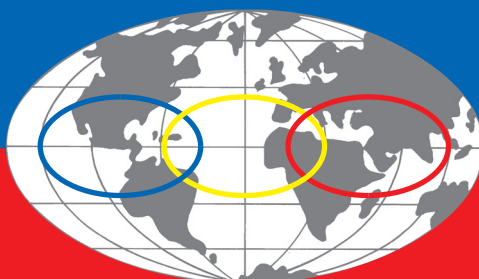# International Angiology

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MANAGEMENT OF CHRONIC VENOUS DISORDERS OF THE LOWER LIMBS

GUIDELINES ACCORDING TO SCIENTIFIC EVIDENCE

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EDIZIONI MINERVA MEDICA

CHAPTER 1

Introduction

Chronic venous disorders (CVDs) is a term which includes the full spectrum of morphological and functional abnormalities of the venous system irrespective of whether they produce symptoms.

Chronic venous disease (CVD) includes any morphological and functional abnormalities of the venous system of long duration manifested by symptoms and or signs indicating the need for the investigation and/or care.[1] Symptoms include aching, heaviness, leg-tiredness, cramps, itching, burning sensations, swelling and the restless leg syndrome, venous claudication as well as cosmetic dissatisfaction. Signs include telangiectasias, reticular and varicose veins, edema, and skin changes such as pigmentation, lipodermatosclerosis, dermatitis and ulceration.[2, 3]

CVD is usually caused by primary abnormalities of the venous wall and/or valves and/or secondary abnormalities resulting from previous deep venous thrombosis (DVT) that can lead to reflux, obstruction or both. Rarely, congenital malformations lead to CVD.[4]

Chronic venous insufficiency (CVI) is a term reserved for advanced CVD due to functional abnormalities of the venous system producing edema, skin changes and venous ulceration.

The clinical history and examination do not always indicate the nature and extent of underlying abnormalities. Consequently, several diagnostic techniques have been developed to define the anatomic extent and functional severity of obstruction and/or reflux, as well as calf muscle pump dysfunction. Difficulties in deciding which investigations to use and how to interpret the results stimulated a consensus statement on investigations for CVD in 2000.[5] This was updated and expanded to include the management of CVD in 2008.[6] The current document aims to provide an account of current concepts on CVDs and an update of guidelines for management.

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CHAPTER 2

Pathophysiology

Changes in Superficial and Deep Veins

Varicose veins are a common manifestation of CVD and are believed to result from abnormal distensibility of connective tissue in the venous wall. Veins from patients with varicosities have different elastic properties than those from individuals without varicose veins.[1, 2] There is hypertrophy of the venous wall with increased collage content,[3] fragmentation of elastin fibers,[4] with degradation and accumulation of extracellular matrix.[5]

Primary varicose veins result from venous dilatation and/or valve damage without previous DVT. Secondary varicose veins are the consequence of DVT or, less commonly, superficial vein thrombosis. Recanalization may give rise to relative obstruction and reflux in deep, superficial and perforating veins.[6]

Approximately 30% of patients with deep-venous reflux shown by imaging appear to have primary valvular incompetence rather than detectable post-thrombotic damage.[7, 8] Rarely, deep venous reflux is due to valve agenesis or aplasia.[9] Varicose veins may also be caused by pelvic vein reflux in the absence of incompetence at the saphenofemoral junction, or perforating veins of the calf or thigh. Retrograde reflux in ovarian, pelvic, vulvar, pudendal or gluteal veins may be also associated with clinical symptoms and signs of pelvic congestion.[10-13]

Following DVT, spontaneous lysis over days or weeks and recanalization over months or years can be observed in 50% to 80% of patients.[14-16] Rapid thrombus resolution after DVT is asso-ciated with a higher incidence of preservation of valve competency.[14, 17] Such rapid resolution depends on thrombus extent, location, local inflammation, potency of local fibrinolytic agents and proinflammatory mediators.[18, 19] Inadequate recanalization following DVT can lead to outflow obstruction. Less frequently, obstruction results from extramural venous compression (most commonly left common iliac vein compression by the right common iliac artery), intra-luminal changes,[20-23] or rarely from congenital agenesis or hypoplasia.[24]

Most post-thrombotic symptoms result from venous hypertension due to valvular incompetence, outflow obstruction or a combination of both. Venous hypertension increases transmural pressure in post-capillary vessels leading to damage of the skin capillaries and increased microvascular permeability,[25] followed by lipodermatosclerosis and, ultimately, ulceration.[26]

The prevalence of post-thrombotic syndrome following DVT has been reported to have a wide variation (35% to 69% at 3 years and 49% to 100% at 5 to 10 years) and depends on the extent and location of thrombosis as well as treatment, but also on the definition used.[27-37] Patients with a combination of chronic obstruction and reflux have the highest incidence of skin changes and ulceration.[37] The risk of ipsilateral post-thrombotic syndrome is higher in patients with recurrent thrombosis and is often associated with congenital or acquired thrombophilia.[38-41] An old and more recent studies report that post-thrombotic skin changes and/or ulceration in pa-

tients with proximal DVT occur less frequently (4% to 8% in 5 years) with adequate anticoagulation, early mobilization, and long-term compression therapy.[42-44]

Mechanical dysfunction of the calf muscle pump may enhance the development of leg ulceration suggesting the importance of the range of ankle motion[45] and patient activity[46] in relation to progression of disease.

Incompetent Perforating Veins

Incompetent perforating veins (IPV) can be defined as those that penetrate the deep fascia and permit flow from the deep to the superficial veins. The flow of calf IPVs is often bidirectional, outward during muscular contraction and inward during relaxation. In normal legs and in the majority of patients with primary uncomplicated varicose veins the net flow is inward from the superficial to the deep veins (re-entry perforators), as first demonstrated in 1891 by Trendelenburg [47] and more recently by Bjordal who used electromagnetic flow meters during exercise.[48] The inward net flow during exercise is the basis of the Perthes test. The net flow is also inward even in patients with femoral vein reflux, provided the popliteal valves are competent. However, in the presence of popliteal valve incompetence (axial reflux) and especially when there is associated deep vein obstruction, the flow is predominantly outward.[48, 49]

IPVs are associated with superficial and/or deep-vein reflux but are rarely found in the absence of reflux.[50-52] The prevalence, diameter, volume flow and velocity of IPVs increase with clinical severity of CVD whether or not there is co-existing deep venous incompetence.[48, 53-58]

Up to 10% of patients, often women, presenting with CEAP clinical class 1 to 3 CVD, have non-saphenous superficial reflux in association with unusually located IPVs.[59]

Vascular Biology and Pathophysiology of the Venous Wall

As mentioned above, varicose veins have different elastic properties from normal veins.[1, 2] The ratio of collagen I to collagen III is altered and so do dermal fibroblasts from the same pa-

tients, suggesting a systemic disorder with a genetic basis.[60]

Leukocyte activation, adhesion and migration through the endothelium as a result of altered shear stress [61-63] contribute to the inflammation and subsequent remodeling of the venous wall and valves.[64-67]

Reduction in shear stress also stimulates production of tumor growth factor-β1 (TGF-β1) by activated endothelial cells and smooth muscle cells (SMCs) inducing SMC migration into the intima and subsequent proliferation. Fibroblasts proliferate and synthesize matrix metalloproteinases (MMPs) overcoming the effect of tissue inhibitors of metalloproteinases (TIMPs). The MMP/TIMP imbalance results in degradation of elastin and collagen.[62, 68, 69] This may contribute to development of hypertrophic and atrophic venous segments and valve destruction seen in varicose veins. Remodelling of the venous wall and abnormal venous distension prevents valve leaflets from closing properly resulting in reflux.

Genetic factors may also play a role in progression to advanced CVD. A relationship between the C282Y polymorphism in hemochromatosis (HFE gene) and venous ulceration has been described.[70]

Changes in Microcirculation as a Result of Venous Hypertension

Techniques such as laser Doppler [71, 72] measurements of transcutaneous PO_2 [73] interstitial pressure capillaroscopy,[74] microlymphography [75] and skin biopsy [76, 77] have provided the means to study the extent of changes in skin microcirculation of limbs with CVD.

In patients with venous hypertension, capillaries become markedly dilated, elongated, and tortuous, especially at skin sites with hyperpigmentation and lipodermatosclerosis. These changes are associated with a high overall microvascular blood flow [69, 78] in the dermis and a decreased flow in nutritional capillaries.[79, 80] A striking feature in the skin of patients with venous hypertension is a "halo" formation around dilated capillaries observed on capillaroscopy. This is associated with microedema, pericapillary fibrin,[81] and other proteins that possibly prevent normal nutrition of skin cells predisposing to ulceration. Microlymphangiopathy [82, 83] and

outward migration of leucocytes exacerbate micro-edema and inflammation.[84-88]

As a late phenomenon, capillary thromboses successively lead to a reduction in the number of nutritional skin capillaries and reduction in transcutaneous PO_2 readings.[89]

The function of endothelium is negatively affected with dilatation, hypervolemia and high pressure. Decreasing of pressure gradient between arteriolar and venular side leads to slower blood flow. The overload of fluid through capillary wall increases procoagulation and secretion of vasoactive mediators.[66, 90] The capillary tone is regulated via the sympathetic and parasympathetic systems. Stretching of the endothelial cells of the postcapillary venules due to dilatation causes the constriction of precapillary arterioles due to endothelial mediators, the veno-arteriolar axon reflex and metabolic inducers.[91, 92] It seems logical to postulate that peripheral neuropathy may be a contributory factor in the cause of CVI.[93]

Pathophysiology of Stasis Dermatitis and Dermal Fibrosis

As stated above, CVD is caused by persistent venous hypertension leading to chronic inflammation. The primary injury is extravasation of macromolecules (*i.e.*, fibrinogen and α_2-macroglobulin) and red blood cells into the dermal interstitium.[77, 94-96] Red blood cell degradation products and interstitial protein extravasation are potent chemoattractants that represent the initial underlying chronic inflammatory signal responsible for leukocyte recruitment. These cytochemical events are responsible for increased expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells of microcirculatory exchange vessels observed in dermal biopsies of patients with CVD.[97, 98] ICAM-1 is the activation dependent adhesion molecule utilized by macrophages, lymphocytes and mast cells for diapedesis.

Cytokine Regulation and Tissue Fibrosis

As indicated above, CVD is characterized by leukocyte recruitment, tissue remodeling and dermal fibrosis. These physiologic processes are prototypical of disease states regulated by trans-

forming growth factor beta (TGF-β_1). The TGF-β_1 is present in pathologic quantities in the dermis of patients with CVD and increases with disease severity.[99] TGF-β_1 is secreted by interstitial leukocytes and binds to dermal fibroblasts and extracellular matrix proteins. Platelet-derived growth factor receptor alpha and beta (PDGFR-α and PDGFR-β) and vascular endothelial growth factor (VEGF) have also been identified in the dermis of CVD patients.[100] It has been postulated that these molecules regulate leukocyte recruitment, capillary proliferation and interstitial edema in CVD by upregulation of adhesion molecules leading to leukocyte recruitment, diapedesis and release of chemical mediators.

Dermal Fibroblast Function

Aberrant phenotypic behavior has been observed in fibroblasts isolated from venous ulcer edges when compared to fibroblasts obtained from ipsilateral thigh biopsies of normal skin in the same patients.[101] Collagen production by fibroblasts is increased by 60% in a dose-dependent manner in control skin whereas venous ulcer fibroblasts are unresponsive. Unresponsiveness in ulcer fibroblasts is associated with a fourfold decrease in TGF-β_1 type II receptors. This is associated with a decrease in phosphorylation of TGF-β_1 receptor substrates SMAD 2 and 3 as well as p42/44 mitogen activated protein kinases [102] and also a decrease in collagen and fibronectin production from venous ulcer fibroblasts when compared to normal controls.[103] Venous ulcer fibroblast growth rates become markedly suppressed when stimulated with bFGF, EGF and IL-1 [104] and this growth inhibition can be reversed with bFGF.[105] The proliferative response of fibroblasts to TGF-β_1 in patients with CVI decreases with increased disease severity [106] and phenotypically, venous ulcer fibroblasts appear to become morphologically similar to fibroblasts undergoing cellular senescence.

Role of Matrix Metalloproteinases (MMPs) and their Inhibitors in CVD

The signaling event responsible for development of a venous ulcer and the mechanisms

responsible for slow healing are poorly understood. Wound healing is an organized process that involves inflammation, re-epithelialization, matrix deposition and tissue remodeling. Matrix deposition and tissue remodeling are processes controlled by matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs). In general, MMPs and TIMPs are induced temporarily in response to exogenous signals such as various proteases, cytokines or growth factors, cell-matrix interactions and altered cell-cell contacts. Gelatinases MMP-2 and MMP-9 as well as TIMP-1 appear to be increased in exudates from venous ulcers compared to acute wounds.[107-109] However, analyses of biopsy specimens have demonstrated variable results. Herouy *et al.* reported that MMP-1, 2 and TIMP-1 are increased in patients with lipodermatosclerosis compared to normal skin.[110] In a subsequent investigation, biopsies from venous ulcer patients were found to have increased levels of the active form of MMP-2 compared to normal skin.[111] In addition, increased immunoreactivity to extracellular inducer of MMP (EMMPRIN), membrane Type 1 and 2 metalloproteinases (MT1-MMP and MT2-MMP) were detected in the dermis and perivascular regions of venous ulcers.[112] Saito *et al.* were unable to identify differences in overall MMP-1, 2, 9 and TIMP-1 protein levels or activity in CVD patients with clinical CEAP class 2 through 6 disease compared to normal controls.[113]

However, within a clinical class, MMP-2 levels were elevated compared to MMP-1, 9 and TIMP-1 in patients with CEAP class 4 and 5 disease. These data indicate that active tissue remodeling is occurring in patients with CVD. Which matrix metalloproteinases are involved and how they are activated and regulated is currently unclear. It appears that MMP-2 may be activated by urokinase plasminogen activator (uPA). Herouy *et al.* observed increased uPA and urokinase-type plasminogen activator receptor (uPAR) mRNA and protein levels in venous ulcers compared to normal skin.[114] Elevated levels of active TGFβ-1 in the dermis of CVI patients suggest a regulatory role for TGFβ-1 in MMP and TIMP synthesis and activity but this needs to be verified by further studies.

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CHAPTER 3

Magnitude of the problem

Early epidemiological studies have shown that CVD has a considerable socio-economic impact in western countries due to its high prevalence, cost of investigations and treatment, and loss of working days.[1, 2] Varicose veins (VVs) are present in 25-33% of female and 10-40% of male adults.[3-13] In the Framingham study, the incidence of VVs per year was 2.6% in women and 1.9% in men.[14] Similar incidence figures have been reported from the Bonn vein study 2 in which 4% of patients with established CVD progressed into a higher CEAP clinical class each year.[15] The prevalence of edema and skin changes such as hyperpigmentation and eczema due to CVD varies from 3.0%[3] to 11%[5] of the population.

Venous ulcers occur in about 0.3% of the adult population in western countries.[6, 14, 16-25] The prevalence of active and healed ulcers combined is about 1%.[26, 27] Healing of venous ulcers may be delayed in patients of low social class and those who are single.[28] More than 50% of venous ulcers require therapy for more than one year.[29] Data from the Brazilian social security system show that CVD is the 14th most frequently quoted disease for temporary work absenteeism and the 32nd most frequent cause of permanent disability and public financial assistance.[30]

Some older studies were based on clinical assessment or questionnaires only. Different definitions of venous disease were used and populations selected contained different age groups and other non-representative factors so that it was difficult to compare epidemiological data. Introduction of the CEAP classification and improved diagnostic techniques have allowed studies to become more comparable.

Thus, in recent studies from France,[31] Germany[32] and Poland[33] the CEAP classification (see below) has been used to differentiate between the different classes of CVD even although selection criteria remain different. The prevalence in the French, German and Polish studies are shown in Table I.

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TABLE I.—*Prevalence of CVD (% of population) stratified by CEAP clinical class (C_2-C_6).*

CEAP class	Men			Women		
	France	Germany	Poland	France	Germany	Poland
C_2	23.7	12.4	51.6	46.3	15.8	47.7
C_3	1.1	11.6	9.2	2.2	14.9	10.5
C_4	4.0	3.1	13.2	2.1	2.7	10.3
C_5	1.4	0.6	4.2	0.7	0.6	2.2
C_6	0	0.1	2.1	0	0.1	1.1

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CHAPTER 4
Socioeconomic aspects

The considerable socioeconomic impact of CVD is due to the large number of individuals affected, cost of investigations and treatment, morbidity and suffering, which are reflected by deterioration in the quality of life and loss of working days. The problem is compounded by the fact that CVD is progressive and has a propensity to recur.

Measures to reduce the magnitude of the problem include awareness of the problem, early diagnosis and care, careful consideration of the necessity and choice of investigations, discipline in the choice of treatment based on clinical effectiveness and cost. These requirements imply specific training in all aspects of this condition.

Costs

Direct costs are associated with medical, nursing and ancillary manpower together with costs for investigations and treatment whether in hospital or as an outpatient. Indirect costs relate to loss of working days. The cost in human terms must also be considered and this can be quantified by assessment of quality of life. Manpower costs alone are important: 22% of district nurses' time is spent treating ulcers of the legs.[1] Estimations of the overall annual costs of CVD vary from 600-900 million € (US$720 million-1 billion) in Western European countries,[2-5] representing 1-2% of the total health care budget, to € 2.5 billion (US$3 billion) in the USA.[6] Often, the costs for treatment include reimbursements by

the State and are affected by government policies.[7]

Detailed figures for France in 1991 [8] showed a total expenditure for CVD of € 2.24 billion (US$2.7 billion) of which 41% was for drugs, 34% for hospital care and 13% for medical fees. There were 200,000 hospitalizations for CVD during that year of which 50% were for varicose veins which was the 8th most common cause for hospitalization. These costs represented 2.6% of the total health budget for that year. A prospective study from France has broken down the cost for treating venous ulceration and of the total cost, 48% was for care, 33% for medications, 16% for hospitalization and 3% for loss of work.[9]

Similarly high costs have been reported for Germany [10] which have increased by 103% between 1980 and 1990 to reach about € 1 billion (US$1.2 billion) with inpatient direct costs of € 250 million (US$300 million), outpatient costs of € 234 million (US$280 million) and drug costs of € 207 million (US$248 million). Similar costs were reported for 2002 (€ 1 billion) with a 20% reduction for 2006 (€ 808 million), due to a 37% decrease of inpatient costs.[5]

In a population-based study on chronic leg ulceration, a cohort of 371 patients was identified and the mean annual treatment cost (including expenditure for medications) for the period 2007-2010 was € 1,646, with wound dressings (€ 257) and analgesics (€ 225) being the most costly for this primary care study.[11]

The real cost however seems to be higher, as demonstrated by a prospective study performed

in 23 specialized wound centers throughout Germany involving a total of 218 consecutive patients (62.1% female).[12] The mean annual total cost of the ulcer was € 9,569 [€ 8,658.10 (92%) direct and € 911.20 (8%) indirect costs]. Major cost factors were hospitalization, outpatient nursing fees and non drug treatments (mainly due to wound dressings).

In Belgium, medical care costs for CVD in 1995 amounted to € 250 million (US$300 million) which is 2 to 2.25% of total health care budget.[13]

In Sweden, the average weekly cost for treating venous leg ulcers in 2002 was € 101 (US$121) with an estimated annual cost of € 73 million (US$88 million) [14] and these costs were slightly less than in previous years which was attributed to a more structured management program.

In the USA, a study showed that the average total medical cost per patient with a leg ulcer in 1999 was $9,685 (median: $3,036).[15] Home health care, hospitalizations and home dressing changes accounted for 48%, 25% and 21% of total costs, respectively. Total costs were related to duration of active therapy, ulcer size and the presence of at least one comorbidity (P<0.05). Also in the USA, a cost estimate of long-term complications for DVT after total hip replacement gave figures varying from € 700 to € 3,180 (US$ 839 to 3,817) per patient in the first year and € 284 to € 1,400 (US$ 341 to 1,677) in subsequent years depending on the severity of the post-thrombotic syndrome.[16]

Many of the above costs are based on estimations and assumptions and strict comparisons are difficult as there is no agreed definition of "costs". The impact of different cost assessments on endovenous treatments for VVs was assessed using top-down and bottom-up approaches.[17] The cost differences between laser and foam were substantial using micro-costing approaches. When national reimbursement data were used there was very little discrepancy between the two treatments.

Furthermore, the figures need to be related to the country's population or to Gross National Product. However, they do illustrate the considerable cost of venous diseases.

Phlebotropic drugs that are prescribed as an alternative to elastic stockings essentially for relief of leg heaviness, pain and edema [18] in women who are either standing or sitting for long periods at work result in considerable expenditure.[6] This cost amounts to € 63.2 million (US$76 million) in Spain, € 25 million (US$30 million) in Belgium and € 457 million (US$548 million) in France [13, 19] representing 3.8% of the sales of reimbursable medicines. Two very similar surveys in Germany [20] and France [21, 22] showed that nearly 50% of the population aged over 15 years reported venous problems of whom 90.3% purchased a venotonic drug: 71% were women of whom 30% were "obese, relatively underprivileged in terms of age, occupational status, hours of work, working conditions, leisure, income and health".

Indirect costs of venous diseases in terms of working days lost is quoted as "the most important cost factor" in Germany, amounting to € 270 million (US$324 million).[10] In the USA, venous ulcers cause loss of 2 million work-days per year.[6] In France, 6.4 million days of work were lost in 1991.[8] Another study in France found that about 7% of the working population is off work because of venous disease (CEAP: C1-C6) with an overall "estimation" of 4 million working days lost in a year at an estimated cost of € 320 million (US$384 million) to the economy.[18, 23] These costs are higher than the amount spent for the treatment of arterial disease.

In recent years, evidence has emerged that proper education and provision of guidelines in the field of phlebology and ulcer treatment carry a significant cost-effectiveness.[24] In Sweden, after the introduction of early surgical intervention in patients with superficial venous reflux (SVR) or SVR combined with deep venous reflux or occlusion, the population of patients with venous ulcer decreased by 46% within fourteen years. The point prevalence was reduced from 0.16% down to 0.09%.[25] A recent study carried out in Poland has shown that education and provision of European Wound Management Association (EWMA) guidelines in patients with ulceration were beneficial. In total 309 patients were identified with a chronic leg ulcer (CLU) at the start of the study (120 men, 189 women). Both regions of country taken into consideration had a similar profile of patients having a median (IQR) duration of ulceration of 96 (30-168) months. A model of care was developed based on guidelines, including the appropriate education of health professionals treating patients,

access to non-invasive methods to determine the ulcer etiology, compression therapy in those with proven venous ulceration. Two years after implementation, the numbers of patients had reduced to 205 (86 men, 119 women), a reduction of 33%, while after implementation more patients were treated at home (49.3% *versus* 19.5%) with a corresponding reduction in those seen at health centers (35.6% *versus* 63.3%). The mean (SD) number of visits was reduced to 1.3 (0.7). During implementation the healing rate at 30 weeks improved from 73.3% to 82.9%. While the cost per patient was higher post-implementation, the overall cost of treating patients within the service reduced from €3,847 to €2,913 per week. The development and implementation of an evidence based system of care for patients with CLU in Poland was both clinically and cost effective.[26]

Quality of Life

Good quality of life (QoL) has been defined by the World Health Organization (WHO) as "a state of complete physical, mental and social well-being".[27] The QoL reflects the patient's perception of "well-being" at any time. Thus, it is an important element in the general assessment of any patient. Illness has repercussions on QoL. In this way, a measure of QoL is also a measure of the "cost" of any disease in terms of human suffering. It also considerably helps to assess a patient's perception of the result of any treatment.

Various quantitative instruments in the form of questionnaires, either generic or specific for venous disease, both assessing health-related QoL (HRQoL) have been developed and some of them have been validated.[27-32] They conclusively show that QoL is adversely affected by venous disease.[18, 27-35]

Similarly, reduction in severity of disease, for example after treatment, is reflected in the QoL.[27, 33, 35-37] There is a significant association between QoL and severity of venous disease and also with the CEAP classification.[27, 33, 36-42] A study also shows an association in women between venous disease and working conditions which is reflected in the QoL.[18] Currently there is no evidence that QoL can be used to identify who will progress, since QoL is not directly related to venous incompetence.

Optimal cost-effective quality of care for prevention and treatment of venous ulcers is lacking, and better economic data are needed. Such data are needed to convince government agencies, payers, and other stakeholders in the healthcare system (HCS) on the importance of venous ulcer prevention and quality care.[43]

However, generic QoL is significantly improved with superficial vein surgery,[44, 45] and so does HRQoL.[46, 47] Ultrasound-guided foam sclerotherapy leads to significant improvements in generic and disease-specific HRQoL for at least 12 months after treatment [48] and so does EVLA.[47] Similarly, radiofrequency ablation is associated with significant improvement of generic QoL [49] and HRQoL.[49, 50]

In conclusion, CVD is very costly both economically and in terms of human suffering. However, prevention of the condition and cost-effective management should lead to a reduction in costs.

Cost-effectiveness of Prevention and Treatment

The need to contain the high cost of CVD is evident. The methods used, whether aimed at prevention or treatment must essentially be shown to be *effective* but must also take into consideration the *cost* in relation to the proven effectiveness.

The two main and costly manifestations of CVD are varicose veins with or without skin changes and venous ulceration. At the present time, there is no way to effectively prevent the onset of varicose veins. However, there are known *risk factors*, some of which are proven (heredity, gender, pregnancies and age) and others are not (*e.g.*, obesity). Much work has been done to prevent CVD developing in patients with early varicose veins or following venous thrombosis and all measures that contribute to preventing a venous ulcer will have a strong impact on the human and socioeconomic costs.

There is a growing awareness of the need to demonstrate cost-effectiveness in many aspects of the management of CVD and this is shown by the volume of publications on this subject. Cost-effectiveness in CVD takes into consideration the progressive nature of the symptoms and their ten-

dency to recur and this implies continuous follow-up. In the case of venous ulcers, assessment of the recurrence rate is as important as the healing rate.

Superficial venous surgery has been shown to be cost-effective compared to conservative management.[51] Endoluminal ablation methods are also cheaper and thus cost-effective when compared to stripping, the latter frequently performed as an inpatient.[52-54] Additionally it has been shown that EVLA is as effective as surgery for varicose veins, but has a less negative impact on early postintervention QoL.[47]

In a randomized trial investigating the cost and effectiveness of EVLA with phlebectomies compared with foam sclerotherapy in superficial venous insufficiency, UGFS is 3.15 times less expensive than EVLA (£230.24 *vs.* £724.72) with comparable effectiveness but 56% (*versus* 6%) required additional foam.[55]

In a randomized clinical trial, 246 patients with uncomplicated varicose veins and evidence of saphenofemoral or saphenopopliteal reflux were randomly allocated to receive either conservative management or surgical treatment.[51] Total NHS costs during a 2-year study period were higher for patients who had surgery (£733) than for those who had conservative treatment (£345). The mean incremental health gain from surgical treatment at 2 years was 0.083 QALYs, leading to a base-case estimate of £4,682 per QALY gained. Assuming an implicit threshold maximum willingness-to-pay value of £20,000 for a QALY, the probability of surgical treatment for varicose veins falling below this threshold value was 70%. Another study showed that compared to conservative management, surgery had an incremental cost-effectiveness ratio (ICER) of £7,175 per QALY. Economic modelling suggested that surgery produced a still greater benefit when considered with a 10-year time horizon, with an ICER of £1,936 per QALY.[46]

Similar results were more recently reported from Finland, where the mean cost per QALY gained during a 6-month period following superficial vein surgery was € 3,248,[56] well below the uniformly accepted ceiling of € 20,000 per QALY gained.

Selection of the most appropriate investigation has been established.[57] Initial outlay for duplex ultrasound has a cost but this is justified by its cost-effectiveness.[58, 59]

Hospital admissions are costly; for example, treatment of a venous ulcer costs 24 times more in hospital than at home.[60]

Realization of this fact has led to more management outside hospital whenever possible and has opened new fields such as day surgery for varicose veins and home treatment of DVT in suitable cases. Prevention and management of venous thrombosis outside the hospital has been shown to be not only as clinically effective as in hospital but also more cost-effective.[61] It has also been shown that treatment of venous ulcers in dedicated centers with a set protocol of treatment is very cost-effective and gives faster healing times than treatment in non-dedicated centers without a set protocol.[6, 60, 62, 63]

Introduction of specialized leg ulcer clinics could significantly reduce costs of treatment. These savings could be estimated as about $780 (€ 610) per patient treated.[64]

The most cost-effective method to manage venous ulcers is by dressings and adequate compression (see chapter on Compression).[6, 65-77] A RCT [78] concluded that for long-term management of venous ulcers, education of the patient and good compression with effective compliance would save € 5,270 (US$6,326) in medical costs per patient per whole life together with a further saving of € 14,228 (US$17,080) due to fewer working days lost. A systematic review [66] demonstrated that high compression hosiery was more cost-effective than moderate compression for preventing ulcer recurrence and was particularly cost-saving if combined with patient education.[78]

There is now evidence for cost-effectiveness of phlebotropic drugs when used as adjuvant therapy to increase the rate of healing of venous ulcers.[79, 80]

Many women suffering from CVD have found that their working conditions aggravated their symptoms, leading them to take many days off work. It has been suggested that simple changes in working conditions such as providing high stools, adequate rest periods and medical counseling could be very cost-effective.[18, 21, 22]

A new era in the treatment of primary superficial venous insufficiency started 15 years ago. Introduction of new endovenous procedures such as laser, radiofrequency and steam offered advantages over the conventional stripping op-

erations in terms of reduced postoperative pain, shorter sick leaves and faster return to normal activities. It provides benefits for societies and cost savings among employed patients. Because the procedures are associated with shorter convalescence, these new methods are now replacing conventional varicose vein surgery.[53]

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CHAPTER 5

Classification, severity scoring systems and terminology of chronic venous disorders

Ceap classification and definition of terms

The CEAP (Clinical, Etiological, Anatomical, Pathophysiological) classification was published in the mid 1990s in 25 journals and books in 13 languages and has been revised in 2004.[1] Several revisions by the ad hoc committee of the American Venous Forum in conjunction with the International ad hoc committee have resulted in the classification summarized in that has been adopted worldwide. The aim of the CEAP classification was to facilitate meaningful communication and description of all forms of CVD.[1]

DATE OF CLASSIFICATION

CEAP is not a static classification, and the patient can be reclassified at any point in time. Therefore, the classification should be followed by the date it was performed.

LEVEL OF INVESTIGATION

A Roman numeral (*e.g.* LII) describes the level (L) of intensity of investigation (see below) and will be discussed in the next section.

Basic and advanced CEAP

Basic CEAP: includes all four components shown in Table I. Use of the C-classification alone describes CVD inadequately. The majority of patients have a duplex scan that provides data on E, A, and P. The highest descriptor is used for clinical class.

Advanced CEAP: For the researcher and for reporting standards, this is a more detailed and precise classification where the extent of disease can be allocated to one or more 18 named venous segments.

Example

A patient presents with painful swelling of the leg and varicose veins, lipodermatosclerosis and active ulceration. Duplex scanning on August 14, 2012 showed axial reflux in the GSV above and below the knee, incompetent calf perforating veins and axial reflux in the femoral and popliteal veins. No signs of post-thrombotic obstruction.

Classification according to basic CEAP: C6, S, Ep, As,p,d, Pr (2012-08-14, LII)

Classification according to advanced CEAP: C2,3, 4b,6,S, Ep, As,p,d, Pr2,3,18,13,14 (2012-08-14, LII).

Need to further develop the CEAP classification

In chronic deep venous insufficiency (CDVI) venous claudication is an important symptom. However, it is poorly defined. In the next revision of CEAP we need to better classify the severity of venous claudication as well as the other symptoms of venous disease, *e.g.* absent (0), mild (1), moderate (2) or severe (3). For evaluation of venous claudication a treadmill could be utilized.

The pathophysiologic classification (P) with Pr, Po, and Pro for different anatomic locations is satisfactory but we need an addition of the severity, and not only the presence of reflux and obstruction.

