lez S. A randomised trial of different compression dressings following varicose veins surgery. Phlebology 1999;14:9-11.
125. Travers JP, Makin GS. Reduction of varicose vein recurrence by use of postoperative compression stockings. Phlebology 1994;9:104-9.
126. Mariani F, Marone EM, Gasbarro V, Bucalossi M, Spelta S, Amsler F, *et al.* Multicenter randomized trial comparing compression with elastic stocking versus bandage after surgery for varicose veins. J Vasc Surg 2011;53:115-22.
127. Lugli M, Cogo A, Guerzoni S, Petti A, Maleti O. Effects of eccentric compression by a crossed-tape technique after endovenous laser ablation of the great saphenous vein: a randomized study. Phlebology 2009;24:151-6.
128. Mosti G, Mattaliano V, Arleo S, Partsch H. Thigh compression after great saphenous surgery is more effective with high pressure. Int Angiol 2009;28:274-80.
129. Travers JP, Rhodes JE, Hardy JG, Makin GS. Postoperative limb compression in reduction of haemorrhage after varicose vein surgery. Ann R Coll Surg Engl 1993;75:119-22.
130. Raraty MGT, Greaney MG, Blair SD. There is no benefit from 6 weeks' postoperative compression after varicose vein surgery: a prospective randomised trial. Phlebology 1999;14:21-25.
131. Rodrigus I, Bleyn J. For how long do we have to advise elastic support after varicose veins surgery? A prospective randomized study. Phlebology 1991;6:95-8.
132. Biswas S, Clark A, Shields DA. Randomised clinical trial of the duration of compression therapy after varicose vein surgery. Eur J Vasc Endovasc Surg 2007;33:631-7.
133. Pittaluga P and Chastanet S. Value of postoperative compression after mini-invasive surgical treatment of varicose veins. J Vasc Surg Venous Lymphat Disord 2013;1:385-91.
134. Bakker NA, Schieven LW, Bruins RM, van den Berg M, Hissink RJ. Compression stockings after endovenous laser ablation of the great saphenous vein: a prospective randomized controlled trial. Eur J Vasc Endovasc Surg 2013;46:588-92.
135. Huang TW, Chen SL, Bai CH, Wu CH, Tam KW. The optimal duration of compression therapy following varicose vein surgery: a meta-analysis of randomized controlled trials. Eur J Vasc Endovasc Surg 2013;45:397-402.
136. Reich-Schupke S, Feldhaus F, Altmeyer P, Mumme A, Stücker M. Efficacy and comfort of medical compression stockings with low and moderate pressure six weeks after vein surgery. Phlebology 2014;29:358-66.
137. Elderman JH, Krasznai AG, Voogd AC, Hulsewe KW, Sikkink CJ. Role of compression stockings after endovenous laser therapy for primary varicosis. J Vasc Surg Venous Lymphat Disord 2014;2:289-96.
138. Krasznai AG, Sigterman TA, Troquay SAM, Houtermans-Auckel JP, Snoeijs MGJ, Rensma HG, *et al.* A randomised controlled trial comparing compression therapy after radiofrequency ablation for primary great saphenous vein incompetence. Phlebology 2016;31:118-24.
139. Ayo D, Blumberg SN, Rockman CR, Sadek M, Cayne N, Adelman M, *et al.* Compression *versus* No Compression after Endovenous Ablation of the Great Saphenous Vein: A Randomized Controlled Trial. Ann Vasc Surg 2017;38:72-7.
140 Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, *et al.* Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349:759-62.
141. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, *et al.* Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004;141:249-56.
142. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. J Vasc Surg 2008;47:1015-21.
143. Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, *et al.* Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med 2001;161:2105-9.
144. Prandoni P, Noventa F, Quintavalla R, Bova C, Cosmi B, Siragusa S, *et al.* Thigh-length versus below-knee compression elastic stockings for prevention of the post-thrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. Blood 2012;119:1561-5.
145. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR *et al.* Compression stockings to prevent post-thrombotic syndrome: a randomized placebo-controlled trial. Lancet 2014;383:880-8.
146. Tie HT, Luo MZ, Luo MJ, Li K, Li Q, Wu QC. Compression Therapy in the Prevention of Postthrombotic Syndrome: A Systematic Review and Meta-Analysis. Medicine (Baltimore) 2015;94:e1318.
147. Burgstaller JM, Steurer J, Held U, Amann-Vesti B. Efficacy of compression stockings in preventing post-thrombotic syndrome in patients with deep venous thrombosis: a systematic review and meta-analysis. Vasa 2016;45:141-7.
148. Jayaraj A, Meissner M. Impact of graduated compression stockings on the prevention of post-thrombotic syndrome - results of a randomized controlled trial. Phlebology 2015;30:541-8.
149. Skervin AL, Thapar A, Franchini AJ, Prandoni P, Shalhoub J, Davies AH. Systematic review and meta-analysis of utility of graduated compression stockings in prevention of post-thrombotic syndrome. Eur J Vasc Endovasc Surg 2016;51:838-45.
150. Subbiah R, Aggarwal V, Zhao H, Kolluri R, Chatterjee S, Bashir R. Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. Lancet Haematol 2016;3:293-300.
151. Berntsen CF, Kristiansen A, Akl EA, Sandset PM, Jacobsen EM, Guyatt G, *et al.* Compression Stockings for Preventing the Postthrombotic Syndrome in Patients with Deep Vein Thrombosis. Am J Med 2016;129:447.e1-447.e20.
152. Jin YW, Ye H, Li FY, Xiong XZ, Cheng NS. Compression Stockings for Prevention of Postthrombotic Syndrome: A Systematic Review and Meta-Analysis. Vasc Endovascular Surg 2016;50:328-34.
153. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, Mostard GJM, *et al.* Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised,single-blind, allocation-concealed, non-inferiority trial. Lancet Haematol 2018;5:e25-e33.
154. O`Donnell Jr TF, Passmann MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, *et al.* Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum J Vasc Surg 2014;60 (Suppl) 3S-59S.
155. Mosti G, De Maeseneer M, Cavezzi A, Parsi K, Morrison N, Nelzen O, *et al.* Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology. Int Angiol 2015;34:202-18.

