96.94%) interventions were performed within 2 weeks of randomisation, 1 intervention happened within 3 weeks and the remaining 2 within 5 weeks. All participants underwent their assigned intervention. Two patients in the ablation group underwent repeat ablation before completing follow-up due to persistent reflux with poor progress with their VLU.

Primary Outcome

Within six months of treatment, 39 of 55 (70.9%) VLU in the axial ablation group had fully healed, while 29 of 39 (74.36%) VLU in the TIRS cohort had fully healed. This was not statistically significant; unadjusted odds ratio (OR) = 0.84; (95%CI, 0.295-2.31); p=0.449. Logistic regression did not indicate a significant impact on this outcome for any of the following variables: age, current smoking, diabetes, obesity, ulcer size, ulcer duration and history of previous ipsilateral VLU.

Secondary Outcomes

There was similarly no significant difference in time to ulcer healing. Among those who had a confirmed date when their VLU healed, median time to healing was 68 days (IQR, 41-86) in the axial ablation group and 72 days (IQR, 35-91) in the TIRS group. Kaplan-Meier time to event analysis was used to demonstrate cumulative hazard (figure 3), with censorship of non-healed VLU at 182 days and on this basis median time to ulcer healing was similar in both groups; Axial Ablation 84 days (95%CI, 74.67 to 93.33) Vs TIRS 84 days (95%CI, 73.016-94.983). Hazard ratio = 0.963 for Axial Ablation Vs TIRS (95%CI, 0.595-1.56); p=0.485).

The BWAT was used as both an objective method to assess for a baseline difference in VLU severity, as well as providing a less simplistic impression than size alone to indicate if any significant difference in VLU improvement existed between the groups, especially among those VLU that did not fully heal. BWAT scores improved significantly in both arms, median improvement of 18.5 (IQR, 16-21) points with Axial Ablation and 15.5 (IQR, 12-18.5) with TIRS, p<0.001 for each. There was no significant between-group difference in BWAT score p=0.322 overall, or among those whose VLU did not heal p=0.206.

Finally, there was there was no significant reduction in VLU size in either group among those whose VLU did not heal; Axial Ablation, p=0.5, TIRS, p=0.375.

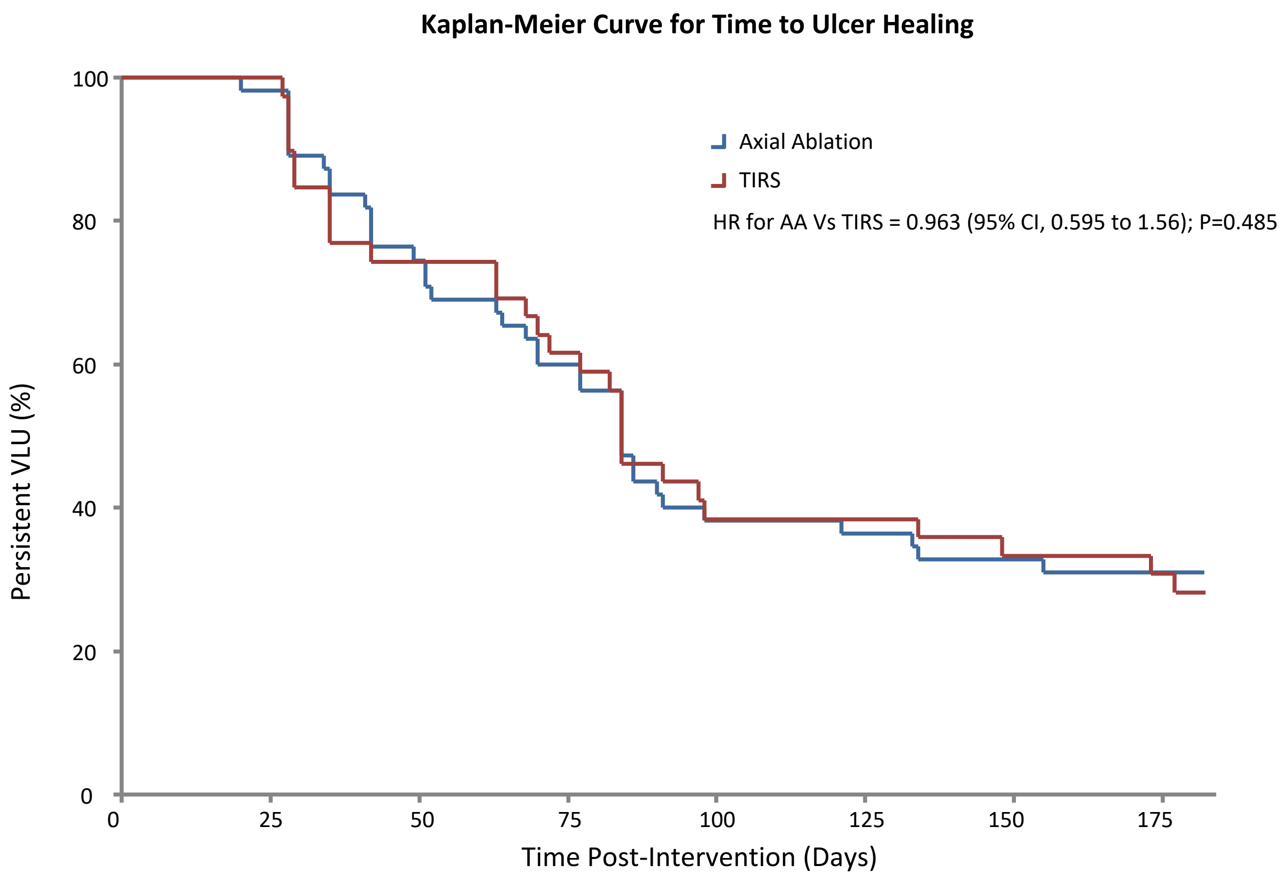

Figure 3: Kaplan-Meier Curve for Time to Ulcer Healing X-axis = Percentage of VLU remaining unhealed Y-axis = Time since intervention (censored at 6 months); HR= Hazard Ratio AA = Axial Ablation, TIRS = Terminal Interruption of the Reflux Source

<u>Quality of Life</u>

Quality-of-life outcomes are summarized in table 6. At baseline, mean CCVUQ scores did not differ significantly between the treatment arms, Axial Ablation 51 (IQR, 36-60) Vs TIRS 55 (IQR, 39-62); p=0.567. Likewise VCSS was similar in both treatment arms; Axial Ablation 13 (IQR, 11-15) Vs TIRS 12 (IQR, 10-15); p=0.584.

Both groups had a significant overall reduction in CCVUQ and VCSS, i.e. an improvement in quality of life. Median improvement in CCVUQ in the Axial Ablation group was 11 (0.5 to 22); p=0.042, and 11.5 (IQR, 3-22); p=0.009 in the TIRS group. Median improvement in VCSS in both groups at completion was 6.5 (IQR, 5-8); p<0.001. VCSS was assessed monthly, with no significant between-group difference at any stage during follow up, and indeed both groups followed a similar pattern with an initial reduction in VCSS from enrolment to first follow-up, with a late return towards baseline VCSS from 4 months.

		Valid n	Median (IQR)	Valid n	Median (IQR)
VCSS					
	At enrolment	54	13 (11-15)	39	12 (10-15)
	1 Month	35	8 (6-13)	31	10 (7-14)
	2 Months	18	9 (6-12)	21	11 (7-12)
	3 Month	17	11 (5-14)	14	9 (6-13)
	4 Months	6	10.5 (10-14)	5	10 (9-11)
	5 Months	6	12 (11-14)	5	11 (10-16)
	At Completion	36	6 (5-7.5)	28	5.5 (4-8.5)
CCVUQ					
	At Enrolment	45	51(36-60)	30	55 (39-62)
	At Completion	33	31 (23-48)	24	35.5 (25-51)

Table 6: Quality of Life Scores
VCSS= Venous Clinical Severity Score, CCVUQ= Charing Cross Venous Ulcer Questionnaire
IQR= Inter-Quartile Range

At completion (i.e. healing or completion of six months of follow up) there was no statistically significant between-group difference in either CCVUQ, 31 (23-48) Vs 35.5 (25-51); p=0.497 or VCSS 6 (IQR, 5-7.5) Vs 5.5 (IQR, 4-8.5); p=0.753.

While quality of life improved for both treatment groups overall, these results were not shared by the cohort in whom VLU did not heal, with no significant improvement in VCSS or CCVUQ in either group; for VCSS, p=0.5 with Axial Ablation and p=0.25 with TIRS, and for CCVUQ, p=0.203 with Axial Ablation and p=0.812 with TIRS. Once again there were no significant between-group differences in VCSS, p=0.584, or CCVUQ, p=0.453.

There were no ulcer recurrences documented by six months.

Discussion

This single centre randomised trial found no significant difference, over up to six months of follow-up, in rates of venous leg ulcer healing between those treated with ablation of reflux in the saphenous veins compared with those treated with terminal interruption of the reflux source using foam sclerotherapy. Patients reported a significant improvement in their ulcer specific and venous disease specific quality of life with both treatments, without a significant difference between treatment groups. This quality of life benefit was not shared by participants whose VLU did not heal.

Two large randomised trials have demonstrated the benefits of treating superficial venous reflux in patients with VLU. The ESCHAR study showed that superficial venous surgery plus compression reduced the rate of ulcer recurrence compared to compression alone, but did not show a significant difference in healing, while the EVRA trial showed that early endovenous ablation of reflux improved time to ulcer healing and healing rates at six months[91].

Since the publication of the EVRA trial we have endeavoured, at our centre, to offer reflux ablation where feasible. The typical patient presenting with VLU at our centre is elderly with multiple comorbidities and often, when offered ablation of superficial venous reflux, intervention has been declined. This provides some explanation for the overall trial recruitment rate of about 17% (99 of 585 patients screened). Many patients do not want 'an operation', but are more than happy to have foam injections. While the EVRA trial showed that early reflux ablation is effective in reducing the time to ulcer healing, there has been a lack of quality evidence to justify the use of TIRS. This led us to conduct this trial to better understand whether TIRS would achieve similar benefits.

