MANAGEMENT OF CHRONIC VENOUS DISORDERS OF THE LOWER LIMBS

GUIDELINES ACCORDING TO SCIENTIFIC EVIDENCE

PART I

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The European Venous Forum
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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 range from Level A to Level C and strength of recommendation is either 1 or 2.[1, 2]

Level A evidence derives from two or more scientifically sound randomized controlled trials (RCTs) or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population. Level A evidence implies that further research is very unlikely to change our confidence in the estimate of effect.

Level B evidence is provided by one well conducted RCT or more than one RCT with less consistent results, limited power or other methodological problems, which are directly applicable to the target population as well as by RCTs extrapolated to the target population from a different group of patients. Level B evidence implies that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Level C evidence results from poorly designed trials, observational studies or from small case series. Level C evidence implies that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

A strong recommendation (1) is made if benefits outweigh the risks. A weak recommendation is made (2) if the benefits and risks are closely balanced or if there is uncertainty about the magnitude of the benefits and risks.

GLOSSARY

AVVSS: Aberdeen Varicose Vein Severity Score
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
EVLA: Endovenous laser ablation
GSV: Great saphenous vein
SSV: Small saphenous vein
ICAM-1: Intercellular adhesion molecule-1
IL-1: Interleukin-1
IPC: Intermittent pneumatic compression
IPVs: 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: Radiofrequency
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
VVs: Varicose veins

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CHAPTER 1

Introduction

Chronic venous disorders (CVDs) is a term that includes the full spectrum of morphological and functional abnormalities affecting the venous system, irrespective of whether they produce symptoms. Chronic venous disease (CVD) is a term that includes any morphological or functional abnormality of long duration affecting the venous system, manifest by symptoms and/or signs indicating a need for investigation and treatment.[1] Symptoms include pain or aching, throbbing, tightness, heaviness, feeling of swelling, muscle tiredness, itching, cramps, burning sensations, restless legs, tingling or venous claudication, as well as secondary symptoms and cosmetic dissatisfaction.[2] Signs include telangiectases, reticular and varicose veins or edema, and skin changes such as pigmentation, lipodermatosclerosis, atrophie blanche, corona phlebectatica, eczema or ulceration.[3, 4] CVD is usually caused by primary abnormalities of the venous wall and/or valves, or secondary abnormalities resulting from previous deep vein thrombosis (DVT) that can lead to reflux, obstruction or both. Rarely, CVD results from congenital malformations.[5] Chronic venous insufficiency (CVI) is a term reserved for advanced CVD due to venous functional abnormalities producing edema, skin changes or venous ulceration.

The clinical history and examination may not indicate the nature and extent of underlying abnormalities. Consequently, several diagnostic techniques have been developed that define the anatomic extent and functional severity of reflux and obstruction as well as calf muscle pump dysfunction. Difficulties in deciding which investigations to use and how to interpret results stimulated a consensus statement on investigations for CVD in 2000.[6] This was updated and expanded to guidelines that included management of CVDs in 2008,[7] revised in 2014.[8] Such guidelines need to be updated to better serve practitioners as new procedures are constantly being developed. This current document aims to describe current concepts for CVDs, update guidelines for management, and indicate the strength of evidence supporting the recommendations.

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CHAPTER 2

Pathophysiology

Changes in superficial and deep veins

Varicose veins are a common manifestation of CVD and are believed to result from remodeling of the venous wall. Veins from patients with varicosities have different elastic properties than those from individuals without varicose veins.[1, 2] Hypertrophy of the venous wall is associated with increased collagen content,[3] fragmentation of elastin fibres,[4] and degradation and accumulation of extracellular matrix [5] in the vein.

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

Approximately 30% of patients with deep venous reflux shown by imaging appear to have primary valvular incompetence rather than detectable post-thrombotic damage.[7, 8] Rarely, deep venous reflux is due to valve agenesis or aplasia.[9] Varicose veins may be caused by pelvic vein reflux with no evidence of incompetence at the saphenofemoral junction, or in perforating veins of the calf or thigh. Reflux in ovarian, pelvic, vulvar, pudendal or gluteal veins may be associated with clinical symptoms and signs of pelvic congestion.[10-13]

Endogenous lysis occurs after DVT and persists for days or weeks, so that recanalization can be observed over months or years in 50% to 80% of patients.[14-16] Rapid thrombus resolution can occur after DVT depending on thrombus extent, location, local inflammation, potency of local fibrinolytic activity and proinflammatory mediators,[18, 19] and this results in a higher incidence of preserved valve competence.[14, 17] Venous outflow obstruction can result from inadequate recanalization following DVT, less frequently from extramural venous compression, most commonly left common iliac vein compression by the right common iliac artery, from intra-luminal changes,[20-23] or rarely from congenital agenesis or hypoplasia.[24]

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

The prevalence of the post-thrombotic syndrome following DVT has been reported to have a wide variation of 35% to 69% at three years and 49% to 100% at five to ten years, and this depends on the extent and location of thrombosis, efficacy of treatment, and other definition issues.[27-37] Patients with a combination of chronic obstruction and reflux have the highest incidence of skin changes and ulceration.[37] The risk of the post-thrombotic syndrome is higher in patients with recurrent thrombosis, and is often associated with congenital or acquired thrombophilia.[38-41] Past and recent studies report that post-thrombotic skin changes and/or ulceration in patients with proximal DVT occur less frequently, with a risk of 4% to 8% in five years with adequate anticoagulation, early mobilization, and long-term compression.[42-44] Mechanical dysfunction of the calf muscle pump may enhance development of leg ulceration suggesting the importance of the range of ankle motion [45] and patient activity.[46]

Incompetent perforating veins

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

IPVs are associated with superficial and/or deep-vein reflux, and are rarely found if there is no superficial or deep reflux.[50-52] The prevalence, diameter, volume flow and velocity of IPVs increase with the clinical severity of CVD, whether or not there is co-existing deep venous reflux.[48, 53-58] However, up to 10% of patients, often women, presenting with CEAP clinical class 1 to 3 CVD, have non-saphenous superficial reflux in association with unusually located IPVs.[59]

Vascular biology and pathophysiology of the venous wall

As referred to above, varicose veins have different elastic properties to normal veins.[1, 2] The ratio of collagen I to collagen III is altered in both the veins and dermal fibroblasts from the same patients, indicating a probable systemic disorder with a genetic basis.[60]

Altered shear stress causes leukocyte activation, adhesion and migration through the endothelium [61-63] which contributes to inflammation and subsequent remodeling of the venous wall and valves.[64-67] Reduced 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 also proliferate and synthesize matrix metalloproteinases (MMPs) which overcome the effect of their tissue inhibitors (TIMPs), and the MMP/TIMP imbalance results in degradation of elastin and collagen.[62, 68, 69] This may contribute to development of hypertrophic and atrophic venous segments and valve destruction which are both seen in varicose veins. Venous wall remodelling leading to abnormal venous distension prevents valve leaflets from closing properly resulting in venous reflux.

There is a well-recognized familial inheritance of varicose veins. The genetic basis for this remains unclear. Monogenic abnormalities such as mutation in the FOXC2 gene on chromosome 16q24.3 is associated with failure of venous valve formation and varicose veins which are well described. However, varicose veins appears to be a polygenic disorder. Despite several attempts to identify genetic variations by Genome-wide Association studies (GWAS), no genes that are clear contenders have been verified. Several studies have been reported where possible genes have been tested based on their likelihood to be involved in the molecular pathology of venous disease,[70] based on different types of molecular and genetic research including gene expression in varicose vein tissue.[60, 70] The “candidate gene approach” has thrown up several possibilities but all need further validation. Unravelling the genetics of venous disease has not moved as far as seen with other vascular diseases.

Changes in the microcirculation as a result of venous hypertension

The skin changes and leg ulcers of chronic venous insufficiency are related to a specific pathophysiological disturbance in the venous microcirculation termed venous hypertensive microangiopathy. Techniques such as laser Doppler,[71, 72] measurements of transcutaneous PO_2,[73] capillaroscopy,[74] microlymphography,[75] and skin biopsy [76, 77] have provided the means to study the changes in the skin microcirculation of limbs with CVD. Venous hypertension causes capillaries to become markedly dilated, elongated and tortuous, especially at skin sites with hyperpigmentation and lipodermatosclerosis. These changes are associated with a high microvascular blood flow in the dermis,[69, 78] and a decreased flow in nutritional capillaries.[79, 80] A striking feature in the skin of patients with venous hypertension is a "halo" formation around dilated capillaries observed on capillaroscopy, associated with microedema, pericapillary fibrin,[81] and deposition of other proteins. Microlymphangiopathy [82, 83] and outward migration of leucocytes exacerbate microedema and inflammation.[84-88] All of these changes are likely to prevent normal nutrition to skin cells predisposing to ulceration. Capillary thromboses are a late phenomenon which successively lead to reduction in the number of nutritional skin capillaries shown by reduced transcutaneous PO_2 readings.[89]

From a hemodynamic viewpoint, the most striking feature of venous microangiopathy is the contrast between an abnormally increased skin blood flow and decreased oxygen delivery to the tissues.[90-97] This decrease in tissue oxygen is explained by a reduced subepidermal capillary density and increased oxygen diffusion distance.[97] The increase in flow, confirmed by several laser-Doppler studies,[98-102] takes place in the deeper layers of the dermis, probably related to abnormal vasomotor regulation, or stimulated by tissue hypoxia and acidosis, and by inflammation.[100, 103]

Alteration of interstitial capillaries, edema and ulceration

Hemodynamic changes that result in venous hypertension are transmitted to the microcirculation to increase hydrostatic pressure in capillaries. This results in transcapillary filtration that exceeds lymphatic drainage so as to cause interstitial edema. Venous hypertension slows blood flow in capillaries prompting leukocyte adhesion to capillary endothelium, initiating an inflammatory reaction.[104] The consequent increase in macromolecular permeability causes plasma, fibrinogen and red blood cell leakage which impairs nutrient exchange.[96, 98] Sustained venous stasis and hypertension lead to chronic inflammation in the capillary bed and surrounding tissues, and chronic edema.[105, 106] Subsequent reduced capillary density could cause trophic disorders and leg ulceration.

Over the past ten years, an improved capillaroscopic technique, the OPS imaging technique used as the Cytoscan (Lekam Medical Ltd, UK) has allowed alterations of skin capillaries to be studied in limbs assigned C_1 to C_6 of the CEAP classification. The Cytoscan has a small handheld probe which can be noninvasively applied to any body surface to evaluate microcirculatory parameters such as functional capillary density (FCD - capillaries/mm^2), diameter of dermal papilla (DDP - µm) to quantify edema, the largest diameter of the capillary bulk (DCB - µm) to assess its degree of change, capillary limb diameter (CD - µm) to describe diameter changes, and capillary morphology (CM - % of abnormal capillaries per field). It has been demonstrated that these values are all progressively altered from C_1 to C_6 limbs, and that values in CVD patients are significantly different to these in healthy subjects ($P<0.05$).[107]

Alterations of lymphatic vessels

Daily lymphatic fluid turnover reaches up to two-thirds of the total volume of interstitial fluid.[108] Skin of the lower extremities contains a more dense and extensive lymphatic capillary network than skin of the upper extremities.[109] Lower extremities have a higher filtration pressure and fluid influx, and it is thought that this greater capacity for lymph transport in the lower extremities compensates for a higher influx of interstitial fluid due to orthostatism and gravity.

Spontaneous lymphatic vessel contractility contributes to lymph transport. Regular contractions of lymph vessels at a frequency of 2-4 per minute are observed *in vitro,* and spontaneous contractions of prenodal lymphatic vessels that drive lymph have been observed in human legs.[110] Internal extensions of lymphatic endothelial cells act as valves and guarantee oneway lymph flow.[108]

In a steady state, fluid and protein extravasation from blood vessels is balanced by lymphatic drainage that returns them to the blood stream. In patients with advanced CVD, tissue fluid accumulates in the interstitium to cause edema if microvascular filtration from capillaries and venules exceeds the capacity for lymphatic drainage for sufficiently long periods. In addition, varicose veins are associated with lymphatic dysfunction and structural damage to the lymphatic network, and subsequent lymph stasis and reduced lymph transportation lead to inflammation.[111] Inflammatory lipids accumulate in the media of diseased veins, and these may cause further damage to lymphatic vessels.

Skin blood flow and the veno-arterial response in limbs with venous hypertension

In normal limbs, the precapillary resistance in the skin of the foot and perimalleolar region increases on standing producing a decrease in capillary blood flow.[112, 113] This response limits the increase in capillary pressure determined by the vertical column of blood between the heart and the foot.[114] and minimizes the number of capillaries exposed to the high pressure in the standing position, This vasoconstrictor or venoarteriolar response (VAR) is mediated by a sympathetic axon reflex.[112, 113] Reduction or absence of the VAR exposes a large number of capillaries to high pressure on standing which causes increased capillary leakage and ankle edema.

Laser Doppler flowmetry has been used to study normal limbs and limbs with venous hypertension. In normal limbs with normal vasomotor activity, only some of the capillaries, say five out of ten, are open at any time when the limb is horizontal, while the VAR results in "closing down" of two or three further capillaries on standing so that only two or three capillary loops bear high pressure as the venous system becomes full. Thus, capillary flow is greatly reduced, and capillary leakage is minimal. In limbs with venous hypertension, skin red cell flux increases at rest indicating increased skin blood flow, and vasomotor activity in the supine position is reduced followed by absence of the VAR on standing.[100-102] Limbs with severe venous hypertension have an increased skin blood flow on average by three times, and vasomotor activity is minimal indicating that most capillaries, say nine out of ten, are open, not unlike an inflammatory reaction. On standing, the VAR is minimal so that a large number of capillaries, say eight out of ten, remain open resulting in increased capillary leakage proportional to the area of capillary endothelium exposed to the high flow and pressure.

Pathophysiology of venous symptoms

The most common leg symptoms in CVD are aching, pain, heaviness and discomfort. Other less common symptoms are throbbing, tightness, fatigue, feeling of swelling, cramps, itching, restless legs, tingling and burning.[115] However, these symptoms are common in the general population, especially in the elderly, and can be observed in many other conditions,[116] so that they are not specific to CVD.[117, 118] It should be stressed that their absence does not exclude CVD.

Pain which is vague and unpleasant is considered to result from increased venous pressure transmitted to the microcirculation resulting in activation of sensory multimodal nociceptors of myelinated Aδ and unmyelinated C fibres [119, 120] *via* local inflammatory mediators. Throbbing frequently occurs in patients with varicose veins and indicates a hemodynamic mechanism. Tightness is common in patients with iliocaval venous obstruction and is thought to be related to increased pressure from fluid accumulation in the anatomical compartments. Venous claudication results from severe venous outflow obstruction when the arterial inflow exceeds the venous outflow, and the recovery time is long often more than 15 minutes.[121] Heaviness and feeling of swelling are often related to edema but can be present without apparent edema. It is thought that they result from microedema in the microcirculation since they are relieved by venoactive drugs without actual reduction in leg volume.[122] Itching is often associated with skin changes but can be an isolated symptom, and inflammation, cytokine and MMP activation have all been implicated in the pathophysiology. [123] The exact cause of cramps, restless legs, tingling and burning is not clear.

Because the definition of varicose veins (CEAP 2) is based on inspection or palpation, CVD affecting the great or small saphenous veins cannot always be identified, a scenario seen in every-day practice so that such limbs may be classified into C_0 or C_1 CEAP categories. Such "occult" but symptomatic venous disease may sometimes affect IPVs, and varicose veins are diagnosed exclusively on the basis of duplex ultrasound scanning (see Chapter 14 for C_{0s} patients).

Progression of CVD

Several prospective epidemiological studies have demonstrated that CVD is progressive. In the Bochum study, 740 children who were 10-12 years of age without any CVD were seen every five years up to a total of 20 years.[124] Clinical examination was combined with Doppler ultrasound examinations and photo-plethysmography refilling time for reflux. Key conclusions were: 1) there was a gradual increase in the presence of reflux from 2.4% to 20.6% accompanied by an increase in truncal varices from 0% to 11%; 2) manifestation of a truncal varicose vein was preceded by reflux in the same vein; 3) reflux started predominantly at the saphenofemoral and saphenopopliteal junctions; 4) reflux started at about puberty; and 5) preclinical reflux represented a 30% risk of developing truncal varicose veins within four years.

In the Edinburgh vein study, 4.3% of subjects with CVD progressed each year to a more severe CEAP clinical class.[125] Another prospective five-year follow-up study of the contralateral normal limb of 73 patients who had operation for varicose veins showed that varicose veins and reflux developed in 52% with an associated deterioration in CEAP class.[126]

Progression is faster in patients with a history of DVT. A five-year follow-up study in 1560 patients who had symptoms of CVD for one year showed that ulceration developed at five years in 3.6% of 1435 without a history of DVT and 14.4% of 125 who had a history of DVT ($P<0.05$).[127] Another case-control study demonstrated that progression was even faster in patients who had developed proximal DVT.[128] In 50 limbs with varicose veins, the prevalence of skin changes progressed from zero at one year to 6% at five years, and this was in contrast to 46 limbs with proximal DVT in which skin changes increased from 4.3% at one year to 23% at five years.

Risk factors associated with progression of CVD are: family history for CVD, female gender, previous episode of DVT or SVT, lifestyle including standing occupations and poor physical activity, obesity, multiparity, oral contraceptives and constipation or low fiber intake.[129-130]

Varicose veins associated with pelvic vein reflux

Minimal or noninvasive imaging now reveals that there is a refluxing pelvic venous source in a significant percentage of women with de novo leg varicose veins, and many more with recurrent varicosities.[131] The most clinically obvious cases are those with leg varices arising in the vulvar area in the presence of a competent and normal great saphenous vein.

