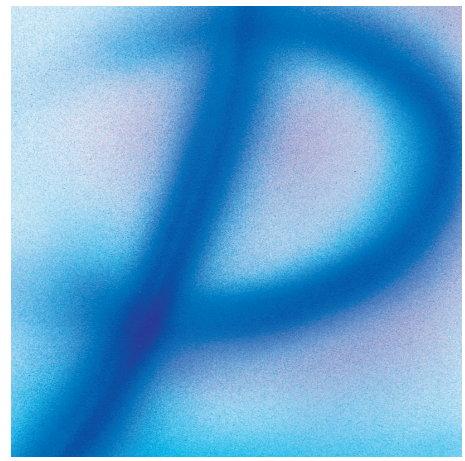
PHLEBOLYMPHOLOGY

ISSN 1286-0107



Proceedings of a satellite symposium "Management of chronic venous disease: therapeutic recommendations"

XVIth world meeting of the UIP, Monaco , Tuesday September 1st, 2009

Vol 16 • No.4 • 2009 • p311-346

AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

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Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in EMBASE, PASCAL, and Scopus databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, news, and a congress calendar.

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Indexed in EMBASE, PASCAL, and Scopus

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ISSN 1286-0107

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"Management of chronic venous disease: therapeutic recommendations"

Proceedings of a satellite symposium held during the XVIth world meeting of the Union Internationale de Phlébologie
Monaco, Tuesday September 1st, 2009

Guest-editor : A. Nicolaides

EDITORIAL

The symposium and these proceedings were made possible by an unrestricted educational grant from Servier

Advances in the Management and Prevention of Chronic Venous Disease

Major advances in the management and prevention of chronic venous disease have been made in the last few years. The stimulus has been the realization of the magnitude of the problem and better understanding of the pathophysiology of the condition at the macrocirculatory, microcirculatory, and molecular levels. Although deep vein thrombosis is responsible for some of the most severe forms of chronic venous disease, especially if its treatment is suboptimal, it should be remembered that in most cases, including those with venous ulceration, chronic venous disease is not the result of previous thrombosis, but of chronic changes in the venous wall that damage valves and produce reflux and venous hypertension.

The most important advance in understanding chronic venous disease pathophysiology has been the realization that changes in blood shear stress with activation of leukocytes and endothelial adhesion followed by subendothelial migration, stimulation of proteolytic enzymes such as MMPs, and accumulation of extracellular material have a key role in the development of chronic venous disease. These changes are associated with the production of IGF-β_1 and FGF-β_1, which stimulate collagen synthesis and smooth muscle cell migration. In addition, the increased plasma level of VEGF promotes capillary growth, increased capillary permeability resulting in the characteristic skin changes and lipodermatosclerosis. With this as background knowledge, drugs have been developed which can counter the above changes.

The development and availability of appropriate tools to assess the severity of symptoms, and the objective determination of the effects of treatment on signs such as edema, venous ulceration, and quality of life, have enabled us to embark on appropriate randomized clinical trials. The results have provided level I evidence and grade A recommendations for therapies: compression, medication, and surgery. Medications such as Daflon 500 mg have now a proven place with grade A recommendations for the whole spectrum of chronic venous disease, ie, early disease, as an adjunct to surgery in moderate and advanced disease and in the treatment of leg ulcers. Recommendations are now available in guidelines for the management and prevention of chronic venous disease drawn up in North America and Europe.

The four articles that follow provide a clear and comprehensive review of the latest advances in this field.

Andrew Nicolaides

Treatment of chronic venous disease of the lower extremities: what's new in guidelines?

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Keywords:
chronic venous disease, guidelines, recommendations, thromboembolic disease

Phlebolymphology. 2009;16(4):313-320.

INTRODUCTION

Guidelines for patient care offer recommendations to physicians for diagnosis and management of common diseases that generally apply to the typical patient. This manuscript addresses some of the newer guidelines to help clinicians manage patients with chronic venous disease of the lower extremities. The two important documents, "Management of Chronic Venous Disorders of the Lower Limbs: Guidelines According to Scientific Evidence"[1] prepared by an international consensus group under the auspices of the leading societies for venous disease, and, "Antithrombotic Therapy for Venous Thromboembolic Disease,"[2] as part of the American College of Chest Physicians (ACCP) 8th consensus conference, have recently been published to help physicians care for patients with venous disease. While there is broad overlap of these two documents, the recent ACCP guidelines have made specific changes with recommendations and suggestions linked to objective grades, which form the basis of this discussion.

The method of determining the strength and quality of the recommendations deserves mention. Recommendations are generally accompanied by a number, which refers to the *strength* of the recommendation, and a letter, which refers to the *quality of the evidence* supporting the recommendation. The guidelines for chronic venous disorders use three levels of strength: Grade I is a strong recommendation, Grade II a moderate, and Grade III a weak recommendation. The recent ACCP guidelines use only two levels for the strength of their recommendations: Grade 1 for strong and Grade 2 for weak.[3] They further indicate that statements accompanied by a Grade 1 level are "recommendations" and statements accompanied by a Grade 2 level are "suggestions."

The quality of evidence upon which the strength of the recommendation is based ranges from "A" for high quality, which is consistent evidence from randomized trials, to "B" for moderate quality, which is evidence from nonrandomized trials or inconsistent evidence from randomized trials. Level "C" is low quality, which is suggestive evidence from nonrandomized trials, observational reports, or expert opinion. Guideline-writing committees are

becoming increasingly aware of costs of care and patient values and preferences, as are physicians. It stands to reason that a clear-thinking, well-informed patient will agree with treatment recommendations that follow strong guidelines (Grades 1A), whereas when physicians are faced with atypical clinical circumstances or weak guideline recommendations (ie, suggestions), cost of care and patient values and preferences should be considered in addition to the risks and benefits of the treatment.

MAGNITUDE OF THE PROBLEM

Venous disease is one of the most common disorders afflicting the populations of developed and developing countries. New studies show that acute venous thrombosis resulting in fatal pulmonary embolism kills more people than acute myocardial infarction or acute stroke.[4] Over one million people per year will suffer acute deep venous thrombosis (DVT) in the United States alone. The postthrombotic morbidity that follows is substantial and is proportional to the extent of venous thrombosis. [5-7]

Chronic venous disease is a common condition with major socioeconomic impact due to its high prevalence. The cost of chronic venous disease includes its investigation, its treatment, and the loss of working days by the afflicted patients.[8, 9] Mild forms of venous disease, such as reticular veins and telangiactasias, are present in 80-85% of the population, varicose veins are present in 40% of men and 60% of women, and ankle edema is found in 7% of men and 16% of women.[10] Venous ulceration will occur in 0.3% of the population on an annual basis and approximately 1% of the population in Western countries will have either an active or healed venous ulcer.[9-11]

The prevalence of chronic venous disease increases with age. Age can be considered a "dose-related risk factor." [9, 10] However, the most impressive risk of chronic venous disease is a history of DVT. DVT increases the odds ratio of chronic venous disease by a factor of 25.[12]

The proportion of patients presenting with chronic venous symptoms increases linearly with the Clinical scale of the CEAP classification.[13]

Quality-of-life studies have shown that chronic venous disease is associated with increased pain, reduced physical function and mobility, and increased feelings of depression and social isolation.[14] The quality-of-life (QOL) assessment is directly associated with the severity of venous disease.[15] Patients who have or have had venous ulcers report a QOL similar to patients suffering with congestive heart failure.[16] Acute DVT often leads to chronic postthrombotic morbidity, and the severity of postthrombotic venous disease correlates directly with the extent of the acute DVT. Treatment of acute DVT is relevant to this discussion, because extensive DVT results in severe chronic morbidity unless patients are treated to eliminate the acute clot.

CLASSIFICATION AND SEVERITY SCORING OF CHRONIC VENOUS DISEASE

There is a broad range of signs and symptoms associated with chronic venous disease. A number of classification systems have been proposed. A widely accepted, objective, and standardized classification system is crucial for accurate and reproducible description of patients. Lack of precision in diagnosis and description leads to conflicting reports of disease distribution and a poor understanding of the management of specific venous pathology. A standardized classification facilitates improved precision of communication and serves as a foundation for accurate reporting of the severity of disease and response to treatment. The CEAP classification (Clinical, Etiology, Anatomy, Pathology) was proposed and subsequently adopted worldwide as a basis for improved patient description.[17] This is a point-in-time assessment which includes the clinical assessment (C), an etiologic assessment of the patient's disease (E), an anatomic assessment of location of the pathology (A), and the pathophysiologic basis for the underlying disease (P). The CEAP classification provides a broad-based, objective, anatomic, and physiologic basis for classification of venous disease. This has improved standardization, communication, decision making, and reporting of venous disease.

The *Villalta classification* is a clinical scale using subjective scores of 0 (absence) to 3 (severe) for symptoms of pain, cramps, itching, and physical findings of edema, pigmentation, venous ectasia, erythema, and induration. This has been used specifically for patients with postthrombotic syndrome. Studies have reported good interobserver agreement and the ability to differentiate moderate versus severe disease.[18] This

instrument is limited by its subjective rather than objective scoring for the clinical features mentioned and appears to have been applied only to patients with postthrombotic syndrome.

The Venous Clinical Severity Score (VCSS) includes nine attributes which are graded from 0 to 3. Attributes include pain, varicose veins, edema, pigmentation, inflammation, induration, active ulcers and size, and compression therapy. The use of a properly designed disease severity scoring system allows patients with similar degrees of chronic venous disease to be selected for entry into clinical trials and to have their outcomes assessed objectively following treatment. Properly applied, a venous severity scoring system is a valuable tool in venous outcome assessment.

