European and American guidelines on primary chronic venous disease: what's new?

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Primary chronic venous disease (CVD) is defined as morphological and functional abnormalities of the venous system of long duration, manifested by symptoms, signs, or both. CVD is extremely common in most countries and has a considerable socioeconomic impact in Western countries. Venoactive drugs (VADs) are a heterogenic group of drugs of vegetal or synthetic origin. The objective of this article is to highlight the role and impact of VADs in the management of primary CVD according to recent European and American guidelines. Following analysis of the recent guidelines on primary CVD and their recommendations regarding the place of VADs in the management of primary CVD, three VADs were given the highest level of recommendation. Calcium dobesilate, micronized purified flavonoid fraction (MPFF), and hydroxyethylrutoside (ie, oxerutins) were assigned a Grade A recommendation, the highest level of recommendation by the International Consensus Statement (Siena, 2005) and the Consensus Statement led by Nicolaides in 2008, with regard to CVD-related symptoms. The guidelines detailed evidence of the efficacy of several VADs in CVD-related edema, and the efficacy of MPFF as an adjunct to standard treatment in the healing of venous ulcers. The use of MPFF and pentoxifylline in combination with compression in longstanding or large venous ulcers was recommended and assigned Grade 1B in the latest edition of the Handbook of Venous Disorders (2009). Suggestions regarding expected improvements in future guideline documents are also presented.

Medicographia. 2011;33:285-291 *(see French abstract on page 291)*

Primary chronic venous disease (CVD) is defined as morphological and functional abnormalities of the venous system of long duration, manifested by symptoms, signs, or both. Symptoms related to CVD are diverse1: tingling, aching, burning, pain, muscle cramp, sensation of swelling, sensation of throbbing or heaviness, itching skin, restless

legs, leg tiredness, and fatigue. They are not pathognomonic, but may be suggestive of CVD if they get worse as the day progresses or are exacerbated by heat, and relieved with leg rest and elevation.[1]

Clinical signs include telangiectasias, reticular and varicose veins, edema, skin changes, and venous ulcers. They are categorized into seven classes designated C0–C6 according to the CEAP (Clinical–Etiological–Anatomical–Pathophysiological) classification (*Table I, page 286*).[2] Each clinical class is characterized by a subscript letter indicating the presence of symptoms (S, symptomatic) or absence of symp- toms (A, asymptomatic). All classes of CVD can be associated with symptoms. Epidemiological studies have shown that CVD is extremely common in most countries and has a considerable socioeconomic impact in Western countries. In some studies, the majority of the adult population showed some degree of CVD. In the Edinburgh Vein Study,[3] more than 80% of people aged 8 to 64 years had mild hyphenweb or reticular varices, while a study carried out in 24 Italian cities[4] showed that only 3% of subjects examined were free of visible signs of CVD. In the San Diego Population Study,[5] featuring 2211 people, visible disease was present in 84% of women and 57% of men.

CEAP classification	Clinical description
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, divided into 2 sub-classes to better define the differing severity of venous disease: C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer

Table I. *Clinical descriptions of the revised CEAP classification.*

Abbreviations: *CEAP, Clinical-Etiological-Anatomical-Pathophysiological; CVD, chronic venous disease.*
Modified from reference 2: *Eklöf et al; American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. J Vasc Surg. 2004; 40:1248-1252. © 2004, The Society for Vascular Surgery.*

Reported prevalences of the clinical manifestations of CVD vary widely. The prevalence of edema and skin changes, such as hyperpigmentation and eczema, due to CVD varies from 3% to 11% of the population. In Western countries, it is estimated that 1% of the population will develop one or more episode(s) of leg ulcer. The economic cost of CVD is thought to be very high. It has been estimated that the cost of managing CVD represents 1%–3% of the total health-care budget in Western countries,[6–9] with treatment costs amounting to approximately US $3 billion annually in the USA.[10] In addition, venous leg ulcers cause the loss of some 2 million working days per year in the USA.[10]

Venoactive drugs

Venoactive drugs (VADs) are a heterogenic group of drugs of vegetal or synthetic origin. They can be classified in 4 major categories (*Table II*): benzopyrones; saponins; other plant extracts; and synthetics drugs.[11]

_ ***Main categories of VADs***

_ *Benzopyrones*

There are two classes of VAD in this category: alpha-benzopyrones and gamma-benzopyrones. Coumarin is the most notable alpha-benzopyrone. Gamma-benzopyrones, which are also known as flavonoids, include diosmin, micronized purified flavonoid fraction (MPFF), and rutosides, such as rutin, troxerutin, and hydroxyethylrutosides (HRs).