Pelvic venous reflux is usually the underlying cause for pelvic varices, often manifest as the pelvic venous congestion syndrome.[132] This results either from damage to pelvic vein valves during parturition,[133] or more rarely from congenital venous stenosis or webs, stenosis such as in May-Thurner syndrome,[134] acquired venous stenosis associated with iatrogenic or other trauma,[135] tumors or DVT.[136]

Recent studies have identified that as many as 15-20% of varicose veins are partly or completely associated with pelvic venous reflux.[137] However, the percentage of such patients rises to up to 30% [137-140] if they have recurrent varicose veins, irrespective of whether they were originally treated by conventional surgery or more contemporary endovenous procedures.

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CHAPTER 3

Magnitude of the problem

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

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

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

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

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

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

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CHAPTER 4

Classification, severity scoring systems and assessment for efficacy of therapies

Changes in superficial and deep veins

Varicose veins are a common manifestation of CVD and are believed to result from remodeling of the venous wall. Veins from patients with varicosities have different elastic properties than those from individuals without varicose veins.[1, 2] Hypertrophy of the venous wall is associated with increased collagen content,[3] fragmentation of elastin fibres,[4] and degradation and accumulation of extracellular matrix [5] in the vein.

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

Approximately 30% of patients with deep venous reflux shown by imaging appear to have primary valvular incompetence rather than detectable post-thrombotic damage.[7, 8] Rarely, deep venous reflux is due to valve agenesis or aplasia.[9] Varicose veins may be caused by pelvic vein reflux with no evidence of incompetence at the saphenofemoral junction, or in perforating veins of the calf or thigh. Reflux in ovarian, pelvic, vulvar, pudendal or gluteal veins may be associated with clinical symptoms and signs of pelvic congestion.[10-13]

Endogenous lysis occurs after DVT and lasts for days or weeks, so that recanalization can be observed over months or years in 50% to 80% of patients.[14-16] Rapid thrombus resolution can occur after DVT depending on thrombus extent, location, local inflammation, potency of local fibrinolytic activity and proinflammatory mediators,[18, 19] and this results in a higher incidence of preserved valve competence.[14, 17] Venous outflow obstruction can result from inadequate recanalization following DVT, less frequently from extramural venous compression, most commonly left common iliac vein compression by the right common iliac artery, from intra-luminal changes,[20-23] or rarely from congenital agenesis or hypoplasia.[24]

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

The prevalence of the post-thrombotic syndrome following DVT has been reported to have a wide variation of 35% to 69% at three years and 49% to 100% at five to ten years, and this depends on the extent and location of thrombosis, efficacy of treatment, and other definition issues.[27-37] Patients with a combination of chronic obstruction and reflux have the highest incidence of skin changes and ulceration.[37] The risk of the post-thrombotic syndrome is higher in patients with recurrent thrombosis, and is often associated with congenital or acquired thrombophilia.[38-41] Past and recent studies report that post-thrombotic skin changes and/or ulceration in patients with proximal DVT occur less frequently, with a risk of 4% to 8% in five years with adequate anticoagulation, early mobilization, and long-term compression.[42-44] Mechanical dysfunction of the calf muscle pump may enhance development of leg ulceration suggesting the importance of the range of ankle motion[45] and patient activity.[46]

Incompetent perforating veins

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

IPVs are associated with superficial and/or deep-vein reflux, and are rarely found if there is no superficial or deep reflux.[50-52] The prevalence, diameter, volume flow and velocity of IPVs increase with the clinical severity of CVD, whether or not there is co-existing deep venous reflux.[48, 53-58] However, up to 10% of patients, often women, presenting with CEAP clinical class 1 to 3 CVD, have non-saphenous superficial reflux in association with unusually located IPVs.[59]

Vascular biology and pathophysiology of the venous wall

As referred to above, varicose veins have different elastic properties to normal veins.[1, 2] The ratio of collagen I to collagen III is altered in both the veins and dermal fibroblasts from the same patients, indicating a probable systemic disorder with a genetic basis.[60]

Altered shear stress causes leukocyte activation, adhesion and migration through the endothelium [61-63] which contributes to inflammation and subsequent remodeling of the venous wall and valves.[64-67] Reduced 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 also proliferate and synthesize matrix metalloproteinases (MMPs) which overcome the effect of their tissue inhibitors (TIMPs), and the MMP/TIMP imbalance results in degradation of elastin and collagen.[62, 68, 69] This may contribute to development of hypertrophic and atrophic venous segments and valve destruction which are both seen in varicose veins. Venous wall remodelling leading to abnormal venous distension prevents valve leaflets from closing properly resulting in venous reflux.

There is a well-recognized familial inheritance of varicose veins. The genetic basis for this remains unclear. Monogenic abnormalities such as mutation in the FOXC2 gene on chromosome 16q24.3 is associated with failure of venous valve formation and varicose veins which are well described. However, varicose veins appears to be a polygenic disorder. Despite several attempts to identify genetic variations by Genome-wide Association studies (GWAS), no genes that are clear contenders have been verified. Several studies have been reported where possible genes have been tested based on their likelihood to be involved in the molecular pathology of venous disease,[70] based on different types of molecular and genetic research including gene expression in varicose vein tissue.[60, 70] The "candidate gene approach" has thrown up several possibilities but all need further validation. Unravelling the genetics of venous disease has not moved as far as seen with other vascular diseases.

Changes in the microcirculation as a result of venous hypertension

The skin changes and leg ulcers of chronic venous insufficiency are related to a specific pathophysiological disturbance in the venous microcirculation termed venous hypertensive microangiopathy. Techniques such as laser Doppler,[71, 72] measurements of transcutaneous PO_2,[73] capillaroscopy,[74] microlymphography,[75] and skin biopsy [76, 77] have provided the means to study the changes in the skin microcirculation of limbs with CVD. Venous hypertension causes capillaries to become markedly dilated, elongated and tortuous, especially at skin sites with hyperpigmentation and lipodermatosclerosis. These changes are associated with a high microvascular blood flow in the dermis,[69, 78] and a decreased flow in nutritional capillaries.[79, 80] A striking feature in the skin of patients with venous hypertension is a “halo” formation around dilated capillaries observed on capillaroscopy, associated with microedema, pericapillary fibrin,[81] and deposition of other proteins. Microlymphangiopathy [82, 83] and outward migration of leucocytes exacerbate microedema and inflammation.[84-88] All of these changes are likely to prevent normal nutrition to skin cells predisposing to ulceration. Capillary thromboses are a late phenomenon which successively lead to reduction in the number of nutritional skin capillaries shown by reduced transcutaneous PO_2 readings.[89]

From a hemodynamic viewpoint, the most striking feature of venous microangiopathy is the contrast between an abnormally increased skin blood flow and decreased oxygen delivery to the tissues.[90-97] This decrease in tissue oxygen is explained by a reduced subepidermal capillary density and increased oxygen diffusion distance.[97] The increase in flow, confirmed by several laser-Doppler studies,[98-102] takes place in the deeper layers of the dermis, probably related to abnormal vasomotor regulation, or stimulated by tissue hypoxia and acidosis, and by inflammation.[100, 103]

Alteration of interstitial capillaries, edema and ulceration

Hemodynamic changes that result in venous hypertension are transmitted to the microcirculation to increase hydrostatic pressure in capillaries. This results in transcapillary filtration that exceeds lymphatic drainage so as to cause interstitial edema. Venous hypertension slows blood flow in capillaries prompting leukocyte adhesion to capillary endothelium, initiating an inflammatory reaction.[104] The consequent increase in macromolecular permeability causes plasma, fibrinogen and red blood cell leakage which impairs nutrient exchange.[96, 98] Sustained venous stasis and hypertension lead to chronic inflammation in the capillary bed and surrounding tissues, and chronic edema.[105, 106] Subsequent reduced capillary density could cause trophic disorders and leg ulceration.

Over the past ten years, an improved capillaroscopic technique, the OPS imaging technique used as the Cytoscan (Lekam Medical Ltd, UK) has allowed alterations of skin capillaries to be studied in limbs assigned C_1 to C_6 of the CEAP classification. The Cytoscan has a small handheld probe which can be noninvasively applied to anybody surface to evaluate microcirculatory parameters such as functional capillary density (FCD - capillaries/mm^2), diameter of dermal papilla (DDP - µm) to quantify edema, the largest diameter of the capillary bulk (DCB - µm) to assess its degree of change, capillary limb diameter (CD - µm) to describe diameter changes, and capillary morphology (CM - % of abnormal capillaries per field). It has been demonstrated that these values are all progressively altered from C_1 to C_6 limbs, and that values in CVD patients are significantly different to these in healthy subjects ($P<0.05$).[107]

Alterations of lymphatic vessels

Daily lymphatic fluid turnover reaches up to two-thirds of the total volume of interstitial fluid.[108] Skin of the lower extremities contains a more dense and extensive lymphatic capillary network than skin of the upper extremities.[109] Lower extremities have a higher filtration pressure and fluid influx, and it is thought that this greater capacity for lymph transport in the lower extremities compensates for a higher influx of interstitial fluid due to orthostatism and gravity.

Spontaneous lymphatic vessel contractility contributes to lymph transport. Regular contractions of lymph vessels at a frequency of 2-4 per minute are observed *in vitro,* and spontaneous contractions of prenodal lymphatic vessels that drive lymph have been observed in human legs.[110] Internal extensions of lymphatic endothelial cells act as valves and guarantee oneway lymph flow.[108]

In a steady state, fluid and protein extravasation from blood vessels is balanced by lymphatic drainage that returns them to the blood stream. In patients with advanced CVD, tissue fluid accumulates in the interstitium to cause edema if microvascular filtration from capillaries and venules exceeds the capacity for lymphatic drainage for sufficiently long periods. In addition, varicose veins are associated with lymphatic dysfunction and structural damage to the lymphatic network, and subsequent lymph stasis and reduced lymph transportation lead to inflammation.[111] Inflammatory lipids accumulate in the media of diseased veins, and these may cause further damage to lymphatic vessels.

Skin blood flow and the veno-arterial response in limbs with venous hypertension

In normal limbs, the precapillary resistance in the skin of the foot and perimalleolar region increases on standing producing a decrease in capillary blood flow.[112, 113] This response limits the increase in capillary pressure determined by the vertical column of blood between the heart and the foot.[114] and minimizes the number of capillaries exposed to the high pressure in the standing position, This vasoconstrictor or venoarteriolar response (VAR) is mediated by a sympathetic axon reflex.[112, 113] Reduction or absence of the VAR exposes a large number of capillaries to high pressure on standing which causes increased capillary leakage and ankle edema.

Laser Doppler flowmetry has been used to study normal limbs and limbs with venous hypertension. In normal limbs with normal vasomotor activity, only some of the capillaries, say five out of ten, are open at any time when the limb is horizontal, while the VAR results in “closing down” of two or three further capillaries on standing so that only two or three capillary loops bear high pressure as the venous system becomes full. Thus, capillary flow is greatly reduced, and capillary leakage is minimal. In limbs with venous hypertension, skin red cell flux increases at rest indicating increased skin blood flow, and vasomotor activity in the supine position is reduced followed by absence of the VAR on standing.[100-102] Limbs with severe venous hypertension have an increased skin blood flow on average by three times, and vasomotor activity is minimal indicating that most capillaries, say nine out of ten, are open, not unlike an inflammatory reaction. On standing, the VAR is minimal so that a large number of capillaries, say eight out of ten, remain open resulting in increased capillary leakage proportional to the area of capillary endothelium exposed to the high flow and pressure.

Pathophysiology of venous symptoms

The most common leg symptoms in CVD are aching, pain, heaviness and discomfort. Other less common symptoms are throbbing, tightness, fatigue, feeling of swelling, cramps, itching, restless legs, tingling and burning.[115] However, these symptoms are common in the general population, especially in the elderly, and can be observed in many other conditions,[116] so that they are not specific to CVD.[117, 118] It should be stressed that their absence does not exclude CVD.

Pain which is vague and unpleasant is considered to result from increased venous pressure transmitted to the microcirculation resulting in activation of sensory multimodal nociceptors of myelinated Aδ and unmyelinated C fibres [119, 120] *via* local inflammatory mediators. Throbbing frequently occurs in patients with varicose veins and indicates a hemodynamic mechanism. Tightness is common in patients with iliocaval venous obstruction and is thought to be related to increased pressure from fluid accumulation in the anatomical compartments. Venous claudication results from severe venous outflow obstruction when the arterial inflow exceeds the venous outflow, and the recovery time is long often more than 15 minutes.[121] Heaviness and feeling of swelling are often related to edema but can be present without apparent edema. It is thought that they result from microedema in the microcirculation since they are relieved by venoactive drugs without actual reduction in leg volume.[122] Itching is often associated with skin changes but can be an isolated symptom, and inflammation, cytokine and MMP activation have all been implicated in the pathophysiology.[123] The exact cause of cramps, restless legs, tingling and burning is not clear.

Because the definition of varicose veins (CEAP 2) is based on inspection or palpation, CVD affecting the great or small saphenous veins cannot always be identified, a scenario seen in every-day practice so that such limbs may be classified into C_0 or C_1 CEAP categories. Such "occult" but symptomatic venous disease may sometimes affect IPVs, and varicose veins are diagnosed exclusively on the basis of duplex ultrasound scanning (see Chapter 14 for C_{0s} patients).

Progression of CVD

Several prospective epidemiological studies have demonstrated that CVD is progressive. In the Bochum study, 740 children who were 10-12 years of age without any CVD were seen every five years up to a total of 20 years.[124] Clinical examination was combined with Doppler ultrasound examinations and photo-plethysmography refilling time for reflux. Key conclusions were: 1) there was a gradual increase in the presence of reflux from 2.4% to 20.6% accompanied by an increase in truncal varices from 0% to 11%; 2) manifestation of a truncal varicose vein was preceded by reflux in the same vein; 3) reflux started predominantly at the saphenofemoral and saphenopopliteal junctions; 4) reflux started at about puberty; and 5) preclinical reflux represented a 30% risk of developing truncal varicose veins within four years.

In the Edinburgh vein study, 4.3% of subjects with CVD progressed each year to a more severe CEAP clinical class.[125] Another prospective five-year follow-up study of the contralateral normal limb of 73 patients who had operation for varicose veins showed that varicose veins and reflux developed in 52% with an associated deterioration in CEAP class.[126]

Progression is faster in patients with a history of DVT. A five-year follow-up study in 1560 patients who had symptoms of CVD for one year showed that ulceration developed at five years in 3.6% of 1435 without a history of DVT and 14.4% of 125 who had a history of DVT ($P<0.05$).[127] Another case-control study demonstrated that progression was even faster in patients who had developed proximal DVT.[128] In 50 limbs with varicose veins, the prevalence of skin changes progressed from zero at one year to 6% at five years, and this was in contrast to 46 limbs with proximal DVT in which skin changes increased from 4.3% at one year to 23% at five years.

Risk factors associated with progression of CVD are: family history for CVD, female gender, previous episode of DVT or SVT, lifestyle including standing occupations and poor physical activity, obesity, multiparity, oral contraceptives and constipation or low fiber intake.[129-130]

Varicose veins associated with pelvic vein reflux

Minimal or noninvasive imaging now reveals that there is a refluxing pelvic venous source in a significant percentage of women with de novo leg varicose veins, and many more with recurrent varicosities.[131] The most clinically obvious cases are those with leg varices arising in the vulvar area in the presence of a competent and normal great saphenous vein.

Pelvic venous reflux is usually the underlying cause for pelvic varices, often manifest as the pelvic venous congestion syndrome.[132] This results either from damage to pelvic vein valves during parturition,[133] or more rarely from congenital venous stenosis or webs, stenosis such as in May-Thurner syndrome,[134] acquired venous stenosis associated with iatrogenic or other trauma,[135] tumors or DVT.[136]

Recent studies have identified that as many as 15-20% of varicose veins are partly or completely associated with pelvic venous reflux.[137] However, the percentage of such patients rises to up to 30% [137-140] if they have recurrent varicose veins, irrespective of whether they were originally treated by conventional surgery or more contemporary endovenous procedures.

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CHAPTER 5

Functional measurements to assess disease severity

Introduction

Venous hypertension is the main factor that determines development and severity of symptoms and signs in CVD. Ambulatory venous pressure (AVP) measurements were used to examine the prevalence of active or healed venous ulceration in a study of 251 legs in patients with symptoms due to superficial and/or deep venous disease.[1] No ulceration occurred in limbs with AVP <30 mmHg, but there was a linear increase in ulcer prevalence with raised AVP, 14% in limbs with AVP between 31 and 40 mmHg, and 100% with AVP >90 mmHg, (r=0.79). The high correlation between ulceration and AVP occurred irrespective of whether the patients had superficial or deep venous disease. Skin changes are rare in the presence of AVP <35 mmHg and frequent with AVP >65 mmHg.[1]

The effects of venous hypertension are modified by three compensatory mechanisms. The first is the ability of the lymphatic system to compensate for the increased lymph volume that is produced. In patients with the same degree of severe venous hypertension, lymphatic drainage can increase by up to ten times and yet the leg may look normal in some, whereas an increase by just two times may cause overt skin changes in others. The second mechanism is the variable fibrinolytic activity in the blood and tissues that removes excess extracellular protein and particularly fibrin. Fibrinolytic activity was measured in 37 patients with moderate venous hypertension with AVP in the range of 35-65 mmHg. Euglobulin lysis time (ELT) was normal (<240 min) in 12 patients of whom only two had lipodermatosclerosis (LDS) but no ulceration, in contrast to the remaining ten patients with low fibrinolytic activity (ELT >240 min) of whom nine had LDS and seven had both LDS and ulceration (P<0.001).[2] The third factor which exerts an adverse effect on the microcirculation is progressive deterioration with time.[3]

Hemodynamic abnormalities responsible for venous hypertension are reflux, obstruction, efficacy of the calf muscle pump and how well the collateral circulation develops if obstruction is present. Compensatory mechanisms have variable efficacy and coexisting hemodynamic abnormalities may be present, so that it is not surprising that if only one of the above parameters is measured then it is likely to have a relatively poor correlation with the severity of disease (see below).

Correlation of measurements of reflux with clinical severity

Results from most studies indicate that the more extensive the reflux, the more severe the disease and the higher is the prevalence of skin changes and ulceration. In patients with deep venous reflux, the presence of a competent popliteal valve appears to protect the leg from skin changes and ulceration even in the presence of proximal obstruction.