AAVTIRS was planned to be adaptive because of the paucity of evidence underpinning the initial power calculation. The evidence around TIRS was considered optimistic at best, and so in the absence of better evidence the decision was taken to base the initial recruitment target on these studies which indicated a non-inferiority trial with an assumption of 80% healing in both trials arms with a 10% non-inferiority limit was reasonable. An interim analysis was planned after the first 50 patients completed follow up to allow for a more robust power calculation. Fairly standard limits for estimating sample size at the outset of trials, 80% power at the 5% significance level, were utilised as it was accepted from the outset that because the original power calculation was likely flawed, this interim calculation would represent the first robust power calculation. It was also accepted that because the initial recruitment target for non-inferiority was based on optimistic and probably quite selective series, the change from non-inferiority to a superiority target might be necessary. At the interim analysis 96.4% (27/28) had healed in the Axial Ablation arm compared to 78.26% (18/23) in the TIRS arm. As outlined above, the sample size was recalculated, suggesting that 98 patients would provide sufficient power to detect significant superiority with 80% power at the 5% significance level. The trial was, therefore, continued until 99 patients had been recruited. The actual healing rates observed (70 to 75%) were lower than originally assumed or suggested by the interim power calculation. Assuming a healing rate of 70% in each arm and a 5% non-inferiority limit, a further trial would require 1040 patients in each arm (2080 patients plus 10% for withdrawals and dropouts). Based upon the observed recruitment rate in AAVTIRS, achieving this sample would require screening approximately 12000 patients. Healing rates in the AA arm fell dramatically after the interim analysis from 96.4% to an overall healing rate of 70.9%. Nothing in our analysis accounts for this discrepancy.

Healing rates in our trial are less than that seen in either arm of the EVRA trial. We attribute this to the chronicity of many of the ulcers in our cohort. An important and often overlooked element of the

EVRA trial is its focus on early intervention. The excellent healing rates seen in the compression-only group in particular suggest that early high-quality compression can go a long way to achieving exceptional healing results. The decision was taken at the outset of the AAVTIRS trial not to restrict eligibility based on VLU chronicity on a very practical basis. Prior experience within the unit was that the majority of patients were not referred until their wound was persistent for a few months at least. This decision was later justified by the fact that even with prioritised appointments and same-day assessment and treatment, median ulcer duration was 5.5 months at enrolment.

Routine duplex assessment after intervention was not performed. While useful information can be gathered from technical success rates, the outcome of concern was VLU healing. There were also more practical reasons. The TIRS cohort would all be expected to have ongoing proximal reflux, difficult to distinguish from failed AA. As the accepted standard treatment, AA would be indicated for patients found to have ongoing reflux unless staff performing duplex knew the treatment groups in advance, otherwise mislabelling of TIRS as failed AA could have caused inordinate numbers of crossovers. In the context of the Covid-19 pandemic, only blinded clinic staff (assessors and trial coordinator) met with patients during follow up to minimise healthcare contacts and these staff could not assess for failed ablation while remaining blinded. Hospital based duplex scans were not feasible during Covid-19 restrictions when only clinically essential hospital attendances could be justified.

No VLU recurrences were noted during follow-up of this cohort. All participants were asked, and many have given their consent to be contacted for longer term follow up in future to look at recurrence rates.

The VCSS is an objective measure of the severity of venous disease, encompassing both ulceration and wound factors, as well as non-wound related signs and symptoms[167] while the CCVUQ is a quality of life questionnaire specific to venous leg ulcers.[168] Both of these were improved significantly in both groups, but not among those whose VLU did not heal. This seems to suggest that in this cohort the benefits are derived predominantly from healing, while treatment of great and/or small saphenous venous reflux does not confer a significant benefit in and of itself. Low numbers in the non-healing cohort however make it difficult to draw any strong statistical inference.

Strengths and Limitations

Several difficulties were encountered in the running of this trial. Recruitment was slower than anticipated and efforts to gather robust secondary outcome data were hampered by reductions in the number of patients attending all outpatient clinics due to Covid-19 restrictions combined with a nationwide health service cyberattack and data loss in 2021. The primary outcome could be affected by having been obtained through phone calls in some instances. Despite planned 1:1 randomisation, the two treatment groups were unbalanced. Block randomisation was not employed. There is some risk of selection bias given the relatively large number of patients screened, with only 17% of screened patients being enrolled. The majority of these were patients with arterial or mixed ulcers unsuitable for compression.

The trial does have some strengths. Ulcer duration was not an exclusion criterion, resulting in a trial population more representative of daily practice in many centres, particularly in rural settings. Assessor blinding of the outcome measures removes the possibility of observer bias influencing the results. To date, this trial provides the only randomised efficacy data comparing VLU outcomes in patients receiving axial ablation versus TIRS.

Conclusion

In conclusion this assessor-blinded randomised controlled trial did not show ablation of superficial venous reflux in the saphenous veins to be superior to foam sclerotherapy, injected into the peri-ulcer venous plexus, in the treatment of VLU as there was no significant difference in rates of healing at six months.

Hyperbaric Oxygen as an Adjunct in the Treatment of Venous Ulcers: A Systematic Review and Meta-Analysis

Background

The use of Hyperbaric Oxygen Therapy (HBOT) as an adjunct in wound care is not a novel concept but the majority of research into this field focuses on ischaemic and in particular, diabetic wounds. The most common cause of lower limb ulcers however is Chronic Venous Insufficiency (CVI), and Venous Leg Ulcers (VLU) pose a massive burden on health services internationally. Literature surrounding the use of HBOT in VLU remains scant.

In ischaemic ulcers, or diabetic wounds where ischaemia is commonly a factor, it is easy to rationalise the benefit of HBOT. In VLU however the benefits are less intuitive. There is a sound scientific rationale however to suggest that hyperbaric oxygen may benefit patients with VLU. Reduced partial oxygen tension has been shown in the tissues surrounding VLU[169] and while the precise mechanisms by which venous insufficiency leads to ulceration have not been fully elucidated, many of the prevailing explanations implicate local hypoxia[170].

Chronic wounds of differing aetiology have many similar characteristics and heal by numerous similar processes and HBOT has been shown to have potential benefits in many of these. Acute inflammation requires the formation of a provisional fibrin and fibronectin extracellular matrix but this process must be halted appropriately, before normal tissue is damaged by the inflammatory response. This can happen when chronic inflammation disrupts normal repair, leading to excessive fibrosis. This inflammatory response can be down-regulated in response to Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which decrease synthesis of chemokines by monocytes and alter inflammatory modulators such as hypoxia inducible factor-1, Haem oxygenase-1, and heat shock proteins. ROS and RNS can also up-regulate neovascularisation by a combination of increased synthesis of growth factors within the wound, e.g., Vascular Endothelial Growth Factor[171] and by increased mobilization from bone marrow of stem and progenitor cells[172]. HBOT leads to increased intracellular oxygen, which produces an increase in ROS and RNS. The effect of HBOT on ROS and RNS is independent of hypoxia, and so the effects of HBOT on chronic wounds should not be expected to be confined to hypoxic wounds. Excessive ROS production can lead to oxidative stress however, which has detrimental effects on wound healing and elevated, sustained ROS have been detected in vivo and have been associated with impaired wound repair in chronic, non-healing wounds[173].

HBOT is delivered across multiple sessions, the number of which can be quite variable. Likewise, the duration of sessions can vary from less than an hour, to four hours or more. Pressure within the chamber pressure is maintained between 2.5 and 3.0 atmospheres for most uses. Acute therapy for decompression sickness or carbon monoxide poisoning usually only require a short course of longer treatments, while chronic wounds may require up to 40 or more sessions of shorter durations[174]. There remains considerable heterogeneity in the process of delivering HBOT.

Objectives

The objective of this review was to investigate if; in patients with VLU, the addition of hyperbaric oxygen to patients' existing wound care was associated with improved healing versus continuing existing pre-study wound care alone.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines[175]. Studies were considered eligible for inclusion if they reported original research comparing patients with an active VLU receiving HBOT, against a control group receiving the same therapy with the single exception of the HBOT. Studies were excluded if they were not published in English and no English language translation could be obtained, or if no abstract could be obtained.

There were two primary outcomes for this review; the proportion of VLU healed in the HBOT Vs Non-HBOT groups, and reduction in VLU area in the HBOT Vs Non-HBOT groups

Search Strategy

The database search was carried out using three databases: PubMed, Scopus and Embase. No significant or landmark articles pertaining to the subject were known in advance so it was considered particularly important that smaller studies not be overlooked, as might happen with a more refined search strategy. Search terms were therefore intentionally kept broad. Searches sought any combination of the terms 'Hyperbaric Oxygen', 'HBOT' or 'Hyperbaric O_2', with any of the terms 'Vein' or 'Venous' or 'Varicose' and the term 'Ulcer'.

After removal of duplicates, titles were screened by two authors (CK and MT), blind to each other, and disputes mediated by a third author (FN). When a list of likely relevant titles was agreed, the same authors screened the abstracts of these. The same reviewers then independently extracted relevant data from the included studies.

Where results were presented at multiple time-points in an individual study, all data were extracted provisionally to allow synthesis of results at similar time-points where possible.

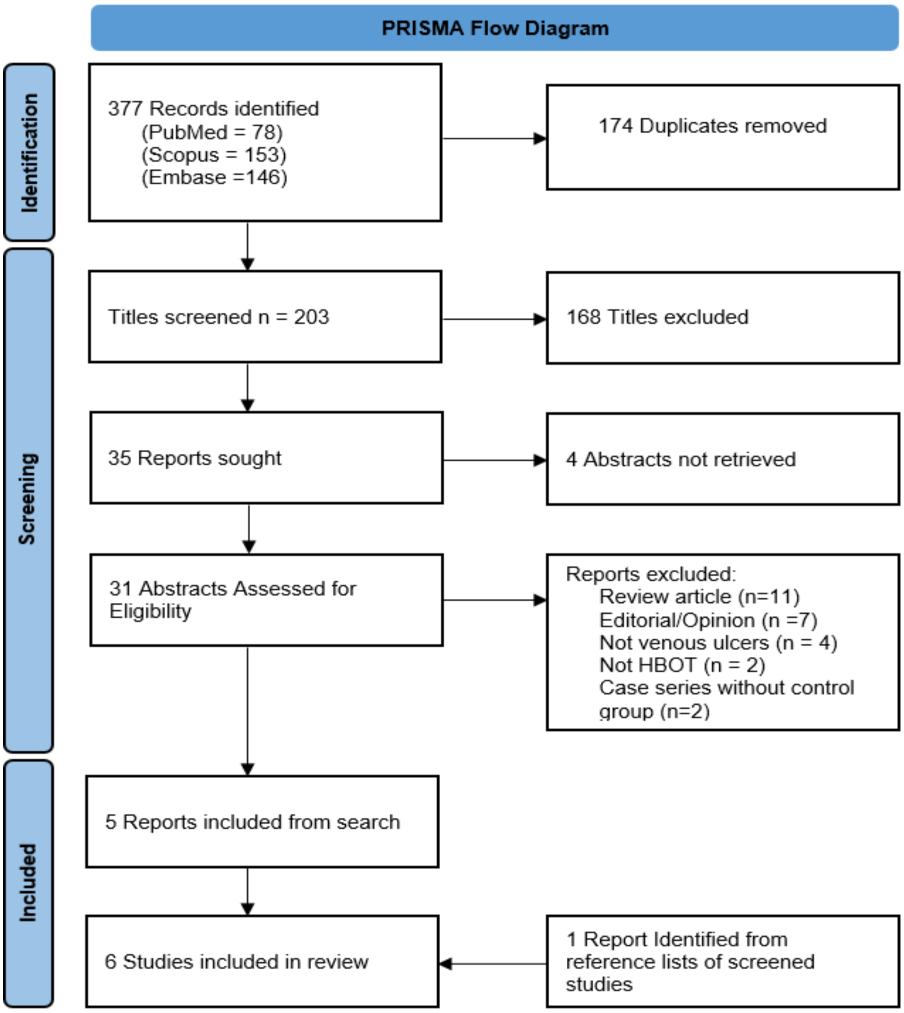

Figure 4: PRISMA flow diagram charting the literature search

<u>Risk of bias</u>

The Risk of Bias-2 (RoB-2)[176] tool was used to assess bias in the randomly allocated studies, while non-random studies were assessed using the Risk Of Bias In Non-randomized Studies (ROBINS-I) tool[177]. These were graphically represented using the Cochrane traffic light system[178].