156. Franks PJ, Barker J, Collier M, Gethin G, Haesler E, Jawien A, *et al.* Management of Patients With Venous Leg Ulcers: Challenges and Current Best Practice. J Wound Care 2016;25 Suppl 6:S1-S67.
157. Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, *et al.* What's new: Management of venous leg ulcers: Approach to venous leg ulcers. J Am Acad Dermatol 2016;74:627-40;quiz 641-2.
158. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev 2012;11:CD000265.
159. Mauck KF, Asi N, Elraiyah TA, Undavalli C, Nabhan M, Altayar O, *et al.* Comparative systematic review and meta-analysis of compression modalities for the promotion of venous ulcer healing and reducing ulcer recurrence. J Vasc Surg 2014;60(2 Suppl):71S-90S.e1-2.
160. Mosti G, Mattaliano V, Partsch H. Influence of different materials in multicomponent bandages on pressure and stiffness of the final bandage. Dermatol Surg 2008;34:631-9.
161. Wong IK, Andriessen A, Charles HE, Thompson D, Lee DT, So WK, *et al.* Randomized controlled trial comparing treatment outcome of two compression bandaging systems and standard care without compression in patients with venous leg ulcers. J Eur Acad Dermatol Venereol 2012;26:102-10.
162. Partsch H and Horakova MA. [Compression stockings in treatment of lower leg venous ulcer]. Wien Med Wochenschr 1994;144:242-9.
163. Jünger M, Wollina U, Kohnen R, Rabe E. Efficacy and tolerability of an ulcer compression stocking for therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. Curr Med Res Opin 2004;20:1613-23.
164. Kapp S, Miller C and Donohue L. The clinical effectiveness of two compression stocking treatments on venous leg ulcer recurrence: a randomized controlled trial. *Int J* Low Extrem Wounds 2013;12:189-98.
165. Dolibog P, Franek A, Taradaj J, Polak A, Dolibog P, Blaszczak E, *et al.* A randomized, controlled clinical pilot study comparing three types of compression therapy to treat venous leg ulcers in patients with superficial and/or segmental deep venous reflux. Ostomy Wound Manage 2013;59:22-30.
166. Finlayson KJ, Courtney MD, Gibb MA, O'Brien JA, Parker CN, Edwards HE. The effectiveness of a four-layer compression bandage system in comparison with Class 3 compression hosiery on healing and quality of life in patients with venous leg ulcers: a randomised controlled trial. Int Wound J 2014;11:21-7.
167. Ashby RL, Gabe R, Ali S, Adderley U, Bland JM1, Cullum NA, *et al.* Clinical and cost-effectiveness of compression hosiery *versus* compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet 2014;383:871-9.
168. Clarke-Moloney M, Keane N, O'Connor V, Ryan MA, Meagher H, Grace PA,*et al.* Randomised controlled trial comparing European standard class 1 to class 2 compression stockings for ulcer recurrence and patient compliance. Int Wound J 2014;11:404-8.