Anatomic extent of reflux

The anatomic extent of reflux in the pre-ultrasound era could be determined with descending phlebography. Pathological reflux through the popliteal vein was shown to be associated with symptoms but the association was not clear-cut.[4]

Duplex ultrasound scanning, which combines B-mode imaging with directional color flow and gated Doppler, is a sensitive method for detecting reflux and its extent in both superficial and deep veins. In the absence of deep venous obstruction, limbs with reflux confined to the proximal (above knee) superficial or deep veins rarely develop skin changes or ulceration.[5, 6] In contrast, even in the presence of normal deep veins, symptoms and signs of CVI are more often found when the entire length of the great saphenous vein is involved or when reflux is present in both great and small saphenous veins.[5, 6] In limbs with reflux confined to the superficial system, aching, ankle edema and skin changes are predominantly associated with reflux in below knee veins, ulceration is found only when the entire great saphenous vein is involved or when reflux is extensive in both great and small saphenous veins, and multi-segmental reflux is more prevalent in legs with ulcers than in non-ulcerated limbs (75% *vs.* 22%).[7] A pattern of reflux that involves two or more of the venous systems (superficial and deep, superficial and perforating or superficial, perforating and deep) is found in approximately two-thirds of patients with skin changes or ulceration.[6-11] Although these studies were performed prior to the introduction of CEAP or other clinical severity scoring systems, available evidence suggests that there is a strong association between the severity of CVI and the anatomic distribution and extent of venous reflux.

The anatomic extent of reflux was investigated in a study involving 98 limbs (83 patients), with active chronic venous ulcers. Reflux was present in all limbs except one. Isolated reflux in one system (superficial=3, deep=4, perforator=3) was seen in ten legs (10%), while incompetence in all three systems was seen in 51 legs (52%). Superficial reflux with or without involvement of other systems was seen in 84 legs (86%), 72 legs (73%) had deep reflux with or without involvement of other systems, and incompetent perforating veins were identified in 79 limbs (81%). Axial reflux (continuous reverse flow from the groin region to below knee) was found in 77 limbs (79%). Thus, axial distribution of disease was found in the majority of cases and no patient had isolated deep venous incompetence below the knee.[12]

The significance of popliteal reflux in relation to development of symptoms was investigated in two studies. The first performed in the late 1970s involved 51 patients (55 limbs) who had had deep venous thrombosis (DVT) extending into the femoral or iliofemoral segment three to five years earlier and ten limbs of ten healthy volunteers.[13] AVP was measured by inserting a needle in a vein on the foot and the presence of reflux in the popliteal vein was determined by a directional Doppler ultrasonic blood velocity detector. All patients had ascending venography. Those limbs with iliofemoral recanalization and competent popliteal valves had an ambulatory venous pressure of 30±10 mmHg. In limbs with iliofemoral recanalization and incompetent popliteal valves, the mean AVP was 61±8 mmHg. In patients with persistent iliofemoral occlusion and competent popliteal valves, the mean AVP was 38±15 mmHg, while those limbs with proximal occlusion and incompetent popliteal valves had the highest AVP of 85±15 mmHg. In limbs with competent popliteal valves, the incidence of ulceration was nil even in the presence of proximal occlusion. In limbs with incompetent popliteal valves, ulceration had developed in three-quarters of the limbs at some time. The results of this study indicated that the most important factor in determining a high AVP and ulceration was the condition of the popliteal valves. The extent of DVT and recanalization or the failure of recanalization was of secondary importance.[13]

A second study involved 50 patients who had venographic DVT confined to the calf during the years 1990-1994 and were seen again 6-10 years after the acute event. A significant association was found between popliteal reflux and skin changes. Popliteal reflux on duplex ultrasound was present in 20 limbs of which 12 (71%) were classified as C4-C6. Popliteal reflux was absent in 30 limbs of which only 5 (29%) were C4-C6 ($P<0.05$).[14]

Refilling time, velocity at peak reflux and volume flow

The cut-off point for the diagnosis of pathological reflux for superficial and deep veins is acknowledged to be 0.5 and 1.0 seconds respectively.[5, 15]

A study of 244 limbs with reflux demonstrated an increase in peak reflux velocity (PRV), time of average rate of reflux (TAR) and absolute displaced volume (ADV) in C4-C6 compared with C1-C3, but reflux time (RT) was not significantly different between these groups. There was no significant correlation between RT, PRV, TAR and ADV *versus* clinical severity in limbs with GSV reflux only. However, in limbs with axial deep reflux to below the knee, that is with concomitant reflux at the knee level, only the PRV and TAR had a significant but weak correlation with clinical severity (r=0.32, P=0.0036 and r=0.22, P=0.049, respectively). The conclusion is that RT cannot quantify severity of reflux and is a purely qualitative measurement.[16] This is because RT depends on the size of the reservoir to be filled and the diameter of the refluxing vessel. A small diameter refluxing vessel with a low volume flow will be associated with a long RT. For the same size reservoir, a large diameter vein which allows a high-volume flow will be associated with a shorter RT.

Quantification of venous reflux was attempted by Yamaki *et al.*[17] who stratified 1,132 limbs in 914 patients with primary valvular incompetence into C1-C3 and C4-C6. The mean±SD of RT, PRV and peak reflux flow (PRF) at the saphenofemoral junction in C1-C3 *versus* C4-C6 were 4.05±2.42 *versus* 3.42±1.87 s (P=0.532), 27.4±21.1 *versus* 49.7±35.3 cm/s (P<0.0001) and 26.3±35.6 *versus* 64.7±73.4 mL/s (P<0.0001) respectively. The corresponding results at the saphenopopliteal junction were 4.55±2.45 *versus* 3.73±1.92 s (P=0.213), 30.5±16.8 *versus* 39.5±24 cm/s (P=0.0002) and 16.5±15.2 *versus* 22.2±23 mL/s (P=0.0029) respectively. The data demonstrated considerable overlap. Nevertheless, they concluded that although the PRV and PRF improved the discrimination power between early and advanced CVI, RT was unable to achieve this result.[17] A similar study by the same group used the same parameters in 686 limbs that included patients with secondary as well as primary CVI.[18] In secondary (post-thrombotic) CVI, they showed that the mean±SD PRV had significant discrimination power between C1-C3 *versus* C4-C6 at the femoral vein (14.8±10.1 *versus* 32.4±16.1 cm/s, P=0.017) and popliteal vein (18.0±11.2 *versus* 28.9±19.0 cm/s, P=0.0003). The same was true for the PRF at the common femoral vein (34.5±4.2 *versus* 66.0±19.1 mL/s, P=0.011), femoral vein (21.3±34.3 *versus* 43.8±43.2 mL/s, P=0.027) and popliteal vein (15.0±14.6 *versus* 20.1±16.9 mL/s, P=0.016).

Flow volume at peak reflux in mL/s was measured in the great saphenous vein in 19 legs. A total reflux greater than 10 mL/s was associated with a high prevalence of skin changes (66%) irrespective of whether this was in the superficial or deep veins, whereas reflux less than 10 mL/s was not associated with skin changes.[19]

Air plethysmography (APG®) provides quantitative measurements of reflux using the venous filling index (VFI) in mL/s and the venous filling time to 90% of the venous volume (VFT90) in seconds. It was shown by Christopoulos *et al.* that the VFI increased with increasing severity from control subjects to patients with varicose veins to those with post-thrombotic sequelae.[20] In a series of 134 limbs with CVD and C1-C6, the prevalence of chronic swelling and skin changes were both zero if VFI was <3.0 mL/s,12% and 19% when VFI was 3-5 mL/s, 46% and 61% when VFI was 5-10 mL/s and both 76% when VFI was greater than 10 mL/s.[21]

VFI was also significantly higher in classes C2-C6 compared with C0-C1 in a study of 294 limbs by Nishibe *et al.* but they were unable to discriminate the clinical severity.[22] Similarly, the mean±SD [range] of the VFI in a study by van Bemmelen *et al* was higher in limbs with ulcers (N.=16, 5.4±3.8 mL/s) and dermatitis (N.=6, 7.7±4.6 mL/s) compared with those with varicose veins (N.=10, 2.6±1.7 mL/s). The differences were significant between varicose veins *versus* ulceration (P=0.003) and *versus* dermatitis (P=0.034). However, there was a large amount of overlap between these groups.[23] In a study by Welkie *et al.*, VFI was progressively larger (P<0.0001) and VFT90 was shorter (P<0.0001) in a series of control legs (N.=94), legs with varicose veins and mild swelling (N.=109) and legs with pigmentation and moderately severe swelling (N.=67).[24] They noted that no additional hemodynamic deterioration occurred between the skin pigmentation stage and venous ulceration.

A recent study using APG on 93 consecutive patients/legs awaiting endovenous treatment confirmed that VFT90 decreased with increasing clinical disease.[25] The VFT90 decrease correlated with increasing C class (r=0.343, P=0.001) and increasing VCSS (0.197, P=0.05). Interestingly, none of the 25 (26.9%) patients with a VFT90>25 seconds were among the 17 (18.3%) patients in categories C4b-C6 or with a VCSS>9. The authors hypothesized that the VFT90 may represent the time taken for the anti-gravitational mechanisms in the leg to fail and concluded that the VFT90 may have discriminatory usefulness in stratifying patients with early clinical disease.[25]

However, in a recent study in 443 legs there was no correlation between the venous refill time (VFT) using photo-plethysmography (PPG) and the AVVQ -0.042 (P=0.606).[26] This is not too surprising because APG has been reported as a better method for evaluating clinically significant venous reflux than PPG.[18] In the comprehensive longitudinal vein study known as the Bochum study, it was concluded that PPG was not a means for assessing malfunction in the venous system during childhood and adolescence [27] although a short VFT had some predictive value in the development of ulceration ten years later.

The presence of saphenous pulsatile flow has been shown by one group to be more helpful than the presence of reflux in discriminating severe disease.[28] The most likely explanation of this pulsatile flow, often seen in patients with severe CVD when examined in the standing position, is the result of maximum dilatation of the arterioles allowing the *vis a tergo* to manifest itself on the venous side.

Neglen and Raju studied the morphologic distribution of venous incompetence (erect duplex ultrasound and descending venography), results of AVP measurement, venous refilling time, the Valsalva test and air-plethysmography VFI for correlation with the clinical severity class as defined by the authors in 118 consecutive limbs (class 0, N.=34; class 1, N.=42; class 2, N.=11; class 3, N.=31).[29] There was pure deep incompetence in 29% of limbs with severe venous disease (class 2/3), only 6% had pure superficial disease and the remainder had a combination. A history of previous thrombosis and the presence of posterior tibial vein incompetence were markedly common with ulcer disease (84% and 42%, respectively). The duplex ultrasound multisegment score correlated strongly with clinical severity classification (r=0.97). The venous refilling time and VFI had the highest sensitivity in identifying severe venous disease (class 2/3), and the AVP had excellent specificity. The authors concluded that for noninvasive determination of reflux, a combination of VFI and duplex ultrasound scanning not only localized reflux but also separated severe from mild clinical vein disease, with high sensitivity and specificity.

Elevation of venous pressure at rest and during exercise

Elevation of venous pressure at rest and during exercise is often present in patients presenting with swelling and venous claudication as a result of severe outflow obstruction. Outflow obstruction is always suspected when swelling is the predominant symptom. It may be associated with a history of DVT and development of prominent collateral venous channels in the groin above the pubis or the anterior abdominal wall. Severe outflow obstruction is particularly suspected in patients with post-thrombotic limbs and venous claudication.

Simple leg elevation with the patient supine can provide an estimate of the resting venous pressure by observing the height (in cm) of the heel from the heart level at which the prominent veins in the foot collapse. During direct femoral vein pressure measurements in patients with venographic iliofemoral occlusion and poor pelvic collaterals, the average resting pressure in the supine position was found to be 5.5±10.5 mmHg higher than the unobstructed opposite limb. In the presence of good collateral veins, the gradient between the two limbs was 0.6±1.4 mmHg.[30] The arm-foot pressure differential in the horizontal position at rest and after reactive hyperemia has been explored by Raju.[31, 32] Four grades of obstruction were identified. In grade IV, the arm/foot pressure differential was greater than 5 mmHg (often 15-20 mmHg) and there was no further increase with reactive hyperemia. Most limbs with venous claudication belonged to this group.

During exercise, elevation of the resting pressure in the dorsal vein of the foot by an average of 22 mmHg has been found in thrombotic deep vein occlusion involving the femoral vein.[33] Increase in venous pressure at rest and during exercise in patients with venous claudication is associated with increase in intramuscular pressure.[34] In a recent study, 22 patients with unilateral obstruction of the iliac and common femoral veins underwent a standardized treadmill test with simultaneous bilateral invasive pressure measurements in the common femoral vein and dorsal foot vein. Post-thrombotic limbs showed a mean common femoral vein (CFV) pressure increase of 28.1±21.0 mmHg after walking compared with 2.1±6.2 mmHg in control limbs (26.0 mmHg difference; 95% confidence interval [CI], 17.1-34.9). Less difference was observed in the dorsal foot vein (net drop of 36.8±22.7 mmHg in affected limbs *vs*. 48.7±23.1 mmHg in non-affected limbs, 11.9 mmHg difference; 95% CI, -1.3 to 25.0).[35]

Combined quantitative measurements of reflux and outflow resistance

As indicated above, attempts to correlate individual venous hemodynamic measurements with symptoms and signs of CVD have produced poor or at best moderate results, probably because of lack of methods to quantify obstruction. The authors of a recent study hypothesized that the combination of quantitative measurements of (a) overall limb reflux (superficial and deep) and (b) overall limb outflow resistance *i.e.* including the collateral circulation would provide a hemodynamic index that should be related to the severity of disease.[36] Twenty-five limbs with CVD and one limb from a healthy volunteer (VCSS 0-13) were studied. The clinical CEAP classification was C0 in one limb, C1 in two limbs, C2 in 10 limbs, C3 in three limbs, C4 in one limb, C5 in six limbs and C6 in three limbs. Air-plethysmography was used to measure reflux (VFI in mL/s) when the subject changed position from horizontal to standing. Subsequently, with the subjects horizontal and the foot elevated 25 cm, simultaneous recordings of pressure and volume were made on release of a proximal thigh cuff inflated to 70 mmHg. Pressure change was recorded with a needle in the foot and simultaneous volume change with air plethysmography. Flow (Q in mL/min) was calculated at intervals of 0.1 seconds from tangents on the volume outflow curve. Outflow resistance (R) was calculated at 0.1 second intervals by dividing pressure by the corresponding flow (R=P/Q). R increased markedly at pressures lower than 30 mmHg due to decrease in vein diameter, so resistance at 30 mmHg (R_{30}) was used in this study. In a multivariable linear regression analysis with VCSS as the dependent variable, both VFI and R_{30} were independent predictors ($P<0.001$). Using the constant (0.333) and regression coefficients, the regression equation provided a hemodynamic Index (HI) or estimated VCSS=0.333+(VFI x 0.44) + (R_{30} x 158). Thus, HI could be calculated for every patient by substituting VFI and R_{30} in the equation. HI or calculated VCSS was linearly related to the observed VCSS (r=0.83). The results indicate that the combination of quantitative measurements of reflux and outflow resistance provide a hemodynamic index which is linearly related to the VCSS. These findings need to be confirmed in a bigger series.

Conclusions

The authors of many of the papers quoted above have spent a lot of time trying to find out if one hemodynamic measurement or another can discriminate between different clinical severity classes (*e.g.* C of CEAP). This approach belongs to the pre-duplex ultrasound era when hemodynamic measurements were used as noninvasive diagnostic tests. Currently, duplex ultrasound provides accurate information about the presence and anatomic extent of reflux or obstruction. Hence, there is no longer a need for hemodynamic measurements to be used as diagnostic tests. However, there is an increasing need for them to be used as measurements that tell us how much reflux and/or how much functional obstruction there is, after the ultrasound examination has been made. Future studies are needed to investigate whether such hemodynamic tests can be used to improve clinical decisions and refine the indications for different therapeutic procedures (see Chapters 6-12).

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Note: This chapter is based on the UIP Consensus document on venous hemodynamic changes in lower limb venous disease.[37]

CHAPTER 6

Investigations

General remarks

Understanding the pathophysiology is the key to selecting appropriate investigations for CVD. However, there is not a single test that can provide all information needed to guide clinical decisions and formulate management strategies. A physician should answer a number of clinically relevant questions when a patient presents with symptoms and signs suggestive of CVD. The first is to ascertain whether symptoms are likely to be a result of CVD. In the absence of obvious varicose veins, a pocket continuous-wave Doppler or duplex ultrasound scan can be used in the office to determine the presence of disease. Investigations should then determine the presence or absence and the severity of reflux, obstruction and calf muscle pump dysfunction.[1]

Detection of reflux and obstruction

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

Duplex ultrasound scanning

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

1. standing position for the femoral and great saphenous veins, sitting or standing position for popliteal, small saphenous and calf veins and supine position for the inferior vena cava and iliac veins;
2. measurement of the duration of peak velocity or volume flow of reflux, after standard calf compression and its release;
3. size and competence of perforators;
4. diameters of saphenous veins;
5. size and competence of major saphenous tributaries;
6. anatomic extent of reflux in the superficial or deep veins;
7. anatomic extent of intraluminal deep venous obstruction (post-thrombotic trabeculae) below and, if feasible, above the inguinal ligament;
8. presence or absence of phasic flow in the common femoral vein;
9. evidence of vulval varices with or without refluxing veins arising from the pelvis and communicating with leg veins (with consideration of transvaginal or transperineal ultrasound) especially with pelvic congestion syndrome symptoms.

Obstruction

It is difficult to quantify venous obstruction (see Chapter 5). Traditional methods that measure arm-foot pressure differential,[11] outflow fraction [12, 13] and limb outflow resistance by plethysmography[1, 14] express global functional obstruction including the effect of the collateral circulation, but do not quantify local anatomic obstruction. IVUS more reliably demonstrates relative degrees of obstruction at the involved venous segment, but it does not provide a measure of overall limb outflow resistance since this depends on how well the collateral circulation develops.