<u>Synthesis</u>

As a dichotomous variable, healing was reported as the Odds Ratio (OR) with 95% confidence interval (95%CI), and underwent meta-analysis using the OR. The change in VLU size, a continuous measurement, required an effect size meta-analysis. To achieve this despite some studies reporting the change in VLU size as absolute area, while others reported only percentage change, the Standardized Mean Difference (SMD) was used. Random effects models were used for both meta-analyses. Forest plots were used to graphically represent the synthesised data.

Due to the reporting of variable follow up periods two separate groups were devised based on follow-up duration. Where results were presented at different time-points within a study, the results which conformed most closely to one of these groups were used.

All statistical analysis was performed using StatsDirect™ Statistical Package version 3 (StatsDirect Ltd., Cambridge, UK.)

Study Title	Study Type	Intervention	Control	Treatment Course	Follow Up	No. healed/ Sample	
						HBOT	Control
Hammarlund 1994	RCT	HBOT at 2.5 ATA for 90 minutes	Hyperbaric air at 2.5 ATA for 90 minutes	5 sessions /week over 6 weeks	6 weeks	0/8	0/8
Batora 2005	Comparative, allocation unspecified	HBOT at 1.8-2 (reported as 0.18-0.2 MPa) for 72 minutes plus unspecified 'conventional therapy'	Unspecified 'Conventional Therapy'	'Average 26 treatments' over 6 weeks	6 weeks	0/13	0/12
Ahmad 2008	3-arm RCT	HBOT for 90 minutes daily	Wound cleansing twice daily	2 sessions /day for 5 weeks	5 weeks	0/10	0/10
Thistlethwaite 2018	RCT	HBOT at 2.4 ATA for 80 minutes, plus compression and decompression phases. Compression therapy and dressings	Hyperbaric air at 1.05-1.2 ATA for 80 minutes. Compression Therapy	30 sessions	12 weeks	6/14	6/15
Longobardi 2020	3-arm RCT	HBOT at 2.4 ATA for 66 minutes plus compression and decompression phases. Compression therapy	Compression Therapy	One HBOT cohort received 2 sessions /day for 3 weeks, the other 1 /day for 6 weeks	3 and 6 weeks	5/25	1/26
ElSharnoby 2022	Parallel prospective cohort study	HBOT at 2.5 ATA for 1 hour plus compression and decompression phases. Treatment of venous reflux. Compression therapy and dressings. Debridement where necessary.	Treatment of venous reflux. Compression therapy and dressings. Debridement where necessary.	5 sessions /week, 20-40 sessions	12 weeks	5/12	3/13

Table 7: Summary of study characteristics, interventions for HBOT and control groups, follow up and reported rates of complete VLU healing
ATA= Absolute Atmospheric Pressure, mmHg= millimetres of Mercury

Results

The database search of Scopus, PubMed, and Embase identified 377 titles for consideration. The last search was performed on July 7th, 2022. There were 203 unique publications remaining after removal of duplicates. 168 of these were excluded based on their title with a further 4 studies removed as no abstract could be obtained for review, 31 abstracts were screened for relevance. 5 studies were identified for inclusion[33, 179-182]. Figure 4 illustrates a flow diagram of this process.

One of these included studies[182] was found to be a published abstract which was never published as a full journal article. Efforts to contact the authors were unsuccessful. The decision was taken to include data from this abstract by Batora et al in the effect size meta-analysis, as sufficient primary outcome data was provided. This of course comes with the caveat that the risk of bias is higher due to the limited methodological information provided in the abstract. A further search through reference lists of included studies and excluded abstracts yielded 1 further relevant study, by Hammarlund et al[183].

Two of the included studies contained a three-arm design. Ahmad et al[179] included a cohort receiving laser-based treatment which was excluded from analysis. The control 'standard wound care' cohort and HBOT plus 'standard wound care' cohort were included. Longobardi et al[181] primarily investigated markers of progress in VLU healing, but randomised participants to one non-HBOT cohort, and two cohorts of participants receiving different regimens of HBOT. Change in VLU area was reported, but it was reported as change in median VLU area. For the purposes of including this study in the meta-analysis these were converted to mean and standard deviation using the methods described by Luo et al[184] and Wan et al[185].

<u>Risk of Bias</u>

Two separate tools were used to assess risk of bias. Figure 5 shows a graphic representation of the risk of bias in randomized studies included in the analysis, calculated using the RoB-2 tool and the risk of bias in non-randomized studies is shown in figure 6, calculated using ROBINS-I.

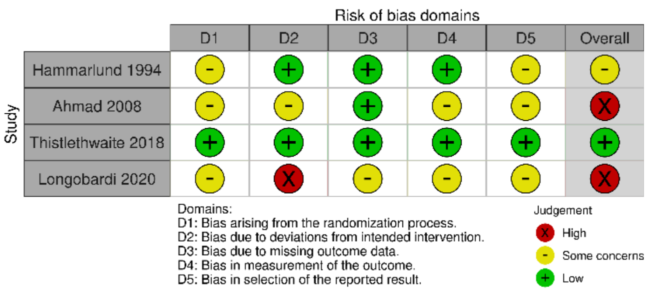

Figure 5 Risk of bias in randomized studies using RoB-2 tool

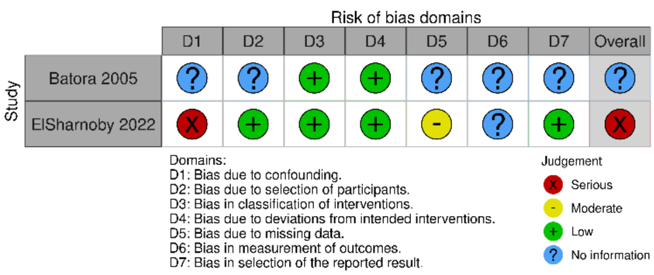

Figure 6 Risk of bias in non- randomized studies using the ROBINS-I tool

There were some concerns of bias in nearly all studies. Only the randomized trial by Thistlethwaite et al [180] was found to have a low risk of bias. In general, concerns arose from the non-reporting of appropriate measures to prevent or limit bias, rather than an actual concern of bias in the study design. The one exception to this is ElSharnoby et al[33]. This prospective study used patients' ability to afford HBOT to determine segregation into treatment and control groups.

Interventions

There is inconsistency in the schedule of HBOT treatment course administered across the included studies but with the exception of Ahmad et al, where the HBOT delivery is unclear, the treatments are broadly similar. The care given to control groups is much more variable however. Hammarlund et al and Thistlethwaite et al went as far as providing a sham treatment in the form of hyperbaric air, while Ahmad et al provided no compression or other therapy that would be considered standard therapy for VLU. The treatments received by both the HBOT and control groups in each study are summarized in table 7.

Outcome 1: Complete Healing of VLU

Only three of the studies reported any VLU having healed completely during the study period[181,33, 180]. Follow-up was heterogeneous, with some studies reporting a 12 week follow up period, while others reported outcomes only at the end of the treatment course of three, five, or six weeks. To minimise the effect of this, studies were pooled in two groups according to the follow-up period employed in each; a 5-6 week group and a 12 week group, with exclusion of one three week group. Table 7 shows the number of participants in each of the studies, and their outcomes. Pooled OR for this group was 5.39 (95%CI, 0.57–259.57); p=0.114, indicating no significant difference in VLU healing between the HBOT and non-HBOT cohorts.

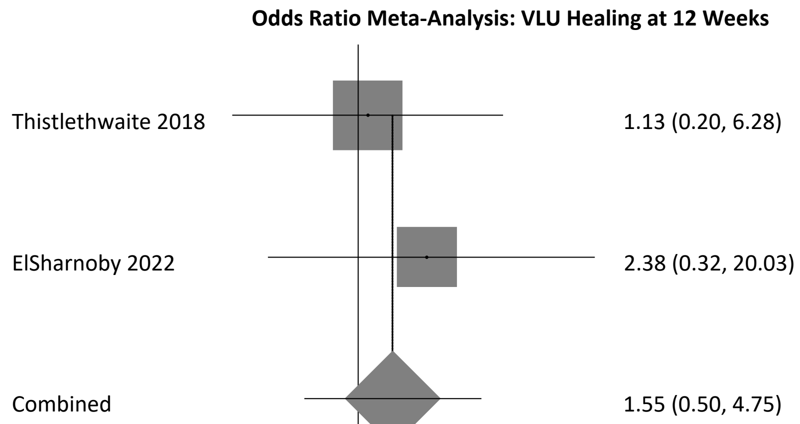

Figure 7: Odds ratio meta-analysis of complete VLU healing at 12 Weeks. OR >1 favours HBOT OR <1 favours control

Thistlethwaite et al and ElSharnoby et al reported 12 weeks of follow up from the commencement of treatment. Pooled OR for this 12 week follow-up group was 1.54 (95%CI, 0.50-4.75); p=0.448, again showing no significant difference in VLU healing rates. Figure 7 contains a forest plot representing this pooled analysis.

Hammarlund et al and ElSharnoby et al both reported longer term follow up than that included in the meta-analysis. There were a number of losses to follow up in the study by Hammarlund et al from the end of treatment until delayed follow up at week 18 (16 weeks after commencement of treatment). While 2 VLU did heal completely within this period, any losses from such a small cohort were felt to pose a significant risk of bias. In order to avoid this, the initial end-of-treatment result was used in the primary analysis. ElSharnoby et al reported one year follow up and at that stage, 10/12 VLU had healed in the HBOT arm, and 7/13 with venous intervention and compression.