The VCSS has been studied and shown to be valid in that its scores increase in a linear fashion with CEAP clinical class.[19] The VCSS is reliable as demonstrated in tests of intraobserver variability.[20-25] Therefore, a change in score of this instrument can be used as an outcome measure assessing treatment. Unfortunately, responsiveness of the VCSS has not been adequately evaluated; therefore, it cannot be used as yet to calculate sample sizes for clinical trials.[26]

PATHOPHYSIOLOGY OF CHRONIC VENOUS DISEASE

Understanding the pathophysiology of a disease state is basic to effective treatment. Results from studies that demonstrate treatment efficacy lead to guideline recommendations. The apparently simple concept of venous hypertension being responsible for chronic venous disease belies the complex cellular and molecular processes set into motion by the abnormal venous hemodynamics. Ambulatory venous hypertension is the hemodynamic pathology, with its underlying components being venous valvular incompetence, luminal obstruction, and failure of the calf muscle pump. Calf muscle pump failure is generally the consequence of obesity or other immobilization, often a reflection of high central venous pressures. A progressive increase in soft tissue findings and skin damage has been reported with increasing exercise venous pressures. In patients with chronic venous disease with ambulatory venous pressures <30 mm Hg, no ulcers were observed.[27] However, nearly all patients with exercising venous pressures of >90 mm Hg experienced venous ulceration. The consequence of venous hypertension is relative stasis with marked reduction in shear stress at the vein wall. Vein distension and reflux allow venous flow reversal. The reduced shear stress, structural changes in vein walls, and areas of disturbed and turbulent flow establish an environment to initiate and maintain inflammation. Shear stress governs leukocyte behavior and endothelial cell function. The resulting changes in endothelial cell signaling through a variety of pathways alter gene expression and the production and release of cytokines, proteases, and other factors that impact inflammation.[28]

The seminal role of leukocyte activation as a result of venous hypertension was recognized following basic animal experiments and human research. Animal models of venous hypertension demonstrated increased numbers of leukocytes in the skin of extremities with venous hypertension.[29,30] Both humans and animals have shown increased macrophages, mast cells, and T-lymphocytes in the skin affected by chronic venous disease.[29,30] When leukocytes are activated as a result of venous hypertension, they shed L-selectin and produce other integrins which bind to intracellular adhesion molecules (ICAMs). This permits endothelial cell adhesion of leukocytes and initiates their migration through the vessel wall into the extravascular tissues, leading to degranulation. Studies of induced venous hypertension (standing for 30 minutes) in humans have demonstrated reduced levels of L-selectin and CD11b on the leukocyte membrane, while at the same time plasma levels of L-selectin increased.[31] Interestingly, patients with chronic venous disease show a systemic increase in leukocyte adhesion. Plasma from patients with chronic venous disease induces more leukocyte activation of otherwise normal white cells than plasma from normal patients.[32] Activated neutrophils produce and stimulate the production of proteolytic enzymes such as matrix metalloproteinases (MMPs) and other serine proteases. Inhibitors of MMPs are also produced, often in greater proportion, which leads to the accumulation of extracellular matrix material, resulting in the characteristic lipodermatosclerosis of chronic venous disease.

Increased production of transforming growth factor beta (TGF-β_1) and fibroblast growth factor beta (FGF-β_1) also occurs. TGF-β_1 stimulates collagen synthesis and further increases tissue inhibitor of MMP production,

whereas FGF-β_1 is a stimulus for smooth muscle cell migration.[33,34] The sum of these events also results in increased soft tissue sclerosis.

Limb blood flow is altered in patients with chronic venous disease.[35] Plasma levels of vascular endothelial growth factor (VEGF) are increased in patients with chronic venous disease who have skin changes compared with patients with normal skin.[36] VEGF may promote the growth of capillaries which are observed in patients with lipodermatosclerosis and further promote the extravasation of fluid into the interstitial space by increasing permeability. The fibrin cuff around capillaries in damaged skin also contains collagen, laminin, fibronectin, and tenascin,[37] which reflects the altered cellular metabolic functions previously discussed.

This brief overview of the pathophysiology of chronic venous disease should improve understanding of treatment modalities which have shown efficacy and have therefore led to guideline recommendations.

WHAT'S NEW IN GUIDELINES?

Treatment of iliofemoral venous thrombosis

The writing committee for Antithrombotic Therapy for Venous Thromboembolic Disease of the 2008 ACCP guidelines recognized the excess morbidity of this particular distribution of disease. It is important to understand the anatomy of lower extremity venous drainage, which functionally resembles a funnel, with distal veins draining into larger but progressively fewer veins as blood moves cephalad. The common femoral and iliac veins represent the spout of the funnel, which is the single common channel of lower extremity venous drainage. If this channel is obstructed, it will affect the entire leg, with adverse functional consequences on all distal veins.

The greatest change in guidelines is the recommendation for consideration of a strategy of thrombus removal in patients with iliofemoral DVT. This is a reversal of the statements from guidelines published in 2004.[38]

Venous thrombectomy

The 2008 ACCP guidelines recommend considering venous thrombectomy for acute iliofemoral DVT in patients with symptoms for <7 days, good functional status, and a life expectancy ≥1 year.

Rationale: This is based upon level 1 data emanating from a large randomized study by Plate et al.[39-41] Patients were followed up and reported at 6 months, 5 years, and 10 years following randomization to venous thrombectomy or anticoagulation. Patients randomized to thrombectomy showed improved patency, lower venous pressures, less leg swelling, and fewer postthrombotic symptoms than patients treated with anticoagulation alone. Other, nonrandomized series also reported favorable outcomes of contemporary venous thrombectomy. Long-term observational results from 10 reports with the mean of 41 months of follow-up demonstrated a 76% patency, with 8 reports demonstrating functional venous valves in the femoropopliteal segment in 63%.[42]

Since venous thrombectomy is infrequently performed, the committee suggested that "catheter-directed thrombolysis is usually preferable to operative venous thrombectomy" (Grade 2C).

Catheter-directed thrombolysis

The recommendation for catheter-directed thrombolysis (CDT) for acute iliofemoral DVT in patients with a low risk of bleeding, symptoms <14 days, good functional status, and a life expectancy ≥1 year is also proposed to reduce acute symptoms and postthrombotic morbidity.

Rationale: A small randomized trial of catheter-directed lytic therapy versus anticoagulation demonstrated significantly better patency and preservation of valve function in patients treated with CDT versus anticoagulation.[43] Large single-center series and multicenter venous registries demonstrate an 80-90% success rate, with progressively lower bleeding complications over time.[44-46] A case-controlled cohort study, which followed the National Venous Registry, demonstrated significantly improved QOL in patients with iliofemoral DVT treated with CDT compared with those treated with anticoagulation.[47] The improved QOL was directly related to lytic success.

The committee suggested correction of underlying venous lesions using balloon angioplasty and stents (Grade 2C). While there are no objective data supporting this statement, the collective clinical observations and expert opinion suggest that residual (uncorrected) venous lesions increase the likelihood of rethrombosis.

Alternatively, correction of focal lesions in the proximal system is associated with good long-term outcome. This suggestion applies to both venous thrombectomy and CDT.

The committee recommends the same intensity and duration of anticoagulation following thrombectomy and CDT as patients who do not undergo these treatments (Grade 1C). This is a uniformly strong opinion by the experts, which underscores the need to avoid recurrence, although proper trials of intensity and duration of anticoagulation following interventional therapy have not been performed.

Early ambulation and compression

Early ambulation in patients with acute DVT is now recommended in preference to initial bed rest (Grade 1A).

Rationale: Randomized trials of early ambulation and leg compression have demonstrated reduced pain, edema, and postthrombotic morbidity compared with patients treated with bed rest and anticoagulation.[48-52]

For patients who have symptomatic proximal DVT, elastic compression stockings of 30-40 mm Hg are recommended (Grade 1A).

Rationale: Two randomized trials treating patients after a first episode of acute symptomatic proximal DVT demonstrated significant reduction (50%) of postthrombotic symptoms in patients wearing compression stockings compared with those treated without compression.[53,54] A Cochrane review of compression following acute DVT also concluded that compression stockings substantially reduced the incidence of the postthrombotic syndrome after two years.[55]

The early application of a snug wrap from the base of the toes to the upper thigh combined with ambulation and anticoagulation is the method described by Partsch et al,[56] which has been shown to be effective in the early management of patients with acute proximal DVT.

Intermittent pneumatic compression

For patients with severe edema of the leg due to postthrombotic syndrome, a course of intermittent pneumatic compression (IPC) is suggested (Grade 2B).

Rationale: In a crossover study[57] in patients with severe postthrombotic syndrome, IPC of 40 mm Hg proved more effective than placebo pressures. Patients uniformly preferred therapeutic pressures to placebo.

In patients with venous ulcers resistant to healing with wound care and standard compression, the addition of IPC is suggested (Grade 2B).

Rationale: IPC has been shown to increase venous velocity, reduce edema, increase TcPO2, increase popliteal artery blood flow, and increase endothelial nitric oxide synthase. These basic effects of IPC have translated into improved healing of venous leg ulcers in clinical trials. Randomized trials in patients with persistent venous ulcers have demonstrated significantly increased healing[58,59] and more rapid healing of venous leg ulcers when IPC was used in addition to standard wound care and compression wraps. Compression pressures and cycles have varied in the studies reported; therefore, IPC prescription for the treatment of postthrombotic syndrome and venous ulcers has not been standardized.

Pentoxifylline

Pentoxifylline at a dose of 400 mg PO TID in addition to local care and compression and/or IPC is recommended in patients with venous leg ulcers.

Rationale: The pharmacologic effect of pentoxifylline improves the rheology of blood flow in the microcirculation by altering the stiffness of the red blood cell membrane.[60] Eight randomized studies were tabulated by a Cochrane review evaluating pentoxifylline versus placebo in patients with venous leg ulcers, using objective measurements of wound healing.[61] There was uniform observation that pentoxifylline improved wound healing.

Micronized Purified Flavonoid Fraction or Sulodexide

In patients with persistent venous ulcers, rutosides, in the form of micronized purified flavonoid fraction (MPFF) given orally, or sulodexide, administered intramuscularly and then orally, is suggested to be added to local care and compression.

Rationale: Five studies (three published, two unpublished) have been performed using MPFF in the management of patients with venous ulcers.[62-66]

Two studies were placebo-controlled. A meta-analysis of these five studies has been reported.[67] Ulcer healing occurred in 61% of the MPFF patients at 6 months compared with 48% of controls (P=0.03). The benefit of MPFF appeared greatest in ulcers ≥5 square cm and those existing >six months.

The mechanism of benefit of MPFF is likely related to increased venous tone[68,69] and improved lymphatic flow,[70-72] resulting in diminished capillary hyperpermeability and increased capillary resistance,[73,74] which results in decreased edema.

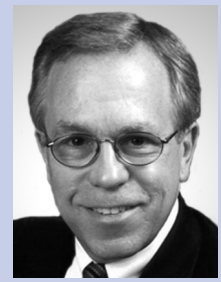
The importance of leukocyte activation as part of the cellular pathophysiology of venous disease was previously discussed. MPFF has been shown to reduce neutrophil adhesion in the post-capillary venules[75] and inhibit leukocyte adhesion and migration in the microcirculation.[76,77]

The glycosaminoglycan sulodexide, when given intramuscularly and orally, improved venous leg ulcer healing as demonstrated in a placebo-controlled trial.[78] There did not appear to be adverse side affects.

SUMMARY

The recent ACCP guidelines have added important new recommendations and suggestions for the management of patients with acute and chronic venous disease. The recommendations regarding acute DVT will have a major impact on reducing the frequency and virulence of postthrombotic chronic venous disease.

The physical and pharmacologic measures recommended will substantially improve the care of patients with chronic venous disease. These measures are consistent with the international guidelines published in *International Angiology* and the revised and updated UIP guidelines currently under development.



