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Pharmacological Treatment of Primary Chronic Venous Disease: Rationale, Results and Unanswered Questions

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Abstract *Aim:* The aim of this article was first to review the complex pathophysiological mechanisms responsible for symptoms and signs of primary chronic venous disease (CVD) that allow the identification of targets for pharmacological treatment. The results of CVD treatment with venoactive drugs (VADs) were emphasised and presented in the form of recommendations. The last section raises key questions to be answered to improve protocols for good clinical trials and to draw up future guidelines on these agents.
Methods: The literature has been reviewed here using PubMed and Embase.
Results: Venous hypertension appears to underlie all clinical manifestations of primary CVD. Inflammation is key in wall remodelling, valve failure and subsequent venous hypertension. Changes in the haemodynamics of veins are transmitted to the microcirculation, resulting in capillary alteration leading to oedema, skin changes and eventually venous ulceration. Venous symptoms may be the result of interplays between pro-inflammatory mediators and nerve fibres located in the venous wall. Therefore, venous inflammation constitutes a promising therapeutic target for pharmacological intervention, and some available VADs could attenuate various elements of venous inflammation. Based on recent studies, reviews and guidelines, tentative recommendations for the use of VADs were proposed and strong recommendations were given to two of them (micronised purified flavonoid fraction and oxerutins).
Conclusion: VADs should be accorded a better role in the management of CVD. However, larger and more definitive clinical trials are needed to improve the existing recommendations.

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Introduction

This article addresses the drug treatment of chronic venous disease (CVD) of primary aetiology. Primary CVD is defined as morphological and functional abnormalities of the venous system of long duration, manifested by symptoms or signs or both, indicating the need for investigation and/or care.[1] This is a common condition with a major impact on the health-care system due to its high prevalence,[2] not to mention the human impact in terms of worsened quality of life (QoL). Unlike secondary CVD, which is the result of thrombosis, the origin of primary CVD is unknown.[3]

There is a broad range of symptoms and signs associated with primary CVD, the most obvious of which are varicose veins and venous leg ulcers, but which also include oedema and skin changes (venous eczema, ankle skin pigmentation, atrophie blanche and lipodermatosclerosis).

Clinical presentations of CVD can be described according to the clinical, etiologic, anatomical and pathophysiological (CEAP) classification, which provides an orderly framework for communication and diagnosis.[3,4] The clinical signs in the affected legs are categorised into seven classes designated C0–C6 (Table 1). Leg symptoms associated with CVD include tingling, aching, burning, pain, muscle cramps, sensation of swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness and/or fatigue.[1] Although not pathognomonic, these may be suggestive of CVD, particularly if they are exacerbated by heat or dependency during the course of the day and relieved with leg rest and/or elevation.[1] Limbs categorised in any clinical class may be symptomatic (S) or asymptomatic (A). CVD encompasses the full spectrum of signs and symptoms associated with classes C0s–C6, whereas the term 'chronic venous insufficiency' (CVI) is generally restricted to disease of greater severity (i.e., classes C3–C6).[1]

The last revision of the CEAP classification in 2004 included a new descriptor—n—for the E, A and P of the CEAP classification, when no anomaly is found in aetiology, anatomy or pathophysiology of the disease.[4] This introduced new categories such as C0s ('symptoms only'), En, An, Pn ('no aetiology, no location, no pathophysiology identified'), reflecting those subjects complaining from leg symptoms before appearance of any sign, reflux or even obstruction. The latter is usually difficult to identify. These patients are frequently encountered in primary care practice and represent the largest target population for venoactive drug (VAD) treatment.

Understanding the pathophysiology of a disease state is basic to effective treatment. Therefore, the aim of this article is first to review the complex molecular processes set in motion by haemodynamic pathology in CVD that warrant pharmacological treatment. Then, we will emphasise the results of such treatment and, more particularly, of VADs. The last section will deal with controversies about this type of treatment, the lack of data that needs to be addressed by future studies and the key questions to be answered to draw up future guidelines on pharmacological agents.