_ *Saponins*

This category includes horse chestnut seed extract (HCSE) and *Ruscus* extracts.

_ *Other plant extracts*

All these plant extracts, such as extracts of *Ginkgo biloba*, *Centella asiatica*, and

Hamamelis, contain flavonoids, such as anthocyans and proanthocyanidins, together with other active substances.

_ *Synthetic drugs*

The principal synthetic drugs are calcium dobesilate, naftazone, and benzarone.

_ ***Mode of action of VADs***

VADs have multiple effects on the venous system.[11] The mode of action varies depending on the drug. They attenuate macrocirculatory changes in the venous wall and venous valves that cause hemodynamic disturbances leading to venous hypertension and attenuate microcirculatory effects of venous hypertension that lead to venous microangiopathy. They also have effects, eg, anti-inflammatory, on venous tone, venous wall, venous valves, capillary leakage, the lymphatic network, and hemorrheologic parameters.

Recently, attention has focused on the roles of oxidative stress and inflammation in causing adverse changes in the vein wall and venous valves, which lead to subsequent skin changes.[12] Some VADs have free-radical scavenging actions and can interfere with inflammatory cascades, notably in the case of MPFF by inhibiting leukocyte-endothelial interactions.[13] An- imal studies suggest that these actions of VADs can protect the vein wall and valves from deleterious changes, with the potential for slowing or preventing the progression of primary CVD.[14]

Selected abbreviations and acronyms

CEAP	Clinical-Etiological-Anatomical-Pathophysiological
CIVIQ	Chronlc Venous dIsease Questionnaire
CONSORT	CONSOlidated standards of Reporting Trials
CVD	chronic venous disease
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HCSE	horse chestnut seed extract
HR	hydroxyethylrutoside
MPFF	micronized purified flavonoid fraction
QOL	quality of life
RCT	randomized controlled trial
SF-12	Short Form 12-item [health survey]
SF-36	Short Form 36-item [health survey]
VAD	venoactive drug

Group	Substance	Origin
Benzopyrones		
Alpha-benzopyrones	Coumarin	Melinot *(Melilotus officinalis)* Woodruff *(Asperula odorata)*
Gamma-benzopyrones (flavonoids)	Diosmin	Ciprus sp *(Sophora japonica)*
	Micronised purified flavonoid fraction (MPFF)	*Rutaceae aurantiae*
	Rutin and rutosides	*Sophora japonica*
	O-(β-hydroxyethyl)-rutosides	Eucalyptus sp *Fagopyrum esculentum*
Saponins	Escin	Horse chestnut *(Aesculus hippocastanum)*
	Ruscus extract	Butcher's broom *(Ruscus aculeatus)*
Other plant extracts	Anthocyans	Bilberry *(Vaccinium myrtillus)* Grape pips *(Vitis vinifera)*
	Proanthocyanidins (oligomers)	Maritime pine *(Pinus maritima)*
	Extracts of ginkgo, heptaminol, and troxerutin	*Ginkgo biloba*
Synthetic products	Calcium dobesilate	Synthetic
	Benzarone	Synthetic
	Naftazone	Synthetic

Table II. *Classification of the main venoactive drugs.*

Modified from reference 11: *Nicolaides et al. Int Angiol. 2008;27:1-59. © 2008, Edizioni Minerva Medica.*

_ ***Recent guidelines on VADs***

Numerous randomized, controlled, double-blind studies have demonstrated the improvement of CVD-related symptoms by VADs, and the antiedema effect of VADs has also been objectively demonstrated in double-blind trials. The main indications for VADs are symptoms related to CVD and edema in patients at any stage of CVD. VADs may also have a role in the treatment of leg ulcers. A meta-analysis of MPFF, from the benzopyrone category of VADs, confirmed its value as an adjunct to standard treatment for healing leg ulcers.[15]

This article will assess the role and impact of VADs in the management of primary CVD in light of the recent European and American guidelines. Two guidelines have been published recently discussing the therapeutic efficacy of VADs on CVDrelated symptoms and venous edema.[11,16,17] The latest edition of the *Handbook of Venous Disorders: Guidelines of the American Venous Forum*[18] includes a chapter on drug treatment of varicose veins, venous edema, and ulcers. Elsewhere, Perrin and Ramelet[19] have proposed their own recommendations for the use of VADs, based on the principle of the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system.