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Management of chronic venous disease: the example of Daflon 500 mg

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ABSTRACT

Chronic venous disease (CVD) is a common condition and represents a spectrum of disorders. The CEAP classification has been adopted worldwide to facilitate meaningful communication about the disease and to serve as a basis for more scientific analysis of treatment options. In addition to improved methods of defining CVD, there is also now increased understanding of the pathological processes involved in its development. Leukocyte-endothelium interactions are one of the earliest pathophysiological mechanisms at work and appear to be important in many aspects of the disease. The sequence of leukocyte adhesion, endothelial interaction, activation, and migration, and its association with valvular damage has focused attention on available molecules with activity known to modify this chain of events. The micronized purified flavonoid fraction (MPFF, Daflon 500 mg), consisting of 90% diosmin and 10% other flavonoids expressed as hesperidin, diosmetin, linarin, and isorhoifolin, currently possesses the most appropriate profile. It has been shown to reduce leukocyte interaction with the endothelium in acute venous hypertension and inflammation and is used clinically to treat CVD.

INTRODUCTION

Chronic venous disease (CVD) is a common presenting condition in industrialized countries, although prevalence estimates vary depending on the design of the particular study, the population sampled, and the disease definition used.[1] This is illustrated by data from the most representative epidemiological studies of the last 10 years, which have observed prevalence rates ranging from 40% to 90%. General population-based surveys in Germany,[2] Italy,[3] Scotland,[4] and the USA[5] have reported CVD prevalence rates of 90%, 77%, 85%, and 71%, respectively. These surveys recruited adults on a spontaneous and voluntary basis, by selecting them from registers[2,4] or by print or television advertising.[3,5] The high prevalence of disease in these surveys might indicate that respondents were more likely to have a history of diagnosed venous disease than nonrespondents.[4]

Keywords:
chronic venous disease, management, drugs, flavonoids

Phlebolymphology. 2009;16(4):321-330.

Although CVD is often mild in presentation, it is potentially a progressive condition.

Despite this it is often deemed a minor problem and frequently ignored by patients and physicians alike. In the past, one of the reasons for this may have been the lack of a standard definition for a disease, which covers a broad spectrum of venous complaints, from telangiectasias to varicose veins and ultimately to chronic venous ulcers, all of which are grouped in the same category of diseases. However, over the past decade the diagnosis and treatment of CVD has developed rapidly. An important aspect of this has been the development of a universal classification system that allows physicians to clearly delineate between the different types of venous complaints, thus facilitating comparisons between studies. The CEAP classification was introduced in 1994[6] and characterized each of the seven clinical classes (C0-C6) by a subscript for the presence of symptoms (S, symptomatic) or absence of symptoms (A, asymptomatic) (see *Table I*).

In 2004, a revision of the classification further refined the definitions of CVD, important amendments being the introduction of subclasses in skin changes (C4a and C4b) and the addition of a new descriptor, n, for E, A, and P items when no venous abnormality is identified.[7] This made it possible to classify the often encountered C0s, En, An, Pn subject, which describes a patient with so-called venous symptoms but without any visible or detectable sign of CVD (usually termed "C0s patient").

Most recently, the VEIN TERM consensus document has been developed to provide universal agreement on the definition of many widely used clinical venous terms.[8] In this document, the term chronic venous disorder encompasses the full spectrum of venous abnormalities, while CVD is reserved for the major subset of individuals with venous complaints and/or manifestations requiring investigation or care or both.[8] The term chronic venous insufficiency is reserved for those with advanced signs. The document also provides recommendations for venous clinical terminology based on the type of symptoms as well as aggravating factors. Thus, venous symptoms are defined as tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness and/or fatigue, which may be exacerbated during the course of the day or by heat, but is relieved with leg rest or elevation or both. The document defines venous signs as visible manifestations of venous disorders, which include dilated veins (telangiectasias, reticular veins, varicose veins), leg edema, skin changes, and ulcers, as described in the CEAP classification.[7]

CVD may be associated with a wide range of lower limb symptoms, which may be present from the outset even before any visible signs of CVD have been identified. The recent clarifications of the definitions of CVD should help physicians identify patients who may be amenable to effective medical therapy. A number of venoactive drugs of plant or synthetic origin are available for the treatment of the symptoms of CVD, as illustrated in *Table II*.[9,10] Using the example of micronized purified flavonoid fraction (MPFF, Daflon 500 mg, Servier, France), this review will provide an update on the pathological processes involved in CVD and illustrate the benefits of treating the underlying disease process.

• C0: No visible or palpable signs of venous disease.
• C1: Telangiectasias or reticular veins.
• C2: Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more.
• C3: Edema.

• C4: Changes in skin and subcutaneous tissue secondary to CVD, now divided into 2 subclasses to better define the differing severity of venous disease:
  • C4a, pigmentation and eczema
  • C4b, lipodermatosclerosis or atrophie blanche

• C5: Healed venous ulcer.
• C6: Active venous ulcer.

Table I. Clinical definitions of the CEAP classification.[7]

Group	Substance	Origin	Dose	Number of doses/day
Benzypyrones				
Alpha-benzopyrones	Coumarin	Melilot *(Melilotus officinalis)* Woodruff *(Asperula odorata)*	90 combined with troxerutin (540)	3
Gamma-benzopyrones (flavonoids)	Diosmin	Citrus spp. *(Sophora japonica)*	300-600	1 or 2
	Micronized purified flavonoid fraction (MPFF)	*Rutaceae aurantiae*	1000	1 or 2
	Rutin and rutosides	*Sophora japonica*	1000	1 or 2
	0-(β-Hydroxyethyl)-rutosides (troxerutin, HR)	*Eucalyptus spp.* *Fagopyrum esculentum*	2 x 500 2 x 1000	1 or 2
Saponins	Escin	Horse chestnut *(Aesculus hippocastanum L)*	Initially 120, then 60	3
	Ruscus extract	Butcher's broom *(Ruscus aculeatus)*	2 to 3 tablets	2 to 3
Other plant extracts	Anthocyans	Bilberry *(Vaccinium myrtillus)*	116	2
	Proanthocyanidins (oligomers)	Maritime pine *(Pinus maritimus)* Grape pips *(Vitis vinifera)*	100 to 300 300 to 360	1 to 3 3
	Extracts of Ginkgo	*Ginkgo biloba*	2 sachets (Extracts of Ginkgo, heptaminol, and troxerutin)	2
Synthetic products	Calcium dobesilate	Synthetic	1000 to 1500	2 to 3
	Benzaron	Synthetic	400 to 600	2 to 3
	Naftazon	Synthetic	30	1

Table II. Classification of the main venoactive drugs.[9,10]

RECENT ADVANCES IN OUR UNDERSTANDING OF THE PATHOPHYSIOLOGY OF CHRONIC VENOUS DISEASE

The venous inflammatory theory

Despite the diversity of signs and symptoms associated with CVD, venous hypertension appears to underlie most or all signs of the condition and in most cases, is caused by reflux through incompetent venous valves.[11] While the valves and vein walls can withstand raised venous pressure for limited periods, when it is prolonged adverse effects occur. A number of theories have been put forward to explain how venous hypertension may lead to venous reflux through failed valves, but a prominent role for an inflammatory reaction in the process of venous valve destruction emerged when it was observed that the valve leaflets and venous wall from vein specimens of patients with CVD were infiltrated with monocytes and macrophages, whereas control specimens were not.[12] Over the past decade evidence for the inflammatory theory has accumulated and it is now widely recognized to play a key role in the pathogenesis of CVD.[11]

The trigger for the inflammatory process is thought to be abnormal venous flow in the form of altered shear stress. While shear stress is important in maintaining healthy vasculature, low shear stress, such as that associated with venous hypertension, promotes the expression of inflammatory gene products by the endothelium[11] and results in enhanced leukocyte activation, adhesion, and migration through the endothelium of venous valves and the vein wall.[12,13] The acute effects of increased venous pressure cannot be readily studied in man, but a number of animal models are available and have provided information on the mechanisms involved in

valve destruction. In a rat model of venous occlusion, the effects of venous hypertension could be observed by comparing regions on either side of the occlusion.[14] Venous pressure was only elevated on the upstream side of the occlusion and was associated with increased rolling, adherent, and migrating leukocytes as well as with increased numbers of apoptotic cells in the parenchyma, which are markers of the inflammatory cascade and tissue injury.[14]

Elevation of femoral venous hypertension by a femoral arterial-venous fistula for a period of 3 weeks in a rat saphenous vein model has revealed that valve failure occurs as a result of dilation of the venous wall and shortening of valve leaflets eventually leading to incomplete valve closure and subsequent reflux.[15] Examination of the valves revealed infiltration with leukocytes including granulocytes, monocytes, and T-lymphocytes. In addition, the expression of the endothelial cell membrane adhesion molecules, P-selectin and ICAM-1, on the endothelial cells of the saphenous vein wall was increased. Activated leukocytes on the venous endothelium migrate into the venous wall and produce toxic metabolites and free oxygen radicals that participate in valve destruction and venous wall weakening. Enzymatic degradation of the valve leaflets and venous wall by metalloproteinases is thought to play a key role in this process through their degradation of elastin and collagen.[16] The leukocyte-endothelium interaction resulting from altered shear stress contributes to the inflammation and subsequent remodeling of the venous wall and valves. Incompetent valves allow reflux to occur, reinforcing venous hypertension and perpetuating disease progression (*Figure 1*).

Hypotheses on venous pain and the C fiber theory

Venous pain is a common complaint in patients with CVD and is associated with all stages of the disease. It is now thought that the pain related to CVD may mirror endothelial activation and the cascade of inflammatory mediators released early in the disease process.[17] Pain of venous origin can be induced by both mechanical and chemical stimuli and it is suggested that the release of proinflammatory mediators as part of the inflammatory cascade may activate nociceptors located in the venous wall and in the connective tissue, as well as causing capillary damage and leakage resulting in swelling and pressure on nerve endings. In later stages of the disease,

