Pubblicazione periodica trimestrale - Poste Italiane - Sped. in a.p. - D.L. 353/2003 (Conv. in L. 27/02/2004 n° 45) art. 1, comma 1 DCB/CN - ISSN 0392-9590 Tasse Perçue

Reprinted from VOLUME 26 . 2007

International Angiology

The Journal of Vascular Biology, Medicine, Surgery and Phlebology

OFFICIAL JOURNAL OF

UNION INTERNATIONALE DE PHLEBOLOGIE

INTERNATIONAL UNION OF ANGIOLOGY

CENTRAL EUROPEAN VASCULAR FORUM

MANAGEMENT OF CHRONIC VENOUS DISORDERS OF THE LOWER LIMBS

GUIDELINES ACCORDING TO SCIENTIFIC EVIDENCE

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EDIZIONI MINERVA MEDICA

Management of Chronic Venous Disorders of the Lower Limbs Guidelines According to Scientific Evidence

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Disclaimer

Due to the evolving field of medicine, new research may, in due course, modify the recommendations presented in this document. At the time of publication, every attempt has been made to ensure that the information provided is up to date and accurate. It is the responsibility of the treating physician to determine the best treatment for the patient. The authors, committee members, editors, and publishers cannot be held responsible for any legal issues that may arise from the citation of this statement.

Rules of evidence

Management of patients with chronic venous disorders has been traditionally undertaken subjectively among physicians, often resulting in less than optimal strategies. In this document, a systematic approach has been developed with recommendations based upon cumulative evidence from the literature. Levels of evidence and grades of recommendation range from Level I and Grade A to Level III and Grade C. Level I evidence and Grade A recommendations derive from scientifically sound randomized clinical trials in which the results are clear-cut. Level II evidence and Grade B recommendations derive from clinical studies in which the results among trials often point to inconsistencies. Level III evidence and Grade C recommendations result from poorly designed trials or from small case series.[1, 2]

Meta-analysis

Meta-analyses are included in the present document but there should be caution as to their possible abuse. Certain studies may be included in a meta-analysis carelessly without sufficiently understanding of substantive issues, ignoring relevant variables, using heterogenous findings or interpreting results with a bias.[3] It has been demonstrated that the outcomes of 12 large randomized controlled trials were not predicted accurately 35% of the time by the meta-analyses published previously on the same topics.[4]

Document developed under the auspices of the American Venous Forum, the American College of Phlebology, the European Venous Forum, the International Union of Angiology, the Cardiovascular Disease Educational and Research Trust (UK), the Cyprus Cardiovascular Disease Educational and Research Trust, Union Internationale de Phlébologie.

PART I
PATHOPHYSIOLOGY AND INVESTIGATION

Introduction

Chronic venous disease (CVD) of the lower limbs is often characterized by symptoms and signs as a result of structural or functional abnormalities of the veins. Symptoms include aching, heaviness, leg-tiredness, cramps, itching, burning sensations, swelling and the restless leg syndrome, as well as cosmetic dissatisfaction. Signs include telangiectasias, reticular and varicose veins, edema, and skin changes such as pigmentation, lipodermatosclerosis, dermatitis and ultimately ulceration.[5, 6]

CVD is usually caused by primary abnormalities of the venous wall and 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.[7]

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 has previously stimulated a consensus statement on investigations for CVD.[8] The current document aims to provide an account of current concepts of CVD and guidelines for management.

Pathophysiology

Changes in superficial and deep veins

Varicose veins are a common manifestation of CVD and are believed to result from abnormal dis-

tensibility of connective tissue in the vein wall. Veins from patients with varicosities have different elastic properties than those from individuals without varicose veins.[9, 10]

Primary varicose veins result from venous dilatation and valve damage without previous DVT. Secondary varicose veins are the consequence of DVT or, less commonly, superficial thrombophlebitis. 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.[11-13] Rarely, deep venous reflux is due to agenesis or aplasia. Varicose veins may also be caused by pelvic vein reflux in the absence of incompetence at the saphenofemoral junction, thigh or calf perforators. Retrograde reflux in ovarian, pelvic, vulval, pudental or gluteal veins may be also associated with clinical symptoms and signs of pelvic congestion.[14-17]

Following DVT, spontaneous lysis over days or weeks and recanalization over months or years can be observed in 50% to 80% of patients.[18-20] Rapid thrombus resolution after DVT is associated with a higher incidence of valve competency.[18, 21] Such resolution depends on thrombus extent and location.[22] 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,[23-27] or rarely from congenital agenesis or hypoplasia.[28]

Most post-thrombotic symptoms result from venous hypertension due to valvular incompetence and/or outflow obstruction. Venous hypertension increases transmural pressure in post-capillary vessels leading to skin capillary damage, lipodermatosclerosis and, ultimately, ulceration.[29]

The reported prevalence of post-thrombotic syndrome following DVT has been variable (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.[30-40] Patients with both chronic obstruction and reflux have the highest incidence of skin changes or ulceration.[40] The risk of ipsilateral post-thrombotic syndrome is higher in patients with recurrent thrombosis and is often associated with congenital or acquired thrombophilia.[41-44] In recent studies, skin changes or ulceration have been less frequent (4% to 8% in 5 years) in patients with proximal thrombosis treated with adequate anticoagulation, early mobilisation, and long-term elastic compression.[45]

Incompetent perforating veins

Incompetent perforating veins (IPV) can be defined as those that penetrate the deep fascia and permit deep to superficial flow. The flow in IPV is often bidirectional. It is outward during muscular contraction and inward during relaxation. In the majority of patients with primary uncomplicated varicose veins the net flow is inward from superficial to deep. However, in the presence of severe damage to deep veins especially with persisting deep vein obstruction, the flow is predominantly outward.[46, 47]

IPVs can result from superficial and/or deep venous reflux but are rarely found in isolation.[48-50] The prevalence of IPVs, their diameter, volume flow and velocity increase with clinical severity of CVD whether or not there is co-existing deep venous incompetence.[47, 51-56] Up to 10% of patients, often women, presenting with clinical CEAP 1 to 3 disease have non-saphenous superficial reflux in association with unusually placed IPVs.[57]

Molecular mechanisms affecting the venous wall

As mentioned above, varicose veins have different elastic properties to normal veins.[9, 10] The ratio between collagen I and collagen III is altered as are dermal fibroblasts from the same patients suggesting a systemic disorder with a genetic basis.[58]

Leukocyte activation, adhesion and migration through the endothelium as a result of altered shear stress [59-61] contribute to the inflammation and subsequent remodeling of the venous wall and valves.[7, 62-64] 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 metaloproteinases (MMPs) overcoming the effect of tissue inhibitors of metaloproteinases (TIMPs). The MMP/TIMP imbalance results in degradation of elastin and collagen.[60, 65] This may contribute to hypertrophic and atrophic venous segments and valve destruction as observed in varicose veins.[60,

[65, 66] Remodelling of the venous wall and abnormal venous distension prevents valve leaflets from closing properly resulting in reflux.

Changes in microcirculation as a result of venous hypertension

Techniques such as laser Doppler,[67, 68] measurements of transcutaneous PO_2,[69] interstitial pressure capillaroscopy,[70] microlymphography [71] and skin biopsy [72, 73] 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 [66, 74] in the dermis and a decreased flow in nutritional capillaries.[75, 76] 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 [77] and other proteins that possibly prevent normal nutrition of skin cells predisposing to ulceration. Microlymphangiopathy [78, 79] and outward migration of leucocytes exacerbate microedema and inflammation.[80-84] As a late phenomenon, capillary thromboses successively lead to reduction in nutritional skin capillaries and transcutaneous PO_2.[70, 85]

Pathophysiology of stasis dermatitis and dermal fibrosis

Mechanisms modulating leukocyte activation, fibroblast function and dermal extracellular matrix alterations have been the focus of investigation in the 1990s. As stated above, CVD is caused by persistent venous hypertension leading to chronic inflammation. It is hypothesized that the primary injury is extravasation of macromolecules (*i.e.* fibrinogen and α_2-macroglobulin) and red blood cells into the dermal interstitium.[73, 86-88] 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 CVI dermal biopsies.[89, 90] 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 TGF-β1. TGF-β1 is present in pathologic quantities in the dermis of patients with CVD and increases with disease severity.[91] TGF-β1 is secreted by interstitial leukocytes and becomes bound 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.[92] 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, diapidesis and release of chemical mediators.[91]

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.[93] 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-β1 type II receptors.[93] This is associated with decrease in phosphorylation of TGF-β1 receptor substrates SMAD 2 and 3 as well as p42/44 mitogen activated protein kinases,[94] and decrease in collagen and fibronectin production from venous ulcer fibroblasts when compared to normal controls.[95]

Venous ulcer fibroblast growth rates become markedly suppressed when stimulated with bFGF, EGF and IL-1[96] and this growth inhibition can be reversed with bFGF.[97] The proliferative response of CVI fibroblasts to TGF-β1 decreases with increased disease severity,[98] and phenotypically, venous ulcer fibroblasts appear to become morphologically similar to fibroblasts undergoing cellular senescence.

TABLE I.—*Prevalence (% of population) of chronic venous disease in CEAP classes C2-C6.*

CEAP class	Men			Women		
	France	Germany	Poland	France	Germany	Poland
C2	23.7	12.4	51.6	46.3	15.8	47.7
C3	1.1	11.6	9.2	2.2	14.9	10.5
C4	4.0	3.1	13.2	2.1	2.7	10.3
C5	1.4	0.6	4.2	0.7	0.6	2.2
C6	0	0.1	2.1	0	0.1	1.1

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 orderly 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.[99-101] 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.[102] 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.[103] In addition, increased immunoreactivity to extracellular inducer of MMP (EMMPRIN), membrane Type 1 and 2 metaloproteinases (MT1-MMP and MT2-MMP) were detected in the dermis and perivascular regions of venous ulcers.[104] 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.[105] 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 uPAR mRNA and protein levels in venous ulcers compared to normal skin.[106] Elevated levels of active TGFβ-1 in the dermis of CVI patients suggest a regulatory role for TGF,-1 in MMP and TIMP synthesis and activity but this, needs to be verified by further studies.

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.[107, 108] Varicose veins are present in 25-33% of female and 10-20% of male adults.[109-119] In the Framingham study, the incidence of varicose veins per year was 2.6% in women and 1.9% in men.[120] The prevalence of edema and skin changes such as hyperpigmentation and eczema due to CVD varies from 3.0% [109] to 11% [111] of the population.

Venous ulcers occur in about 0.3% of the adult population in western countries.[112, 120-128] The prevalence of active and healed ulcers combined is about 1%.[129, 130] Healing of venous ulcers may be delayed in patients of low social class and those who are single.[131] Data from the Brazilian 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.[132]

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 in the mid 1990s and improved diagnosic techniques have allowed studies to become more comparable.

Thus, in recent studies from France,[133] Germany [134] and Poland [135] 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.

Socioeconomic aspects

The considerable socioeconomic impact of CVD is due to the large numbers concerned, cost of investigations and management and morbidity, and suffering it produces which are reflected in a deterioration in 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 management 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 out-patient. 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.[136] Estimations of the overall annual costs of CVD vary from 600 to 900 million €* (US$720 million-1 billion) in Western European countries [137-139] representing 1-2% of the total health care budget, to 2.5 billion € (US$3 billion) in the USA.[140] Often, the costs for treatment include reimbursements by the State and are affected by government policies.[141]

Detailed figures for France in 1991 [142] 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 medication, 16% for hospitalization and 3% for loss of work.[143]

Similarly high costs have been found in Germany [144] which have increased by 103% between 1980 and 1990 to reach about 1 billion € (US$1.2 billion) with in-patient direct costs of 250 million € (US$300 million), out patient costs of 234 million € (US$280 million) and drug costs of 207 million € (US$248 million).

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.[145]

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) [146] and these costs were slightly less than in previous years which was attributed to a more structured management program.

In the USA, a cost estimate of long-term complications for deep vein thrombosis (DVT) after total hip replacement gave figures varying from 700 € to 3180 € (US$839 to 3817) per patient in the first year and 284 € to 1400 € (US$341 to 1677) in subsequent years depending on the severity of the postthrombotic syndrome.[147] The cost of a pulmonary embolus (PE) was 5500 € (US$6604).

Many of the above costs are based on estimations and assumptions and strict comparisons are difficult as there is no agreed definition of "costs". 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 [148] in women who are either standing or sitting for long periods at work result in considerable expenditure. 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,[145, 149] representing 3.8% of the sales of refundable medicines. Two very similar surveys in Germany [150] and France [151, 152] showed that nearly 50% of the population aged over 15 years reported leg vein problems of whom 90.3% purchased a phlebotropic drug: 71% were women of whom 30% were "obese, relatively underpriviledged in terms of age, occupational status, hours of work, working conditions, leisure, income and health".

Indirect costs of venous disease in terms of working days lost is quoted as "the most important cost factor" in 1990 in Germany, amounting to 270 million € (US$324 million).[144] In the USA, venous ulcers cause loss of 2 million work-days per year.[140] In France, 6.4 million days of work were lost in 1991.[142] 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.[148, 153] These costs are higher than the amount spent for the treatment of arterial disease.