Study Title	Participants	HBOT		Control		SMD	95%CI	
	(n=)	Mean Δ VLU area	SD	Mean Δ VLU area	SD			
Thistlethwaite 2018	29	95(%)	6.53	54	6.78	5.98	4.28	7.69
ElSharnoby 2022	25	5.46	2.03	4.42	1.92	0.51	-0.29	1.31
Pooled	54					3.21	2.12	8.54

Table 8: Reduction in VLU area in studies included in the effect size meta-analysis with 12 weeks of follow up. Δ VLU area= change in venous leg ulcer area SD=Standard Deviation 95% CI=95% Confidence Interval SMD=Standardized Mean Difference

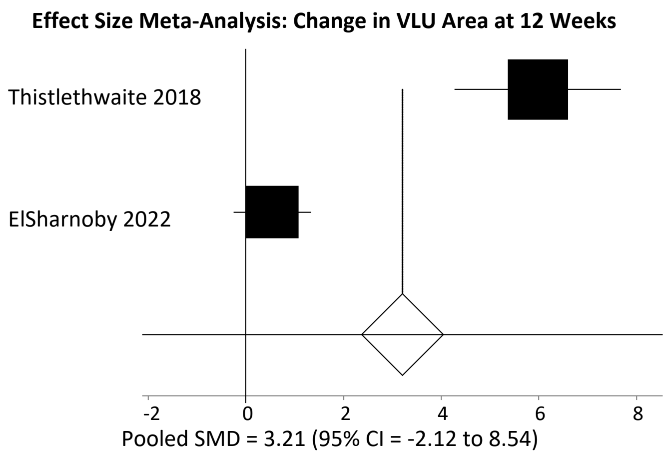

Figure 8: Effect size meta-analysis of change in ulcer area at 12 weeks. SMD > 0 favours HBOT, SMD < 0 favours control. In this case the pooled effect is not statistically significant

Outcome 2: Reduction in VLU Area

All included studies reported change in VLU area over time, but again pooled analysis is limited by variable follow up. Results were therefore separated again into two groups, interrogating the change in VLU area over 12 weeks of follow up (table 8, figure 8) and 5-6 weeks of follow up (table 9, figure

9). A further pooled analysis of change in VLU area over reported follow up was also performed (table 10) to allow a single pooled analysis of all participants. Finally a pooled analysis of all RCTs was performed (figure 10).

Study Title	Participants	HBOT		Control		SMD	95%CI	
	(n=)	Mean Δ VLU area	SD	Mean Δ VLU area	SD			
Hammarlund 1994	16	35.17(%)	17	2.7	11	2.18	0.94	3.42
Batora 2005	25	60.8(%)	42.7	29.3	6.5	0.98	0.15	1.8
Ahmad 2008	20	1.68	0.27	0.77	0.23	3.47	2.09	4.86
Longobardi 2020 (6 weeks)	48	67.46	40.05	59.72	33.86	0.20	-0.34	0.76
Pooled	109					1.59	0.30	2.89

Table 9: Reduction in VLU area; effect size meta-analysis with shorter follow up. Δ VLU area= change in venous leg ulcer area SD=Standard Deviation 95% CI=95% Confidence Interval SMD=Standardized Mean Difference

Study Title	Participants	HBOT		Control		SMD	95%CI	
	(n=)	Mean Δ VLU area	SD	Mean Δ VLU area	SD			
Hammarlund 1994	16	35.17(%)	17	2.7	11	2.18	0.94	3.42
Batora 2005	25	60.8(%)	42.7	29.3	6.5	0.98	0.15	1.8
Ahmad 2008	20	1.68	0.27	0.77	0.23	3.47	2.09	4.86
Thistlethwaite 2018	29	95(%)	6.53	54	6.78	5.98	4.28	7.69
Longobardi 2020 (6 weeks)	48	67.46(%)	40.05	59.72	33.86	0.20	-0.34	0.76
Longobardi 2020 (3weeks)	51	29.75(%)	26.48	31.3	15	-0.06	-0.63	0.50
ElSharnoby 2022	25	5.46	2.03	4.42	1.92	0.20	-0.34	0.76
Pooled	214					1.7	0.60	2.79

Table 10: Reduction in VLU area over any follow up period; effect size meta-analysis. Δ VLU area= change in venous leg ulcer area SD=Standard Deviation 95% CI=95% Confidence Interval SMD=Standardized Mean Difference

Among participants with 12 weeks of follow up the pooled SMD was not significantly different; SMD = 3.21 (95%CI, -2.12-8.54); p=0.238. However, in the 5-6 week follow up group there was a significant difference in favour of the HBOT group, meaning greater reduction in VLU area; SMD = 1.59 (95%CI, 0.30-2.89); p=0.016. These results are represented in figure 5 and figure 6 respectively. Finally pooling of only RCT data, again without segregation by follow up duration, also showed a statistically significant reduction in VLU area with HBOT; SMD = 2.20 (95%CI, 0.55-3.84); p=0.009. These results are represented in figure 7.

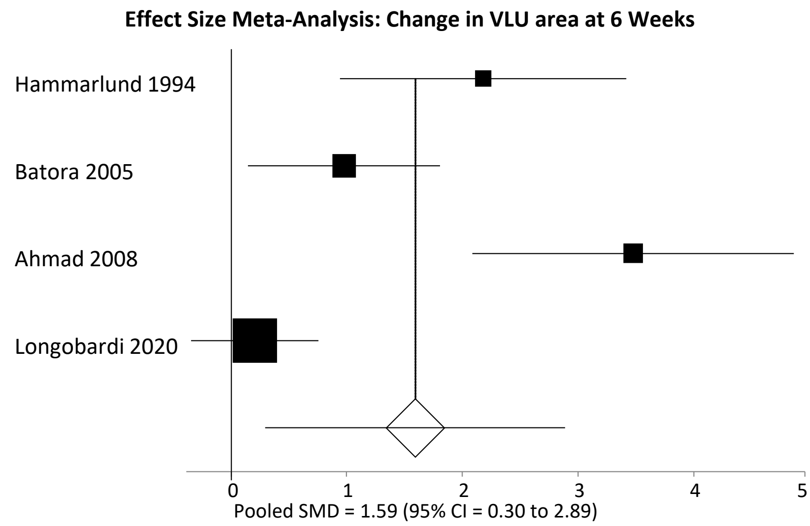

Figure 9: Effect size meta-analysis of change in ulcer area at 12 weeks. SMD > 0 favours HBOT, SMD < 0 favours control. In this case the pooled effect is statistically significant

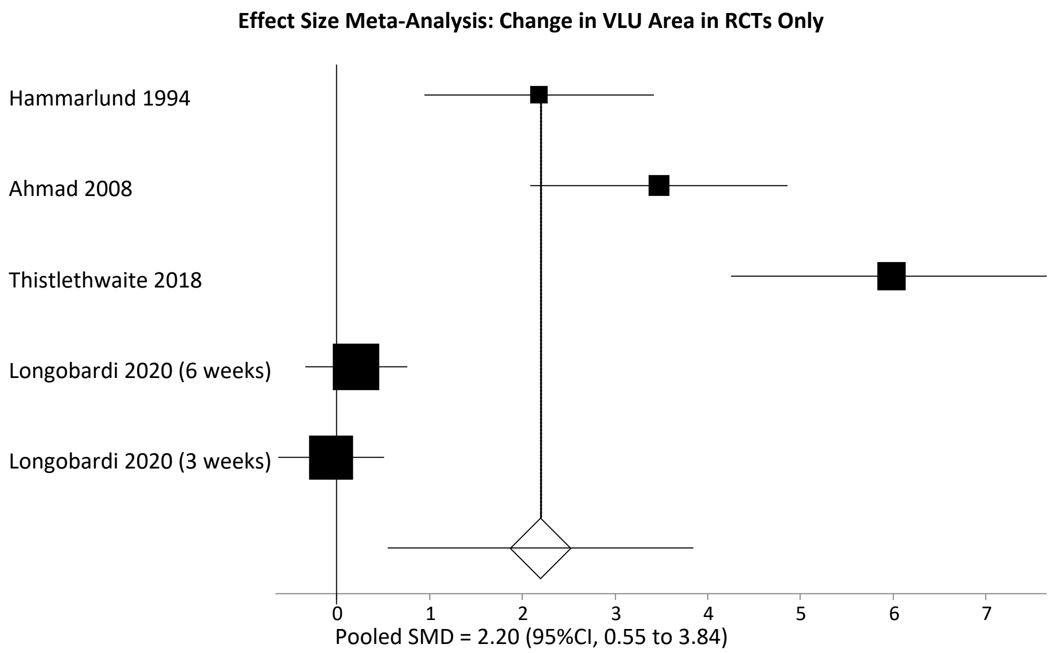

Figure 10: Effect size meta-analysis of change in ulcer area by the end of the study in included RCTs. SMD > 0 favours HBOT, SMD < 0 favours control. In this case the pooled effect is statistically significant

Discussion

A quick glance at the included studies in this review might lead one to believe that that HBOT is a useful adjunct in the management of VLU. With the exception of Ahmad et al, the focus of whose trial was evaluation of laser therapy, all of the included studies concluded in favour of the use of HBOT, stating that HBOT 'may have a role', was 'promising', or was 'a valuable adjunct' in VLU healing. Our analysis however shows no statistically significant difference in the number of VLU healed by the addition of HBOT to existing wound care, suggesting limited, if any, clinical benefit. Our analysis is limited by the heterogeneity in multiple aspects of the included studies, in particular the outcome reporting measures and the duration of follow up.

Variable follow-up means direct comparisons are more difficult to make, in particular for a dichotomous outcome like complete healing of VLU. The lack of complete healing in many studies is probably at least partly attributable to brief follow up. This is borne out by the fact that included studies in which no VLU healed at all, involved no follow up beyond six weeks. However in the best-designed of the included studies, with adequate follow up and the lowest risk of bias, Thistlethwaite et al showed no difference in VLU healing rates at three months.

A serious flaw in an otherwise well-designed study by ElSharnoby et al is the use of patients' ability to afford HBOT to dictate allocation. This has serious potential to confound any results because the ability of patients to afford expensive treatment suggests intuitively that this cohort must come from a higher socio-economic background than the control arm. Lower socioeconomic class has been shown to be significantly associated with reduced VLU healing[186]. Even despite this potential confounding in favour of HBOT, the pooled analysis of healing rates at 12 weeks showed no significant difference between HBOT and controls.

Change in VLU area is a reasonable surrogate marker of treatment effect in VLU, which by their nature tend to be slow to fully heal. Change in VLU area outcomes were reported in some studies as an absolute change from baseline VLU area, while others reported the percentage change from baseline. This necessitated the use of SMD instead of weighted mean difference. While SMD is a perfectly valid statistical method for this comparison, it is much easier to assess the clinical relevance based on the weighted mean difference. The pooled analysis of these studies shows a statistically significant benefit to HBOT. It may well be the case that with sufficient follow up this statistical benefit would translate to a greater number of VLU healing completely, but given that this has not been seen in the groups with the longest follow up, the current data shows a statistically significant benefit without sufficient evidence of a clinically significant benefit.