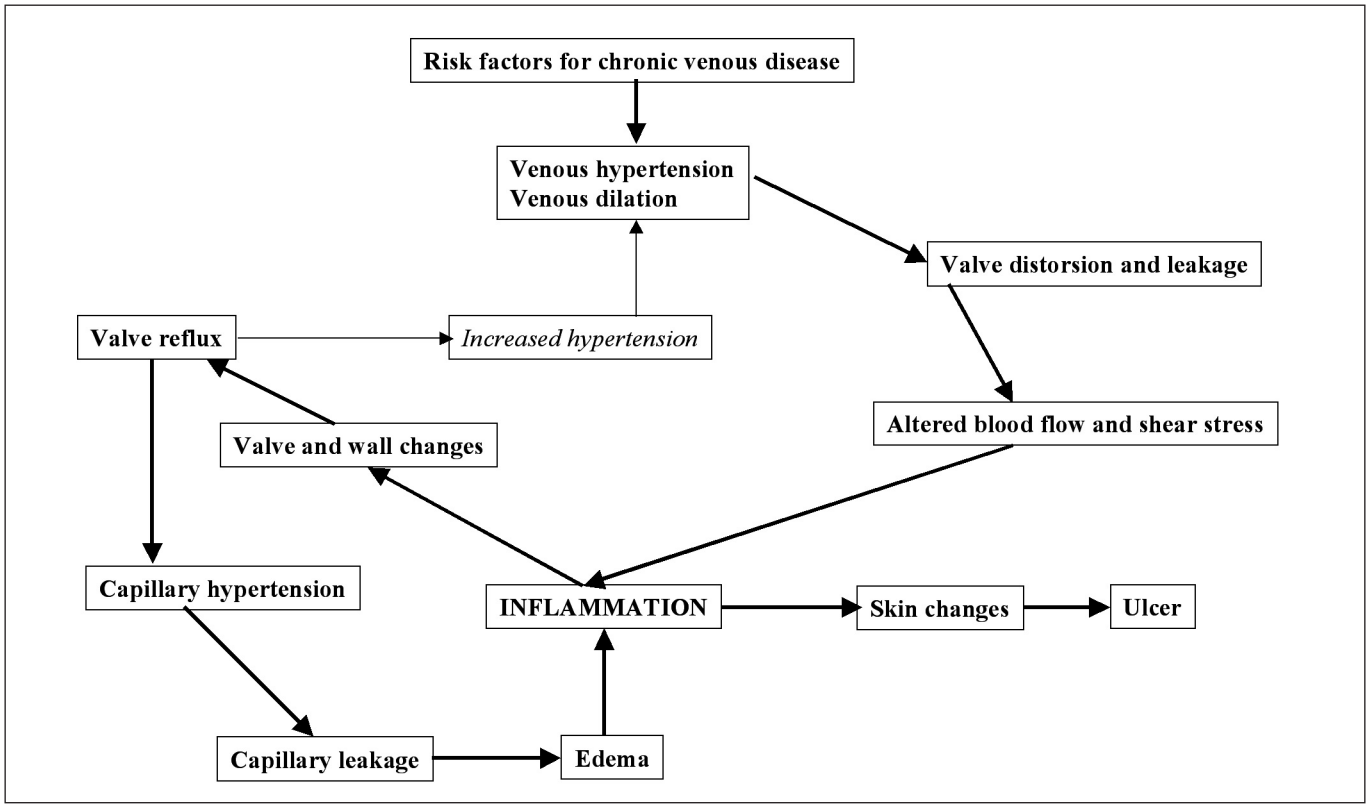


Figure 1. The vicious circle of venous hypertension/venous inflammation. Adapted from Bergan et al, 2006.[11]

remodeling and stretching of the venous wall due to the inflammatory process may also stimulate nociceptors in the venous wall. With such a theory, it would be expected that the levels of some inflammatory markers would be correlated with the intensity of pain in CVD. However, no such correlation has been found, and there is also no association between pain and the severity of the disease. For example, pain is often more severe in the early stages of CVD when superficial venous distensibility is slight than in more advanced stages when pressure on the venous wall is high. This has led researchers to suggest that the cascade of inflammatory reactions that activate venous nociceptors can occur before any significant remodeling of large venous vessels arises. This may account for the occurrence of pain from the earliest stages of CVD. The fact that venous pain is not closely correlated with vein remodeling or incompetent valves suggests that the primary activation site of venous nociceptors may not be in the large venous vessels, but in the microcirculation, where contact between nerve endings, the arteriole, the vein, and the capillary is much closer.[17] The involvement of an inflammatory process in the pain related to CVD is important as it suggests that pharmacological treatments acting on venous inflammation may provide relief from this symptom.

THE MECHANISM OF ACTION OF VENOACTIVE DRUGS AND MPFF (DAFLON 500 MG)

Most venoactive drugs prolong the vasoconstrictor effect of noradrenaline on the vein wall, increasing venous tone, and thereby reducing venous capacitance, distensibility, and stasis. This increases the venous return and reduces venous pressure in patients suffering from CVD. Studies of the mechanism of action of MPFF have shown that it prevents or delays the occurrence of CVD by: (i) increasing venous tone (this results in restoration of normal blood flow, dispersion of red cell aggregates, and better oxygenation); (ii) improving capillary hyperpermeability and lymph flow thus protecting the microcirculation and decreasing the risk of edema; and (iii) inhibiting leukocyte adhesion to endothelial cells and the transmigration of leukocytes into the venous wall (an effect seen only with MPFF).

Venous tone

The beneficial effects of MPFF on venous tone have been studied in three double-blind, placebo-controlled trials in patient populations with varying degrees of CVD including women with venous insufficiency related to a postthrombotic syndrome,[18] venous insufficiency related to pregnancy,[19] and women without any venous pathology.[20] MPFF at a dose of two tablets per day had an acute effect on increasing venous tone beginning 1 hour after administration in all three groups of women. In the trial of women without any venous pathology,[20] MPFF significantly improved venous distensibility for 4 hours after administration compared with placebo ($P<0.05$). When treatment was continued for 1 week, the significant effect on venous distensibility compared with placebo was maintained for 24 hours ($P<0.05$).

In a study aimed at determining the effect of MPFF in 25 female volunteers aged 18-35 years with abnormal venous elasticity, but without varicose veins,[21] twelve women received a single dose of two tablets of MPFF for 4 weeks and 13 women in the control group received no treatment. Venous tone was significantly improved compared with baseline in patients receiving MPFF ($P<0.02$). In contrast, venous elasticity did not change significantly from baseline in patients in the control group.

Capillary hyperpermeability

When subjected to prolonged venous hypertension, capillaries become elongated and dilated and develop abnormal permeability. The increased permeability causes interstitial edema. The beneficial effects of MPFF on capillary hyperpermeability have been demonstrated in two trials.[22,23] In a 6-week, placebo-controlled trial in 30 patients with idiopathic cyclic edema, MPFF significantly improved capillary hyperpermeability (as measured by labeled albumin retention) compared with placebo ($P<0.05$).[22] This was accompanied by a mean weight loss of at least 1.5 kg and a decreased sensation of swelling indicating a concomitant decrease in edema. In a 4-week study in patients with venous hypertension, MPFF given either two or three times daily significantly decreased the capillary filtration rate from baseline values in a dose-dependent manner ($P<0.05$).[23]

Lymphatics

In patients with advanced CVD, there is an increase in intralymphatic pressure and diameter, and in permeability of lymphatic capillaries leading to the transendothelial diffusion of fluids.[24] MPFF is thought to improve lymph flow by increasing both the frequency and amplitude of contraction of lymphatic capillaries, as well as increasing the number of functional capillaries.

This reduces edema by facilitating the drainage of interstitial fluid into the lymphatic system. In a 4-week study in 24 patients with severe CVD, but no active ulceration, MPFF significantly decreased the diameter of lymphatic capillaries and the intralymphatic pressure from baseline ($P<0.001$).[25] In addition, the number of functional lymphatic capillaries was also significantly increased ($P<0.001$).

Leukocyte-endothelial interactions

The well-established role of leukocytes in the pathophysiology of CVD has focused attention on drugs able to block leukocyte adhesion to the venous valves and wall and thereby stop venous inflammation very early in the disease process. MPFF is up to now the only available venoactive drug with documented evidence of its ability to attenuate the effects of various mediators of the inflammatory cascade, particularly leukocyte-endothelial interactions, which are important in many aspects of the disease.

For more than 10 years it has been accepted that CVD is related to a primary failure of venous valves that are affected by inflammation.[15,16] As a result, guidelines now mention that early pharmacological treatment directed towards preventing or inhibiting the inflammatory response at all stages of the disease may play a significant role in preventing or slowing the development and recurrence of the signs and symptoms of CVD.[26] Key findings were those provided by the rat fistula model of venous hypertension with MPFF.[15] In this model, venous hypertension caused by a femoral arterial-venous fistula resulted in the development of venous reflux and an inflammatory reaction in venous valves. In animals treated with MPFF there was a significant, dose-dependent reduction in the reflux rate. MPFF also inhibited the expression of the endothelial cell adhesion molecules P-selectin and ICAM-1, reduced leukocyte infiltration, and decreased the level of apoptosis in the valves in a dose-dependent manner. These data suggest that in the rat model of venous hypertension, MPFF delays the development of reflux and suppresses damage to the valve structures by decreasing the interaction between leukocytes and endothelial cells.

The above observations were confirmed in a study using the same animal model.[16] The administration of MPFF reduced the edema and the fistula blood flow produced by the acute arterial-venous fistula. MPFF also reduced granulocyte and macrophage infiltration of valves.

As a consequence of these findings, the most recent guidelines on the management of chronic venous disorders of the lower limbs have expanded the recommendations for the use of venoactive drugs following the realization that the beneficial effects of these agents is not just due to their effects on venous tone.[26]

INDICATIONS FOR VENOACTIVE DRUGS

CVD may be associated with a wide range of lower limb symptoms, and these may be present in patients suffering from any class of the CEAP classification for CVD (C0s–C6s). Leg heaviness, discomfort, itching, cramps, pain, paresthesia, and edema are the most frequent manifestations of CVD and a major reason for medical consultation.

Venoactive drugs may be indicated as a first-line treatment for CVD-related symptoms and edema in patients at any stage of disease.[9,26] In the most recent guidelines for the management of chronic venous disorders of the lower limbs, three agents receive a Grade A level of evidence for their effects on venous symptoms: calcium dobesilate, hydroxyethyl-rutosides, and MPFF.[9,26]

In patients with advanced CVD, venoactive drugs may be used in conjunction with sclerotherapy, surgery, compression therapy or a combination thereof.[9,26] MPFF is useful for first-line management of edema as well as associated symptoms of CVD. It continues to be effective at all subsequent stages of the disease and is the only venoactive drug proven to have an additional beneficial effect on leg ulcer healing in a meta-analysis of 5 trials.[27] On the basis of this meta-analysis, MPFF was assigned a grade 2B in the treatment of venous leg ulcers in patients with venous thromboembolic disease[28] and a grade 1B in the healing of long-standing or large venous ulcers.[29] In these guidelines, the authors had reviewed the evidence for therapies added to conventional compression.

CLINICAL EFFICACY OF THE VENOACTIVE DRUGS: THE EXAMPLE OF MPFF (DAFLON 500 MG)

Symptoms of CVD

A review of the data for MPFF show that it is effective from the earliest stages of CVD, including in patients

with a C0s classification, and that symptom relief is achieved rapidly and sustained. The efficacy of MPFF's relief of clinical symptoms has been evaluated in two placebo-controlled trials in which the following symptoms were considered: functional discomfort, leg heaviness, pain, fatigue when standing, night cramps, paresthesia, burning sensation, itching, sensation of edema in the evening (summarized in *Table III*).[30,31] In the first trial of 40 patients with CVD, MPFF was associated with a significantly greater improvement in many of the symptoms of CVD compared with placebo with P-values for the global scores of $P<0.001$.[30] In a second placebo-controlled trial of 160 patients with CVD, MPFF was again associated with a significant improvement in symptoms compared with placebo.[31] For the symptoms of functional discomfort, sensation of heaviness, nocturnal cramps, and sensation of swelling, these changes were significant after 4 weeks of treatment.

The effects of MPFF on the symptoms of CVD have also been compared with nonmicronized diosmin in a study of 88 patients.[32] While statistically significant improvements in all subjective symptoms were noted in both treatment groups at the end of 2 months, MPFF was more effective than diosmin for the majority of response measures.