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".[154] 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, both generic and specific for venous disease, have been developed and some have been validated.[108, 154-157] They show conclusively that QOL is adversely affected by venous disease.[108, 148, 154-160] Similarly, reduction in severity of disease, for example after treatment, is reflected in the QOL.[154, 158, 160-162] There is a significant association between QOL and severity of venous disease and also with the CEAP classification.[154, 158, 161-165] A recent study also shows an association in women between venous disease and working conditions which is reflected in the QOL.[148] 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 increasing 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 (*e.g.* obesity), and many are not (heredity, gender, pregnancies, age). 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 tendency 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. However, at present there is a paucity of evidence-based studies of the most cost-effective way to manage primary varicose veins.

Selection of the most appropriate investigation has been established.[8] Initial outlay for duplex ultrasound has a cost but this is justified by its cost-effectiveness.[166, 167]

Hospital admissions are costly; for example, treatment of a venous ulcer costs 24 times more in hospital than at home.[168] 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 hospital has been shown to be not only as clinically effective as in hospital but also more cost-effective.[169] 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.[140, 168, 170, 171] The most cost-effective method to manage venous ulcers is by simple dressings and multi-layered bandaging to provide good pressure.[140, 172-185] A recent study [185] concluded that for long-term management of venous ulcers, education of the patient and good compression with effective compliance would save 5270 € (US$6326) in medical costs per patient per whole life together with a further saving of 14228 € (US$17080) due to fewer working days lost. A further study [173] 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.[186]

There is now evidence for cost-effectiveness of phlebotropic drugs when used as adjuvant ther-

apy to increase the rate of healing of venous ulcers.[187, 188]

Many women suffering from CVD have found that their symptoms were made worse by their working conditions resulting in 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.[148, 151, 152]

The CEAP classification of chronic venous disorders (CVD)

The CEAP classification was published in the mid 1990s in 25 journals and books in 8 languages (Table II). 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 below that has been adopted worldwide to facilitate meaningful communication about and description of all forms of CVD. The term CVD includes all morphological and functional abnormalities of the venous system in the lower limb. Some of these like telangectasia 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) of the venous system and 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 [189] the previous overall structure of CEAP has been maintained but more precise definitions have been added. The following recommended definitions apply to the clinical C classes in CEAP.

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

Reticular veins: dilated bluish subdermal veins usually from 1 mm in diameter 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 venulectasies.

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.

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.

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.

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.

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

TABLE II.—*Journals and books in which the original CEAP classification has been published.*

— Actualités Vasculaires Internationales 1995;31:19-22
— Angiologie 1995;47:9-16
— Angiology News 1996;19:4-6
— Australia and New Zealand Journal of Surgery 1995;65: 769-72
— Clinica Terapeutica 1997;148:521-6
— Dermatologic Surgery 1995;21:642-6
— Elliniki Angiochirurgiki 1996;5:12-9
— European Journal of Vascular and Endovascular Surgery 1996;12:487-91
— Forum de Flebologia y Limphologia 1997;2:67-74
— Handbook of Venous Disorders 1996;652-60
— International Angiology 1995;2:197-201
— Japanese Journal of Phlebology 1995;1:103-8
— Journal of Cardiovascular Surgery 1997;38:437-41
— Journal of Vascular Surgery 1995;21:635-45
— Journal des Maladies Vasculaires 1995;20:78-83
— Mayo Clinic Proceedings 1996;71:338-45
— Minerva Cardioangiologica 1997;45:31-6
— Myakkangaku 1995;31:1-6
— Phlébologie – Annales Vasculaires 1995;48:275-81
— Phlebologie (German version) 1995;24:125-9
— Phlebology 1995;10:42-5
— Przeglad Flebologiczny 1996;4:63-73
— Scope on Phlebology and Lymphology 1996;3:4-7
— VASA 1995;24:313-8
— Vascular Surgery 1996;30:5-11

leg. Eczema is usually caused by CVD or by sensitization to local therapy.

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.

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.

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

Revised CEAP [189]

Clinical classification

C0: no visible or palpable signs of venous disease.
C1: telangiectasies 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: perforator 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 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

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.

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.

EXAMPLE

A patient presents with painful swelling of the leg and varicose veins, lipodermatosclerosis and active ulceration. Duplex scanning on May 17, 2004 showed axial reflux of GSV above and below the knee, incompetent calf perforators 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 (2004-05-17, LII)

Classification according to advanced CEAP: C2,3,4b,6,S, Ep, As,p,d, Pr2,3,18,13,14 (2004-05-17, LII).

Basic and advanced CEAP

Basic CEAP includes *all four* components. Use of the C-classification alone inadequately describes CVD. 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 is 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.

Investigations

General remarks

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

When a patient presents with symptoms and signs suggestive of CVD, a physician should ask a number of clinically relevant questions. The first question is to ask whether CVD is present. If it is then investigations should follow that determine the presence or absence of reflux, obstruction, calf muscle pump dysfunction and the severity of each.[8]

Detection of reflux and obstruction

The clinical presentation is assessed with the history and physical examination which may include an initial evaluation with a 'pocket' Doppler or duplex scan. Such an evaluation helps to identify the presence and sites of reflux and potential occlusion of proximal veins. A proportion of patients may require additional investigation (see below).

Duplex scanning

Duplex ultrasound is superior to phlebography and is considered to be the method of choice to detect reflux in any venous segment.[56, 190-197] Imaging is usually performed with colour flow scanners using high frequency probes for superficial veins and lower frequency probes when deep penetration is required. 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 and calf veins;
2. measurement of the duration of reflux;
3. size of perforators;
4. diameter of saphenous veins;
5. size and competence of major saphenous tributaries.

Obstruction

Quantification of venous obstruction is difficult. Traditional methods that measure arm-foot pressure differential,[198] outflow fraction [199, 200] and outflow resistance by plethysmography [8] express functional obstruction but do not quantify local anatomic obstruction. Intravascular ultrasound (IVUS) and direct pressure measurements demonstrate relative degrees of obstruction at the involved venous segment more reliably, but they are 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 may include use of a 'pocket' Doppler or a color flow duplex.

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

Level III: The addition of invasive investigations or complex imaging studies including ascending and descending phlebography, varicography,

venous pressure measurements, CT scan, venous helical scan, MRI 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.

CLASS 0/1 NO VISIBLE OR PALPABLE SIGNS OF VENOUS DISEASE; TELANGIECTASIES OR RETICULAR VEINS PRESENT

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

CLASS 2 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.

CLASS 3 EDEMA WITH OR WITHOUT VARICOSE VEINS AND WITHOUT SKIN CHANGES

Level II investigations are utilized to determine 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 should be considered. Lymphoscintigraphy may be indicated to confirm the diagnosis of lymphedema in certain patients.

CLASS 4,5,6 SKIN CHANGES SUGGESTIVE OF VENOUS DISEASE INCLUDING HEALED OR OPEN 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 venous 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.

TABLE III.—*Compression classes and pressure at the ankle region as recommended by the European Prestandard of the Commité Européen de Normalisation (CEN, 2001).*

CEN class	Pressure in mmHg	Level of compression
A	10-14	Light
I	15-21	Mild
II	23-32	Moderate
III	34-46	Strong
IV	>49	Very strong

The values indicate the compression exerted by the hosiery at a hypothetical cylindrical ankle.

PART II
THERAPEUTIC METHODS

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 Velcro devices do not extend at all.[201]

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 (panty style). They may be custom-made or off the shelf and are available in standard sizes.

Different compression classes are available according to the pressure exerted. The pressure profile for each compression class varies among different countries and is measured by various non-standardized methods. The European Prestandard on medical compression hosiery proposed by the Commité Européen de Normalisation (CEN) provides five compression classes as shown in Table III.[202]

Measurement of interface pressure and stiffness in vivo [203]

There is a need to standardize measurements of interface pressures and fabric stiffness *in vivo* to allow comparison between different compres-

sion systems, both for clinical practice and research. Fabric stiffness is determined by the increase of interface pressure per centimetre increase of the leg circumference due to muscular contraction during walking or standing.[202] 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 develops a sufficiently high pressure peak during walking to enable intermittent compression of the veins while allowing a tolerable resting pressure. Bandages should maintain their nominal pressures during application for several days and nights. They should be washable and reusable.

Multilayer bandages better meet the above requirements than single layer 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 situated 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. Different devices have been developed to facilitate application of stockings. They are best put on in the morning.[204] New stockings should be prescribed after 3-6 months if used daily.

Intermittent pneumatic compression devices (IPC)

IPC devices consist of single or preferably multiple inelastic cuffs that are intermittently and/or sequentially inflated. Limited data based on randomized controlled studies are currently available demonstrating encouraging clinical outcome when IPC is used as part of the care for venous ulcers.[205]

TABLE IV.—*Effects of compression therapy.*

Parameter	Investigative method
Sub-bandage pressure	MST-tester [203, 212]
Reduced edema	Volumetry, isotopes, ultrasound [160, 213-216]
Reduced venous volume	Phlebography, blood pool scintigraphy, air plethysmography (APG) [217-222]
Increased venous velocity	Circulation time (isotopes), Duplex [223, 224]
Blood shift into central compartments	Blood pool scintigraphy, cardiac output [225]
Decreased venous reflux	Duplex, APG [220, 226]
Improved venous pump	Foot volumetry, APG, venous pressure [217, 218, 227-231]
Decreased arterial flow	Duplex, Xenon-clearance, Laser Doppler [232-234]
Effect on microcirculation	Capillaroscopy, $tcPO_2$, laser Doppler [233, 235-237]
Increased lymphatic drainage	Isotopic and indirect lymphography [238]
Effect on ultrastructure and cytokines	Microscopy and histochemistry [239-242]

Quality of life and compliance

Several studies have shown improvement in quality of life with compression treatment.[160, 162, 206, 207] Compliance is crucial to prevent ulcer recurrence.[45, 208-211] Regular daily use of compression stockings for at least two years after DVT can reduce the incidence and severerity of the post-thrombotic syndrome.[45, 210]

Mode of action

The beneficial effects of compression treatment and methods used to measure these effects are summarized in Table IV.

Clinical applications

A summary of evidence-based indications for compression therapy is listed in Table V.

Grade A recommendations for the use of compression therapy are available for management of venous ulceration and prevention of the post-thrombotic syndrome. Application of continuous compression may be contraindicated in patients with advanced peripheral arterial disease or severe sensory impairment. Grade B and C recommendations apply to other frequent indications for compression treatment such as venous edema and lymphedema (Table VI).

TABLE V.—*Evidence-based indications and grade of recommendation (A-C) for compression therapy.[243] (Below Knee Stockings Class A, I, II, III: mmHg according to CEN).*

Indication and CEAP class	References	Comparisons (0=controls)	Bandage	Stockings Class (pressure in mmHg)			
				A (10-14)	I (15-21)	II (23-32)	III (34-46)
C0S, C1 S	Weiss *et al.*, 1999 [244]	0 *vs* A *vs* I for 4 weeks		B	B		
	Vayssairat *et al.*, 2000 [160]	3-6 *vs* 10-15 mmHg for 4 weeks		B			
	Benigni *et al.*, 2003 [162]	0 *vs* A for 15 days		B			
C1 Sclerotherapy	Weiss *et al.*, 1999 [245]	0 *vs* 3 *vs* 7 *vs* 21 days				(B[1])	
	Scurr *et al.*, 1985 [246]	Stockings *vs* bandages					B
C2A	Hartmann *et al.*, 1997 [247]	Compression+physical therapy *vs* 0				C[2]	
C2S	Anderson *et al.*, 1990 [248]	Stockings *vs* drug *vs* 0					(C[3])
C2	Thaler *et al.*, 2001 [249]	0 *vs* I *vs* II			B	B	
Pregnancy	Young and Jewell, 2000 [250]	External pneumatic compression *vs* 0					C
C2 Surgery	Shouler *et al.*, 1989 [251]	I *vs* III			C		C
	Travers *et al.*, 1994 [252]	0 *vs* II				C	
	Rodrigus, 1991 [253]	Bandages 1 *vs* 3 *vs* 6 weeks	(C[1])				
	Bond *et al.*, 1999 [254]	Bandages *vs* A *vs* III	(C[4])	(C[4])			(C[4])
	Raraty *et al.*, 1999 [255]	Bandages *vs* A	C				
	Travers *et al.*, 1993 [256]	Bandages *vs* bandages	C[5]				
C2 Sclerotherapy	Shouler *et al.*, 1989 [251]	I *vs* III			C		C
	Scurr *et al.*, 1985 [246]	Bandages *vs* III					B
	Stanley *et al.*, 1991 [257]	Local pads	(C[6])				
C3	Diehm *et al.*, 1996 [258]	II *vs* drug				B[7]	
C4b (LDS)	Vandongen *et al.*, 2000 [259]	0 *vs* II				B	
C5	Nelson *et al.*, 2000 Review* [209]	Multiple			B	B	B
C6	Cullum *et al.*, 2001 Review* [173]	Multiple	A			B	
	Cochrane Reviews Review* [260-269]	Multiple		A-B	A-B		
DVT Therapy	Aschwanden *et al.*, 2001 [270]	0 *vs* bandages	B				
	Partsch and Blattler, 2000 [271]	0 *vs* II *vs* bandages	B			B	
PTS Prevention	Brandjes *et al.*, 1997 [45]	0 *vs* III					A
	Ginsberg *et al.*, 2001 [272]	0 *vs* A *vs* I		(B[8])	(B[8])		
	Prandoni *et al.*, 2004 [210]	0 *vs* II				A	
	Kolbach *et al.*, 2003 [273]	Intermittent pneumatic compression					C
Lymphedema	Badger *et al.*, 2000 [274]	Bandages *vs* stockings	B				
	Johansson *et al.*, 1999 [275]	Bandages *vs* bandages + MLD	(B[9])				
	Bertelli *et al.*, 1991 [276]	II *vs* II+electric stimulation				(C[10])	
	Andersen *et al.*, 2000 [277]	III *vs* III+MLD					(C[11])
	Badger *et al.*, 2004 [278]	Multiple	C				
	McNeely *et al.*, 2004 [279]	Bandages *vs* bandages + MLD	C				