Pathophysiology of Primary CVD

Primary CVD is the result of increased and unabated venous hypertension caused mostly by reflux through incompetent valves, and sometimes by primary non post-thrombotic obstruction and reflux.[5] Venous hypertension is central to alterations mostly in superficial veins (less frequently in deep veins), in capillaries and, eventually, in skin. We will endeavour to outline these three aspects of pathogenetic mechanisms of CVD. Secondary CVD will intentionally not be broached in the present review.

Valve and vein wall changes

Valves are present in both superficial and deep venous systems to ensure that blood flows in a single direction, from the superficial to the deep system, towards the heart and against gravity.[6] Damage to and alterations in the saphenous vein valves are more frequently seen in varicose than in non-varicose veins.[7,8] The causes of such valve failure are still under investigation, and several theories have been put forward. It has been postulated that valvular dysfunction causing reflux was the initial pathological change in CVD.[7,9] This hypothesis has been challenged recently, and evidence seems to favour pre-existing weakness in the vessel wall, which produces dilation and, in turn, causes secondary valvular incompetence.[6,10]

Histologic and ultrastructural studies of varicose veins have found structural changes in the vein wall. Intimal hyperplasia and areas of hypertrophy with increased collagen

Table 1 Revised CEAP Clinical Classification of Chronic Venous Disease of the Leg.[4]

Clinical class	Description [4]
C0	No visible or palpable signs of venous disease
C1	Telangiectases or reticular veins • Telangiectases defined by dilated intradermal venules <1 mm diameter • Reticular veins defined by dilated, nonpalpable, subdermal veins ≤3 mm in diameter
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 subclasses 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

content alternate with hypotrophic segments with fewer smooth muscle cells (SMCs) and reduced extracellular matrix (ECM).[6,7] Degradation of ECM proteins is caused by an array of proteolytic enzymes including matrix metalloproteases (MMPs). The production of MMPs is increased by venous hypertension secondary to blood stasis,[11] and their activity is inhibited by tissue inhibitors of MMPs (TIMPs). MMP—TIMP imbalance has been observed in varicose disease,[12] together with collagen disruption, elastin loss and proliferation, rearrangement and migration into the intima of SMCs. SMCs in varicose veins become dedifferentiated and lose their ability to contract, while dysregulated apoptosis occurs. All these phenomena contribute to venous dilation, venous relaxation and loss of venous tone.

The triggers for such structural changes in the vein wall remain unclear, although inflammatory events in venous valves and wall are likely to be the initial culprits.[7] The venous leg system is subject to frequent postural pressure changes in daily life. In particular, prolonged standing leads to pooling of blood, which causes distension of veins and distortion of venous valves. Leakage through such valves exposes endothelial cells to flow reversal, which initiates endothelial and leucocyte activation, the starting point of venous inflammation (Fig. 1).[7] Repeated inflammatory stresses on the venous endothelium lead to chronic recurring injury to the vein wall, maintaining an inflammatory state at vein level.[7]

Evidence has accumulated in the past years that inflammation could be key in wall remodelling, valve failure and subsequent venous hypertension.[8,11,13] Various types of inflammatory mediators and growth factors are released, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), transforming growth factor beta (TGF-β_1), fibroblast growth factor beta (FGF-β_1) and vascular endothelial growth factor (VEGF). The inflammatory cascades in the vein wall and venous valves can cause progressive valvular incompetence and eventual valvular destruction.[13] Once initiated, venous valve damage will be self-reinforcing, exacerbating venous hypertension and disturbance of venous flow and causing further inflammation (Fig. 2). As a result, reflux appears and may occur in the superficial or deep venous system or in both.[2] It is not ascertained whether deep vein incompetence in primary CVD is a congenital or acquired phenomenon.[14]