Symptoms after stripping surgery

The benefits of MPFF as part of the pharmacological pre-operative care and post-operative recovery for patients with varicose veins who undergo phlebectomy have been evaluated in two trials.[33-36] In both studies, MPFF helped to attenuate pain, decrease postoperative hematomas and accelerate their resorption, and to increase exercise tolerance in the early post-operative period. Pre-operative management included prolonged administration of MPFF (4-6 weeks) and compressive therapy in cases of varicose veins with lymphostasis. Post-operatively, MPFF was continued for at least 4 weeks.[33,34]

Symptoms associated with pelvic congestion syndrome

Venous dysfunction and stasis may be pathophysiologic components of pelvic pain in women with pelvic congestion syndrome. As venous leg disorders have been reported in cases of pelvic congestion syndrome, MPFF treatment has been evaluated in a trial of 20 women with chronic pelvic pain diagnosed with pelvic congestion syndrome by laparoscopy.[37] In a cross-over study, 10 women were randomized to receive MPFF 500 mg twice daily for 6 months, and ten a vitamin pill for placebo effect. After 6 months, mean pain scores were significantly lower in the MPFF group compared with placebo ($P<0.05$).

Leg edema

In the three trials assessing the efficacy of MPFF's relief of the symptoms of CVD, measures of edema were also taken and all three trials demonstrated a significant correlation between the improvements in the symptom score of sensation of swelling and a decrease in ankle circumference (*Table IV*).[30-32] Three further studies that have used different methods to quantify leg edema have also demonstrated beneficial effects of MPFF. In two placebo-controlled trials of patients with either symptoms or signs of CVD, MPFF resulted in significant reductions in ankle circumference compared with placebo.[30,32] In a third study, edema was assessed using a volumeter in 20 patients with varicose veins or postthrombotic syndrome. MPFF was associated with a significant decrease in volume of the more affected lower leg of 263 ml (8%) in all patients and 392 ml (12%) in patients with varicose veins.[39] Finally, edema, measured

Reference	Regimen (n)	Symptoms improved by MPFF			
		Pain	Functional discomfort	Sensation of swelling	Leg heaviness
Chassignolle et al, 1987[30]	MPFF (18) vs placebo (18)	NA	+++	NA	+
Gilly et al, 1994[31]	MPFF (76) vs placebo (74)	+	+++	+++	+++
Cospite et al, 1989[32]	MPFF (43) vs single diosmin (45)	+	NA	NS	+

NS, not significant. NA, not assessed. +$P<0.05$; ++$P<0.01$; +++$P<0.001$ MPFF vs comparator.

Table III. Clinical efficacy of MPFF in alleviating venous symptoms (adapted from Chassignole et al, 1987;[30] Gilly et al, 1994;[31] Cospite et al, 1989[32])

Reference	Regimen (n)	Decrease in edema with MPFF		
		Ankle circumference	Calf circumference	Volume
Chassignolle et al, 1987[30]	MPFF (18) vs placebo (18)	+++	+++	NA
Gilly et al, 1994[31]	MPFF (76) vs placebo (74)	+++	+++	NA
Cospite et al, 1989[32]	MPFF (43) vs single diosmin (45)	+++	+++	NA
Blume et al, 1992[39]	Open (20)	NA	NA	+++
Laurent et al, 1988[38]	Open (200)	+	NA	NA
Jantet, 2002[40]	Open (3101)	NA	+++	NA

+*P*<0.05; +++*P*<0.001 MPFF vs comparator (or Day 60 [Blume et al, 1992; Laurent et al, 1988] or Day 120 [Jantet, 2002] vs Day 0 for open studies). NA, not available.

Table IV. Clinical efficacy of MPFF in reducing venous edema (adapted from Chassignole et al, 1987;[30] Gilly et al, 1994;[31] Cospite et al, 1989;[32] Blume et al, 1992;[39] Laurent et al, 1988;[38] Jantet, 2002[40]).

by leg circumference, was also significantly decreased compared with baseline in the Reflux assEssment and quaLity of lIfe improvEment with micronised Flavonoids (RELIEF) study.[40]

Leg ulcer healing

MPFF remains of significant benefit for patients at advanced stages of CVD where it may be used with conventional therapy to promote ulcer healing. The efficacy of MPFF in augmenting the healing of venous ulcers has been demonstrated in three randomized, controlled, multicenter trials in which MPFF plus standard venous leg ulcer management was compared with standard venous leg ulcer management (compression therapy plus local treatment) alone[41,42] or in addition to placebo[43] (*Table V*).

In all three studies, there was a significantly higher ulcer healing rate in patients treated with MPFF than in the control group. In the Glinski et al study, ulcers with a diameter less than 3 cm were cured in 71% of the MPFF group and 50% of the standard therapy group.[41] In the Roztocil et al study, the time to achieve complete healing was significantly shorter in the MPFF group (137 days for MPFF versus 166 days for the control group, *P*=0.042), and a significantly greater number of patients had complete ulcer healing with MPFF (64.6%) compared with the control group (41.2%, *P*=0.04).[42]

A meta-analysis in which 723 patients with venous ulcers treated with MPFF were pooled confirmed that venous ulcer healing is accelerated by adding MPFF to conventional treatments.[27] At 6 months, the chance of a healing ulcer was 32% better in patients treated with adjunctive MPFF than in those managed by conventional therapy alone (relative risk reduction: 32%; 95% CI, 3% to 70%; *P*=0.03). Subgroup analyses suggested that the benefits of MPFF were greatest in ulcers ≥ 5 cm² and > 6 months in duration.

Reference	Design (n)	Study duration (months)	Results
Guilhou et al, 1997[43]	RCT, placebo-controlled (105)	2	Healed ulcers: MPFF 32%, placebo 13% (*P*=0.028)
Glinski et al, 1999[41]	RCT, open-label (140)	6	Healed ulcers: MPFF 47%, placebo 28% (*P*<0.05)
Roztocil et al, 2003[42]	RCT, open-label (150)	6	Healed ulcers: MPFF 65%, placebo 41% (*P*=0.004)
Coleridge-Smith et al, 2005[27]	Meta-analysis (723)	2-6	Healing rate increased by 32% with MPFF and healing shortened by 5 weeks

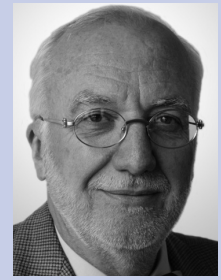
RCT, randomized clinical trial

Table V. Clinical efficacy of MPFF in healing venous ulcers (adapted from Kearon et al, 2008[28]).

CONCLUSION

CVD is a common condition, but epidemiological studies often only focus on one aspect of the disorder, for example varicose veins, and therefore true prevalence rates are difficult to determine. In reality, CVD represents a spectrum of disorders ranging in severity from leg pain, swelling, edema, and skin changes, to venous ulcers. While the CEAP classification has been paramount in providing a uniform basis on which to present diagnostic and treatment results, it is less useful for epidemiological research because of the many subgroups of CVD it distinguishes. In this regard, the recent VEIN-TERM consensus document might prove invaluable in providing uniform recommendations for venous terminology. The use of a common scientific language to allow the global dissemination of knowledge is essential in the rapidly developing field surrounding the investigation and management of CVD.

In order to develop effective treatment regimens for CVD, a clear understanding of the underlying pathological processes is required. Research advances have led to an appreciation of the importance of chronic inflammatory processes throughout the course of the disease and have clarified some of the mechanisms involved in its progression. The wealth of preclinical studies that have been conducted with MPFF have been instrumental in establishing that an interaction between leukocytes and endothelial cells marks the beginning of all pathophysiology in venous disorders and that the resulting inflammation leads to primary failure of venous valves. This discovery has important implications for preventing the development of CVD and, in particular, for treating the C0s class in which patients have symptoms despite the absence of any visible signs of CVD. Patients in this class may be presenting with the earliest form of CVD and treating them may therefore delay further development of the disease. Optimal therapy for CVD would normalize venous physiology, resolving the inflammatory cascade that results in adverse effects on valves and vein walls. While a number of venoactive drugs are available, currently only MPFF has an evidence base demonstrating that it has both acute and long-term anti-inflammatory effects on the venous valves in chronic conditions of venous hypertension. This is translated into clinical benefits with a number of randomized, controlled, double-blind studies demonstrating MPFF's efficacy in treating the symptoms of CVD, skin changes (C4a-b, C5), and venous leg ulcers (C6). The strength of the evidence is reflected in recent international guidelines, which are strongly evidenced-based and assign MPFF high levels of recommendation for the treatment of patients at all stages of CVD. The management of CVD has therefore reached a point where improved definitions of the disease and understanding of the pathophysiological processes involved have come together to facilitate earlier treatment of CVD with targeted agents. In the long term this may prevent the more serious consequences of the disease, while at the same time improving patient quality of life.



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Unmet needs in the assessment of symptoms and signs related to chronic venous disease

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ABSTRACT

Chronic venous disease (CVD) is a disorder highly prevalent among populations of Western countries and with which both general practitioners and specialists have to deal. It induces pain, causes discomfort, significantly reduces the quality of life for the affected patient, and lacks specific and consensual instruments able to adequately assess its signs and symptoms.

This article presents these needs that are still unmet in clinical practice and that relate to the tools currently available for the assessment of the therapeutic efficacy of drugs on the disease symptoms and signs. Suggestions are presented regarding new endpoints and tools to be used in further clinical trials designed to assess the effect of therapies on CVD, in particular studies with Daflon 500 mg.

INTRODUCTION

Chronic venous disease (CVD) is common among general populations[1-5] and its prevalence is likely to increase with population ageing.[6] For a long time, wide differences have been observed between the reported rates of prevalence, probably due to recruitment biases and to the use of a definition of CVD that has long remained nonuniform. The Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification, published in 1995[7] and updated in 2004,[8] provides a descriptive clinical classification that describes CVD in all its aspects, using a coding system. Recent population-based surveys based on this classification report prevalence rates of CVD of 49% in Poland,[9] 71% in the US,[10] 77% in Italy,[11] 85% in Scotland,[12] and 90% in Germany.[13]

Both general practitioners and specialists have to deal with CVD. Its treatments are usually evaluated on the basis of clinical outcomes, but such evaluation does not take into account the patients' perception of the disease and the treatment impact on their quality of life (QOL), which is significantly altered by the disease. Specific tools capable of assessing the full spectrum of

Keywords:
chronic venous disease, signs, symptoms, assessment tools, management, patient-related outcome, quality of life, classification

Phlebolymphology. 2009;16(4):331-339.

CVD, its signs and symptoms, impact on QOL, and treatment effects are the key for efficient management of the disease.

This article describes those instruments that are currently available to practitioners to assess the efficacy of therapy on symptoms and signs related to CVD. It highlights also what needs to be better assessed in terms of CVD symptoms and signs, the main need being a consensus about the tools to use so as to be able to compare treatment effects between studies, and to assess which have the best specificity regarding CVD.