*Cochrane reviews. MLD: manual lymph drainage. The level of recommendation as plotted in the table also indicates the class of compression applied. [1]Variable duration of the same compression compared. [2]Compression+physical therapy compared with no therapy. [3]Stocking + drug better than either treatment on its own. [4]Comparison between 3 types of compression for one week: no difference of pain level. [5]Panelast had less bleeding than non-adhesive crepe. [6]Comparison of different pads under the same bandage. [7]No significant difference between drug and stocking. [8]"Placebo" stocking =1-2 sizes too large stocking. [9]Both groups had bandages, MLD+bandage is more effective than bandage alone. [10]Both groups had stockings, additional electrostimulation: no benefit. [11]Both groups had sleeves, MLD does not add benefit.

TABLE VI.—*Summary of clinical studies on compression and the effect of addition of IPC.*[280]

Authors	Number of patients (N.)	Type of Compression	Type of IPC	Result
Hazarika *et al.*, 1981 [281]	21	Compression bandage	Flowtron Mk2 (A/C2002)	Subjective improvement
Dillon, 1986 [282]	17	—	The circulator boot system An end-diastolic pneumatic compression boot	All patients improved or healed
Pekanmaki,1987 [283]	8	Elastic bandage	Sequential and graded pressure IPC	Shortens ulcer healing time markedly (P<0.05)
Coleridge Smith *et al.*, 1990 [284]	45	GEC	SCD (Kendall) [1]	Increased ulcer healing rate (P<0.05)
McCulloch *et al.*, 1994 [285]	22	Unna boot	A single chamber IPC [2]	Improved healing rate
Schuler *et al.*, 1996 [286]	53	Unna boot	GEC/IPC (HomeRx, Kendall)	Equally effective in ulcer healing rates
Rowland, 2000 [287]	16	Compression bandage	IPC	Equally effective in ulcer healing rates
Kumar *et al.*, 2002 [288]	47	4-layer bandage	IPC	Faster healing (P<0.05)
Alpagut and Dayoglou, 2005 [289]	76	GEC	Flowtron plus (AC2002)	IPC shortens mean treatment time and improves quality of life
Nikolovska *et al.*, 2005 [290]	104	—	Rapid *versus* slow IPC	Rapid IPC healed ulcers more rapidly (P=0.0002) and in more patients (P=0.003) than slow IPC

[1]Compression stockings (30-40 mmHg) plus sequential IPC used daily, achieved healing in 10 over 21 (48%) patients after 3 months *versus* 1 over 24 (4%) among the control (P=0.009). [2]Unna boot plus IPC used one hour twice weekly, n=12, (50 mmHg, inflation 90 seconds, deflation 30 seconds) achieved a healing rate of 0.15 cm^2/day *versus* 0.08 cm^2/day in the control limbs, n=10, (P<0.05). After 3 months follow up all limbs receiving IPC healed (12 over 12) *versus* 8 over 10 in the control group.

Drugs

VENOACTIVE DRUGS

Introduction

Venoactive drugs (VADs) are a heterogenic group of drugs from vegetal or synthetic origin (Table VII).[291, 292]

Numerous randomized controlled double blind studies have demonstrated the anti-edematous effect and effective attenuation of symptoms of CVD such as heavy legs, pain and restless legs by VADs so that they have become an established component of the therapeutic armamentarium for all stages of disease. VADs may accentuate the effects of compression on symptoms and some of them accelerate healing of leg ulcers.

Mode of action

VADs have two pathophysiological mechanisms of action. They alter macrocirculatory changes in the venous wall and venous valves that cause hemodynamic disturbances to produce venous hypertension[6] and they alter microcirculatory effects of venous hypertension that lead to venous microangiopathy.[6] The mode of action varies depending on the drug product.

Action at the macrocirculatory level

Mechanisms of action on the venous wall and valves are summarised in Table VIII.[293-325] Until recently, the most popular theory was that weakness of the vein wall produced venous dilatation causing secondary valvular incompetence. For this reason, research on VADs was focused for a long time on their effect on venous tone. Most VADs have been shown to increase venous tone by a mechanism related to the noradrenaline pathway. Micronized purified flavonoid fraction (MPFF) [293, 294, 303-305] prolongs noradrenergic activity, hydroxyethylrutosides [295, 314] act by blocking inactivation of noradrenaline, and ruscus extracts

TABLE VII.—*Classification of the main venoactive drugs.*

Group	Substance	Origin	Dosage (mg/day)	Number of doses/day
Benzopyrones				
Alpha-benzopyrones	Coumarin	Melilot (*Melilotus officinalis*) Woodruff (*Asperula odorata*)	90 combined with troxerutin (540)	3
Gamma-benzopyrones (flavonoids)	Diosmin	Citrus spp. (*Sophora japonica*)	300-600	1 or 2
	Micronised purified flavonoid fraction	*Rutaceae aurantiae*	1000	1 or 2
	Rutin and rutosides	*Sophora japonica*	1000	1 or 2
	O-(β-hydroxyethyl)-rutosides (troxerutin, HR)	*Eucalyptus spp.* *Fagopyrum esculentum*		
Saponins	Escin	Horse chestnut (*Aesculus hippocastanum* L)	Initially 120, then 60	3
	Ruscus extract	Butcher's broom (*Ruscus aculeatus*)	2 to 3 tablets	2 to 3
Other plant extracts	Anthocyans	Bilberry (*Vaccinium myrtillus*) Grape pips (*Vitis vinifera*)	116	2
	Proanthocyanidins (oligomers)	Maritime pine (*Pinus maritima*)	100 to 300 300 to 360	1 to 3 3
	Extracts of Ginkgo, heptaminol and troxerutin	Ginkgo biloba	2 sachets	2
Synthetic products	Calcium dobesilate	Synthetic	1000 to 1500	2 to 3
	Benzaron	Synthetic	400 to 600	2 to 3
	Naftazon	Synthetic	30	1

[296-302] act by agonism on venous α1-adrenergic receptors. A high affinity for the venous wall was found for MPFF [326] and hydroxyethylrutosides.[309-311] The precise mechanism by which other drugs increase venous tone is not known.

More recently, as indicated in Part I, it has been realized that chronic venous disease is related to primary failure of venous valves that are affected by inflammation.[308, 327] Currently available drugs have been shown to attenuate various elements of the inflammatory cascade, particularly the leucocyte-endothelial interactions [306, 317-319, 322, 325] that are important in many aspects of the disease.[63, 328, 329] Results of a recent trial performed on an animal model of acute venous hypertension revealed that MPFF showed an anti-inflammatory effect under this acute situation that may result in protection of venous valves in chronic conditions.[307]

Action on the microcirculation.-VAD effects on capillary resistance, lymphatic drainage, protection against inflammation, and blood flow are summarized in Table IX.[330-395]

Capillary resistance.—Numerous studies have shown that VADs are able to increase capillary resistance and reduce capillary filtration. This is seen for MPFF,[330-347] rutosides,[351-355] escin,[379] ruscus extracts,[349, 350, 356] proanthocyanidines,[348, 358, 359] and calcium dobesilate.[382-385] The capillary protective effect of MPFF may be related to inhibition of leukocyte adhesion to capillaries.[334, 335, 343, 345-347] This is enhanced by micronisation.[364]

Lymphatic drainage.—The efficacy of coumarin on lymphedema has been described by Casley Smith.[395] Coumarin combined with rutin reduce high protein edema by stimulating proteolysis.[377] MPFF improves lymphatic flow and increases the number of lymphatic vessels [361-363] and calcium dobesilate enhances lymphatic drainage.[386-389]

Protection against inflammation.—In animal models of skin inflammation, VADs appear to attenuate the inflammatory response by various mechanisms. Numerous reports have confirmed free-radical-scavenging, anti-elastase and anti-hyaluronidase properties of most VADs (rutosides,[357, 360] escin,[380] ruscus extracts,[381] proanthocyanidines,[358, 359] calcium dobesilate,[390-392] and MPFF [366-368]).

TABLE VIII.—*Modes of action of venoactive drugs on venous tone and the venous wall.*

Group	Compound	Effect on venous tone	Effect on venous wall and venous valve
Benzopyrones			
Gamma-benzopyrones (Flavonoids)	Micronised purified flavonoid fraction	Increases venous tone by prolonging noradrenergic activity [293, 294, 303-305]	Protects human saphenous endothelial cells from hypoxia [306]
		Attracted to venous endothelium [326]	Prevents appearance of reflux by inhibiting the adhesion of leukocytes on the endothelium of the wall and venous valve [307]
	Rutin and rutosides O-(β-hydroxyethyl-rutosides (troxerutin, HR)	High affinity for venous wall [309-311] increases venous wall tone [314] by blocking the inactivation of noradrenaline [295]	—
Association of α-benzopyrones and γ-benzopyrones	Coumarine and rutin	Increase of venous flow [312]	—
Saponins	Escin (Horse chestnut seed extract)	Increases venous wall tone [313-316]	Protects human saphenous endothelial cells from hypoxia [317, 318]
	Ruscus extract	Venoconstrictive effect [302] and by agonism on venous α1-adrenergic receptors [296-301]	Protects human saphenous endothelial cells from hypoxia [319]
Other plant extracts	Proanthocyanidines (oligomers) (*Vitis vinifera*)	—	— Protects endothelial cells against hypoxia [306]
	Pycnogenol (Pinus maritima Lank)	Petrassi,[320]	—
	Ginkgo biloba	—	Protects human saphenous endothelial cells from hypoxia [306, 321, 322]
Synthetic products	Calcium dobesilate	Increases venous tone [323, 324]	—
	Naftazone	—	Accelerates endothelial cells proliferation [325]

Hemorrheological disorders.—Hemorrheological changes are constant in CVD appearing as a basic trait with increased blood viscosity due to plasma volume contraction and increased fibrinogen as a consequence of inflammation.[396] The presence of huge red cell aggregates in the vicinity of venules reduces blood flow to cause poor oxygen delivery from red cells. Erythrocyte aggregability and blood viscosity increase with greater severity of disease.[396] Some VADs limit red cell aggregation (Gingko biloba),[396] decrease blood viscosity (MPFF,[374, 375] calcium dobesilate,[394]), and increase red cell velocity (MPFF).[375]

Therapeutic efficacy of oral VADs on venous-related symptoms

The main indications for VADs are symptoms related to varicose veins or attributed to CVD (heavy legs, "heaviness", "discomfort", pruritus, pain along varicose vein paths) or less specific but frequently associated symptoms (paresthesiae, night time cramps or restless leg syndrome) and edema.[292, 396, 397]

Two reviews of VADs published recently by Martinez *et al.*. [398] (Cochrane review) and by Ramelet *et al.*. [291] studied the efficacy of the drugs in detail. The paper by Ramelet *et al.* represented proceedings of an International Medical Consensus Meeting on "Veno-active drugs in the management of chronic venous disease" held in the framework of the 13th Conference of the European Society for Clinical Hemorrheology (ESCH) in Siena, Italy.[291]

Data from randomized, double-blind, placebo-controlled trials (RCTs) for the efficacy of VADs at any stage of disease were extracted by independent reviewers who also assessed the quality of trials according to quality criteria specified in the Cochrane Handbook [398] or evidence-based

TABLE IX.—*Modes of action of the main venoactive drugs on the microcirculation, lymphatic network and other areas.*