TABLE I.—*Revised CEAP (1).*

Clinical Classification
C0: no visible or palpable signs of venous disease.
C1: telangiectasiae or reticular veins.
C2: varicose veins.
C3: edema.
C4a: pigmentation and/or eczema.
C4b: lipodermatosclerosis and/or atrophie blanche.
C5: healed venous ulcer.
C6: active venous ulcer.

S: symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction.
A: asymptomatic.

Etiologic Classification
Ec: congenital.
Ep: primary.
Es: secondary (post-thrombotic).
En: no venous etiology identified.

Anatomic Classification
As: superficial veins.
Ap: perforating veins.
Ad: deep veins.
An: no venous location identified.

Pathophysiologic Classification
Basic CEAP:
Pr: reflux.
Po: obstruction.
Pr,o: reflux and obstruction.
Pn: no venous pathophysiology identifiable.

Advanced CEAP:
Same as Basic CEAP with the addition that any of 18 named venous segments can be utilized as locators for venous pathology:

Superficial veins:
1. Telangiectasies/reticular veins.
2. Great saphenous vein (GSV) above knee.
3. GSV below knee.
4. Small saphenous vein.
5. Non-saphenous veins.

Deep veins:
6. Inferior vena cava.
7. Common iliac vein.
8. Internal iliac vein.
9. External iliac vein.
10. Pelvic: gonadal, broad ligament veins, other.
11. Common femoral vein.
12. Deep femoral vein.
13. Femoral vein.
14. Popliteal vein.
15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired).
16. Muscular: gastrocnemial, soleal veins, other

Perforating veins:
17. Thigh
18. Calf

Definition of terms

During the development of the CEAP classification it was realized that a number of descriptive and anatomical terms, which were often used in different contexts, needed a more pre-cise definition. This initial list of definitions was extended to create a more precise common scientific language for the investigation and management of CVD in October 2007 on board M/S Trollfjord where the Arctic Fjords conference and workshops on chronic venous disease took place. During this voyage an interdisciplinary faculty of experts under the auspices of the European Venous Forum, the American Venous Forum, the International Union of Phlebology, the International Union of Angiology, the American College of Phlebology, and the Society for Vascular Surgery met in order to provide recommendations for fundamental venous terminology. The group met again in February 2008 at the AVF meeting in Charleston, South Carolina, USA to finalize the document, which was endorsed by the organizations and eventually published as the VEIN-Term consensus document in the Journal of Vascular Surgery.[2] The definitions produced are summarised in the Appendix at the end of this chapter.

Disease Severity Scoring Systems

The **V**enous **S**everity **S**coring (**VSS**) system with its three components, Venous Disability Score (VDS), Venous Segmental Disease Score (VSDS) and Venous Clinical Severity Score (VCSS) was developed in 2000 by the American Venous Forum ad hoc committee on venous outcomes assessment in order to supplement the CEAP classification by providing an instrument for assessment of the patient's condition during follow-up.[3] In contrast to CEAP, VSS includes symptoms as well as signs. The good intraobserver and interobserver variability and validation of VSS, [4, 5] its applicability to all CEAP clinical classes and its ability to demonstrate subtle changes[6] makes it an ideal tool to evaluate clinical outcome in RCTs.

The **Venous disability score (VDS)** has a maximum of 3, defined as: 0 = asymptomatic, 1 = symptomatic but able to carry out usual activities without compressive therapy, 2 = can carry out usual activities only with compression and/ or limb elevation, 3 = unable to carry out usual activities even with compression and/or limb elevation. Usual activities are defined as patient's activities *before* onset of disability from venous disease.

The **Venous Segmental Disease Score (VSDS)** combines the anatomic and pathophysiologic components of CEAP. VSDS is based on venous segmental involvement with major venous segments being graded according to presence of reflux and/or obstruction. This scoring scheme is entirely based on venous imaging, primarily duplex scanning but also venographic findings, and weights 11 venous segments for their relative importance when involved with reflux and/or obstruction. There is one VSDS score for reflux (maximum score of 10) and another one for obstruction (also a maximum score of 10).

The **Venous Clinical Severity Score (VCSS)** is based on nine clinical characteristics (pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, and number, duration and size of active ulcers), all graded from 0 to 3 and additionally use of conservative therapy (compression and elevation), using the same points, to produce a 30 point-maximum flat scale.[2, 3]

Validation of the VSS scoring systems has been reported in the past.[5, 7-9]

It has been shown that the venous severity scores are significantly higher in advanced venous disease, demonstrating correlation with anatomic extent. VCSS has been found to be equally sensitive and significantly better for measuring changes in response to superficial venous surgery than the CEAP clinical class, while VDS demonstrated comparable and even better performance.[5] It has been suggested that VCSS may have a more global application in determining the overall severity of venous disease.[9] Additionally a clear association between VCSS and Duplex findings has been demonstrated, suggesting that this score can be used as a screening tool. In 2010 VCSS was revised in the sense of clarifying mainly its pain, inflammation and induration components.[10] Pain attribute for example was expanded to include other less severe symptoms and discomfort (ie, aching, heaviness, fatigue, soreness, burning), presumably of venous origin.

Scoring systems for assessing the post-thrombotic syndrome (PTS)

Three further different scoring systems have been proposed that are specific for the assessment of the PTS: the **Brandjes**,[11] the **Ginsberg**,[12] and the **Villalta**.[13] All three systems use symptoms and signs, which are present or absent in the Brandjes system but graded in the other two. The Ginsberg system identifies the presence or absence of PTS without grading its severity. In contrast, the Villalta scale grades symptoms and signs and classifies patients into different PTS severity groups. Because of its reliability, high correlation with relevant health outcomes, acceptability, responsiveness to changes in the severity of PTS and successful use in clinical trials [14] the subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis recommended that the Villalta scale should be used in clinical studies to diagnose and grade the severity of PTS.[15]

The Villalta Scale

This was first introduced in 1994 as a score for the PTS.[13] It scores both symptoms (cramps, pruritus, pain, heaviness, paraesthesia) and signs (pretibial oedema, induration of the skin, hyperpigmentation, new venous ectasia, redness and pain during calf compression), by rating their severity from 0 (not present or minimal) to 3 (severe), for a maximum of 33 points, while the presence of a venous ulcer of the lower limb is also recorded. A total score of 15 or more on two consecutive visits or the presence of a venous ulcer indicates severe PTS. A total score of 5 to 14 on two consecutive visits indicates mild PTS. In patients with bilateral thrombosis, the higher score was used. The Villalta scale has been uniformly accepted and it has shown to be reproducible,[13] including a good inter-observer reliability of measures to assess the post-thrombotic syndrome.[16]

In a recent study assessing the Villalta, Ginsberg, Brandjes, Widmer, CEAP, and VCSS systems in terms of interobserver reliability, association with ambulatory venous pressures, ability to assess severity of PTS, ability to assess change in condition over time, and association with patient-reported symptom severity, only the Villalta score was able to fulfill all the above criteria,[17] findings that endorse its generalized use in PTS.

REVAS classification

REVAS is another classification which is specific for recurrent varices after operative treatment. Recurrent varicose veins are a common, complex and costly problem for both the patients and the physicians who treat venous diseases. To deal with this problem an international consensus meeting was held in Paris in 1998, which proposed definition, classification and management of **Re**current **Va**rices after **S**urgery (**REVAS**) [3] to be used in combination with CEAP classification. REVAS classification was evaluated in terms of intra- and inter-observer reproducibility [4] and a worldwide survey was conducted in 2006.[3]

The **REVAS** classification system takes into account six main items (sites, nature and sources of recurrence, the magnitude of the reflux and other possible contributory factors), shown in detail below.[18]

T is for topographical sites of REVAS (**g** is for Groin, **t** for Thigh, **p** for Popliteal Fossa, **l** for Lower leg (including ankle and foot), **o** for Other).

S is for Source of recurrence (**0** is for no source of reflux, **1** for pelvic/abdominal, **2** for sapheno-femoral junction, **3** for thigh perforating veins, **4** for sapheno popliteal junction, **5** for popliteal fossa perforating veins, **6** for gastrocnemius veins, **7** for lower leg perforating veins).

R is for Reflux (**1** is for clinical significance probable, **2** for clinical significance.

? (unlikely/uncertain). This estimate should be based on both the duplex and venographic information, and an evaluation as to how the degree of reflux relates to the overall clinical situation.

N is for Nature of sources

Ss is for Same Site (**1**: technical failures, **2**: tactical failures, **3**: neovascularization, **4**: uncertain, **5**: mixed) and

Ds is for Different (new) Site (**1**: persistent, known to have been present at the time of previous surgery, **2**: new, known to have been absent at the time of previous surgery, **3**: uncertain/not known, insufficient information at the time of previous surgery). This classifies the source as to whether or not it is the site of previous surgery and describes the cause and timescale of recurrence respectively.

C is for Contribution from persistent incompetent saphenous trunks

AK: great saphenous (above knee), **BK**: great saphenous (below knee), **SSV**: short saphenous, **Ø**: neither/other.

Certain clinical data should be gathered and reported in the medical file: **F is for possible contributory Factors; GF: General Factors:** family history, obesity, pregnancy, hormones; **SF: Specific Factors:** primary deep venous incompetence, post-thrombotic syndrome, iliac vein compression, congenital (angiodysplasiae), lymphatic, calf pump dysfunction.

In an intra- and inter-observer reproducibility study of the 8 items in REVAS, intra-observer reproducibility was excellent for three items and good for five, and inter-observer reproducibility was good for 6 items and moderate for two.[19]

Classic surgery is not anymore the most frequent operative procedure used for treating varicose vein in several countries. Chemical and thermal ablation on one hand and mini invasive surgery including CHIVA and ASVAL on the other hand have decreased the use of high ligation (HL) and stripping tremendously in most parts of the world. To deal with this problem recurrent and residual varices were defined as listed in the terminology list below and a new acronym **PREVAIT** (**PRE**sence of **V**arices (residual or recurrent) **A**fter operat**I**ve **T**reatment) was coined. The term **PREVAIT** was created for two reasons: firstly because it is frequently difficult to classify correctly the results of initial procedures done by others and consequently to differentiate recurrent varices from residual varices. Secondly the previous acronym **REVAS** was only applicable to patients previously treated by surgery, while nowadays a variety of operative treatment need to be assessed by a same protocol. Since 1998 more than ninety new articles in English and French have been published on the topic including 19 randomized controlled trials. Obviously there is a need for a new classification taking into account patients with PREVAIT.

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APPENDIX

Defined terms

The term CVDs includes all morphological and functional abnormalities of the venous system in the lower limb. Some of these like telangiectasiae are highly prevalent in the adult population and in many cases the use of the term 'disease' is, therefore, inappropriate. The term chronic venous insufficiency (CVI) is entrenched in the literature and has been used to imply a functional abnormality (reflux, obstruction or a combination of both) of the venous system and it is usually reserved for patients with more advanced disease including those with edema (C3), skin changes (C4) or venous ulcers (C5/6). In the revised CEAP classification (1) the previous overall structure of CEAP has been maintained but more precise definitions have been added. The definitions used in the CEAP classification and the VEIN-Term consensus document are listed below in alphabetical order.

Atrophie blanche or white atrophy: Localized, often circular whitish and atrophic skin areas surrounded by dilated capillary spots and sometimes with hyperpigmentation. This is a sign of severe chronic venous disease. Scars of healed ulceration are excluded from this definition.

Axial reflux: uninterrupted retrograde venous flow from the groin to the calf.

Superficial: confined to the superficial venous system.

Deep: confined to the deep venous system.

Combined: involving any combination of the three venous systems (superficial, deep, perforating).

Chronic venous disease: morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care.

Chronic venous disorders: this term includes the full spectrum of morphological and functional abnormalities of the venous system.

Chronic venous insufficiency (C3-C6): a term reserved for advanced chronic venous disorders, which is applied to functional abnormalities of the venous system producing edema, skin changes or venous ulcers.

Corona phlebectatica: this term describes a fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot. This is commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare.

Eczema: erythematous dermatitis, which may progress to a blistering, weeping, or scaling eruption of the skin of the leg. It is often located near varicose veins but may be located anywhere in the leg. Eczema is usually caused by CVD or by sensitization to local therapy.

Edema: this is defined as a perceptible increase in volume of fluid in the skin and subcutaneous tissue characterized by indentation with pressure. Venous edema usually occurs in the ankle region, but it may extend to the leg and foot.

Endophlebectomy: removal of post-thrombotic residue from the venous lumen.

Lipodermatosclerosis (LDS): localized chronic inflammation and fibrosis of the skin and subcutaneous tissues sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin which may be painful and which is often referred to as hypodermitis. This condition needs to be distinguished from lymphangitis, erysipelas or cellulitis by their characteristic local signs and systemic features. LDS is a sign of severe chronic venous disease.

High ligation and division: ligation and division of the great saphenous vein (GSV) at its confluence with the common femoral vein, including interruption of all upper GSV tributaries.

Iliac vein obstruction syndrome: venous symptoms and signs caused by narrowing or occlusion of the common or external iliac vein.

May-Thurner syndrome: venous symptoms and signs caused by obstruction of the left common iliac vein due to external compression at its crossing posterior to the right common iliac artery.

Miniphlebectomy: removal of a vein segment through a small skin incision.

Neovascularization: presence of multiple new, small tortuous veins in anatomic proximity to a previous intervention.

Pelvic congestion syndrome: chronic symptoms, which may include pelvic pain, perineal heaviness, urgency of micturition, and postcoital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices.

Perforating vein ablation: disconnection or destruction of a perforating vein by mechanical, thermal or chemical means.

Perforating vein interruption: disconnection of a perforating vein by mechanical, thermal or chemical means.

Perforating vein ligation: interruption of a perforating vein by mechanical means.

Perforator incompetence: perforating veins with outward flow of abnormal duration.

Pigmentation: brownish darkening of the skin initiated by extravasated blood, which usually occurs in the ankle region but may extend to the leg and foot.

Post-thrombotic syndrome: chronic venous symptoms and/or signs secondary to deep vein thrombosis.

PREVAIT: this acronym stands for **PRE**sence of **V**arices (residual or recurrent) **A**fter operat**I**ve **T**reatment.

Recanalization: development of a new lumen in a previously obstructed vein.

Recurrent varicose veins: reappearance of varicose veins in an area previously treated successfully.

Residual varices: varicose veins remaining after treatment.

Reticular veins: dilated bluish subdermal veins usually from 1 mm to less than 3 mm in diameter. They are usually tortuous. This excludes normal visible veins in people with transparent skin. Synonyms include blue veins, subdermal varices, and venulectasiae.

Sclerotherapy: obliteration of a vein by introduction of a chemical agent (liquid or foam).

Segmental reflux: localized retrograde flow in venous segments of any of the three venous systems (superficial, deep or perforating) in any combination in the thigh and/or the calf, BUT not in continuity from the groin to the calf.

Stripping: removal of a long venous segment, usually most of the GSV or the small saphenous vein by means of a device.

Telangiectasia: a confluence of dilated intradermal venules of less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins.

Varicocele: presence of scrotal varicose veins.

Varicose veins: subcutaneous dilated veins equal to or more than 3 mm in diameter in the upright position. These may involve saphenous veins, saphenous tributaries, or non-saphenous veins. Varicose veins are usually tortuous, but refluxing tubular saphenous veins may be classified as varicose veins. Synonyms include varix, varices, and varicosities.

Venous ablation: removal or destruction of a vein by mechanical, thermal or chemical means.

Venous aneurysm: localized saccular or fusiform dilatation of a venous segment with a caliber at least 50% greater than the normal trunk.

Venous compression: narrowing or occlusion of the venous lumen as a result of extraluminal pressure.

Venous obstruction: partial or total blockage of venous flow.

Venous occlusion: total obliteration of the venous lumen.

Venous reflux: retrograde venous flow of abnormal duration in any venous segment.

Primary: caused by idiopathic venous valve dysfunction.

Secondary: caused by thrombosis, trauma, or mechanical, thermal, or chemical etiologies.

Congenital: caused by the absence or abnormal development of venous valves.

Venous signs: visible manifestations of venous disorders, which include dilated veins (telangiectasiae, reticular veins, varicose veins), leg edema, skin changes, and ulcers, as included in the CEAP classification.

Venous symptoms: complaints related to venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, and leg tiredness and/or fatigue. Although not pathognomonic, these may be suggestive of chronic venous disease, particularly if they are exacerbated by heat or dependency in the day course, and relieved with leg rest and/or elevation.

Venous ulcer: full thickness defect of the skin most frequently at the ankle that fails to heal spontaneously sustained by CVD.

Venous valvular incompetence: venous valve dysfunction resulting in retrograde venous flow of abnormal duration.

CHAPTER 6
Investigations

General Remarks

There is no single test that can provide all information needed to guide clinical decisions and formulate a management strategy. Understanding the pathophysiology is the key to select the appropriate investigations.

When a patient presents with symptoms and signs suggestive of CVD, a physician should answer a number of clinically relevant questions. First, one should ascertain whether CVD is present. If it is, then investigations should determine the presence or absence of reflux, obstruction, calf muscle pump dysfunction and the severity of each one of the above.[1]

Detection of Reflux and Obstruction

The clinical presentation is assessed by obtaining a detailed history and performing a meticulous physical examination followed by duplex scanning. Such an evaluation helps the physician to identify the presence, sites and anatomical extent of reflux and/or occlusion of veins. A proportion of patients may require additional investigations.

Duplex Scanning

Duplex ultrasound is superior to phlebography and is considered to be the gold standard to detect reflux in any venous segment.[2-10] Imaging is usually performed with colour flow scanners with high frequency probes used for superficial veins and lower frequency probes used when deeper veins are to be visualized. The entire superficial and deep venous systems as well as the communicating and perforating veins are examined. Elements of the examination that are often germane to further management include:

1. standing position for the femoral and great saphenous veins or sitting position for popliteal, small saphenous and calf veins;

2. measurement of the duration, peak velocity or volume flow of reflux, after standard calf compression and its release;

3. size and competence of perforators;

4. diameter of saphenous veins;

5. size and competence of major saphenous tributaries;

6. anatomic extent of reflux in the deep veins.

Obstruction

Quantification of venous obstruction is difficult (Chapter 5). Traditional methods that measure arm-foot pressure differential,[11] outflow fraction [12, 13] and outflow resistance by plethysmography [1] express global functional obstruction including the effect of the collateral circulation, but do not quantify local anatomic obstruction. IVUS demonstrates relative degrees of obstruction at the involved venous segment more reliably, but it is not useful for infra-inguinal obstruction.

Investigation of Patients in Different CEAP Clinical Classes

A precise diagnosis is the basis for correct classification of the venous problem. A way to organize the diagnostic evaluation of the patient with CVD is to utilize one or more of three levels of testing, depending on the severity of the disease.

Level I: The office visit with history and clinical examination, which could include a hand held Doppler or color flow duplex.

Level II: The non-invasive vascular laboratory with detailed duplex scanning, with or without plethysmography.

Level III: The addition of invasive investigations or complex imaging studies including ascending and transfemoral (antegrade and retrograde) phlebography, varicography, venous pressure measurements, computerized tomographic venography, magnetic resonance venography or IVUS.

A simple guide to the level of investigation in relation to CEAP clinical classes is given below. This may be modified according to clinical circumstances and local practice.

Clinical Class C0/1—No visible or palpable signs of venous disease; telangiectasiae or reticular veins present.

Level I investigations are usually sufficient. However, symptoms such as ache, pain, heaviness, leg-tiredness and muscle cramps in the absence of visible or palpable varicose veins are an indication for detailed duplex scanning to exclude reflux which often precedes the clinical manifestation of varices.

Clinical Class C2—Varicose veins present without any edema or skin changes.

Level II (duplex scanning) should be used in the majority of patients and is mandatory in those being considered for intervention. Level III may be needed in certain cases.

Clinical Class C3—Edema with or without varicose veins and without skin changes.

Level II investigations are utilized to determine the severity of reflux and obstruction and whether or not reflux or obstruction in the deep veins is responsible for the edema. If obstruction is demonstrated or suspected as a result of duplex scanning, level III studies to investigate the deep venous system must be considered. Whether or not obstruction is demonstrated, or suspected as a result of duplex scanning, level III studies to in-

vestigate the deep venous system may be considered. Lymphoscintigraphy may be indicated to confirm the diagnosis of lymphedema in certain patients with suspected phlebolymphedema.

Clinical Class C4,5,6—Skin changes suggestive of venous disease including healed or active ulceration with or without edema and varicose veins.

Level II investigations will be required in virtually all patients. Selected cases, such as those being considered for deep-vein intervention, will proceed to level III. Level I investigations may be sufficient in some patients with irreversible muscle pump dysfunction due to neurological disease, severe and non-correctable reduction of ankle movement or where there is a contraindication to surgical intervention. Some investigations may have to be deferred, particularly in patients with painful ulcers. The evaluation of significant pigmentation in the gaiter region (C4a) as a marker of advanced venous disease requires a level II investigation because clinical appearances alone can be highly misleading.[14]

Measurement and Reporting of Reflux

There are several ways to measure reflux.

1. Global non-invasive indirect investigations based on volume changes, *e.g.* plethysmography (VFI in ml/sec). Simultaneous measurements of venous filling time using air-plethysmography (APG) have been shown to correlate highly with GSV reflux time using duplex.[15] Thus duplex ultrasound in a single superficial vein has been validated against a leg's overall hemodynamic status.

2. Global invasive investigation, (*e.g.* dorsal foot venous pressure) where one can differentiate between superficial and deep reflux using below and above knee cuffs with recordings of ambulatory venous pressure (AVP) and recovery time (RT). Although AVP is the gold standard for hemodynamic function in venous disease in terms of ambulatory venous pressure, it cannot provide a quantitative measurement of reflux.

3. Non-invasive duplex ultrasound which offers morphologic and functional evaluation of different vein segments that mainly gives qualitative information about presence or absence and extent of reflux in individual veins; however, semi-quantitative evaluation of reflux in terms of

peak velocity and quantitative reflux in terms of volume flow throughout reflux or volume flow at peak reflux can be used.

4. Using descending venography Kistner classified deep vein reflux in 5 grades:

— grade 0: competent valves with no reflux;

— grade 1: wisps of reflux limited to upper thigh;

— grade 2: definite reflux, but limited to upper thigh by competent valves in the distal thigh or the popliteal vein;

— grade 3: reflux through the popliteal vein and into the calf;

— grade 4: massive cascading reflux through the popliteal vein into the calf, and frequently through incompetent perforating veins.

Note: Kistner's classification can be applied to the duplex findings. Segmental reflux includes Kistner 1 and 2, while axial reflux includes Kistner 3 and 4.

Measurement and Reporting of Obstruction

The pathophysiologic classification of obstruction needs additional information on severity, particularly at the level of the iliocaval segment. Venous occlusion is defined as total obliteration of the venous lumen, while venous obstruction is defined as partial or total blockage of venous flow. *There is no gold standard for the functional assessment of venous obstruction.* No adequate hemodynamic test exists presently to delineate a local hemodynamically significant obstruction. A positive global test, *e.g.* plethysmography (outflow fraction or outflow resistance), hand-foot pressure differential (Raju test) or hyperemia pressure differential may indicate global obstruction to venous outflow, but a normal result because of a well-developed collateral circulation does not rule out a significant stenosis. Recently, duplex ultrasound assessments of the femoral vein have been shown to change in response to increasing levels of experimentally induced venous obstruction.[16] Analysis of femoral vein velocity profiles in patients during intermittent pneumatic compression of the calf could be developed as a test to quantify the degree of venous obstruction. Duplex ultrasound can describe obstructions and collaterals in the venous system of the leg, but it is less valuable above

the inguinal ligament. Bilateral dynamic femoral vein pressure measurement was previously considered to evaluate the degree of obstruction to venous outflow where the best parameters were pressure elevation and difference before and during exercise, and immediately after exercise, as well as time for pressure to return to pre-exercise level. The pressure measurements can be performed simultaneously with the biplane femoral venograms which will demonstrate the morphological changes of the iliocaval outflow. The method of choice to evaluate the **morphologic** changes of the iliocaval outflow today is IVUS. There is an interesting development of CTV and MRV. In classification of iliocaval morphologic changes we should differentiate between occlusion and obstruction as well as the development of collaterals.

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CHAPTER 7

Compression therapy

Therapy that applies pressure to the lower extremities is a fundamental component for managing CVD.

Bandages

Long stretch bandages extend by more than 100% of their original length, *short-stretch bandages* extend to less than 100% and *stiff bandages* such as zinc plaster bandages (Unna's boot) and some Velcro devices do not extend at all.[1] Textiles may be covered with adhesive (sticking to the skin) or cohesive material (sticking to the bandage) to prevent slippage. Composite bandages consist of several components usually including a padding layer (multi-component bandages).[2] While most of these bandages need to be applied by specialized staff, velcro-band wraps can be handled and adjusted by the patients.[3]

Medical Compression Hosiery and Classes

Medical compression stockings are made of elasticated textile. According to their length, they are classified as *knee-length, thigh-length and tights* (pantihose style). These may be custom-made or off the shelf, which are available in standard sizes.[4] Most compression stockings are round-knitted. Flat knitted products are usually custom-made products for patients with lymphoedema providing higher stiffness.

Different compression classes are available according to the pressure exerted. The pressure profile for each compression class varies among different countries. Therefore it is recommended to classify stockings rather by mmHg than by compression classes.[2] Table I shows a proposal for an international terminology as used in the United States. A recent study compared the hemodynamic efficiency of a standard stocking designed to exert a high pressure at the ankle and a 20% lower pressure at the calf, *i.e.* graduated compression (GC) with a stocking designed to exert a 50% higher pressure at the calf, *i.e.* negative graduated compression (NGC), both composed of the same short-stretch material.[5] In this study 30 patients with great saphenous vein (GSV) incompetence and candidates for surgery (CEAP C_2-C_5), the ejection fraction of the venous calf pump was measured using strain-gauge plethysmography during a standardized walking test without compression, with GC and NGC. Substocking pressures were measured simultaneously over the distal leg and over the calf. NGC with median pressures higher at the calf (29 mmHg) than at the distal leg (18.5 mmHg) achieved a significantly higher increase of ejection fraction (median increase 75%) compared with GC (32% increase) with a distal pressure of 22 mmHg and a calf pressure of 19 mmHg (P<0.001).

Measurement of Interface Pressure and Stiffness [6]

The compression pressure given by the producers of stockings is measured in textile-labora-

TABLE I.—*Proposal to classify compression classes of medical compression stockings based on the pressure (mmHg) exerted at the distal lower leg.*

Class	Pressure in mmHg	Level of Compression
I	10-20	Mild
II	21-30	Moderate
III	31-40	Strong
IV	>40	Very strong

tories by calculating the force of a fabric exerted on a theoretical cylinder model depending on its stretch using different extensiometers. Stiffness is defined as the increase of pressure due to an increase of the leg circumference by one centimetre.[4]

To allow comparison between different compression systems, both for clinical practice and research, interface pressures and fabric stiffness can also be measured *in vivo*.[2] Fabric stiffness is determined by the increase of interface pressure per centimetre increase of the leg circumference due to muscular contraction during walking (walking pressure) or standing.[2, 4] For equal resting pressures, the peak pressure and bandwidth of pressure change at the ankle is much higher with short stretch material. Addition of several layers of compression bandages and superimposition of stockings increase both the interface pressure and stiffness of the cumulative compression.

PRACTICAL USE OF BANDAGES

There are no definitive data on the superiority of different bandaging techniques (spiral, figure of eight, circular, etc). However, an important feature of a good compression bandage is that it provides a sufficiently high pressure peak during walking ("working pressure") to exert a pronounced massaging effect while allowing a tolerable resting pressure. Due to edema reduction, bandages are losing pressure after application. Therefore bandages should initially be applied with high enough pressure and should be renewed when the pressure decreases into an ineffective range. They should be washable and reusable. Multi-component bandages meet better the above requirements than single component bandages. Pads or rolls of different materials can be used to increase the local pressure over a treated venous segment following sclerotherapy or over a venous ulcer located behind the medial malleolus.

PRACTICAL USE OF COMPRESSION STOCKINGS

Stockings should only be prescribed if patients are able to apply them on a regular basis. They are best put on in the morning,[7] and replaced with new stockings after 3-6 months if used daily. A variety of devices have been developed to facilitate application of stockings. While bandages are mainly used for the initial phases of compression therapy, stockings are recommended for maintenance and long term management in chronic conditions.

Quality of Life and Compliance

Several studies have shown that compression treatment improves the quality of life in patients with CVD.[8-12] Compliance is crucial to prevent ulcer recurrence.[11-16] Regular daily use of compression stockings for at least two years after DVT can reduce the incidence and severity of the PTS.[13-15, 17]

Mode of Action

Several beneficial effects of compression treatment and methods used to measure these effects are summarized in Table II. Experimental studies have helped to understand the performance of various compression devices on the normal and the diseased leg.

Clinical Applications

Effect on symptoms and QoL in patients with mild to moderate CVD

A prospective crossover trial of symptom evaluation in 19 flight attendants was performed in which participants rated their symptoms on a visual analog scale.[18] During the initial phase, participants wore no compression for 2 weeks. They then wore 8-15 mmHg and 15-20 mmHg gradient compression support hose while flying over a

TABLE II.—*Effects of compression therapy.*

Parameter	Investigative method
Sub-bandage pressure	MST-tester, Picopress, Kikuhime [4, 61, 62]
Reduced edema	Volumetry, isotopes, ultrasound [63-65]
Reduced venous volume	Phlebography, MRI, blood pool scintigraphy [44-5]
	Air plethysmography (APG) [44, 45, 66-71]
Increased venous velocity	Circulation time (isotopes), Duplex [72, 73]
Blood shift into central compartments	Blood pool scintigraphy, cardiac output [74]
Decreased venous reflux	Duplex, APG [69, 70, 75]
Improved venous pump	Foot volumetry, plethysmography, venous pressure [66, 67, 70, 71, 76-82]
	Duplex, Xenon-clearance, Laser Doppler [50, 83-88]
Increased arterial flow	Capillaroscopy, tcPO2, Laser Doppler [86, 89-92]
Improvement of microcirculation	Isotopic and indirect lymphography [93, 94]
Increased lymphatic drainage	Microscopy and histochemistry [95-97]
Effect on ultrastructure and cytokines	Laboratory investigations [98-100]

Note: The compression pressure should never exceed perfusion pressure.

4-week period. Use of lightweight (low compression) ready-to-wear gradient compression hosiery was very effective in improving symptoms of discomfort ($P<0.01$), swelling (almost $P<0.05$), fatigue ($P<0.05$), aching ($P<0.01$), as well as leg tightness. Improvement of symptoms was statistically significant compared to no compression when hosiery was worn regularly during waking hours for 4 weeks. The difference between the 8-15 mmHg and 15-20 mmHg compression was not statistically significant.

In a 4-week multicentre, randomized, double-blind, placebo-controlled clinical trial conducted in two parallel groups of 341 women presenting with mild chronic venous insufficiency CEAP grade C(1-3S) E(p) A(S1-5).[9] Class 1 graduated elastic compression (GEC) stockings (pressure at the ankle 10 to 15 mmHg) were compared with placebo stockings (pressure at the ankle 3 to 6 mmHg). Treatment efficacy was assessed by global impairment on a visual analogue scale (primary efficacy parameter), Quality of Life (QoL) measured by the CIVIQ questionnaire, symptoms index (sum of individual scores for pain, limb heaviness, paresthesiae, cramps and evening limb edema) and limb volume measured by volumetry. A statistically significant improvement of QoL and a decrease of limb edema were demonstrated in patients with class 1 GEC stockings.

Another prospective multicentre randomized double blind crossover study involving 125 female patients presenting with early-stage chronic CVD (CEAP classification of C1-3$_S$EpA$_s$1-5) compared the efficacy of Class 1 (10-15 mmHg at the ankle) compression stockings with that of reference stockings of identical appearance.[11] There was a significant improvement in global painful discomfort as well as in quality-of-life criteria.

In another study 108 hairdressers were randomized to wear medical compression stockings (MCS; 15-20 mmHg) in a crossover study.[19] Wearing MCS reduced the symptom score for pain and feelings of swelling (range 0-4) by an average of 0.22 (12%, $P<0.001$). Sleep disturbance, feeling of unattractive legs and depressiveness also improved and there was a decrease of lower leg volume by an average of 19 mL ($P<0.001$), mostly in older hairdressers ($P<0.001$).