169. van Gent WB, Catarinella FS, Lam YL, Nieman FH, Toonder IM, van der Ham AC, *et al.* Conservative *versus* surgical treatment of venous leg ulcers: 10-year follow-up of a randomized, multicenter trial. Phlebology 2015;30(1Suppl):35-41.
170. Partsch H, Mosti G, Uhl J. Unexpected venous diameter reduction by compression stocking of deep, but not of superficial veins. . Veins and Lymphatics 2012;1:e3.
171. Partsch H, Damstra RJ, Mosti G. Dose finding for an optimal compression pressure to reduce chronic edema of the extremities. Int Angiol 2011;30:527-33.
172. Kalodiki E, Giannoukas AD. Intermittent pneumatic compression (IPC) in the treatment of peripheral arterial occlusive disease (PAOD)--A useful tool or just another device? Eur J Vasc Endovasc Surg 2007;33:309-10.
173. Rabe E, Partsch H, Junger M, Abel M, Achhammer I, Becker F, *et al.* Guidelines for clinical studies with compression devices in patients with venous disorders of the lower limb. Eur J Vasc Endovasc Surg 2008;35:494-500.
174. Mani R, Vowden K, Nelson EA. Intermittent pneumatic compression for treating venous leg ulcers. Cochrane Database Syst Rev 2001:CD001899.
175. Kalodiki E. Use of intermittent pneumatic compression in the treatment of venous ulcers. Future Medicine 2007;3:185-91.
176. Hazarika EZ, Wright DE. Chronic leg ulcers. The effect of pneumatic intermittent compression. Practitioner 1981;225:189-92.
177. Coleridge Smith P, Sarin S, Hasty J, Scurr JH. Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial. Surgery 1990;108:871-5.
178. McCulloch JM, Marler KC, Neal MB, Phifer TJ. Intermittent pneumatic compression improves venous ulcer healing. Adv Wound Care 1994;7:22-4, 26.
179. Schuler JJ, Maibenco T, Megerman J, Ware M, Montalvo J. Treatment of chronic venous ulcers using sequential gradient intermittent pneumatic compression. Phlebology 1996;11:111-6.
180. Rowland J. Intermittent pump *versus* compression bandages in the treatment of venous leg ulcers. Aust N Z J Surg 2000;70:110-3.
181. Nelson EA, Hillman A, Thomas K. Intermittent pneumatic compression for treating venous leg ulcers. Cochrane Database Syst Rev 2014;CD001899.
182. Nikolovska S, Arsovski A, Damevska K, Gocev G, Pavlova L. Evaluation of two different intermittent pneumatic compression cycle settings in the healing of venous ulcers: a randomized trial. Med Sci Monit 2005;11:CR337-43.
183. Kessler CM, Hirsch DR, Jacobs H, MacDougall R, Goldhaber SZ. Intermittent pneumatic compression in chronic venous insufficiency favorably affects fibrinolytic potential and platelet activation. Blood Coagul Fibrinolysis 1996;7:437-46.
184. Andriessen A, Apelqvist J, Mosti G, Partsch H, Gonska C, Abel M. Compression therapy for venous leg ulcers: risk factors for adverse events and complications, contraindications - a review of present guidelines. J Eur Acad Dermatol Venereol 2017;31:1562-8.