Group	Compound	Effect on capillary leakage	Effect on lymphatic network	Anti-inflammatory effect	Hemorrheologic parameters
Benzopyrones					
Gamma-benzopyrones (Flavonoids)	Micronised purified flavonoid fraction	Reduces capillary hyperpermeability.[330-333, 336-342] The underlying mechanism is an inhibition of leukocyte adhesion to capillaries.[334, 335, 343, 345-347] The capillary protective effect is enhanced by micronisation [344]	Increases lymphatic flow and number of functional lymphatic vessels [361-363]	Reduces release of inflammatory mediators.[364-369] The mechanism is by inhibition of the rolling and thus the adhesion of leukocytes at the level of the microcircula-tion [63, 328, 370-372]	Decreases hemoconcentration [373, 374] and increases red cell velocity [375]
	Rutin and rutosides O-(β-hydroxye-thyl-rutosides (troxerutin, HR)	Reduces capillary hyperpermeability [351, 352, 376]	—	Inhibits free radical generation [353]	
Association of α-benzopyro-nes and γ-benzopyrones	Coumarine and rutin	Beneficial effects on the microcirculation [357 355]	Stimulates high-protein edema proteolysis [354, 377] Increases lymphatic flow [312]	—	—
Saponins	Escin	Decreases capillary filtration [378]	—	Free radical scavenging properties. [379, 380] Anti-elastase and anti-hyaluronidase properties [381]	—
	Ruscus extract	Antipermeability effect [349, 350, 356]	—	—	—
Other plant extracts	Proanthocyanidines (oligomers)	Reduces hyperpermeability [348, 358]	—	Free radical scavenging effect [359]	
	Ginkgo biloba	—	—	—	Improves hemorrheology [360]
Synthetic products	Calcium dobesilate	Increases capillary resistance [382, 383] by mitigating reactive oxygen species in capillaries [384] and histamine effect [385]	Improves lymphatic drainage [386-388]	Anti-oxydant and angioprotective effects. [389-391] Enhances nitric oxide synthetase activity in endothelial cells [392]	Decreases blood viscosity [393, 394]
	Naftazone				
	Synthetic diosmins				

medicine predefined criteria or their own experience.[291] Outcomes included edema, venous ulcers, trophic disorders, and symptoms (pain, cramps, restless legs, itching, heaviness, swelling and paraesthesiae) [398] or symptoms only at any stage of the disease.[291]

Many VADs consisting of natural products (flavonoids: rutosides, french maritime pine bark extract, grape seed extract, micronized diosmine and hidrosmine, disodium flavodate; saponosides: centella asiatica) and synthetic products (calcium dobesilate, naftazone, aminaftone and chromocarbe) [398] were explored. Escin was excluded from the Cochrane review of Martinez *et al.*. [398] but was evaluated in the Cochrane review of Pittler and Ernst [399] and was covered by the consensus paper.[291]

Studies were classified as level I (low risk of

TABLE X.—*Summary of VAD effects on symptoms, edema and skin changes by category of drugs (adapted from ref.[291, 398, 399]).*

Compound	Positive results* on the following indications [398, 399]	Randomised Controlled Trials (RCTs) [398, 399]	Recommendation [291]**	Trials and Meta-analyses [291]**
Calcium dobesilate	Cramps, restless legs, sensation of swelling, edema	Marinello and Videla, 2004 [405] Casley Smith *et al.*, 1988 [410] Hachen and Lorenz, 1982 [407] Widmer *et al.*, 1990 [406]	Grade A	Labs *et al.*, 2004 [424] Ciapponi *et al.*, 2004 [425]
MPFF	Pain, cramps, heaviness, sensation of swelling, trophic changes, venous leg ulcer	Danielsson *et al.*, 2002 [400] Gilly *et al.*, 1994 [408] Guilhou *et al.*, 1997 [411] Laurent *et al.*, 1988 [412] Tsouderos, 1989 [420]	Grade A	Coleridge-Smith *et al.*, 2005 [445]
Hydroxyethyl-rutosides	Itching, edema	Van Cauwenberge, 1972 [402] de Jongste *et al.*, 1989 [457] MacLennan *et al.*, 1994 [458] Burnand *et al.*, 1989 [459] Cloarec *et al.*, 1996 [403] Pulvertaft, 1983 [414] Balmer and Limoni, 1980 [417] Pedersen *et al.*,1992 [418] Schultz-Ehrenburg and Muller, 1993 [419] Unkauf *et al.*, 1996 [409]	Grade A	Unkauf *et al.*, 1996 [409] Kranendo *et al.*, 1993 [426] Grossmann, 1997 [427] Poynard and Valterio, 1994 [428]
Escin, HSCE	Pain, edema	—	Grade B	Diehm *et al.*, 1996 [258] Pittler and Ernst, 2006 [399] Siebert *et al.*, 2002 [429]
Ruscus extracts	Pain, edema	Parrado and Buzzi, 1999 [421] Vanscheidt *et al.*, 2002 [415]	Grade B	Boyle *et al.*, 2003 [430]
Synthetic diosmins			Grade C	Carpentier et Mathieu, 1998 [431]
Troxerutin		Vin *et al.*,1994 [422]	Grade C	Rehn *et al.*, 1993 [432]
Gingko biloba	—	—	Grade C	
Proanthocyanidines	Pain	Ihme *et al.*, 1996 [404] Arcangeli, 2000 [416] Petrassi *et al.*, 2000 [320]	Grade C	Kiesewetter *et al.*, 2000 [433]
Troxerutin-coumarin	—	Vanscheidt *et al.*, 2002 [415]	Grade C	
Naftazone	—	—	Grade C	Vayssairat *et al.*, 1997 [434]

MPFF: micronized purified flavonoid fraction; HCSE: horse chestnut seed extract. *Homogeneity of results with relative risk (RR) <1; **only symptoms have been considerred.

bias), level II (moderate risk of bias) or level III (high risk of bias).[398] Alternatively, they were associated with grade of recommendations: grade A (RCTs with large sample sizes, meta-analyses combining homogeneous results), grade B (RCTs with small sample size, single RCT) or grade C (other controlled trials, non-randomized controlled trials).[291]

One hundred and ten RCTs were identified in the Cochrane review,[398] but eventually only 44 of them were included in the efficacy analysis. Eighty three trials of VADs were analysed in the consensus paper [291] with 31 of these retained [258, 399, 400, 403, 406, 408-411, 415, 421-434] for assessing the grade of recommendations for each medication (25 RCTs and 6 meta-analyses). The efficacy of VADs on both symptoms and signs related to CVD estimated by relative risk applying a random effects statistical model is displayed in columns 2 and 3 of Table X [398] with the grade of recommendations per individual medication shown in columns 4 and 5.[291]

One of the limitations in the Cochrane reviews [398] is that while all studied the full spectrum of conditions seen in CVD, only 23% of the studies reported the diagnostic classification used. Of the

studies that did report it, Widmer's classification was used most frequently,[403, 409, 410, 415, 421] followed by the CEAP classification.[400, 405] Only symptoms were considered in the consensus paper [291] allowing a better uniformity of outcomes.

Therapeutic efficacy of oral VADs on edema of venous origin

Although edema is a non-specific sign, it is one of the most frequent and typical complaints of CVD. All other causes should be excluded to confirm the venous origin of edema. Chronic venous disease-related edema is described as a sporadic unilateral or bilateral edema limited to the legs which may also involve proximal parts of the lower extremities. It is enhanced by prolonged orthostatic posture and improved by leg elevation.[435]

Several well-conducted, controlled trials *versus* placebo [404, 406, 412, 415, 436-438] or stockings [409, 439] have shown efficacy of oral VADs such as micronized purified flavonoid fraction,[412] rutosides,[436, 437, 439] horse chestnut seed extract,[438] calcium dobesilate,[406] proanthocyanidines [404] and coumarin rutin.[415] In these trials, evaluation of the anti-edema efficacy was based on objective measures such as leg circumference assessment, strain-gauge plethysmography and water displacement. Other large-scale trials performed internationally,[154] on air-travel edema,[440, 441] on healthy volunteers [432] or in patients with varicose veins or postthrombotic syndrome [442] have shown the value of VADs in reducing leg edema. Results of meta-analyses have confirmed the anti-edema efficacy of such medications.[398, 443]

Pharmacological treatment of leg ulcers

Healing of venous leg ulcers (stage C6) has been shown to be accelerated in double-blind studies using "micronised purified flavonoid fraction"(MPFF).[187, 411, 444] This was confirmed in 2005 by a meta-analysis of 5 trials using MPFF as an adjunct to standard treatment in 723 patients of stage C6 of the CEAP classification.[445]

Among VADs, the use of horse chestnut seed extract or of hydroxyrutosides failed to demonstrate superiority over compression in advanced chronic venous insufficiency [258, 446] or in preventing venous ulcer recurrence.[447]

A small number of other drugs have been used with varying success. Stanozolol, a fibrinolytic anabolic steroid was expected to break down pericapillary fibrin cuffs but did not increase the rate of ulcer healing.[448] Abnormalities of coagulation observed in patients with venous disease have been improved by aspirin [449] but there is a lack of data supporting its use for preventing thromboembolic events in patients with CVD.[6] A thromboxane receptor antagonist (Ifetroban) failed to show benefit over compression therapy in ulcer healing.[450] Several trials have suggested that pentoxifylline may improve venous ulcer healing rates although the magnitude of the effect appears to be small and its role in patient management is unclear.[6, 451, 452]

Safety of oral VADs

Safety of VADs is in general good, except for hepatotoxicity from coumarin and benzarone. Adverse events most commonly associated with VADs are gastrointestinal (*e.g.* abdominal pain, gastric discomfort, nausea, dyspepsia, vomiting and diarrhoea) or autonomic (*e.g.* insomnia, drowsiness, vertigo, headache and tiredness). They occur in approximately 5% of patients treated (Table XI).[453-455] Some VADs have been used without any problems during the second and third trimester of pregnancy but there are no long-term series documenting this. Thus, caution is recommended when administering VADs to patients who are breast feeding because of absence of data concerning diffusion of these medications into breast milk.

Indications for oral VADs

In France where VADs are widely prescribed, recommended prescribing practices for "Venotropics in venous insufficiency of the legs" [456] state that it is not appropriate to prescribe VADs in the absence of disease-related symptoms (heavy legs, pain, restless legs on going to bed) or in varicose veins if they are not associated with symptoms. In addition, VADs should not be prescribed for more than 3 months except in the event of recurrence of symptoms after treatment discontinuation. It is not appropriate to combine several VADs in the same prescription.

Although trials of VADs on the improvement of symptoms are numerous, the anti-edema effect of VADs has been objectively demonstrated in dou-

TABLE XI.—*Adverse effects of VADs - (reproduced from Ramelet* et al.*, 2004 [292]).*

Coumarin* and O-(β-hydroxyethyl)rutosides	Hepatotoxicity (high-dose coumarin alone) Gastrointestinal disorders Skin rash
Rutin and rutosides O-(β-hydroxyethyl)rutosides	Gastrointestinal disorders Skin rash
Escin (horse chestnut)	Gastrointestinal disorder Urticaria
Ruscus extracts	Gastrointestinal disorders
Anthocyans	Gastrointestinal disorders
Proanthocyanidines and Pycnogenol	Gastrointestinal disorders Skin rash
Ginkgo biloba	Gastrointestinal disorders Skin rash
Diosmin and micronised purified flavonoid fraction	Gastrointestinal disorders Skin rash
Calcium dobesilate	Gastrointestinal disorders Skin rash Fever
Benzarone	Photosensitization Skin rash Gastrointestinal disorders Hepatitis
Naftazone	Gastrointestinal disorders Headache Dizziness

*Coumarin is not identical with dicoumarol, which has also potential hepatotoxicity. Coumarin has no anticoagulant effect.

ble-blind trials. VADs may be indicated as a first-line treatment for CVD-related symptoms and edema in patients at any stage of disease. In more advanced stages, VADs may be used in conjunction with sclerotherapy, surgery and/or compression therapy.[291, 453]

A meta-analysis of micronised purified flavonoid fraction further confirmed its valuable contribution for healing leg ulcers as an adjunct to standard treatment.[445]

Combination of oral VADs with other methods such as compression

VADs may accentuate the effect of compression. A double-blind trial demonstrated that the combination of compression and VADs was more effective than compression alone [409, 439] and may be prescribed instead of compression when compression is contra-indicated as in the presence of arterial insufficiency or neuropathies or where compression is poorly tolerated (individual reactions, summer heat). There is only one randomized study comparing VADs *versus* stockings to prevent edema.[258]

Topical treatment

VADs and heparinoids are blended in topical preparations. The formulation, especially in gels, has a relieving effect on some symptoms. Natural heparin and heparinoids have anti-inflammatory properties, an analgesic effect by inactivating histamine, and anti-thrombotic effects. The transcutaneous effectiveness of VADs and heparinoids depends on their concentration. Several brands are associated with other active substances such as polidocanol or a local anesthetic agent. A double blind study has been performed to prevent edema in long flights with a rutoside gel, which proved to be more effective than its excipient.