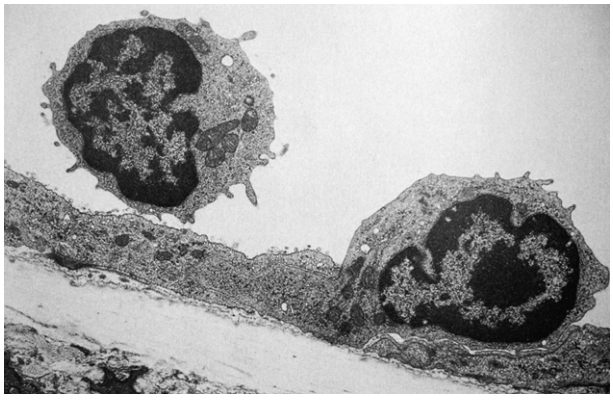

Figure 1 Rolling and adhesion of leukocytes at the surface of the endothelium, starting point of an inflammatory cascade causing vein wall remodelling and eventually progression to complications. *Am J Pathol*. 1983; 113:341—358. Copyright the American Journal of Pathology.

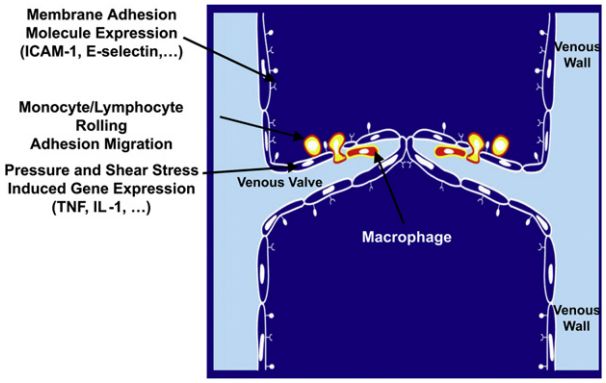

Figure 2 Schematic illustration of key events that may lead to valve damage in primary venous disease; inflammatory gene expression in the endothelium may be induced by a shift in venous hydrostatic pressure and fluid shear stress. This supports leukocyte rolling, adhesion, and migration together with free radical formation, apoptosis, and tissue necrosis. In the process, macrophages become the instruments of tissue damage.

Capillary alteration

Venous hypertension increases hydrostatic pressure in capillaries resulting in transcapillary filtration that exceeds lymphatic flow. This contributes to the formation of interstitial oedema. Venous hypertension alters blood flow in capillaries, prompting leucocyte adhesion to capillary endothelium and initiating an inflammatory reaction.[15] One theory holds that inflammation would open the gaps between the endothelial cells via a mechanism involving VEGF, nitric oxide synthetase (NOS) and the contraction of actin and myosin filaments that are present in endothelial cells.[16] The gaps would become very large, greatly raising capillary permeability to fluid, macromolecules and extravasated red blood cells, resulting in their flow into the interstitial space and in oedema formation. Based on the observation that inter-endothelial gap junctions of capillaries from either the gaiter zone or thigh of CVI patients were not widened, Pappas refuted this theory and proposed an alternative explanation involving the formation of transendothelial channels for macromolecule transport.[17] Fragmentation and destruction of lymphatic vessels may further impair drainage from the extremity, whereas dysfunction of local nerve fibres may alter regulatory mechanisms (Fig. 3).[2]

Skin changes

Several mechanisms for the development of venous ulceration have been postulated, of which the theory of 'leucocyte trapping' is the most likely,[18] although challenged today. It is hypothesised that the primary injury to the skin (which is the final target of chronic venous hypertension) is extravasation of macromolecules, such as fibrinogen and α-macroglobulin, and red blood cells into the dermal interstitium. Red-blood-cell-degradation products and extravasated interstitial

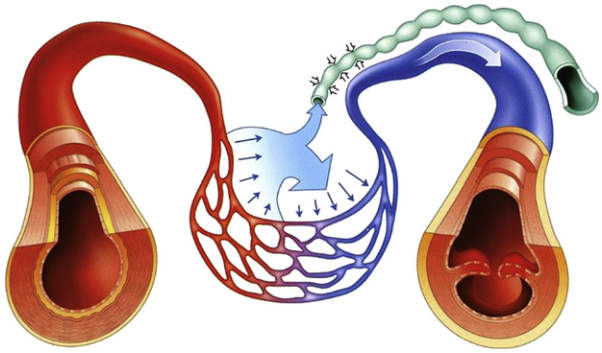

Figure 3 Venous hypertension is transmitted to the microcirculation and prompts leukocyte adhesion to capillary endothelium. This initiates an inflammatory reaction which dramatically increases capillary permeability. When transcapillary filtration exceeds lymphatic flow, an interstitial edema occurs. Copyright Impact Médecin.