Investigation of patients in different CEAP clinical classes

A precise diagnosis is the basis for correct classification of the venous problem. One or more of three levels of testing need to be used tto evaluate a patient with CVD, depending on the severity of disease:

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

— ***Level II:*** The non-invasive vascular laboratory with detailed duplex ultrasound scanning which can include transabdominal ultrasound,[15] with or without plethysmography.

— ***Level III:*** The addition of invasive investigations or complex imaging studies including ascending and transfemoral (antegrade and retrograde) phlebography, varicography, venous pressure measurements, CT venography scanning, MR venography or IVUS.

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

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

Level I investigations are usually sufficient in asymptomatic patients. However, symptoms such as aching, pain, heaviness, leg-tiredness and muscle cramps in the absence of visible or palpable varicose veins are an indication for detailed duplex ultrasound scanning (Level II) to exclude reflux which often precedes the clinical manifestation of varices. In certain cases (C0s), ultrasound scanning may have to be repeated at the end of the day.[16]

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

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

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

Level II investigations are used to determine the severity of reflux and obstruction and whether or not reflux or obstruction in the deep veins is responsible for the edema. Level III studies to investigate the deep venous system must be considered if obstruction is demonstrated or suspected as a result of duplex scanning of the lower limbs and of transabdominal ultrasound scanning, Lymphoscintigraphy may be indicated to confirm a diagnosis of lymphedema in certain patients with suspected phlebolymphedema.

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

Level II investigations, often including transabdominal ultrasound scanning, is required in all patients. Selected cases such as those being considered for deep-vein intervention should proceed to level III. Level II 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. Evaluation of significant pigmentation in the gaiter region (C4a) as a marker of advanced venous disease always requires a level II investigation because clinical appearances alone can be highly misleading.[14]

In the presence of collateral veins on the abdominal wall or in the suprapubic area in symptomatic patients, even without signs of CVI (C3-C6), level II investigations including transabdominal ultrasound scanning are warranted, and additional level III investigations may be considered.[17] The same strategy is also applicable for patients with venous claudication.[18]

Measurement and reporting of reflux

There are several ways to measure reflux:

1. Global non-invasive indirect investigations can be used based on volume changes such as plethysmography (VFI in mL/s). Simultaneous measurements of venous filling time using APG have been shown to correlate highly with GSV reflux time using duplex ultrasound.[15] Thus, duplex ultrasound changes in a single superficial vein has been validated against the leg's overall hemodynamic status.
2. Global invasive investigation such as dorsal foot venous pressure can differentiate between superficial and deep reflux using below and above knee cuffs with recordings of ambulatory venous pressure (AVP) and recovery time (RT). Although AVP is the gold standard for hemodynamic function in venous disease, it cannot provide a quantitative measurement of reflux.
3. Non-invasive duplex ultrasound which offers morphologic and functional evaluation of different vein segments. It mainly gives qualitative information about the presence or absence and extent of reflux in individual veins. In addition, it can provide semi-quantitative evaluation of reflux in terms of peak velocity, and quantitative volume flow throughout reflux or volume flow at peak reflux.
4. Using descending venography, Kistner classified deep vein reflux in five grades:
   - grade 0: competent valves with no reflux;
   - grade 1: wisps of reflux limited to the upper thigh;
   - grade 2: definite reflux, but limited to the upper thigh by competent valves in the distal thigh or the popliteal vein;
   - grade 3: reflux through the popliteal vein and into the calf;
   - grade 4: massive cascading reflux through the popliteal vein into the calf, and frequently through incompetent perforating veins.

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

Measurement and reporting of obstruction

The pathophysiologic classification of obstruction needs additional information about its severity, particularly for the iliocaval segment. Venous obstruction is defined as partial or total blockage of venous flow, while venous occlusion is defined as total obliteration of the venous lumen. A positive global test such as plethysmography (outflow fraction or outflow resistance), hand-foot pressure differential (Raju test) or hyperemia pressure differential may indicate global obstruction to venous outflow, but a normal result does not rule out a severe local stenosis if there is a well-developed collateral circulation.

Bilateral dynamic femoral vein pressure measurement was previously considered to evaluate the degree of obstruction to venous outflow. The best parameters were pressure elevation and difference before and during exercise, and immediately after exercise, as well as time for pressure to return to pre-exercise level. Pressure measurements can be performed simultaneously with biplane femoral venography which will demonstrate the morphological changes of the iliocaval outflow.

The venous drainage index (VDI) in mL/s is a recently introduced parameter of APG.[19] It is the exact opposite to the VFI. The VDI quantifies the rate of calf decompression from a position of dependency to elevation. It is intuitive that a slow rate of calf decompression, which occurs in obstruction, will have a poor response to gravitational drainage. This has been validated in healthy controls using graduated thigh-cuff pressures to simulate degrees of obstruction.[20] Using a tilt-table comparing healthy controls with patients of known obstruction, the cut-off point in determining presence of obstruction was a VDI <11 mL/s.[21] In a subsequent study, VDI was reduced significantly in response to iliac venous stenting.[22]

Although several tests are available to assess the overall severity of outflow obstruction for a limb, especially outflow resistance (see Chapter 5), no adequate hemodynamic test presently exists to identify a local hemodynamically significant obstruction. There is no data available to indicate whether it is the local stenosis in the common femoral vein or the overall outflow resistance, which takes into account the collateral circulation, that would clinically matter. The method of choice to evaluate the morphologic changes of the iliocaval outflow today is IVUS.

Measurements of reflux using APG and outflow resistance using pressure and APG volume changes were developed in the 1980s and 1990s when valve reconstruction was in its infancy and venous stenting for relief of obstruction was not available so that the need for clinical applications were limited. Now that valve reconstruction and stenting for iliac obstruction have not only been demonstrated to be feasible but have also become more widely used, reflux and resistance or VDI should be measured before and after deep venous reconstruction so that objective criteria can be developed to assess clinical benefit. Such criteria will help us refine the indications for deep venous surgery.

Investigations in patients with pelvic congestion syndrome

The following investigations should be considered to assess pelvic venous reflux which is the underlying cause of the pelvic congestion syndrome: endovaginal duplex sonography, transperineal duplex sonography, magnetic resonance imaging (MRI), catheter venography and CT venography (CTV).

Endovaginal or transperineal Doppler ultrasound is a dynamic study allowing provocative manouvres to demonstrate pelvic venous reflux. Experienced operators suggest that they can consistently specifically identify an ovarian or hypogastric vein or their branches as the source of reflux,[23] although others have found this difficult to reproduce, while some define specific "leak points."[24]

A more reproducible technique is MRI which can be enhanced with newer protocols, protein-bound gadolinium contrast agents, and where available "upright" MRI scanners. CTV is not recommended for diagnosing pelvic vein reflux as it is not dynamic, requires iodinated contrast and exposes the patient to ionizing radiation.

Transjugular or transfemoral catheter venography is usually reserved for confirming sources of pelvic vein reflux identified by non-invasive imaging prior to therapeutic sclerotherapy or embolization, rather than for primary assessment. Unfortunately, agreement is lacking for consistent criteria for the presence of significant reflux.

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CHAPTER 7

Compression therapy

Treatment to apply pressure to the lower extremities is a fundamental component for managing CVD. The following devices are available: 1) compression bandages; 2) compression stockings; 3) self-adjustable Velcro-devices; 4) compression pumps; 5) hybrid devices.[1]

Compression bandages

Long stretch bandages (“elastic”) 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) do not extend at all.[2] The latter two groups are also called “inelastic”. Textiles may be covered with adhesive (sticking to the skin) or cohesive (sticking to the bandage) material to prevent slippage. Composite bandages consist of several components, usually including a padding layer (multi-component bandages).[3] Inelastic bandages are usually applied too loosely and need special training.[4-6]

Printed ovals or rectangles that change to circles or squares at a particular bandage extension,[7] and markings that are matched to a specific pressure may facilitate application by showing adequate stretch, and may help to achieve even intended pressures.[8] By superimposing velcro patches, bandages may achieve a predefined resting pressure and a high working pressure.[9]

Medical compression hosiery and classes

Medical compression stockings (MCS) are made of elasticated textile. According to their length, they are classified as *knee-length, thigh-length and tights* (pantyhose style). They may be custom-made or off the shelf which are available in standard sizes.[10] Most compression stockings are round-knitted. Flat-knitted products provide higher stiffness and are usually custom-made for lymphedema patients.

Different compression classes are available according to the pressure they exert. The pressure profile for each compression class varies between different countries. A Consensus meeting from the International Compression Club on the classification of compression stockings has criticized this confusion and the fact that the customer does not get any information concerning the stiffness of the individual stocking declared on the box. Several practical proposals were made.[11, 12] It was recommended to classify stockings by mmHg rather than by compression classes.

Producers ruled that MCS should achieve higher pressures in the ankle region than proximal over the calf. This dogma of graduated compression was to avoid impeding venous return, but this has been questioned by several studies. Couzan et al have shown that “antigradient” or “progressive” stockings are more effective and also easier to apply than usual degressive compression stockings for improvement of pain and lower leg symptoms in patients with CVI [3] Mosti *et al.*[14] showed hemodynamic superiority for such "progressive stockings" compared to conventional medical compression stockings, and also demonstrated that the inverse pressure profile did not cause increased leg edema.[15] However, using different methodology, Riebe *et al.* reported that venous pumping function showed greater improvement with graduated than with "progressive stockings", but the latter were easier to apply and take off.[16] These authors described superior effects for conventional graduated stockings over "progressive" stockings for edema reduction and subjective complaints.[17] Despite these discrepancies concerning the issue of a pressure gradient in medical stockings, the concept of antigradient compression for mobile patients may be of increasing relevance in the field of compression bandages [18] and of compression devices used in sport.[19-22]

Velcro-devices

CircAid® products were introduced in the United States, and several other brand names then turned up on the international market which all are based on the concept to provide a short-stretch product that can be handled by the patients themselves. They have two main advantages compared to a stiff inelastic bandage. The first is that the compression pressure does not depend on the skill and experience of a bandager but on the subjective feeling of the patient. One manufacturer includes pressure cards that inform the patient how strong the straps need to be applied to achieve a specific pressure range, which can be adjusted to the individual needs. After a short demonstration, patients are able to apply the devices with a lower degree of variability than even an experienced bandager.[23]

The second advantage is that in contrast to inelastic bandages that start to lose compression pressure immediately after application, Velcro products keep their pressure due to repeated self-adjustment by the patients.[24] It has been shown that Velcro compression during the acute phase of leg swelling is more effective than inelastic compression for reducing edema. The ability to readjust these devices as swelling subsides helps maintain the high pressure that effectively reduces swelling and improves symptoms.[24]

These Velcro devices are useful for managing venous leg ulcers where the use of bandages is not feasible, either due to lack of personnel or for those far from wound centers. The Velcro can be changed as necessary, the wound cleansed, then dressed by the patient or local carer. The proper pressure profile can be maintained by proper reapplication of the devices. These Velcro devices are also useful for managing mixed ulcers and are much safer than elastic bandaging. It has also been reported that they improve the microcirculation in the area of the ulcer.[24]

Finally, there are many patients who need ongoing effective leg compression for swelling but who physically are unable to apply and remove stockings. Velcro devices are easily managed by many of these individuals and allow control of their symptoms over the long term.

Intermittent Pneumatic Compression Pumps (IPC)

IPC devices consist of single or multiple inelastic cuffs that are intermittently and/or sequentially inflated.

Devices consist of an inflatable cuff wrapped around the leg or foot and an electrical pneumatic pump that inflates the cuff with air, compressing the deep veins and displacing blood proximally.

Several devices are used in clinical practice including pneumatic garments designed to compress the foot, calf, or thigh, or combinations of these. The garments incorporate single- or multi-chamber compression bladders that are intermittently pumped up to pressures of varying magnitudes, with different durations of inflation, deflation and maintained pressure. The bladders may inflate simultaneously or sequentially with fluctuating times of overlapped applied pressures. IPC devices range from simple single-chamber or multi-chamber devices with limited adjustability, to advanced devices with more treatment options. Few studies are available comparing the efficiency of different devices, but single cell compression is less effective than multiple cells [25] and sequential multi-compartmental programmable device, so called advanced pneumatic compression devices (APCDs) provide faster and more succinct cycles of pres-

TABLE I.—*Compression classes for stockings in different countries.*

Compression class (US Standard)	Compression class (AFNOR)	Compression class (AFNOR)	Compression class (RAL-GZG/ENV)	Compression at the ankle*	
Ccl	Ccl	Ccl	Ccl	HPa	mmHg
15/20	I légère	10/15	Not applicable	20 to 23	15 to 17
20/30	II moyenne	15/20	I mild high	14 to 28	18 to 21
30/40	III forte	20/36	II moderate	31 to 43	23 to 32
40/50	IV extra forte	>36	III strong	45 to 61	34 to 46
50 high			IV very strong	65 and higher	49 and higher

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

sure and relaxation and seem superior to standard systems.[26] The main mechanisms of action for IPC are to have a hemodynamic effect that promotes venous return, increases arterial flow, and removes edema, and that enhances fibrinolytic activity and release of TFPI to reduce the tendency for blood to thrombose.[27]

Hybrid compression devices

This new concept combines sustained compression exerted by inflated pressure chambers. This compression is kept constant with further intermittent pneumatic pressure and can be used after a working day for several hours in the sitting position. First experiences concerning edema reduction and ulcer healing have been published.[28-30]

Measurement of interface pressure and stiffness

The compression pressure given by stocking producers is measured in textile laboratories using different extensometers that calculate the force that fabrics exert on a theoretical cylinder model, which depends on its stretch.[31]

As shown in Table I, values for the different compression classes provided by the stocking producers vary considerably between different countries. It is therefore recommended that for future publications, pressure ranges be provided, in mmHg rather than a compression class. The International Compression Club proposed three classes for pressures exerted by bandages: mild <20 mmHg, moderate 20-40 mmHg and strong 40-60 mmHg. These recommended pressure values are measured at the medial distal lower leg ("B1 point") in the resting position.[3, 31] While most prescribed compression stockings are in a pressure range between 20 and 30 mmHg,[32] the intended pressure range of compression bandages should usually be higher than 40 mmHg.[3, 6]

Different pressure probes that are commercially available can be used to measure interface pressures of a compression device *in vivo* [31] Among different possible locations to measure pressure, we recommend the area where the muscular part or the medial gastrocnemius muscle turns into the tendinous part ("B 1 point"). The cross-section of the leg is approaching a circle in this segment, so that results from point measurements can be extrapolated to the whole circumference.[3, 31]

Fabric stiffness is determined by the increase in interface pressure per centimetre increase of the leg circumference, either at rest or from muscular contraction during walking ("walking pressure"). The peak pressure and bandwidth of pressure change at the ankle is highest with short-stretch material. Adding several layers of compression bandages and superimposing stockings increase both the interface pressure and stiffness of the cumulative compression.[31, 33]

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 for good compression from a bandage is that it provides a sufficiently high-pressure peak during walking ("working pressure") to exert a pronounced massaging effect while allowing a tolerable resting pressure. Bandages lose pressure after application due to edema reduction. Therefore, bandages should initially be applied at relatively high pressure and should be renewed when the pressure decreases into an in-effective range. When bandage pressures were measured in different institutions, on average three out of four bandages applied by medical staff were too loose, and only a small proportion of the bandagers reached a given target range of 40-60 mmHg.[4-6] These data clearly demonstrate the importance of adequate training for bandagers.

Multi-component bandages better meet the above requirements than single component bandages. Pads or rolls of different materials can be used to increase the local pressure over a treated venous segment following sclerotherapy or over a venous ulcer situated behind the medial malleolus. Bandages should be washable and reusable.

Practical use of compression stockings

Stockings should only be prescribed if patients can apply them on a regular basis. They are best put on in the morning.[34] New stockings should be prescribed after 3-6 months if used daily. Different devices have been developed to help patients put them on.[35] Wearing two or more stockings over each other or superimposable leggings may be a way to facilitate putting them on, and this creates a dose-adjustable compression according to the indication and the patient's tolerance.[36]

While bandages are mainly used for the initial phases of compression therapy, stockings are recommended for maintenance and long-term management of chronic conditions.

Quality of life and compliance

Several studies have shown that quality of life improves with compression treatment.[37-41] Different questionnaires are available:[42-47] besides general quality-of-life forms, such as Short Form Health Survey 36 (SF-36), Nottingham Health Profile (NHP), Euroqol 5D (EQ-5D), while disease-specific quality-of-life questionnaires have been published for deep vein thrombosis (VEINES-QOL/Sym questionnaire), chronic venous insufficiency (Chronic Venous Insufficiency Quality of Life questionnaire (CIVIQ)),[46] and venous leg ulcers (Health-related quality of life in chronic wounds or Wound-QoL questionnaire).[47-49]

Compliance with compression is a major issue, especially when the efficacy of devices is assessed in long-term studies such as after ulcer healing or for preventing the post thrombotic syndrome.[50-51]

Mode of action

Several beneficial effects of compression treatment, and methods used to measure these effects, are summarized in Table II.[52-101] Experimental studies have helped to understand how various compression devices perform for the normal and the diseased leg. Basically, three main effects of compression can be identified:

1) an effect preventing and reducing edema and inflammation for which relatively low pressure may be sufficient;

2) a hemodynamic effect to reduce venous re-

TABLE II.—*Effects of compression therapy.*

Parameter	Investigative method
Sub-bandage pressure	MST-tester, Picopress, Kikuhime [52, 53]
Reduced edema	Volumetry, isotopes, ultrasound [54-58]
Reduced venous volume	Phlebography, blood pool scintigraphy, Air plethysmography (APG) [59-65] MRI [66-67]
Increased venous velocity	Circulation time (isotopes), Duplex [68, 69]
Blood shift into central compartments	Blood pool scintigraphy [70]
Decreased venous reflux	Duplex, APG [59, 60, 71]
Improved venous pump	Foot volumetry, plethysmography, venous pressure [72-78]
Increased arterial flow	Xenon-clearance, Laser Doppler [79-85]
Improvement of microcirculation	Capillaroscopy, tcPO2, Laser Doppler [86-89]
Increased lymphatic drainage	Isotopic and indirect lymphography Indocyanin green lymphography [90-93]
Effect on ultrastructure and cytokines	Microscopy and histochemistry, Laboratory investigations [94-99]
Patients compliance	Thermocouple, Pressure sensors [100, 101]

flux and enhance pumping capacity which requires venous narrowing in the upright position and during walking, therefore with higher pressures required;

3) the effect of a stiff compression material which will cause compression to increase sharply during calf muscle expansion, resulting in an extra boost from the venous return pumping mechanism.