_ ***Therapeutic efficacy of VADs and impact on guidelines***

A Cochrane review of VADs by Martinez et al (2005) examined the efficacy of such drugs in detail.[20] Clinical trials of a range of different VADs were analyzed. Studies of HCSE were excluded because they were covered in a separate Cochrane review (see below).[21] The authors identified 110 randomized, placebo-controlled trials, 44 of which were included in the final analysis. Studies were classified level A (low risk of bias), level B (moderate risk of bias), or level C (high risk of bias). A wide range of outcome variables, including objective signs and subjective symptoms, were analyzed using a random effects statistical model. For every outcome variable except venous ulcer, the analyses showed significant treatment benefits for VADs compared with placebo when analyzed as either a dichotomous or a continuous variable, or both in some cases. The analyses

showed that VADs had significant treatment benefits compared with placebo with regard to pain, cramps, heaviness, and sensations of swelling and paresthesia, despite a lack of homogeneity between trials.[19] The only nonsignificant effects were for venous ulcer, itching assessed as a continuous variable, and paresthesias assessed as a continuous variable. For edema (relative risk [RR], 0.72; 95% confidence interval [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 a significant benefit with VAD treatment, with no evidence of heterogeneity among the studies. This was in contrast to most of the analyses, which showed evidence of heterogeneity.[19]

_ *The Cochrane review of horse chestnut seed extract* [21]

Randomized clinical trials (RCTs) of HCSE, whose main active component is the triterpenic saponin iscin, were the subject of a Cochrane review published by Pittler and Ernst in 2006. Twenty-nine studies were identified, 17 of which were included in the review. The authors concluded that HCSE was efficacious compared with placebo and of similar efficacy to compression therapy in the short-term treatment of CVD. Adverse effects were generally mild and infrequent, so the overall risk/benefit ratio for HCSE was favorable. On the basis of publications, including Cochrane reviews, VADs as a whole have been assigned a weak recommendation (Grade 2B) for improving symptoms and edema associated with CVD in the latest edition of the Handbook of Venous Disorders.[18]

Compound	Recommendation	Number of influential studies	
		RCTs	*Meta-analyses*
Calcium dobesilate	Grade A	3	2
MPFF	Grade A	4	1
Hydroxyethylrutosides	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	
Ginkgo biloba	Grade C	2	
Proanthocyanidines	Grade C	2	
Troxerutin + coumarin	Grade C	1	
Centella asiatica	Grade C	1	
Naftazone	Grade C	1	

Table III. *Grades of recommendation of the International Consensus Statement. Based on data from reference 11.*

Abbreviations: *HCSE, horse chestnut seed extract; MPFF, micronized purified flavonoid fraction; RCT, randomized clinical trial.*

International consensus

The International Consensus Statement in 2005[16] represents the outcome of the International Medical Consensus Meeting on Venoactive Drugs in the Management of Chronic Venous Disease, held during the 13th Conference of the European Society for Clinical Hemorheology in Siena, Italy, from 26–29 June, 2005.

A group of 14 experts, from countries in which VADs were available and with experience of their clinical use, analyzed a total of 83 studies. Three grades of recommendation were considered, based on the following levels of evidence: grade A (several RCTs with large sample sizes, meta-analysis of homogenous results); grade B (RCTs with small sample sizes, or a single RCT); and grade C (other controlled trials, nonrandomized controlled trials, and observational studies). Outcomes included only symptoms at any stage of CVD.

As a result of the analysis, calcium dobesilate, MPFF, and HR were all assigned the highest level (Grade A) recommendation, while HCSE and Ruscus extracts were assigned Grade B (*Table III*).

_ ***Management of CVD of the lower limbs***

A consensus statement on the management of chronic venous disorders of the lower limbs was prepared in 2008[11] under the auspices of several learned societies, including the American Venous Forum, the American College of Phlebology, and the European Venous Forum. A set of guidelines arising from the consensus statement covers most aspects of the management of CVD, including investigations, treatment, and management strategy.

With respect to VADs, the guidelines largely summarized and endorsed the positive findings of the recent Cochrane reviews[20,21] and the grades of recommendation of the International Consensus Statement of Siena.[16] These guidelines used the same grading system as the Siena Consensus, except for meta-analyses, which were considered to have a grade B level of evidence. Outcomes this time included not only symptoms, but also edema and venous ulcer healing.