protein are potent chemoattractants and presumably generate the initial inflammatory signal, which results in leukocyte recruitment and migration into the dermis.[17]

Pathologic events occur during leucocyte migration into the dermis and the end product of these is dermal fibrosis. One of the pathologic events is an increase in TGF-β_1 which is either released by macrophages and mast cells or auto-induced by dermal fibroblasts. An increase in TGF-β_1 causes an imbalance in tissue remodelling, which results in increased collagen synthesis and affects MMPs as well as TIMPs. It is hypothesised that an imbalance in MMPs and their regulation may cause or contribute to venous ulcer formation.[17]

A cascade of inflammatory events results in cutaneous changes, which include skin hyperpigmentation caused by haemosiderin deposition and eczematous dermatitis. Fibrosis may develop in the dermis and subcutaneous tissue (lipodermatosclerosis) (Fig. 4). There is an increased risk of cellulitis and leg ulceration.[2]

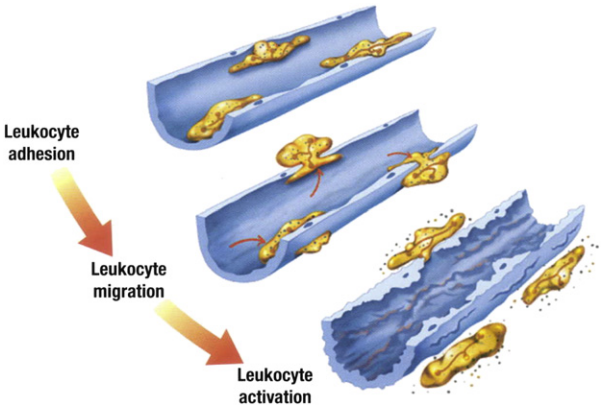

Figure 4 Early cellular events leading to the skin changes of chronic venous insufficiency may begin with venous hypertension inducing low shear stress, which favors leukocyte adhesion and spreading on the endothelium. Degranulation occurs as cytoplasmic granules containing proteolytic enzymes are released. Subsequent tissue damage may induce a secondary stimulation of leukocytes and endothelial cells in the lipodermatosclerotic skin.

There is some evidence that the severity of venous reflux may be related to the risk of ulceration in CVI patients. A linear relationship between ulceration rate and ambulatory venous pressure has been shown.[19]

Symptoms of CVD

Symptoms may accompany all stages of CVD. Pain in venous disease is the chief complaint that leads to the diagnosis of CVD. Current hypotheses on venous pain mechanisms focus on a local inflammatory origin. It has been postulated that pro-inflammatory mediators released locally by leucocytes can activate nociceptors located in the venous wall (between endothelial cells and smooth muscle cells of the media) and in the connective tissue that forms the perivenous space, in close contact with the microcirculation.[20] Unmyelinated C fibres were identified in the wall of varicose veins, seemingly arranged as a wide mesh arising from the adventitia and spreading out into the external part of the media.[21] Such nervous fibres may play a key role in symptom onset.

Implications for Treatment of CVD

Understanding of the pathophysiological processes suggests potential therapeutic targets that could be effective not only in relieving symptoms and signs of CVD but also in slowing its progression.

Compression stockings improve venous haemodynamics,[22] and reduce oedema.[23] There is some evidence that surgery aimed at preventing superficial venous reflux can aid in preventing the recurrence of ulcers.[24] On the other hand, and in patients presenting with a combination of primary venous obstruction and deep or superficial reflux, Raju et al. consider that the treatment of obstruction alone by stent placement, without correction of associated reflux, often provides satisfactory relief rates.[5,25] However, whatever the technique used to heal or prevent an ulcer, it is not known how many patients in C2, C3 or C4 (according to the CEAP classification) must be treated to prevent the occurrence of a venous ulcer. Therefore, cost-effectiveness studies on the techniques described above have not been performed.