A meta-analysis of 11 RCT involving 1,453 subjects (794 healthy people exposed to various forms of stress, 552 patients with CVD and 141 patients after varicose vein surgery) compared stockings exerting an ankle pressure of 10-20 mmHg with placebo or no treatment and with stockings exerting a pressure of more than 20 mmHg.[20] Compression with 10-20 mmHg had a clear effect on edema and symptoms as compared with <10 mmHg pressure, placebo stockings, or no treatment ($P<0.0001$). Stockings applying pressure between 10-20 mmHg and over 20 mmHg had similar efficacy in all studies. The authors concluded that despite important methodological heterogeneity and sometimes suboptimal reporting, the meta-analysis suggests that leg compression with 10-15 mmHg is an effective treatment for CVD. Less pressure is less effective and higher pressure may be of no additional benefit.

A recent Cochrane review of 7 studies involving 356 patients (CEAP C1-4) concluded that symptoms subjectively improved with the wear-

ing of stockings across trials that assessed this outcome, but these assessments were not made by comparing one randomized arm of a trial with a control arm and are therefore subject to bias.[21] The conclusion was that there is insufficient, high quality evidence to determine whether or not compression stockings are effective as the sole and initial treatment of varicose veins or whether any type of stocking is superior to any other type.

The efficacy of negative GEC stockings in relieving symptoms of moderate to severe CVD was tested in a study that included 401 patients (CEAP C_{2b} to C_5) randomized to degressive compressive stockings (30 mmHg at ankle, 21 mmHg at upper calf) or progressive compressive stockings (10 mmHg at ankle, 23 mmHg at upper calf).[22] The primary outcome, evaluated after 3 months, was a composite success outcome, including improvement of pain or heavy legs without onset of either ulcer, deep or superficial vein thrombosis of the lower limbs, or pulmonary embolism. The rate of success was higher in the progressive compressive stocking group compared to the degressive compressive stocking group (70.0% vs. 59.6%; relative risk, 1.18; 95% confidence interval, 1.02-1.37; P=0.03). This was mainly due to more frequent symptom improvement in the progressive compressive stocking group. In addition, the compressive stockings were considered easy to apply by 81.3% of patients in the progressive compressive stocking group vs. 49.7% of patients in the degressive compressive stocking group (P<0.0001).

The available evidence suggests that compression relieves the symptoms and reduces edema in patients with mild to moderate (CEAP C1-2) CVD (Grade B). Further studies are needed to determine the optimum type of compression in different CEAP classes of patients.

Effect of compression stockings in pregnancy

A prospective randomized controlled study involving 42 pregnant women compared a no-stockings control group (N.=15) with two treatment groups: group 1 (N.=12) wore compression class I stockings (18-21 mm Hg) on the left leg and class II stockings (25-32 mmHg) on the right; in group 2 (N.=15), the compression classes were reversed.[23] Both classes of compression

stockings failed to prevent the occurrence of superficial varicose veins. However, GSV reflux at the sapheno-femoral junction was observed in the third trimester in only 1/27 treated women vs. 4/15 controls (P=0.047); in addition, more treated women reported improved leg symptoms (7/27 vs. 0/15 controls; P=0.045). The authors concluded that although compression stockings did not prevent the occurrence of gestational varicose veins, they decreased the incidence of GSV reflux at the sapheno-femoral junction and improved leg symptoms and that more RCTs are needed.

Effect of compression stockings in patients having sclerotherapy

Two studies addressed the effect of compression stockings and its duration following sclerotherapy of reticular veins and telangiectasiae in similar locations. The first study included 40 patients, 30 patients who did and 10 control patients who did not receive compression therapy.[24] The compression group consisted of three subgroups (each having 10 patients) based on compression duration: 3 days, 1 week, and 3 weeks. Patients were evaluated at 1 week, 2 weeks, 6 weeks, 12 weeks, and 24 weeks for degree of improvement and side effects. The three compression subgroups showed significantly greater improvement at 6 weeks compared to control (P=0.004). The patients treated with compression for 3 days and 1 week showed better improvement than the control patients while the patients treated for 3 weeks of continuous compression had the most improvement. In terms of side effects, the 1 week and 3 week compression groups experienced the least amount of post-sclerotherapy hyperpigmentation.

In the second study 100 female patients seeking treatment of telangiectasiae and reticular veins and presenting comparable areas of telangiectasiae on the lateral aspect of the thigh (C1A or SEPAS1PN) were randomized to wear medical compression stockings (23 to 32 mmHg) daily for 3 weeks or no such treatment following a single session of standardized liquid sclerotherapy.[25] Outcome was assessed by patient satisfaction analysis and quantitative evaluation of photographs taken from the lateral aspect of the thigh before and again at 52 days on the av-

erage after sclerotherapy by two blinded expert reviewers. Wearing compression stockings (23 to 32 mm Hg) for 3 weeks enhanced the efficacy of sclerotherapy of leg telangiectasiae by improving clinical vessel disappearance.

It appears that three weeks of continuous compression leads to the best results, although even 3 days of compression results in greater improvement than no compression. Compression leads to a statistically significant reduction of post-sclerotherapy hyperpigmentation.

Two studies compared high compression stockings with bandages after liquid sclerotherapy. The first one was a RCT comparing a standard bandaging technique with a high pressure compression stocking.[26] Efficacy was judged on the success of injections, complications of the treatment and patient satisfaction. In the stockinged legs 144 of 156 injections were successful, compared with 117 of 147 in the bandaged group (P<0.001). The incidence of superficial vein thrombosis was also reduced in the stocking group. In the second study, high compression stockings alone produced results comparable to Elastocrepe bandages with stockings.[27] It was concluded that after sclerotherapy, bandaging is not required if a high compression stocking is used.

Two studies compared the effect of compression bandaging or stockings in patients undergoing foam sclerotherapy. In the first study, 124 legs were randomized to 24 h or 5 days of bandaging.[28] There was no significant difference in the incidence of superficial thrombophlebitis after 2 weeks or skin discoloration after 6 weeks (46% versus 40%, P=0.546). There was no significant difference in the change in AVV_{S}.S from baseline to 2 weeks or to 6 weeks or in change in Burford pain score from baseline to 2 weeks, or in change in Short Form 36 score from baseline to 6 weeks. In the second study, 60 patients with incompetent GSV or small saphenous vein (SSV) were randomized to compression stockings (15-20 mmHg worn during the day, for 3 weeks) or no compression.[29] On days 14 and 28, clinical and duplex ultrasound assessments were performed by independent experts. Patients also completed QoL and symptom questionnaires. There was no difference between compression and control groups in terms of efficacy, side effects, satisfaction scores, symptoms and QoL. Further RCTs

are required to establish the role of compression in patients having foam sclerotherapy.

Effect of compression stockings in patients having varicose vein surgery

Two studies investigated the value of class III compression stockings after varicose vein surgery. In a trial of high versus low compression stockings (40 mmHg *vs*. 15 mmHg at the ankle level) both were equally effective in controlling bruising and thrombophlebitis, but low compression stockings proved to be more comfortable.[27] In the second study patients were randomized to bandages *vs*. class I *vs*. class III stockings.[30] There was no difference in terms of pain and costs.

Two studies investigated the value of class II compression stockings after varicose vein surgery. A reduction in recurrent varicose veins was produced by postoperative stockings worn for three months to a year in a RCT study involving 76 limbs.[31] The incidence of recurrence was reduced from 61% in the control group to 12% in the stocking group. In the second study, 60 patients CEAP $C2_{S}$ were randomized for postoperative compression therapy with a stocking system or standard stretch bandages for two weeks.[32] Primary end points were incidence of venous thromboembolism, hemorrhage, limb hematoma or edema. There was no difference in the mean area of thigh hematoma on postoperative days 7 and 14 in the two groups. On postoperative day 7, edema was found in 50% of the patients wearing bandages and in 20% of the patients wearing the stocking kit, which was a significant reduction. No statistical difference was recorded for postoperative pain; however, better patient acceptance and quality of life after the operation were recorded in the stocking group.

Two studies investigated the addition of local pressure pads under the compression bandages or stockings after varicose vein surgery. In the first study 200 patients were randomized to receive an eccentric compression applied in the medial aspect of the thigh *vs*. no such compression.[33] Patients were scheduled for a seven-day examination to assess the level of pain experienced. Pain intensity was measured using a visual analogue scale giving a numerical grade from 0 (no pain) to 10 (worst pain ever). The intensity

of postoperative pain was significantly reduced (P<0.001) in the eccentric compression group compared with the control group. In the second study, 54 patients undergoing stripping of the GSV and side branch avulsion under local anesthesia were treated postoperatively in sequential order by A) thigh length compression stockings; B) adhesive bandages; and C) newly developed eccentric compression pads fixed with tapes and a superimposed thigh length stocking.[34] The lowest sub-bandage pressure of around 15 mmHg at the thigh level in the lying position was found in group A under the compression stockings. Group B and group C showed significantly higher values (median values of 47 and 68 mmHg respectively in lying position, P<0.001). Major adverse events were seen in a total of 10 of 18 patients in group A, in 1/18 in group B, and in 0/18 in group C. It appears that the best results with respect to the reduction of pain and hematoma were obtained when eccentric compression pads were taped to the skin of the thigh and a superimposed compression stocking.

Conflicting results have been obtained on the value of compression bandages after varicose vein surgery. One study showed that high compression reduces thigh hematoma using 99mTc-labelled red blood cells.[35] However, there was no difference between bandages and class I compression stockings,[36] or groups of different duration of compression (1 week *vs.* 3 weeks *vs.* 6 weeks).[37, 38]

As presented above the evidence evolving from different RCTs and meta-analyses may occasionally be divergent. The most relevant reason for this is the fact that therapeutic interventions are often ill defined, *e.g.* comparing good stockings with poor bandage technique. The characteristics of compression (pressure and stiffness) are rarely provided, so that the conclusions drawn need to be interpreted with caution.

Effect of compression stockings in the prevention of PTS

Four RCTs investigated the efficacy of compression stockings in preventing the development of PTS in patients with proximal deep venous thrombosis (DVT) who received conventional anticoagulant treatment.

In the first study 194 patients were random-ized to compression stockings (class III) or no stockings.[13] The median follow-up was 76 months (range 60-96) in both groups. Mild-to-moderate PTS occurred in 19 (20%) patients in the stocking group and 46 (47%) in the control group patients (P<0.001). Severe PTS occurred in 11 (11%) patients in the stocking group and 23 (23%) patients in the control group (P<0.001). In both groups, most cases of PTS occurred within 24 months of the acute thrombotic event.

In the second study 180 patients were random-ized to wear or not to wear below-knee compression elastic stockings (class III) for 2 years.[14] Follow-up was performed for up to 5 years. Post-thrombotic sequelae developed in 44 (49%) of 90 controls (severe in 10) and in 23 (26%) of 90 patients wearing elastic stockings (severe in 3). All but 1 event developed in the first 2 years (P=0.011).

The third study assessed the effect of pro-longed compression therapy after a standard anticoagulant treatment for 6 months.[39] At the end of anticoagulation 169 patients were random-ized to wear compression stockings (grade II) or not. Primary efficacy analysis was performed on the end point of emerging skin changes (CEAP C4-C6). The primary end point occurred in 11 (13.1%) of 84 patients in the treatment group and 17 (20.0%) of 85 in the control group (P=0.30). Within subgroup analyses of the primary end point, we observed a large sex-specific difference between women (HR, 0.11; 95% CI, 0.02-0.91) and men (HR, 1.07; 95% CI, 0.42-2.73).

The fourth study randomized one group of 47 patients to compression stockings (class II) or placebo stockings and a second group of 35 patients to compression stockings (class III) or placebo.[40] PTS developed in 11 (27%) of 40 controls and in 11 (26%) of 42 patients wearing elastic stockings (P=0.91).

Clear cut results have been obtained from the first two studies in which class III stockings were used. However, considering all four studies which include 628 patients, compression stockings reduce the incidence of PTS from 37% to 21% (RR 0.55; 0.43 to 0.72).

In a recent RCT 267 patients with a first episode of proximal DVT were randomized to wear either thigh-length or below-knee compression stockings for 2 years.[41] After 3, 6, 12, 18, 24, and 36 months, they were assessed for PTS manifes-

tations according to the Villalta scale. PTS developed in 44 (32.6%) of the 135 patients randomized to thigh-length and in 47 (35.6%) of the 132 allocated to below-knee stockings. Severe PTS developed in 3 patients in each group. Stocking-related complications developed in 55 (40.7%) of the 135 patients allocated to thigh-length GEC stockings and in 36 (27.3%) of those randomized to the below-knee group (P=0.017), and led to premature discontinuation of their use in 29 (21.5%) and 18 (13.6%) patients, respectively. The authors concluded that thigh-length stockings do not offer a better protection against PTS than below-knee stockings and are less well tolerated.

A multicentre placebo controlled RCT involving 794 patients with a first DVT has been recently published casting doubt on the effectiveness of compression in the prevention of PTS. The interpretation of the results by the authors was "Elastic compression stocking (ECS) did not prevent PTS after first proximal DVT, hence our findings do not support routine wearing of ECS after DVT". This assertion should be confirmed by further studies.[101]

Effect of compression in the healing of venous ulcers

There is a large number of publications on the efficacy of compression in healing venous leg ulcers. The results are summarized by the Cochrane database systematic review updated in 2009.[42] In this review, ulcer healing was the primary endpoint. Compression was more effective than no compression in 4 out of 6 trials. When multi-layer systems were compared, elastic compression was more effective than non-elastic compression (5 trials). There was no difference in healing rates between 4-layer bandaging and other high compression multi-layer systems (3 trials). There was no difference in healing rates between elastomeric multi-layer systems (4 trials). Multi-layer high compression was more effective than single layer compression (4 trials). The authors concluded that compression increases ulcer healing rates compared with no compression. Multi-layer systems are more effective than single-layer systems. High compression is more effective than low compression. However, there are no clear differenc-

es in the effectiveness of different types of high compression.

The above Cochrane Database Systematic Review was updated in 2012 [43] reporting on forty eight RCTs which included a total of 4,321 patients. The authors concluded that "compression increases ulcer healing rates compared with no compression. Multi-component systems are more effective than single-component systems. Multi-component systems containing an elastic bandage appear to be more effective than those composed mainly of inelastic constituents. Two-component bandage systems appear to perform as well as the four layer bandage (4LB). Patients receiving the 4LB heal faster than those allocated the short stretch bandage (SSB). More patients heal on high-compression stocking systems than with the SSB. Further data are required before the difference between high-compression stockings and the 4LB can be established".

Recent experimental studies

Recent experimental studies have questioned some conventional concepts on compression.

— Compression of superficial and deep veins depends very much on the body position: in the horizontal prone position and in standing deep veins are mostly more affected than superficial veins.[44-46]

— Higher pressure over the calf leads to a stronger effect on the venous pump than a pressure gradient.[47]

— In chronic venous edema lower pressure may be more effective than very high pressure.[48]

— Not only intermittent pressure waves,[49] but also sustained pressure up to 40 mmHg improve arterial flow, both in normal individuals and in patients with arterial occlusive disease, *e.g.* in patients with mixed, arterial-venous leg ulcers.[50]

In contrast to drug therapy, compression treatment never had to pass any pharmacological phase I and phase II trials to confirm clinical efficacy and determine the therapeutic dose range. Although some insight concerning the mechanisms of action of compression has emerged from several studies during the last years, a lot more has to be learnt in order to tailor and to optimize this important treatment modality in different clinical indications.[51]

Intermittent Pneumatic Compression (IPC)

IPC devices consist of single or multiple inelastic cuffs that are intermittently and/or sequentially inflated. Limited data based on RCTs are currently available demonstrating encouraging clinical outcome when IPC is used as part of the care for venous ulcers.[52, 53]

The first study was reported in 1981.[54] It was a prospective controlled, but not randomised trial involving 21 patients. Eight out of 9 (89%) patients treated with IPC (single chamber used for 2-3 hours per day for 10 to 44 weeks) were healed, compared with only 1 (9%) of 11 control patients.

A RCT involving 45 patients was subsequently performed in 1990.[55] Both groups included ulcer debridement, cleaning, nonadherent dressing, and GEC stockings. In one group, sequential gradient IPC was applied for 4 hours each day for 3 months. In the IPC group 10 (48%) of 21 patients had complete healing of all ulcers compared with 1 (4%) of 24 patients in the control group. The median rate of ulcer healing in the control group was 2.1% of the ulcer area per week compared to 19.8% of the ulcer area per week in the IPC group.

In another RCT, 22 patients were assigned to IPC (used for 1 hour twice weekly at 50 mmHg for 90 s followed by 30 s deflation) for 6 months and a control group.[56] Both groups received local wound care and application of an Unna boot. At 6 months, all 12 patients (100%) in the IPC group had healing of their ulcers compared with 8 out of 10 patients (80%) in the control group. The healing rate was 0.15 cm²/day in the IPC group compared with 0.06 cm²/day in the control group.

In a third RCT, 53 patients were assigned to IPC (sequential gradient) for 3 hours each day with an elastic stocking for 6 months or an Unna boot.[57] At 6 months, 20 (71%) of 28 patients in the IPC group had healing of their ulcers compared with 15 (60%) of 25 patients in the control group.

A more recent RCT with a crossover design compared IPC (uniform compression) with elastic bandages but it was underpowered because of its small size (N.=16) and further interpretation of the poor healing results (persisting even after cross-over) in both study arms was further hampered by the number of patient dropping out (N.=5), which left 11 patients into the study.[58]

A recent systematic review identified seven RCTs (including 367 patients in total).[59] However, only one trial was at low risk of bias having reported adequate randomization, allocation concealment and blinded outcome assessment. The authors concluded that IPC may increase healing compared with no compression, but it is not clear whether it increases healing when added to treatment with bandages, or if it can be used instead of compression bandages.

A RCT compared two different IPC regimens on ulcer healing.[60] One hundred and four patients were randomized to rapid (3 cycles per minute) or slow (1 cycle per 3 minutes) compression IPC devices for one hour daily. Both devices applied the same pressure and no other compression treatment was applied during the study period. Complete healing occurred in 45 of the 52 patients treated with rapid IPC, and in 32 of the 52 patients treated with slow IPC. Life table analysis showed that the proportion of ulcers healed at six months was 86% in the group treated with the rapid IPC compared with 61% in the group treated with slow IPC (P=0.003, log-rank test). The mean rate of healing per day in the rapid IPC group was found to be faster compared to the slow IPC group (0.09 cm² *vs*. 0.04 cm², P=0.0002).

Although IPC is an attractive alternative modality, at present it can be recommended for venous leg ulcers that have failed to heal with proper use of elastic bandages or patients who cannot tolerate them. Further trials are required to determine the optimum type of IPC and optimum type of compression stockings it should be combined with.

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CHAPTER 8

Venoactive drugs

Introduction

Venoactive drugs (VADs) comprise a heterogeneous group of drugs, some of which are synthetic but most are of plant origin. Five main categories of VADs have been described in recent publications;[1, 2] their source and dosages are summarised in Table I. Some VADs are commonly taken as mixtures; for example, marketed ruscus extracts are a mixture of ruscus aculeatus, hesperidine, methyl chalcone and ascorbic acid, while micronised purified flavonoid fraction (MPFF) is a micronised mixture of diosmin (90%) and flavonoids (10%), expressed as hesperidin, diosmetin, linarin, and isorhoifolin, and gingko biloba extracts are mixed with heptaminol and troxerutin.

A number of dietary supplements allegedly considered as therapies have created confusion in recent years. Dietary supplements, unlike registered VADs, have not been shown to be efficient and therefore they have not received any marketing authorization from health authorities. For these reasons, we will not consider products that are exclusively dietary supplements in this document. On the other hand, some VADs described in the present chapter are considered as medicinal products in some countries and as food supplements in others. For example, red vine leaves extracts (*Vitis vinifera*) is registered as therapeutic drug in seven member states of the European Union (EU), and as food supplement in eight different EU countries.

In this chapter, the various pharmacological actions of VAD are summarized, and the evolu-

tion of recommendations for their therapeutic use is tracked. Finally, a new set of recommendations based on current evidence is proposed. The emphasis throughout this document is on recent experimental and clinical advances that have altered our understanding of the effects of VADs and their therapeutic use. A more comprehensive review of the older literature was given in the previous guidelines.[3]

Mode of action

Although not all actions of VADs are fully understood, it seems clear that they can act at both the macrocirculation and microcirculation levels, affecting the changes in the venous wall and venous valves that lead to the development of venous hypertension (VH), and altering the effects of VH on small vessels that lead to venous microangiopathy.[4-6] Traditionally, VH was thought to result primarily from valvular incompetence related to excessive venous dilation due to weakness of the vein wall and/or low venous tone. Consequently, much of the earlier research on VADs was centred on their effects on venous tone. More recently, research interest has shifted towards the action of VADs on chronic inflammatory processes that can affect large and small venous vessels and valves.

Actions on venous tone

Most of the main types of VADs have been shown to increase venous tone, including

TABLE I.—*Main categories of venoactive drugs (modified from Ramelet et al.[1]).*

Category	Drug	Origin	Dosage (mg/day)	Doses/day
Flavonoids (gamma-benzopyrones)	Micronised purified flavonoid fraction	*Rutacae; Citrus aurantium, ssp amara*	1000	1-2
	Diosmin	Citrus species	300-600	1-2
	Rutin and rutosides, O-(β-hydroxyethyl)-rutosides (troxerutin, HR)	*Sophora japonica* Eucalyptus species *Fagopyrum esculentum*	1000	1-2
	Quercetine glucuronide, kaempferol glucoside	Red-vine-leaf extracts *(Vitis vinifera)*	100-300	1-3
	Proanthocyanidins	Grape pips *(Vitis vinifera)*	100-300	1-3
		French maritime pine *(Pinus pinaster*, formerly *P. maritima)*	300-360	3
	Anthocyans	Red-vine-leaf extracts *(Vitis vinifera)*	100-300	1-3
		Bilberry *(Vaccinium myrtillus)*	116	2
Alpha-benzopyrones	Coumarin	Melilot *(Melilotus officinalis)* Woodruff *(Asperula odorata)*	90 combined with troxerutin (540)	3
Saponins	Horse chestnut seed extract; escin	Horse chestnut *(Aesculus hippocastanum)*	Initially 120, then 60	3
	Ruscus extract	Butcher's broom *(Ruscus aculeatus)*	2-3 tablets	2-3
Other plant extracts	Gingko extracts	*Gingko biloba*	2 sachets (extracts of Gingko, heptaminol and troxerutin)	2
Synthetic products	Calcium dobesilate	Synthetic	1000-1500	2-3
	Benzarone	Synthetic	400-600	2-3
	Naftazon	Synthetic	30	1

MPFF,[7-9] rutin and rutosides,[10] escin,[11] *Ruscus* extract [12] and calcium dobesilate.[13] Most act by modulating noradrenergic signalling, by reducing norepinephrine metabolism in the cases of MPFF and hydroxyethyl-rutosides,[7, 8, 14-16] or by agonism of venous α1-adrenergic receptors in the case of *Ruscus* extracts.[17, 18] By contrast, horse chestnut seed extract induces calcium-dependent contractions in rat vena cava preparations, but inhibits the action of the α-adrenergic agonist phenylephrine.[19]

Actions on inflammatory processes in venous valves and the vein wall

Most VADs have now been demonstrated to have anti-inflammatory effects. Some act on multiple steps of inflammatory pathways, and their ability to inhibit inflammatory mechanismsisms may be a common factor underlying many of their various beneficial effects in CVDs.

As a group, flavonoids are known to have potent antioxidant properties which have been investigated in several therapeutic areas other than CVD, including cancer, arthritis and cardiovascular disease.[20-24] These properties may include prevention of oxidant production, scavenging of free radicals thereby preventing them from attacking cellular targets, blocking the propagation of oxidative reactions, and reinforcing inherent cellular antioxidant capacity.[24] More specifically, the VAD MPFF and rutosides have shown powerful free-radical scavenging properties in various assay systems,[25-28] and VADs from other groups including escins,[11, 29] proanthocyanidines from grape seeds,[30, 31] French maritime pine bark,[32-35] and calcium dobesilate,[36-38] have also shown similar properties.

In addition to actions that reduce oxidative stress, several VADs also act at various points in inflammatory cascades. As examples, grape seed proanthocyanidin reduced expression of cell adhesion molecules by activated cultured vein endothelial cells,[39] and MPFF decreased expression of adhesion molecules by neutrophils and monocytes in patients with CVD.[40, 41] Similarly, rutoside reduced inflammation-related gene expression by activated human macrophages,[42] and French maritime pine bark extract reduced ICAM-1 expression and adherence of cultured T-lymphocytes to human keratinocytes.[43]

Perhaps the most detailed and comprehensive analysis of the importance of inflammatory processes and the ability of VADs to inhibit them was provided by a series of experiments by Bergan *et al.*,[44] in rodent models of VH. In venular occlusion experiments, markers of inflammation, such as leukocyte attachment and migration, were elevated with 1 hour of the onset of the increase in venous pressure. In experiments involving placement of an arterio-venous fistula, reflux flow through venous valves exposed to elevated pressure was detected after 7 days and markedly increased at 21 and 42 days. Morphological changes developed with a parallel time course, and complete disappearance of valvular structures as seen at 42 days. Treatment with oral MPFF decreased the signs of inflammation and markedly reduced reflux, in a dose-dependent manner.

These experiments have illustrated how inflammatory processes may be central to many of the deleterious effects of VH, and also show that some VADs such as MPFF have at least the potential to prevent the development and progression of CVDs and its different manifestations.

Actions on capillary permeability (edema)

The control of microvascular permeability is complex and is an active field of research. However, it is clear that hyperpermeability and resulting edema are induced by more than just elevated microvessel pressure. In particular, recent research has highlighted the importance of inflammatory mechanisms, involving neutrophil-endothelial interactions including activation, adherence, attachment, migration and release of reactive oxygen species, in producing hyperpermeability.[45-49] Given their antioxidant and anti-inflammatory effects, it is not surprising that many of the major VADs have been shown to reduce capillary hyperpermeability, including MPFF,[50-52] rutosides,[53-55] escin,[11, 56] *Ruscus* extract,[57-59] grape seed extract[31] and calcium dobesilate.[60, 61]

Vascular endothelial growth factor (VEGF) is known to play a key role as a regulator of capillary permeability.[62, 63] VEGF levels in plasma are elevated in patients with CVD, especially those with skin changes.[64-66] MPFF treatment significantly reduces plasma VEGF in patients with skin changes, and plasma VEGF has been proposed as a marker of MPFF therapy.[65]

Skin changes related to capillary abnormalities

The chronic inflammation that results from sustained venous hypertension is also thought to be important in the skin changes associated with CVD.[67, 68] Expression of endothelial adhesion molecules can lead to perivascular infiltration of leukocytes, resulting in fibroblast-mediated skin tissue remodelling and damage, including proliferation of dermal capillaries and fibrosis.[65, 69-71] Sustained oxidative stress, primarily due to the release of reactive oxygen species from neutrophils and macrophages, together with resultant fibroblast senescence, is thought to be important in the eventual formation of active venous leg ulcers and their chronic persistence.[68, 72-75]

Interest in the mechanisms underlying skin changes has received new impetus with the increasing recognition of the importance of venous valves in small veins and venules. It is now appreciated that small superficial veins of the human lower limb contain abundant, typical bicuspid venous valves, with the majority occurring in vessels less than 100 µm in diameter and present in vessels as small as 18 µm.[76, 77] A recent study has shown that incompetence can occur in human small superficial venous valves independently of reflux within the great saphenous vein and major tributaries. Importantly, degenerative changes and incompetence in these microvenous valves can allow reflux into the microvenous networks in the skin, which may be critical in the development of severe skin changes in CVD.[78]

The ability of VADs to reduce inflammation and oxidative stress could protect small venous valves and prevent reflux, as demonstrated in the rodent models of VH described above,[44] and also act at the level of preventing the adverse remodelling of skin tissue that ultimately may lead to the development of active ulcers in CVD.

Role of nociceptors in the development of venous symptoms

Most recent studies have found that the prevalence and severity of CVD symptoms are greater with increasing severity of CVDs or CEAP clinical class.[79-83] However, other studies have found

TABLE II.—*Evidence-based modes of action of the main venoactive drugs.*

Category	Drug	Effect on:					
		Venous tone	Venous wall and valve	Capillary leakage	Lymphatic drainage	Hemorheological disorders	Free radical scavengers
Flavonoids (gamma-benzopyrones)	Micronised purified flavonoid fraction	+	+	+	+	+	+
	Nonmicronised or synthetic diosmins*						
	Rutin and rutosides, O-(β-hydroxyethyl)-rutosides (troxerutin, HR)	+		+	+	+	+
	Anthocyans (Vitis vinifera)						+
	Proanthocyanidins (Vitis vinifera)			+			+
Alpha-benzopyrones	Coumarin			+	+		
Saponins	Horse chestnut seed extract; escin	+		+			+
	Ruscus extract	+		+			
Other plant extracts	Gingko extracts*						
Synthetic products	Calcium dobesilate	+		+	+	+	+
	Benzarone*						
	Naftazon*						

*No data available

only weak correlations,[84, 85] or that symptom scores were actually higher in individuals with less severe CVDs.[86] A possible confounding factor is the occurrence of peripheral neuropathy in some patients with severe CVD, which may decrease the perception of pain and other symptoms.[87-89] What seems clear is that typical leg symptoms of CVDs are common in those with even the least severe forms of CVDs (CEAP clinical classes 0_s and 1).[90-92] In a random sample of the population of Edinburgh, Scotland, aged between 18 and 64 years with no visible or palpable signs of CVDs, 32.8% and 28.9% had symptoms of leg aching and cramps, respectively.[91] In a recent report from the Vein Consult Program, a large cohort of over 90,000 consecutive outpatients from 20 countries who were consulting their general practitioner for any reason were screened for CVDs. Of these, 19.7% had typical CVDs leg symptoms without signs and were assigned to CEAP class C_{0s}, and a further 21.7% were assigned to class C_1.[93]

The exact mechanisms by which CVDs, particularly the earliest stages, gives rise to pain and other typical venous symptoms are not yet understood, but recent studies suggest that inflammation plays a key role.[94-96] Sympathetic C fibers are found in the venous intima and media and wrapped around cutaneous venules, and act as nociceptors that can respond to inflammatory mediators. Inflammatory processes seem to be involved in all stages and severity classes of CVDs, even before obvious tissue damage has occurred, and could be responsible for many of the symptoms experienced. Thus, the anti-inflammatory properties of VADs have the potential to improve symptoms in patients at all stages of the disease, including those in CEAP class C_{0s}.

Lymphatic drainage

Lymphatic function is known to be compromised especially in patients with the more advanced stages of CVD,[97-99] and has been shown to improve in patients with varicose veins after reduction of venous reflux by saphenous vein ablation.[100] A recent study has suggested that abnormal accumulation of lipid molecules, elevated tissue pressure and chronic inflammation in varicose veins may combine to produce lym-

TABLE III.—*Global results of combined analyses for all venoactive drugs, for all outcomes analyzed as percentage of improved patients (adapted from Schoonees et al.[111] and Guyatt et al.[116]).*

Outcome variable	Number of patients in the Cochrane review.[111]	Number in treatment group	Number in placebo group	Patients with no symptom (%) in treatment group	Patients with no symptom (%) in placebo group	Test for treatment effect (P value)	Heterogeneity of studies
Edema	1245	626	619	59.4	42.5	5.81 (<0.00001)	no
Trophic disorders	705	355	350	33.8	23.7	3.76 (<0.0001)	no
Pain	2247	1294	953	63.4	37.0	4.70 (<0.00001)	yes
Cramps	1793	1072	721	67.6	45.5	3.02 (0.003)	yes
Restless legs	652	329	323	46.2	33.4	2.77 (0.006)	no
Itching	405	206	199	64.6	41.2	0.83 (NS)	yes
Heaviness	2166	1257	909	59.8	33.1	5.38 (<0.00001)	yes
Swelling	1072	544	528	62.9	38.4	3.86 (<0.0001)	yes
Paresthesia	1456	896	560	71.0	50.7	2.82 (0.005)	yes

phatic dysfunction and a decrease in the number of lymphatic vessels.[101] Several VADs, including α-benzopyrones (coumarin) either alone or combined with rutin,[102, 103] MPFF [104] and calcium dobesilate [105] have all been shown to improve lymphatic drainage in animal models.