Other drugs

Pentoxifilline

Method of action.—Pentoxifylline is a vasoactive drug that reduces leucocyte adhesion and has rheological action on erythrocytes and a mild fibrinolytic action.[460]

Effectiveness.—In a systematic review, Jull *et al.*. identified 8 clinical trials (547 adults) published from 1983 to 1999 comparing pentoxifylline to placebo, either associated with compression (n=445) or not (n=102).[461] They conclude that "our results suggest that pentoxifylline gives additional benefit to compression for venous leg ulcers, and possibly is effective for patients not receiving compression". However, positive global findings are strongly influenced by old studies with obsolete methodology. Diagnostic methods confirming a venous etiology of the ulcers are not reported in 2 of the 8 trials; while the diagnosis is based on clinical signs only in 4 and by Doppler ultrasound in only 2 of the 8 trials.

Results of recent studies are not conclusive. One trial with pentoxifylline and placebo did not reach statistical significance.[452] However, the placebo double blind studies of Falanga [462] and Belcaro [463] indicated that pentoxifylline was effective for healing leg ulcers. In an open randomized trial with debatable methodology (inpatients were not distinguished from outpatients), Nikolovska [464] obtained good results from treating ulcers with pentoxifylline in the absence of compression. In one study,[462] a higher dose of pentoxifylline (800 mg three times a day) was more effective than the lower dose (1200 mg daily).

Combination with other methods such as compression.—Pentoxyfilline therapy increased the rate of ulcer healing when combined with compression in some studies [451, 452, 462, 463, 465, 466] or given on its own.[464, 467] However, the use of such an adjuvant drug without adequate compression therapy should be considered only when compression is not tolerated or contra-indicated.

General recommendations for use.—Although pentoxyfilline is relatively well tolerated, its value for treating leg ulcers remains debatable until new data become available.

Prostaglandins E

Introduction.—Few studies have been devoted to the efficacy of prostaglandins (PG) for venous leg ulcers. Systemic or local PG are rather indicated for arterial ischemic ulcers. The method of action of PG is not well defined in published trials. Probable actions may include small vessel dilatation and augmented blood flow in the capillaries, increased fibrinolytic activity, effects on reducing platelet and leucocyte aggregation and adherence to endothelium, and reduction of white cell activation.

Intra-venous PGE.—In a double-blind, placebo-controlled study by Rudofsky,[468] 42 patients were randomly given either one i.v. infusion over 3 hours of 3 ampoules of Prostavasin (60 micrograms PGE1) or 3 ampoules of placebo daily diluted in 250 ml saline over a 6 week period. In the PGE1 group (n = 20) there was a significant improvement in the ulcer status compared to placebo (n = 22) ($P<0.001$) being assessed by a detailed, multivariated score. Ulcers healed completely in 8 out of 20 patients on PGE1 (40%) compared to only 2 out of 22 patients on placebo (9%). Concomitant clinical symptoms also improved. In the PGE1 group, edema completely resolved in 17 of 20 patients (85%) whereas this occurred in only 7 of 20 patients in the placebo group (35%). Calf cramps were controlled in 80% and 87.5% respectively and eczema in 50% and 9% respectively. Parallel to this was an increase of $tcPO_2$ in the ulcer area by a mean of 46%. No side effects were noted after PGE1 infusion throughout the treatment period.

Topical PGE2.—Eriksson *et al.*[469] applied topical PGE2 dispersed in hydrocolloid granules in 9 patients with chronic leg ulcers and evaluated the healing process by stereophotogrammetry. Ulcers healed completely in eight patients after topical application and almost completely in the ninth.

Topical prostacyclin analogues - Iloprost.—In a multicenter, randomized, double-blind, placebo-controlled study in patients with venous leg ulcers, the efficacy and tolerability of topical applications of a prostacylin hydrogel (iloprost) was investigated [470] with 34 patients allocated to placebo treatment and 65 patients to iloprost treatment given in two concentrations. Both iloprost concentrations were well tolerated. In a second paper,[471] the same team compared placebo to two iloprost concentrations in a larger number of patients with 49 patients allocated to treatment 1 (placebo solution), 49 patients to treatment 2 (0.0005% iloprost solution) and 50 patients to treatment 3 (0.002% iloprost solution). The solu-

tions were applied to the ulcer edge and surrounding skin twice weekly for eight weeks. No significant difference was found in favor of the iloprost treatment in either study.

Absorption of topical iloprost may be variable. In a study by Meyer,[472] iloprost could not be detected in the plasma in 40% of patients, whereas iloprost was absorbed through the ulcer base in variable degrees in the others. There was no direct relation between the ulcer size and amount of iloprost absorbed.

Intravenous or perilesion injection of PGE1.—In a study by Tondi,[473] 80 patients suffering from ischemic ulcers were enrolled. Treatment for 25 patients was with injection of low doses of alprostadil around the ulcers and intravenous saline infusion, and in a further 25 by intravenous alprostadil infusion and local injections of saline, while the control group of 30 patients received saline injections around the ulcers and intravenous saline infusions. All patients treated with PGE1 showed statistically significant improvement in ulcer diameter, pain, and transcutaneous oxygen pressure compared to controls. Both intravenous and local subcutaneous alprostadil may be useful for treating ischemic leg ulcers, but subcutaneous administration is less expensive and easier to perform. A similar study in patients with venous ulcers has not been performed.

Indications.—Chronic leg ulcers (C6) may be an indication for either intravenous or topical PG but there are only few data on this topic and no recent studies for venous ulcers.

General recommendations for use of PG.—As the efficacy has not yet been fully demonstrated, no recommendation can be made.

Topical therapy for venous ulcers

A wide range of topical agents and dressings has been advocated to promote desloughing, granulation and re-epithelialization of venous ulcers, including hydrogels, alginates, hydrocolloids, enzymatic agents, growth factors, foams and films.[474-498] Tissue-engineered skin equivalents based on cultured keratinocytes and fibroblasts have been shown to accelerate healing.[499-501] However, there is no level I evidence that the other agents 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.[474, 502] However, systemic antibiotics are indicated in the presence of β-hemolytic streptococcus and evidence of soft tissue infection. Topical antiseptics exhibit cellular toxicity that exceeds their bactericidal activities and they have been found to impair wound epithelialization.[503]

Sclerotherapy

Liquid sclerotherapy

Outcome after treatment of varicose veins is commonly described by the rate of recurrence. It is generally accepted that sclerotherapy is effective for treating C1 and some C2 CVD. However, sclerotherapy is reported to fail for all other clinical levels with increased frequency the longer patients are followed reaching 90% at 10 years.[504-507] In this respect, randomized trials have shown surgery to be superior to sclerotherapy for treating main stem GSV and SSV disease [508-510] unless the incompetent saphenofemoral junction is ligated first.[504, 505] Ultrasound-guided techniques may improve early results [511, 512] but long-term benefit has not been established.[513] In practice, sclerotherapy is frequently combined with other interventions.

Foam sclerotherapy

When delivered as foam, detergent sclerosant is more active within the vein because it is not diluted by blood and persists in the treated vessels. Foam can be readily visualized by ultrasound and can be used to treat C2-C6 CVD.[514-516] Results out to more than 5 years demonstrate clinical effectiveness rates exceeding 80%.[517-519] Foam has been shown to be superior to liquid sclerotherapy in the GSV in terms of clinical and hemodynamic outcome.[520, 521] Treatment of C4-6 has been particularly rewarding.[518, 522] There are two RCT's published. Varisolve foam sclerotherapy was superior to conventional sclerotherapy, but surgery was superior to Varisolve sclerotherapy.[523] In the second study foam sclerotherapy combined with sapheno-femoral ligation was less expensive,

involved a shorter treatment time and resulted in more rapid recovery than high ligation and stripping.[524] Serious complications including DVT appear to be uncommon.[525] One case of ischemic stroke in a patient with a patent foramen ovale has been reported.[526]

Endovascular therapy

Various electrosurgical devices have been used in an endeavor to develop a minimally invasive alternative for treating varicose veins, first introduced by Politowski.[527] All employed monopolar energy either via an extravenous [528-531] or endovenous route.[532-534] Full-thickness skin burns, saphenous nerve injuries and recurrence were common postoperative complications.[535]

More recently, radiofrequency (RF) ablation using bipolar energy has evolved for endoluminal obliteration for GSV reflux.[536-538] With growing experience, RF can also be used to treat refluxing side branches of the GSV [539] and recurrent varicose veins where an incompetent GSV persists.[538] A new RF catheter named Closure FAST™ is now available which speeds up the procedure (Supplement to Endovascular Today, January 2007). The 810nm diode laser was FDA approved for endovenous laser treatment (EVLT) in 2002 followed by the 940, 980, 1064 and 1320 nm lasers. In the treatment of varicose veins both procedures are used in conjunction with phlebectomies or sclerotherapy.

Mode of action

RF ablation induces resistive heating (85°C) causing contraction of collagen fibres with associated circumferential endothelial denudation and muscle necrosis.[539] EVLT uses thermal energy to boil blood producing thermochemical destruction of the venous wall.[540]

Method

RF ablation can be performed under local, tumescent, regional or general anesthesia. EVLT is performed under tumescent anesthesia to prevent thermal injury to the skin and saphenous nerve. Both methods involve prograde introduction of a catheter through a venepuncture at the ankle or knee level under ultrasound guidance.[537, 539, 541] Duplex ultrasound is indispensable not only to assess the patient's suitability for the procedure (usually a straight GSV with no tortuous or thrombosed sections) but also as a procedural tool to assess catheter tip position and as a post procedural tool to confirm the immediate and long-term efficacy of this technique.[536, 539, 542-544] It should be noted that the Laser fiber cannot be identified with duplex ultrasound. There are many studies comparing RF to EVLT.[545-555]

Complications

Transient sensory disturbances are the most common problem following VNUS closure although the rate can be reduced by ultrasound-guided tumescent infiltration of especially superficial segments of the GSV that reduces the thermal insult to perivenous tissue during treatment. Recanalization of the GSV, treatment failure, skin burns and common femoral vein stenosis are potential complications but should not occur in the hands of an experienced operator. Clinical DVT is an uncommon postoperative complication.[537, 538, 543, 556] However, Hingorani *et al.* and Mozes *et al.* found a 16% and 7.7% DVT rate respectively on routine screening using ultrasound.[557, 558]

Results

Single center studies [538, 559, 560] reported a GSV occlusion rate at 1 and 2 years between 90 and 99% after RF. One multicentre study involving 1222 limbs from 34 clinical sites achieved complete occlusion of GSV in 87% of 117 patients at 5 years.[561]

In a systematic review article involving 18 clinical studies for treatment of varicose veins by EVLT, occlusion of the saphenous vein abolition of venous reflux occurred in 88-100% of limbs with low rates of recanalization and retreatment.[562] Vuylsteke *et al.*[563] have also reported their experience.

Two randomized controlled trials demonstrated that endovenous obliteration by RF with additional phlebectomies or sclerotherapy appears to provide a safe and effective minimally invasive method avoiding the morbidity of the traditional high ligation and stripping of the GSV. It is also associated with reduced postoperative pain and a shorter return to work and to normal daily activities in comparison to conventional varicose vein surgery.[559, 564, 565] This was confirmed in a German randomized controlled trial where RF ablation

was superior to surgery [566] and in a British study on patients with recurrent varicose veins after previous bilateral high ligation without stripping where their recommendation was that RF ablation should be considered the treatment of choice for recurrent GSV veins.[567] There are more studies comparing RF to classical surgery.[568-570]

There are two randomized controlled trials [571,572] and a non-randomized trial [573] comparing EVLT with surgery showing that laser ablation is safe and well tolerated with results comparable to conventional stripping.

There is one RCT comparing RF with laser ablation showing a significantly higher occlusion rate of GSV for the RF group after 1 year.[549]

Surgery

Surgery for varicose veins

The goals of surgery are to relieve presenting symptoms, prevent adverse effects of continuous venous hypertension, and normalize venous physiology by eradicating main stem reflux and removing visible varices.

There is no indication for surgery in patients with C0 and C1 CVD. In patients with superficial reflux causing C2 to C6 CVD, flush ligation and division of the saphenofemoral junction (SFJ) combined with stripping of the GSV to the knee [574-581] is clearly superior to SFJ ligation alone.[577, 582, 583] Treatment of superficial reflux involving the SSV usually involves saphenopopliteal junction (SPJ) ligation and division following pre-operative duplex marking. Stripping of the SSV and of the GSV below knee may reduce VV recurrence but are associated with increased risk of sural or saphenous nerve injury.[575, 584] Remaining GSV and SSV varices can be either excised by phlebectomies or managed by sclerotherapy.