Treatment to inhibit inflammation may offer the greatest opportunity to prevent disease-related complications. Currently available medication such as VADs can attenuate various features of the inflammatory cascade,[2,7] particularly the leucocyte—endothelium interactions that are important in many aspects of the disease. These agents and their mode of action deserve more detailed explanation.

Introduction to VADs and their Mode of Action

VADs are a heterogeneous group of synthetic or plant-based drugs (Table 2).[26]

Action of VADs on venous tone

Most VADs have been shown to increase venous tone by a mechanism related to the noradrenaline pathway.[27] Micronised purified flavonoid fraction (MPFF) prolongs

noradrenergic activity, hydroxyethylrutosides act by blocking inactivation of noradrenaline and ruscus extracts are agonists at venous α1-adrenergic receptors. A high affinity for the venous wall was found for MPFF and hydroxyethylrutosides. The precise mechanism by which other drugs increase venous tone is not known.

Action of VADs on capillary resistance

Numerous studies have shown that VADs are able to increase capillary resistance and reduce capillary filtration.[27] This is seen for MPFF, rutosides, escin, ruscus extracts, proanthocyanidines and calcium dobesilate. The capillary protective effect of MPFF may be related to inhibition of leucocyte adhesion to capillaries.

Action of VADs on lymphatic drainage

The efficacy of coumarin on lymphoedema has been described by Casley Smith.[28] Coumarin alone or combined with rutin improves lymph flow and reduces high-protein oedema by stimulating proteolysis.[27] MPFF improves lymphatic flow and increases the number of lymphatic vessels, and calcium dobesilate enhances lymphatic drainage.[27]

Action of VADs on haemorrheological disorders

Haemorrheological changes are constant in CVD, appearing as a basic trait with increased blood viscosity due to plasma volume reduction and increased fibrinogen as a consequence of inflammation. The presence of huge red cell aggregates in the vicinity of venules reduces blood flow and impairs oxygen delivery from red cells. Erythrocyte aggregability and blood viscosity increase with greater severity of disease. Some VADs limit red cell aggregation (Gingko biloba), decrease blood viscosity (MPFF and calcium dobesilate) and increase red cell velocity (MPFF).[27]

Action of VADs on inflammation

As described above in the section entitled 'Pathophysiology of primary CVD', recent research has highlighted the central role of inflammation and elucidated some processes involved in the progression of CVD. Of all the currently available drugs, only MPFF has shown an anti-inflammatory effect in acute venous hypertension created by a venous fistula in rats. In this model, MPFF treatment reduced reflux flow in a dose-dependent manner. In animal models of ischaemia/reperfusion, MPFF reduced the release of inflammatory mediators such as oxygen free radicals, prostaglandins and thromboxane.[13]

Therapeutic Efficacy of VADs

Effects of oral VADs on venous symptoms

The main indications for VADs are symptoms related to CVD and oedema.[29] A Cochrane review on VADs by Martinez et al. examined the efficacy of such drugs in detail.[30] Another Cochrane review of Pittler and Ernst was published for escin only (horse chestnut seed extract, HCSE).[31] Studies were classified as level A (low risk of bias), level B (moderate risk of bias) or level C (high risk of bias). In the review of 44 controlled studies versus placebo,[30] the analyses showed significant treatment benefits for the VADs compared with placebo on pain, cramps, heaviness, sensation of swelling and paraesthesia, despite the lack of homogeneity between trials (Table 3). The only non-significant effects were for itching, while for restless legs the analyses showed significant benefit of VADs, with no evidence of heterogeneity among studies. Tests of heterogeneity were not performed in the review by Pittler.[31]

Two randomised clinical trials were not included in the review of VADs.[30] One deals with MPFF,[32] and the other is a large study with calcium dobesilate,[33] respectively, in 101 symptomatic patients and in 509 patients in CEAP classes