Hemorheological disorders

Hemorheological changes, including increased blood viscosity and erythrocyte aggregation, are common in CVDs. Several VADs have been shown to reduce blood viscosity and/or erythrocyte aggregation, including MPFF,[106] troxerutin [107] and calcium dobesilate.[108] The pharmacological effects of VADs are summarized in Table II.

Therapeutic efficacy of VADs on venous symptoms and edema

The efficacy and safety of VADs in the treatment of symptoms and edema associated with CVDs have been evaluated in a large number of generally small clinical studies. As a result, overall conclusions on their efficacy have relied heavily on meta-analyses, reviews and consensus statements rather than individual large clinical trials. In this section, we track the evolution of recommendations for the use of VAD through

the various landmark publications, before proposing a set of recommendations based on currently available evidence.

Cochrane reviews

Meta-analysis represents the most formal and objective way of combining the results of multiple small clinical studies, and Cochrane meta-analyses. They have been influential in the development of recommendations for use of different VADs. A total of 59 randomized clinical trials involving several different types of VADs were included in the 2005 Cochrane review and meta-analysis.[109] Of these, 44 studies were considered to be of suitable design and quality, including 23 trials on rutosides, 10 on MPFF and 6 on calcium dobesilate. The outcome variables considered included objective signs such as edema and trophic disorders, together with a range of subjective symptoms, including pain, heaviness, cramps, restless legs and the sensation of swelling. When all VADs were considered together, significant benefits of treatment were demonstrated for all outcome variables except for itching and venous ulceration. The percentage of patients with complete pain relief was significantly greater in the VAD group compared with placebo (63% *versus* 37%, P<0.00001); and so were heaviness (60% *versus*

TABLE IV.—*Results of the 2005 Cochrane review [111] showing significant (P<0.05) results for main types of venoactive drugs.*

Drug	Variable	Dichotomous/continuous	Single/multiple studies	RR/SD
Calcium dobesilate	Edema	Continuous	Multiple	SD=-0.64
	Pain	Dichotomous	Multiple	RR=038
	Cramps	Dichotomous	Multiple	RR=0.65
	Restless legs	Dichotomous	Multiple	RR=0.73
	Swelling	Dichotomous	Multiple	RR=0.17
MPFF	Edema	Continuous	Multiple	SD=-0.58
	Trophic disorders	Dichotomous	Multiple	RR=0.88
	Cramps	Dichotomous	Multiple	RR=0.83
	Cramps	Continuous	Single study	SD=-0.46
	Heaviness	Continuous	Single study	SD=-0.69
	Swelling	Dichotomous	Multiple	RR=0.70
	Swelling	Continuous	Single study	SD=-0.92
	Global assessment	Continuous	Single study	SD=-0.81
Rutosides	Edema	Dichotomous	Multiple	RR=0.73
	Pain	Dichotomous	Multiple	RR=0.63
	Pain	Continuous	Multiple	SD=-0.71
	Cramps	Dichotomous	Multiple	SD=-0.83
	Itching	Continuous	Single study	SD=-0.58
	Heaviness	Dichotomous	Multiple	RR=0.60
	Heaviness	Continuous	Multiple	SD=-1.11
	Swelling	Dichotomous	Multiple	RR=0.67
	Paresthesias	Dichotomous	Multiple	RR=0.55
	Global assessment	Dichotomous	Multiple	RR=0.49
	Global assessment	Continuous	Multiple	SD=-1.02
French maritime pine bark extract	Pain	Dichotomous	Single study	RR=0.65
	Pain	Continuous	Single study	SD=-1.39
	Heaviness	Continuous	Single study	SD=-1.50
	Swelling	Continuous	Single study	SD=-1.65

RR: relative risk (for dichotomous variables); SD: standard deviation.

33%, P<0.00001), sensation of swelling (63% *versus* 38%, P<0.0001), cramps (68% *versus* 45%, P=0.003), and restless legs (46% *versus* 33%, P<0.006). For most variables there was evidence of heterogeneity among studies, although this is not surprising given that studies of different drugs, designs and with different patient inclusion criteria were combined. Results are summarized in Table III. The overall incidence of adverse events was not different from placebo, although it was pointed out that most studies were of relatively short duration.

Subgroup analyses for individual VAD were also performed, in which calcium dobesilate, MPFF and rutosides all showed significant treatment benefits for edema, based on multiple studies, and were effective for a range of symptoms, based on multiple or single studies (Table IV). French maritime pine bark extract showed ef-

ficacy against symptoms of pain, heaviness and swelling based on a single acceptable study (standard deviation=-1.39 for pain; -1.50 for heaviness and -1.65 for swelling). Adverse events were analyzed for calcium dobesilate, MPFF and rutosides, and the incidence was not different from placebo for all of them.

Separate Cochrane reviews have been published subsequently for horse chestnut seed extract[110] and French maritime pine bark.[111] Regarding horse chestnut seed extract, a meta-analysis of 6 trials indicated significant efficacy against edema measured in terms of leg volume, and 7 controlled trials showed reduction in leg pain compared with placebo. Adverse events were generally mild and infrequent. The review of French maritime pine bark included only 2 trials in CVD, and concluded that current evidence was insufficient to support its use.

TABLE V.—*Summary of recommendations from the 2005 International Consensus Statement,[2] and the 2008 Guidelines.[3]*

Drug	2005 International Consensus Statement[2]	2008 Guidelines[3]	
	Recommendation	Indications	Recommendation
Calcium dobesilate	Grade A	Cramps, restless legs, sensation of swelling, edema	Grade A
Micronised purified flavonoid fraction	Grade A	Pain, cramps, heaviness, sensation of swelling, trophic changes, venous leg ulcer	Grade A
Hydroxyethyl-rutosides	Grade A	Itching, edema	Grade A
Horse chestnut seed extract; escin	Grade B	Pain, edema	Grade B
Ruscus extracts	Grade B	Pain, edema	Grade B
Synthetic diosmin	Grade C	–	Grade C
Troxerutin	Grade C	–	Grade C
Gingko biloba extract	Grade C	–	Grade C
Proanthocyanidines	Grade C	Pain	Grade C
Troxerutin-coumarin	Grade C	–	Grade C
Centella asiatica extract	Grade C	–	–
Naftazone	Grade C	–	Grade C

The 2005 International Consensus Statement

Published evidence relating to the efficacy, safety and role of VADs was evaluated by a panel of 14 experts from different countries where such drugs were in clinical use, who met within the framework of the 13th Conference of the European Society for Clinical Hemorheology in Siena, Italy in June, 2005 and published an international consensus statement.[2] Results of 83 randomized controlled studies and meta-analyses relating to the effectiveness of VADs on symptoms linked to CVD were considered and interpreted, drawing on the experts' clinical experience. The drugs were then assigned to one of three recommendation levels according to the following levels of evidence:

Grade A — randomized clinical trials with large sample sizes, meta-analyses combining homogeneous results;

Grade B — randomized clinical trials with small sample sizes, single randomized trial only;

Grade C — other controlled trials, non-randomized controlled trials.

All published conclusions reflected the views of all or a large majority of panel members.

On this basis, calcium dobesilate, MPFF and hydroxyethyl-rutosides were classified as Grade A, horse chestnut seed extract and *Ruscus* extract as Grade B, and other VADs as Grade C (Table V). The authors stressed that all the drugs listed in Table IV had demonstrated efficacy in at least one randomized trial; those in Grades A and B had better documentation of their effectiveness in the published literature, and so could be recommended more strongly. The experts also considered the indications of VAD, and concluded that they are indicated to relieve symptoms in all classes of CVD, from CEAP class C_{0s} to C_{6s}.

2008 Guidelines for the management of chronic venous disorders of the lower limbs

The 2008 Guidelines,[3] also evaluated the efficacy and safety of VADs. Regarding efficacy against edema and symptoms related to CVDs, they essentially restated and combined the conclusions of the various Cochrane reviews and the 2005 International Consensus Statement described above (Table V).

The guideline authors also considered VADs in the treatment of C_6. Several studies have suggested the effectiveness of MPFF in venous leg ulcers. A meta-analysis of 5 trials, in which oral MPFF was given as adjunctive therapy in conjunction with compression and local wound care, concluded that MPFF accelerates venous ulcer healing, particularly in larger ulcers (RRR=40; 95% CI=6-87, in ulcers between 5 and 10 cm²) and those of long standing (RRR=44; 95% CI=6-97, in ulcers between 6 and 12 months).[112] Although not generally classified as a VAD, pentoxifylline has also been shown in the 2012 Cochrane review of 11 studies of variable quality to be an effective adjunct to compression therapy for treat-

ing venous ulcers (RR=2.2; 95% CI=1.5-3.4), and may be effective in the absence of compression (RR=1.6; 95% CI=1.1-2.1).[113]

Regarding safety, the guidelines concluded that the safety of VADs was generally good, with the exceptions of the hepatotoxicity of coumarin and benzarone. For the other main types of VADs, the most frequent adverse events were reported to be gastrointestinal disorders, skin rash and autonomic disorders including headache, dizziness and insomnia.

These guidelines also provided the following recommendations on the indications of VADs:

— VADs may be indicated as first-line treatment for CVD-related symptoms and edema in patients at any stage of disease;

— in more advanced disease stages, VADs may be used in conjunction with surgery, endovenous treatment including sclerotherapy, thermal ablation, and/or compression therapy; they may accentuate the effects of compression;

— it is not appropriate to combine several VADs on the same prescription.

The 2011 review

Perrin and Ramelet [114] recently proposed a tentative set of recommendations for the use of VAD, based on the 'Grading of recommendations assessment, development and evaluation' (GRADE) system.[115, 116] The GRADE system differs from the other schemes described in these guidelines in that separate levels are assigned for the recommendation for treatment and for the quality of evidence on which the recommendation is based. Recommendations are classified as either strong (grade 1) or weak (grade 2), and quality of evidence as high (grade A), moderate (grade B) or low (grade C). Importantly, the GRADE system recognises that large observational studies may provide evidence of moderate or even high quality, particularly if the estimate of the magnitude of the treatment effect is very large.[115]

Regarding their efficacy in relieving venous symptoms and CVD-related lower limb edema, the authors suggested that for MPFF and rutosides there was substantial evidence from relatively small trials supported by meta-analyses and, in the case of MPFF, a large observational study the RELIEF study.[117] Therefore, MPFF

and rutosides were given strong recommendations based on moderate evidence (overall grade 1B for both drugs). The volume of evidence for horse chestnut seed and *Ruscus* extracts was considered less, and these two drugs were given weak recommendations based on low quality evidence (grade 2C). None of the above drugs have obvious safety concerns, but the authors drew attention to the rare cases of agranulocytosis associated with calcium dobesilate. In consequence, calcium dobesilate was given only a weak recommendation, although the quality of evidence in support of its efficacy was moderate, and the overall grade for this drug was 2B. The authors also confirmed the recommendation of MPFF as adjuvant treatment of active venous ulcers, giving a strong recommendation based on moderate evidence (grade 1B).

Finally, it was concluded that there was insufficient evidence to specify which CEAP classes would benefit most from VAD therapy, but it was reasonable to assume that patients at all stages of the disease might benefit.

2014 guidelines update: the present position

EFFICACY AND SAFETY RECOMMENDATIONS FOR VAD

In the current update of the guidelines, we propose recommendations for the use of VADs using the GRADE system. Our recommendations are derived from the tentative recommendations of Perrin and Ramelet,[114] with modifications made partially in the light of additional recent evidence and partially based on a re-evaluation of previous data, in order to provide a better discrimination between the different drugs.

Among the evidence that recently became available is a meta-analysis of the impact of four VADs (MPFF, hydroxyethyl-rutosides, *Ruscus* extract and diosmin) on venous edema, assessed as the decrease in ankle circumference.[118] All four drugs achieved reduction in ankle circumference that was superior to placebo. This was significant for MPFF (-0.80±0.53 cm), hydroxyethyl-rutosides (-0.58±0.31 cm), *Ruscus* extract (-0.58±0.47 cm) (P <0.0001 in each case) but not for simple diosmin (-0.20±0.5 cm). In between-drug comparisons, MPFF was significantly superior to hydroxyethyl-rutosides and *Ruscus* extract, which were not different from each other.

In a recent open-label study of the combination of *Ruscus* extract, hesperidin methylchalcone and ascorbic acid in 65 women in CEAP classes C_{2s} and C_{3s}, significant improvements in plethysmographic venous filling time were correlated with improvements in subjective symptoms.[119]

The benefits of calcium dobesilate on edema and venous symptoms have been evaluated recently in four randomized clinical trials, with contradictory results. In three studies, involving 256,[120] 253,[121] and 49,[122] patients, calcium dobesilate produced a significantly higher reduction in lower calf volume or circumference compared with placebo (respectively -64.7 cm³ at week 8, P<0.0002;[120] -12.2 mL/L at week 4, P=0.011,[121] and -1.6 cm at week 7 after treatment, P<0.05),[122] and in two of these studies,[120, 122] there was also a significant improvement in venous symptoms. In the fourth study, in 509 patients in CEAP classes C_1 to C_6, there were no significant differences between the calcium dobesilate and placebo groups on quality of life (scores were 37.8 in the VAD group *versus* 38.2 in the placebo), edema (reduction of ankle circumference=-3.3 cm in both groups) or CVD-related symptom severity (mean decrease on the VAS scale= 9 to 13.2 mm) at the end of the 3-month treatment period.[123]

Finally, two placebo-controlled study on redvine-leaf extract in 248,[124] and 71,[125] patients in CEAP classes $C_3 – C_{4a}$ demonstrated significant reductions in lower limb volume (-19.9±8.9 mL, 95% CI=-37.5-2.3, P=.027) and leg pain (-6.6±3.3 mm on VAS, 95% CI=-13.1-0.1, P=.047) after 12 weeks of treatment,[124] and in ankle circumference (-0.39±0.09 cm in the treatment group *versus* 0.29±0.09 cm in the placebo group, P<.0001) after 6 weeks.[125]

Two items included in the Perrin and Ramelet review,[114] warrant detailed consideration. First, the RELIEF observational study was a large prospective study in which 5,052 patients in CEAP classes C_0 to C_4 in 23 countries were given MPFF for 6 months.[117] All patients were assessed for the presence of venous reflux at baseline. Outcome variables included the proportions of patients with various venous symptoms, leg pain severity assessed by visual analogue scale, edema assessed by measurements of leg circumference, and changes in CEAP clinical class and quality of life. Results were expressed separately for patients with and without reflux at baseline. All outcome variables improved significantly during the study, and some of the treatment effects were very large. For example, the proportion of patients with leg cramps decreased from 71.2% to 23.2% in patients with reflux, and from 72.3% to 15.1% in patients without reflux (P<0.001 for both). Pain severity decreased from 3.89 cm to 1.43 cm in patients with reflux, and from 3.59 cm to 1.12 cm in those without. In addition, the proportion of patients in CEAP classes C_3 and C_4 decreased and those in the less severe classes $C_0 – C_2$ increased significantly. There were also substantial improvements in quality of life (QoL). The main improvement in QoL was noted after 2 months (mean progression of 8.5 in the Global Index Score (GIS) which has a range from 0 (bad QoL) to 100 (good QoL) but further improvements were noted after 4 months (additional mean progression of 5.0 in the GIS) and after 6 months (additional mean progression of 4.0 in the GIS). The RELIEF also provided longer-term evidence of the safety of MPFF in a large patient sample. Overall, it could be argued that the large size of the study, together with the consistency and magnitude of the treatment effects observed, constitute evidence of moderate quality of the efficacy and safety of MPFF, despite the open-label design of the trial.

The second item concerns the reported association of cases of agranulocytosis with calcium dobesilate treatment. Initially three anecdotal reports during the 1990s, two of which involved positive association with calcium dobesilate, caused concern.[126-128] Subsequent analyses have produced different estimates of the prevalence and risk associated with calcium dobesilate.[129-131] Nonetheless, agranulocytosis is a serious condition with a case fatality of approximately 10%. A population-based case-control study in Spain identified calcium dobesilate as one of a limited number of drugs with the largest relative increases in risk that were thought to account for nearly 70% of cases.[132] Given that other effective VADs with no known serious safety concerns are available, even a low risk of agranulocytosis compromises the benefit-risk balance of calcium dobesilate.

It must be mentioned that VADs containing coumarine and benzarone as unique active in-

TABLE VI.—*Summary of the present guideline recommendations for the use of venoactive drugs, according to the GRADE system.*

Indication	Veno-active drug	Recommendation for use	Quality of evidence	Code
Relief of symptoms associated with CVD in patients in CEAP classes C0s to C6s and those with venous edema (CEAP class C_3)	Micronized purified flavonoid fraction	Strong	Moderate	1B
	Nonmicronized diosmins or synthetic diosmins	Weak	Poor	2C
	Rutosides (O-betahydroxyethyl)	Weak	Moderate	2B
	Red-vine-leaf extracts (Vitis vinifera)	Weak	Moderate	2B
	Calcium dobesilate	Weak	Moderate	2B
	Horse chestnut seed extract	Weak	Moderate	2B
	Ruscus extracts	Weak	Moderate	2B
	Gingko biloba	Weak	Poor	2C
	Other VADs	Weak	Poor	2C
Healing of primary venous ulcer (CEAP class C_6), as an adjunct to compressive and local therapy	Micronized purified flavonoid fraction	Strong	Moderate	1B

CEAP: clinical, etiological, anatomical, and pathophysiological classification; CVDs: chronic venous disorders; GRADE: Grading of Recommendations Assessment, Development and Evaluation; VADs: venoactive drugs.

gredients have been withdrawn from the market for their potential to cause severe (even fatal) hepatotoxicity.[133, 134]

Taking into account the issues outlined above, we now propose the GRADE recommendations summarized in Table VI. It should be noted that the recommendation for MPFF is strong, based on benefits that clearly outweigh the risks and evidence of moderate quality (grade 1B), to reflect the need for additional evidence,[135] despite the contribution of a recent study.[118] Secondly, the recommendation for calcium dobesilate is now weak based on the uncertainty on the estimates of risks and moderate quality evidence (grade 2B). In this case, this reflects the compelling nature of the adverse evidence regarding the safety concerns associated with the drug. Hydroxyethyl-rutosides, horse chestnut seed extract, *Ruscus* extract and red vine leaves extracts are all given weak recommendations based on moderate evidence (grade 2B), and other VADs are given weak recommendations based on low quality evidence (grade 2C).

The above recommendations are given for the indication of relief of symptoms associated with CVD in patients in CEAP classes C_{0s} to C_{6s} and those with CVD-related edema. MPFF retains its strong recommendation based on moderate evidence (grade 1B) for use as adjuvant therapy in treating venous leg ulcers.[114]

PLACE OF VADS IN THE MANAGEMENT OF CVDs

This guideline update serves to underline the conclusion of the 2008 guidelines,[3] that VADs may be used to relieve CVD-related symptoms and edema in patients at any stage of disease. We would now go further and stress the central and unique role that VADs have in the management of symptomatic patients at the earliest stages of CVD, given that compression therapy may be the only other appropriate form of therapy for such patients. However, in view of the poor compliance with compression therapy in certain countries with hot climate,[136] VADs may be the only alternative available. The importance of effective treatment of patients in CEAP class C_{0s} was highlighted in the recent study,[93] who found that approximately 20% of all patients consulting their general practitioner for any reason could be assigned to class C_{0s}. In more advanced stages of CVD, VADs may be used in conjunction with sclerotherapy, surgery and/or compression therapy, and MPFF may be considered as adjunctive therapy in patients with active venous leg ulcers, especially in those with large, long standing ulcers.[112]

The studies of Bergan *et al.*,[44] have shown that VADs, by reducing oxidative stress and inhibiting inflammatory cascades, can prevent degenerative changes in venous valves and the vein wall. It remains to be demonstrated whether the early

use of VAD can prevent or delay the progression of CVDs in patients. This should be investigated in future clinical trials. Overall, recently acquired evidence has only strengthened the case for a greater role for VADs in the management of patients with CVDs.

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CHAPTER 9

Topical therapy for venous ulcers

A wide range of topical agents and dressings has been advocated to promote desloughing, granulation and epithelialization of venous leg ulcers, including hydrogels, alginates, hydrocolloids, enzymatic agents, growth factors, foams, aminoacids, platelet rich plasma gels, fibrin sealant and films.[1-50] Tissue-engineered skin equivalents based on cultured keratinocytes and fibroblasts have been shown to accelerate healing.[51-64] However, there is no level I evidence that the above therapies provide additional benefit over simple wound dressing and compression therapy.

The use of topical antibiotics in patients with venous ulcerations is discouraged because of emergence of resistant organisms and increased risk of contact dermatitis.[11, 65] At present, there is no evidence to support the routine use of systemic antibiotics to promote healing in venous leg ulcers. However, systemic antibiotics are indicated in the presence of soft tissue infection. In light of the increasing problem of bacterial resistance to antibiotics, current guidelines recommend that antibacterial preparations should only be used in cases of clinical infection and not for bacterial colonization.

In terms of topical preparations, there is some evidence to support the use of povidone iodine, octenidine, phenytoin, crystacide, sucralfate, peroxide-based preparations, topical wound oxygen, ethacridine lactate, mupirocin and chlorhexidine in healing venous ulceration.[66-74] Topical antiseptics exhibit cellular toxicity that exceeds their bactericidal activities and they have been found to impair wound epithelialization.[75]

There is some evidence than hyaluronic acid and amniotic membrane may have a positive impact on venous ulcer healing.[76-80]

During the last few years negative pressure wound therapy gained an increased popularity and there is growing evidence than this kind of therapy promotes ulcer healing.[81-86]

Electric stimulation therapy, radio frequency electromagnetic energy, low and high frequency ultrasound, phototherapy, laser and water-filtered infrared wave therapy may have an influence on ulcer healing especially in refractory and difficult to heal venous ulcers.[87-101] Extracorporeal shock wave therapy is reported to accelerate venous ulcer healing.[102, 103] However, the vast majority of these studies are based on case reports or small patient cohorts.

In order to achieve pain relief, use of an ibuprofen slow-release foam dressing was introduced.[104-107] Some authors suggest larval and maggot therapy for wound debridement,[108-111] whilst others suggest honey as a topical treatment for venous ulcers.[112-115]

Although there is a large number of publications related to the topical treatment for venous ulcers, evidence is limited in terms of efficacy and cost effectiveness of the treatment. In order to clarify true benefit of these treatment modalities, more randomized trials are needed.

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CHAPTER 10

Treatment of superficial and perforating vein incompetence

A treatment of superficial incompetence

Introduction

For the last 100 years, open surgery (OS) has been the most recommended and used procedure for treating varicose veins (VVs). During the past 15 years, the development of minimally invasive correction of primary superficial venous reflux in patients with chronic venous disease (CVD) of the lower limbs by endovenous techniques has provided a patient-friendly means to treat this disorder as an office-based procedure with ablation of the saphenous veins and varicosities including radiofrequency ablation (RFA), endovenous laser ablation (EVLA) and sclerotherapy. In addition, surgery preserving the GSV was developed in parallel including the "Cure Hemodynamique de l'Insuffisance Veineuse en Ambulatoire" (CHIVA) [1] and "Ablation Selective des Varices sous Anesthésie Locale" (ASVAL) [2] techniques.

Surgery

Modern open surgery is performed under local anesthesia, based on preoperative assessment and mapping using Duplex ultrasound. The traditional flush ligation of the sapheno-femoral junction (SFJ) is completed by invagination stripping of the proximal (to the knee level) saphenous vein. Stripping can be also done by using a cryo-probe. Treatment of the incompetent small saphenous vein (SSV) usually involves ligation of the sapheno-popliteal junction (SPJ) and proximal stripping by invagination. Stripping of the distal SSV or the GSV below the knee may reduce VV recurrence but is associated with increased risk of sural or saphenous nerve injury, respectively.[3, 4] The necessity of flush ligation has been recently called into question.[5, 6] The remaining non truncal varicosities can be either excised by phlebectomy or managed by sclerotherapy in the same session or later.

There is general agreement for recommending elastic compression stockings up to one week postoperatively.[7, 8]

Complications of surgery

The early complications of surgery include discomfort (common), bruising (common), bleeding (rare), lymphatic vessel complications (rare), femoral vein injury (very rare), wound infections (2-6%), and injury of the saphenous or sural nerve (10%). Deep venous thrombosis (DVT) and pulmonary embolism (PE) rates, symptomatic or asymptomatic, following OS vary from 0.4% to 5.3% and from 0% to 0.5%, respectively. Late complications include permanent neuropraxia (5%) and recurrence, increasing with duration follow-up (20-50%).

Radiofrequency ablation (RFA)

Ablation of the treated vein is achieved by heat delivered into the vein through the percutaneously placed radiofrequency catheter. The heat

causes a direct thermal injury to the vein wall, resulting in destruction of the endothelium, collagen denaturation of the media, and finally thrombotic and fibrotic occlusion of the vein. The RFA is performed under local-tumescent anesthesia with ultrasound-guided percutaneous catheter placement as an outpatient procedure. The first generation device was a bipolar electrode that looked like a flower, located at the tip of the endovenous catheter (ClosurePlus) that was heated to 85 degrees Celsius and slowly withdrawn. The current ClosureFast RF catheter (VNUS/Covidien), introduced in 2007, is user-friendly and treatment is performed in a shorter time compared to ClosurePlus. A temperature of 120 degrees Celsius is generated and the entire pullback time is 3-4 minutes. A second RFA system of bipolar RF-induced closure, Celon RFITT, is available (Olympus Medical Systems). This system generates heat at 60-85 degrees Celsius and operates with a continuous pullback speed of 1cm/s. The RFA requires local tumescent anesthesia. It is performed under ultrasonic guidance using percutaneous catheter placement as an outpatient procedure.

Endovenous laser ablation (EVLA)

Similar to RFA, the heat generated by laser causes a direct thermal injury to the vein wall, however EVLA also provides direct heat injury to the blood. Blood coagulates at 70 to 80 °C, steam bubbles form at 100 °C and carbonization of the coagulum is observed at 200 to 300 °C. Currently available laser fibers include hemoglobin-specific laser wave lengths (810, 940, and 980 nm) and water-specific laser wavelengths (1319, 1320, and 1470 nm). Initially, the fibers were bare-tipped, but the new radial or jacket-tipped fibers have now become the standard. Laser devices are made by a number of manufacturers, *e.g.* Angiodynamics (VenaCure), Biolitec (ELVeS), CoolTouch (CoolTouch CTEV), Dornier (Medilas), Sciton (Pro-V) and Vascular Solutions (Vari-lase). Like RFA, EVLA is also performed under local-tumescent anesthesia with ultrasound-guided percutaneous catheter placement as an outpatient procedure. The techniques for EVLA and RFA are similar and preferably involve use of a micro-access kit with placement of a 4 Fr or 5 Fr micro sheath which is exchanged for a 5 Fr sheath. Then the laser fiber can be introduced with the tip positioned at 2 cm distal to the SFJ or SPJ. The laser fiber is activated and withdrawn at a rate of 1 to 2 mm/s for the first 10 cm and 2 to 3 mm/s for the remaining vein length. Energy settings of 50 to 70 J/cm are recommended. The post-ablation procedures are similar to RFA.

Complications of thermal ablation

Reviews analyzing RCTs involving RFA (N.=317 patients), EVLA (N.=1057 patients) and OS (N.=975 patients) provided a list of short-term complications. There was a significantly higher rate of wound infection for OS (2.3%; 95% CI, 1.3%-3.1%) *vs.* EVLA (0.5%; 95% CI, 0.3%-1.3%; P=0.006), but not between OS and RFA (1.5%; 95% CI, 0.4%-3.0%; P=0.094). The incidence of paresthesiae was significantly lower with EVLA (3.8%; 95% CI, 2.4%-4.5%) compared with RFA (5.2%; 95% CI, 3.1%-7.9%; P<0.001) and OS (7.4%; 95% CI, 5.3%-8.3%; P<0.001). The incidence of thrombophlebitis was significantly lower for OS (3.0%; 95% CI, 2.9%-4.0%) compared with RFA (5.5%; 95% CI, 3.0%-7.8%; P=0.003) and EVLA (5.6%; 95% CI, 4.2%-7.0%; P=0.003). There was no difference in the rate of thermal skin burns between RFA and EVLA.[9-11]

Steam ablation

Steam is the latest of the thermal endovenous techniques to enter clinical use. It was introduced in 2006 by R. Milleret as a less expensive alternative to laser and radio frequency.[12] The principle is to inject inside the vein pulses of water vapor at 120 °C, each pulse delivering 60 Joules of energy into the lumen. Steam is injected under pressure: the first pulse dislodges the blood and the next ones heat the vein wall. A 5 Fr stainless steel catheter is used, which it is flexible enough to navigate through tortuosities without using a guidewire. Two lateral holes close to the tip eject the steam, avoiding the risk of heating-up the deep veins when the catheter is used close to the SFJ. A comparative animal study by Thomis *et al.*[13] showed that immediate shrinking was more

pronounced with steam than with both Closure Fast® RF and 1470 nm TULIP® fiber laser catheters. Perivenous damage occurred less often, although the number of cases was not sufficient to obtain statistical significance.

A pilot study by van den Bos [14] showed full obliteration in 11 out of 19 veins treated at 6 months with partial reopening in the other cases, but the energy delivered was too low, 1 pulse/cm instead of 2 to 4 advised by the promoters of the technique.

In a series of 75 patients the complications included a thrombus protrusion into the femoral vein, one ecchymosis at the entry site in one case and moderate pain for 8 days in 6 patients.[12] In this study obliteration of the treated vein at 6 months was achieved in 96% of the patients.

Sclerotherapy

Injection of a sclerosing agent into the vein to achieve endoluminal fibrosis and obstruction of the vein has been used for almost a century. Although liquid sclerotherapy has been used primarily for obliteration of spider veins or telangiectasiae, interest in the use of sclerotherapy greatly increased when Cabrera [15] reported in 1995 and 2000 that foam prepared by mixing gas with the detergent polidocanol was effective for obstruction of larger veins. Ultrasound guided foam sclerotherapy (USGFS) has rapidly spread for treatment of primary and recurrent varicose veins, including the GSV and SSV, perforating veins and venous malformations.

The mechanisms of action of sclerosing solutions are the destruction of venous endothelial cells, exposure of subendothelial collagen fibers, and ultimately, the formation of fibrotic obstruction. Delivery of the solution as a foam prolongs the time of contact and amplifies the effect of the chemical. In Europe approved agents for sclerotherapy include sodium tetradecyl sulphate (STS), polidocanol, sodium morrhuate, and glycerine. Hypertonic saline, has also been used for many years.

Sodium tetradecyl sulphate is a detergent that destroys the endothelium by denaturation of the cell surface proteins. The solution is safe and painless when injected. When the solution is injected in higher concentration, extravasation

may result in tissue necrosis. Hyperpigmentation, matting, and allergic reactions have been described. Foaming of this agent is easy.

Polidocanol is another detergent which is safe and painless when injected, with a low risk of tissue necrosis when used in low concentration. It may cause hyperpigmentation, but has a very low rate of allergic or anaphylactic reactions.

Sodium morrhuate is a detergent that is used less frequently because of the relatively higher incidence of skin necrosis observed with extravasation and because of the higher risk of anaphylactic reactions.

Glycerine is a corrosive agent that destroys the cell surface proteins by affecting chemical bonds. Chromated glycerine is used most frequently as a solution of glycerine, sterile water, and benzyl alcohol. Chromated glycerine is safe and rarely leads to tissue necrosis, hyperpigmentation, or allergy. It is suitable for treatment of small veins or telangiectasiae.

Hypertonic saline is a weak sclerosing agent that causes dehydration of endothelial cells through osmosis, which leads to endothelial cell death. Burning pain is frequent during injection. Extravasation may cause skin ulcers and tissue necrosis.