Descending ovarian phlebography should be considered for patients presenting with varicose veins with reflux through pelvic and vulvar veins and a normal great saphenous vein. Ovarian vein embolisation for reflux followed by sclerotherapy or surgery for the varicose veins has been recommended.[16, 17]

Surgical ligation of perforating veins

Methods of ligation.—If surgery to interrupt perforating vein is to be performed then it is now 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.[585-599] Paratibial fasciotomy to access the deep compartment is required.[594, 600-603] There is currently no consensus as to the benefits of pre-operative marking or which marking method should be used.[48, 56, 193, 604-614]

Sub-fascial endoscopic perforator surgery (SEPS).—Numerous uncontrolled series have suggested that SEPS might have a beneficial effect upon the natural history of CVD and in particular chronic venous ulceration.[615-624] 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.[625-628] In addition, it has been suggested by data from uncontrolled series that deep venous reflux (especially if post-thrombotic) might diminish the benefits of SEPS [626, 629] although this has not been a universal finding.[625] In patients with deep post-thrombotic or occlusive venous disease, results of SEPS in terms of ulcer healing and recurrence in the uncontrolled NASEPS registry have been similar to those that might be expected from compression bandaging alone.[630-632] The performance of SEPS in patients with the post-thrombotic syndrome remains controversial.[633-635]

It has never been shown that interrupting perforators in addition to standard saphenous surgery confers additional benefit in patients with CEAP C2 disease in terms of symptom relief, hemodynamic improvement and quality of life or recurrence.[578-580, 629, 630, 636-639] This may be because in the absence of deep venous reflux, complete eradication of superficial venous reflux will result in most incompetent perforators regaining competence.[47, 639]

Furthermore, there is no evidence that addition of perforator surgery to standard saphenous surgery confers additional benefit in patients with CEAP C4-6 disease in terms of symptom relief, hemodynamic improvement,[640, 641] quality of life, ulcer healing or recurrence.[48, 638, 642-649] This may be because appropriate sub-groups that might benefit have not yet been defined. A prospective, randomized multicentre 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.[650]

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.[651, 652] 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 [653] and with 34% in another.[654]

Deep venous reflux

Surgery for deep venous reflux in the lower limb has had a much more limited development than open or endovascular arterial surgery. The significance and frequency of deep venous reflux in CVD has only been fully realised in the last 20 years thanks to duplex ultrasound scanning.

It is difficult to identify patients with deep venous reflux who are suitable candidates for deep venous reconstruction on clinical grounds. This may explain why deep venous reconstructive surgery is performed in only a few units, the world experience is small, and the indications remain controversial. Furthermore, it is difficult to assess specific benefits from deep reconstructive surgery as it is usually combined with superficial and perforator surgery.[655, 656]

Venous reflux involving deep veins only is found in less than 10% of patients with skin changes and ulceration (C4-C6) [657] and is associated with superficial reflux and/or perforator incompetence in most patients. The most common cause of deep venous reflux is the post-thrombotic syndrome 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.[657] A very rare cause of reflux is congenital absence of valves. Reflux may be associated with obstruction in patients with the PTS. Most authors agree that significant obstruction must be treated first if it is localized above the inguinal ligament.

Surgical techniques for treating deep venous reflux can be classified into two groups. The first group involves phlebotomy and includes internal valvuloplasty,[658-661] transposition,[662] auto-transplantation,[655, 663, 664] neo valve creation [665, 666] and cryopreserved allografts.[667, 668] The second group does not require phlebotomy and includes wrapping,[669, 670] external valvuloplasty which can be transmural or transcommissural,[671] angioscopy assisted [672,673] and percutaneous placed devices.[674]

Indications for treating deep venous reflux by surgery depend on clinical severity, hemodynamics and imaging. Most authors recommend surgery in patients graded C4b and C5-6. Associated superficial and perforator reflux must also be treated.

Investigations

It is not always possible to distinguish between superficial or deep venous reflux on clinical grounds. In addition, it is difficult to distinguish between primary and secondary deep reflux.

Duplex scanning provides both hemodynamic and anatomic information. Photoplethysmography, air plethysmography and strain gauge plethysmography can help identify the predominant physiopathological component between superficial and deep venous reflux when the latter coexist. It would seem logical to go beyond these investigations only in patients being considered for surgery for deep venous reflux, where ambulatory venous pressure measurements and ascending or descending phlebography are frequently indicated. The choice of investigation is determined by the clinical context and whether or not there are contraindications for surgical intervention such as uncorrectable coagulation disorders or ineffective calf muscle pump.

The aim of surgery for deep venous reflux is to correct the reflux at a subinguinal level. However, it must be kept in mind that deep venous reflux is frequently combined with superficial and perforator reflux, and several sites need to be corrected to reduce the increased venous pressure. The most frequent procedure performed for primary deep venous reflux is valvuloplasty. This is

TABLE XII.—*Valvuloplasty results.*

	Surgical technique	Number of limbs (number of valves repaired)	Etiology PVI/total	Follow-up months (mean)	Ulcer recurrence or non healed ulcer (%)	Hemodynamic results	
						Competent valve (%)	❑ AVP ■ VRT
Eriksson and Almgren, 1988 [677]	I	27	27/27	(49)	—	19/27 (70)	❑ ↗ 81% (av) ■ ↗ 50% (av)
Perrin, 2000 [656]	I	85 (94)	65/85	12-96 (58)	10/35 (29)	64/83(77)	❑ Normalized 63 %(av)
Raju, 1985 [678]	I	68 (71)	—	12-144	16/68 (26)	30/71 (42)	—
Raju, 1985 [678]	TMEV	47 (111)	—	12-70	14/47 (30)	72/111	—
Raju, 2000 [671]	TCEV	141 (179)	98/141	1-42	(37)	(59)	❑ ↗ 15% (av) ❑ Normalized 100%.
Rosales, 2006 [676]	TMEV	17 (40)	17/17	3-122 (60)	3/7 (43)	(52)	❑ ↗ 50% (av)
Sottiurai, 1988 [659]	I	143	—	9-168 (81)	9/42 (21)	107/143 (75)	—
Tripathi, 2004 [675]	I	90 (144)	96/118	(24)	(32)	(79.8)	—
	TMEV TCEV	12 (19)			(50)	(31.5)	—

I: internal valvuloplasty; PVI: primary venous insufficiency; TMEV: transmural external valvuloplasty; TCEV: transcommissural external valvuloplasty; ❑ AVP: ambulatory venous pressure; ■ VRT: venous refill time; av: average; ↗: improved.

TABLE XIII.—*Banding, cuffing, external stent, wrapping results.*

Author Material used	Number extremities treated (number of valves repaired)	Site	Etiology PVI/total	Follow-up months (average)	Ulcer recurrence or non healed ulcer (%)	Hemodynamic results	
						Competent valve (%)	❑ AVP ■ VRT
Akesson (Venocuff I) 1999 [683]	20 (27)	F, P	7/20	5-32 (19)	2/10 (20) both PTS	PVI 7/7 (100) PTS 7/10 (4)	PVI ❑ ↗ 10% (av) ■ ↗ 10% (av) PTS ❑ ↗ 10% (av) ■ ↗ 100%
Camilli (Dacron) 1994 [684]	54	F	54/54	4-63	—	41/54 (76)	—
Lane (Venocuff II) 2003 [669]	42 (125)	F, P	36/42	64-141 (93)	(20)	(90)	❑ ↗ ? ■ ↗ 100% (av)
Raju 1996 [680]	28	F, P, T	—	12-134	6/22	60/72 (83)	—

PVI: primary venous insufficiency; ❑ AVP: ambulatory venous pressure; ■ VRT: venous refill time; av: average; ↗: improved; F: femoral; P: popliteal; T: tibial (posterior); PTS: post-thrombotic syndrome; absence of reflux or minimal reflux (<1 s).

credited with achieving a good result in 70% of cases (Table XII) [656, 659, 671, 675-678] in terms of clinical outcome defined as freedom of ulcer recurrence and reduction of pain, valve competence, and hemodynamic improvement over a follow-up period of more than 4 years. [656, 659, 676-678] 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.[682]

Wrapping has been used both in primary venous reflux and PTS providing variable results. (Table XIII).[669, 680, 683, 684]

Long -term results after surgery for PTS are also available for transposition [656, 658, 681, 685, 686] and transplantation.[656, 659, 663, 677, 678, 687] In terms of clinical results and valve competence, a meta-analysis demonstrates that a good result is achieved in 50% of cases over a follow-up period of more than 5 years (Tables XIV, XV), with a poor correlation between clinical and hemodynamic outcome. Other

TABLE XIV.—*Transposition results.*

	Number extremities treated	Etiology PVI/total	Follow-up in months	Ulcer recurrence or non healed ulcer (%)	Hemodynamic results	
					Competent valve (%)	❑ AVP ■ VRT
Cardon *et al.*, 1999 [685]	18	18/18	24-120	4/9 (44)	12/16 (75)	—
Johnson *et al.*, 1987 [686]	16	16/16	12	4/12 (33)	3/12 (25)	❑ unchanged ■ unchanged
Kistner, 1975 [658]	14	—	48-252	7/14 (50)	10/13 (77)	❑ ↗ 70% (av) ■ ↗ 70% (av)
Perrin, 2000 [656]	18	16/18	12-168	2/8 (25)	9/17 (53)	—
Sottiurai, 1996 [681]	16	—	9-149	9/16 (54)	8/20 (40)	—

PVI: primary venous insufficiency;❑ AVP: ambulatory venous pressure; ■ VRT: venous refill time; av: average; ↗: improved.

TABLE XV.—*Transplantation results.*

	Number of extremities treated	Site	Etiology PVI/total	Follow-up in month (average)	Ulcer recurrence or non healed ulcer (%)	Hemodynamic results	
						Competent valve (%)	❑ AVP ■ VRT
Eriksson and Almgren, 1988 [677]	35	F, P	35/35	6-60	—	11/35 (31)	❑ unchanged
Nash, 1988 [687]	25	P	25/25	—	3/17 (18)	18/23 (77)	❑ ↗ 18% (av)
Perrin, 2000 [656]	32	F	31/32	12-124 (66)	9/22 (41)	8/32 (25)	■ ↗ 19% (av)
Raju, 1985 [678]	83Ξ	F, P, T	83/83	12-180	(40) 6 yrs	(38) 4 yrs	❑ unchanged
Sottiurai, 1988 [659]	18	F, P	—	7-144	6/9 (67)	6/18 (33)	—
Taheri *et al.*, 1982 [663]	71	F, P	—	—	1/18 (6)	28/31 (90)	❑ ↗ 15% (av)

PVI: primary venous insufficiency;❑ AVP: ambulatory venous pressure; ■ VRT: venous refill time; av: average; ↗: improved; F: femoral; P: popliteal; T: tibial (posterior); Ξ: axillary vein transfer in trabeculated (poorly recanalized) vein.

techniques including neovalve [666, 690] and cryopreserved valves have a shorter follow-up.[667, 668]

Maleti and Lugli reported neovalve competence in 17/18 cases after a mean follow-up of 22 months.[690]

Hemodynamic and imaging criteria.—Only patients with deep venous reflux graded 3-4 according to Kistner [657] are usually treated by deep valve reconstractive surgery. To be significantly abnormal, it is generally recognized that, values for venous refill time must be less than 12 seconds and the difference between pressures at rest and after standardized exercise in the standing position must be less than 40%.

Indications according to etiology.—The indications for surgery can be simplified according to the clinical, hemodynamic and imaging criteria described above. However, the decision to operate should be based on the clinical status rather than non-invasive data since the patient's symptoms and signs may not correlate with the laboratory findings.[691]

In primary reflux, reconstructive surgery should be considered after failure of conservative treatment and in young and active patients who are reluctant to wear permanent compression. Valvuloplasty is the most suitable technique, with Kistner,[679] Perrin [656] Sottiurai [681] and Tripathi [661] favoring internal valvuloplasty, and Raju [671] and Rosales [676] transcommissural external valvuloplasty.

Secondary deep venous reflux, mainly from the PTS, may be treated only after failure of conservative treatment. Valvuloplasty is very frequently not feasible so that alternative techniques to be used in order of recommendation are valve transposition, valve transplantation and neovalve insertion. Patients must be informed that surgery for reflux after PTS has a relatively high failure rate.

Because results achieved by subfascial endoscopic perforator surgery with or without superficial venous surgery are not convincing,[692] it is recommended that this procedure is considered and carried out in combination with deep reconstructive surgery.

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. A grade 2B recommendation (according to the new grading system by Guyatt et al.) has been provided.[2] Better results from surgery are obtained for primary compared to secondary reflux.

Relief of obstruction

Obstruction is the principal cause of symptoms in approximately one-third of postthrombotic limbs. It is associated with reflux in 55% of symptomatic patients with CVD.[40, 693] This combination leads to the highest levels of venous hypertension and the most severe symptoms as compared to either reflux or obstruction alone.[694] Proximal obstruction, especially in the iliac vein is more likely to cause symptoms than lower segmental blockages.[695] Following iliofemoral DVT, only 20-30% of iliac veins completely recanalize spontaneously, while the remaining veins have residual obstruction and varying degrees of collaterals.[696, 697] The main aim from intervention is to relieve proximal outflow obstruction.

Diagnosis and selection of patients.—It is important for the physician to be aware that there may be venous occlusion. Patients presenting with classes C 3-6 should be considered for further studies, particularly those with venous claudication on challenged exercise.[698] Unfortunately, there are no 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 importance of chronic outflow obstruction is the major obstacle to selecting limbs for treatment and evaluating outcome. Although a positive noninvasive or invasive test may indicate the need to proceed with further investigations, a negative test should not discourage it. 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.[699-701] Iliocaval obstruction and underlying abnormalities can be detected by MRI and spiral CT venography.[702, 703]

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 rarely 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.[704, 705]

The cross-over bypass

The autogenous femoro-femoral venous bypass [706] appears to be less thrombogenic with better patency than prosthetic grafts.[707] However, most series have small numbers of patients with inconsistent clinical and venographic follow-up (Tables XVI-XVIII) .