Table IV summarizes VAD effects on symptoms, edema, and skin changes by category of drug. Grade A status was assigned to three VADs: calcium dobesilate, MPFF, and HR, but only symptoms were considered. Generally, no reservations were voiced regarding the safety of VADs, except for a couple of specific cases: coumarin-rutin and benzarone (hepatotoxicity) and calcium dobesilate (some cases of transcient agranulocytosis were reported from 1992 to 2005).[11]

Guidelines and VADs for venous edema

Although edema is a nonspecific 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 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.[22]

Several well-conducted controlled trials versus placebo or stockings[11,16] have shown the efficacy of oral VADs such as MPFF, rutosides, HCSE, calcium dobesilate, proanthocyanidines, and coumarin-rutin. In these trials, the evaluation of antiedematous efficacy was based on objective measures, such as measurement of leg circumference, strain-gauge plethysmography, and water displacement. Results of meta-analyses, including the Cochrane reviews,[20,21] have confirmed the antiedematous efficacy of VADs.

The guidelines highlighted the evidence of efficacy of several VADs (calcium dobesilate, MPFF, rutosides, HCSE, proanthocyanidines, and coumarin + rutin) in CVD-related edema, andthe efficacy of MPFF as an adjunct to standard treatment in the healing of venous ulcers (although only symptoms have been considered in the assignation of a grade of recommendation) (*Table IV*).[11]

Compound	Positive results on the following indications*	RCTs	Recommendation**	Trials and meta-analyses**
Calcium dobesilate	Cramps, restless legs, sensation of swelling, edema	4	Grade A	2
MPFF	Pain, cramps, heaviness, sensation of swelling, trophic changes, venous leg ulcer	5	Grade A	1
Hydroxyethylrutosides	Itching, edema	10	Grade A	4
Escin, HCSE	Pain, edema	-	Grade B	3
Ruscus extracts	Pain, edema	2	Grade B	1
Synthetic diosmin	-	-	Grade C	1
Troxerutin	-	1	Grade C	1
Ginkgo biloba	-	-	Grade C	-
Proanthocyanidines	Pain	3	Grade C	1
Troxerutin-coumarin	-	1	Grade C	-
Naftazone	-	-	Grade C	1

* Homogeneity of results with relative risk (RR) <1.
** Only symptoms have been considered.

Table IV. *Summary of VAD effects on symptoms, edema, and skin changes by category of drugs.*

Abbreviations: *HCSE, horse chestnut seed extract; MPFF, micronized purified flavonoid fraction; RCT, randomized controlled trial.*
Modified from reference 11: *Nicolaides et al. Int Angiol. 2008;27:1-59. © 2008, Edizioni Minerva Medica.*

Guidelines and VADs for venous leg ulcers

Acceleration of venous leg ulcer healing (stage C6 of the CEAP classification) has been demonstrated in a double-blind study using MPFF in combination with compression.[23] This result was confirmed in 2005 by a meta-analysis of five trials in which MPFF was used as an adjunct to standard compression treatment in 723 class C6 patients.[15] HCSE and HRs were not superior to compression in advanced chronic venous insufficiency[24] or in the prevention of venous ulcer recurrence.[25]

The latest edition (3rd edition) of the Handbook of Venous Disorders[18] includes a chapter on drug treatment of varicose veins, venous edema, and ulcers. The method of determining the strength and quality of recommendations in this document was based on GRADE.[26] GRADE recommendations consist of a number ("1" for a "strong" or "we recommend" recommendation, and "2" for a "weak" or "we suggest" recommendation) and a letter, which refers to the "quality of evidence" supporting the recommendation. There are three grades: "A" for high-quality evidence; "B" for moderate-quality evidence; and "C" for low-quality evidence. The GRADE system is based on the distinction between the strength of a recommendation and the quality of the evidence on which it is based, although in practice the separation is not absolute and the quality of evidence is an important determinant of the strength of a GRADE recommendation.

The use of MPFF in combination with compression in longstanding or large venous ulcers was recommended and assigned a grade 1B. 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 mentioned above.15 At 6 months, complete ulcer healing had occurred in 61%ofMPFF patients and in 48%of 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 in ulcers of >6 months' duration.

Pentoxifylline, a drug indicated for the management of peripheral arterial disease, has also been used in the management of venous ulcers. Its use in combination with compression in long-standing or large venous ulcers has a grade 1B recommendation.