Clinical applications

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

A prospective crossover trial was performed in 19 flight attendants who rated their symptoms on a visual analog scale.[102] Initially, participants wore no compression for two weeks, after which they wore 8-15 mmHg and 15-20 mmHg gradient compression support hose while flying over a 4-week period. Use of lightweight (low compression) ready-to-wear gradient compression hosiery was very effective for improving symptoms of discomfort (P<0.01), swelling (almost P<0.05), fatigue (P<0.05), aching (P<0.01), and leg tightness. Symptom improvement when hosiery was worn regularly during waking hours for four weeks was statistically significant compared to no compression. The difference between 8-15 mmHg and 15-20 mmHg compression was not statistically significant.

Blättler *et al.* measured leg volume increase and subjective complaints in healthy volunteers with a standing test and showed that symptoms are reduced independent to the pressure exerted by compression and the volume increase that this prevented.[103]

A study of industry workers showed that very light compression “placebo stockings” with less than 10 mmHg compression also significantly reduces occupational evening edema after a working day.[54] In a 4-week multicenter, randomized, double-blind, placebo-controlled clinical trial conducted on two parallel groups of 341 women presenting with mild chronic venous disease CEAP class C1-3s Ep As Pr1-5 [38] class 1 elastic compression stockings (pressure at the ankle 10-15 mmHg) were compared with placebo stockings (pressure at the ankle 3-6 mmHg). The primary treatment efficacy was assessed by global impairment on a visual analogue scale, while quality of life was measured by the CIVIQ questionnaire, a symptoms index included sum of individual scores for pain, limb heaviness, paresthesiae, cramps and evening limb edema, and limb volume was measured by volumetry. A statistically significant improvement of quality of life and a decrease of limb edema was demonstrated in patients with class 1 elastic compression stockings.

Another prospective multi-center randomized double-blind crossover study involved 125 female patients presenting with early-stage chronic CVD (CEAP classification of C1-3s Ep As Pr1-5) and compared the efficacy of class 1 (10-15 mmHg at the ankle) compression stockings with that of reference stockings of identical appearance.[104] There was a significant improvement in global painful discomfort as well as quality-of-life criteria. In a further study, 108 hairdressers were randomized to wear medical compression stockings (MCS;15-20 mmHg) in a crossover study.[105] Wearing medical compression stockings reduced the symptom score for pain and feelings of swelling (range 0-4) by an average of 0.22 (12%, P<0.001). Sleep disturbance, feeling of unattractive legs and depression also improved and there was a decrease of lower leg volume by an average of 19 mL (P<0.001), with preference in older hairdressers (P<0.001).

A meta-analysis of 11 RCT involving 1453 subjects (794 healthy people exposed to various forms of stress, 552 patients with CVD and 141 patients after varicose vein surgery) compared stockings exerting an ankle pressure of 10-20 mmHg with placebo or no treatment and with stockings exerting a pressure of more than 20 mmHg.[55] Compression with 10-20 mmHg had a clear effect on edema and symptoms compared to <10 mmHg pressure, placebo stockings, or no treatment (P<0.0001). No study showed a difference between 10-20 and >20 mmHg stockings. The authors concluded that despite important methodological heterogeneity and sometimes sub-standard reporting, the meta-analysis suggests that leg compression with 10-15 mmHg is an effective treatment for CVD, that lower degrees pressure is not effective and that higher pressure may be of no additional benefit.

A Cochrane review of seven studies involving 356 patients (CEAP C1-4) concluded that symptoms subjectively improved with wearing stockings across trials that assessed this outcome, but these assessments were not made by comparing one randomized arm of a trial with a control arm and are therefore subject to bias.[106] The conclusion was that there is insufficient, high-quality evidence to determine whether compression stockings are effective as the sole and initial treatment of varicose veins or whether any type of stocking is superior to any other.

In a recent randomized double-blind placebo controlled trial, 30 patients with no experience of elastic stockings presenting with primary varicose veins causing calf pain or aching were randomized to a GECS (18-21 mmHg at the ankle level, N.=15) or a placebo stocking (“0 mmHg”, N.=15). The primary outcome measure was pain or aching of the index leg after one week. After one week, GECS were more effective than placebo stockings in reducing pain or aching (VAS score 1.7±3.0 *vs.* 4.5±2.8 for placebo, p=0.02), while non-significant trends were observed for some of the remaining symptoms of the index leg, including feeling of swelling (VAS score 0.9±1.9 *vs.* 3.3±3.5 for placebo), paresthesiae (VAS score 0.2±0.6 *vs.* 2.1±3.1 for placebo), and a number of symptoms other than pain or aching (1.3±1.1 *vs.* 2.8±1.7 for placebo). The number needed to treat (95% CI) for a 50% or complete improvement of pain or aching in the index leg was two (95% CI 1.2-5.5) and two (95% CI 1.2-5.3), respectively. Mean daily use of the placebo stockings and GECS was 8.0 hours and 10.2 hours respectively (P=0.13).[107]

The efficacy of negative graduated compression stockings for relieving symptoms of moderate to severe CVD has been studied. Based on experiences from a previous study,[108] 401 patients (CEAP C2b to C5) were randomized to degressive compressive stockings (30 mmHg at ankle, 21 mmHg at upper calf) or progressive compressive stockings (10 mmHg at ankle, 23 mmHg at upper calf).[13] The primary outcome, evaluated after three months was a composite success outcome including improvement of pain or heavy legs without onset of either ulcer, deep or superficial vein thrombosis of the lower limbs, or pulmonary embolism. The rate of success was higher in the progressive compressive stocking group compared to the digressive compressive stocking group (70.0% *vs.* 59.6%; relative risk, 1.18; 95% confidence interval, 1.02-1.37; P=0.03). This was mainly due to more frequent symptom improvement in the progressive compressive stocking group. In addition, the stockings were considered easy to apply by 81.3% of patients in the progressive compressive stocking group *vs.* 49.7% of patients in the digressive compressive stocking group (P<0.0001).

An update concerning the efficacy of compression stockings in patients with symptoms due to mild to moderate CVD was published recently.[109] The available evidence suggests that compression relieves the symptoms and reduces edema in patients with mild to moderate CVD (C1-C4).

Effect of compression stockings in pregnancy

According to a Cochrane review, only few studies are available.[110]

A prospective randomized controlled study involving 42 pregnant women compared a “no-stockings” control group (N.=15) with two treatment groups: group 1 (N.=12) wore compression class I stockings (18-21 mmHg) on the left leg and class II stockings (25-32 mmHg) on the right; in group 2 (N.=15), the compression classes were reversed.[111] Both classes of compression stockings failed to prevent emergence of superficial varicose veins. However, reflux at the sapheno-femoral junction to the great saphenous vein was observed in the third trimester in only 1/27 treated women *vs.* 4/15 controls (P=0.047). In addition, more treated women reported improved leg symptoms (7/27 *vs.* 0/15 controls; P=0.045). The authors concluded that although compression stockings did not prevent emergence of gestational varicose veins, they decreased the incidence of reflux at the sapheno-femoral junction to the great saphenous vein and improved leg symptoms (Grade B). More RCTs are needed.

A retrospective study from Italy using 15-20 mmHg stockings revealed reduction of leg pain and improvement for quality of life in two-thirds of pregnant women who agreed to wear compression stockings.[112] A recent study described reduced nausea associated with wearing stockings in the early stage of pregnancy.[113]

Effect of compression stockings in patients having sclerotherapy

Two studies addressed the effect of compression stockings and its duration following sclerotherapy for reticular veins and telangiectases in similar locations. The first study included 40 patients, 30 patients who did and ten control patients who did not receive compression therapy.[114] The compression group consisted of ten in each of three duration groups: three days, one week, and three weeks. Patients were evaluated at 1, 2, 6, 12 and 24 weeks for degree of improvement and side effects. The three compression groups showed significantly greater improvement at six weeks (P=0.004). The patients treated with compression for three days and one week had more improvement than the control patients while the patients treated for three weeks of continuous compression had the most improvement. In terms of side effects, the one week and three-weeks compression groups experienced the least amount of post-sclerotherapy hyperpigmentation. In the second study, 100 female patients seeking treatment for telangiectases and reticular veins and presenting comparable areas of telangiectasia on the lateral aspect of the thigh (C1a or C1a Ep As1 Pn) were randomized to wear medical compression stockings (23 to 32 mmHg) daily for three weeks or no such treatment, following a single session of standardized liquid sclerotherapy.[115] Outcome was assessed by patient satisfaction analysis and quantitative evaluation of photographs taken from the lateral aspect of the thigh before and again at 52 days on average after sclerotherapy by two blinded expert reviewers. Wearing compression stockings (23 to 32 mmHg) for three weeks enhanced the efficacy of sclerotherapy of leg telangiectasies by improving clinical vessel disappearance.

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

Two studies compared high compression stockings to bandages after liquid sclerotherapy. In the first study, a standard bandaging technique was compared with a high pressure compression stocking in a RCT.[116] Efficacy was judged by success of injections, complications of treatment and patient satisfaction. For the stockinged legs, 144 of 156 injections were successful compared to 117 of 147 in the bandaged group (P<0.001) (Chi squared). The incidence of superficial thrombophlebitis was also reduced in the stocking group. In the second study after sclerotherapy, high compression stockings alone produced comparable results to Elastocrepe bandages with stockings.[117] It was concluded that bandaging is not required after sclerotherapy if a high compression stocking is used.

Two studies compared the effect of compression stockings in patients having foam sclerotherapy. In the first, 124 legs were randomized to 24 hours or five days of bandaging.[118] There was no significant difference in the incidence of superficial thrombophlebitis after two weeks or skin discoloration after six weeks (46% *versus* 40%; P=0.546). There was also no significant difference in the change in AVVSS from baseline to two weeks or to six weeks or in change in Burford pain score from baseline to two weeks, or in change in Short Form 36 score from baseline to six weeks. In the second study, 60 patients with incompetent great or small saphenous veins were randomized to compression stockings (15-20 mmHg worn during the day for three weeks) or no compression.[119] Clinical and duplex ultrasound assessments were performed by independent experts on days 14 and 28. Patients also completed QOL and symptom questionnaires. There was no difference between compression and control groups in terms of efficacy, side effects, satisfaction scores, symptoms and QOL. It is questionable if a stocking exerting a pressure of about 10 mmHg on the thigh can achieve any effect in an ambulant patient. However, recent consensus papers recommend the use of compression after sclerotherapy.[120-123]

Duration of compression therapy after sclerotherapy

In the absence of convincing evidence, we recommend best clinical judgment to determine the duration of compression therapy after sclerotherapy.

However, further RCTs are required to establish the role of compression in patients having foam sclerotherapy.

Effect of compression stockings in patients having varicose vein surgery or endovenous procedures

Two studies investigated the value of grade III compression stockings after varicose vein surgery. In a trial of high- *versus* low-compression stockings (40 mmHg *vs.* 15 mmHg at the ankle) both were equally effective for controlling bruising and thrombophlebitis, but low compression stockings proved to be more comfortable.[123] In the second study, patients were randomized to bandages or grade I or grade III stockings,[124] and there was no difference in terms of pain and costs.

Two studies investigated the value of grade II compression stockings after varicose vein surgery. A RCT involving 76 limbs found that recurrent varicose veins were reduced by postoperative stockings worn for three months to one year.[125] The incidence of recurrence was reduced from 61% in the control group to 12% in the stocking group. In the second study, 60 patients (CEAP classification C2s) were randomized to postoperative compression therapy with a stocking system or standard stretch bandages for two weeks.[126] Primary end-points were incidence of venous thromboembolism, hemorrhage, limb hematoma, or edema. There was no difference in the mean area of thigh hematoma on postoperative days seven and 14 in the two groups. On postoperative day seven, edema was found in 50% of patients wearing bandages and in 20% of patients wearing the stocking kit which was a significant reduction. No statistical difference was recorded for postoperative pain; but better patient acceptance and quality of life after the operation were recorded in the stocking group.

Two studies investigated addition of local pressure pads under the compression bandages or stockings after endovenous laser and varicose vein surgery. In the first study, 200 patients undergoing endovenous laser ablation of the GSV were randomized to receive an eccentric compression applied in the medial thigh or not.[127] Patients were scheduled for a seven-day examination to assess the level of pain experienced, measured using a visual analogue scale giving a numerical grade from 0 (no pain) to 10 (worst pain ever). The intensity of postoperative pain was significantly reduced ($P<0.001$) in the eccentric compression group compared with the non-compression group. In the second study, 54 patients underwent stripping of the GSV and side branch avulsion under local anesthesia and were treated postoperatively in sequential order by 1) thigh length compression stockings; 2) adhesive bandages; and 3) newly developed eccentric compression pads fixed with tapes and a thigh length stocking.[128] The lowest sub-bandage pressure of around 15 mmHg at thigh level in the lying position as found in group A under the

TABLE III.—*Studies on post-procedural compression published since 2013.*

Pittaluga (2013) [133]	MCS 18 mmHg for 36 hrs *vs.* one week after mini-invasive surgery	100 patients	No benefit from wearing the compression stocking beyond the first postoperative day for pain, ecchymosis, quality of life, and DVT
Bakker (2013) [134]	MCS for 48 hrs *vs.* MCS for seven days (after EVL ablation)	86 patients	Compression for longer than 48 hrs reduces pain and improves physical function during the first week after treatment
Huang (2013) [135]	Short-duration (3-10 d) *vs.* long-duration (3-6 wk) compression after GSV surgery	Meta-analysis 4 RCTs (1991-2009) 686 patients	No benefits to long-term compression therapy regarding postoperative pain, leg volume, incidence of complications, and duration of absenteeism from work
Reich-Schupke (2014) [136]	Low pressure MCS 18-22 mmHg) *vs.* moderate pressure MCS (23-32 mmHg)	88 patients	23-32 mmHg MCS are superior to 18-21 mmHg MCS in faster resolution of edema and feelings of pain, tightness, and discomfort of the leg in the first week after varicose vein surgery, but not in the longer post-surgical period up to six weeks
Elderman (2014) [137]	MCS (23-32 mmHg) two wks *vs.* no MCS after 24 hrs bandage	111 patients	MCS for two wks: significant reduction of postoperative pain and use of analgesics compared with not wearing compression
Krasznai (2016) [138]	MCS (23-32 mmHg, thigh high) 4 hrs *vs.* 72 hrs after laser	50 patients 4 h 51 patients 72 h	4 h not inferior to 72 h concerning swelling and pain
Ayo (2017) [139]	Radiofrequency (91%) and laser ablation (9%) one wk 30-40 mmHg *vs.* no compression	85 limbs (72 patients)	No difference of patient-reported and clinical outcomes May be an unnecessary adjunct following GSV ablation

compression stockings, Group B and group C showed significantly higher pressures (median values of 47 and 68 mmHg respectively in lying position, P<0.001). Major adverse events were seen in a total of 10 of 18 patients in group A, in 1/18 in group B, and in 0/18 in group C. It appears that the best results with respect to reduction of pain and hematoma were obtained when eccentric compression pads were taped to the skin of the thigh and a compression stocking was worn on top.

Conflicting results have been obtained for the value of compression bandages after varicose vein surgery. One study using 99mTc-labelled red blood cells showed that high-compression can reduce thigh hematoma.[129] However, other studies showed no difference between bandages and grade I compression stockings [130] or the duration of their use (1 *vs.* 3 *vs.* 6 weeks).[131, 132]

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

Table III [133-139] shows an update on studies concerning post-procedural compression published since 2013.

Effect of compression stockings in the prevention of PTS

Four RCTs investigated the efficacy of compression stockings for preventing development of the PTS in patients with proximal DVT who received conventional anticoagulation.

In the first study, 194 patients were randomized to grade III (40-50 mmHg) compression stockings or no stockings.[140] The median follow-up was 76 months (range 60-96) in both groups. Mild-to-moderate PTS occurred in 19 (20%) patients in the stocking group and 46 (47%) in the control group (P<0.001). Severe PTS occurred in 11 (11%) patients in the stocking group and 23 (23%) patients in the control group (P<0.001). In both groups, most cases of PTS occurred within 24 months of the acute thrombotic event. In the second study, 180 patients were randomized to wear or not wear below-knee compression elastic stockings (30-40 mmHg) for two years.[141] Follow-up was performed for up to five years. Post-thrombotic sequelae developed in 44 (49%) of 90 controls (severe in 10) and in 23 (26%) of 90 patients wearing elastic stockings (severe in three). All but one event developed in the first two years (P=0.011). The third study assessed the effect of prolonged compression therapy after standard anticoagulation for six months.[142] At the end of anticoagulation, 169 patients were randomized to wear grade II compression stockings or not. Primary efficacy analysis was for emerging skin changes (C4-C6 per the CEAP classification). The primary end occurred in 11 (13.1%) of 84 patients in the treatment group and 17 (20.0%) of 85 in the control group (P=0.30). Within subgroup analyses of the primary end showed a large sex-specific difference between women (HR, 0.11; 95% CI, 0.02-0.91) and men (HR, 1.07; 95% CI, 0.42-2.73). The fourth study randomized one group of 47 patients to compression stockings (20-30 mmHg) or placebo stockings and a second group of 35 patients to compression stockings (30-40 mmHg) or placebo.[143] PTS developed in 11 (27%) of 40 controls and in 11 (26%) of 42 patients wearing elastic stockings (P=0.91).