Table 2 Classification of the main venoactive drugs.[26]

Group	Substance	Origin
Alpha-benzopyrones	Coumarin	Melilot (*Melilotus officinalis*)
		Woodruff (*Asperula odorata*)
Gamma-benzopyrones (flavonoids)	Diosmin	Citrus spp. (*Sophora japonica*)
	Micronized purified flavonoid fraction	*Rutaceae aurantiae*
	Rutin and rutosides	*Sophora japonica*
	0-(β-hydroxyethyl)-rutosides (troxerutin, HR)	*Eucalyptus* spp.
		Fagopyrum esculentum
Saponins	Escin	Horse chestnut seed extracts (*Aesculus hippocastanum* L)
	Ruscus extract	Butcher's broom (*Ruscus aculeatus*)
Other plant extracts	Anthocyans	Bilberry (*Vaccinium myrtillus)*
	Proanthocyanidins (oligomers)	Red wine leaves extracts, Maritime pine (*Pinus maritimus*)
	Extracts of Ginkgo, heptaminol and troxerutin	Ginkgo biloba
	Total triterpene fraction	Centella asiatica
Synthetic products	Calcium dobesilate	Synthetic
	Benzaron	Synthetic
	Naftazon	Synthetic

Table 3 Global results of combined analyses for all venoactive drugs, for all outcomes analysed as percentage of improved patients, adapted from the Cochrane review of phlebotonics for venous insufficiency[30] and the meta-analysis of adjunctive MPFF on venous ulcer.[39]

Outcome variable	N patients in the Cochrane review.[30]	N in treatment group	N in placebo group	Patients with no symptom (%) in Tt group	Patients with no symptom (%) in placebo group	Test for treatment effect (*P* value)	Heterogeneity of studies
Oedema	1245	626	619	59.4	42.5	5.81 (<.00001)	No
Trophic disorders	705	355	350	33.8	23.7	3.76 (<.0001)	No
Pain	2247	1294	953	63.4	37.0	4.70 (<.00001)	Yes
Cramps	1793	1072	721	67.6	45.5	3.02 (=.003)	Yes
Restless legs	652	329	323	46.2	33.4	2.77 (=.006)	No
Itching	405	206	199	64.6	41.2	.83 (NS)	Yes
Heaviness	2166	1257	909	59.8	33.1	5.38 (<.00001)	Yes
Swelling	1072	544	528	62.9	38.4	3.86 (<.0001)	Yes
Paresthesias	1456	896	560	71.0	50.7	2.82 (=.005)	Yes
	N patients in the meta-analysis.[39]	N in treatment group	N in control group	Patients with no ulcer (%) in Tt group	Patients with no ulcer (%) in control group	Test for overall effect (*P* value)	Heterogeneity of studies
Venous ulcer at month 6	616	318	298	61.3	47.7	.03	Yes

C_1—C_6. No significant difference between the treatment and the placebo groups in the reduction of CVD-related symptoms were recorded after a 2-month treatment with MPFF (except for night cramps and oedema),[32] or in QoL, oedema and symptom severity at the end of the 3-month treatment period with the calcium dobesilate.[33] But neither the aetiology (primary or secondary) nor the pathophysiological and anatomical anomalies of studied lower limbs were reported in these two trials despite the CEAP classification being available at the time, weakening the valuability of such results.

On the basis of a large collection of publications including Cochrane reviews, VADs, as a whole, were assigned a weak recommendation in the improvement of symptoms and oedema associated with CVD in the latest edition of the Handbook of Venous Disorders.[29] In the Siena consensus paper on efficacy of VADs in symptom relief,[34] data from randomised, controlled trials (RCTs) were selected according to the predefined criteria of evidence-based medicine and on the basis of 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-RCTs). Outcomes included only symptoms at any stage of the disease. In this consensus document, a grade A was assigned to calcium dobesilate, MPFF and O-(beta-hydroxyethyl)rutosides (HR)-oxerutins, a grade B to escin and ruscus extracts and a grade C to the remaining VADs.