_ *Tentative recommendations for VADs*

Building on recent reviews and meta-analyses and taking into account additional evidence that was either not available or not included in them, Perrin and Ramelet have proposed tentative recommendations for the use of VADs based on the principles of the GRADE system.[19] They stress that these recommendations reflect their own opinions and

judgements, and have not been endorsed by learned societies or other organizations to date.

These recommendations are summarized in *Table V (page 290)*.[19] A grade 1B was assigned to MPFF and rutosides for the relief of symptoms associated with CVD in $C0_S$ to $C6_S$ patients with CVD-related edema. A grade 1B recommendation was also given for the use of MPFF as an adjunct to compressive and local therapy for healing large or long-standing venous ulcers.[18]

Indication	Venoactive drug	Recommendation for use	Quality of evidence	Code
Relief of symptoms associated with CVD in $C0_S$ to $C6_S$ patients with CVD-related edema	MPFF	Strong	Moderate	1B
	Rutosides	Strong	Moderate	1B
	Calcium dobesilate	Weak	Moderate	2B
	HCSE	Weak	Low	2C
	Ruscus extracts	Weak	Low	2C
Healing of large or long-standing venous ulcers as an adjunct to compression and local therapy	MPFF	Strong	Moderate	1B

Table V. *Summary of tentative recommendations, according to Perrin and Ramelet.*

Abbreviations: *CVD, chronic venous disease; HCSE, horse chestnut seed extract; MPFF, micronized purified flavonoid fraction.*
Modified from reference 19: *Perrin and Ramelet. Eur J Vasc Endovasc Surg. 2011;41:117-125. © 2011, European Society for Vascular Surgery.*

Future challenges[17,19]

_ ***Assessing the efficacy of treatment***

An update of the guidelines for testing drugs for CVD[27] is needed to enable the pharmaceutical industry to invest the resources required to perform large and definitive clinical trials, with a view to improving the recommendations. Recommendations are useful to clinicians and organizations involved in decision-making in this important field. Such guidelines could:

_ Reiterate the basic principles that should prevail when reporting (and setting up) a

clinical trial, using the CONSORT (CONSOlidated standards of Reporting Trials) statement. This statement is designed to help authors and investigators file reports using a published checklist and flow diagram,28 available on the Web site: www.consort-statement.org.

_ Describe patients comprehensively at study selection using the advanced CEAP classification. This implies that not only the "C" (Clinical) of CEAP should be completed, but also items "E" (Etiological), "A" (Anatomical), and "P" (Pathophysiological), together with mandatory duplex color, with or without plethysmography (a level 2 investigation, according to Eklöf et al),[2] and in certain cases, invasive (level 3) investigations; the addition of new descriptors for the "E", "A", and "P" items when no venous abnormality is identified may be useful when describing patients with leg complaints, but no visible or detectable signs of CVD.[2]

_ Promote the use of validated tools to assess symptoms,[29] edema,[30] and venous leg ulcer.[31]

_ Reach a consensus on the standard use of dressings, compression therapy, and local antiseptics in venous leg ulcer. In addition, there is a need for consensus on the following end points:

_ Symptoms: how great does the decrease on the visual analogue scale have to be in order to consider there is clinical improvement?

_ Edema: how great does the reduction in ankle volume have to be in order to consider it as clinically relevant?

_ Varicose veins: which criteria should be used to consider whether a drug treatment for varicose veins works?

_ Venous leg ulceration: when should we consider the ulcer to be healed?

_ Adapted patient-reported outcome tools

Early stages of CVD are difficult to assess objectively, particularly in C0s patients, as symptoms are by definition subjective. The assessment of patients' perception of their quality of life (QOL) is desirable in such cases. Both generic and specific QOL scales should be used: the generic SF-12 (Short Form 12-item [health survey]) or SF-36 (Short

Form 36-item [health survey]) are validated tools that could be adopted, while if a specific scale is required, the CIVIQ-20 (ChronIc Venous dIsease Questionnaire) QOL is a good choice. It has been extensively validated,[32] is the scale most often used in CVD, and has currently been validated in 13 languages.

Conclusion

The role of VADs in the prevention of the natural history of CVD progression remains to be fully determined: are all VADs able to protect CVD patients against the progression of the disease to severe complications? The use of human-sized experimental animals, such as pigs, might allow for better evaluation of the key processes involved.[33] Where grading is concerned, the consensual adoption of a simple and universally understood system of grading is desirable.[26] _