Suggestions are made regarding new end points and instruments of assessment for further clinical trials assessing the therapeutic effects of venoactive drugs.

ASSESSING THE EFFICACY OF TREATMENT ON CVD-RELATED SYMPTOMS

Symptoms are defined as what patients complain of. In a world epidemiological survey (the Vein Consult Program) which is to be set up under the aegis of the *Union Internationale de Phlébologie* Scientific Society during the year 2009, the symptoms that will be screened for are listed in *Tables I and II*. Symptoms can be self-assessed, using Patient-Related Outcome or Patient-Reported Outcome (PRO) tools,[14,15] or reported by physicians. In the latter situation, questioning of the patient is crucial.

There are currently, three types of instruments for the assessment of CVD-related symptoms.

I. Ascribing symptoms to CVD

In fact, symptoms are not pathognomonic but may be suggestive of CVD, particularly if they are exacerbated by heat or dependent on the time of day, and relieved by leg rest and/or elevation. Simple questions can be asked by the practitioners to ascribe symptoms to CVD (*Table II*).

The scoring system by Carpentier,[16] presented in *Table III*, is a patient-administered diagnostic tool designed to ascribe leg symptoms to CVD. This system "might also help predict the usefulness of treatment in patients with CVD seeking medical help for their symptoms". It combines four criteria: 1) sensation of heavy or swollen legs, 2) associated sensation of itching, restless legs, or phlebalgia, 3) sensation worsened by a hot environment or improved by a cold environment, and 4) sensation not worsened by walking. Scores range from 0 to 4. With a threshold level of >3, this scoring system had a high specificity (0.95) and a fair sensitivity (0.75) for CVD (*Table III*).

Do you have any of the following leg problems now?
One or more boxes can be ticked

a.	☐	Heavy legs
b.	☐	Pain in the legs
c.	☐	Sensation of swelling
d.	☐	Sensation of burning
e.	☐	Cramps
f.	☐	Itching
g.	☐	Sensation of "pins and needles" in the legs

Table I. Symptoms screened for in the future VEIN CONSULT PROGRAM to be set up under the aegis of the scientific society UIP (Union Internationale de Phlébologie)

When are your leg problems more intense?
One or more boxes can be ticked

a.	☐	At the end of the day
b.	☐	During nighttime
c.	☐	After prolonged standing
d.	☐	After prolonged sitting
e.	☐	During summer
f.	☐	After warm baths
g.	☐	When walking
h.	☐	Before menstrual periods (women only)

Table II. Ascription of symptoms to CVD, as screened for in the VEIN CONSULT PROGRAM to be set up under the aegis of the UIP (Union Internationale de Phlébologie)

The VEINES-Sym, developed by DL Lamping,[17] is a 10-item self-administered questionnaire that includes questions on the frequency of 9 CVD-related symptoms (heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling sensation), and the intensity of leg pain. The scores range from 0 to 10, with higher values indicating better outcomes.

The Phleboscore® developed by P. Blanchemaison[18] is an 11-item self-administered questionnaire which helps predict the risk of developing CVD. It includes questions

Sensation of heavy or swollen legs …	… associated with itching, restless legs, or phlebalgia…	… worsened by a hot environment or improved by a cold environment …	… and not worsened by walking
1 mark	1 mark	1 mark	1 mark

Score ≥3: symptoms are of venous origin *Score <1: symptoms are not of venous origin*

Table III. The scoring system for venous symptoms. Adapted from Carpentier PH et al[16]

about risk factors (gender, age, sedentary life, weight excess, number of pregnancies, working conditions, family history, sporting activities), as well as questions about the frequency of symptoms (heavy legs, sensation of swelling) and the circumstances in which symptoms worsen (heat, birth pill, long-haul travel). The scores range from 0 to 31. A score >12 identifies patients at risk of CVD, while a score >23 pinpoints a need for venous investigation.

II. Tools adapted to patient-reported outcome

The tools used to assess PRO consist mainly of quality of life (QOL) scales that may be either generic or disease-specific.[15]

The 13-item Aberdeen Varicose Veins Questionnaire[19] (AVVQ) is a disease-specific approach to measuring the patient's perception of outcome for varicose veins. This questionnaire addresses all features of varicose vein disease: physical symptoms and social issues, pain, ankle edema, ulcers, compression therapy use, and the effect of varicose veins on daily activities, in addition to the effect of varicose veins from a cosmetic standpoint. In studies conducted to test the validity and the reliability of this instrument, the Aberdeen Questionnaire was shown to have good levels of validity and test-retest reliability and to be the most responsive to changes in health status.[19,20] A recent Dutch study conducted to test the translated version of the questionnaire obtained interesting results with very satisfactory levels of feasibility (0.6% of missing answers and 0.2% of non-unique answers), internal consistency (Cronbach's alpha =0.76 indicating a high level of concordance between the questions); test-retest reliability (Spearman's r=0.87, showing a significant strong association between test and retest scores), and discriminative validity since AVVQ score was able to differentiate between subgroups of patients with different severity of venous disease according to the CEAP classification (Mann-Whitney U test, $P<0.01$).[20]

The 20-item ChronIc Venous disease quality of lIfe Questionnaire (CIVIQ) gives a global score, plus a score for each of the 4 areas in which QOL is likely to be affected: physical, psychological, social, and pain. CIVIQ has been extensively used, as reported in numerous studies[22-41] among which some included large samples of patients.[22-26] Launois initially developed with rigorous methods a practical, scientifically rigorous patient-reported outcome measure CIVIQ in a clinical trial of 934 patients and an epidemiologic survey of 26 681 patients.[22] Lurie used it to compare two surgical procedures (stripping vs Closure").[24] Jantet tested it in the RELIEF study (Reflux assEssment and quaLity of life improvEment with micronized Flavonoids), in 3948 C0 to C4 patients.[23] Guex et al used the CIVIQ questionnaire in a study aimed at describing the health status of 1045 female patients suffering from CVD, and to assess the care impact,[25] and Neglén used it before and after intervention, along with the CEAP classification in an 8-year study on venous outflow stenting performed in 982 chronic non-malignant obstructive lesions of the femoroiliocaval vein.[26] CIVIQ has been extensively used in many CVD-related conditions.[27-42] CIVIQ is validated in 13 languages including Canadian English, English for Singapore, British English, American English, French Canadian, French for France, German for Austria, Greek, Italian, Polish, Portuguese for Portugal, and Spanish for Spain and for the USA.

The Charing Cross Venous Ulceration Questionnaire was developed to provide a valid QOL measure for patients with venous ulcers and to assess the effects of the many treatments available for venous ulcers.[15,42] A study aimed at testing the validity of this questionnaire showed a high correlation with all eight domains of the gold standard SF-36 general health measure ($r>0.55$, $P<0.001$). The factor analysis identified four important health factors: social function, domestic activities, cosmesis, and emotional status. This study also demonstrated its good reliability (internal consistency: Cronbach's alpha=0.93),

test-retest reliability (r=0.84), and good responsiveness (significant reduction in the score on the ulcer questionnaire as ulcers healed at 6 and 11 weeks; $P<0.05$).[42]

The VEnous INsufficiency Epidemiological and Economic Study (VEINES), an international, prospective cohort study conducted in 166 general practices and 116 specialist clinics in Belgium, France, Italy, and Canada, has developed the VEINES-QOL/Sym to evaluate QOL and symptoms across the range of conditions (eg, telangiectasias, varicose veins, edema, skin changes, leg ulcers) in lower limb CVD.[17] It consists of 35 items distributed in 2 categories to generate 2 summary scores: the VEINES-QOL questionnaire comprises 25 items that estimate the effect of disease on QOL, and the 10-item VEINES symptom questionnaire (VEINES-Sym) measures symptoms. The focus of this instrument is on physical disconfort as opposed to psychological and social aspects. This measure of QOL and symptoms is available in four languages (English, French for Belgium and France, Italian, and Canadian French). It has been used in only 3 studies of Kahn et al to assess the health-related QOL of large samples of CVD patients with and without prior venous thromboembolism,[43] and patients with deep venous thrombosis.[44-46]

All these four disease-specific assessment tools were used in conjunction with the 36-item Medical Outcome Study Health Survey Short Form (MOS SF-36), a generic health-related QOL instrument of which the validity, reproducibility, and responsiveness to changes over time have been well demonstrated.[47,48] It is the most widely used and validated generic QOL instrument, whatever the medical field. The SF-36 has been developed over time with questions in the following two categories: physical health (assessed as the patient's level of functioning) and mental health (assessed as an indication of well-being). These two groups have been broken down into 8 areas that include evaluation of physical and social functioning, role limitations due to physical or emotional problems, mental health, pain, vitality, and health perception. When complete, the survey generates a score ranging from 0 to 100, with higher scores indicating best general health perception. The SF-36 has proven to be a good fit for generic QOL assessment in patients with CVD.[20,49-52]

III. Tools available to physicians to measure symptoms

Among the various instruments that are available to physicians to measure symptoms such as pain, assessing the consumption of analgesic drugs may be valuable but only if assessed by the practitioner. Such a criterion is unreliable when assessed by the outpatient and reported during history taking only: no instrument has been validated for the measurement of outpatients' consumption of analgesic medication.[53,54]

Practitioners may use visual analogue scales (VAS) – such as the 10-cm VAS – for measuring CVD-related pain.[37] This type of scale provides patients with easy and rapid way to express the intensity of their pain and has been validated[55-57] and used in numerous applications. Regarding CVD, since pain related to this disease is mostly below 4 cm, the adequacy of this measurement may be questioned; the amplitude of pain may not be large enough in CVD to assess the therapeutic effects using such means.

The numerical rating scales are usually graded from 0 to 5, or 0 to 4, or 0 to 10. These scales that measure pain during the medical visit and in a retrospective manner[58] are often used in the evaluation of treatment in CVD.[59-61]

ASSESSING THE EFFICACY OF TREATMENT ON CVD-RELATED SIGNS

Disease-related signs are visible or palpable; they are usually reported by the physician, not by the patient.

I. The CEAP classification, a universally adopted classification of CVD signs

The CEAP classification[7,8] has become a universal method of classification of venous disease. This classification can be used by the clinician in keeping office records of diagnostic information. Adoption of this single classification worldwide based on correct diagnosis has facilitated meaningful communication about the disease and served as a basis for a more scientific analysis of management alternatives.