Liquid sclerotherapy is performed using small tuberculin syringes and a 30- or 32 gauge needle. Treatment is usually started with larger varicose veins and ends with reticular veins and telangiectasiae. The proximal part of the leg is treated first followed by the distal part. Use of loupes for magnification and transillumination helps intraluminal injection and avoids extravasation of the drug. Severe pain during injection may signal extravasation, and further injection should be avoided. The patient is instructed to wear high compression class (30-40 mmHg) graduated compression stockings for 1-3 days after treatment for telangiectasiae and reticular veins and at least 1 week after treatment for varicose veins and perforating veins.

The USGFS of the saphenous vein is the least invasive of the endovenous ablation techniques. The European consensus meeting on foam sclerotherapy in 2008 reported that foam was an effective, safe and minimally invasive endovenous treatment for varicose veins with a low rate of complications. The most popular technique currently in use was developed by Tessari using a

three-way stopcock connected with two syringes. Experts recommend a ratio of one part solution of STS or polidocanol to four or five parts of air. Mixing the drug with air using the two syringes and pushing the mixture from one syringe into the other 20 times results in an approximate bubble size of less than 100 micrometers. The veins are cannulated in supine patients and then the limb is elevated 30 degrees to inject the foam. Ultrasonography is used to monitor the movement of foam in the veins. The great or small saphenous vein is injected first, followed by varicose veins and perforating veins if indicated. A maximum of 10 mL of foam is injected during one session. The procedure is completed by placing a short stretch bandage or a 30 to 40 mmHg graduated compression stocking on the limb. Most experts recommend compression for 1 to 2 weeks. Complications of USGFS are usually classified into two categories (a) severe complications: anaphylaxis (extremely rare), large tissue necrosis (extremely rare), stroke and transient ischemic attack (extremely rare), distal DVT (very rare), PE (extremely rare), motor nerve injury (extremely rare); and (b) benign complications: visual disturbances (uncommon), headaches and migraines (uncommon), sensory nerve injury (rare), chest tightness (very rare), dry cough (very rare), superficial thrombophlebitis (unclear), skin reaction (very rare), matting (common), residual pigmentation (common), minimal skin necrosis (very rare), embolia cutis medicamentosa (very rare).[16]

Cyanoacrylate glue ablation

A new non-ablative procedure using a formulation of cyanoacrylate (CA) adhesive delivered intravenously, has been developed to improve some of the limitations with RF, EVL and sclerotherapy ablation. Upon intravascular injection, CA rapidly solidifies via a polymerization reaction and results in an inflammatory reaction of the vein wall. In an experimental model a granulomatous foreign body reaction was observed in the venous lumen. At 60 days fibroblasts were seen invading the contents of the vein lumen and 100% occlusion was observed. The primary potential advantage with this new technique is that it does not require tumescent anesthesia, and the patients do not need postoperative compression stockings.

The disposable Sapheon Closure System (SCS) includes 4 mL of Sapheon Cyanoacrylate Adhesive (SCA) and a Sapheon Delivery System (SDS). The SDS consists of a 7-Fr introducer sheath/dilator, a 5-Fr delivery catheter, a 3-mL syringe, and a dispenser gun. The 5-Fr delivery catheter has a hydrophobic design to help prevent CA adhesion to the vein wall and a novel configuration with air-filled micro-channels to enhance sonographic visibility. The dispenser gun will deliver either 0.08 or 0.16 mL of SCA with each trigger pull. The venous system is mapped under ultrasound guidance and the GSV is accessed percutaneously with a micropuncture introducer kit followed by insertion of a 0.035" J guidewire. Using ultrasound control the 7-Fr introducer sheath/dilator is advanced to the SFJ and positioned 1.5-2 cm caudal to the SFJ. After extracting the SCA with a 3-mL syringe, the latter is attached to the delivery catheter. The catheter is primed with the dispenser gun to fill all but the final 3 cm of catheter tubing; this step ensures that the catheter tip is empty upon venous insertion to prevent premature contact of SCA with blood. The primed delivery catheter is inserted into the introducer sheath and secured with spin-lock mechanism. The 5 cm of the catheter tip is exposed distal to the tip of the sheath and positioned 4 cm from the SFJ. The technique basically consists of segmental pullback and compression of the vein after glue injection via the catheter. Prior to delivery of the SCA, the ultrasound transducer is positioned transversely just cephalad to the catheter tip near the SFJ. Once positioned, pressure is applied on the transducer to compress the vein leading to vein wall coaptation 4 cm caudal to the SFJ. Using continuous compression, 2 injections of 0.08 mL of SCA are delivered into the vein by depressing and holding the dispenser gun trigger. The entire delivery system is immediately retracted by 3 cm, and the vein walls are coapted using compression over the treatment segment for three minutes. The next segment is then treated by repositioning the ultrasound transducer just cephalad to the catheter tip, compression applied, and another 0.08 mL is delivered with one trigger depression, followed by 3 cm catheter pullback and compression of the treated vein for 30 seconds. This injection/retraction process is repeated until the entire length of the target segment is treated. After venous closure is confirmed by ultrasound, the

catheter is removed and compression applied to catheter entry site until hemostasis is achieved. A single band-aid is applied; compression stockings are not required. The patient is discharged and instructed to resume normal activities but avoid strenuous exercise.[17]

Mechanochemical ablation

A new mechanochemical device (ClariVein) is developed to minimize the negative aspects of both endothermal ablation and USGFS for treatment of saphenous incompetence, while incorporating the benefits of each. The advantages of this hybrid system are claimed to be standard percutaneous access, endovenous treatment, local anesthesia only without the need for tumescent anesthesia and short procedure time. Since the system does not use thermal energy, the potential for nerve damage is minimized. The mechanochemical method achieves venous occlusion utilizing a wire rotating within the lumen of the vein at 3500 rpm which injures the intima to allow for better efficacy of the sclerosant. A liquid sclerosant (sodium tetradecyl sulphate) is concomitantly infused through an opening close to the distal end of the catheter near the rotating wire. These two modalities, mechanical and chemical, achieve venous occlusion results equal to endothermal methods. The system includes an infusion catheter, motor drive, stopcock and syringe. The dispersion wire extends through the catheter lumen. It is connected to an interface cartridge unit for connection to the 9 V DC battery motorized handle unit on the proximal end, which controls wire rotation. The handle unit also provides a grip and syringe holder to facilitate physician-controlled infusion. The wire plus the catheter sheath are inserted into the vein percutaneously with the patient in reversed Trendelenburg position. The catheter sheath is retracted to expose the wire tip, which is positioned 2 cm from the SFJ. The patient is then placed into the supine position for the remainder of the procedure. The catheter motor is turned on and, with the wire rotating and the sclerosant being infused, the catheter is pulled down the vein at a rate of approximately 1-2 mm per s. After removal of the catheter, occlusion of the GSV and patency of the common femoral vein is checked by duplex ultrasound. Compression is applied for 2 weeks without restriction of patient activity. In a small series of 26 patients no complications were identified except 3 ecchymoses.[18]

Surgery with preservation of the saphenous trunk

CHIVA

The CHIVA technique is a conservative approach to redistribute the reflux from superficial to deep system through staged ligations on the GSV or tributaries in order to avoid ablation of the GSV as a possible future vascular graft.[1] CHIVA is a complex approach demanding careful mapping and understanding of the anatomy and function of the superficial system by well trained and experienced physicians.

ASVAL

Stab phlebectomy of all varicose tributaries can lead to an improvement or abolition of the saphenous vein reflux. Most patients operated upon with this method had less advanced stage of varicose veins. The ASVAL method is a procedure based on the ascending or multifocal approach of the CVD whereas the CHIVA is based on the descending theory. The goal of ASVAL is to remove the distal venous reservoir by phlebectomy of incompetent tributaries and preserve the GSV.[2]

Pelvic and ovarian vein embolization

When VVs are fed by incompetent pelvic and ovarian veins, embolization of the refluxing veins by coils and sclerosing agent is a minimal invasive method. Nevertheless when reflux is related to iliac vein compression, iliac stenting is also a useful non-invasive technique.

Outcome after operative treatment
RFA *vs.* open surgery

There are 7 RCTs in 9 articles comparing RFA with OS and almost all of them conclude that after radiofrequency ablation there was less postoperative pain, faster recovery and earlier return to work and normal activities, as well as higher patient satisfaction (Table I).[19-27] The longest follow-up was 3 years and there was no difference in terms of

TABLE I.

Operative Procedure	Article	Conclusions
OS *versus* RFA	Hinchliffe *et al.* 2006 [20]	16 patients presenting REVAS with persistent GSV trunk RF VNUS Closure bipolar catheter *versus* redo-groin surgery + S. Anesthesia: no standardization F-U 10 days <u>With RFA</u> Procedure shorter P=0.02 Less post-operative pain. P=0.02 Less bruising P=0.03
	Kianifard *et al.* 2006 [21]	GSV 55 patients treated by VNUS closure bipolar catheter *versus* HL+S (control group) Anesthesia: no information F-U 1 year <u>After RFA</u> Absence of neovascularization 11 % after HL+S. P=0.028
	Lurie *et al.* 2003 [22]	GSV 86 patients VNUS Closure bipolar catheter *versus* HL+S Anesthesia: no standardization F-U 4 months <u>With RFA</u> Return to normal activity shorter P=0.02 Return to work shorter P=0.05 Better health-related QoL
	Lurie *et al.* 2005 [23]	GSV 65 patients VNUS Closure bipolar catheter *versus* HL+S Anesthesia: no standardization F-U 2 years <u>With RFA</u> Clinical and DUS results at least equal to those after HL+S Better health-related QoL
	Rautio *et al.* 2002 [24]	GSV VNUS Closure bipolar catheter (N.=15) *versus* HL+S (N.=13) General anesthesia F-U 2 months <u>With RFA</u> Less post-operative pain P=0.017–0.036 Shorter convalescence. P<0.001 Cost-saving for society in employed patients
	Perala *et al.* 2005 [19]	GSV VNUS Closure bipolar catheter (N.=15) *versus* HL+S (N.=13) General anesthesia <u>With RFA</u> F-U 3 years No difference in terms of clinical result
	Stötter *et al.* 2006 [25]	GSV VNUS Closure bipolar catheter (N.=20) *versus* HL+ invagination S (N.=20) *versus* HL+ cryostripping (N.=20) General anesthesia F-U 1 year No difference in the physician-assessed clinical status between the 3 groups <u>With RFA</u> Patients continued to be significantly more satisfied with both their operative procedure (P=0.001) and the cosmetic appearance (P=0.006)
	Subramonia & Lees. 2010 [26]	GSV VNUS closure bipolar catheter (N.=47) *versus* HL+S (N.=41) General anesthesia <u>With RFA</u> Duration procedure was longer. P<0.001 Hospital cost more expensive Earlier return to work. P=0.006
	Helmy Elkaffas *et al.* 2011 [27]	GSV 180 patients Incompetent SFJ+ saphenous reflux VNUS closure bipolar catheter *versus* HL+S RFA local anesthesia OS general anesthesia <u>With RFA</u> Lower overall complication rate Shorter hospitalization. P=0.001 More expensive P=0.003 F-U 2 years No difference in term of recurrence

Abbreviations: OS= Open surgery: High ligation + Saphenous stripping+/ - Perforating vein ligation +/ - Tributary phlebectomy; DUS= duplex ultrasound; F-U= follow up; GSV= Great saphenous vein ;HL= High ligation; S=Stripping; RFA=Radiofrequency ablation

TABLE II.—*RCT's comparing EVLA with OS.*

Operative Procedure	Article	Conclusions
OS *versus* EVLA	de Medeiros & Luccas. 2005 [32]	GSV Spinal anesthesia 980 nm diode laser, bare fiber, stepwise laser withdrawal (N.=20) *versus* open surgery (N.=20) Follow-up 9 months (mean) No difference in postoperative pain After endovenous laser Fewer swellings and less bruising P not given Better outcome. P not given
	Vuylsteke *et al.* 2006 [33]	GSV General anesthesia 980-nm diode laser bare fiber, stepwise laser withdrawal (N.=118) *versus* open surgery (N.=124) Follow-up 1, 8 weeks, 9 months After endovenous laser ablation Less postoperative complications Sick leave shorter. P< 0.001 Total cost lower
	Ying *et al.* 2007 [46]	GSV General anesthesia for both procedures 980-nm diode laser, bare fiber pulse mode (N.=40) *versus* OS (N.=40) Follow-up 1 year *After EVLA* Less bleeding P <0.01 Less postoperative pain P<0.05 Hospitalization shorter P<0.05 No APG difference
	Rasmussen *et al.* 2007 [34]	GSV Local tumescent anesthesia for both procedures Diode 980-nm diode laser, bare fiber, stepwise laser withdrawal (N.=62) *versus* OS (N.=59) Follow-up 1, 2, 6 months No difference in terms of efficacy and safety *After EVLA* Less postoperative pain and bruising. P=0.05
	Darwood *et al.* 2008 [31]	GSV OS general anesthesia EVLA local tumescent anesthesia 980-nm diode laser, bare fiber, stepwise laser withdrawal (N.=42) continuous laser withdrawal (N.=29) *versus* OS (N.=32) Follow-up 3 months No difference between EVLA and OS in terms of reflux abolition and QoL (specific questionnaire) *After EVLA* Earlier return to normal activity in both laser groups. P=0.005
	Kalteis *et al.* 2008 [35]	GSV Anesthesia : incomplete information Diode 810-nm diode laser, bare fiber, stepwise laser withdrawal+ HL (N.=47) *versus* OS (N.=48) Follow-up 1, 4, 16 weeks *After EVLA* Less bruising. P=0.001 Longer period of time until return to work P=0.054 QoL (CIVIQ) no difference
	Theivacumar *et al.* 2009 [36]	GSV OS general anesthesia EVLA local tumescent anesthesia 980-nm diode laser , bare fiber, pulse mode (N.=69) *versus* OS (N.=60) Follow-up 2 years Recurrence rates similar

(Continued)

TABLE II.—*RCT's comparing EVLA with OS.*

Christenson *et al.* 2010 [37]	*After EVLA* Neovascularization less frequent P=0.001 GSV General or spinal anesthesia for both procedures 980-nm diode laser, bare fiber, stepwise mode (N.=100) *versus* OS (n=100) under general or spinal anesthesia Follow-up 12 days No difference in postoperative pain, use of analgesics and time return to normal activity More hematoma in OS group More bruising in the EVL group Follow-up 1 and 2 years No difference in terms of symptoms, VCSS or QoL. GSV treatment failure EVL =7%. OS=0%. P=0.051
Pronk *et al.* 2010 [38]	GSV Local tumescent anesthesia for both procedures 980-nm diode laser, bare fiber, continuous laser withdrawal + postoperative sclerotherapy for persistent varices (N.=62) *versus* OS : HL +pin-stripping +tributary stab avulsion + (N.=68) For both local tumescent anesthesia Follow-up 1 -14 days *After EVLA* More postoperative pain P<0.01 More hindrance in mobility and daily activities P≤0.01 Follow-up 1 year No difference in terms of DUS recurrence
Rasmussen *et al.* 2010 [39]	GSV Local tumescent anesthesia for both procedures 980-nm diode laser , bare fiber, pulse mode (N.=62) *versus* OS (N.=59) Follow-up 2 years No significant differences in - Clinical or DUS recurrences - Clinical severity scores (VCSS) - AVQQ
Carradice *et al.* 2011 [40]	GSV OS General anesthesia EVLA Local tumescent anesthesia Incompetent saphenofemoral junction 810-nm diode, bare fiber, continuous laser withdrawal, continuous power delivery 14W (N.=140) under local tumescent anesthesia *versus* HL+ inversion stripping (n=140) under general anesthesia Tributaries phlebectomy + perforator ligation in both groups Follow-up 1 week -1year Both groups significant improvement after treatment VCSS & QALY gain P<0.001 *After EVLA* Less pain P<0.001 Better SF-36 in 6 out 8 domains P=0.004 QALY P=0.04 Shorter return to work P<0.001
Carradice *et al.* 2011 [30]	GSV OS General anesthesia EVLA Local tumescent anesthesia Incompetent saphenofemoral junction 810-nm diode, bare fiber, continuous laser withdrawal, continuous power delivery 14 W (N.=140) *versus* HL+ inversion stripping (N.=140) Tributaries phlebectomy + perforator ligation in both groups Follow-up 1 week - 1 year *After EVLA* Better initial technical results

(Continued)

TABLE II.—*RCT's comparing EVLA with OS.*

	99.3 % *versus* 92.4%. P=0.005 *At 1-year* Clinical recurrence rate was lower 4.0% *versus* 20.4 % P<0.001. Clinical recurrence was associated with worse AVVQ scores P<0.001
Rass *et al.* 2012 [41]	GSV Tumescent local anesthesia for both procedures Incompetent saphenofemoral junction + saphenous reflux at least down the knee level 810-nm diode laser, bare fiber, continuous laser withdrawal, applied energy 20 J/cm² vein surface (N.=185) *versus* OS (N.=161) Follow-up 2 years PREVAIT: *After EVLA* 16.2%, OS 23.1 %. P=NS DUS recurrence: reflux at the SFJ: EVLA 17.8% (clinically silent in 81%), OS 1.3%. P<0.001 Clinical venous severity scoring (HVSS): no difference QOL (CIVIQ), Recovery time, ability to work : NS difference
Samuel *et al.* 2013 [29]	SSV SPJ incompetent +SSV reflux 56 OS vs 56 EVLA Follow-up 1 week -1 year *After EVLA* Better initial technical results 96.2 % *versus* 71.7%. P<0.001 Postoperative pain lower P<0.05 Earlier return to work and normal function P <0.001 Minor sensory disturbance. P=0.009 *At 1-year* VCSS and QoL no difference
Rasmussen *et al.* 2013 [42]	CEAP C2-4EpAsPr GSV Local tumescent anesthesia for both procedures Diode 980-nm diode laser, bare fiber, stepwise laser withdrawal (N.=69) *versus* OS (N.=68) Follow-up 1, 2, 6 months, 1-5 years *At 5 years* DS examination: GSV persistent reflux; no significant difference between the 2 groups (P=0.21) Clinical recurrence: No significant difference between the 2 groups (P=0.72) Repeat treatment: no significant difference between the 2 groups (P=0.99) VCSS improved in both groups and lasted from 1month to 5 years without difference between the 2 groups. AVVSS improved significantly in both groups from 3 month and onwards (P<0.0001), with no difference between the groups at any point in time SF-36 scores improved in all domains and in both groups
Flessenkämpfer *et al.* 2013 [43]	CEAP C2-6EpAsPr GSV with incompetent SFJ HL+ ST group 1, N.=159 EVLA group 2, N.=142 EVLA+HL group 3, N.=148 Diode 980-nm diode laser, bare fiber, continuous mode Anesthesia: group 1 not stated group 2 and 3 local tumescent anesthesia In the immediate post operative course day 1 Post-operative pain was higher in group 3. P=0.0069 Follow-up 2 months VCSS no difference Presence of inguinal reflux in GSV Group 1=0%. Group 2= 26.7%. Group 3=6.7% Group 1 *versus* group 2. P<0.0001 Group 1 *versus* group 3. P< 0.009

(Continued)

TABLE II.—*RCT's comparing EVLA with OS.*

| Roopram *et al.* 2013 [44] | Group 2 *versus* group 3. P<0.0001
CEAP C2-6
SSV Diameter >10 mm with incompetent SPJ
EVLA (N.=118) 810-nm diode laser, bare fiber, continuous
laser withdrawal under LA
versus
SPJ ligation (n=57)
Follow-up 2-6 weeks
Difficulty of procedure
in favor of EVLA, P=<0.001
Immediate post operative course and short term results
EVLA 91% complete occlusion
SPJ ligation 21% persistent reflux
Pain VAS in favor of EVLA. P=0.03 AVQQ no difference
Return to work in favor of EVLA P<0.05
At 6 weeks
Neurologic complications
in favor of EVLA P<0.001
Infection in favor of EVLA P<0.05 |

APG=Air Plethysmography; AVVQ: Aberdeen varicose vein questionnaire; AVVSS= Aberdeen varicose vein severity score; DUS= duplex ultrasound ; EVLA=endovenous laser ablation; GSV=Great saphenous vein; HL= high ligation; HVSS= Homburg varicose vein severity score; LA= local anesthesia; PREVAIT= Presence of varices after operative treatment; OS= Open surgery: High ligation + Saphenous stripping+/ - Perforating vein ligation +/ - tributary phlebectomy; QALY=quality adjusted life year ; QoL= quality of life; ST= GSV stripping; SFJ= saphenofemoral junction; SFP= saphenopopliteal junction; SSV=short saphenous vein; VCSS=Venous clinical severity scoring.

clinical result between OS and RFA. It must be noted that in all series the bipolar catheter (Closure Plus) was used. We now know that the new ClosureFast® catheter has demonstrated better results in published observations.[28] It should however be pointed out that modern less invasive open surgery under local tumescent anesthesia in the office setting is showing similar good outcomes.

EVLA *vs*. open surgery

13 RCTs (17 publications) compared EVLA with OS and all used bare tipped fibers (Table II).[29-46] Quality of safety and early efficacy was high with no significant difference between the groups. After two years no significant difference was found in clinical or duplex scanning recurrence, clinical severity or QoL. These results are maintained in a five year follow-up by Rasmussen *et al.* in a paper published in the Journal of Vascular Surgery.[42] No RCT has been reported with the new radial or jacket-tipped laser fibers compared to open surgery.

EVLA variations

Six RCTs compared modifications of EVLA (Table III).[47-52] High ligation in association with EVLA did not modify the 2 year outcome.

EVLA that included the below knee GSV needed less complementary sclerotherapy and was not associated with saphenous nerve injury. A 1470 nm radial fiber was superior to a 980 nm bare-tip fiber in terms of pain, ecchymosis and induration in the immediate postoperative course.[48] In another study, a 1500 nm bare-tip fiber had a better immediate postoperative course, with reduced induration around the treated vein and use of analgesics, and better quality of life compared with the 980 nm bare-tip fiber.[47] At 6 months the occlusion rate was similar in both groups. In a study on the 1470 bare tip fiber there was no difference in occlusion rate between warm or cold tumescence anesthesia.[51] The cold tumescence group had pain reduction with a reduced need for analgesics. A comparison between the bare tip and the tulip tip (1470 nm laser) concluded that the latter had less postoperative pain and better QoL scores.[47] Compression for one week (compared with 2 days) provided less postoperative pain.[52]

RFA *vs*. EVLA

Five RCTs compared RFA with EVLA (Table IV).[53-57] There was less bruising and less pain with ClosureFast. Subsequently, new laser fibers were developed, *e.g.* radial or jacket-tip fibers. Kabnick has reported on a pilot study comparing RFA

TABLE III.—*EVLA versus EVLA variations.*

Operative procedure	Article	Conclusions
HL+ EVLA *versus* EVLA without HL	Disselhoff *et al.* 2008 [49]	GSV 33 patients Anesthesia: general (day case procedure) or local (outpatient procedure) HL+ EVL (N.=43) *versus* EVL without HL (N.=43) 810-nm diode laser, bare fiber, continuous laser withdrawal Follow up 2 years No difference in terms of recurrence and VCSS between the 2 groups
EVLA GSV ablation AK *versus* GSV ablation AK+BK	Theivacumar *et al.* 2008 [50]	GSV 68 lower limbs C_2-C_6 Local tumescent anesthesia 810-nm diode laser, bare fiber, stepwise laser withdrawal AK and BK GSV reflux and BK VV randomized in 3 groups Group A: AK-EVLA (N.=23) Group B: AK+BK EVLA (N.=23) Group C: AK-EVLA+BK-FS (N.=22) Follow up 6 weeks AVVSS improved in all groups Complementary Sclerotherapy Group A 61% Group B 17% Group C 36% BK-EVLA was not associated with saphenous nerve injury.
EVLA 980 nm bare-tip fiber *versus* EVLA 1470 nm radial fiber	Doganci *et al.* 2010 [48]	GSV 106 limbs Intravenous sedation EVLA 980 nm bare-tip fiber *versus* EVLA 1470 nm radial fiber Follow up 1month With 1470 nm radial fiber Less postoperative pain and better VCSS scores
EVLA 1470nm Warm *versus* Cold tumescence anesthesia	Pannier *et al.* 2010 [51]	GSV 85 limbs Group A Warm=37 C° (N.=42) Group B Cold=5 C°(N.=43) No difference in terms of occlusion Group B Postoperative course Light pain reduction Significant intake of analgesic reduction
EVLA 980 nm *versus* EVLA 1500 nm	Vuylsteke *et al.* 2011 [47]	GSV 180 limbs Local tumescent anesthesia EVLA 980 nm bare-tip fiber *versus* EVLA 1500 nm bare-tip fiber Follow up Immediate postoperative course With 1500 nm Less induration. P=0.0002 Less need to take analgesics Better quality of Life CIVIQ 2 P=0.018 6 months No difference in terms of occlusion
EVLA 2 days post operative compression *versus* 7 days	Bakker *et al.* 2013 [52]	GSV 109 patients Local tumescent anesthesia EVLA 810 nm bare-tip fiber Postoperative compression stocking Group I 2 days Group II 7 days Follow up 48 hours - 6 weeks Group II better VAS and SF 36 at one week 100 % vein obliteration and no DVT in both groups

Abbreviations: AK= above knee; AVVS= Aberdeen varicose vein severity scores; BK= below knee; BK-FS= below knee foam sclerotherapy; EVLA=endovenous laser; HL= High ligation: VAS= Visual analogue scale; VCSS= venous clinical severity score

TABLE IV.—*RCT's comparing RFA with EVLA.*

Operative Procedure	Article	Conclusions
RFA *versus* EVLA	Almeida JI *et al.*[54] 2009	69 patients GSV Local tumescent anesthesia for both procedures RFA Closure Fast® vs EVLA Diode 980-nm barefiber Follow up 2 weeks <u>With RFA</u> All scores referable to pain, ecchymosis, and tenderness were statistically lower in the ClosureFAST group at 48 hours, 1 week, and 2 weeks. Minor complications were more prevalent in the EVL group P =0.0210 Venous clinical severity scores and QOL measures were statistically lower in the Closure- FAST group No difference in terms of postoperative vein occlusion and truncal elimination reflux between RFA and EVLA
	Shepherd AC *et al.*[55] 2010	131 patients GSV General anesthesia for both procedures RFA Closure FastÒ v EVLA Diode 980-nm, barefiber Follow up 6 weeks <u>With RFA</u> Less postoperative pain (3-10 days. P= 0,012-P=0.001) Less analgesic tablets (3-10 days. P=0,003-P=0.00) <u>RFA vs EVLA</u> QoL: AVVQ et SF-12 No difference
	Gale SS *et al.*[53] 2010	141 lower extremities GSV Local tumescent anesthesia for both procedures RF ClosurePlus® vs EVLA Diode 810-nm barefiber. 24 bilateral. 94 unilateral: 49 RFA,48 EVLA Follow up 1-4 weeks -1year <u>With RFA</u> Less bruising and disconfort Recanalization more frequent à 1 year. P =0.002
	Goode SD *et al.*[57] 2012	70 lower extremities GSV General anesthesia for both procedures CELON RFiTT RFA vs EVLA Diode 810-nm barefiber 17 bilateral. 36 unilateral: 19 RFA,17 EVLA Follow up 6 weeks – 6 months <u>With RFA</u> Less postoperative pain and bruising in the bilateral group QoL and activity score no difference Follow-up 9 months Same occlusion rate 74% vs 78%.
	Nordon IM *et al.*[56] 2011	GSV 80 patients laser (Vari-Lase Bright tip 810 nm laser fiber); 79 patients RFA (ClosureFast). General anesthesia. F-U 1 week: all GSV's occluded. Pain and bruising significantly less after RFA. 3 months: 3/68 laser and 2/70 RFA reopened (P= ns)

Abbreviations AVVQ = Aberdeen varicose vein questionnaire ; EVLA = endovenous laser ablation ; GSV= great saphenous vein ;RFA = radiofrequency ablation ; QoL = Quality of Life

(ClosureFast in 50 patients) *versus* EVLA (980 nm jacket-tipped fiber in 35 patients).[58] At 72 hours there was 100% closure in both groups. At one week pain and bruising scores were identical in the two groups. His results suggested that jacket-tipped laser fibers generated a uniform thermal

TABLE V.—*RCT comparing OS with cryostripping.*

Operative Procedure	Article	Conclusions
OS *versus* Cryostripping	Menyhei G *et al.* 2008 [80]	OS (n =86) *versus* HL+ cryostripping (N.=79) Follow-up 6 months No difference in terms of - Postoperative pain - Clinical results. Less hematoma with cryostripping, P=0.01
	Klem *et al.* 2009 [81]	OS (N.=245) *versus* HL+ cryostripping (N.=249) Follow-up 6 months No difference between the 2 groups

Abbreviations: OS= Open surgery: High ligation + Saphenous stripping+/ - Perforating veins ligation +/ - Tributary phlebectomies; HL= High ligation; SFJ= Saphenofemoral junction

TABLE VI.—*RCT comparing high ligation and cryostripping with EVLA.*

Operative procedure	Article	Conclusions
EVLA *versus* cryostripping	Disselhoff *et al.* 2008 [59]	GSV 33 patients Anesthesia: general (day case procedure) or local (outpatient procedure) 810-nm diode laser, bare fiber, continuous laser withdrawal (N.=17) *versus* HL+ cryostripping (N.=16) Follow-up 6 months One complication in cryostripping group Lymphedema grade 1
	Disselhoff *et al.* 2008 [60]	GSV 120 patients Anesthesia: general (day case procedure) or local (outpatient procedure) 810-nm diode laser, bare fiber, continuous laser withdrawal *versus* HL+ cryostripping Post operative course Cryostripping Procedure quicker (P<0.001) After EVLA Less postoperative pain (P=0.003) Return to normal activity quicker (P<0.001) Follow-up 2 years No difference in terms of recurrence and QoL questionnaire (VCSS, AVVSS) between the 2 groups
	Disselhoff *et al.* 2009 [61]	GSV bilateral 120 patients Anesthesia: general (day case procedure) or local (outpatient procedure) 810-nm diode laser bare fiber, continuous laser withdrawal *versus* HL+ cryostripping Follow-up 2 years Cryostripping was less costly and more effective regarding costs (P=0.234), QALY (P=0.824), and cost effectiveness ratio (P=0.788)

Abbreviations: AVVSS= Aberdeen varicose vein severity score; EVL=endovenous laser; HL=high ligation; QoL= quality of Life; QaLY(SF-6D); VCSS= venous clinical severity score

reaction similar to that generated by ClosureFast. His conclusion was that the most current RFA and jacket-tip laser methods and devices are similar regarding efficacy and short-term complications. With procedure time and tumescent anesthesia also equivalent, these procedures present no genuinely significant difference to patients.