There was a lack of homogenous control treatments across the included studies. This limits our ability to assess HBOT as an alternative to existing therapies. Only one study involved treatment of venous reflux which is increasingly becoming a standard part of management in VLU care, while only three studies involved compression therapy, which is well established as standard of care.

No indication was provided to suggest there was any stratification based on VLU size in any of the included studies. Given the small sample sizes this is probably unsurprising, but nevertheless has the potential to be a source of bias.

A single, well designed, sufficiently powered RCT would provide much more compelling evidence than the aggregate of existing evidence. A power calculation based on the VLU healing rates at three months in our analysis suggests that such a trial would require close to a thousand participants[187]. Given the costs associated with HBOT, such a trial seems unlikely.

Limitations

The main limitations of this review are the small sample size in the included studies, the high risk of bias within most of the studies, the lack of consistency in control treatments and the short follow up periods. There are some concerns regarding the risk of bias for each study except for Thistlethwaite et al, while ElSharnoby et al is at particularly high risk because of their method of allocation, making socio-economic status a significant confounding factor. Finally, the inconsistency in control treatments limits the applicability of any findings in the real-world setting.

Interpretation

This review has found that while some existing evidence supports the use of HBOT as an adjunct in managing VLU, most of this evidence is of poor quality and therefore, questionable reliability. The addition of HBOT to existing treatment has not been shown to lead to any significant improvement in VLU healing rates in the short term. It has been shown that the addition of HBOT to existing treatment is associated with a statistically significant reduction in area of VLU versus controls, but this does not necessarily translate to a significant clinical benefit.

Conclusion

Poor quality evidence from individual studies suggests a potential benefit from the use of HBOT in managing VLU, but the synthesis of this data does not support its widespread use.

Conclusion

Patients attending LUCI have been receiving consultant-led treatment delivered by experienced nursing staff, with reflux assessment and ablation where appropriate, or diversion to a tertiary centre for management of arterial or outflow vein pathology when necessary. Experience derived from this service has been the guiding force for this body of research. As outlined previously, our goal was to assess the impact of the service and identify opportunities to progress the management of patients with VLU in the West of Ireland beyond compression alone, the long-accepted standard of care. This thesis investigated three distinct domains.

First we wished to assess the impact of the LUCI service itself and whether the dedicated rapid access service provided had an effect on the healthcare needs of VLU patients. The benefits of treating superficial venous reflux in patients with VLU have been established but among patients attending LUCI, TIRS was sometimes favoured by patients as an alternative to axial ablation. The intention of the AAVTIRS trial was to test whether the efficacy of TIRS was sufficient to justify its continuing place in the clinic's armamentarium, or whether all patients considering an intervention should be encouraged to undergo axial ablation. Finally we wished to explore the evidence available for existing methods not already in use in LUCI that might add value within the service by augmenting compression or serving as an alternative in those unsuitable for compression. This was particularly relevant for those with hard-to heal VLU. This inquiry into the evidence for adjuncts to compression was intended to be a wide ranging network meta-analysis but several Cochrane and other systematic reviews had examined dressings and pharmacological agents, finding little in the way of convincing evidence of any benefit.

HBOT had been the subject of a Cochrane review but this looked at undifferentiated wounds. As we wished to look specifically at VLU an up to date and more specific systematic review was considered, and felt to be an attractive area to investigate for two reasons. First, this prior Cochrane review had suggested that HBOT may reduce the size of VLU in the limited studies included that had differentiated wound types. Second, the proximity of the National Hyperbaric Medicine Unit meant that if the existing literature was indicative that HBOT was helpful in the care of VLU, then there was scope to either try to introduce it for LUCI patients, or if there was an inconclusive but promising signal, then there was the potential to investigate its use further in conjunction with the National Hyperbaric Medicine Unit.

Individually, the studies included in this review found HBOT to be a useful adjunct in the management of VLU. This was based on a statistically significant reduction in ulcer area. The key concern of VLU management is healing. Without complete healing, patients continue to feel the adverse effects of their VLU on their quality of life. They also continue to require compression, wound care, nursing inputs and therefore continue to be high cost users of the health system. Reduction in VLU area is a logical surrogate marker of treatment effect, as many VLU will take months to heal, but there is no benchmark for how much of a reduction in area should be considered clinically significant. Logically, a greater reduction in area should translate to quicker healing, but even in the groups with the longest follow-up in this review, this was not seen. It may be the case that insufficient follow-up has impacted healing outcomes in these studies, and longer follow-up may show a benefit in healing, but the evidence to date does not show a clinically significant benefit.

The evidence pertaining to HBOT is tenuous. The studies in the review were of poor quality, with high risk of bias generally and heterogeneity in treatment delivery, follow-up, and controls. The maxim that the quality of a systematic review depends on the quality of the included studies certainly applies. Only three studies involved compression therapy, and only one involved treatment of venous reflux, increasingly part of evidence based VLU care. Treatment and follow-up durations varied, and the reporting of outcomes did not allow for direct comparison between all studies.

Arranging services to maximize access and deliver the necessary quality of care early in a patient's journey is essential for patients with VLU. There is plenty of evidence to support this. One often overlooked yet compelling piece of evidence is the EVRA trial where the deferred treatment arm was found to have the highest healing rates of any cohort being managed with compression alone ever reported in a randomised trial for VLU. These rates are unlike anything seen in our everyday practice where patients are typically seen in vascular outpatients or dressing clinics only after their VLU has progressed from the more easily managed early stages to chronic wounds that have become almost self-perpetuating. In EVRA, VLU were enrolled and treatment begun on average three months from the appearance of their VLU and for some as soon as six weeks. While the ablation cohort healed faster, the results in the compression arm were exceptional and the most obvious explanation for this is commencement of high-quality compression early on in the patient's journey. Early access to this kind of high-quality service was one of the founding principles of LUCI.

Assessing the impact of this rapid access service, we found a fall in the number of inpatient admissions across the Saolta hospital group. This was also associated with a fall in the number of bed-days occupied by patients admitted primarily for management of their VLU. Length of stay remained unchanged and the number of admissions or bed-days used by patients with infection did not change. This is reasonably unsurprising as infected ulcers will still requiring inpatient antibiotic treatment and admissions such as these remain the responsibility of the local hospital there was no reason to suspect that management of these cases hospital would have changed in any respect likely to affect length of stay.

Accurate data are not available for the number of VLU healed in the early years of the clinic, but observed healing rates having changed little in the region, certainly not enough to have made a measurable difference in prevalence of VLU. The number of patients experiencing complications could not therefore be expected to have changed as a result of the clinic's efforts. The decline in the overall number of VLU admissions does suggest however, that LUCI has had some effect. Population-level analyses such as this can never establish causation but the most likely explanation is the availability of an alternative referral pathway. For patients with difficult-to-manage VLU, there was previously no alternative to the emergency department for rapid assessment and expert management. These patients can now be referred to LUCI. No other changes in the management of VLU in this catchment area have been observed or instituted that we feel would account for this reduction in admissions.

Operating in a health system where access to inpatient beds and emergency department trolley numbers are perennial problems, our priority was to assess whether the clinic contributed in any way to alleviating these pressures. Financial costs are of course a key consideration in good governance of any service, but the observed extra bed-days are, in an Irish context, arguably more important. The fall in bed occupancy for patients with VLU suggests there may be significant value in providing the dedicated rapid access service. The data provided around these potential savings are somewhat rudimentary. Aggregated costs per night of hospital stay provide a decent guide to potential savings and served as a useful secondary outcome which we were able to assess using readily available information. A complete cost-benefit analysis incorporating the costs associated with the running of the clinic would of course provide a better picture of its overall economic impact and this is something to look at going forward.

Operating LUCI from Roscommon University Hospital, away from the busy emergency departments of larger hospitals in the region, avoids the risk of cancellations which are a common occurrence in other hospitals to help alleviate pressure on the emergency department, especially during winter surges. This allows the service to function predictably with space for add-ons when urgent assessment is required.

Finally, the availability of same-day treatment aims to minimize delays for those keen to proceed. A 2014 analysis using US data estimated the daily cost of VLU treatment in the outpatient setting at $86[125]. Adjusted for inflation this amounts to €736 per week today. Same-day assessment and treatment is one of the aims of the LUCI service to reduce the otherwise unnecessary waiting time in between. It is not possible in all cases. Many patients will wish to take time to consider their options or try compression alone before going ahead with an intervention. Education of patients prior to arrival to anticipate the possibility of a procedure and ensure that they can be somewhat mentally prepared for it is one simple measure to increase the uptake of same-day treatment. Prioritizing appointments for new VLU patients is another simple measure that most services could easily adopt to optimize treatment as early as possible, even if this is with high quality compression alone.

The purpose of the AAVTIRS trial was to evaluate whether the treatment of venous reflux in the management of VLU required formal endovenous ablation of the axial veins in all cases, or if a less invasive approach with local foam sclerotherapy might achieve a comparable benefit. Some patients attending LUCI were reluctant to undergo what they perceived as a 'bigger' intervention or an 'operation'. This was particularly seen among older patients. The trial encountered numerous difficulties and is by no means perfect. One particular difficulty was that recruitment took place largely during Covid-19 lockdowns when the number of patients able to attend clinics of all types was curtailed. While this probably slowed recruitment, there was a clear effect on follow up. Clinic appointments for new VLU who might require treatment were prioritised over appointments for patients who had already been treated and were due in for trial follow up rather than on the basis of a clinical need. Some primary outcome data was therefore gathered by phone calls to the patient, while monthly complete wound assessments were not documented for many more. This no doubt introduces a risk of bias, though it is reasonable to expect that the relatively dichotomous nature of healed versus not-healed as an outcome should protect against this to some degree.

The trial found no significant difference in the primary outcome, rate of VLU healing within six months, or the secondary outcomes, time to ulcer healing and quality of life.

The lack of a significant difference in VLU healing was somewhat surprising and there are two possible explanations for this. The first is that there is no significant benefit of axial ablation over TIRS. The alternative explanation is that the trial is underpowered to detect a difference. Comparison of our findings with pre-existing evidence does not help in resolving this question as the existing evidence for TIRS is poor quality and this trial is the first time it has been evaluated with comparative data to the best of our knowledge.

At the outset of the trial the evidence for TIRS was considered to be insufficient to inform a reliable power calculation, consisting of potentially selective case-series and small studies which were considered to be poor quality and/or at risk of bias. It was because of this lack of quality evidence that an interim analysis was planned to give a more robust power calculation. Our expectation was that axial ablation would prove superior as it is has shown excellent results when tested against compression therapy alone. Despite this expectation we based our initial recruitment target on a calculation for non-inferiority because taking the evidence for TIRS at face value indicated approximately similar results. The results of the interim analysis however suggested that a recruitment target of 98 would be sufficient to demonstrate a significant difference in a superiority trial and so, as had been planned from the outset, the recruitment target was adapted accordingly. There was a significant difference between the healing rates in the axial ablation cohort before and after the interim analysis. There is no explanation for this that we have been able to discern from the data. The overall success rate with axial ablation would suggest that the power calculation based on the interim analysis is overly optimistic and the trial may well be underpowered.