CHAPTER 8

Venoactive drugs

Introduction

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

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

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

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

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

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

Mode of action

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

Actions on venous tone

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

Actions on inflammatory processes in venous valves and the vein wall

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

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

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

Perhaps the most detailed and comprehensive analysis of the importance of inflammatory processes and the ability of VADs to inhibit them

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

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

Actions on capillary permeability (edema)

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

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

Skin changes related to capillary abnormalities

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

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

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

Role of nociceptors in the development of venous symptoms

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

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

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

*No data available.

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

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

Lymphatic drainage

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

Hemorheological disorders

Hemorheological changes including increased blood viscosity and erythrocyte aggregation, are common in CVDs. Several VADs have been

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

Therapeutic efficacy of VADs on venous symptoms and edema

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

Cochrane reviews

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

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

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

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

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

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

The 2005 International Consensus Statement

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The 2011 review

Perrin and Ramelet[114] proposed a tentative set of recommendations for the use of VADs based on the 'Grading of recommendations assessment, development and evaluation' (GRADE) system.[115, 116] The GRADE system differs from

the other schemes described in these guidelines in that separate levels are assigned for the recommendation for treatment and for the quality of evidence on which the recommendation is based. Recommendations are classified as either strong (grade 1) or weak (grade 2), and quality of evidence as high (grade A), moderate (grade B) or low (grade C). Importantly, the GRADE system recognizes that large observational studies may provide evidence of moderate or even high quality, particularly if the estimate of the magnitude of the treatment effect is very large.[115]

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

The 2014 guidelines update – efficacy and safety recommendations for VAD

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

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

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

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

Finally, two placebo-controlled studies on red-vine-leaf extract in 248,[124] and 71,[125] patients in CEAP classes C_3 – C_{4a} demonstrated significant reductions in lower limb volume (-19.9±8.9 mL; 95% CI: -37.5 to 2.3; P=0.027) and leg pain (-6.6±3.3 mm on VAS; 95% CI -13.1 to 0.1,

P=0.047) after 12 weeks of treatment,[124] and in ankle circumference (-0.39±0.09 cm in the treatment group *versus* 0.29±0.09 cm in the placebo group, P<0.0001) after six weeks.[125]

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

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

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

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

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

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

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

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

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

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

Introduction

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

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

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

MPFF

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

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

Heaviness was reduced with the use of MPFF compared to placebo when assessed as a continuous variable in two studies, both significant

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ruscus+HMC+AA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hydroxyethylrutosides (HR) (also known as Oxerutins)

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

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

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

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

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

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

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

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

Horse chestnut seed extract (HCSE)

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

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

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

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

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

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

Calcium dobesilate

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

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

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

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

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

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

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

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

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

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

The second positive study performed by Flota-Cervera *et al.* in 2008 [122] involved 49 patients with "lymphovenous vascular edema" (CVI Wid-

mer grade I to V classes) and investigated the effect of 49-day therapy on lymph flow and pain. By the end of the treatment period, patients treated with dobesilate had normalization of lymphogammagraphy and a statistically significant reduction in the circumference of the leg, calf and ankle. There was complete relief of pain in 68% of patients in the dobesilate group and 0% in the placebo group.