The in-line bypass.—Anatomic in-line bypass reconstruction can be used in the femoro-iliocaval axial outflow axis with segmental obstruction in the presence of a sufficient venous inflow and outflow of the graft.

The only study presenting cumulative success rates by Jost *et al.*[707] 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.

Sapheno-popliteal bypass.—Sapheno-popliteal vein bypass is a rarely performed operation for outflow obstruction. The few reported series of patients,[708, 711, 722] show clinical success and patency rates of 31-58% and 56-67% for follow-up at one to five years respectively.

Endophlebectomy of the deep veins.—Endophlebectomy may be performed to improve inflow and

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

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Husni, 1970 [708]	78	7-144	74	73
Hutschenreiter *et al.*, 1979 [709]	20	6-28	69	44
O'Donnell *et al.*, 1987 [655]	6	24	100	100
Halliday *et al.*, 1985 [710]	47	60	89	75
AbuRahma *et al.*, 1991 [711]	24	66	88	75

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

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Eklof *et al.*, 1985 [705]	7	2-31	86	17
Yamamoto *et al.*, 1986 [712]	5	1-18	60	60
Comerota *et al.*, 1994 [713]	3	40-60	67	67
Gruss and Hiemer, 1992 [714]	32	—	85	85

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

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Husfeldt, 1981 [715]	4	4-30	100	100
Dale *et al.*, 1984 [716]	3	1-30	100	100
Ijima *et al.*, 1985 [717]	5	22-36	60	60
Eklof *et al.*, 1985 [705]	7	2-31	86	29
Plate *et al.*, 1985 [718]	3	1-11	67	33
Okadome *et al.*, 1989 [719]	4	17-48	100	100
Gloviczki *et al.*, 1992 [720]	12	1-60	67	58
Alimi *et al.*, 1997 [721]	8	10-45	88	88
Jost *et al.*, 2001 [707]	13	1-150	49	54

outflow in association with bypass and stenting procedures.[723, 724]

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. Studies of venous stenting in peer review publications often have similar shortcomings as reports for open surgery. Most are case reports and very few are sizable, the follow-up is short-term with patency not reported as cumulative success, stented sites in the upper and lower extremities are mixed, and the majority of reported series have not differentiated between etiologies or management of acute and chronic conditions. Patency rates assessed by duplex ultrasound or phlebography in successfully stented limbs of mixed groups of patients are shown in Table XIX.

Stented limbs with non-thrombotic disease appear to do far better than those with thrombotic disease, with reported primary, assisted-primary and secondary cumulative patency rates of 89%, 100% and 100% and 65%, 85% and 88% respectively at 36 months.[733, 734]

Severe in-stent recurrent stenosis defined as greater than 50% diameter decrease on single plane antero-posterior venogram was infrequent occurring in only 15% at 42 months in one study.[733] Gender and side of limb involved did not affect outcome. Higher rates of severe in-stent recurrent stenosis were found in thrombotic compared to nonthrombotic limbs, reported as 23% and 4% respectively at 36 months in this study, and 18% and 12%, respectively in the presence of thrombophilia. Long stents (>13 cm) and extension of stent to below the inguinal ligament had a cumulative rate of severe in-stent recurrent stenosis of 25% at 36 months and 40% at 24 months respectively. These three major risk factors of throm-

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

Author	Number of limbs	Etiology and adjuvant treatment	Duration of follow-up	Patency rate		
				Primary	Assisted	Secondary
Nazarian *et al.*, 1996 [725]	56	Mixed	4 years, (cumulative)	50%	—	75%
Binkert *et al.*, 1998 [726]	8	With and without thrombectomy	10-121 months	100%	—	—
O'Sullivan *et al.*, 2000 [727]	34	With and without trombolysis	1 year		—	92-94%
Patel *et al.*, 2000 [728]	10	After thombolysis	1.5 years	60%	—	100%
Hurst *et al.*, 2001 [729]	18	With and without trombolysis	1.5 years		—	79%
Juhan *et al.*, 2001 [730]	15	With and without thrombectomy	5-52 months	87%	—	93%
Lamont *et al.*, 2002 [731]	15	With and without thrombectomy	41 months (cumulative)		—	87%
Blattler and Blattler 1999 [732]	12	Chronic non-malignant obstruction	1-43 months	92%	—	—
Neglen and Raju, 2004 [733]	324	Chronic non-malignant obstruction	4 years (cumulative)	57%	92%	93%
Delis *et al.*, 2004 [698]	41	With and without thrombolysis/ thrombectomy	6 months	58%	71%	76%

botic obstruction, thrombophilia, and long stents for development of in-stent recurrent stenosis were similar for late occlusion and limbs with these three risk factors show a 61% rate of severe in-stent restenosis at 24 months post-stenting, while none developed in the their absence.[733]

The reports describing patency rates indicate clinical improvement in the intermediate term in most patients (>72%).[726, 727, 729] The incidence of ulcer healing after iliac vein balloon dilation and stent placement in 304 limbs with active ulcer was 68% and the cumulative ulcer recurrence-free rate at 2 years was 62%.[735] Median swelling and pain severity scores decreased significantly. The frequency of limbs with any swelling decreased from 88% to 53% and limbs with any pain from 93% to 29%. 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

Stenting technology is relatively recent so that the follow-up period is limited. Because long-term effects of stents in the venous system are not fully known, monitoring for several more years is required to assess efficacy and safety.

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 well-powered studies. These clinical outcome parameters should have been previously validated.

The method of choice to assess clinical outcome after treatment for 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.[736]

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

Available methods for measurement are summarized below.

Evaluation of signs

Telangiectasia and reticular veins.—Telangiectasia 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.[737] This is an old [738, 739] but recently updated noninvasive technique. Volumetry does not quantify edema, but measures short-term variations which reflect changes in edema.[740-742] 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 intra-individual variability is 1.3% under the same conditions.[741]

Volumetry has already demonstrated that legs that ache are those that swell the most,[743] that leg volume increases during daily activity and that this increase correlates with the severity of CVD;[741] that leg volume may increase during long distance flights and that it diminishes after venous surgery [744] and after different drug treatments for venous or lymphatic insufficiency.[395, 745, 746]

Other methods to assess edema include leg circumference measurements using tape [258, 395, 747] and opto-electronic volumetry.[442, 748, 749]

Skin changes and lipodermatosclerosis.—The degree of induration caused by lipodermatosclerosis can be measured by different techniques including high resolution ultrasound B-scan,[213] and a "durometer".[750, 751] Goniometry of ankle joint movements can be performed.[752, 753] However, none of these techniques are yet validated for therapeutic measurements in CVD.

Ulcer healing.—Complete healing of an ulcer is the most clinically significant outcome measurement for C6 patients [736] and can be assessed using life table analysis.

Surface area reduction is the surrogate criterion most often used. 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.[754] 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 $\pi/4$ the calculated rectangular area is transformed to an elliptic one. Gillman published a method for calculating wound healing rates that corrects for differing sizes and shapes by dividing the ulcer area by its perimeter.[755]

The above changes in geometrical measurements per unit time are often used in clinical trials.[756, 757] However, complete healing and the initial healing rate are the most common endpoints used.[758, 759] 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.[756] However, the Gillman equation corrects for different initial ulcer sizes so that it meets the needs of clinical studies for standardized and comparable measurements.[759-761]

Ulcer recurrence.—Ulcer recurrence is the most important end-point in C5 patients and can be assessed in long-term follow-up studies using cumulative ulcer-free survival times.[263, 642]

Evaluation of symptoms and quality of life

Symptoms.—Symptoms can be evaluated by the clinician and/or by a patient self-report. 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 [412] 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 question-

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

CEAP "C" Class	Clinical *	Morphology	Function
C1	Photographic analysis	—	—
C2	idem C1	Duplex: 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 + chromometry, durometry, goniometry	idem C2 + US: Skin thickness + Capillaroscopy : cpl 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.

naire 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.[762, 763] In a study by Garratt *et al.*[762] 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 sample from the normal population.

Because specific complaints from patients with CVD were 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.[155, 764] The most recent of these is the Chronic Venous Insufficiency Questionnaire (CIVIQ) used by Launois *et al.*[155] The 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.

Health-related quality of life studies should be used in the future to assess overall outcome and justify treatment for CVD.[578, 765]

Venous Clinical Severity Score (VCSS)

The CEAP related VCSS[766] was designed to measure outcomes after surgical treatments and seems adequate for patients with advanced CVD. Its short-term repeatability has been validated.[767] Validity of construct and responsiveness remain to be evaluated.

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, plethysmographic techniques, pressure measurements and microvascular techniques. Their use depends on the C class and on the specific target of the treatment assessed (Table XX).

PART III
MANAGEMENT

Prevention of post-thrombotic chronic venous disease

CVD is either primary or secondary. Science has not advanced to the point where we can effectively prevent primary venous disease although it has clarified much of the pathophysiology of secondary CVD. Treatment modalities have demonstrated that the virulence of post-thrombotic CVD can be

TABLE XXI.—*Thrombus resolution in patients with acute DVT treated with anticoagulation or thrombolytic therapy: pooled data from 14 reports.*[779-787, 789-795]

R_x	N.	Thrombus resolution		
		None/Worse	Partial	Significant/Complete
Anticoagulation	301	253 (84%)	38 (13%)	10 (3%)
Thrombolysis	387	147 (38%)	74 (19%)	166 (43%)

substantially reduced and in many cases avoided. In most cases, this must be achieved at the time the patient is managed for acute deep venous thrombosis.

Anticoagulation is the main therapy for acute DVT. Establishing and maintaining a therapeutic level of anticoagulation is important for best management and to reduce recurrence.[768] This is critical to reduce the severity of the PTS as ipsilateral recurrence of DVT increases the likelihood of PTS six-fold.[41] Randomized trials have shown that the longer the duration of anticoagulation, the fewer are the episodes of recurrence.[769-773]

In addition to anticoagulation, randomized trials have shown that lower leg compression stockings with an ankle pressure of 30-40 mmHg significantly reduce the severity of the PTS.[41, 45, 774]

It has already been mentioned that the underlying pathophysiology of post-thrombotic CVD is ambulatory venous hypertension.[8] Its two components are venous obstruction and valvular incompetence and investigators have found that the most severe PTS symptoms are likely to occur when both are present.[40, 775] Although recanalization of a thrombosed venous segment may restore "patency", significant luminal obstruction remains because the recanalized channel may be only a fraction of the original luminal diameter. Though this may not present significant functional obstruction at rest, its physiologic importance is magnified during exercise.

A natural history study [19] demonstrated that valvular incompetence develops progressively from the time of acute DVT. This study observed that valvular incompetence was more likely to develop in patients with occlusive rather than non-occlusive DVT, and more likely to occur with more extensive thrombosis. In subsequent prospective studies of the natural history of acute DVT treated with anticoagulation, it was found that patients who preserved their valvular function had early lysis of their previously thrombosed veins.[776] Therefore, the natural history studies for acute DVT indicate that persistent obstruction increases the severity of the PTS, and that early clot lysis not only eliminates obstruction but also potentially preserves valvular function. It appears intuitive then that treatment specifically designed to eliminate thrombus should reduce the severity of the PTS, and this is supported by available evidence. Scandinavian investigators performed a randomized trial of venous thrombectomy plus AV fistula *versus* anticoagulation alone for patients with iliofemoral DVT and demonstrated significant benefit both early and at 10-year follow-up [696, 777, 778] in patients in whom the thombus was removed.

Successful fibrinolytic therapy for acute DVT may reduce or avoid post-thrombotic CVD. Systemic fibrinolytic therapy was studied into the 1980s [779-794] and although it was associated with better recanalization rates than anticoagulation alone, it was perceived to be disappointing since 50% or more of patients failed to have a good outcome. There are 14 reports that compare thrombolysis with anticoagulation for acute DVT (Table XXI). In patients treated with anticoagulation alone, significant or complete thrombus resolution occurred in 3%, partial thrombus resolution in 13% and no thrombus resolution or worsening in 84%. In patients treated with thrombolytic therapy, 43% had significant or complete lysis, another 19% demonstrated partial lysis, and 38% had no thrombus resolution or worsened. Although a large percentage of patients treated with thrombolysis failed to achieve the desired outcome, it was demonstrated by randomized trials that successful lysis significantly reduced post-thrombotic symptoms and preserved venous valvular function [789, 795] (Table XXII).