Another factor which may have affected the power of the trial is the unbalanced randomization. This may have resulted in too small a cohort in the TIRS arm. Having looked more closely at this, with hypothetical analyses we found that if by some anomaly the next 10 patients recruited were to fall into the TIRS arm, balancing out the two arms, no combination of outcomes would lead to a statistically significant finding. It is unlikely, therefore, that the randomization had a material effect on the outcome of the trial, but this cannot be guaranteed.

A power calculation based on the final results suggests that a full non-inferiority trial would require 680 participants.

TIRS at the very least compares more favourably with formal ablation than we would have suspected at the outset. It may well be that the evidence guiding the initial power calculation was actually not as far from the mark as expected. There is some other evidence that would support the view that axial ablation is not as vital as it may seem to improve overall lower limb venous function. The results seen with CHIVA an ASVAL suggest that axial ablation is not uniformly necessary to manage reflux, and that managing problematic veins without treating the axial veins can be a successful strategy. The use of foam in the EVRA trial is also worth considering. Results were comparable whether foam or thermal techniques such as RFA or Laser were used even though foam is known to achieve inferior rates of closure of the axial veins. This suggests that successful axial ablation may not be as essential as expected.

VLU healing in the EVRA trial was greater in both arms than that seen in AAVTIRS, but the eligibility criteria for the two trials mean that they are not directly comparable. The restriction of the EVRA trial to patients with VLU for less than six months is often levelled as a criticism of the trial design, but this is unfair. Randomized trials are a test not only of treatments but of treatment strategy. EVRA tested whether an early ablation strategy made a difference, not just treatment with ablation. We made the decision not to restrict the AAVTIRS trial to a similar early cohort as the only benefit of this would be to allow a more direct comparison. We felt it would be more useful to assess treatment options in all patients. There were two reasons for this. First, we wanted to include hard-to-heal ulcers as these are the real targets of aggressive VLU care strategies. These include the large and the chronic. Second, early access to appropriate services remains a significant challenge. It is difficult to ensure that patients are referred early enough, and so while the benefits of early intervention have been shown, a pragmatic trial involving the same case-mix as the patients we treat in our normal practice would include VLU at any duration. With these harder-to-heal VLU included it is hardly surprising that our results were not as impressive.

Patients treated with either modality experienced significant improvement in their quality of life. Improvements were not significant among patients whose VLU did not heal. One might have anticipated some benefit to axial ablation over TIRS among participants whose VLU did not heal because treatment of axial reflux might improve other symptoms of venous insufficiency. This would not be achieved with a limited treatment like TIRS which leaves residual venous reflux. This was not borne out by our findings, though the trial was not powered to detect this and the numbers in each cohort who did not heal were too small for any significant inference to be made.

It is important to note when interpreting the AAVTIRS trial that it was not, in the end, powered to demonstrate non-inferiority, and so it would be incorrect to assert that there is no difference between TIRS and axial ablation. However, because the AAVTIRS trial does not show axial ablation to achieve superior outcomes in management of VLU, TIRS can at least be considered a viable option.

In the cohort of patients for whom we have been using TIRS over the last number of years in LUCI, the AAVTIRS trial provides sufficient justification to continue to do so as one of a number of available treatment options.

TIRS is a valid treatment option, in addition to compression, for management of VLU.

Areas for Further Research

A single, well-designed, sufficiently powered randomized trial would provide much more compelling evidence regarding the use of HBOT than the existing evidence. This was one of the attractions of investigating HBOT, as the National Hyperbaric Medicine Unit is based in Galway, in the same catchment area as LUCI. The failure of HBOT to surpass the medley of state-of-the-art, standard, and sub-par controls employed in the studies to date suggests that it would not compare favourably in a larger trial against good-quality compression with treatment of reflux where appropriate. In Ireland, HBOT costs in the region of €150 per session in the private sector, and while at scale this could presumably be delivered for less, the cost of weeks or months of treatment in a trial would be difficult to justify based on the evidence of this systematic review. Such a trial would also require close to a thousand participants.

There are a number of areas that need to be explored in the realm of venous ablation for VLU. The results of AAVTRS suggest that a trial with 680 participants would be required to demonstrate non-inferiority. Unfortunately, this is not something for which we have the resources as a single unit. Based on recruitment rates seen in AAVTIRS, 12,000 patients would need to be screened. This would necessitate a multi-centre approach and therefore significant funding for administration and coordination alone. Further small trials to confirm or dispute the results of AAVTIRS would be welcome, and different primary endpoints, such as time to ulcer healing, may yield different results. Other areas of interest include the question of whether management of varicosities is necessary when treating reflux for VLU. A combination of TIRS plus axial ablation may prove more effective than either modality alone, though there is presumably a point at which increasingly aggressive attempts at ablation will lead to an increased VTE risk.

Finally there is growing awareness in the vascular community, among those with a venous subspecialist interest in particular, of the importance of improving the efficiency and quality of care available to patients with VLU. It has long been known that the sooner a VLU heals the less it costs for the health service. In assessing the impact of the LUCI service on admissions we have provided some evidence of benefit, though the focus was on admissions and bed-days. A formal cost-benefit analysis would provide a more firm business case for rollout of similar services throughout Ireland.

Appendix A

Axial Ablation Versus Terminal Interruption of the Reflux Source (AAVTIRS): A Randomised Controlled Trial

Study Protocol for an Assessor Blinded Randomised Controlled Trial

Keohane C.R., Westby D., Twyford M., Ahern T., Tawfick W., Walsh S.R.

Principal Investigator:	Mr Colum Keohane Lambe Institute for Translational Research, National University of Ireland Galway
Supervising Investigator/ Primary Sponsor:	Professor Stewart R. Walsh Consultant Vascular Surgeon, University Hospital Galway, and Associate Director, Lambe Institute for Translational Research, National University of Ireland Galway.
Protocol Date:	26 April 2022
Protocol Version:	3
Trial registration:	Clinicaltrials.gov registration NCT04484168

Trial Synopsis

Title:	Axial Ablation Versus Terminal Interruption of the Reflux Source in Venous Ulcer Management: A Randomised Controlled Trial in Venous Ulcer Management
Public Title	AAVTIRS trial
Medical Condition Under Investigation	Lower Limb Venous Ulcers
Purpose of Trial	To evaluate whether there is a clinically significant difference between Axial Ablation of varicose veins and peri-ulcer Terminal Interruption of the Reflux Source in promoting healing of lower limb venous ulcers.
Primary Objective	To determine if the proportion of ulcers healed within six months of endovenous treatment differs between patients undergoing axial ablation of varicose veins, or terminal interruption of the reflux source by peri-ulcer foam sclerotherapy.
Secondary Objectives	To determine whether there is a significant advantage to either treatment, in reduction in ulcer size, encouraging wound regeneration, and venous disease severity, or a significant difference in patient-assessed quality of life, between the two interventions
Trial Design	Prospective Single Centre Assessor Blinded Randomised Controlled Trial
Primary Endpoint	Proportion of ulcers healed within six months of intervention
Secondary Endpoints	Absolute and relative reduction in ulcer size Time to ulcer healing BWAT score progression VCSS progression over time Change in Charing Cross Venous Ulcer Questionnaire score from treatment to completion of follow-up
Sample Size	320 individual ulcers
Summary of Eligibility	Patients with a leg ulcer, attributable to venous insufficiency, without any contraindication to compression or either of the comparator treatment modalities will be included
Screening Process	All patients with a venous ulcer attending a Leg Ulcer Centre Ireland- a dedicated venous ulcer assessment clinic in Roscommon University Hospital will be considered for enrolment.
Randomisation	Affected legs will be randomised in a 1:1 ratio to Axial Ablation, or Terminal Interruption of the Reflux Source

Treatment	Patients will be treated on the same day as randomisation according to their assignment to either group
Follow-Up	Patients will be followed monthly for six months
End-of-Study	The trial will end when all patients have been enrolled and completed both treatment and six month follow-up
Safety Monitoring	The principal investigator will be notified of any serious adverse events, and they will liaise with all investigators and the ethics committee.
Criteria for Stopping Trial on Safety Grounds	Unacceptable risk to participants due to unexpected serious adverse events Unacceptable rate of adverse events Interim demonstration of a significant difference in efficacy Interim demonstration of a significant difference in rate of adverse or serious adverse events Intolerable discomfort during treatment or compression, or inability to adhere to protocol for any other safety related reason leading to insufficient compliance with randomisation
Registration	Clinicaltrials.gov registration NCT04484168. Registered 23/7/2020
Recruitment	Commenced 21/7/20 –ongoing. Planned completion 1st quarter of 2022, last patient last visit 3rd quarter of 2022
Recruiting Country	Ireland
IPD Sharing	Not planned
Funding	No funding has been received for this research
Ethics	Approved by Galway University Hospitals Clinical Research Ethics Committee 18/6/2020, ref. no. C.A. 2416

Background

Venous ulceration poses a massive burden on health services internationally [140, 145-147]. In Ireland, prevalence of leg ulcers is 1 per 800 people in the general population, rising to 1 per 100 over the age of 70 years[145]. Compression therapy has been shown to expedite healing of venous ulcers[149, 150]. However, it is time consuming for patients and practitioners and requires significant community support.

Superficial venous reflux is frequently present in patients with venous leg ulcers[151]. Surgical treatment of varicose veins, in combination with compression, has been shown to improve the rate of ulcer recurrence, but the ESCHAR trial didn't show any benefit in ulcer healing from surgery[89, 90]. Therefore many guidelines only recommend surgery as a means to reduce recurrence[188]. Numerous observational studies[153-156] and in particular the EVRA (Early Venous Reflux Ablation) trial have demonstrated that after endovenous treatment of reflux, ulcers do tend to heal faster, reducing ulcer persistence at six months[91]. This has important implications both for the patient in the psychosocial burden of venous ulceration[160], and for the economic burden of ulcer management on community, outpatient and inpatient services.