II. The adjuncts to the CEAP as tools for physicians

Some limitation exists regarding the use of the CEAP classification in the evaluation of patients with CVD. The CEAP classification is descriptive, but cannot be used for venous severity scoring because many of its components are static and do not change in response to treatment. A disease severity scoring scheme needs to be quantifiable, with gradable elements that can change

in response to treatment.[62] Therefore, a venous severity scoring system (VSSS) has been proposed by the American Venous Forum (AVF) ad hoc committee on outcomes, consisting of three scores: the Venous Clinical Severity Score (VCSS), which includes 10 hallmarks of venous disease that are likely to show the greatest change in response to therapy and are scored on a scale of severity graded 0-3, and the Venous Segmental Disease Score (VSDS), which uses the anatomic and pathophysiological classifications in the CEAP system to generate a grade based on venous reflux or obstruction, and the Venous Disability Score (VDS), which refers to ability to work with or without a "support device".[62]

Among the various comments and recommendations presented by B. Eklöf[63] at the San Diego Consensus meeting of 2003 regarding the use of these tools (the CEAP classification and the VSSS), the following points for which consensus was reached should are worthy of particular attention:

- The CEAP classification is a descriptive instrument to categorize patients into different groups of severity of CVD;
- The VSSS is a useful complement to the CEAP classification, and should be used for research;
- The use of all CEAP components should be encouraged. However, use of only the clinical component (C) at the time of the initial evaluation is appropriate, and the E, A, and P components can be added as the diagnostic evaluation progresses.

Although reportedly easy to use, in the view of angiologists the VSSS is more likely to be of value in severe CVD.[64] The descriptive CEAP and the VSSS, particularly the VCSS, are valid but imperfect instruments for evaluation of the early stages of CVD and treatment outcome. It seems that the time has come to revise the VCSS to allow proper reporting of common patient symptoms.

Another element appears to be lacking in the evaluation of CVD patients based on the CEAP and VSSS systems only: the patient's perception of anxiety or psychological apprehension.[65] A study that used both systems to evaluate venous disease in patients undergoing primary ambulatory surgery for varicose veins noted that despite careful patient selection, psychological distress could not be prevented or predicted; 11% of the patients experienced distress and anxiety, and a significant difference was observed regarding the complication rate in the recovery room (p=0.04) between patients with or without anxiety.[65] Thus, taking emotional factors into consideration in outpatient surgical practice appears to be essential.

III. The assessment of treatment efficacy on edema and venous ulcer

Some tools assess leg edema by measuring either leg circumference or volume (volumetry).[66] Leg circumference can be assessed using a tape measure or the Leg-O-Meter, an inexpensive and reproducible method validated in the RELIEF study[23] and the VEINES study.[68] Its limitation is that the circumference is not always correlated with leg volume measurement.[66] The leg volume can be assessed simply and reproducibly by water displacement volumetry, optoelectronic methods, CT scanning, MRI, and dual X-ray absorptiometry. Assessing the volume is preferable, but the methods of assessment have not all been validated and lack sensitivity in CVD.

Numerous techniques are available for the assessment of venous ulcer, ranging from the simple use of tracings to more sophisticated methods requiring cameras, videos, and computers.[68] The parameters most frequently used to measure a wound are the length of the principal axes (length and width of the wound), the projected surface area, and the perimeter.[68]

ASSESSMENT OF TREATMENT EFFICACY IN CVD: A NEED FOR CONSENSUS ABOUT TOOLS TO BE USED

I. Regarding the tools used to assess symptoms

This is the most problematic issue since symptoms are subjective by definition. Moreover, pain in CVD is diffuse, unpleasant, with a high negative impact on QOL. This is seen in the many symptoms reported (sensation of swelling, of burning, of leg heaviness, etc.) and in the fact that the wording used to describe the complaints is vague. This may be due to the underlying mechanisms of venous pain.[69]

In general, what is still needed is:

- the validation of Carpentier's scoring system (*Table III*);[16]

- the inclusion of questions regarding the circumstances of appearance of symptoms as part of the usual patient questioning; this will be done (with a more comprehensive Q) in the VEIN-Consult programme (*Tables I and II*);
- the Phleboscore[18] is an interesting way of warning patients about the risk factors, but it has never been validated;
- it is acknowledged that both generic and specific QOL scales should be used: the generic SF-12 (or 36) is a validated tool that could be adopted, while for specific scales, the CIVIQ that has been extensively used in CVD is the most often used scale up to now, with 13 languages validated;[15]
- quantitative and semi-quantitative scales were included in the comprehensive document of the ANAES,[53] but much remains to be done to choose the most adapted scale. The VAS has been the most extensively validated tool in different diseases, but rare are the CVD patients whose scores exceed 5 cm.

II. Tools used to assess signs

The CEAP has been a great leap in the classification of venous signs. It allows the description of patients at the entry in a study, and the comparison of patients' profiles between studies. Despite the progress the CEAP represents, it has weaknesses, such as:

- a certain difficulty in distinguishing between C1 and C2 patients as shown by the epidemiological studies in which the prevalence of the disease at these stages varies greatly from one paper to another;
- it is not clearly stated in the CEAP whether the edema of C3 patients is a permanent edema (as a preliminary stage towards skin changes and CVD complications) or if a reversible edema that occurs at the end of the day and disappears after rest can be included in the C3 stage.
- Although corona phlebectatica (corona) is a clinical sign associated with chronic venous disease, it is not yet included in the CEAP classification. Corona is defined as fan-shaped intradermal telangiectasias in the medial and sometimes lateral portions of the ankle and foot. It has been shown that corona strongly correlates with the clinical severity and hemodynamic disturbances of the disease.[70] The inclusion of corona in the C3 class should probably improve the reliability of the CEAP clinical classes.

III. Methods of assessment

In addition to the limitations related to the methods of assessment of leg edema (see above), there is a lack of consensus regarding the definition of wound healing in assessing the treatment of leg ulcers: should we consider healing as a simple wound re-epithelization or as skin re-epithelization + return to daily activities?[71,72] Standards for the measurement of wound healing are needed.

USING CURRENT AND NEW TOOLS IN FURTHER CLINICAL TRIALS ASSESSING THE EFFECTS OF DAFLON 500 MG ON SYMPTOMS AND SIGNS

One of the main objectives of any new clinical trial with Daflon 500 mg is to assess the benefits of this treatment at the early stages of CVD: C0, C1 and C3. Taking into account the following suggestions should improve the assessment of treatment outcome.

- Quantifying symptoms:
  - which symptoms? The most frequently encountered ones such as pain, heaviness, and sensation of swelling, separately;
  - use of rating scales such as VAS, and simple verbal scales + assessment of the influence of symptoms on QOL using the SF-12 or CIVIQ questionnaire.

- New approach to symptom assessment:
  - Since pain of venous origin is often multifaceted and is frequently associated with other unpleasant sensations like swelling, heaviness, burning, etc., which are often difficult to describe and usually expressed with a vague terminology, it is likely that such unpleasantness belongs to the range of symptoms of nociception. Therefore, the use of a composite score that would include pain, heaviness, and sensation of swelling would be desirable;
  - Given the high negative impact unpleasantness and symptoms may have on patients' daily lives, and the fear for the future that patients express when they report their anxiety, the use of a complementary psychological screening tool to measure the improvement of CVD-related anxiety disorders would be an interesting complement to the QOL scales. In this view, the Hospital Anxiety and Depression Scale (HADS) that has been extensively

validated in many illnesses and is used in routine care in many countries[73] could be helpful;
- both the CIVIQ and the HADS are likely to provide the best answer to the difficulty of assessing subjective symptoms.

- Reporting signs:

  - telangiectasias: educating primary care investigators using slides and clear-cut definitions;
  - edema: by distinguishing edema of venous origin from nonvenous edema (pitting edema);[74]
  - edema assessment by associating leg circumference measures and volume measurement as in the method of the truncated cone.[75]

CONCLUSION

As a common disease with which both general practitioners and specialist doctors have to deal, CVD and outcomes of CVD treatment should be better assessed, especially at early stages of the disease. As stated by the AVF, "the cornerstone for management of CVD is a proper diagnosis and accurate classification of the underlying venous problem, which creates the base for correctly directed treatment". Taking emotional factors into consideration in the patient's management has been shown to be essential also, given the significant impact of this disease on the patient's QOL. Numerous instruments and tools are available to practitioners both to assess signs and symptoms of the disease and to assess the patients' perception of their health-related QOL, but none is fully satisfactory and some remain to be validated. Much is yet to be done to improve the management of this disease by a more proper use of the existing diagnostic and assessment means and by taking account of the full spectrum of the disease including its impact on the patient's QOL.

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Venoactive medications and the place of Daflon 500 mg in recent guidelines on the management of chronic venous disease

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ABSTRACT

Because the venous system is in many respects more complex than the arterial system, because chronic venous disease (CVD) is common in Western populations, and because both specialists and general practitioners have to deal with this disease, there is a need for practical support regarding CVD management in daily practice. This article summarizes the most recent guidelines regarding the place of venoactive drugs (VADs) such as Daflon 500 mg in the management of this disease. In addition, it makes suggestions regarding expected improvements in future guideline documents.

INTRODUCTION

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

Epidemiological studies have shown that CVD has a considerable socio-economic impact in Western countries due to its high prevalence, cost of investigations and treatment, and loss of working days.[1,2] Varicose veins are present in 25-33% of female and 10-20% of male adults. In the Framingham study, the incidence of varicose veins per year was 2.6% in women and 1.9% in men.[3] The prevalence of edema and skin changes such as hyperpigmentation and eczema due to CVD varies from 3.0% to 11% of the population and venous ulcers occur in as many as 0.3% of the adult population in Western countries.[4]

The considerable socioeconomic impact of CVD is due to the large numbers concerned, cost of investigations and management and morbidity, and the

Keywords:
chronic venous disease, venoactive drugs, guidelines, Daflon 500 mg

Phlebolymphology. 2009;16(4):340-346.

suffering it produces, all of which is reflected in deterioration of quality of life and in working days lost. The problem is compounded by the fact that CVD is progressive and has a propensity to recur. Measures to reduce the magnitude of the problem include awareness of the problem, early diagnosis and care, careful consideration of the necessity and choice of investigations, and discipline in the choice of management based on clinical effectiveness and cost. These requirements imply specific training in all aspects of this condition. Estimations of the overall annual costs of CVD vary from 600 to 900 million euros in Western European countries, representing 1-2% of the total health care budget, to 2.5 billion euros (US$3 billion) in the USA.[5]

Two recent guidelines have reviewed the place of venoactive drugs (VADs) in the management of CVD[5,6] and another has made recommendations for venoactive drugs in chronic venous leg ulceration.[7] This article summarizes their recommendations regarding the place of VADs in the management of CVD.

SUMMARY OF THE RECENT GUIDELINES ON VADS

Numerous randomized, controlled, double-blind studies have demonstrated the anti-edematous effect and the effective attenuation by VADs of the symptoms related to CVD, such as heavy legs, pain in the legs, sensation of swelling, of burning in the legs, itching and restless legs. Currently, VADs are an established component of the therapeutic armamentarium for all stages of CVD.