Clear-cut results have been obtained from the first two studies in which strong stockings were used. However, considering all four studies which include 628 patients, compression stockings reduced the incidence of PTS from 37% to 21% (RR 0.55; 0.43 to 0.72). In a RCT, 267 patients with a first episode of proximal DVT were randomized to wear either thigh-length or below-knee compression stockings for two years.[144] After 3, 6, 12, 18, 24, and 36 months, they were assessed for PTS manifestations using the Villalta scale. PTS developed in 44 (32.6%) of the 135 patients randomized to thigh-length and in 47 (35.6%) of the 132 allocated to below-knee stockings. Severe PTS developed in three patients in each group. Stocking-related side effects developed in 55 (40.7%) of the 135 patients allocated to thigh-length CES and in 36 (27.3%) of those randomized to the below-knee group (P=.017), and this led to premature discontinuation of their use in 29 (21.5%) and 18 (13.6%) patients respectively. The authors concluded that thigh-length stockings do not offer a better protection against PTS than below-knee stockings and are less well tolerated.

A multicenter placebo-controlled RCT involving 794 patients with a first DVT has-been recently published casting doubt on the efficacy of compression for preventing the PTS. Interpretation of the results by the authors was that "elastic compression stockings (ECS) did not prevent PTS after first proximal DVT, hence our findings do not support routine wearing of ECS after DVT". This assertion should be confirmed by further studies.[145] This large multicenter study which contradicts previous publications has stimulated several groups to publish reviews and meta-analyses on this subject, all with the conclusion that further studies will be needed to achieve clear recommendations.[146-152]

Table IV [147-152] shows a summary of new publications concerning the effect of compression stockings to prevent PTS.

Prerequisites of future studies should include the following considerations:

— clear characterization of location, duration and treatment of acute DVT;

— exclusion of chronic venous insufficiency (CEAP 3-6);

— immediate use of compression in the acute DVT phase;

— optimal care concerning best compliance;

— outcome parameters: pain, edema, QOL, CEAP, Villalta, VCCS, registration of walking distances.

In the recently published IDEAL DVT study individualised duration of wearing compression stockings was compared with ongoing compression for 2 years after a first episode of proximal DVT in patients in whom CEAP classes >3 were excluded. 666 from 856 patents started with compression in the acute phase of DVT. Treatment could be stopped in 55% of patients at 6 months and in an additional 11% of patients at 12 months because of two consecutive Villalta scores of 4 or less. Post-thrombotic syndrome occurred in 125 (29%) of 432 patients receiving individualised duration of therapy and in 118 (28%) of 424 receiving standard duration of therapy, (odds ratio 1·06, 95% CI 0·78 to 1·44). The authors conclude that individualising the duration is effective and could shorten the length of therapy needed, potentially enhancing patients wellbeing.[153]

Effect of compression on the healing of venous ulcers

Several recent guidelines have emphasized that appropriate compression therapy is the keystone to treating patients with leg ulcers. Once healing has completed, compression should be continued as a basic management.[154-157]

The Cochrane Database Systematic Review, updated in 2012,[158] reports on 48 RCTs which include a total of 4321 patients. The authors concluded that "compression increases ulcer healing rates compared with no compression. Multi-component systems are more effective than single-component systems. Multi-component systems containing an elastic bandage appear to be more effective than those composed mainly of inelastic constituents. Two-component bandage systems appear to perform as well as the four-layer bandage. Patients receiving the four-layer bandage heal faster than those allo-

TABLE IV.—*Summary of new publications concerning the effect of compression stockings to prevent PTS.*

Jayaraj A (2015) [148]	GECs *vs.* no compression	69 patients after acute DVT for 2 y, Villalta + VCSS	Lower incidence of PTS after one month, but not later.
Skervin AL (2016) [149]	Review meta-analysis	3 RCTs inclusive of 1,177 patients	Uncertainty because of sampling variability and heterogeneity was too high to conclude in favour or against an effect of wearing compression stockings in preventing PTS.
Burgstaller (2016) [147]	Review meta-analysis	5 RCTs with a total of 1393 patients	It is not justifiable to entirely abandon the recommendations regarding compression stockings to prevent PTS.
Subbiah (2016) [150]	Review meta-analysis	3 RCTs, 1462 patients	Use of elastic compression stockings does not significantly reduce the development of PTS, more studies needed.
Berntsen (2016) [151]	Review meta-analysis	5 RCTs, 1418 patients	Moderate-quality evidence including all 5 studies suggest no effect of elastic compression stockings on recurrent venous thromboembolism or death.
Jin (2016) [152]	Review meta-analysis	6 RCTs, 1465 patients	Evidence is not strong enough to draw a reliable conclusion.

TABLE V.—*Update of references for leg ulcer healing published since 2013.*

Kapp (2013) [164]	MCS moderate pressure *vs.* MCS high pressure	100 patients: dropouts: 69	Non-compliant patients: wound recurrence 9 times more likely Moderate compression: risk recurrence 3 times greater than with high compression
Dolibog (2013) [165]	IPC *vs.* MCS *vs.* bandages	70 patients:	Wound size reduction and percentage of wounds healed significantly higher in groups receiving IPC or MCS than in groups using short-stretched bandages
Finlayson (2014) [166]	MCS (Cl III) *vs.* 4 layer bandages	103 patients: dropouts: 16	Healing of venous leg ulcers equally effective with both systems, but more rapid response with bandages
Ashby (2014) [167]	Double layer MCS *vs.* bandages	457 patients: (2954 excluded)	Both treatments equally effective at healing venous leg ulcers Higher rate of treatment changes in MCS group
Clarke-Moloney (2014) [168]	Ulcer-recurrence: MCS class 1 (18-21 mmHg) *vs.* MCS class 2 (23-32 mmHg)	100 patients: dropouts: 1	Ulcer recurrence rates: no group difference Compliance: no group difference Ulcer recurrence rates: lowest in compliant patients, regardless of compression levels
Van Gent (2015) [169]	Ulcer recurrence after RCT 10 y before: surgery *vs.* compression	80 patients after 10y surgery	Ulcer free: surgical group (58.9%), compared to the conservative group (39.6%)

cated the single stretch bandage. More patients heal on high-compression stocking systems than with the single stretch bandage. Further data are required before the difference between high-compression stockings and the four-layer bandage can be established".

In a recent review of the literature to determine which compression method is superior to promote ulcer healing, Mauck *et al.* described that at least moderate-quality evidence supports compression over no compression, multicomponent systems over single-component systems, and systems with an elastic component over those without, and that only low-quality evidence supports the effect of compression on ulcer recurrence.[159]

The superiority of bandages containing an elastic component may be better explained by the easier handling rather than by physical factors, since all tested multicomponent bandages exert high stiffness due to friction between the multiple layers and the fact that they are covered by an adhesive layer on top.[160] A study from Hong Kong reported healing rates at 24 weeks for short stretch bandages of 72.0% (77/107) *vs.* 67.3% in the four-layer bandage group (72/107) and 29.0% (31/107) with "usual care" without compression, demonstrating that successful results can be achieved without an elastic component.[161]

Compression bandages should be applied by trained staff. Due to the immediate reduction of edema, it loses pressure and should therefore be renewed frequently. Special ulcer kits consisting of a light stocking to keep the ulcer dressing in place and a stronger 20-30 mmHg stocking have been developed, with reports that they have better healing rates than different compression bandages, especially in patients with small and short duration ulcers.[162, 163] The under-stocking is used overnight, while the additional over-stocking is usually worn just during the day. Larger ulcers may benefit from ulcer stockings if they are wrapped over by stronger bandages.[164]

Table V [164-169] shows an update of references on healing of leg ulcers with different stockings published since 2013.

In a prospective clinical pilot study, Dolibog *et al.* randomized 70 patients with unilateral venous leg ulcers to compression therapy by intermittent pneumatic compression (IPC), medical compression stockings or short-stretch compression bandages for 15 days. All patients received saline-soaked gauze dressings along with oral Daflon 500 mg once daily.[165] Wound size reduction and percentage of wounds healed were significantly higher in groups receiving IPC or stockings than in groups using short-stretch bandages.

Ashby *et al.*[167] randomised 457 patients out of a total of 3411 ulcer patients presenting with small venous leg ulcers of median areas 4.1 cm² and 3.7 cm² to either two-layer ulcer kit or four-layer bandage treatment. Median time to ulcer healing was 99 days (95% CI 84-126) in the hosiery group and 98 days (95% CI 85-112) in the bandage group. The healing rate was similar in the two groups (70.9% hosiery and 70.4% bandage). Finlayson *et al.*[166] reported results that were similar to these, although in their study the four-layer system showed a more rapid response.

Based on the current literature, the healing rates of venous leg ulcers are comparable between ulcer medical compression stockings (ulcer kit) and crepe bandage systems for relatively small ulcers.

It is essential to continue compression therapy to prevent ulcer-recurrence.[168]

However, abolishing reflux by surgical or endovenous intervention is more effective than compression therapy alone.[169]

Recent experimental studies

Recent experimental studies have questioned some conventional concepts concerning compression:

— Compression of superficial and deep veins depends very much on the body position. Deep veins are more affected by compression than superficial veins in both the horizontal prone position and standing.[67, 170]

— Higher pressure over the calf leads to a stronger effect on the venous pump than a pressure gradient.[18, 19]

— Lower pressure may be more effective than very high pressure for chronic venous edema.[171]

— Compression has an anti-inflammatory effect that deserves more consideration.[98, 99]

— Both intermittent pressure waves [172] and sustained pressure up to 40 mmHg improve arterial flow, in normal individuals [81, 82] and also in patients with occlusive arterial disease, for example in patients with mixed, arterial-venous leg ulcers.[79]

In contrast to drug therapy, compression treatment never had to pass any pharmacological phase I and phase II trials to confirm clinical efficacy and determine the therapeutic dose range. Although some insight concerning the mechanisms for action of compression has emerged from several studies during the past years, a lot more must be learned to tailor and to optimize this important treatment modality for different clinical indications.[173]

Intermittent pneumatic compression devices (IPC)

Limited data based on RCTs are currently available that demonstrate encouraging clinical outcome when IPC is used as part of the care for venous ulcers.[174-182]

The first study was reported in 1981,[176] and was a prospective controlled but not randomised trial involving 21 patients. Eight of nine (89%) patients treated with IPC (single chamber used for two to three hours per day for ten to 44 weeks) healed but only 1 (9%) of 11 control patients healed. A RCT involving 45 patients was subsequently performed in 1990.[177] Both groups were managed with ulcer debridement, cleaning, nonadherent dressings, and graduated compression stockings. In one group, sequential gradient IPC was applied for four hours each day for three months. In the intermittent pneumatic compression group, 10 (48%) of 21 patients had complete healing of all ulcers compared to one (4%) of 24 patients in the control group. The median rate of ulcer healing in the control group was 2.1% area per week compared to 19.8% area per week in the IPC group.

In another RCT, 22 patients were assigned to IPC (one hour twice weekly at 50 mmHg for 90 s followed by 30 s deflation) for six months, and a control group.[178] Both groups received local wound care and application of Unna boots. At six months, 12 (100%) of 12 patients in the IPC group had healing of ulcers compared to eight (80%) of ten patients in the control group. The healing rate was 0.15 cm^2/d in the IPC group compared with 0.06 cm^2/d in the control group. In a third RCT, 53 patients were assigned to IPC (sequential gradient) for three hours each day with an elastic stocking for six months or Unna boot.[179] At six months, 20 (71%) of 28 patients in the IPC group had healing of ulcers compared with 15 (60%) of 25 patients in the control group.

A more recent RCT with a crossover design compared IPC (uniform compression) with elastic bandages, but it was underpowered because of its small size (N.=16), while interpretation of the poor healing results (persisting even after cross-over) in both study arms was further hampered by the number of patients dropping out (N.=5), which left 11 patients in the study.[180]

An updated Cochrane review identified nine randomized controlled trials including 489 patients,[181] However, only one trial was at low risk of bias by reporting adequate randomization, allocation concealment and blinded outcome assessment. The authors concluded that IPC may increase healing compared with no compression, but it is not clear whether it increases healing when added to treatment with bandages, or if it can be used instead of compression bandages. There is some limited evidence that IPC may improve healing when added to compression bandages. Rapid IPC was better than slow IPC in one trial: A RCT which compared two different IPC regimens for ulcer healing.[182] randomized 104 patients to rapid (three cycles per minute) or slow (one cycle per three minutes) compression IPC devices for one hour daily. Both devices applied the same pressure and no other compression treatment was applied during the study period. Complete healing occurred in 45 of 52 patients treated with rapid IPC, and in 32 of 52 patients treated with slow IPC. Life table analysis showed that the proportion of ulcers healed at six months was 86% in the group treated with the rapid IPC compared with 61% in the group treated with slow IPC (P=0.003, log-rank test). The mean rate of healing per day in the rapid IPC group was found to be faster compared to the slow IPC group (0.09 cm^2 *vs.* 0.04 cm^2, P=0.0002).

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

Different detected hematologic, hemodynamic and endothelial effects of IPC are a promising basis for using such devices in addition to conventional compression therapy in different stages of CVD.[27, 183]

Contraindications to compression therapy

A recent publication has summarized the contraindications as quoted in several guidelines and consensus papers from recent years.[184] There is general agreement that severe occlusive arterial disease with an arterial ankle pressure less than 50 mmHg or ankle-brachial pressure index of <0.5 is an absolute contraindication while less severe stages of mixed, arterial-venous disease may be a good indication for "modified compression by inelastic material applied with an initial pressure lower than 40 mmHg, plus frequent check of the compressed skin regions. Caution should be observed in patients with cardiac failure, diabetes, or local infection such as erysipelas., In these situations, careful compression can be very valuable to reduce edema, but should be handled and controlled by experts only.

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CHAPTER 8

Venoactive drugs

Introduction

Venoactive drugs (VADs) comprise a heterogeneous group of drugs, some of which are synthetic whereas most are of plant origin. Five main categories of VADs have been described in recent publications;[1, 2] their source and dosages are summarized in Table I. Some VADs are commonly taken as mixtures; for example, marketed Ruscus extracts are a mixture of *Ruscus aculeatus*, hesperidine methyl chalcone (HMC) and ascorbic acid, while micronized purified flavonoid fraction (MPFF) is a micronized mixture of diosmin (90%) and flavonoids (10%), expressed as hesperidin, diosmetin, linarin, and isorhoifolin, while Gingko biloba extracts are mixed with heptaminol and troxerutin. Two additional drugs that are not venoactive, pentoxifylline and sulodexide, are included because of their beneficial effect on the healing of venous leg ulcers.

A number of dietary supplements allegedly considered as therapies have created confusion in recent years. Dietary supplements, unlike registered VADs, have not been shown to be efficient

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

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

and therefore have not received any marketing authorization from health authorities. For these reasons, we will not consider products that are exclusively dietary supplements in this document. On the other hand, some VADs described in the present chapter are considered as medicinal products in some countries and as food supplements in others. For example, red vine leaves extracts (*Vitis vinifera*) is registered as therapeutic drug in seven member states of the European Union (EU), and as food supplement in eight other EU countries.

In this chapter, the various pharmacological actions of VADs are summarized, and the evolution of recommendations for their therapeutic use is tracked. The emphasis throughout this document is on recent experimental and clinical advances that have altered our understanding of the effects of VADs and their therapeutic use. A more comprehensive review of the older literature was given in the previous guidelines.[3]

Mode of action

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

Actions on venous tone

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

Actions on inflammatory processes in venous valves and the vein wall

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

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

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

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

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

Actions on capillary permeability (edema)

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

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

Skin changes related to capillary abnormalities

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

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

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

Role of nociceptors in the development of venous symptoms

Most recent studies have found that the prevalence and severity of CVD symptoms are greater with increasing severity of CVDs or CEAP clinical class.[79-83] However, other studies have found only weak correlations,[84, 85] or that symptom scores were actually higher in individuals with

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

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

*No data available.

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

The exact mechanisms by which CVDs, particularly in the earliest stages, gives rise to pain and other typical venous symptoms are not yet understood, but recent studies suggest that inflammation plays a key role.[94-96] (see Chapter 2). Sympathetic C fibers are found in the venous intima and media and wrapped around cutaneous venules, and act as nociceptors that can respond to inflammatory mediators. Inflammatory processes seem to be involved in all stages and severity classes of CVDs, even before obvious tissue damage has occurred, and could be responsible for many of the symptoms experienced. Thus, the anti-inflammatory properties of VADs have the potential to improve symptoms in patients at all stages of the disease, including those in CEAP class C_{0s}.

Lymphatic drainage

Lymphatic function is known to be compromised, especially in patients with more advanced stages of CVD,[97-99] and has been shown to improve in patients with varicose veins after reduction of venous reflux by saphenous vein ablation.[100] A recent study has suggested that abnormal accumulation of lipid molecules, elevated tissue pressure and chronic inflammation in varicose veins may combine to produce lymphatic dysfunction and a decrease in the number of lymphatic vessels.[101] Several VADs, including α-benzopyrones (coumarin) either alone or combined with rutin,[102, 103] MPFF,[104] Ruscus extracts[202] and calcium dobesilate[105] have all been shown to improve lymphatic drainage in animal models.

Hemorheological disorders

Hemorheological changes including increased blood viscosity and erythrocyte aggregation, are common in CVDs. Several VADs have been shown to reduce blood viscosity and/or erythrocyte aggregation, including MPFF,[106] troxerutin,[107] Ruscus extract[203] and calcium dobesilate.[108] The pharmacological effects of VADs are summarized in Table II.