Endovenous management of reflux is achieved by ablation of the main superficial veins of the leg, or Axial Ablation (AA). If incompetent, the long or short saphenous veins, or their larger tributaries, contribute to venous ulceration by raising venous pressure, and therefore capillary hydrostatic pressure, leading to oedema, relative under-perfusion and hypoxia, and triggering an inflammatory cascade[189]. AA encourages healing by reducing venous reflux, decreasing venous pressure in distal veins, which improves the perfusion pressure at the capillary level. This improves oxygen and nutrient delivery to ulcerated areas, facilitating wound healing. Terminal Interruption of the Reflux Source (TIRS) aims to target those veins in the distal leg which are directly responsible for transmitting the raised venous pressure to the ulcerated area, and by only treating these specific veins, achieve the necessary improvement in perfusion locally. While a review of the level 1 evidence has shown less anatomical success with ultrasound-guided foam sclerotherapy, clinical success was similar[190]. Foam sclerotherapy has been shown to be safe and effective in the management of venous ulcers [191, 192]. The ability to deliver foam via a small needle without anaesthetic makes foam sclerotherapy ideal for TIRS, and studies of perilesional sclerotherapy have found it to be safe and effective[98-100].

Treatments

<u>TIRS</u>

TIRS will be achieved using foam sclerotherapy. This involves ultrasound assessment of the ulcerated area and identification of veins which allow reflux into the ulcer itself. Under ultrasound guidance a small needle is used to inject a sclerosant foam directly into those veins identified for treatment. The sclerosant Sotradecol (Sodium-Tetradecyl-Sulphate) will be used for all patients in the trial. The liquid form of sotradecol will be made into foam by agitating 1ml sotradecol with 4ml air in two 5ml syringes in a modified Tessari method[165].

Axial Ablation

All patients randomised to AA will have Mechanical Occlusion with Chemical Assistance (MOCA). Because this technique is non-thermal, it can be used in more superficial veins, facilitating use in a wider range of anatomies than a thermal technique. Clarivein™ (Vascular Insights LLC, Quincy, USA) is a device consisting of a rotating wire within a catheter. The catheter allows the infusion of sclerosant, while the rapid rotation of the wire scores the intima of the vein, generating an inflammatory response. The infusion of the sclerosant via the same catheter as the wire ensures that it is spread around the full circumference of the vein by the wire as it rotates, further augmenting the inflammatory response, causing occlusion of the vein initially, followed by obliteration. Sotradecol will also be used as the sclerosant in these patients.

Aim

The aim of this trial is to answer the following research question:

In adult patients with venous ulcers, are TIRS and AA equivalent in their ability to increase the proportion of ulcers that heal completely within six months of treatment.

Null hypothesis; there is a clinically significant difference in ulcer healing

Alternative hypothesis; there is no clinically significant difference in ulcer healing.

Objectives

Primary Objective

To determine if the proportion of ulcers healing within six months of treatment with AA of varicose veins by MOCA or TIRS by peri-ulcer foam sclerotherapy is equivalent

Secondary Objectives

To determine if there is a significant difference between the two treatments in

1. Absolute reduction in ulcer size
2. Relative reduction in ulcer size
3. Time to ulcer healing, in those patients whose ulcer has fully healed by the end of the trial
4. Wound regeneration

5. Objective venous disease severity
6. Patient-assessed quality of life

Methods

Statement of Trial Design

This is a prospective, assessor blinded randomised controlled trial. The primary trial centre will be Leg Ulcer Centre Ireland operating in Roscommon University Hospital, with oversight from the Department of Vascular Surgery, University Hospital Galway (UHG). Other centres may come on board in the future.

Randomisation

Once enrolled, patients will be stratified by ulcer size (<5cm^2, 5.1 to 10cm^2, 10.1 to 25cm^2, >25cm^2) and will be randomised to either arm on a 1:1 basis.

<u>Sequence Generation</u>

Randomisation will be done using a computer generated random number sequence, stratified by ulcer size

<u>Allocation Concealment</u>

Randomisation will be performed using sealed opaque envelopes containing treatment allocation, sequentially marked within each stratification level, to be opened by the operating surgeon immediately before intervention.

Implementation

On enrolment the principal investigator will assign a trial number to the patient and be informed of the ulcer's size. An envelope will then be taken from the appropriate stratum. The trial number will be written on the envelope, and the envelope passed to the surgical team. The team performing the procedure will sign the envelope sealed, and open it in the operating room immediately before the procedure. A member of the surgical team will then take appropriate consent from the patient for the specific procedure being carried out.

Sample Size

Power calculation[164] was informed by existing evidence[91, 154-156], predominantly the EVRA trial[91]. EVRA showed a 95% success rate for ulcer healing at 24 weeks. We anticipated a more modest success rate because our exclusion criteria did not limit participants to those with new ulcers. In addition, TIRS has very limited existing evidence with reporting healing ranging from 83% to 100% [98, 99]. An 80% success rate was felt to be reasonable for both treatments in a non-inferiority trial. A cohort of 308 patients (154 per arm) was required to ensure that if the null hypothesis should be rejected, the limits of a two-sided 90% confidence interval would exclude a difference between the groups of more than 15%, with 90% power at 5% significance level.

Given that existing evidence for TIRS consists mainly of small case series with widely varying healing rates, we planned once the first 50 cases exited the trial (either healed or completed 6 months of follow-up) as a pilot to inform a further power calculation for both superiority and non-inferiority outcomes.

Outcomes

Primary Outcome

The proportion of ulcers which have healed by the time they are reviewed at 24 weeks.

Secondary Outcomes

1. Time to ulcer healing; in those ulcers where complete healing is achieved
2. Absolute reduction in ulcer size
3. Relative reduction in ulcer size as a percentage of original ulcer area
4. Wound regeneration as indicated by changes in Bates-Jensen Wound Assessment Tool (BWAT) score over time
5. Change in Venous Clinical Severity Score (VCSS) monthly from randomisation to exit from the study
6. Changes in Charing Cross Venous Ulcer Questionnaire (CCVUQ) score from randomisation to exit from the study

The BWAT is a tool originally derived for assessing pressure ulcers [166], but which has been validated for venous ulcer use[193].

The VCSS is an objective measure of the severity of venous disease, encompassing both ulceration and wound factors, as well as non-wound related signs and symptoms[167].

The CCVUQ is a quality of life questionnaire specific to venous leg ulcers [168]

Safety

Definition of an Adverse Event

Any medical misadventure encountered as a direct or indirect result of treatment received as part of the trial.

Definition of a Serious Adverse Event

Any adverse event, as defined, that results in hospitalisation or prolonged hospital stay, permanent or prolonged incapacity, significant disruption to daily life, threat to life, death, or any congenital abnormality arising from treatment, will be deemed a serious adverse event.

Anticipated Adverse Events

The procedures involved in this trial are typically safe and well tolerated. Though any serious adverse event is unlikely, there are known potential adverse events with both treatments. These include:

1. Pain
2. Bleeding
3. Infection
4. Phlebitis
5. Staining of skin
6. Palpable subcutaneous lumps
7. New ulceration
8. Deep vein thrombosis
9. Pulmonary embolism, including life threatening or fatal embolism
10. Stroke
11. Nerve injury leading to pain/paraesthesia/reduced sensation
12. Skin breakdown or hypersensitivity reaction secondary to compression/dressings
13. Adverse or hypersensitivity reaction to local anaesthetic or sotradecol

Adverse Event Reporting

The principal investigator should be notified of all adverse events. In the event of multiple similar adverse events, or any serious adverse event the trial monitoring committee and local ethics committee will be notified, and risk analysis performed.

Trial treatment

Patients enrolling in the trial will treated with either TIRS or AA according to their randomly assigned group and will then be placed in compression. Compression will take the form of two- or four-layer compression bandaging, using either Profore™ (Smith & Nephew, London, UK) or Coban™ (3M, Maplewood, Minnesota, USA).

Trial Monitoring

The principal investigator will take responsibility for the day-to-day management of the trial supervised by the supervising investigator. Meetings will be held every two weeks between the principal investigator and supervising investigator to monitor recruitment, data collection and problems as they arise. The trial monitoring committee will meet as necessary to review safety issues. An independent data monitoring committee has not been established as the trial interventions are low-risk and consist of already-available and recognised treatment strategies. Any safety or equipoise concerns will be reported to those members of the Department of Vascular Surgery in University Hospital Galway who are not involved in the conduct of the trial for their consideration. This will include the results of the interim analysis.

Personnel

The principal investigator will manage this trial, along with help from the on-site tissue viability nurse, and the co-authors. The principal investigator will specifically have responsibility for screening and enrolment of patients, data collection at randomisation and follow-up, and statistical analysis.

The trial nurse(s) will assess all wounds prior to allocation and perform blinded assessment at each subsequent follow-up visit.

Method of Blinding

The trial will be assessor blinded. The trial nurse(s) will assess all wounds prior to randomisation, and will be blinded to treatment allocation throughout, performing assessments at each follow-up visit. Patients will be instructed not to reveal the nature of their treatment in follow-up. The operation note from the intervention will be filed in the patient notes to allow intentional or emergency access. All members of the trial team involved in data collection and analysis, will not be present when the envelope is opened at the time of treatment.

Any treatment decisions required beyond the trial protocol will be made by a member of the surgical team who is already unblinded.

Ultrasound assessment of treated veins will be avoided unless otherwise indicated, to minimise risk of inadvertent unblinding of assessors.

Ethical Approval

Ethical approval has been obtained through Galway University Hospitals Clinical Research Ethics Committee, the Research Ethics Committee governing Roscommon University Hospital. Approval was granted on 18/6/2020, ref. no. C.A. 2416, before recruitment commenced.

Screening of Patients

Patients will be recruited from Leg Ulcer Centre Ireland, a dedicated leg ulcer clinic in Roscommon University Hospital, drawing referrals from the entire Saolta Hospital Group in the West of Ireland. General Practices in the area will receive written information in advance of the trial commencing to encourage direct referral to the clinic. All patients attending this clinic with a leg ulcer will be screened for eligibility including an ultrasound assessment by a member of the surgical team. Written trial information will be provided to each eligible patient, and the option to defer enrolment for a period of consideration will be offered.

Inclusion criteria

Patients will be eligible for the trial provided that the following criteria are met:

- Primary or recurrent venous leg ulcer
- Long or short saphenous vein reflux confirmed on ultrasound assessment, defined as retrograde flow lasting for >0.5 seconds in the standing position
- Ankle-Brachial pressure Index (ABI) ≥ 0.8 (if ulceration prevents ABI, Toe-Brachial Index (TBI) ≥ 0.5 acceptable), or a palpable pulse
- Ulcer size between 1 and 200 cm^2
- Patient suitable for full compression bandaging

Exclusion criteria

Patients will be excluded if any of the following apply:

- Pregnancy (or breastfeeding and needing to feed within 48 hours of treatment)
- Active infection of ulcer, or infection within the last two weeks
- Leg ulcer of non-venous aetiology as determined by clinical assessment
- Isolated perforator vein reflux only
- Evidence of deep venous insufficiency or thrombosis
- Known hypersensitivity to Sotradecol or similar sclerosants
- Previous inability to tolerate compression bandages
- Presence of any contraindications for the use of compression bandages:
    - Absence of a palpable pulse, and Ankle Brachial Index (ABI) <0.8
    - Decompensated congestive cardiac failure (NYHA Class IV)

    - Known hypersensitivity to any of the component materials

- Patients unable to provide informed consent
- Patients attending the leg ulcer clinic already will be excluded from enrolment with the same ulcer but will be eligible to enrol with a contralateral ulcer. Recurrent ipsilateral ulcers will not be excluded.