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

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

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

NS: not significant.

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

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

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

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

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

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

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

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

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

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

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

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

Pentoxifylline

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

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

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

MPFF

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

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

Sulodexide

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

in only one study was the personnel completely blinded. Adverse effects with sulodexide were low (4.4%) and statistically not different from the control group (3.1%).

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

Hydroxyethylrutosides (HR)

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

Place of VADs in the management of CVDs

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

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

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

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

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

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

Combination of VADs and compression has

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

References

1. Ramelet AA, Kern P, Perrin M. Varicose veins and telangiectasias. Paris: Elsevier, 2004.
2. Ramelet AA, Boisseau MR, Allegra C, Nicolaides A, Jaeger K, Carpentier P, *et al.* Veno-active drugs in the management of chronic venous disease. An international consensus statement: current medical position, prospective views and final resolution. Clin Hemorheol Microcirc 2005;33:309-19.
3. Nicolaides AN, Allegra C, Bergan J, Bradbury A, Cairols M, Carpentier P, *et al.* Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. Int Angiol 2008;27:1-59.
4. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation 2005;111:2398-409.
5. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355:488-98.
6. Atta HM. Varicose veins: role of mechanotransduction of venous hypertension. Int J Vasc Med 2012;2012:538627.
7. Ibegbuna V, Nicolaides AN, Sowade O, Leon M, Geroulakos G. Venous elasticity after treatment with Daflon 500 mg. Angiology 1997;48:45-9.
8. Gargouil YM, Perdrix L, Chapelain B, Gaborieau R. Effects of Daflon 500 mg on bovine vessels contractility. Int Angiol 1989;8(4 Suppl):19S-22S.
9. Tsouderos Y. Venous tone: are the phlebotonic properties predictive of a therapeutic benefit? A comprehensive view of our experience with Daflon 500 mg. Z Kardiol 1991;80(Suppl 7):95-101.
10. Frick RW. Three treatments for chronic venous insufficiency: escin, hydroxyethylrutoside, and Daflon. Angiology 2000;51:197-205.
11. Guillaume M, Padioleau F. Veinotonic effect, vascular protection, antiinflammatory and free radical scavenging properties of horse chestnut extract. Arzneimittelforschung 1994;44:25-35.
12. Bouskela E, Cyrino FZ, Marcelon G. Effects of Ruscus extract on the internal diameter of arterioles and venules of the hamster cheek pouch microcirculation. J Cardiovasc Pharmacol 1993;22:221-4.