EVLA *vs.* cryostripping

Disselhoff and his team presented the results of 2 RCTs in three papers comparing high ligation and cryostripping *versus* EVLA (Table V).[59-61] Cryostripping was significantly faster while EVLA was associated with significantly less

TABLE VII.—*RCT comparing foam sclerotherapy with surgery*

Type of procedure	Article	Conclusions
CA (USGFS) + HL *versus* HL + S	Bountouroglou *et al.* 2006 [62]	GSV General anesthesia for all procedures USGFS + HL (n=30) *versus* HL+S (N.=30) Follow-up 3 months Early recanalization in 13% after CA treated by complementary injection CA+HL less expensive, more rapid return to normal activities P<0.0001 No difference in terms of complication and occlusion
	Abela *et al.* 2008 [63]	GSV General anesthesia for all procedures HL+ reverse foam sclerotherapy (N.=30), HL + invagination S (N.=30), HL+ standard S (N.=30) Follow-up 2 weeks HL+ reverse foam sclerotherapy fewer post operative complications and better patient satisfaction
	Liu *et al.* 2011 [64]	GSV C_2-C_6 General anesthesia for all procedures HL+ S+/- TP (N.=30) S group HL+ USGFS (N.=30) F group Complementary foam sclerotherapy treatment Group F n=5 Follow-up 6 months F group Shorter operation time, return-to work time and less analgesia treatment; P<0.01 Obliteration F group: 80% S group: 89.5%
	Kalodiki E *et al.* 2012 [65]	GSV C_2-C_6 Classical surgery general anesthesia HL+ USGFS local anesthesia HL+ S+/- TP (N.=39) group S HL+ USFGS (N.=41) group F Complementary foam sclerotherapy treatment Group S (N.=25) Group F (N.=33) Follow-up 3-5 years VCSS no difference VSDS no difference AVVQ better in Group S, P<0.0005 SF 36 Physical component no difference
CA (USGFS) *versus* HL + S	Figueiredo *et al.* 2009 [66]	GSV C_5, Ep, As, Pr patients Surgery under local anesthesia Foam sclerotherapy (N.=27) 1–3 sessions 10 mL/session *vs.* HL+S (N.=29) Follow-up 6 months Significant clinical improvement in both groups. Vein ablation CA 78%, HL+S 90%. P=ns related to the small number of patients included
	Shadid *et al.* 2012 [67]	Incompetent SFJ +GSV incompetence at least 20 cm at the thigh USGFS (n=230). Polidocanol 3% . 1 mL *versus* HL+S (n=200). Partial GSV stripping+/- tributary phlebectomy under general anesthesia Follow-up 2 years PREVAIT Symptoms +QoL HL+S 9% (16/177). USGFS 11, 3% (24/213) P=0.407 REFLUX More than 2 cm in the length of the GSV treated HL+S 21%. USGFS 35% P=0,003 Cost HL+S €1824; USGFS €774

(Continued)

TABLE VII.—*RCT comparing foam sclerotherapy with surgery*

Type of procedure	Article	Conclusions
CA *versus* HL or HL + S or Phlebectomy	Wright *et al.* 2006 [68]	GSV and SSV. C_{2s}-C_6 Surgery : no information on anesthesia 710 patients randomized to foam sclerotherapy (Varisolve polidocanol), surgery (HL 92%, stripping 88%, phlebectomies 53%) or conventional sclerotherapy (92% home-made foam) Endpoint ultrasound determined occlusion of truncal veins and elimination of reflux; Follow-up 12 months Surgery superior to Varisolve foam (86 vs 63%) Varisolve foam superior to conventional sclerotherapy (90% *vs*. 76%, P=0.001) Foam resulted in less pain and earlier returns to work than surgery.

Abbreviations: AVVQ=Aberdeen Varicose Vein Questionnaire; CA=chemical ablation; HL=high ligation; S=saphenous stripping; SSV=small saphenous vein; TP=tributary phlebectomies; USGFS=ultrasound guided foam sclerotherapy; VCSS=venous clinical severity score; VSDS=venous segmental disease score.

postoperative pain and quicker return to normal activities. However, there was no significant difference in terms of recurrence, quality of life, or cost.

Foam sclerotherapy *vs*. open surgery

6 RCTs (7 publications) compared foam sclerotherapy with surgery (Table VI).[62-68] The outcome up to 12 months follow-up did not give any conclusive results. Geroulakos' group recently reported their 5 year follow-up and concluded that the treatment was equally effective in both groups as demonstrated by improvements in venous clinical severity score (VCSS), venous segmental disease score (VSDS), and the physical component of the SF-36 score.[65] Aberdeen varicose vein questionaire (AVVQ) score was better in the surgical group. Given that foam is less expensive, one can conclude that the cost effectiveness ratio is in favour of foam sclerotherapy.

Foam sclerotherapy *vs*. EVLA

Again in RCTs from Geroulakos' group the effectiveness and costs were compared between USGFS and EVLA (Table VII).[69-71] There were no differences in occlusion rate, AVVQ, VCSS or venous filling index (VFI) between the two procedures, but USGFS outperformed EVLA in cost, treatment duration, pain, analgesia requirements and recovery.

OS *vs*. thermal and chemical ablation

In one RCT, which compared open surgery (OS) with thermal and chemical ablation, outcome was assessed at 1 and 3 years (Table VIII).[42, 72, 73] Results after 1 year showed that all treatments were effective with a higher technical failure rate after foam sclerotherapy; RFA and foam sclerotherapy were associated with a faster recovery, less postoperative pain and superior QoL scores compared with EVLA and surgery. At three years the results were similar with less occlusion rate and higher re-operation rates after foam sclerotherapy. However, according to ardent supporters of foam the short catheter used as well as the injection site were not the ideal techniques for USGFS. There was no difference in clinical recurrence rate and all groups improved in VCSS, AVVSS and QoL.

Another RCT compared OS with laser and US-GFS. The complication rate as well as improvement at 1 year follow-up were comparable in the 3 groups.[73]

OS *vs*. microwave ablation

One single center RCT has reported the results of OS compared with microwave ablation with a 2-year follow-up (Table IX).[74] The recurrence rate was 14.3% in the microwave ablation and 28.2% on the OS group and there was no difference in the AVVQ and VCSS between the two groups. However, skin burns 10.2% were related to subcutaneous tributaries treated by microwave.

TABLE VIII.—*RCT comparing ultrasound guided foam sclerotherapy with EVLA.*

Operative procedure	Article	Conclusions
EVLA + Phlebectomy *versus* CA	Lattimer *et al.* 2012 [70]	66 patients C2-C6 GSV incompetence with refluxing SFJ randomized USGFS *versus* EVLA + phlebectomy under local anesthesia F-U 3 weeks-3 months At 3 months Patients were evaluated by DUS and APG to build a Saphenous treatment score (STS) There was no difference in AK in terms of STS improvement between the 2 procedures
	Lattimer *et al.* 2012 [69]	100 patients C2-C6 GSV incompetence with refluxing SFJ randomized UGFS *versus* EVLA + phlebectomy under local anesthesia F-U 3 weeks-3 months At 3 months AK GSV obliteration rate, AVVQ, VCSS, VFI no significant difference UGFS significantly outperformed EVLA in cost, treatment duration, pain, analgesia requirements and recovery.
	Lattimer *et al.* 2013 [71]	100 lower limbs presenting superficial vein reflux+/- perforator incompetence 50 UGFS *versus* 50 EVLA + phlebectomy under local anesthesia F-U at 15 months EVLA and UGFS were equally effective in abolishing global venous reflux with overall success of 41% and 43%, respectively. Despite the high reflux rate there was no difference in terms of VCSS and AVVQ improvement between the 2 procedures

Abbreviations: AK=above knee; AVVQ=Aberdeen varicose vein questionaire; EVLA=endovenous laser ablation; GSV=great saphenous vein; SFJ=saphenofemoral junction; USGFS=ultrasound guided sclerotherapy; VCSS=venous clinical severity score; VFI=venous filling index

Results of non-RCTs endovenous treatment

RCTs concerning the other endovenous procedures including steam, glue ablation and ClariVein are not available, but case series have been reported. With steam ablation the obliteration rate was 96.1% (72/75 patients) at 12 months[12] A RCT is ongoing. At 12 months, Kaplan-Meier analysis showed an occlusion rate of 92% (38 patients) with glue ablation.[17, 75]

A RCT is ongoing. At 280-day follow-up (mean) the obliteration rate was 96.7% (29/30 GSV) with mechanochemical ablation.[76]

OS *vs*. conservative treatment

A RCT compared conservative treatment limited to life style advice *versus* OS in C_{2s} patients (Table X).[77, 78] After 2-year follow-up OS was credited with cosmetic and QoL improvement, and symptomatic relief. However, the benefit was modest for relatively little national health service cost.

OS *vs*. CHIVA

Two RCTs have compared OS with CHIVA (Table XI).[79, 80] The Carandina RCT[79] was limited to shunt I+II varicose veins according to the CHIVA nomenclature, while the article by Parés *et al.*[80] encompasses all kinds of primary varicose veins. Nevertheless, this large, well-documented randomized, open-label, controlled, single-center study raises some questions. First, more than 90% of patients present-

TABLE IX.—*RCT comparing OS with thermal and chemical ablation.*

Operative procedure	Article	Conclusions
	Rasmussen *et al.* 2011 [72]	CEAP $C_{2\text{-}4}E_pA_sP_r$ GSV with SFJ reflux 580 lower limbs All procedures under local anesthesia OS (group 1) *versus* EVLA 980 and 1470 nm, bare fiber *versus* (group 2) RFA Closure Fast™ (group 3) *versus* USGFS, one or 2 sessions when needed (group 4) All procedures accompanied by phlebectomies F-U 3 days and 1 month Better QoL (SF 36) as well as less pain score (P<0.001) and shorter time off work (P<0.001) in groups 3 and 4 1 year DS examination: GSV occlusion better in groups 1,2,3 compared to group 4 (P<0.001) Clinical recurrence: No significant difference
OS *versus* EVLA *versus* RFA *versus* USGFS	Rasmussen *et al.* 2013 [73]	CEAP $C_{2\text{-}4}E_pA_sP_r$ GSV with SFJ reflux 580 lower limbs All procedures under local anesthesia OS (group 1) *versus* EVLA 980 and 1470 nm, bare fibre (group 2) *versus* RFA Closure Fast™ (group 3) *versus* USGFS, one or 2 sessions when needed (group 4) All procedures accompanied by phlebectomies F-U 3 years DS examination: GSV occlusion better in groups 1, 2, 3 compared to group 4 (P<0.001) Clinical recurrence: no significant difference (P= 0.66) Reoperations were more frequent in group 4 (P<0.001) but were mainly treated by USGFS in all groups VCSS improved in both groups and with no significant difference between the groups. AVVSS improved significantly in both groups from 3 days and onwards (P<0.0001), with no difference between the groups at any point in time SF-36 scores improved in all domains and in both groups SF-3
OS *versus* EVLA *versus* UGFS	Biemans *et al.* 2013 [74]	240 consecutive CEAP $C_{2\text{-}6}$ symptomatic patients GSV with SFJ reflux OS under general or spinal anesthesia (group 1) *versus* EVLA 940 nm, bare fibre, continuous laser withdrawal (group 2) *versus* UGFS complementary session after 3 months when needed (group 3) F-U 1 year Occlusion rate Group 3=72.7% lower than group 1 (88.22%) and group 2 (88.5%); P<0.02 The complication rate was low and comparable between the groups. EuroQoL and EQ5D, all groups showed significant improvement with no difference between the groups.

Abbreviations: AVVSS= Aberdeen varicose vein severity score; CIVIQ = chronic venous insufficiency quality-of –life questionnaire; DS = duplex ultrasound; Euro Qol 5D= EQ -5D; EVLA = endovenous laser ablation; GSV= great saphenous vein; OS= Open Surgery: saphenofemoral ligation+ stripping, +/- perforating veins ligation+/- tributary phlebectomies; QoL= quality of life; RFA= radiofrequency ablation; UGFS= ultrasound guided sclerotherapy; VCSS= venous clinical severity score

ed uncomplicated varicose veins (C_2). Second, one outcome assessment is not considered in this article, *i.e.* patient's evaluation. This point is particularly important given that one of patients' main complaints after CHIVA is a persistent cosmetic problem.

TABLE X.—*OS compared with microwave ablation.*

Type of procedure	Article	Conclusions
HL+EMA GSV+ EMA Trib Phleb.+ EMA IPVs Lig Versus HL+ S+ Trib Phleb.+ IPVs Lig.	Yang *et al.* 2013 [75]	C_{3-6} patients SFJ incompetence GSV refluxbelow knee 100 patients/108 LL Group 1 HL+EMA GSV+ EMA Trib Phleb.+ EMA IPVs Lig 88 patients/ 98 LL Group 2 HL+ S+ Trib Phleb.+ IPVs lig F-U 1 MONTH-2 YEARS Lost to F-U at 2 years Group 1 8 LL Group 2 9 LL Immediate post operative course Skin burn Group 1 10.2% Ecchymosis P=0.004 in favor of group 1 Sensory impairment P=0.03 in favor of group 1 Recurrence Group 1 2.8 % 6 months 14.3 % 2 years Group 2 10.2% 6 months 28.2 % 2 years P=0.03 and P=0.02 AVVQ and VCSS no difference at any time.

AVVQ : Aberdeen varicose vein questionnaire; EMA=endovenous microwave ablation; F-U=Follow-up ; GSV=great saphenous vein; HL= high ligation; LL= lower limb; IPVs Lig.= perforating veins ligation; S=stripping; SFJ= saphenofemoral junction; Trib phleb.= tributary phlebectomies; VCSS=Venous clinical severity scoring.

TABLE XI.—*Conservative treatment limited to life style advice compared with OS.*

Treatment	Article	Conclusions
OS *vs.* conservative treatment	Michaels *et al.* 2006 [78]	246 patients Non complicated varices (C_{2s}) with saphenofemoral or /and saphenopopliteal junction reflux Conservative treatment (Life style advice) *versus* OS Follow-up 2 years After Surgery QoL improvement Symptoms relief (pain and edema feeling) Cosmetic benefit
	Ratcliffe *et al.* 2006 [79]	246 patients Non complicated varices (C_{2s}) with saphenofemoral or/and saphenopopliteal junction reflux Conservative treatment (Life style advice) *versus* OS Follow-up 2 years Surgery offers a modest health benefit for relatively little National Health Service cost compared to conservative treatment

OS=Open Surgery: saphenofemoral or/and saphenopopliteal junction ligation + stripping, +/- perforator ligation+/- tributary phlebectomies; QoL=Quality of Life.

OS *vs.* cryostripping

Though cryostripping is not at present frequently used, two randomized controlled trials have compared it with OS (Table XII).[80-83] There was no difference between postoperative pain or clinical results. However, postoperative hematoma was less frequent with cryostripping.

OS *vs.* high ligation and phlebectomies

Campanello *et al.* in Sweden in 1996 presented a randomized clinical trial on preservation of the GSV after high ligation, phlebectomies and perforating vein ligation. Later an English team repeated the same RCT with a longer follow-up. In both studies there was no differ-

TABLE XII.—*RCT comparing OS with CHIVA.*

Operative procedure	Article	Conclusions
OS *versus* CHIVA	Carandina *et al.* 2008 [80]	Patients C_{2-6} OS (n =75) *versus* cure CHIVA (N.=75) Follow-up 10 years (mean) After CHIVA Less recurrence OR 2.2, 95% CI 1-5, P=0.04
	Parés *et al.* 2010 [81]	Patients C_{2-6} OS with clinical marking (N.=167) *versus* OS with duplex marking (N.=167) *versus* CHIVA (N.=167) Follow-up 5 years After CHIVA Better clinical outcome (symptoms and signs) - Less recurrence - OR 2.01,CI 1.4-3 , P<0.001

OS= Open surgery: High ligation + Saphenous stripping+/ - Perforating veins ligation +/ - tributary phlebectomies; CHIVA=Ambulatory Conservative Hemodynamic Management of Varicose Veins

TABLE XIII.—*RCT comparing OS with cryostripping.*

Operative procedure	Article	Conclusions
OS versus Cryostripping	Menyhei G *et al.* 2008 [82]	OS (N.=86) versus HL+ cryostripping (N.=79) Follow-up 6 months No difference in terms of - Postoperative pain - Clinical results. Less hematoma with cryostripping, P=0.01
	Klem *et al.* 2009 [83]	OS (N.=245) versus HL+ cryostripping (N.=249) Follow-up 6 months No difference between the 2 groups

OS= Open surgery: High ligation + Saphenous stripping+/ - Perforating veins ligation +/ - Tributary phlebectomies; HL= High ligation; SFJ= Saphenofemoral junction

ence in the rate of recurrence in the two groups (Table XIII).[82, 83] However, high ligation plus tributary phlebectomies with perforating veins ligation is not used today. The explanation lies probably in both the more precise information provided by duplex ultrasound investigation of the SFJ and the outcome after endovenous ablation. Duplex ultrasound has shown that reflux at the SFJ is absent in many patients presenting with VVs and that the terminal valve is competent in about 50% of cases in the presence of GSV reflux. When thermal or chemical ablation is used, the termination of the SFJ remains open and this does not seem to negatively influence the results. Furthermore, high ligation tends to enhance recurrence related to neovascularization.

Table XIV summarizes variations of OS related to technique or anesthesia.[84-91]

Indications for operative treatment

Indications for operative treatment rely both on the clinical status of the patient and information provided by ultrasound investigation.

There is no indication for surgery in patients with C_0 and C_1 CVD. In patients with superficial reflux causing C_2 to C_6 CVD operative treatment should be considered particularly in C_3-C_6 class. The choice of procedure depends on many factors which include personal mastery of a technique, cover/reimbursement by the health services/health insurance which varies from country to country and the patient's own choice, influenced by possible postoperative problems, recovery time and time off work, the procedure type that allows easiest control of recurrences and information from friends, literature or the internet.

TABLE XIV.—*RCT of OS compared with high ligation, phlebectomy, and perforator ligation.*

Operative Procedure	Article	Conclusions
OS *versus* HL + tributary phlebectomy +/- perforator ligation	Campanello et al. 1996 [84]	OS (n =18, group 1) *versus* HL+ tributary phlebectomy +/- IPVs ligation (n =18, group 2) Post operative course Less subjective postoperative discomfort in group 2 Follow-up 4 years No difference in terms of clinical outcome and plethysmography results between group 1 and 2 as far as IPVs had been treated Ultrasound examination: Patent and compressible GSV in group 2
	Dwerryhouse et al. 1999 [85] Winterborn et al. 2004 [86]	OS (n =52, group 1) *versus* HL+ tributary phlebectomy +/- IPVs ligation (n =58, group 2) Follow-up 5 and 11 years No difference rate of recurrence between the 2 groups but more redo surgery in group 2

OS= Open surgery: High ligation + Saphenous stripping+/ - Perforating veins ligation +/ - tributary phlebectomies; HL= high ligation; GSV=Great saphenous vein

Nevertheless in presence of saphenous incompetence and on a technical point of view we recommend

— Thermal ablation (radiofrequency, laser) Grade 1A

— Old type surgery 2A

— Open modern surgery Grade 1B (only one RCT)

— USGFS Grade 1A

— Presently Steam, Cyanoacrylate glue ablations and Clarivein cannot be graded as well as procedures with preservation of the saphenous trunk.

In absence of saphenous incompetence we recommend phlebectomies or USGFS both deserve grade 1C.

Presence of varices after interventional treatment (PREVAIT) represents a particular situation in terms of indications. There is general agreement that USGFS is the first line treatment in almost all cases except in patients presenting with lower limb VVs fed by reflux from pelvic veins. The European guidelines for sclerotherapy gives a Grade 1B to this procedure.[16] However, this recommendation is based on case series.[92, 93]

Guidelines

THE SVS/AVF guidelines [94] were published 3 years ago and their conclusions remain valid although some of the recommendations may not be applicable in Europe.[95] European guidelines for sclerotherapy are also available.[16]

B. TREATMENT OF INCOMPETENT PERFORATING VEINS

Introduction

The hemodynamic and clinical significance of incompetent perforating veins (IPs) when combined with primary superficial incompetence remains debated.

Operative treatment procedures

It is widely accepted that a minimally invasive approach is preferred to reduce morbidity and particularly to avoid delayed wound healing and infection, but there is no consensus as to the best technique.[96, 118]

Outcome after operative treatment

Numerous case-series with no control group have suggested that subfacial endoscopic sur-

TABLE XV.—*Variations of OS related to technique or anesthesia.*

Type of procedure	Article	Conclusions
HL Wound closure with subcuticular absorbable *vs.* interrupted monofilament nylon mattress sutures	Corder *et al.* 1991 [87]	HL Skin closure with subcuticular polyglycolic acid (N.=76) *versus* interrupted monofilament nylon mattress sutures (N.=86) F-U 6 weeks The higher infection rate found with subcuticular polyglycolic acid (P=0.05) appeared to be operator dependent
HL+S+ Trib phleb. *versus* HL+S +Trib phleb. + SEPS	Kianifard *et al.* 2007 [88]	GSV Saphenous reflux+ IPVs reflux (N.=68), HL +S+ Trib phlebec (N.=34) *versus* HL +S+ Trib phleb+ SEPS (N.=34) Excluded patients with isolated SFJ junction reflux or /and deep reflux, C_6, REVAS F-U 1 week to 1 year The addition of SEPS was not associated with significant morbidity. Although it reduced the number of IPVs it had no effect on recurrence rate or QoL
OS General anesthesia + Local anesthesia : Lidocaine + adrenaline *versus* Saline solution	Nisar *et al.* 2006 [89]	GSV General anesthesia+ local lidocaine and adrenaline (N.=50) *versus* saline solution (N.=50) F-U 1 day-6 weeks In group local lidocaine and adrenaline Reduction of hematoma (P=0.007) and postoperative pain (P<0.001)
Saphenous stripping (Babcock) *versus* invaginated stripping	Scheltinga *et al.* 2007 [90]	GSV 92 patients Various anesthesia modality Conventional stripping, Babcock Group I (n=46) *versus* Invaginated stripping. Group II (n=46) Group II Less blood loss. P<0.001 F-U 1-26 weeks No difference in terms of postoperative pain and returned to work
Saphenous stripping (Babcock) *versus* pin stripping (Oesch Stripper)	Buttler *et al.* 2002 [91]	GSV 136 patients HL+S Under general anesthesia Conventional stripping, Babcock Group I (n=68) *versus* Inverting stripping Oesch stripper Group II (n=68) Group II Shorter operative time and less blood loss F-U 1 week No difference in terms of hematoma, postoperative pain, mobility or analgesia consumption

F-U=Follow-up; GSV=great saphenous vein; HL= high ligation; IPVs=Incompetent perforating veins; QoL=Quality of life ; S=stripping ; SEPS=subfascial endoscopic perforator surgery; Trib phleb=tributary phlebectomies

gery (SEPS) might have a beneficial effect upon the natural history of CVD and in particular chronic venous ulceration.[119-128]

However, it is not clear as to whether benefits observed are due to the SEPS procedure or to concomitant saphenous surgery undertaken in most patients.[129-132]

In addition, it has been suggested by data from retrospective case-series that deep venous reflux (especially if post-thrombotic patients) may diminish the benefits of SEPS [129, 131-133] although this has not been a universal finding.

It has never been shown that interrupting perforating veins in addition to standard saphenous surgery confers additional benefit in patients with CEAP C_2 disease in terms of symptom re-

lief, hemodynamic improvement and QoL or recurrence. This may be because in the absence of deep venous reflux, complete eradication of superficial venous reflux will result in some incompetent perforating veins regaining competence.[134, 135]

Three RCTs have shown that perforating veins regain competence in more than one third of legs from GSV treatment alone.[88, 136, 137]

Furthermore, there is no level A evidence that the addition of perforating veins surgery to standard saphenous surgery confers additional benefit in patients with CEAP C_4-C_6 disease in terms of symptom relief, hemodynamic improvement,[139, 139] QoL, ulcer healing or recurrence.[117, 140-144] This may be because appropriate subgroups that might benefit have not yet been identified. Two long-term prospective cohort studies showed however, very low rates of recurrent venous ulceration following superficial venous surgery and SEPS.[145, 146]

The role of perforating veins has been assessed in the short term by one Swedish RCT, where patients with venous ulcers and incompetent GSV and perforating veins incompetence were randomized into GSV high ligation alone or combined with a SEPS procedure. At one year there were no significant differences between the groups regarding healing or recurrence.[137] A prospective, randomized multi-center trial was conducted to study if ambulatory compression therapy with venous surgery including SEPS and superficial vein ligation (97 patients) was a better treatment than compression therapy alone (103 patients) for patients with venous leg ulcers. There was no significant difference in healing rates between the two groups and recurrence rates were the same. However, patients with recurrent ulcers or medially located ulcers in the surgical group had a longer ulcer-free period than those treated conservatively.[147]

Indications for treating incompetent perforating veins

There is no consensus on this point, but in $C_{2,3,4a}$ patients most phlebologists agree to treat only superficial incompetence. In C_{4b}, C_5, C_6 the majority will treat only VVs and reserve perforat-

ing veins ablation to patients whose clinical status is worsening or in case of ulcer recurrence, while others will combine superficial and perforating veins operative treatment.

C. GASTROCNEMIUS VEIN REFLUX

Duplex scanning is mandatory before surgery for superficial vein reflux arising in the popliteal fossa. It determines the anatomy of termination of the SSV and gastrocnemial veins.[148, 149]

Their termination can be separate or they can share a common ostium or terminal trunk. Persistence of an incompetent gastrocnemius vein missed at operation is a common cause of recurrence so that adequate ligation is essential. In one study, it was associated with 42% of SSV recurrence [150] and with 34% in another.[151]

D. FINAL REMARKS

The evolution of materials and devices for the treatment of CVD is rapid, and when long- or medium-term outcomes comparing new treatment techniques become available, the particular material or device employed in the RCT is no longer used.

Most new procedures are operator-dependent and when two or more are tested in a RCTs it is important that the investigators are well trained in all of them.

A brief description of a procedure does not indicate precisely how it was performed, *e.g.* the high ligation and stripping technique has evolved and is now less aggressive and invasive than it was in the past. Unfortunately it is ignored by many surgeons.

RCTs are important in the evaluation of new procedures. Skepticism about conventional RCTs in non-pharmacological interventions such as surgery remains and so called expertise-based RCTs are suggested as an alternative where participants are randomized to clinicians with expertise in intervention A or clinicians with expertise in intervention B, and the clinicians perform only the procedure they are experts in.

Accurate analysis of RCTs is difficult as hid-

den bias can be hard to identify. For illustrating this point in some RCTs, operative procedures for VVs were performed either under local tumescent anesthesia or general anesthesia that should influence short term evaluation.

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CHAPTER 11

Treatment of deep venous reflux

The significance and frequency of deep venous reflux in CVD has only been fully realized in the last 25 years owing to the use of duplex ultrasound scanning.[1, 2]

Venous reflux involving deep veins is found in less than 10% of patients with skin changes and ulceration (C_4-C_6) [3] and is associated with superficial reflux and/or perforating veins incompetence in most patients. The most common cause of deep venous reflux is post-thrombotic changes accounting for an estimated 60-85% of patients. Primary reflux is less common and is the result of structural abnormalities in the vein wall and the valve itself.[3] A very rare cause of reflux is congenital absence of valves. Reflux may be associated with iliac obstruction in both post-thrombotic and non-thrombotic disease.[4]

Surgical techniques for treating deep venous reflux can be classified into three groups.[5] The first group requires phlebotomy and includes internal valvuloplasty,[6-9] transposition [10] and transplantation,[1, 11, 12] neovalve creation.[13, 14] and cryopreserved valves.[15, 16] The second group does not require phlebotomy and includes wrapping,[17, 18] external valvuloplasty (transmural [19] or transcommissural) [20] with or without angioscopy assistance.[21-22] The last group is represented by bioprosthetic valve inserted percutaneously.[23]

Patients who are considered for deep reflux repair should have advanced symptoms of pain, swelling, skin changes, and/or ulcer (C_{4-6}) affecting quality of life despite adequate conservative treatment. Deep valve reconstruction should follow control of superficial incompetence and correction of iliac venous outflow obstruction. It requires detailed mapping of obstruction and reflux and is only indicated in the presence of deep axial reflux (from groin into calf veins).[5, 24]

Investigations

Patients considered for deep valve repair in addition to duplex scanning require preoperative phlebographic evaluation to assess operability (ascending, transfemoral and/or transbrachial phlebography). Pre-operative air-plethysmography and ambulatory venous pressure (AVP) measurements provide baseline quantitative information that may be useful for follow-up. The choice of investigation is determined by the clinical context and whether or not there are contraindications for surgical intervention. The goal of surgery for deep venous reflux is to correct the reflux at a subinguinal level.

Valve repair in primary deep vein insufficiency

The most frequent procedure performed for primary deep venous reflux is internal valvuloplasty. This is credited with achieving a good result in 70% of cases (Table I) [2, 20, 25-32] in terms of clinical outcome defined as freedom of ulcer recurrence and reduction of pain, valve com-

TABLE I.—*Results of valvuloplasty for deep venous reflux.*

Author Year	Surgical technique	Number of limbs (Number of valves repaired)	Etiology PVI /Total	Follow-up months (mean)	Ulcer recurrence or non healed ulcer (%)	Competent valve (%)	AVP □ VRT ■
Masuda & Kistner 1994 [28]	I	32	27/32	48-252 (127)	(28)	24/31 (77) *	□ ↗ 81% (av) ■ ↗ 50% (av)
Raju 1985 [30]	I	68 (71)	/	12-144	16/68 (26)	30/71 (42)	/
Raju et al. 1996 [26]	TMEV	47 (111)	/	12-70	14/47 (30)	72/111	/
Sottiurai 1996 [25]	I	118	/	8-146 (71)	9/42 (21)	89 /118 (75)	/
Perrin 2000 [2]	I	85 (94)	65/85	12-96 (58)	10/35 (29)	72/94(77)	■ Normalized 63% (av)
Raju et al. 2000 [20]	TCEV	141 (179)	98/141	1-42	(37)	(59)	□ ↗ 15% (av) ■ Normalized 100 %
Tripathi et al. 2004 [27]	I TMEV	90 (144) 12 (19)	118	(24)	(32) (50)	(79.8) (31.5)	/ /
Rosales et al. 2006 [32]	TMEV	17 (40)	17/17	3-122 (60)	3/7 (43)	(52)	□ ↗ 50% (av)
Wang et al. 2006 [29]	TMEV	(40)	40/40	(36)	/	(91)	■ ↗ 50% (av)
Lehtola et al. 2008 [31]	I+TMEV I+TMEV	12 7 1	5/12 3/7 0/1	24-78 (54)	/	(55)	/

TABLE II.—*Results of banding, cuffing, external stenting and wrapping for deep venous reflux.*

Author (material used) Year	Number of extremities treated (number of valves repaired)	Site	Etiology PVI/Total	Follow-up Months (average)	Ulcer recurrence or non healed ulcer (%)	Competent valve (%)	□ AVP ■ VRT
Camilli & Guarnera (Dacron) 1994 [35]	54	F	54/54	4-63	/	41/54 (76)	/
Raju et al. (Dacron) 1996 [26]	96	F, P, T	/	12-134	6/22 (27)	60/72 (83)	/
Akesson et al. (Venocuff I) 1999 [34]	20 (27)	F, P	7/20	5-32 (19)	2/10 (20) Both PTS	PVI 7/7 (100) PTS 7/10 (70)	PVI □ ↗ 10% (av) ■ ↗ 10% (av) PTS □ ↗ 10% (av) ■ ↗ 100% (av)
Lane et al. (Venocuff II) 2003 [17]	42 (125)	F, P	36/42	64-141 (93)	(20)	(90)	□ ↗ ■ ↗ 100% (av)
Makhatilov et al. (Vedensky Spiral) 2009 [36]	24(54)	F	28/28	12-60 (29)	No C6		/

petence, and hemodynamic improvement over a follow-up period of more than 5 years. In all series, a good correlation has been observed between these three criteria.