An important advance in the 1990s was the acceptance of catheter-directed intra-thrombus thrombolysis to manage patients with acute DVT, especially those with iliofemoral DVT. Although there are numerous reports in the literature, three large studies demonstrate consistent results,[796-798] with successful outcome in 80-90% (Table XXIII). Patients successfully treated have a significantly improved quality of life compared to those managed with anticoagulation alone and those where catheter-directed thrombolysis fails.[799] A small randomized trial of catheter-directed thromboly-

TABLE XXII.—*Long-term symptomatic outcome of patients with acute DVT treated with thrombolytic therapy or anticoagulation (Results of two randomized studies).*[788, 789]

R_x	N.	Post-thrombotic symptoms		
		Severe	Moderate	None
Anticoagulation	39	8 (21%)	23 (59%)	8 (21%)
Thrombolysis	39	2 (5%)	12 (12%)	25 (64%)

sis and anticoagulation *versus* anticoagulation alone in patients with iliofemoral DVT [21] demonstrated better outcomes and preservation of valve function in those randomized to catheter-directed thrombolysis.

It appears then that for patients where there are no contraindications to thrombolytic therapy, catheter-directed thrombolysis offers the best chance of successful thrombus resolution to reduce the severity of the PTS. In patients with iliofemoral DVT who have contraindications to lytic therapy, percutaneous mechanical means for thrombus removal are being studied, but operative venous thrombectomy appears to be the better option until results from percutaneous treatment improve.

An important caveat for ultimate success with thrombolytic therapy is the need to correct underlying venous stenoses to allow unobstructed venous drainage into the vena cava. Additionally, long-term therapeutic anticoagulation to prevent rethrombosis is important.[768, 770, 772, 773, 788, 800] Ineffective anticoagulation leading to recurrent DVT will eliminate the long-term beneficial effects from lytic therapy.

Management of symptomatic individuals in the absence of signs

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 used complementary investigations engaged in the CEAP classification are assigned to class C0S, An, Pn. Such patients are not uncommon in practice. After a thorough examination to exclude varicose veins or venous reflux, several options are available although none are "evidence based" except for veno-active drugs.

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 these complications. However, the value of reassuring patients has not been demonstrated and studies on Quality of Life (QoL) might improve our knowledge on this point.

TABLE XXIII.—*Results of catheter-directed thrombolysis with urokinase in three contemporary series: efficacy and complications.*

	Bjarnason *et al.*,[796] (N=77)	Mewissen *et al.*,[797] (N=287)	Comerota *et al.*,[799] (N=58)
Efficacy			
Initial success	79%	83%	84%
Iliac	63%	64%	78%
Femoral	40%	47%	-----
Primary patency at 1 yr			
Iliac	63%	64%	78%
Femoral	40%	47%	-----
Iliac stent: patency at 1 yr			
+Stent	54%	74%	89%
–Stent	75%	53%	71%
Complications			
Major bleed	5%	11%	9%
Intracranial bleeding	0%	<1%	0%
Pulmonary embolism	1%	1%	0%
Fatal pulmonary embolism	0%	0.2%	0%
Death secondary to lysis	0%	0.4%	0% (?2%)*

*Death due to multi-organ system failure 30-days post lysis, thought not related to lytic therapy.

Adaptation of lifestyle

In most phlebologists' experience, many symptoms will diminish if patients can adopt a better lifestyle including improving working conditions, choosing walking rather than driving, and developing recreational activities such as walking, swimming or raising the legs during pauses or at night. However, the value of these measures has also not been demonstrated.

Oral veno-active drugs

Their effect on symptoms, either in C0s or for all other classes of the CEAP classification, has been well demonstrated (see above).

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 C0S. In the San Diego Consensus conference,[203] three trials have been considered to provide a Grade B recommendation. In another study,[215] "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". It is then logical to prescribe light compression in COS but we need further trials to assess their effect.

Management of patients with varicose veins

Non-interventional therapy

There is strong evidence for the efficacy of venoactive drugs to relieve symptoms in patients with varicose veins. Compression therapy may also be effective (see above).

Interventional therapy

Intervention for varicose veins by means of surgery, endovenous (radio-frequency, laser) techniques [544, 560, 801, 802] and sclerotherapy [803] aim to eliminate reflux, normalize venous hemodynamics and remove visible varices in order to relieve symptoms,[584] prevent recurrence and minimize the complications of CVD. In practice, this entails eliminating axial reflux [577, 582] and varicose clusters from the circulation. The former is accomplished by surgery, endovenous techniques or foam sclerotherapy and the latter by surgery or sclerotherapy.

Increasingly, varicose veins are 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.[536, 559, 564, 804-806]

Management 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 grade 1A or 1B recommendations (according to the new grading system by Guyatt *et al.*) [2] cannot be made.

Compression is the cornerstone for treating patients with the PTS [219] but the optimal degree of compression is unknown. Below-knee compression is as effective as above-knee in most patients.[215] The grade of compression used is often tailored to the grade of CEAP 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 perforator reflux with superadded obstruction in some [121] 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 methods to relieve obstruction or reflux are targeted to treat specific anatomic areas but various methods are frequently used in combination for superficial, perforator and deep reflux so that it remains difficult to identify which is most beneficial.

Although drug treatment has been effective for reducing edema in short-term studies [442, 457, 807] compression remains the pivotal treatment in patients classified C3. 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 [699] intravascular ultrasound is the most reliable investigation. There is a large consensus for using ballooning and stenting rather than surgical bypass [735, 808] and for treating ilio-caval obstruction or occlusion, whatever the CVD class.

In patients presenting with severe (C4-6) CVD, 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, it should be treated by ballooning and stenting. Recently endophlebectomy has been reported for treating above inguinal obstruction.[724] 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 ran-

TABLE XXIV.—*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: — Compresssion, — Venotonic drugs Treatment of Superficial Reflux: — Sclerotherapy — Surgery
Mild $C_{3\ S,\ AD}$	D	O	Normal	Conservative treatment: — Compression, — Venotonic drugs
Severe $C_{3\ S}$	Above inguinal significant O			Failure of conservative Treatment: — Ballooning and stenting
C_{4-6}	D Above inguinal significant O	O	Normal	Conservative treatment: — Compresssion, — Venotonic drugs Failure of conservative Treatment: — Ballooning and stenting
C_6 Non healing ulcer Recurrent ulcer	D	R+O	Absence of contraindications	Conservative treatment: — Compresssion, — Venotonic drugs Failure of conservative Treatment: — Valve transfer — Treat obstruction first

A: anatomic; P: pathophysiologic; S: superficial; D: deep; P*: perforator; R: reflux; O: obstruction.

domized study comparing perforator surgery with compression the pros and cons remain debatable. Nevertheless if surgery is to be performed there is a large agreement for using SEPS.[594] Echo-guided foam sclerotherapy may be also used for treating incompetent lower leg perforators in PTS.

Deep venous reconstructive surgery for treating reflux remains controversial. Among those that are in favour 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 correctable coagulation disorder). As valvuloplasty is rarely feasible in PTS, transplantation of a valvuled axillary vein segment or vein transposition is the recommended technique to be used. Recently Maleti and Lugli have reported promising middle term good results with the construction of neovalve in PTS.[690] Results provided by the different procedures are reported in sections devoted to deep venous obstruction and reflux. However, surgery for deep vein reflux or obstruction has to be performed in specialized units with highly trained staff (Table XXIV).

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.[173] In addition, high compression is more effective than low compression.[173] A four-layer bandage system produces 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.[208] 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.[261, 268, 809] A weakness of all available trials is that pressures were not measured at the ankle level.

Surgery for superficial veins

In patients with combined superficial and deep venous insufficiency, superficial venous surgery without compression bandaging did not improve venous hemodynamics and failed to achieve ulcer healing.[810] However, if 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.[646]

A randomized study that compared compression with an inelastic bandage (n=24) to superficial venous surgery (n=21) for patients with superficial venous reflux only showed that surgery reduced the recurrence rate at 3 years and in addition accelerated the healing rate of the ulcers.[263]

A randomized controlled trial allocated patients with isolated 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). Multilayer compression bandaging and surgery reduced the rate of recurrence at 12 months when compared to compression alone without affecting the healing rate.[642]

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 above. It is reserved for patients whose ulcers do not respond to compression or compression combined with venoactive drugs.

Prevention of leg ulcer recurrence

Most research has previously been centered on 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 26-69% at 12 months.[811-813] Various studies have reported ulcer recurrence rates at 28%-57% at 2 years,[814] 38% at 3 years [178] and 48% at 5 years.[815]

Compression therapy

Compression therapy is believed to counteract the effects of venous hypertension and to control edema. A recent Cochrane review of compression to prevent ulcer recurrence [173] did not find any randomized controlled studies comparing ulcer recurrence rates with and without compression. There is fairly strong circumstantial evidence that not wearing compression stockings for various reasons is associated with ulcer recurrence.[262, 814, 816, 817] The recurrence rate was 2-3 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. [816, 817] McDaniel *et al.*[815] 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 is included in the Venous Clinical Severity Score (VCSS).[766]

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 ranging from 37-84%.[815-818] Compression is probably of value but the poor compliance in many patients fails to allow satisfactory decrease of ulcer recurrence rates when analysed by "intent-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 heart level. 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 chronic venous disease.[819-821] Greater body weight has been shown to be sta-

tistically associated with poor healing of venous ulcers [822] and proportionally more patients with ulcer have been found to be obese as compared to the general population in a study performed in Sweden.[823]

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.[753] It would seem that improvement of the calf muscle pump by exercise would increase venous return and subsequently help the clinical situation.

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 reduced incidence of ulcer recurrence. In a prospective, non-randomized study by McDaniel *et al.*[815] there was significantly less cumulative recurrence rate at 48 months in limbs treated by a variety of operations compared to those treated without surgery (26% and 52%, respectively). The study found that patients who were not candidates or who elected to forego surgery had 3.4 times higher rate of ulcer recurrence. A prospective, randomized study combining compression with or without simple superficial venous surgery showed that the 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 to those with compression alone (12% and 28%, respectively).[642]

Deep venous insufficiency appears to be a major determinant for ulcer recurrence. The ulcer recurrence rate after superficial venous surgery or perforator 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% respectively in limbs with and without deep venous involvement.[632, 643, 815]

It seems logical that deep valve repair should be beneficial, but the proof is circumstantial. Prospective, randomized studies do not exist. Long-term follow up by Masuda and Kistner [679] after deep valve reconstruction reported 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 post-thrombotic disease in some studies,[656, 679] but Raju *et al.*[680] reported a 6-year cumulative ulcer recurrence rate after deep venous reconstruction of approximately 40% which was similar in primary and secondary disease.

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 4.0ml/s *versus* those with more than 4.0 mL/s were associated with 28% and 53% recurrence respectively.[815] Another study reported that the recurrence rate was only 14% if a venous filling time (VFT) more than 5s could be maintained compared to 45% when VFT was less than 5s.[635]

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.[43] In a series of patients stented for venous obstruction, 51% of those with post-thrombotic occlusion had thrombophilia although thrombophilia was also found in 23% of patients considered to have primary disease.[733] 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.

Key questions to be answered

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

Pathophysiology

Despite the increased interest in the pathophysiological mechanisms for 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 lipodermato-sclerosis 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 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 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 just started to emerge.

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, spiral 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, 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, lymphatic and arterial 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 post-thrombotic syndrome 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, hemodynamic and cost-benefit for 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 these methods are currently unavailable. In view of the clinical efficacy and simplicity of conventional saphenectomy and the increasing implementation of the inexpensive foam sclerotherapy, the higher procedural cost of endovenous therapies needs to be justified.

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

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.

Glossary

bFGF: fibroblast growth factor
CEN: Comité Européen de Normalisation
CVDs: chronic venous disorders
CVD: chronic venous disease
CVI: chronic venous insufficiency
DVT: deep vein thrombosis
EGF: endothelial growth factor
EMMPRIN: extracellular inducer of MMP
EVLT: endovenous laser therapy
GSV: great saphenous vein
ICAM-1: intercellular adhesion molecule-1
IL-1: interleukin-1
IPC: intermittent pneumatic compression
IPV: incompetent perforating veins
IVUS: intravascular ultrasound
LDS: lipodermatosclerosis
MPFF: micronized purified flavonoid fraction`
MMPs: matrix metalloproteinases
MT1-MMP: membrane type 1 MMP
MT2-MMP: membrane type 2 MMP
PDGFR-α: platelet derived growth factor receptor alpha
PDGFR-β: platelet derived growth factor receptor beta
PE: pulmonary embolism
PG: prostaglandins
PGE1: prostaglandin E1
PGE2: prostaglandin E2
Proximal DVT: DVT in popliteal or more proximal veins
QOL: quality of life
PTS: post-thrombotic syndrome
RF: radio-frequency
SEPS: subfacial endoscopic perforator ligation surgery
SFJ: saphenofemoral junction
SMC: smooth muscle cells
SPJ: saphenopopliteal junction
SSV: small saphenous vein
$tcPO_2$: transcutaneous PO_2
TGF-β1: tumor growth factor-β1
TIMPs: tissue inhibitors to metalloproteinases
uPA: urokinase plasminogen activator
VADs: venoactive drugs
VCSS: venous clinical severity score
VEGF: vascular endothelial growth factor
VTE: venous thromboembolism
VV: varicose veins

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