Therapeutic efficacy of VADs on venous symptoms and edema

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

Cochrane reviews

Systematic review and meta-analysis represents the most formal and objective way to combine results of multiple small clinical studies. Cochrane meta-analyses have been influential in developing recommendations for using different VADs. A total of 59 randomized clinical trials involving several different types of VADs were included in a 2005 Cochrane review and meta-analysis.[109] Of these, 44 studies were considered to be of suitable design and quality, including 23 trials on rutosides, ten on MPFF and six on calcium dobesilate. Outcome variables considered included objective signs such as edema and trophic disorders together with a range of subjective symptoms including pain, heaviness, cramps, restless legs and the sensation of swelling. When all VADs were considered together, significant benefits from treatment were demonstrated for all outcome variables except for itching and venous ulceration.[110-116] The percentage of patients with complete pain relief was significantly greater in the VAD group compared to placebo (63% *versus* 37%, P<0.00001); as were heaviness (60% *versus* 33%, P<0.00001), sensation of swelling (63% *versus* 38%, P<0.0001), cramps (68% *versus* 45%, P=0.003), and restless legs (46% *versus* 33%, P<0.006). For most end-points, there was evidence of heterogeneity among studies although this is not surprising given that studies of different drugs, varying designs and different patient inclusion criteria were combined. Results are summarized in Table III.[111, 116] The overall incidence of adverse events was not different from placebo, although it was pointed out that most studies were of relatively short duration.

Subgroup analyses for individual VADs were also performed in which calcium dobesilate, MPFF and rutosides all showed significant treatment benefits for edema based on multiple studies and were effective for a range of symptoms

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

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

based on multiple or single studies (Table IV).[111] French maritime pine bark extract showed efficacy against symptoms of pain, heaviness and swelling based on a single acceptable study: the standard mean deviation (SMD) was -1.39 for pain; -1.50 for heaviness and -1.65 for swelling. Adverse events were analyzed for calcium dobesilate, MPFF and rutosides, and the incidence was not different from placebo for all of them.

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

The 2005 International Consensus Statement

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

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

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

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

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

RR: relative risk (for dichotomous variables); SMD: standardized mean difference.

— Grade C – other poorly designed controlled trials or non-randomized controlled trials.

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

On this basis, calcium dobesilate, MPFF and hydroxyethyl-rutosides (also known as oxyrutins) were classified as Grade A, horse chestnut seed extract and *Ruscus* extract as Grade B, and other VADs as Grade C (Table V).[2, 3] The authors stressed that all drugs listed in Table IV had demonstrated efficacy in at least one randomized trial; those in Grades A and B had better documentation for their effectiveness in the published literature and so could be recommended more strongly. The experts also considered the indications for VADs and concluded that they are indicated to relieve symptoms for all classes of CVD from CEAP class C_{0s} to C_{6s}.

The 2008 guidelines for the management of CVDs of the lower limbs

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

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

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

The guideline authors also considered VADs for treatment of C_6. Several studies have suggested that MPFF is effective for venous leg ulcers. A meta-analysis of five trials in which oral MPFF was given as adjunctive therapy in conjunction with compression and local wound care concluded that MPFF accelerates venous ulcer healing, particularly for larger ulcers (RRR=40; 95% CI: 6 to 87, in ulcers between 5 and 10 cm^2) and those of long standing (RRR=44; 95% CI: 6 to 97, in ulcers between 6 and 12 months).[112] Although not generally classified as a VAD, pentoxifylline was also shown in the 2012 Cochrane review of 11 studies of variable quality to be an effective adjunct to compression therapy for treating venous ulcers (RR=2.2; 95% CI: 1.5 to 3.4), and may even be effective in the absence of compression (RR=1.6; 95% CI: 1.1 to 2.1).[113]

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

These guidelines also provided the following recommendations regarding indications for VADs:

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

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

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

The 2011 review

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

Regarding their efficacy in relieving venous symptoms and CVD-related lower limb edema, the authors suggested that there was substantial evidence for benefit from relatively small trials supported by meta-analyses for MPFF and rutosides, and a large observational study - the RELIEF study, in the case of MPFF.[117] Therefore, MPFF and rutosides were given strong recommendations based on moderate evidence (overall grade 1B for both drugs). The volume of evidence for horse chestnut seed and *Ruscus* extracts was considered less, and these two drugs were given weak recommendations based on low-quality evidence (Grade 2C). None of the above drugs have obvious safety concerns but the authors drew attention to the rare cases of agranulocytosis associated with calcium dobesilate. In consequence, calcium dobesilate was given only a weak recommendation although the quality of evidence in support of its efficacy was moderate, and the overall grade for this drug was 2B. The authors also confirmed the recommendation of MPFF as adjuvant treatment for active venous ulcers, giving a strong recommendation based on moderate evidence (grade 1B). Finally, it was concluded that there was insufficient evidence to specify which CEAP classes would benefit most from VAD therapy, but it was reasonable to assume that patients at all stages of the disease might benefit.

The 2014 guidelines update – efficacy and safety recommendations for VAD

In the 2014 update of the guidelines, the faculty proposed use of the GRADE system. Recommendations were derived from the tentative recommendations of Perrin and Ramelet,[114] with modifications made partially in the light of additional recent evidence and partially based on a re-evaluation of previous data in order to provide better discrimination between different drugs.

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

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

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

Finally, two placebo-controlled studies on red-vine-leaf extract in 248,[124] and 71,[125] patients in CEAP classes C_3 – C_{4a} demonstrated significant reductions in lower limb volume (-19.9±8.9 mL; 95% CI: -37.5 to 2.3; $P=0.027$) and leg pain (-6.6±3.3 mm on VAS; 95% CI -13.1 to 0.1, P=0.047) after 12 weeks of treatment,[124] and in ankle circumference (-0.39±0.09 cm in the treatment group *versus* 0.29±0.09 cm in the placebo group, P<0.0001) after six weeks.[125]

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

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

It was mentioned that VADs containing coumarine and benzarone as unique active ingredients had been withdrawn from the market for

Table VI.—*Summary of the 2014 guideline recommendations for the use of venoactive drugs, according to the GRADE system.*

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

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

their potential to cause severe (even fatal) hepatotoxicity.[133, 134]

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

The above recommendations were given in 2014 for relief of symptoms associated with CVD in patients in CEAP classes C_{0s} to C_{6s} and those with CVD-related edema. MPFF retained its strong recommendation based on moderate evidence (grade 1B) for use as adjuvant therapy in treating venous leg ulcers.[114]

The 2018 approach for the effect of individual drugs on individual symptoms and signs

Introduction

As shown above, several meta-analyses (Table III) and also the most recent Cochrane review of 2016 by Martinez-Zapata *et al.*[137] have looked at individual symptoms by combining venoactive drugs. A drawback for this approach of combining trials of several venoactive drugs is that the effect shown was average or weak because the effect of different drugs is not the same (Table III) or that there was such marked heterogeneity that the authors could not pool the results (Cochrane review 2016).[137] Another approach has been to look at the global effect of individual drugs on symptoms. The drawback of this approach is that information on the effect a specific drug has on individual symptoms could be missed, as it is well known that individual drugs are more effective for certain symptoms than others.

In contrast to the above, the Cochrane review of 2005 [109] and other recent meta-analyses by Allaert,[118] Boyle *et al.*[138] and Kakkos *et al.*[139] demonstrated that looking at the effect of individual drugs on individual symptoms is feasible and can provide a meaningful measurement of the magnitude of the effect as well as the number of patients needed to treat to have benefit in one patient. As a result of the above, the 2018 faculty decided to scrutinize both old and new meta-analyses that provide data so as to allow the level of available evidence for the magnitude of the effect each VAD has on each symptom to be determined.

What emerged by this exercise was that convergent data confirmed the important role of VADs in the management of CVDs, either alone in the early stages or in combination with interventional procedures in the more advanced stages. The evidence for this is presented below.

MPFF

A recent systematic review and meta-analysis of randomized double-blind placebo-controlled trials for the efficacy of MPFF to improve individual venous symptoms identified ten publications reporting seven eligible studies involving 1692 patients.[140] There was generally minimal risk of bias in most of these trials. CEAP clinical class ranged between 0 to 6 with some studies allowing inclusion of patients with the post-thrombotic syndrome.

Pain was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in three studies each one significant and involving 839 patients. Standardized Mean Difference (SMD) was -0.25 (95% CI: -0.38 to -0.11).[141-143] It was also reduced when assessed as a categorical variable in three studies, involving 271 patients, two of which were significant.[141,142,144] Risk Ratio (RR) was 0.53 (95% CI: 0.38 to 0.73). NNT was 4.2 (95% CI: 2.8 to 7.9). Level of evidence high (Grade A).

Heaviness was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in two studies, both significant and involving 254 patients (SMD of -0.80; 95% CI: -1.05 to -0.54).[141,142] It was also reduced when assessed as a categorical variable in three studies involving 283 patients, two of which were significant. RR was 0.35 (95% CI: 0.24 to 0.51). NNT was 2.9 (95% CI: 2.2 to 4.2).[141,142,145] Level of evidence high (Grade A).

Feeling of swelling was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in two studies involving 254 patients, each one significant [141,142] (SMD was -0.99 (95% CI: -1.25 to -0.73). It was also reduced when assessed as a categorical variable in three studies involving 267 patients, two of which were significant.[141,142,144] RR was 0.39 (95% CI: 0.27 to 0.56). NNT was 3.1 (95% CI: 2.3 to 4.8). Level of evidence high (Grade A).

Cramp severity was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in one study [141] involving 150 patients. SMD was -0.46 (95% CI: -0.78 to -0.14). A significant effect was also observed for cramp reduction with the use of MPFF compared to placebo when assessed as a categorical variable in two studies [142,144] involving 119 patients, one of which was significant. RR was 0.51 (95% CI: 0.29 to 0.92). NNT was 4.8 (95% CI: 2.7 to 22.9). Level of evidence moderate (Grade B).

Paresthesiae (tingling) were not reduced with the use of MPFF compared to placebo when assessed as a continuous variable of end of treatment values in one study [141] involving 150 patients. SMD was -0.11 (95% CI: -0.44 to 0.21). However, a significant effect was observed with the use of MPFF compared to placebo when assessed as a categorical variable in another study [142] involving 61 patients. RR was 0.45 (95% CI: 0.22 to 0.94). NNT was 3.5 (95% CI: 1.9 to 20). Level of evidence moderate to low (Grade B/C).

Burning sensation was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in one study [141] involving 150 patients. SMD was -0.46 (95% CI: -0.78 to -0.14). A significant effect was not observed when assessed as a categorical variable in two other studies [142,145] involving 96 patients. RR was 0.67 (95% CI: 0.38 to 1.17). Level of evidence moderate to low (Grade B/C).

Functional discomfort was significantly reduced with the use of MPFF compared to placebo when assessed as a continuous variable in two studies [141,142] involving 254 patients, both being significant. SMD was -0.87 (95% CI: -1.13 to -0.61). It was also significantly reduced in two studies [142,145] involving 134 patients, both being significant. RR was 0.41 (95% CI: 0.25 to 0.67). NNT was 3.0 (95% CI: 2.1 to 5.8). Level of evidence high (Grade A).

Tightness was not significantly reduced with the use of MPFF compared to placebo in a small study [144] involving 56 patients. (RR 0.61; 95% CI: 0.20 to 1.86).

Fatigue was non-significantly reduced with the use of MPFF compared to placebo when assessed as a categorical variable in a small study [145] involving 31 patients. (RR 0.27; 95% CI: 0.07 to 1.09).

Restless leg symptoms were non-significantly reduced with the use of MPFF compared to placebo when assessed as a categorical variable in a small study involving 56 patients [144] (RR 0.36; 95% CI: 0.11 to 1.19).

Global symptoms were not significantly reduced with the use of MPFF compared to placebo when assessed as a continuous variable in one study involving 36 patients. [145] SMD was -0.48 (95% CI: -1.14 to 0.19). It was also not reduced in three studies involving 189 patients when assessed as a categorical variable.[135,144,145] RR was 0.36 (95% CI: 0.09 to 1.53).

Leg redness was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in two studies (one significant) involving 254 patients.[141,142] SMD was -0.32 (95% CI: -0.56 to -0.07). It was also reduced in one study [142] involving 66 patients when assessed as a categorical variable. RR was 0.50 (95% CI: 0.27 to 0.94). NNT was 3.6 (95% CI: 2.0 to 20.6). Level of evidence moderate (Grade B).

Skin changes were improved with the use of MPFF compared to placebo when assessed as a categorical variable in two studies [141,142] involving 61 patients, both being significant. RR was 0.18 (95% CI: 0.07 to 0.46). NNT was 1.6 (95% CI: 1.2 to 2.2). Level of evidence high (Grade A).

Ankle circumference was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in three studies involving 282 patients, one of them being significant. [142,146] SMD was -0.59 (95% CI: -1.15 to -0.02). Level of evidence moderate (Grade B).

Leg or foot volume were not reduced in two studies [135,147] involving 166 patients. SMD was 0.03 (95% CI: -0.28 to 0.33).

Quality of life was improved with the use of MPFF compared to placebo when assessed as a continuous variable in two studies, both significant and involving 601 patients. [143,147] SMD was -0.21 (95% CI: -0.37 to -0.04). Level of evidence high (Grade A).

Ruscus+HMC+AA

Ruscus is the main ingredient of Cyclo 3 Fort®, which combines three active ingredients: the saponine Ruscus aculeatus extract, the flavonoid hesperidine methyl chalcone (HMC) and ascorbic acid (AA).

A recent systematic review and meta-analysis of randomised double-blind placebo-controlled trials for the efficacy of Ruscus+HMC+AA to improve individual venous symptoms identified ten eligible studies involving 719 patients.[139] There was generally no risk of bias in almost all of these trials. CEAP clinical class ranged between 2-5, but it was mostly 3-4 with some studies allowing the inclusion of patients with post-thrombotic syndrome.

Pain was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in two studies, each one significant. [148,149] SMD was -0.80; 95% CI: -1.21 to -0.39. It was also reduced when assessed as a categorical variable in two studies [149,150] involving 111 patients. RR was 0.35 (95% CI: 0.16 to 0.78). NNT was 5.0 (95% CI: 2.9 to 18.1). Level of evidence high (Grade A).

Heaviness was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in three studies involving 136 patients, each one being significant.[148,149,151] SMD was -1.23 (95% CI: -1.60 to -0.86). It was also reduced when assessed as a categorical variable in four studies involving 198 patients,[149, 150, 152, 153] each one significant. RR was 0.26 (95% CI: 0.16 to 0.42). NNT was 2.4 (95% CI: 1.9 to 3.3). Level of evidence high (Grade A).

Fatigue was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in one study [148] involving 60 patients. SMD was -1.16 (95% CI: -1.71 to -0.61). Level of evidence moderate (Grade B).

Feeling of swelling was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in three studies involving 150 patients,[148, 149, 154] each one being significant. SMD was -2.27 (95% CI: -3.83 to -0.70). It was also reduced when assessed as a categorical variable in five studies involving 217 patients [149,150,152-154] two of which were significant. RR was 0.53 (95% CI: 0.40 to 0.71). NNT was 4.0 (95% CI: 2.6 to 8.0). Level of evidence high (Grade A).

Cramp severity was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable (0.0±0.0 *vs.* 0.19±0.40, respectively (P<0.02) in one study [148] involving 60 patients. A non-significant trend was observed for cramp reduction with the use of Ruscus compared to placebo when assessed as a categorical variable in two studies [150,153] involving 87 patients. RR 0.63 (95% CI: 0.38 to 1.05). Level of evidence moderate to low (Grade B/C).

Paresthesiae were reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in one study [149] involving 40 patients. SMD was -0.86 (95% CI: -1.59 to -0.21). They were also reduced when assessed as a categorical variable in two studies involving 79 patients [149, 153] each one significant. RR was 0.27 (95% CI: 0.14 to 0.51). NNT was 1.8 (95% CI: 1.4 to 2.8). Level of evidence high (Grade A).

Pruritus severity was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in one study [148] involving 60 patients (0.0±0.0 *vs.* 0.19±0.40, respectively) (P<0.01). There was not any significant difference when pruritus was assessed as a categorical variable in another small study with 20 patients.[150] RR was 0.43 (95% CI: 0.03 to 5.78). Level of evidence moderate to low (Grade B/C).

Burning sensation was not significantly reduced with the use of Ruscus+HMC+AA compared to placebo, although there was a trend in favour of Ruscus.[148] SMD was -0.42 (95% CI: -0.93 to 0.09).

Global symptoms were reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in two studies involving 97 patients, each one significant.[151, 154]

SMD was -3.12 (95% CI: -4.53 to -1.71). It was also reduced when assessed as a categorical variable in four studies involving 347 patients,[148-150, 155] three of which were significant. RR was 0.54 (95% CI: 0.41 to 0.70). NNT was 4.3 (95% CI: 3.0 to 7.4). Level of evidence high (Grade A).

Ankle circumference was reduced with the use of Ruscus+HMC+AA compared to placebo when assessed as a continuous variable in four studies involving 228 patients, three of four being significant.[148-150, 154] SMD was -0.74 (95% CI: -1.01 to -0.47). Level of evidence high (Grade A).

Foot volume was also reduced in two studies involving 181 patients, both significant.[156, 157] SMD was -0.61 (95% CI: -0.91 to -0.31). Level of evidence high (Grade A).

Hydroxyethylrutosides (HR) (also known as Oxerutins)

A recent systematic review on the efficacy and tolerability of hydroxyethylrutosides (HR) for improving signs and symptoms of CVI [158] identified 15 randomised placebo-controlled trials involving 1643 patients.

Pain was reduced with the use of HR compared to placebo when assessed as a continuous variable in two similar pooled studies involving 132 patients, each one significant.[159, 160] SMD was -1.07 (95% CI: -1.44 to -0.70). However, the combined results of two other trials that recorded pain as improved or not improved [161,162] demonstrated that there was no significant difference between the groups. Odds ratio (OR) was 0.90 (95% CI: 0.50 to 1.62). Level of evidence moderate (Grade B).

Leg heaviness was reduced with the use of HR compared to placebo when assessed in a study that measured leg heaviness as a symptom score.[160] SMD was -1.00 (95% CI: -1.27 to -0.73). Pooling the results of three similar trials involving 254 patients,[160, 161, 163] of which two were not significant showed a beneficial effect on leg heaviness in the HR group. OR was 0.50 (95% CI: 0.28 to 0.91). Level of evidence moderate (Grade B).