International guidelines on the management of CVD use the same grading system as that of the Siena experts, except for meta-analyses, which were grade B.[27] Outcomes included not only symptoms but also oedema and venous ulcer healing. When considering VADs, the guidelines largely summarised and endorsed the positive findings of the recent Cochrane reviews.[30,31] The guidelines highlight the evidence of efficacy of several VADs (calcium dobesilate, MPFF, rutosides, HCSE, proanthocyanidines, escin, coumarin + rutin and synthetic products) in CVD-related oedema, and the efficacy of MPFF as an adjunct to standard compression treatment in the healing of venous ulcers. Given the consistency of the evidence, a grade A was assigned to three VADs: calcium dobesilate, MPFF and HR-oxerutins for their effects on symptoms, oedema and skin changes.[27]

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.[27]

Effect on venous oedema

Although oedema is a nonspecific sign, it is one of the most frequent and typical signs in CVD. All other causes of oedema should be excluded to confirm its venous origin.

CVD-related oedema is described as sporadic, unilateral or bilateral and is more frequently located at the ankle site.

Several well-conducted controlled trials versus placebo or stockings have shown the efficacy of oral VADs such as MPFF, rutosides, HCSE, calcium dobesilate, proanthocyanidines (red grapevine leaves, or bark of maritime pine) and coumarin–rutin.[27,34] In these trials, the effect on oedema was assessed objectively, using leg circumference measurement, strain-gauge plethysmography and water displacement. The analyses of a pool of 1245 patients of the Cochrane review,[30] showed significant benefit of VADs in alleviating oedema (Table 3). However, to the authors' knowledge, none have considered which anatomical and pathophysiological components the drugs act on and to what extent they decrease the venous severity scoring (according to Rutherford).[35]

Pharmacological treatment of leg ulcers

Among VADs, HCSE and hydroxyrutosides have not proven superior to compression in advanced CVI,[36] or in preventing venous ulcer recurrence.[37] Acceleration of the healing of venous leg ulcers (stage C6 of the CEAP classification) has been demonstrated by a double-blind study using micronised purified flavonoid fraction (MPFF) in combination with compression.[38] This was confirmed in 2005 by a meta-analysis of five trials with MPFF as an adjunct to standard compression treatment in 723 patients in class C6, according to the CEAP classification.[39]

Pentoxifylline, which is indicated in the management of peripheral arterial disease, has also been used in the management of venous leg ulcers. In a review of 12 clinical trials involving 864 patients, pentoxifylline improved venous ulcer healing on its own and when used in combination with compression compared with placebo.[29,40]

The last edition (3rd edition) of the Handbook of Venous Disorders includes a chapter on drug treatment of varicose veins, venous oedema and ulcers.[29] The method of determining the strength and quality of the recommendations in this document was based on the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) system,[41] in which recommendations are accompanied by a number (1 for 'strong' and 2 for 'weak' recommendation), and a letter, which refers to the 'quality of the evidence' supporting the recommendation ranging from 'A' for high quality to 'B' for moderate quality and 'C' for low quality of evidence. The use of MPFF and of pentoxifylline in combination with compression in long-standing or large venous ulcers was assigned a 'strong recommendation with evidence of moderate quality' (Grade 1B).[29] The evidence for adjunctive MPFF or pentoxifylline treatment is based on the meta-analyses, respectively by Coleridge Smith et al.,[39] and by Jull et al.[40]

Tentative Recommendation for VADs

Building on recent reviews and meta-analyses, tentative recommendations for the use of VADs, based on the principles of the GRADE system, were proposed. It should be stressed that these recommendations reflect the opinions and judgements of the authors, and have not been endorsed by learned societies or other organisations. These tentative recommendations are summarised in Table 4. To our knowledge, no VAD has been evaluated in a very large RCT of the type that could provide high-quality evidence supporting their use in any indication related to CVD. For MPFF and rutosides, there is substantial evidence from smaller trials,[42] supported by meta-analyses and, in the case of MPFF, a large observational study,[43] for their efficacy in relieving CVD-related symptoms such as pain, heaviness and cramps, and in reducing CVD-related lower limb oedema. There are insufficient data to specify those CEAP clinical classes for which the benefits will be greatest, but it is reasonable to assume that patients at all stages of the disease, and particularly at the early CEAP stages, may benefit. There appear to be no important safety concerns with the use of these drugs; hence, it is possible to propose a strong recommendation, based on evidence of moderate quality, for their use in these indications. HCSE and *Ruscus* extracts have also proven effective against CVD-related symptoms and lower limb oedema, although the volume and quality of evidence are less than for the previous two drugs. In the apparent absence of important safety concerns, these drugs may be given a weak recommendation based on low-quality evidence.