External transmural valvuloplasty does not seem to be as reliable as internal valvuloplasty in providing long-term valve competence or ulcer free-survival.[5, 33] Wrapping has been used both in primary venous reflux and PTS providing variable results (Table II).[17, 26, 34-36]

Valve repair in post-thrombotic disease

Long -term results after surgery for PTS are also available for transposition (Table III).[2, 25, 28, 31, 37, 38] and transplantation (Table IV).[2, 11, 25-27, 31, 39-45] In terms of clinical results and valve competence, a meta-analysis demonstrated that a good result was achieved in 60% and 40% in transposition and transplantation, respectively, over a follow-up period of more

TABLE III.—*Results of transposition for deep venous reflux.*

Author Year	Number of extremities treated	Etiology PTS/Total	Follow-up in month	Ulcer recurrence or non healed ulcer (%)	Competent valve (%)	AVP □ VRT ■
Johnson et al. 1981 [38]	12	12/12	12	4/12 (33)	/	□ unchanged ■ unchanged
Masuda & Kistner 1994 [28]	14	/	48-252	7/14 (50)	10/13 (77)	□ ↗ 70% (av) ■ ↗ 70% (av)
Sottiurai 1996 [25]	20	20/20	9-149	9 /16 (56)	8/20 (40)	/
Cardon et al. 1999 [37]	16	16/16	24-120	4/9 (44)	12/16 (75)	/
Perrin 2000 [2]	17	16/17	12-168	2/8 (25)	9/17 (53)	/
Lehtola et al. 2008 [31]	14	12/14	24-78	/	(43)	/

TABLE IV.—*Results of transplantation for deep venous reflux.*

Author Year	Number of extremities treated	Site	Etiology PTS/Total	Follow-up in month (average)	Ulcer recurrence or non healed ulcer (%)	Competent valve (%)	AVP □ VRT ■
Taheri et al. 1982 [11]	71	F, P	/	/	1/18 (6)	28/31 (90)	□ ↗ 15% (av)
Bry et al. 1995 [42]	15	P	/	15/132	3/14 (21)	7/8 (87)	□ unchanged ■ unchanged
Eriksson & Almgren 1988 [39]	35	F, P	35/35	6-60	/	11/35 (31)	■ unchanged
Kabbani et al. 2011 [43]	19	FC, P, GSV	12/18	(37)	6/8 (80)	8/19 (42)	
Lehtola et al. 2008 [31]	29	F, P	25/29	24-78 (54)	/	(16)	/
Mackiewicz et al. 1995 [44]	18	F	/	43/69	5/14 (36)	/	■ improved ?
Nash 1988 [40]	25	P	25/25	/	3/17 (18)	18/23 (77)	□ ↗ 18% (av)
Perrin 2000 [2]	32	F	31/32	12-124 (66)	9/22 (41)	8/32 (25)	■ ↗ 19% (av)
Raju et al. 1999 [41]	83 X	F, P, T	83/83	12-180	(40) 6 yrs	(38) 4 yrs	□ unchanged
Raju et al. 1996 [26]	54	F	/	12-180	/	16/44 (36)	/
Rosales et al. 2008 [45]	22 including 2 double Tr. Tr.+ other procedure	F, P	22/22	6-108	/	GSV Tr. 14/26 AV Tr. 3/6	/
Sottiurai 1996 [6, 25]	18	F, P	/	7-144	6/9 (67)	6/18 (33)	/
Tripathi et al. 2004 [27]	35	F, P	35/35	(24)	(45)	(41)	/

than 5 years (with a poor correlation between clinical and hemodynamic outcome). Other techniques include neovalve construction (Table V).[14, 46-48]

Nevertheless Maleti and Lugli reported excellent clinical results and neovalve competence in 34/40 cases after mean follow-up of 28.5 months.[46]

Large randomized control trials comparing conservative treatment and surgery for deep venous reflux would be difficult to conduct so that it is necessary to rely on the outcome of available series of deep venous reconstructive surgery. Their analysis provides a grade 1C recommendation in primary etiology and 2C in secondary.

TABLE V.—*Results of neo-valve construction for deep reflux.*

Author Publication Year	Technique	Number of extremities	Etiology PTS/Total (extremity)	F-U month (mean)	Non-healed ulcer or ulcer recurrence (%)	Results Competent Valve (%)	Results Hemodynamics AVP ❑ RT ■
Plagnol *et al.* 1999 [14]	Bicuspid neo valve constructed with superficial vein	44	44/44	6-47 (18)	3/32 (17)	38/44 (86)	/
Opie *et al.* 2008 [47]	Monocuspid neo valve constructed with deep vein wall + PTFE patch	14	?	(48)	0/6	13/14 (92)	
Labas *et al.* 2009 [48]	Wilson technique on transplanted axillary vein +/- FV valvuloplasty + sclerotherapy	56	?	4-21 (10.7)	(18)	51/56	/
Lugli *et al.* 2009 [46]	Monocuspid or bicuspid neo valve constructed with deep vein wall	19+21=40 2 different techniques	40/40	2-78 (28.5)	7/40 (17)	13/19 (68) unimproved in 75% 21/21 (100)	■ 75% (av)

I=Internal Valvuloplasty; PVI=Primary Venous Insufficiency; TMEV=Transmural External Valvuloplasty; TCEV=Transcommissural External Valvuloplasty; Tr.=transposition; GSV=Great Saphenous Vein; AV=Axillary Vein; ❑ AVP=Ambulatory Venous Pressure; ■ VRT=Venous Refill Time; av=average; ↗=Improved; F=Femoral vein; FC= Common femoral vein; P=Popliteal vein; T=Tibial (Posterior) vein; PTS=Post-Thrombotic Syndrome.

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CHAPTER 12

Treatment of venous outflow obstruction

Obstruction is the principal cause of symptoms in approximately one-third of post-thrombotic limbs. It is associated with reflux in 55% of symptomatic patients with chronic venous disease (CVD).[1, 2] This combination leads to the highest levels of venous hypertension and the most severe symptoms as compared to either reflux or obstruction alone.[3] Obstruction of the common femoral and ilio-caval venous outflow (ilio-femoral venous obstruction) is more likely to cause symptoms such as ulcer, pain, edema and venous claudication, and decreased quality of life than femoro-popliteal vein blockages.[4-8] The recurrence rate of DVT is increased.[9] Following iliofemoral DVT, only 20-30% of iliac veins completely recanalize spontaneously, while the remaining veins have residual obstruction and varying degrees of collaterals.[4, 10] The role of chronic obstruction in the pathophysiology of CVD is now emphasized. Correction of obstruction by venoplasty and stent placement alone has been shown to be a sufficient therapy in most patients even in the presence of reflux.[11]

Diagnosis and selection of patients

It is important for the physician to be aware that there may be ilio-femoral venous obstruction. Patients presenting with C classes 3-6 should be considered for further studies, particularly those with venous claudication on challenged exercise,[5] those with pain out of pro-portion to detected lesion and those with post-thrombotic disease. Unfortunately, there are no hemodynamically reliable tests to measure what degree of narrowing constitutes an anatomically significant "critical stenosis" in the venous system. This lack of a "gold standard" to assess the hemodynamic impact of chronic outflow obstruction is the major obstacle for selecting limbs for treatment and evaluating outcome. Although a positive non-invasive or invasive test may indicate the need to proceed with further investigations, a negative test should not discourage it.[12] Ascending or antegrade transfemoral phlebography is the standard method to image the venous outflow tract, showing the site of obstruction and the presence of collaterals. Intravascular ultrasound (IVUS) is superior to standard single-plane and multi-plane phlebography for estimating the morphological degree and extent of iliac vein stenosis and to visualize details of intraluminal lesions.[13-16] Iliocaval obstruction and underlying abnormalities can be detected by MRV and CTV.[17, 18] With new MRV protocols and blood pool (venous) contrast agents, MRV has emerged as a promising new diagnostic option but not been validated by IVUS.[18-24]

Open surgical reconstruction

Results following open reconstructions are usually presented in series with small numbers of treated limbs and short observation times, usually with poor reporting standards and rare-

TABLE I.—*Results of saphenous vein femoro-femoral bypass.*

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Husni 1970 [29]	78	7-144	74	73
Hutschenreiter et al. 1979 [30]	20	6-28	69	44
O'Donnell et al. 1987 [31]	6	24	100	100
Halliday et al. 1985 [32]	47	60	89	75
AbuRahma et al. 1991 [33]	24	66	88	75

TABLE II.—*Results of prosthetic femoro-femoral bypass.*

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Eklof et al. 1985 [26]	7	2-31	86	17
Yamamoto et al. 1986 [34]	5	1-18	60	60
Comerota et al. 1994 [35]	3	40-60	67	67
Gruss & Hiemer 1992 [36]	32		85	85

TABLE III.—*Results of femoro-caval/ilio-caval prosthetic bypass grafting.*

	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Husfeldt 1981 [37]	4	4-30	100	100
Dale et al. 1984 [38]	3	1-30	100	100
Ijima et al. 1985 [39]	5	22-36	60	60
Eklof et al. 1985 [26]	7	2-31	86	29
Plate et al. 1985 [40]	3	1-11	67	33
Okadome et al. 1989 [41]	4	17-48	100	100
Gloviczki et al. 1992 [42]	12	1-60	67	58
Alimi et al. 1997 [43]	8	10-45	88	88
Jost et al. 2001 [28]	13	1-150	49	54

ly presenting cumulative patency and success rates. Bypass grafting appears to have relatively poor long-term patency rates, perhaps for several reasons such as low velocity flow, external compression of the low pressure bypass, inherent thrombogenicity of non-saphenous graft material and poor distal inflow due to extensive distal disease.[25, 26]

The cross-over bypass

The autogenous femoro-femoral venous bypass [27] appears to be less thrombogenic with better patency than prosthetic grafts.[28] However, most series have small numbers of patients with inconsistent clinical and venographic follow-up (Tables I and II).

The in-line bypass

Anatomic in-line bypass reconstruction can be used in the femoro-ilio-caval axial outflow axis with segmental obstruction in the presence of a sufficient venous inflow and outflow of the graft (Table III).

The only study presenting cumulative success rates by Jost et al.,[28] shows a secondary patency rate of 54% at 2 years for prosthetic in-line bypass. This should be compared to 83% patency for saphenous vein femoro-femoral crossover bypass in the same study. Open venous reconstruction for chronic femoro-ilio-caval obstruction should only be considered in patients who have unsuccessful or failed endovenous treatment in surgically fit patients with severe symptoms.[44]

TABLE IV.—*Patency rates following femoro-ilio-caval stenting.*

Author	Etiology	Number of limbs	Cumulative patency rates			
			Primary	Assisted-primary	Secondary	Time of cumulative follow-up
Neglen *et al.* 2007 [51]	All	982	67%	89%	93%	6y
Hartung *et al.* 2009 [49]	All	87	83%	89%	93%	8y
Neglen *et al.* 2007 [51]	NIVL	518	79%	100%	100%	6y
Ye *et al.* 2012 [53]	NIVL	205	99%	100%	100%	4y
Neglen *et al.* 2007 [51]	Post-thrombotic	464	57%	80%	86%	6y
Rosales *et al.* 2010 [52]	Post-thrombotic	32	67%	76%	90%	2y
Kölbel *et al.* 2009 [54]	Post-thrombotic Occlusion	59	70%	73%	80%	5y
Raju & Neglen. 2009 [55]	Post-thrombotic Occlusion	139	30%	56%	66%	4y
Kurklinsky *et al.* 2012 [50]	Post-thrombotic occlusion	91	71%	90%	95%	3y
Knipp *et al.* 2007 [56]	Mixed acute/chronic	58	38%	63%	74%	5y
Oguzkurt *et al.* 2008 [57]	Mixed acute/chronic	36	80%	-	82%	4y
Razavi *et al.* 2000 [58]	IVC obstruction	17	-	-	87%	2y
Raju & Neglen. 2006 [59]	IVC obstruction	106	58%	82%	84%	2y

NIVL = non-thrombotic iliac vein lesions (primary disease, so-called May-Thurner Syndrome or Cockett disease); IVC=inferior vena cava

Sapheno-popliteal bypass

Sapheno-popliteal vein bypass is a rarely performed operation for outflow obstruction. The few reported series of patients,[29, 33, 45] show clinical success and patency rates of 31-58% and 56-67% respectively for follow-up at one to five years.

Endophlebectomy of the deep veins

Endophlebectomy may be performed in limbs with segmental obstruction of the common femoral outflow.[46, 47] It may also be a part of a hybrid procedure to improve the inflow in association with bypass or stenting procedures as a last resort.[44, 48]

Femoro-ilio-caval stenting

The introduction of percutaneous iliac venous balloon dilation and stenting has dramatically expanded the scope of treatment. Complications are minimal and mortality has been nil. It is now the method of choice in the treatment of femoro-ilio-caval obstruction. In recent years several large case series, have been published that confirm the effectiveness of this treatment option.[49-52]

Patency rates assessed by duplex ultrasound or phlebography in successfully stented limbs are shown in Table IV.

Stented limbs with non-thrombotic disease appear to do far better than those with post-thrombotic disease, with reported secondary cumulative patency rates of 100% and 86-90% respectively at 4-6 years (see table IV, NIVL vs post-thrombotic).

Severe in-stent recurrent stenosis defined as greater than 50% diameter decrease on single plane antero-posterior venogram is infrequent occurring in only 5% at 72 months in one study.[51, 60] Gender and side of limb involved did

not affect outcome. Cumulative greater rates of severe in-stent recurrent stenosis were found in thrombotic compared to nonthrombotic limbs, reported as 10% and 1% respectively at 72 months, and was seen more often in post-thrombotic venous occlusion than in non-occlusive disease. Thrombophilia was not associated with increased in-stent restenosis. Although initially thought to be contributing factors, a subsequent study has shown that length of stented vein or extension beneath the inguinal ligament into the common femoral vein are not associated with increased in-stent restenosis.[61] Similar factors seem to be associated with early and late occlusions of stents.[51] The reports describing patency rates indicate clinical improvement in the long-term term in most patients. In one study after iliac vein balloon dilation and stent placement in 148 limbs with active ulcer the cumulative ulcer recurrence-free rate at 5 years was 58%.[51] Cumulative rate of complete relief of pain and swelling at 5 years was 62% and 32%, respectively. Using a quality-of-life questionnaire assessing subjective pain, sleep disturbance, morale and social activities, and routine or strenuous physical activities, patients indicated significant improvement in all major categories after venous stenting. The clinical results are gratifying with substantial decrease in venous clinical severity and disability scores and high cumulative ulcer healing rate.[51, 52, 62, 63]

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CHAPTER 13

Assessment of efficacy of therapies

To validate therapeutic efficacy, it is necessary to evaluate individual signs, symptoms and quality of life as well as morphological and functional venous parameters in properly powered studies. These clinical outcome parameters should have been previously validated.

The method of choice to assess clinical outcome after treatment for chronic venous disease (CVD) depends to a great extent on the clinical presentation. It is difficult to evaluate improvement in cosmetic appearance or subjective symptoms such as cramps, itching, pain or fatigue. Also, the patient's preference and acceptance of different treatments must be considered. It is much easier to accurately measure improvement of clinical signs such as diminishing size, healing or recurrence of an ulcer or change in the circumference or volume of the extremity than to evaluate symptoms.

The efficacy of treatment is best established by documenting improved signs and symptoms supported if possible by laboratory tests, recording all adverse effects of treatment, and with a long-term follow-up especially when prevention of progression is targeted.[1]

Adverse effects from treatment must be recorded. Complications from surgery or sclerotherapy such as mortality, wound infection, superficial thrombophlebitis, cellulitis and saphenous nerve injury should be reported.

Available methods for measurement are summarized below.

Evaluation of signs

Telangiectasiae and reticular veins

Telangiectasiae and reticular veins can be assessed visually with photographs and diagrams.

Varicose veins

Varicose veins can be assessed visually with photographs and diagrams and by venous diameter and area assessments.

Edema and leg volume

An international consensus meeting considered that water displacement volumetry is the gold standard to prove and compare the efficacy of any treatment to reduce edema in CVD.[2] This is an old,[3, 4] but recently updated noninvasive technique. Volumetry does not quantify edema, but measures short-term variations which reflect changes in edema.[5-7] It is reproducible provided measurement conditions are carefully standardized. Volumetry allows accurate comparison of changes in the same leg over time or with changing conditions as displayed by different amounts of edema, e.g. morning *versus* evening (vesperal) edema, supine or standing, resting or after exercise, before and after the application of a venous tourniquet, before and after treatment and at the beginning compared with the end of the follow-up period. The repeatability for the method is 0.7% for two consecutive measurements in the same leg by two different observers, and its in-

tra-individual variability is 1.3% under the same conditions.[6]

Volumetry has already demonstrated that legs that ache are those that swell the most,[8] that leg volume increases during daily activity and that this increase correlates with the severity of CVD;[6] that leg volume may increase during long distance flights and that it diminishes after venous surgery,[9] and after different drug treatments for venous or lymphatic insufficiency.[10-12]

Other methods to assess edema include leg circumference measurements using a tape measure,[13-15] and opto-electronic volumetry.[16-18]

Skin changes and lipodermatosclerosis

The degree of induration caused by lipodermatosclerosis can be measured by different techniques including high resolution ultrasound B-scan,[19] and a "durometer".[20, 21] Ankle joint movements can be quantified by goniometry.[22, 23] However, none of these techniques have been validated so far as tools for comparing therapeutic methods in CVD.

Ulcer healing

Complete healing of an ulcer is the most clinically significant outcome measurement for C6 patients,[1] and can be assessed with life table analysis.[24]

Surface area reduction is the surrogate criterion that is used most often. The area of the ulcer can be measured by planimetry using its outline drawn on a transparent sheet, by scaled photography or by direct ultrasonic digitized measurements using a light pen.[25] Alternatively, it can be approximated by multiplying the two maximal perpendicular diameters to obtain an area in cm^2; if this is then multiplied by n/4 the calculated rectangular area is transformed to an elliptic one. Gillman has published a method for calculating wound healing rates that corrects for differing sizes and shapes by dividing the ulcer area by its perimeter.[26]

The above changes in geometrical measurements per unit time are often used in clinical trials.[27, 28] However, complete healing and the initial healing rate are the most common endpoints used.[29, 30] The initial healing rate is defined as the rate of healing over the course of a first time period.

Percentage of area decrease per unit time is not a valid endpoint, since this depends on the initial size of the ulcer.[27] However, the Gillman equation corrects for different initial ulcer sizes so that it meets the needs of clinical studies for standardized and comparable measurements.[30-32]

Ulcer recurrence

Ulcer recurrence is the most important endpoint in C5 patients and can be assessed in long-term follow-up studies using cumulative ulcer-free survival times,[33, 34] or a life-table analysis of proportion without recurrence over time.[24]

Evaluation of symptoms and quality of life

Symptoms

Symptoms can be evaluated by the clinician and/or by patient self-reporting. In the latter case, a questionnaire should be completed at leisure outside the doctor's office. This method is used most frequently for evaluation before, during and after treatment. Patients can be asked to give global ratings of improvement in symptoms or to use quantitative scales such as a Likert scale,[35] or a visual analog scale. Quantification of analgesic requirements can be useful as an additional assessment of pain.

Quality of life

Quality of life for patients with CVD has been assessed by generic and by disease-specific measures. The most frequently used generic measure is the Medical Outcome Study Short Form Health Survey (SF-36), a 36-item questionnaire that covers eight health dimensions including physical and social functioning, role limitations due to physical and emotional problems, mental health, vitality/energy, bodily pain and general health perceptions. The SF-36 has been used both in patients with varicose veins and with venous ulcers.[36, 37] In a study by Garratt et al,[36] SF-36 satisfied strict psychometric criteria for validity and internal consistency and confirmed a significantly lower quality of life in patients with varicose veins compared to an age-adjusted

TABLE I.—*Outcome parameters for therapeutic studies in patients with CVD.*

CEAP "C" Class	Clinical (*)	Morphology	Function
C1	Photographic analysis		
C2	idem C1	Duplex, MRV, CTV: vein diameter and obstruction	Duplex: reflux and obstruction Plethysmography: pumping function and outflow resistance
C3	idem C1 + Volume measurement	idem C2	idem C2 + Venous Pressure: venous pump impairment and obstruction
C4	idem C3 + use of a chromameter, durometer and goniometer	idem C2 + US: Skin thickness + Capillaroscopy: capillary density + Microlymphography	idem C3 + TcPO$_2$ + laser Doppler fluxmetry
C5	idem C4 + ulcer recurrence rate	idem C4	idem C4
C6	idem C5 + ulcer healing rate	idem C4	idem C4

(*) The standardized evaluation tools for symptoms, quality of life and clinical severity scores can be used in symptomatic patients with C1 to C6 disease.

sample from the normal population. EuroQol-5D (EQ-5D) is a shorter form of a generic QoL questionnaire including only five questions to be answered by patients. This form has been validated against SF-36.[38]

Because specific complaints from patients with CVD are not identified by currently used generic quality of life questionnaires, specific questionnaires have been developed to assess the functional and psychological effects of venous disease.[39, 40] The most recent of these is the Chronic Venous Insufficiency Questionnaire (CIVIQ) used by Launois *et al.*[40] This questionnaire has been validated and found to meet stringent psychometric criteria, including reliability, content, construct validity and responsiveness. In a randomized trial of 934 patients the CIVIQ showed that quality of life scores were significantly lower in patients with venous insufficiency than in controls without venous disease. The Aberdeen varicose vein questionnaire (AVVQ) has been frequently used in the UK.[41]

Health-related quality of life studies should be used in the future to assess overall outcome and justify treatment for CVD.[42, 43]

Venous Clinical Severity Score (VCSS)

VCSS [44] was designed to measure outcomes after surgical treatments and seems adequate for patients with advanced CVD, but is less well adapted for patients with less severe venous disorders. It has been validated,[45] including its short-term repeatability.[46] The score has recently been revised,[47] and validated [48] (see Chapter 5).

Evaluation of morphological and functional venous parameters

Several morphological and functional parameters related to reflux and obstruction of the venous system can be measured by duplex ultrasound,[49] MRV, CTV, plethysmographic techniques, pressure measurements and microvascular techniques. Their use depends on the C class and on the specific target of the treatment assessed (Table I).

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CHAPTER 14

Prevention of post-thrombotic syndrome

Despite conventional anticoagulation therapy of deep venous thrombosis (DVT) (LMWH for at least 5 days followed by warfarin), 30-50% of all patients, depending on the anatomical level, will develop post-thrombotic syndrome (PTS).[1] The symptomatology of PTS includes limb swelling, pain, heaviness, pruritus (itching), venous claudication, skin changes and ulceration,[2] which is the single most predictive clinical finding. It may occur as early as 3 months.[3] Established PTS is a significant cause of chronic incapacity and inability to work with considerable consequences for both the patient and the society.[4-7]

The PTS is the result of venous hypertension produced by reflux (caused by remodelling of the venous wall and/or damaged valves) alone or combined with persisting outflow obstruction.[8] Venous hypertension is associated with chronic inflammation affecting not only the venous wall but also the microcirculation producing excessive capillary leakage and impairment of skin nutrition with skin changes and eventually skin ulceration.[9]

Factors that are associated with the development of the PTS include iliofemoral DVT,[4, 5] especially if chronic iliofemoral vein obstruction persists,[10, 11] increased BMI, older age and female gender,[5, 12] recurrent DVT,[12] which often obstructs part of the collateral circulation and sub-therapeutic anticoagulant therapy which allows DVT recurrence.[13] More recently, it has been demonstrated that elevated inflammatory biomarkers such as IL-6, ICAM-1 and CRP,[14, 15] are also associated with increased rates of PTS following DVT.

Prevention of PTS

Prevention of primary and recurrent DVT

Prevention of DVT should reduce the prevalence of PTS. There is an association between PTS and recurrent DVT and patients with recurrent DVT have a high incidence of PTS.[16] Recurrent DVT in the same leg results in a higher frequency and severity of the PTS. Until recently PTS was viewed as a late complication. However, recent data show that PTS occurs early and that review of signs and symptoms at one month after the onset of DVT is highly predictive of the presence of PTS.[5] Prevention of recurrence in patients with DVT should lessen the severity and frequency of PTS. The evidence and guidelines for primary prevention has been summarized in the international consensus document on the prevention and management of venous thromboembolism in sections 3-12 and for secondary prevention in sections 14, 15, 17 and 18.[17] Guidelines aiming to reduce the PTS and leg ulcers by 50% in the next ten years have been published.[18]

Compression stockings

Effective compression stockings have been shown to reduce venous hypertension, edema and minimise the damage to the microcirculation.[19, 20] Four RCTs involving 745 patients have demonstrated that in patients with proximal (above-knee) DVT, knee length compression stockings used for 2 years reduce the incidence

of PTS from 39% to 19% (RR 0.49; 95% CI 0.38 to 0.62).[21-24] One study has shown no difference between knee and thigh length compression stockings.[25] It appears that treatment with LMWH combined with early ambulation and elastic compression prevents further the development of PTS.[26, 27]

Early thrombus removal

Thrombectomy was popularized 30 years ago. Early surgical thrombectomy in a small series of patients with iliofemoral DVT was associated with increased iliac vein patency compared with standard anticoagulation therapy alone (67% *vs*. 34%) (RR for patency 1.92; 95% CI 1.06 to 3.51) and decreased incidence of PTS from 93% in the absence of thrombectomy to 58% when thrombectomy was performed (RR 0.63; 95% CI 0.44 to 0.90).[28, 29]

A recent study showed that venous thrombectomy for iliofemoral DVT, even with crural involvement in 63% of cases, could achieve acceptable results regarding patency and occurrence of PTS at 5-year mean follow-up. This procedure was combined with peri-operative stenting of an underlying iliac obstruction (not performed by others), but was also combined with an AV fistula.[30]

Catheter directed thrombolysis (CDT) from observational cohort studies and comparative non-randomized studies appears to be associated with increased vein patency, valve preservation and a reduction in the incidence of PTS compared with conventional anticoagulation therapy.[31-34]

Two RCTs compared CDT with standard anticoagulation therapy involving a total of 138 patients with iliofemoral DVT.[35, 36] At six months, the patency rate was 70% in the catheter-directed thrombolysis group and 33% in the standard anticoagulation therapy group (RR 0.48; 95% CI 0.33 to 0.70). The second and more recent RCT continued recruitment to a total number of 209 patients and has recently reported on iliofemoral patency and PTS in 189 patients.[37] Iliofemoral patency at 6 months was 64% in the catheter-directed thrombolysis group and 47% in the conventional treatment group (RR for patency 1.42; 95% CI 1.09 to 1.85). At 24 months PTS was developed in 41% of patients in the catheter-

directed thrombolysis group and 56% of patients in the standard anticoagulation therapy group (RR 0.74; 95% CI 0.55 to 1.00; P=0.047). Clinically relevant bleeding events occurred in 9% of patients. More RCTs are needed with PTS as the primary endpoint to assess the efficacy and safety of CDT. The results of the NIH-sponsored ATTRACT study (NCT00790335) and the Dutch CAVA trial (NCT00970619) are eagerly awaited.

Relief of chronic post-thrombotic iliofemoral obstruction

Prospective observational studies have indicated that percutaneous endovascular venoplasty and stenting to correct chronic venous obstruction may alleviate the symptoms of PTS.[38] More RCTs are needed to demonstrate the efficacy of endovascular venoplasty and stenting on the prevention of symptoms, ulceration and its recurrence.

In the largest published series on 982 lesions,[11] at 72 months, primary, assisted-primary, and secondary cumulative patency rates were 79%, 100%, and 100% in non-thrombotic disease and 57%, 80%, and 86% in post-thrombotic disease, respectively. The frequency of severe leg pain (visual analogue scale >5) and leg swelling (grade 3) decreased from 54% and 44% before present placement to 11% and 18% after stent placement, respectively. At 5 years, cumulative rates of complete relief of pain and swelling were 62% and 32%, respectively, and ulcer healing was 58%. The mean CIVIQ scores of QOL improved significantly in all categories. RCTs are needed to determine the efficacy of pre-emptive endovascular venoplasty and stenting in patients with chronic post-thrombotic iliofemoral obstruction.

Long term anticoagulation with LMWH

Standard treatment of DVT (initial LMWH for at least 5 days followed by VKA) prevents thrombus extension and embolization but does not directly lyse the thrombus, which often results in partial recanalization. A number of studies have compared long-term treatment with LMWH *versus* standard therapy,[39-44] and demonstrated better recanalization in the long-term LMWH groups. A meta-analysis on 5 studies that

reported on total recanalization demonstrated a risk ratio of 0.66 (95% CI 0.57 to 0.77; P<0.0001) in favor of long term LMWH.[45] In a large multicentre study involving 480 patients there was a reduction of the incidence of PTS with long-term LMWH compared to standard therapy (RR 0.77; P=0.001).[46] Pooled analysis of 2 studies reporting on the long-term development of leg ulcers as part of PTS,[46, 47] demonstrated an 87% risk reduction for venous ulcers when long-term LMWH was used instead of standard therapy (P=0.019).[45]

In summary, adherence to the guidelines for the primary prevention of DVT,[17] (and therefore PTS) in hospitalised patients is essential. Adequate intensity and duration of anticoagulation, in addition to compression and early mobilization is recommended. Early thrombus removal using CDT may be used in expert centres in selected patients with iliofemoral DVT. Surgical thrombectomy may be offered if thrombolysis is contraindicated or unavailable. Although conventional anticoagulation therapy (LMWH for at least 5 days followed by VKA) is based on a high level of evidence in terms of VTE recurrence, prolonged therapy with LMWH in patients with proximal DVT is preferable in terms of PTS prevention. In patients with proximal DVT, below-knee graduated compression stockings for at least two years in addition to appropriate anticoagulation are recommended.

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CHAPTER 15

Management of symptomatic individuals in the absence of clinical signs and pathophysiological abnormalities

Patients complaining of "venous" symptoms but who do not have any clinical signs, anatomic anomalies or physiological disorders that can be identified by the currently in use complementary investigations engaged in the CEAP classification are assigned to class $C0_S$, E_n, An, Pn.

Such patients are not uncommon in practice, and the results of the recent international detection programme (Vein Consult Program) indicated that almost 20% of the 91,545 screened adults had CEAP grade $C0_s$.[1] After a thorough examination to exclude non-venous causes of symptoms, confirm the presence of varicose veins or other venous physiopathological anomalies using non-invasive techniques or even invasive investigations if necessary e.g. in the presence of severe symptoms (level III investigation),[2] several options are available although none are "evidence-based" except for veno-active drugs and compression.

Patient reassurance

This measure is self-evident and will help many patients, mostly those with a family history of varicose veins or leg ulcers who are anxious that they may also get venous problems. However, the value of reassuring patients has not been demonstrated and studies on QoL might improve our knowledge on this point.

Adaptation of lifestyle

In most phlebologists' experience, many symptoms will diminish if patients can adopt a better lifestyle including improved working conditions, performing tip-toes when obliged to stand-still, and developing recreational activities such as walking rather than driving, swimming or raising the legs during pauses or at night, and trying to lose weight when appropriate. However, the value of these measures has not been demonstrated.

Oral veno-active drugs

Their effect on symptoms in $C0_S$ classification has been well demonstrated (see Chapter 8).

Topical veno-active drugs and topical heparinoids

These drugs may relieve some complaints of heaviness or swelling. This may be due to the cooling effect of gels.

Compression therapy

Compression therapy, usually by wearing stockings, has been studied in class $C0_S$. In the San Diego Consensus conference, 3 trials have been considered to provide a Grade B recommendation.[3] In another study it was stated that

"calf-length compression stockings with a pressure range between 11 and 21 mmHg were able to reduce or totally prevent evening edema and might therefore be recommended for people with a profession connected with long periods of sitting or standing".[4, 5] It is then logical to prescribe light compression in $C0_S$, however, we need further trials to assess their effect.

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CHAPTER 16

Management of patients with varicose veins

Non-interventional therapy

There is evidence for the efficacy of veno-active drugs to relieve symptoms and improve venous edema in patients with varicose veins. Compression therapy may also be effective (see Chapters 7 and 8).

Non-interventional therapy is usually the main treatment modality during initial patient presentation until all work-up and interventional therapy is performed and for patients not willing to have interventional therapy. The latter group may include patients with transient symptoms, those with minimal symptoms not severe enough to make interventional therapy appealing and in cases of vague or atypical symptoms as a therapeutical trial, awaiting further investigation for other diseases that could explain them. Veno-active drugs are indicated in patients with the characteristics shown above, not able to tolerate compression including pruritic symptoms that worsen when compression is worn and residence in warm climates that prevents use of compression due to heat intolerance, especially during the warm seasons of the year.

Interventional therapy

Intervention for varicose veins by means of surgery, endovenous (radio-frequency, laser) techniques [1-4] and sclerotherapy [5] aim to eliminate reflux, normalize venous hemodynamics and remove visible varices in order to relieve symptoms, prevent recurrence and minimize the complications of CVD (see Chapter 10). In practice, this entails eliminating both axial reflux [6, 7] and varicose clusters. The former is accomplished by surgery, endovenous techniques or foam sclerotherapy and the latter by surgery or sclerotherapy.

Varicose veins are increasingly being treated by minimally invasive alternatives to surgery in the expectation that these methods will reduce morbidity, eliminate hospital stay and accelerate return to normal activity. There is also strong evidence that the new techniques will reduce recurrence caused by neovascularization,[8-13] but so far overall recurrence rates of varicose veins are similar in the available RCTs with 5-year follow-up (see Chapter 10). However, there is more neovascularization in the surgery groups and more SFJ and tributary recurrence in the laser groups. The important remaining question to be answered is whether these differential manifestations of recurrence are equal regarding clinical severity.[14, 15] The hierarchy and relative indications of the above interventional treatment modalities are determined by the presence of saphenous vein reflux and/or varicose veins, availability of particular methods and local experience, and patient preference.