Pooling the results of two trials that reported cramps in terms of symptom scores,[159, 160] showed benefit in favor of HR (SMD -1.7; 95% CI: -1.45 to -0.69), (P<0.0001). However, in three other trials in which cramps were recorded as improved or not [161-163] the outcome was not statistically significant. Level of evidence moderate (Grade B).

Evidence of statistical significance between the groups for symptoms of feeling of swelling, restless legs, itching or paresthesiae were not reported, because high heterogeneity did not allow pooling of trials.

Three trials involving 311 patients reported on presence of edema. The results were significant in favor of HR in two,[160, 163] but not significant in the third study.[164] The pooled effect on ankle circumference in two similar trials [160, 165] showed no benefit by HR (MD -3.63; 95% CI: -9.40 to 2.15).

The adverse effects reported were minor and showed no significant difference between HR and placebo.

The authors concluded that the limitations of the current evidence arising from inadequate reporting indicate that future trials need to be reported according to the CONSORT 2010 statement.[166] A limitation of this review was that only three trials used the Widmer classification of CVD and none of the others reported the diagnostic classification used.

Horse chestnut seed extract (HCSE)

Individual symptoms of leg pain, pruritus and signs of edema, leg volume and circumference were assessed in ten placebo-controlled studies included in the Cochrane systematic review by Pittler *et al.* in 2012.[110]

Leg pain was assessed in seven randomized placebo-controlled trials. Six studies reported a statistical significant reduction of leg pain on different measurement scales in patients treated with HCSE compared to placebo [167-172] and one reported a statistical significant reduction of leg pain compared to baseline.[173] One study [167] included adequate data to provide a weighted mean difference (WMD) of 42.4 mm (95% CI: 34.9 to 49.9) which translates to NNT of 5.1 (95% CI: 3.4 to 9.8). Level of evidence high (Grade A).

Pruritus was assessed in eight randomised placebo-controlled trials.[170-177] Four trials (N.=407) indicated a statistically significant reduction of pruritus in patients treated with HCSE compared to placebo (NNT 6.1; 95% CI: 3.3 to 36.3). Two trials indicated a statistically significant difference compared to baseline. Level of evidence high (Grade A).

Edema was assessed in six placebo-controlled trials.[167-171, 173] Four trials (N.=461) reported a statistically significant reduction of edema in patients treated with HCSE compared to placebo, while one reported an improvement compared to baseline.[173] One study [167] included adequate data to provide a weighted mean difference (WMD) of 40.1 mm (95% CI: 31.6 to 48.6) in favor of HCSE which translates to NNT of 4.0 (95% CI: 2.9 to 6.8). Level of evidence high (Grade A).

Leg volume using water displacement was assessed in seven randomised placebo-controlled trials.[169, 172-177] Meta-analysis of six trials (N.=502) suggested a WMD of 32.1 mL (95% CI: 13.49 to 50.72) in favor of HCSE compared to placebo, with pooled standardized mean difference of -0.34; 95% CI: -0.15 to -0.52. Level of evidence high (Grade A).

The adverse events reported were mild and infrequent. They included gastrointestinal complaints, dizziness, nausea, headache and pruritus and showed no significant difference between HR and placebo.

Calcium dobesilate

A systematic review of calcium dobesilate according to the Cochrane Collaboration guidelines dealing with individual symptoms was published by Ciapponi in 2004.[178] It included seven randomised placebo-controlled trials involving 778 patients, and the magnitude of the effect was expressed as RR for dichotomous variables and SMD for all continuous variables applying a random effects statistical model and NNT to obtain a significant benefit.

Pain was reduced with the use of calcium dobesilate compared to placebo when assessed as a categorical variable in five pooled studies involving 477 patients, three of which showed statistical significance in favor of dobesilate.[179-183] RR for the subgroup of mild pain was 1.32 (95% CI: 0.89 to 1.98) and for subgroup severe pain was 15.76 (95% CI: 3.80 to 57.4). NNT was 1.4. Level of evidence moderate (Grade B).

Limb heaviness was reduced with the use of calcium dobesilate compared to placebo when assessed as a categorical variable in four pooled studies involving 428 patients,[179, 181, 182] each one showing statistical significance in favor of dobesilate. RR for the subgroup of "mild heaviness" was 1.34 (95% CI: 0.84 to 2.14) and for subgroup "severe heaviness" was 14 (95% CI: 2.10 to 93.5). NNT was 1. Level of evidence high (Grade A).

Discomfort was reduced with the use of calcium dobesilate compared to placebo when assessed as a categorical variable in one study [180] involving 225 patients. RR 2.30 (95% CI: 1.51 to 3.52). NNT was 4 (95% CI: 3 to 7). Level of evidence moderate (Grade B).

Paresthesie were not reduced with the use of calcium dobesilate compared to placebo when assessed as a categorical variable in three studies [179, 180, 182] involving 304 patients RR 1.39 (95% CI: 0.87 to 2.22). However, for the subgroup of severe paresthesiae, RR was 3.33 (95% CI: 1.14 to 9.75). NNT 2 (95% CI: 1 to 6). Level of evidence moderate (Grade B).

Lower limb edema was assessed in two studies involving 80 patients,[179, 182] both of them being significant in favor of dobesilate. For the subgroup "mild edema" RR was 2.00 (95% CI: 1.26 to 3.19) and for the subgroup "severe edema" RR was 27.00 (95% CI: 1.75 to 416). NNT 1.2. Level of evidence high (Grade A).

Leg volume was assessed as a continuous variable in three studies [180, 182, 184] involving 486 patients. Larger volume reductions with dobesilate were shown in all. For the subgroup of "mild edema" SMD was -0.26 (95% CI: -0.60 to -0.07) and for the subgroup "severe edema" -11.39 (95% CI: 14.56 to -8.22). It appears that the more severe the edema the more effective is the drug. Level of evidence high (Grade A).

The incidence of adverse effects with dobesilate ranged from 0% to 39%, without any significant differences when compared to placebo.

Five randomized placebo-controlled trials have been performed between 2004 and 2016. [120-123,185] Three were positive in favor of dobesilate and two negative.

The first positive study, performed by Labs *et al.* in 2004,[121] involved 253 patients with CEAP C3-C4 patients and investigated the effect of 4-week treatment with dobesilate on leg volume calculated from calf and ankle circumference based on a truncated cone model. At four weeks, there was a median difference of 12.2 mL/L tissue (95% CI: -21.6 to -2.8) in favour of dobesilate.

The second positive study performed by Flota-Cervera *et al.* in 2008 [122] involved 49 patients with "lymphovenous vascular edema" (CVI Widmer grade I to V classes) and investigated the effect of 49-day therapy on lymph flow and pain. By the end of the treatment period, patients treated with dobesilate had normalization of lymphogammagraphy and a statistically significant reduction in the circumference of the leg, calf and ankle. There was complete relief of pain in 68% of patients in the dobesilate group and 0% in the placebo group.

The third positive study, performed by Rabe *et al.* in 2011,[120] involved 256 patients and investigated the effect of 2-month therapy on leg volume using optoelectronic volumetry and symptoms in CEAP C3-5 patients. At the end of treatment, there was a reduction of leg volume by 2.04±3.4% on average in the dobesilate group compared with an increase of 0.1±4.8% in the placebo group (P<0.001). Pain assessed by VAS was reduced more in the dobesilate than the placebo group (mean±SD: 10.2±26.3 mm *vs.* 0.92±23.0 mm; P=0.007). Leg discomfort was also reduced more in the dobesilate than the placebo group (mean±SD: 19.1±25.4 mm *vs.* 10.2±25.9 mm; P=0.05). However, quality of life at the end of therapy using the CIVIQ score was not statistically different in the two groups.

The first of two negative studies, performed by Martinez-Zapata in 2008,[123] involved 509 patients (CEAP 1-6) and investigated the effect of 3-month therapy on QoL using the CIVIQ score, on edema and on symptoms. At the end of the treatment, there was no difference in all measurements between the two groups. The second negative study, performed by Rabe in 2016,[185] involved 351 patients (CEAP 3-4) and investigated the effect of 3-month therapy on leg volume and QoL using the CIVIC score. At the end of the treatment, there was no difference in all measurements between the two groups.

It should be pointed out that in the study by Martinez-Zapata, QoL was better in the dobesilate group at 12 months, and in the study by Rabe *et al.* in 2016, leg volume was lower in the active drug group at the end of follow up. The authors suggested that further studies are needed to investigate possible long-term effects.

Another observation made by several authors is that the effect of dobesilate is higher in patients with the most advanced stage of disease.

The 2018 approach which determined the magnitude of the effect of individual venoactive drugs on individual symptoms provided evidence that has enabled us to summarize and produce a new table (Table VII). On the basis of the 2018 findings (magnitude of effects on individual symptoms or signs *vs.* side-effects) the strength of recommendations for the main VAD are as follows.

For MPFF, it is 1 (strong) for treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema and quality of life, and it is 2 (weak) for paresthesiae and burning.

For Ruscus+HMC+AA, it is 1 (strong) for treatment of pain, heaviness, feeling of swelling,

TABLE VII.—*2018 update. Level of evidence that merits grade A or B for the effect of the main VADs on individual symptoms, signs and QoL with magnitude of effect: Number needed to treat (NNT) to benefit one patient or Standardized Mean Difference (SMD) are also shown. Only randomized placebo controlled trials and meta-analyses were considered.*

Symptom/sign	MPFF	Ruscus+ HMC+AA	Oxerutins	HCSE	Calcium dobesilate
Pain (NNT)	A (4.2)	A (5)	B	A (5.1)	B (1)
SMD	-0.25	-0.80	-1.07		
Heaviness (NNT)	A (2.9)	A (2.4)	B (17)		A (1)
SMD	-0.80	-1.23	-1.00		
Feeling of swelling (NNT)	A (3.1)	A (4)			
SMD	-0.99	-2.27			
Functional discomfort/discomfort (NNT)	A (3.0)				B (4)
SMD	-0.87				
Leg fatigue (NNT)	NS	B			
SMD		-1.16			
Cramps (NNT)	B (4.8)	B/C	B		
SMD	-0.46		-1.7		
Paresthesiae (NNT)	B/C (3.5)	A (1.8)			B (2)
SMD	-0.11	-0.86			
Burning (NNT)	B/C	NS			
SMD	-0.46				
Pruritus/itching (NNT)		B/C	A (6.1)		
Tightness (NNT)	NS				
Restless legs (NNT)	NS				
Leg redness (NNT)	B (3.6)				
SMD	-0.32				
Skin changes (NNT)	A (1.6)				
Ankle circumference (NNT)	B	A	NS	A (4)	
SMD	-0.59	-0.74			
Foot or leg volume	NS	A	NS	A	A
SMD		-0.61		-0.34	-11.4
QoL	A				NS
SMD	-0.21				

NS: not significant.

leg fatigue, paresthesiae and edema, and it is 2 (weak) for cramps and pruritus.

For oxerutins, it is 1 (strong) for treatment of pain, heaviness and cramps, and it is 2 (weak) for edema.

For HCSE, it is 1 (strong) for treatment of pain, pruritus and edema.

For calcium dobesilate, it is 2 (weak) in view of the possibility of inducing agranulocytosis.[128]

Effect of medications on the healing of leg ulcers: 2018 overview

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

Pentoxifylline

Pentoxifylline is a xanthine derivative. It has a pleomorphic effect. It increases intracellular cAMP, inhibits TNF-α and leukotriene synthesis, and reduces inflammation and innate immunity. It reduces blood viscosity by improving red cell deformability thus increasing blood flow in the microcirculation. In addition, it inhibits platelet aggregation and neutrophil activation.[186]

The 2012 Cochrane Review [113] identified eleven trials involving 864 patients that compared pentoxifylline with placebo or no treatment. Pentoxifylline was more effective than placebo in terms of complete ulcer healing or significant improvement (RR 1.70; 95% CI: 1.30 to 2.24). Pentoxifylline with compression was more effective than placebo with compression (RR 1.56; 95% CI: 1.14 to 2.13). This translates to NNT of 4.3 (95% CI: 3.3 to 6.4). In the absence of compression (three trials), pentoxifylline was more effective than placebo or no treatment (RR 2.25; 95% CI: 1.49 to 3.39). Level of evidence high (Grade A).

Adverse effects were reported in 19.5% of patients receiving pentoxifylline and in 11.3% on placebo (RR 1.56; 95% CI: 1.10 to 2.22). The majority of side-effects (72%) were gastrointestinal.

MPFF

As indicated above, MPFF also has a pleotropic action. It increases venous tone and lymphatic drainage, increases free radical scavengers, reduces inflammation, prevents activation and adhesion of white cells to the endothelium, and decreases capillary leakage.

A meta-analysis of five RCTs involving 723 patients with venous ulcers [112] demonstrated that at six months, ulcers healed faster when MPFF was combined with compression than compression alone. Compression in addition to MPFF was compared with compression plus placebo in two of the studies (N.=309) or with compression alone in three studies (N.=414). At six months, the chance of ulcer healing was 32% better in patients treated with the combined therapy than those managed by compression alone (RRR 32%; 95% CI: 3% to 70%). This translates to NNT of 7.3 (95% CI: 4.6 to 17.1). This difference was present from month two (RRR 44%; 95% CI: 7% to 94%) and was associated with shorter time to healing (16 weeks *vs.* 21 weeks, P=0.0034). Level of evidence high (Grade A).

Sulodexide

Sulodexide is a glycosaminoglycan composed of a fast-moving heparin fraction (80%) with mild affinity for antithrombin and a dermatan sulphate fraction (20%) with affinity for heparin cofactor II. Sulodexide is another drug with pleomorphic properties. It has a profibrinolytic effect, an antiproliferative effect on smooth muscle cells, an antilipemic, antiplatelet and anti-inflammatory effect with a protective effect on the glycocalyx endothelial layer. Several observational studies have demonstrated a beneficial effect for signs and symptoms of chronic venous disease.[187] Due to the absence of randomized placebo-controlled studies in CVD, the level of evidence is low (Grade C). However, this is not the case with ulcer healing. The 2016 Cochrane Database Systematic Review [188] identified three RCTs involving 438 patients with venous leg ulcers which were published as full papers. The studies compared sulodexide + compression with compression alone. Each of the studies was significant, and meta-analysis of the three studies indicated an increase in the proportion of ulcers completely healed with combined treatment (49.4%) compared to compression alone. (RR 1.66; 95% CI: 1.30 to 2.12). This translates to NNT of 5.6 (95% CI: 3.7 to 11.5). There was no heterogeneity but high bias mainly because in only one study was the personnel completely blinded. Adverse effects with sulodexide were low (4.4%) and statistically not different from the control group (3.1%).

A more recent meta-analysis that pooled four RCTs involving 482 patients,[190] with each one of the studies being significant, indicated a RR of 1.70 (95% CI: 1.33 to 2.17) for a random effects model which translated to a NNT of 5.1 (95% CI: 3.6 to 9.0). Level of evidence high (Grade A).

Hydroxyethylrutosides (HR)

A recent systematic review of the efficacy and tolerability of hydroxyethylrutosides (HR) for improvement of signs and symptoms of CVI [158] identified four trials which reported numbers of venous ulcers healed. Three trials compared the effect of HR + compression *vs.* compression alone on the healing of leg ulcers. These studies did not find any significant difference in the number of ulcers healed between the HR and the placebo groups. A fourth trial that compared troxerutin (a component of HR) plus compression with placebo plus compression in a trial involving 149 patients found a significant benefit from the troxerutin group.[190] Level of evidence moderate (Grade B).

Place of VADs in the management of CVDs

This guideline update serves to complement the conclusion of the 2014 guidelines [191] that VADs may be used to relieve CVD-related symptoms and edema in patients at any stage of disease. Knowledge of the specific effect that individual drugs have on different symptoms broadens the armamentarium and confidence in their use. Great emphasis has been placed in the presentation of the evidence that became available, not only in terms of statistical significance but also in terms of the magnitude of the clinical effect.

Two caveats are associated with the above general conclusions and current recommendations.

First, as written in the SYMVein document [192] one cannot always rely on the patient's skill to name symptoms that by their nature are personally-felt-experiences. These feelings are variably expressed and with different intensity, and have different meanings in the minds of individual patients. In addition, words used to describe symptoms are influenced by cultural and linguistic experiences. For these reasons a physician needs great care and experience to interpret the patient's history. For the same reasons, strong scientific evidence for the effect of VADs on symptoms can only be obtained from randomized placebo- controlled blinded trials.

Second, we frequently do not know the exact etiology and mechanism for symptoms, although we understand that the initiating pathophysiological mechanisms are venous hypertension and chronic inflammation. Symptoms may improve with VADs whatever the pathophysiology (reflux or obstruction) by improving venous tone, flow in the microcirculation and reducing capillary leakage.[193] Despite such knowledge, the potential danger is to encourage general practitioners to prescribe VADs based on symptoms alone without considering the CEAP status of the patient and ignoring indications for appropriate investigations that could lead to effective intervention to relieve symptoms and arrest progression of disease. This approach may lead to misuse of VADs causing failures and eventual disrepute.

With these caveats in mind, the faculty wishes to stress the central and unique role that VADs have in the management of symptomatic patients at the earliest stages of CVD, given that compression may be the only other appropriate form of therapy for such patients. In addition, in view of poor compliance with compression therapy in certain countries with hot climates,[136] VADs may be the only alternative treatment available.

The importance of effective treatment of patients in CEAP class C0s was highlighted in a recent study [93] which found that approximately 20% of all patients consulting their general practitioner for any reason could be assigned to class C0s. In more advanced stages of CVD, VADs may be used in conjunction with interventional treatment of varices such as sclerotherapy, surgery, and endovenous treatment. Six articles including 2 RCTs have shown that the combination of interventional procedures and VADs was beneficial.[194-199] Only one study did not show any difference in terms of postoperative pain and daily activities.[200] We have no data on the effect of VADs when associated with other surgical and endovascular procedures, including those on deep veins.

Combination of VADs and compression has

been recommended in several reviews [2, 201] and several meta-analyses [112, 113, 158, 188] that have demonstrated the efficacy of this combination in accelerating the healing of venous ulcers (see section “Effect of Medications on the Healing of Leg Ulcers - 2018 Overview” above).

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