Calcium dobesilate has been associated with a potential safety concern relating to rare cases of agranulocytosis.[27] We consider that it is only possible to give a weak recommendation for its use, given the uncertainty over the

Table 4 Summary of tentative recommendations, according to the principles of the GRADE system.[41]

Indication	Venoactive drug	Recommendation for use	Quality of evidence	Code
Relief of symptoms associated with CVD in patients C0s to C6s and 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 primary venous ulcer, as an adjunct to compressive and local therapy (Coleridge Smith, 2009)[29]	MPFF	Strong	Moderate	1B

HCSE: horse chestnut seed extract; MPFF: micronised purified flavonoid fraction.

balance between benefits and harms. Based on previous guidelines,[29] the use of MPFF in the healing of small (5–10 cm^2) venous ulcer can be given a strong recommendation, based on evidence of moderate quality in ulcer of primary aetiology (1B).

Key Questions to be Answered When Drawing Up Future Guidelines in CVD

Studies of the efficacy of VADs in treating symptoms and oedema related to CVD are rarely comparable, owing to disparities in inclusion criteria and primary end points. The effect of VADs on the natural history of CVD remains to be determined. Prevention of CVD progression by inflammatory pathway inhibition has been established in animal models only, and must now be tested in patients.

Assessing the efficacy of treatment

An update of the 'guidelines for testing drugs for CVD'[44] 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, which are useful to clinicians and organisations involved in decision making in this important field of CVD. Such guidelines could:

- Reiterate the basic principles that should prevail when reporting (and setting up) a clinical trial, using the Consolidated Standards of Reporting Trials (CONSORT) statement; this CONSORT statement is designed to help authors and investigators file reports, by the use of a published checklist and a flow diagramme,[45] available on the Web site www.consort-statement.org.
- Describe patients comprehensively at study selection, 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 mandatory duplex colour, with or without plethysmography (level 2 investigation according to Eklof et al.),[4] and in certain cases, invasive (level 3) 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 with leg complaints but no visible or detectable signs of CVD.[4]
- Promote the use of validated tools to assess symptoms,[46] oedema[47] and venous leg ulcer.[48]
- Have a consensus on a standard treatment for dressings, compression therapy and local antiseptics in venous leg ulcer.

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

- Symptoms: How great does the decrease on the visual analogue scale (VAS) scale have to be to consider there is a clinical improvement?
- Oedema: How great does the reduction in ankle volume have to be to consider it is clinically relevant?
- Varicose veins: Which criteria should be used to consider a drug treatment for varicose veins as successful?
- Venous leg ulceration: When should we consider the ulcer to be healed?

Tools adapted to patient-reported outcome

Early stages of CVD are difficult to assess objectively, particularly in C0s patients, as symptoms are by definition subjective. The assessment of the patients' perception of their QoL is desirable in such cases. It is acknowledged that both generic and specific QoL scales should be used: the generic Short Form (12) Health Survey (SF-12) (or SF-36) is a validated tool that could adopted, while for specific scales, the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20), which has been extensively validated,[49] is the most often used in CVD, and is currently validated in 13 languages.

On the other hand, the role of VADs in the prevention of the natural history of CVD remains to be determined: are all VADs able to protect CVD patients against disease progression to severe complications? Yet, the use of human-sized experimental animals such as the pig allows for better evaluation of the key processes involved.[50] It is to be hoped that such models, together with future clinical research, will accord pharmacological agents the role they deserve in the management of CVD.

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