Consent

Each patient who meets the eligibility criteria will receive a full explanation of the trial aims and rationale, as well as the concept of equipoise. To participate, each patient will have to provide written informed consent to participation, treatment, and data processing. Risks and benefits of both trial treatments will be explained, along with potential complications of compression therapy. At this point they will be given the opportunity to enrol, take time to consider, or not enrol with the assurance that non-participation will not adversely impact further treatment, nor will leaving the trial during follow-up. Three copies of the consent form will be signed, (one each for the patient, the patient's hospital notes, and the trial database). Consent for data storage will be discussed and permission sought to contact patients in the future to seek further consent for any further use of collected data.

Data collection

After screening and enrolment, clinical and demographic data will be collected for each participant using a trial case report form. These data will be entered into the trial database on an on-going basis.

Data Protection/Storage

The trial database will be stored on a password-protected, desktop computer in UHG. A backup copy will be prepared at the end of each data entry session and stored in a locked filing cabinet. The original data-entry case report form will be retained with a copy of the consent form in a locked trial filing cabinet within the Vascular Research Unit. All data shall be monitored by approved trial personnel only and processed and stored in the strictest confidence in accordance with Irish and European Union data protection law. All data will be retained in the care of the principal investigator for a period of five years from the closure of the trial.

Baseline Characteristics

After screening, enrolment and provision of informed consent, the principal investigator or trial nurse will collect the following demographic data:

1. Age

2. Sex
3. Height
4. Weight
5. Body Mass Index (BMI)
6. Diabetes
7. Smoking
8. Anaemia
9. ABI, (or TBI if ulceration prevents cuff application at the ankle)
10. Immunosuppression
11. Medications at time of randomisation and treatment

Ulcer Characteristics

Along with the above baseline characteristics, the following data related to the wound itself will be documented:

1. Ulcer location
2. Ulcer duration
3. Ulcer area (in cm^2)
4. Depth (in terms of tissue layers involved)
5. Condition of Wound edges
6. Undermining
7. Necrotic tissue type
8. Necrotic tissue amount (as a percentage of wound area)
9. Exudate type
10. Exudate amount
11. Surrounding skin colour
12. Surrounding tissue oedema
13. Surrounding tissue induration
14. Granulation (as a percentage of wound area)
15. Epithelialisation (as a percentage of wound area)
16. Pain (present or not, and relieved by medications or not)

At follow-up visits only:

17. Compliance with compression

These data will be recorded by the trial nurse and a BWAT score and VCSS will be calculated.

At each review appointment, the same data will be collected, and progress of the wound assessed using the BWAT. VCSS will also be monitored monthly.

Quality of Life Data

At their initial visit, and when exiting the trial (ulcer healed or completion of six month follow-up), participants will complete a CCVUQ questionnaire[168]

Treatment Regimen

Once patients have been assigned a trial number and randomized their sealed allocation envelope will be retained. Where possible enrolment, allocation and treatment will occur on the same day to maximise adherence to trial treatments.

The interventions being tested involve the following core steps

<u>TIRS</u>

I. Ultrasound guided puncture of the desired vein using a butterfly needle
II. Injection of up to 10ml sotradecol foam (max 2ml 1% sotradecol agitated with 8ml air to give 10ml foam) under ultrasound guidance
III. Massage of the foam as needed into desired vessels

<u>AA</u>

I. Ultrasound guided micropuncture of the desired axial vein
II. Placement of a 5 French-gauge sheath
III. Passage of the Clarivein™ device to the proximal end of the treatment area
IV. Activation of the device, followed by withdrawal at a rate of 1mm/second, while simultaneously infusing sotradecol.

Variations of these treatments are at the discretion of the treating surgeon as long as the above steps are met. After treatment all patients will be placed in compression bandages. They will then be followed up monthly at the same site with changes of their compression bandages in between by their local Public Health Nurse (PHN) weekly, or more frequently as needed. If at any follow-up visit, their ulcer is seen to have healed, the time at which it healed will be noted in weeks from intervention. At this point they will have completed their follow-up and will exit the trial. Patients in whom the ulcer has not fully healed at 24 weeks will also exit the trial. In either case subsequent treatment will be at the discretion of the surgical team.

Statistical Analysis

Statistical analysis will be performed using StatsDirect™ Statistical Package version 3 (StatsDirect Ltd., Cambridge, UK.). All analyses will be performed on an intention to treat basis, but a per-protocol analysis will also be performed. Continuous variables will be presented as mean (±standard deviation) or median (±interquartile range) based on distribution, with 95% confidence intervals. They will be analysed using Student's T-test for parametric and Mann-Whitney U test for non-parametric data. Categorical variables will be described in absolute numbers with percentage frequencies. Chi-squared and Fisher's exact test will be used.

Trial allocation will be concealed during interim statistical analysis unless a significant difference is found at this point which warrants stopping of the trial, or the interim analysis indicates the trial could not be completed within a reasonable timeframe.

Criteria for Discontinuation

Should reasonable justification for termination or suspension of the trial be encountered the principal investigator will notify the regional research ethics committee and all investigators involved in the trial in writing.

- Unacceptable risk to participants due to unexpected significant adverse events
- Interim demonstration of a significant difference in efficacy
- Interim power calculation indicating that significantly more participants would be required, which would prevent the trial being completed within a reasonable timeframe
- Intolerable discomfort during treatment or compression, or inability to adhere to protocol for any other reason leading to insufficient compliance with randomisation
- Incomplete data collection precluding coherent analysis

Protocol Violations

Inability to tolerate AA or TIRS, or compression bandages will constitute a violation of protocol. Failure to attend follow-up on a single occasion will not constitute a protocol violation, and patients will be contacted by phone to arrange further follow-up. All analyses will be performed primarily on an intention to treat basis, but a per-protocol analysis will also be performed.

Losses to Follow Up

At enrolment all patients will be informed of the importance of attending follow-up according to the trial protocol. The principal investigator will endeavour to contact any patients missing a follow-up appointment.

Drop-Out Criteria

Participants will be considered to have left the study if, despite all efforts of the trial team, no reliable determination can be made regarding the primary outcome.

Schedule

Referral

Once referred for ulcer management, patients will be seen within six weeks, with the aim of keeping all waiting periods under one month.

1st Clinic Visit

At their 1st visit to the clinic, patients will be screened and, if found to be eligible, the principal investigator or another designated trial investigator will discuss enrolment. If willing, patients will have their baseline data and wound assessment recorded as above and be randomised and treated on the same day as screening unless they wish to defer enrolment.

Deferred Enrolment

Patients wishing to take time to think about enrolment will be offered the chance and brought back to the clinic at an interval agreeable to them.

Patients already attending the ulcer clinic will be eligible for enrolment if they present with a new contralateral ulcer.

Subsequent Follow-up

Patients will attend monthly follow-up, with instructions to the PHN changing their dressings to continue compression until follow-up in all cases. At follow-up appointments patients will fill a VCSS questionnaire, and the trial nurse will assess their wound and document the BWAT score. Non-healed ulcers will be placed in compression with any other dressings or adjuncts as appropriate and continue follow-up.

Final Follow-up

Once a patient has attended for follow-up and their ulcer has healed, they will exit the trial. If the ulcer does not heal by 24 weeks post intervention these patients will exit the trial at this point. At their final visit patients will have a BWAT score, VCSS, and CCVUQ questionnaire recorded. All patients completing follow-up, either through completion of six months or having healed their ulcer, will be seen by a member of the clinical team in the ulcer clinic who will determine ongoing follow-up management.

Dissemination

Registration

The trial is registered at clinicaltrials.gov, reference number NCT04484168.

Reporting

The trial protocol will be published in a suitable peer-reviewed journal and recorded in keeping with the SPIRIT guidelines[194] . Trial results will be submitted for peer reviewed publication regardless of outcome. The principal investigator will have responsibility for drafting the manuscript and all co-authors will have editorial input.

Discussion

TIRS has not yet been tested in a randomised trial so this will be the first rigorous test of the efficacy of TIRS. By comparing TIRS against AA there is the opportunity for significant savings in healthcare resources because TIRS using sclerosant foam is less expensive and less time consuming than AA, as well as less invasive. If the results of TIRS are comparable to those of AA then a significant savings resources could be made.

The EVRA trial required that all participants undergo treatment to the lowest point of reflux, but did not specify that all participants undergo formal ablation, and patients may have been treated with foam from the lowest point of reflux, in a manner similar to the aim of TIRS. The results of this trial will help to refine best practice in how reflux ablation to aid in ulcer healing is delivered in practice. The results of this trial may also serve to support the findings of EVRA if similar high healing rates are seen with either or both forms of ablation.

Appendix B

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

Ospidéal na h-Ollscoile, Páirc Mheirlinne
Merlin Park University Hospital
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Room 59
1st Floor
HR Building
Merlin Park Hospital
Galway.

18th June, 2020.

Mr. Colum Keohane
Specialist Registrar in Vascular Surgery
Department of Vascular Surgery
Lambe Institute
University College Hospital
Galway.

Ref: C.A. 2416 ***Axial Ablation Versus Terminal Interruption of the Reflux Source (AAVTIRS): A Randomised Controlled Trial***

Dear Mr. Keohane,

I have considered and reviewed the above submission, and I wish to confirm that I am happy to grant Chairman's approval to proceed. The following documentation was reviewed:

- Cover Letter
- CREC Application Form & Signatory Pages, signed both by Mr. Keohane & Professor Walsh
- Study Protocol
- Patient Consent Form, Version 1, dated 15th June, 2020
- Patient Information Leaflet, Version 1, dated 15th June, 2020
- Venous Clinical Severity Score
- Charing Cross Venous Ulcer Questionnaire
- Pates Jensen Wound Assessment Tool
- C.V. for Mr. Keohane

'This submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller and relevant Data Protection Officer to ensure and monitor compliance with any relevant legislation in the country where the study is due to take place or any local policy in the site where the study is due to take place.'

"Chairman's approval is normally ratified at the next Clinical Research Ethics Committee meeting. If any issues with your application are identified at the meeting we will contact you again"

Yours sincerely,

B. Gerard Loftus FRCPI,MD
Emeritus Professor of Paediatrics, NUI,Galway
Adjunct Professor of Paediatrics, IMU, Kuala Lumpur
Chair, Galway Clinical Research Ethics Committee.

c.c Professor Stewart Walsh, Department of Vascular Surgery, Lambe Institute, University College Hospital, Galway.

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