13. Androulakis G, Panoysis PA. Plethysmographic confirmation of the beneficial effect of calcium dobesilate in primary varicose veins. Angiology 1989;40:1-4.
14. Araujo D, Viana F, Osswald W. Diosmin therapy alters the in vitro metabolism of noradrenaline by the varicose human saphenous vein. Pharmacol Res 1991;24:253-6.
15. Araujo D, Gulati O, Osswald W. Effects of two venotropic drugs on inactivation and O-methylation of catecholamines in an isolated canine vein. Arch Int Pharmacodyn Ther 1985;277:192-202.
16. Juteau N, Bakri F, Pomies JP, Foulon C, Rigaudy P, Pillion G, *et al.* The human saphenous vein in pharmacology: effect of a new micronized flavonoidic fraction (Daflon 500 mg) on norepinephrine induced contraction. Int Angiol 1995;14(3 Suppl 1):8-13.
17. Rubanyi G, Marcelon G, Vanhoutte PM. Effect of temperature on the responsiveness of cutaneous veins to the extract of Ruscus aculeatus. Gen Pharmacol 1984;15:431-4.
18. Bouskela E, Cyrino FZ, Marcelon G. Possible mechanisms for the venular constriction elicited by Ruscus extract on hamster cheek pouch. J Cardiovasc Pharmacol 1994;24:165-70.
19. Raffetto JD, Khalil RA. Ca(2+)-dependent contraction by the saponoside escin in rat vena cava: implications in venotonic treatment of varicose veins. J Vasc Surg 2011;54:489-96.
20. Manthey JA, Grohmann K, Guthrie N. Biological properties of citrus flavonoids pertaining to cancer and inflammation. Curr Med Chem 2001;8:135-53.
21. Benavente-Garcia O, Castillo J. Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. J Agric Food Chem 2008;56:6185-205.
22. Garcia-Lafuente A, Guillamon E, Villares A, Rostagno MA, Martinez JA. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflamm Res 2009;58:537-52.
23. Wu CH, Wu CF, Huang HW, Jao YC, Yen GC. Naturally occurring flavonoids attenuate high glucose-induced expression of proinflammatory cytokines in human monocytic THP-1 cells. Mol Nutr Food Res 2009;53:984-95.
24. Akhlaghi M, Bandy B. Mechanisms of flavonoid protection against myocardial ischemia-reperfusion injury. J Mol Cell Cardiol 2009;46:309-17.
25. Shukla VK, Sethi AK, Garg SK, Ganguly NK, Kulkarni SK. Effect of venoruton on hypoxic stress-induced neurotoxicity in mice and oxygen free radical generation by human neutrophils. Arch Int Pharmacodyn Ther 1989;299:127-33.
26. Cypriani B, Limasset B, Carrie ML, Le Doucen C, Roussie M, de Paulet AC, *et al.* Antioxidant activity of micronized diosmin on oxygen species from stimulated human neutrophils. Biochem Pharmacol 1993;45:1531-5.
27. Jean T, Bodinier MC. Mediators involved in inflammation: effects of Daflon 500 mg on their release. Angiology 1994;45(6 Pt 2):554-9.
28. Blasig IE, Loewe H, Ebert B. Effect of troxerutin and methionine on spin trapping of free oxy-radicals. Biomed Biochim Acta 1988;47:S252-5.
29. Matsuda H, Li Y, Murakami T, Ninomiya K, Yamahara J, Yoshikawa M. Effects of escins Ia, Ib, IIa, and IIb from horse chestnut, the seeds of Aesculus hippocastanum L., on acute inflammation in animals. Biol Pharm Bull 1997;20:1092-5.
30. Maffei Facino R, Carini M, Aldini G, Bombardelli E, Morazzoni P, Morelli R. Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneimittelforschung 1994;44:592-601.
31. Maffei Facino R, Carini M, Aldini G, Berti F, Rossoni G, Bombardelli E, *et al.* Procyanidines from Vitis vinifera seeds protect rabbit heart from ischemia/reperfusion injury: antioxidant intervention and/or iron and copper sequestering ability. Planta Med 1996;62:495-502.
32. Packer L, Rimbach G, Virgili F. Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (Pinus maritima) bark, pycnogenol. Free Radic Biol Med 1999;27:704-24.
33. Cho KJ, Yun CH, Packer L, Chung AS. Inhibition mechanisms of bioflavonoids extracted from the bark of Pinus maritima on the expression of proinflammatory cytokines. Ann N Y Acad Sci 2001;928:141-56.
34. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. Int J Clin Pharmacol Ther 2002;40:158-68.