1. Elimination of saphenous reflux, when present, is clearly the initial step, preferably by endoluminal methods and followed by surgery, with the exception of recurrent varicose veins due to incomplete ligation where sclerotherapy is considered an alternative to surgery because

of the potentially hazardous redo nature of the latter. The effectiveness of CHIVA and ASVAL techniques in presence of saphenous reflux is still debated and needs long term prospective RCT comparing their outcome to those provided by endovenous procedures.

2. Any co-existing varicose veins can be managed with avulsions, concurrently with saphenous surgery if this is performed or even at a second stage if endoluminal ablation is performed as it is expected that these will become less prominent and bothersome. Some surgeons instead of varicose vein avulsions prefer sclerotherapy, which can be performed during operative or endoluminal management of the saphenous trunk, or at a later stage in the latter scenario. However, patients should be adequately informed that sclerotherapy is plagued by a higher recurrence rate necessitating re-interventions and this also holds true for sclerotherapy of the main saphenous trunks.

3. In isolated varicose veins (*i.e.*, saphenous vein incompetence does not exist, occurring often in primary varicose veins, recurrent varicose veins and no evidence of trunk incompetence at the time of patient presentation or in varicose veins of non-saphenous origin), avulsion or sclerotherapy are employed. Although sclerotherapy is considered as second choice, it is very often the first choice in recurrent varicose vein. Additional parameters to be considered include potential contraindications of each method that should be discussed with the patient, including post-sclerotherapy skin pigmentation, mostly a problem in patients with fair skin color.

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CHAPTER 17

Treatment of patients with the post-thrombotic syndrome

There are no prospective randomized controlled studies comparing various treatment modalities in most of the CEAP clinical classes for patients with the PTS so that a strong recommendation cannot be made.

Compression is the cornerstone for treating patients with the PTS,[1] (Chapter 7) but the optimal degree of compression is unknown. Below-knee compression is as effective as above-knee in most patients.[2] The grade of compression used is often tailored to the grade of CEAP and patient tolerance but not to the etiology, anatomic lesions or pathophysiological disorders due to lack of data. Anatomic lesions in severe classes of PTS frequently combine deep, superficial and perforating vein reflux with superadded obstruction in some [3] but we do not know precisely the value of compression for treating PTS in relation to these patterns. The same is true for adjuvant therapy with medications, physiotherapy or hydrotherapy.

Surgical or endovascular methods to relieve obstruction or reflux (Chapters 11 and 12) are targeted to treat specific anatomic areas but various methods are frequently used in combination for superficial, perforating veins and deep reflux so that it remains difficult to identify which is most beneficial. Many patients with superficial venous insufficiency also have deep vein insufficiency. There is literature which indicates that treating superficial vein reflux in patients with deep venous reflux in addition to the superficial reflux (and no deep obstruction), will often improve or correct the deep reflux.[4, 5]

Although drug treatment has been effective for reducing edema in short-term studies,[6-8] (Chapter 8) compression remains the pivotal treatment in patients classified C_{3-6}. In practice, compression is tailored according to its efficacy for controlling edema.

Intervention may be considered if severe symptomatic edema is not controlled by compression because of above inguinal ligament obstruction. Unfortunately, the hemodynamic severity is not easy to measure. According to Neglen and Raju [9] intravascular ultrasound is the most reliable investigation (Chapters 6 and 12). There is a large consensus for using balloon venoplasty and stenting rather than surgical bypass,[10, 11] and for treating ilio-caval obstruction or occlusion, whatever the severity of the venous disease is. Raju and Neglen noted a high incidence of non-thrombotic iliac vein obstructions in patients with CVD,[12] and started treating patients with iliac vein obstruction and reflux with stents for the iliac vein obstruction. They found to their surprise that placing iliac vein stents without treatment of the reflux was sufficient to control symptoms in the majority of patients having a combination of reflux and iliac vein thrombosis.[13]

Chronically occluded iliac veins and IVC occlusions are now commonly treated with recanalization and stent placement and several reports have demonstrated high technical success with good clinical response and intermediate to long-term durability (Chapter 12).[14]

In patients presenting with severe C_{4-6} CVD,

TABLE I.—*Management of patients with chronic venous disease according to the CEAP clinical classification.*

C Class	A: S, D P*	P: R, O, O+R	Calf pump	Treatment
C$_{0-2 S}$	S	R without O	Normal	Conservative treatment: Compression, Venotonic drugs Treatment of superficial reflux: Sclerotherapy Surgery
Mild C$_{3 S, AD}$ Severe C$_{3 S}$	D Suprainguinal significant O	O	Normal	Conservative treatment: Compression, Venotonic drugs Failure of conservative treatment: Ballooning and stenting
C$_{4-6}$	D Suprainguinal significant O	O	Normal	Conservative treatment: Compression, Venotonic drugs Failure of conservative treatment: Balloon venoplasty and stenting
C$_6$ Non-healing ulcer Recurrent ulcer	D	R + O	Sometimes Normal	Conservative treatment: Compression, Venotonic drugs (see Chapter 18) Failure of conservative treatment: Treat obstruction first, Valve transfer

A=Anatomic; P=Pathophysiologic; S=Superficial; D=Deep; P*=Perforator; R=Reflux; O=Obstruction.

conservative treatment is also accepted as the basic treatment but surgery should be considered after full investigation when skin or subcutaneous changes are not controlled by compression. If obstruction proximal to the inguinal ligament is identified, recanalization with angioplasty and stent placement should be considered. Recently endophlebectomy has been reported for treating obstruction above the inguinal ligament.[15] When reflux is combined with severe obstruction, the latter has to be managed as first step. There is no consensus for the efficacy and the need for surgical treatment of incompetent perforating veins in PTS. In the absence of a prospective randomized study comparing perforating vein surgery with compression the pros and cons remain debatable. Nevertheless if surgery is to be performed there is a large agreement for using SEPS.[16] Ultrasound-guided foam sclerotherapy may also be used for treating incompetent lower leg perforating veins in PTS and has been demonstrated to be an effective treatment option.[17] Radiofrequency and specially laser mediated perforating vein ablation have become common practice and may replace other forms of perforating vein treatment where the technology is available even though the evidence may still be quite weak (see Chapter 10).[18]

Deep venous reconstructive surgery for treating reflux remains controversial (chapter 11). Among those that are in favor, there is a consensus for selecting only patients in whom conservative treatment has failed to heal the ulcer or patients with recurrent ulcers and other severe symptoms in the absence of contraindications (inefficient calf pump, severe and non-correctible coagulation disorder). As valvuloplasty is rarely feasible in PTS, transplantation of an axillary vein segment with valves or vein transposition are the recommended techniques to be used. Maleti and Lugli have reported promising midterm results with the construction of a neo-valve in PTS.[19] Results provided by the different procedures are reported in the chapters devoted to deep venous obstruction and reflux. However, surgery for deep venous reflux or obstruction has to be performed in specialized units with highly trained personnel.

Exercise training program for patients with acute DVT does not increase the risk of developing pulmonary emboli and does not negatively affect clinical outcome. Present studies do not clearly demonstrate improvement with exercise but there appears to be a trend towards improved outcome with prescribed exercise.[20] For more chronic DVT, an exercise program appears to improve ejection fraction and muscle strength but not valvular reflux, venous clinical

severity sores or quality of life. Further studies are needed in order to clarify this issue (Table I).[21]

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CHAPTER 18

Management of leg ulcers

Compression therapy

The management of venous hypertension and tissue edema with compression bandaging has been shown to encourage healing of venous leg ulcers. A Cochrane review concluded that compression increases ulcer-healing rate compared with no compression.[1] In addition, high grade compression is more effective than low grade compression.[1] A four-layer bandage system may produce a pressure of 42.5 mmHg at the ankle level that can be maintained for one week. After weekly bandaging with four-layer bandages, 110 of 148 legs with chronic venous ulcers healed within 12 weeks.[2] Four-layer bandaging is probably the most widely used method in the UK whereas short-stretch bandaging is the system of choice in most of continental Europe. Several randomized trials have been published that compare different bandaging systems. Some have shown a benefit for ulcer healing using 4-layer bandages *versus* short stretch bandages, while others have shown no difference.[3-5] A weakness of all available trials is that the exerted pressure was not measured at the ankle level.

Surgery for superficial veins

Superficial surgery without compression can heal venous ulcers.[6] A randomized controlled trial (ESCHAR) allocated patients with isolated superficial venous reflux and mixed superficial and deep venous reflux to either compression treatment with multilayer compression bandage (N.=258) *versus* a combination of compression treatment and superficial ablative surgery (N.=242).[7] Multilayer compression bandaging and surgery reduced the rate of recurrence at 12 months when compared with compression alone without affecting the healing rate.

When deep venous reflux is segmental and limited, and is associated with superficial venous reflux and leg ulcers, superficial venous surgery abolishes deep venous reflux in 50% of limbs and healing can be achieved at 12 months in 77% of leg ulcers.[8]

The fact that superficial vein surgery is of benefit in patients with segmental deep vein incompetence was also shown in the ESCHAR RCT, where there also seemed to be a trend favoring surgery in patients with axial reflux.[9] Low recurrence rate of ulcers in that group was also shown in a prospective series from Sweden where also perforators had been treated with SEPS.[10]

There is enough evidence today promoting early surgical intervention for superficial venous incompetence, in combination with effective compression therapy, in patients with venous ulcers, and there is no need to wait for the ulcer to heal. A cross-sectional study performed in Sweden has demonstrated that this approach makes a difference on a population basis, with the prevalence of venous ulcers being reduced by almost one half over a 14-year period.[11]

Surgery for incompetent perforating and deep veins

Ligation of perforating veins (SEPS), deep venous reconstruction and balloon dilatation with or without stenting has been discussed in Chapters 10-12. It is reserved for patients whose ulcers do not respond to compression or compression combined with venoactive drugs.

Oral medications in combination with compression

Several studies have investigated the effect of oral medications when used as adjuvants to compression therapy.

A meta-analysis of 7 RCT involving 659 patients demonstrated that at 8-24 weeks the healing rate increased from 40% in the compression group to 64% in the compression plus pentoxifylline group (RRR 33%; 95% CI 25% to 45%; P<0.001).[12]

A meta-analysis of 5 RCT involving 616 patients demonstrated that at 6 months ulcers healed faster when the phlebotonic micronised purified flavonoid fraction was combined with a two layer compression than compression alone. The RRR was reported as 32% (95% CI 3% to 70%; P=0.03). This difference was present from the second month and was associated with a shorter time to healing (16 weeks *versus* 21 weeks; P=0.0034).[13]

Four RCTs involving 488 patients demonstrated an increase rate of healing at 2-3 months when sulodexide was combined with compression than compression alone. The overall healing rate increased from 32% in the compression group to 54% in the compression plus sulodexide group (RRR 41%; 95% CI 27% to 52%; P<0.001).[14-17]

Intermittent pneumatic compression (IPC)

Four studies involving a total of 142 patients of which three were RCT compared the effect of IPC on ulcer healing when used in conjunction with compression. Despite the small number of patients, considering all four studies IPC appears to increase the incidence of ulcer healing from 35% to 71% (RR for healing 2.23; 95% CI 1.50 to 3.33).[18-21]

A recent systematic review identified seven randomized controlled trials (including 367 patients in total).[22] However, only one trial was at low risk of bias having reported adequate randomization, allocation concealment and blinded outcome assessment. The authors concluded that IPC may increase healing compared with no compression, but it is not clear whether it increases healing when added to treatment with bandages, or if it can be used instead of compression bandages.

A RCT compared two different IPC regimens on ulcer healing.[23] 104 patients were randomized to rapid (3 cycles per minute) or slow (1 cycle per 3 minutes) compression IPC devices for one hour daily. Both devices applied the same pressure and no other compression treatment was applied during the study period. Complete healing occurred in 45 of the 52 patients treated with rapid IPC, and in 32 of the 52 patients treated with slow IPC. Life table analysis showed that the proportion of ulcers healed at six months was 86% in the group treated with the rapid IPC compared with 61% in the group treated with slow IPC (P=0.003, log-rank test). The mean rate of healing per day in the rapid IPC group was found to be faster compared to the slow IPC group (0.09 cm² *vs.* 0.04 cm², P=0.0002).

On the basis of the available evidence the current recommendation is that IPC can be used as alternative method when other methods have failed.[24]

Further trials are required to determine the optimum type of IPC and optimum type of compression stockings it should be combined with.

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CHAPTER 19

Prevention of leg ulcer recurrence

In western countries venous leg ulcers occur in approximately 0.3% of the adult population.[1-3] The combined prevalence of active and healed ulcers is around 1%.[4, 5] The vast majority of previously published studies are related to ulcer healing rate. Only a few studies relate to the problem of ulcer recurrence after healing and these are often not very robust. The incidence of recurrent ulceration after healing with conservative techniques varies in different studies from 24% to 69% at 12 months.[6-9] Various studies have reported ulcer recurrence rates of 28-57% at 2 years,[9, 10] 21-38% at 3 years [11, 12] and 48% at 5 years.[13]

Compression therapy

Compression therapy is believed to counteract the effects of venous hypertension and to control edema. There is fairly strong circumstantial evidence that not wearing compression stockings for various reasons is associated with ulcer recurrence.[10, 14-16]

A recent Cochrane review of compression to prevent ulcer recurrence,[17] identified four trials with 979 participants. One trial in patients with recently healed venous ulcers compared recurrence rates with and without compression and found that compression significantly reduced ulcer recurrence at six months.[18] Two trials compared high-compression hosiery with moderate-compression hosiery.[12, 19] The first study found no significant reduction in recurrence at five years with high-grade compression hosiery compared with moderate-

grade compression,[19] while the second study assessed ulcer recurrence at three years and found that high-grade compression hosiery reduced recurrence compared with moderate-grade compression.[12] There was significantly higher compliance with medium-grade compression than with high-grade compression hosiery in one and no significant difference in the second trial. A third trial found no statistically significant difference in recurrence rates between two types of compression hosiery with moderate-grade compression.[14] No trials of compression bandages for preventing ulcer recurrence were identified.

The recurrence rate was 2-20 times higher in noncompliant patients during an observation period of 1-156 months and the cumulative recurrence rate at 5 years was 29-31% and 83-100% in compliant and noncompliant "limbs", respectively.[15, 16, 20] McDaniel et al.[13] used univariate analysis of risk factors to show that poor compliance for use of stockings did not reach a significant level but tended to be associated with recurrence. Compliance for compression therapy has been included in the venous clinical severity score (VCSS).[21]

It is difficult to assess a patient's daily compliance. Lack of compliance can be due to several factors including lack of cosmetic appeal, discomfort, inability to put stockings on, allergy to material, lack of financial resources, and lack of patient understanding and education about their condition and these need to be addressed to improve compliance. Studies have shown great variations of compliance to stocking use rang-

ing from 37-84%.[13, 15, 16, 22] Wearing compression hosiery was found to be positively associated with the participants' knowledge of the cause of their condition (P=0.002), higher self-efficacy scores (P=0.026) and lower depression scores (P = 0.009).[23] In one study commonly cited factors, such as age, gender, difficulty in applying stockings and cosmetic appearance did not have any influence on stocking use.[24]

Compression is probably of value but the poor compliance in many patients fails to allow satisfactory decrease of ulcer recurrence rates when analyzed by intention-to-treat in a population of ulcer patients.

Bed rest and leg elevation

Leg elevation and bed rest have been recommended to control edema, preferably with the leg elevated above the heart level. Having both full ankle movement and full mobility reduces the risk of recurrence.[25] Leg elevation, compression hosiery, high levels of self-efficacy and strong social support will help prevent recurrence.[26] However, there is no supportive evidence that either prevent ulcer recurrence.

Exercise and body weight

Morbid obesity is an increasing problem in the general population and has been linked to skin changes and ulcers of venous type with or without detection of CVD.[27-29] Greater body weight has been shown to be statistically associated with poor healing of venous ulcers,[30] and proportionally more patients with ulcer have been found to be obese compared with the general population in a study performed in Sweden.[31]

The function of the calf muscle pump is greatly influenced by the mobility of the ankle joint. It has been shown that ankle range of motion decreases with increasing severity of clinical symptoms of CVD, and is associated with poor calf pump function as measured by plethysmography.[22, 32] It would seem that improvement of the calf muscle pump by exercise would increase venous return and subsequently help the clinical situation. One study indicated that the amount of moderately strenuous activity in the study

group was low compared with that of the general Dutch population; 35% of the patients did not have a 10-minute walk even once a week.[33]

Exercise and weight loss are often recommended to prevent or delay recurrence of venous ulcers but there is no conclusive evidence to show that they are effective.

Correction of underlying venous insufficiency

Ulcer recurrence rates have been reported after correcting underlying venous pathology by superficial or deep venous interventions, but few appropriate prospective studies are available to indicate that correction of CVD results in a reduced incidence of ulcer recurrence.

Open surgery

The ESCHAR study compared surgery and compression with compression alone in prevention of venous ulceration. This RCT concluded that overall 24-week healing rates were similar in the two groups, but the 12-month ulcer recurrence rate was significantly reduced in the group with compression and surgery compared with those with compression alone (12% and 28%, respectively).[34] Rates of ulcer recurrence at four years were 56% for the compression group and 31% for the compression plus surgery group (P<0.01).[35]

In a prospective, non-randomized study McDaniel *et al.*,[13] reported a significantly reduced cumulative recurrence rate at 48 months in limbs treated by a variety of operations compared with those treated without surgery (26% and 52%, respectively). The study found that patients who were not candidates or who elected to forego surgery had a 3.4 times higher rate of ulcer recurrence compared to surgical patients.

Subfascial endoscopic perforator surgery (SEPS)

Sundukov *et al.*,[36] reported ulcer recurrence in 2 out of 68 patients treated with SEPS. From the level of evidence available by now it seems that SEPS, used as part of a treatment regimen for severe CVI, benefits most patients in the short term regarding ulcer healing and the prevention of ulcer recurrence.[37] It seems that

SEPS combined with superficial venous surgery leads to healing with a low recurrence rate in patients with open and healed venous ulcers (8% and 18% at 3 and 5 years, respectively).[38] A prospective randomized trial performed by van Gent et al.[39] comparing the treatment of venous ulcers with SEPS and compression therapy *versus* compression therapy alone, revealed during follow-up of a mean of 29 months in the surgical group and 26 months in the conservative group, that in the surgical group, the ulcer-free rate was 72%, whereas in the conservative group this rate was 53% (P=0.11). Some studies are showing similar low recurrence rates for venous ulcers after SEPS procedure (2.4% after 1 year follow up period).[40]

Thermal ablation of incompetent superficial and perforating veins

Recently published studies showed that combined treatment with compression therapy and thermal ablation of incompetent superficial and perforating veins significantly reduces ulcer recurrence compared to historical controls (4.8% and 67%, respectively).[41] Sufian et al. reported ulcer recurrence in one out of 18 patients with 25 venous ulcerations one year after superficial venous laser ablation.[42] Similar results were reported by Marroco et al.: 4.7% recurrence rate in C5 patients and 20% cumulative non-healing and recurrence rate in C6 patients.[43] Teo et al.[44] reported no recurrence at one year in 44 patients with non-healing venous ulcers treated with endovenous thermal ablation.

Ultrasound guided foam sclerotherapy (UGFS)

There is growing evidence that foam sclerotherapy could be beneficial to patients with venous ulcerations not just in terms of healing but in preventing venous ulcers also. One study showed that the 24-week healing rate was 71.1% whilst one- and four-year recurrence rates were 4.7% and 28.1%, respectively.[45] Pang et al. reported a 4.9% Kaplan-Meier estimate of recurrence at 2 years after UGFS of superficial venous reflux,[46] and Darvall et al. reported a 7% recurrence rate in 27 patients with venous ulcers treated with UGFS and compression.[47]

Valve repair

Deep venous insufficiency appears to be a major determinant for ulcer recurrence. The ulcer recurrence rate after superficial venous surgery or perforating veins ligation is markedly increased by associated deep venous disease. Cumulative recurrence rates at 4-5 years are reported to be 67-100% and 6-29% in limbs with and without deep venous involvement respectively.[13, 48, 49] Good results following superficial surgery with or without perforator interruption have been published, which makes surgery a treatment option to be considered also in the group of patients with combined superficial and deep vein incompetence.[35, 38]

It seems logical that deep valve repair should be beneficial, but the proof is circumstantial.[50] Prospective, randomized studies do not exist. Long-term follow up by Masuda and Kistner [51] after deep valve reconstruction reported a 40% ulcer recurrence over a long period but many had long ulcer-free periods for 5-10 years. Results after valve repair were superior for primary disease compared to PTS in some studies,[51, 52] but Raju et al.,[53] reported an approximately 40% 6-year cumulative ulcer recurrence rate after deep venous reconstruction, which was similar in primary and secondary disease.

In one study the ulcer recurrence rate, within the 5-year follow-up was 18% after autogenous venous valve reconstruction.[54] Lugli et al.[55] reported 3 ulcer recurrences in 37 patients who were treated by neovalve construction because of presence of venous ulcer and deep venous incompetence.

Venous stenting in deep reflux disease

Raju and Neglen [56] reported the freedom of ulcer recurrence in legs with healed ulcers (C5) to be 88% at 5-year follow up period after venous stenting in deep reflux disease.

Venous surgery produces beneficial results in prevention of venous ulcers not only in pure venous ulcerations, but also in patients with accompanying arterial disease (4% and 11%, respectively).[57] Treatment should intuitively change underlying pathophysiology to prevent recurrence. A decreased ulcer recurrence rate has been observed in limbs with less reflux as

measured by VFI using air plethysmography where limbs with VFI of less than 4.0 mL/sec *versus* those with more than 4.0 mL/sec were associated with 28% and 53% recurrence, respectively.[13] Another study reported that the recurrence rate was only 14% if a venous filling time (VFT) more than 5 sec could be maintained compared with 45% when VFT was less than 5 sec.[58]

It is concluded that ulcer healing outcome data and physiological test results are circumstantial but they support surgery in patients who have recurrence during conservative treatment or in those who are unable to comply with conservative measures.

Prevention of recurrent DVT

Studies to evaluate whether prevention of recurrent DVT decreases the risk of ulcer recurrence have not been performed. Patients with chronic venous ulceration have a 41% prevalence of thrombophilia (2-30 times higher than the normal population), similar to that reported for patients with previous DVT.[59] In a series of patients who had a stent placed for venous obstruction, 51% of those with postthrombotic occlusion had thrombophilia although thrombophilia was also found in 23% of patients considered to have primary disease.[60] It has been suggested that patients with venous ulceration may have subclinical thrombosis or undetected distal macro- and even micro-vascular disease due to thrombophilia. It is possible that long-term anticoagulation in selected patients may prevent recurrent thrombosis and decrease the risk of recurrent ulceration.

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KEY QUESTIONS TO BE ANSWERED

During the writing up of this document, the faculty identified a lack of data in several areas that need to be addressed by future studies. These are summarized below.

Pathophysiology

Despite the increased interest in the pathophysiological mechanisms for chronic venous disease (CVD) over the past four decades, our knowledge remains rudimentary. The genetic and molecular determinants for development of varicose veins and CVD are largely undetermined. The relationship between the macro-hemodynamics and endothelial function or dysfunction in the vein wall, and the actual impact of flow dynamics on capillary, valve and vein wall remodeling, white cell activation, SMC proliferation and migration as well as extracellular matrix alteration require further investigation. Evidence for the role of senescence and apoptosis in the development of CVD has just started to emerge. Factors defining target-tissue resilience in the development of CVD-related cellular and molecular alterations in the presence of venous hypertension remain poorly understood. The variable manifestations of signs and symptoms in CVD among individuals with similar reflux sites, extent of disease and global hemodynamic impairment have not been explained. The pathophysiological and molecular bases of lipodermatosclerosis and ulceration are only partially understood.

CEAP classification

It is critically important that recommendations for change in the CEAP classification are supported by research enabling progress on levels of evidence rather than levels of investigation. Validating studies underscoring the usefulness of the CEAP classification both in the clinical and research settings are encouraged. The descriptive comparability offered by the CEAP stratification should be used in association with the Venous Clinical Severity Score (VCSS) and Quality of Life (QoL) as instruments for longitudinal research that offer objective assessment of outcomes.

Venous hemodynamics

The significance of corona phlebectatica and its particular types in relation to progression of CVD remains undetermined. The relationship between symptom severity in CVD and venous global hemodynamics across the spectrum of CEAP is currently unavailable. The possible role of incompetent popliteal valves on calf muscle pump function in limbs with CVD requires investigation. Evidence for the potential importance of improving impaired calf muscle pump function by exercise for treating leg ulceration in the presence of deep venous valvular incompetence and considerable reflux has emerged and needs further study.

Obstruction

Methods to measure the degree of a hemodynamically significant stenosis in the venous trunks remains undetermined. There is a compelling need to introduce a dependable test to detect clinically relevant outflow impairment. The comparative diagnostic value of magnetic resonance phlebography, CT venography and emerging imaging technologies in clinical decision-making needs to be established. The long-term patency and clinical outcome of deep venous reconstruction for iliofemoral venous obstruction are still undefined. The clinical outcome following deep venous reconstruction should be determined comprehensively with the application of the accepted reporting standards of CEAP classification, allowing comparability and objectivity. There is paucity of data on the cost-effectiveness of these procedures and their effect on quality of life. Methods to enable enhanced natural process for collateralization in chronic major vein obstruction may emerge as pivotal adjuncts to compression therapy. Hemodynamic studies to determine the impact of outflow reconstruction on venous valvular incompetence and calf muscle pump function are not available.

Perforating veins

The criteria that define perforating vein incompetence require further validation. On the

basis of existing criteria, there is an absence of level I evidence for the clinical significance of incompetent perforating veins (IPV). Evidence in support of IPV surgery at present is weak and circumstantial. Assessment of the hemodynamic role of perforator incompetence in physiological conditions and a comprehensive determination of the clinical and hemodynamic changes generated with IPV ablation in association with established tools for stratification and quantification are required.

Compression

There is a paucity of methods that enable optimal selection or application of compression therapy for patients with CVD. A key to this direction would be development of techniques that enable prompt determination of sub-bandage and interphase pressures as well as compression material stiffness. Newly developed multi-component fabrics made of textiles of different stiffness that offer a higher grade of support on ambulation at a much lower resting pressure than was previously attainable are now available. They require comprehensive trials to assess their efficacy. The effects of compression in CVD at cellular and molecular levels in the endothelium and vessel wall remain poorly understood. Acute and long-term effects of sustained and intermittent compression on the venous circulation need to be determined. The role that intermittent pneumatic compression of the limb, either as an adjunct to elastic compression therapy or used alone, may have in the management of CVD requires clarification.

Randomized controlled trials are needed for clinical efficacy especially for (a) relief of symptoms in small (C1) and large veins (C2) after surgery or sclerotherapy, (b) edema reduction depending on pressure and stiffness, (c) improvement of skin changes (C4) and (d) clinical value of thigh compression.

Drug therapy

Available studies on the efficacy of venoactive medication in CVD are only rarely comparable due to disparities for inclusion criteria and primary end-points. Internationally accepted reporting standards are required to enable standardization and comparability of accrued randomized data.

The role that venoactive medication may have for treating varicose veins, edema or leg ulcers, and their effect on the natural history of CVD remains to be determined.

The impact of inflammatory pathway inhibition to prevent DVT recurrence and deterioration of PTS is still in a primary level of analysis.

The role of thrombophilia in CVD needs to be determined.

Sclerotherapy

The mid- and long-term clinical and hemodynamic results and cost-effectiveness of sclerotherapy (fluid or foam) for treating varicose veins, incompetent perforating veins or valvular incompetence of the saphenous trunks remain undetermined. Pertinent research should aim to advance knowledge about the indications, optimal use of materials, and methods of its application.

Endovenous ablation

The early clinical and hemodynamic results of feasibility studies for methods of endovenous saphenous vein ablation in light of their wide acceptance and application command validation with short-term level I studies. Long-term outcomes on the efficacy of foam sclerotherapy and the recently introduced methods (cryostripping and mechanochemical ablation) have either emerged or are currently unavailable.

Post-thrombotic syndrome

Strategies preventing or limiting development of PTS are critically essential for containment of the personal, social and financial repercussions of secondary CVD. For this purpose, in-depth appreciation of the pathophysiologic cascades underscoring development of PTS and identification of the associated factors are fundamental.

The optimal implementation of lysis, anticoagulation, thrombolysis, thrombectomy and compression therapy remains undetermined. Refinement of methods to assess valvular function may provide an insight to development as well as prevention of the PTS.
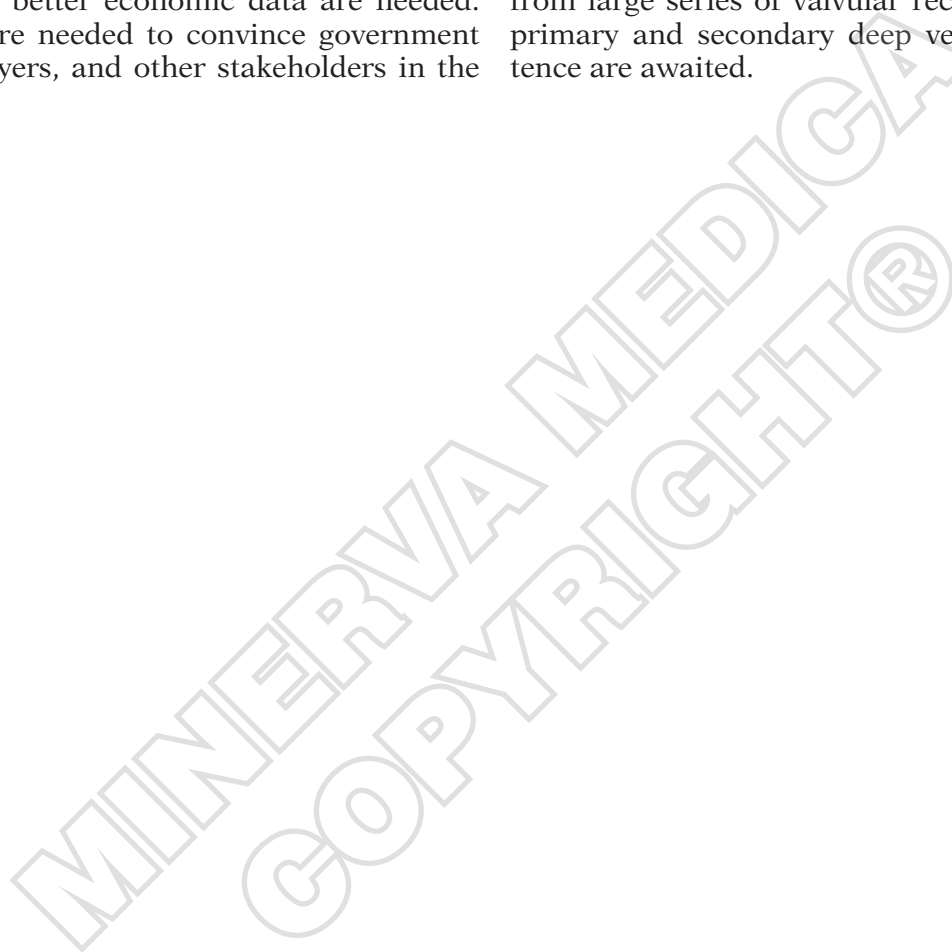
Venous ulcers

Optimal cost-effective quality of care for prevention and treatment of venous ulcers is lacking, and better economic data are needed. Such data are needed to convince government agencies, payers, and other stakeholders in the healthcare system (HCS) on the importance of venous ulcer prevention and quality care.

Valve reconstruction

The efficacy of percutaneously deployed venous valve bioprostheses has been investigated in phase I trials with encouraging results. Large phase II studies are required to determine their actual applicability, optimal deployment and mid- and long-term outcome. Long-term results from large series of valvular reconstruction for primary and secondary deep venous incompetence are awaited.

CHAPTER 20

Key questions to be answered

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