The therapeutic efficacy of oral VADs on venous-related symptoms

The main indications of VADs are symptoms related to varicose veins or attributed to CVD and edema.[8,9]

A Cochrane review on VADs has been published recently by Martinez et al[10] in which the efficacy of such drugs has been examined in detail. Studies were classified as level A (low risk of bias), level B (moderate risk of bias), or level C (high risk of bias). In this review, for every outcome variable except venous ulceration, the analyzes showed significant treatment benefits for the VADs compared with placebo when analyzed as either a dichotomous or a continuous variable or both in some cases. The only non-significant effects were for venous ulceration, itching assessed as a continuous variable, and paresthesia assessed as a continuous variable. For edema (RR 0.72, 95% CI 0.65; 0.81), trophic disorders (RR 0.88, 95% CI 0.83; 0.94) and restless legs (RR 0.84, 95% CI 0.74; 0.95) the analyses showed significant benefit of VAD treatment with no evidence of heterogeneity among studies.

On the basis of this review, the author of the chapter devoted to drug treatment of varicose veins, venous edema, and ulcers of the last (3rd) edition of the Handbook of Venous Disorders, Guidelines of the American Venous Forum, assigned VADs a grade 2B in the improvement of symptoms and edema associated with chronic venous disease.[11]

The article of Ramelet et al[12] represents the proceedings of the International Medical Consensus Meeting on venoactive drugs in the management of chronic venous disease held in the framework of the 13th Conference of the European Society for Clinical Haemorrhoeology (ESCH), Siena, Italy. Data from RCTs were selected according to the predefined criteria of evidence-based medicine and on the experts' own experience. Studies were classified as: grade A (at least two RCTs with large sample sizes, meta-analyses combining homogeneous results), grade B (RCTs with small sample size, single RCT), or grade C (other controlled trials, non-randomized controlled trials) in the Siena consensus paper on efficacy of VADs on symptoms (*Table I*). Outcomes included only symptoms at any stage of the disease.

Escin (horse chestnut seed extract), which was not included in the Cochrane review of Martinez et al,[10] was evaluated in the Cochrane review of Pittler and Ernst[13] and in the Ramelet et al consensus paper.[12]

The international guidelines on the management of CVD[14] used the same grading system as that of the Siena experts except for meta-analyses, which were grade B. Outcomes included not only symptoms but also edema and venous ulcer healing. When considering VADs, the guidelines largely summarized and endorsed the positive findings of the recent Cochrane reviews.[10,13] The guidelines highlighted the evidence of efficacy of several VADs (calcium dobesilate, MPFF, rutosides, HCSE, proanthocyanidines, and coumarin + rutin) in CVD-related edema, and the efficacy of MPFF as an adjunct to standard compression treatment in the healing of venous ulcers.

Compound	Recommendation	Number of influential studies	
		RCTs	Meta-analyses
Calcium dobesilate	Grade A	3	2
MPFF	Grade A	4	1
HR-oxerutins	Grade A	5	1
HCSE (escin)	Grade B	1	2
Ruscus extracts	Grade B	2	1
Diosmin (synthetic)	Grade C	1	
Troxerutin	Grade C	2	
Gingko biloba	Grade C	2	
Proanthocyanidines	Grade C	2	
Troxerutin + coumarin	Grade C	1	
Centella asiatica	Grade C	1	
Naftazone	Grade C	1	

RCTs: randomized clinical trials

Table I. Classification of the RCTs on VADs by grades of recommendation in the international consensus statement (International Medical Consensus Meeting on Veno-active drugs in the management of chronic venous disease, 13th Conference of the European Society for Clinical Haemorrhoeology, Siena, Italy).[6]

According to these two recent guidelines on VADs,[12,14] and given the consistency of their respective files, a grade A was assigned to 3 VADs: calcium dobesilate, MPFF (Daflon 500 mg), and HR-oxerutins for the effects of these VADs on symptoms and skin changes, which are summarized in *Table II*.

No reservations were voiced regarding the safety of VADs, except for coumarin-rutin and benzarone (hepatotoxicity) and for calcium dobesilate with which some cases of transient agranulocytosis were reported from 1992 to 2005.[14]

The therapeutic efficacy of oral VADs on edema of venous origin.

Although edema is a non-specific sign, it is one of the most frequent and typical symptoms and signs in CVD. All other causes of edema should be excluded to confirm its venous origin. CVD-related edema is described as a sporadic, unilateral or bilateral, and limited to the legs, which may also involve proximal parts of the lower extremities. It is enhanced by prolonged orthostatic posture, and improved by leg elevation.[15]

Several well-conducted controlled trials versus placebo or stockings[12,14] have shown efficacy of oral VADs such as micronized purified flavonoid fraction, rutosides, horse chestnut seed extract, calcium dobesilate, proanthocyanidines and coumarin-rutin. In these trials, the evaluation of the anti-edema efficacy was based on objective measures, such as measurement of leg circumference, strain-gauge plethysmography, and water displacement. The results of many meta-analyses have confirmed the anti-edema efficacy of such medications (*Table II*).

Pharmacological treatment of leg ulcers

Among VADs, horse chestnut seed extract and of hydroxyrutosides were not superior to compression in advanced chronic venous insufficiency[16] or in preventing venous ulcer recurrence.[17] Acceleration of the healing of venous leg ulcers (stage C6 of the CEAP) has been demonstrated by several double-blind studies using *micronized purified flavonoid fraction* (MPFF) (Daflon 500 mg) in combination with compression (*Table II*). This was confirmed in 2005 by a meta-analysis of 5 trials with MPFF as an adjunct to standard compression treatment in 723 patients in class C6 according to the CEAP classification.[18]

The third and most recent guidelines of the American College of Chest Physicians (Evidence-Based Practice

Compound	Indications	RCTs (year)	Meta-analyses	Recommendation
Calcium dobesilate	Cramps, restless legs, sensation of swelling, edema	Labs (2004), Marinello (2004), Casley-Smith (1988), Widmer (1990)	Ciapponi (2004)	Grade A
MPFF	Pain, cramps, heaviness, sensation of swelling	Chassignole (1987), Behar (1988), Cospite (1989), Barbe (1992), Galley (1993), Gilly (1994), Danielsson (2002)		Grade A
	Venous leg ulcer healing	Guilhou (1997), Glinski (1999), Roztocil (2003)	Coleridge Smith (2005)	Grade A
Hydroxyethyl-rutosides	Itching, edema	de Jongste (1989), MacLennan (1994), Burnand (1989), Pedersen (1992), Schultz-Ehrenburg (1993), Kranendonk (1993), Cloarec (1996), Unkauf (1996), Grossmann (1997)	Poynard (1994)	Grade A
Escin, HSCE	Pain, edema	Diehm (1996)	Pittler (2006), Siebert (2002)	Grade B
Ruscus extracts	Pain, edema	Parrado (1999), Vanscheidt (2002)	Boyle (2003)	Grade B
Synthetic diosmins		Carpentier (1998)		Grade C
Troxerutin		Rehn (1993), Vin (1994)		Grade C
Gingko biloba	-			Grade C
Proanthocyanidines	Pain, edema	Ihme (1996), Petrassi (2000), Kiesewetter (2000)		Grade C
Troxerutin-coumarin	-	Vanscheidt (2002)		Grade C
Naftazone	-	Vayssairat (1997)		Grade C

HCSE: horse chestnut seed extract; MPFF: micronized purified flavonoid fraction; RCTs: randomized clinical trials.

Table II. Summary of VAD effects on symptoms, edema and skin changes by category of drugs[5,6]

Guidelines (8th edition) published in 2008 in Chest)[7] included a section on the treatment of venous leg ulcers in patients with venous thromboembolic disease, with a review of the evidence for therapies added to conventional compression. It was recommended that in patients with venous ulcers resistant to healing with wound care and compression one should consider the addition of intermittent pneumatic compression (IPC) (Grade 2B) or pentoxifylline (Grade 2B); in patients with persistent venous ulcers MPFF should be added to compression (Grade 2B). The rationale for the Grade 2B recommendation is probably the absence of a single large, randomized, controlled study. The evidence for the addition of IPC was based on 2 randomized, controlled, clinical trials involving 45 and 47 patients.[19,20] The evidence for pentoxifylline was based on the Cochrane meta-analysis of Jull et al[21] of 8 RCTs involving 547 patients. Compression therapy was also used in 5 of the 8 trials.

The last edition (3rd) of the Handbook of Venous Disorders, Guidelines of the American Venous Forum, included a chapter on drug treatment of varicose veins, venous edema, and ulcers. The use of MPFF in combination with compression in long-standing or large venous ulcers was recommended (Grade 1B).[11]

The evidence for the addition of MPFF is based on the meta-analysis of 5 trials with MPFF as an adjunct to standard compression treatment in 723 patients as mentioned above.[18] At 6 months, complete ulcer healing had occurred in 61% of the MPFF patients and in 48% of the control patients (RR reduction for persistent ulceration: 32%; 95% CI 3% to 70% P=0.03). Subgroup

analyses suggested that the benefits of MPFF were greatest in ulcers ≥ 5 cm² and > 6 months in duration.

KEY QUESTIONS TO BE ANSWERED FOR BUILDING FUTURE GUIDELINES IN CVD

An update of the "guidelines for testing drugs for CVD"[22] is needed to allow the pharmaceutical industry investing the necessary resources to perform large and definitive clinical trials, which could improve the recommendations used by clinicians and organizations involved in decision-making in this important field of CVD. Such guidelines could:

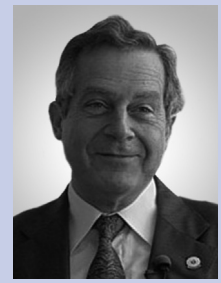
- Reiterate the basic principles applied when reporting from (and setting up) any RCT, using the Consolidated Standards of Reporting Trials (CONSORT) statement. This CONSORT statement helps authors and investigators report trials by the use of a checklist and a flow diagram, available at www.consort-statement.org. Numerous papers have published this checklist.[23-26]
- Describe comprehensively patients at selection in a study, using the advanced CEAP classification, which implies that not only the C of the CEAP should be completed but also items E, A and P, together with a level 1 investigation. The addition of the new descriptor n for E, A and P items, when no venous abnormality is identified, may be useful when describing patients complaining of leg symptoms but with no visible or detectable signs of CVD.[27]
- Promote the use of validated tools to assess symptoms,[28-35] edema and venous leg ulcer.[36-39]

Besides, there is a need for a consensus on the following end points:

- Symptoms: how great does the decrease on the VAS scale have to be in order to consider there is a clinical improvement? (This is useful when drawing a parallel between VAS improvement and quality of life improvement, for example.)
- Edema: how great does the reduction in ankle volume have to be in order to consider it clinically relevant?[22]
- Varicose veins: which criteria should be used to judge whether a treatment for varicose veins has been successful? Cosmetic satisfaction for the patients or the absence of reflux after treatment or the absence of pain and complaints after treatment or the absence of recurrent varicose veins after treatment?

Venous leg ulceration: when should we consider the ulcer has healed?[40]

- The role of VADs in the prevention of the natural history of CVD remains to be determined: are all VADs able to protect the "venous capital"?
- Consensual adoption of a simple and universally understood system of grading would be desirable.[41]



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1 - Ramelet AA, *Clin Hemorheol Microcir.* 2005;33:309-319. **2** - Nicolaides A, *Int Ang.* 2008;27:1-60.

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