der therapeutischen Wirksamkeit von Daflon). Vasa 1982;11:53-8.
145. Chassignolle J-F, Amiel M, Lanfranchi G, Barbe R. Activité thérapeutique de Daflon 500 mg dans l'insuffisance veineuse fonctionnelle. J Int Med 1987;(Suppl 99):32-5.
146. Tsouderos Y. Are the phlebotonic properties shown in clinical pharmacology predictive of a therapeutic benefit in chronic venous insufficiency? Our experience with Daflon 500 mg. Int Angiol 1989;8(Suppl 4):53-9.
147. Belczak SQ, Sincos IR, Campos W, Beserra J, Nering G, Aun R. Veno-active drugs for chronic venous disease: A randomized, double-blind, placebo-controlled parallel-design trial. Phlebology 2014;29:454-60.
148. Parrado F, Buzzi A. A study of the efficacy and tolerability of a preparation containing Ruscus aculeatus in the treatment of chronic venous insufficiency of the lower limbs. Clin Drug Investig 1999;18:255-61.
149. Questel R, Walrant P. Bilan de l'essai randomisé Veinobiase contre placebo dans l'unsuffisance veineuse: observation de la microcirculation per capillarographie conjonctivale. Gazette Medicale de France 1983;90:508-14.
150. Elbaz C, Nebot F, Reinharez D. Insuffisance veineuse des membres inférieurs étude controleé de l'action du Cyclo 3. Phlébologie 1976;29:77-84.
151. Altenkamp H. Efficacy of antivaricotic drugs can be measured objectively. Phlebologie in der praxis 1987;2:9-20.
152. Le Devehat C, Lemoine A, Roux E, Cirette B, Vimeux M, Martinaggi P. Aspects clinique et hémodynamique de Cyclo 3 dans l'insuffisance veineuse. Angéiologie 1984;3:119-22.
153. Sentou Y, Bernard-Fernier MF, Demarez JP, Laurent D, Cauquil J. Symptomatologie et pléthysmographie: Parallélisme des résultants obtenus lors d'un traitement par Cyclo 3 de patientes porteuses d'une insuffisance neineuse chronique (étude en double insu contre placebo). Gazette Medicale de France 1985;92:73-7.
154. Braun R, Hirche H, van Laak H-H. Die therapie der venösen insuffizienz: eine doppelblind-studie mit Phlebodril®. ZFA 1985;61:309-19.
155. Vanscheidt W, Jost V, Wolna P, Lucker PW, Muller A, Theurer C, *et al.* Efficacy and safety of a Butcher's broom preparation (Ruscus aculeatus L. extract) compared to placebo in patients suffering from chronic venous insufficiency. Arzneimittelforschung 2002;52:243-50.
156. Rieger H. Efficacy of a combination drug in patients with chronic venous insufficiency under orthostatic conditions. Phlebology 1988;3:127-30.
157. Rudofsky G, Diehm C, Gruβ JD, Hartmann M, Schultz-Ehrenburg HK, Bisler H. Chronic venous insufficiency. Treatment with Ruscus extract and trimethylhesperidin chalcone. MMW Munch Med Wochenschr 1990;132:205-10.
158. Aziz Z1, Tang WL, Chong NJ, Tho LY. A systematic review of the efficacy and tolerability of hydroxyethylrutosides for improvement of the signs and symptoms of chronic venous insufficiency. J Clin Pharm Ther 2015;40:177-85.
159. Belcaro G, Rulo A, Candiani C. Evaluation of the microcirculatory effects of Venoruton in patients with chronic venous hypertension by laserdoppler flowmetry, transcutaneous PO2 and PCO2 measurements, leg volumetry and ambulatory venous pressure measurements. Vasa 1989;18:146-51.
160. Cloarec M, Clement R, Griton P. A double-blind clinical trial of hydroxyethylurosides in the treatment of the symptoms and signs of chronic venous insufficiency. Phlebology 1996;11:76-82.
161. Pedersen FM1, Hamberg O, Sørensen MD, Neland K. Effect of 0-(beta-hydroxyethyl)-rutoside (Venoruton) on symptomatic venous insufficiency in the lower limbs. Ugeskr Laeger 1992;154:2561-3.
162. Welsh W, Moriau M, van Gysel JP. A double blind placebo-controlled trial of o-(beta-hydroxyethyl)-rutosides in patients with chronic venous insufficiency. Basel: Novartis; 1985.
163. Petruzzellis V, Troccoli T, Candiani C, Guarisco R, Lospalluti M, Belcaro G, *et al*. Oxerutins (Venoruton): efficacy in chronic venous insufficiency--a double-blind, randomized, controlled study. Angiology 2002;53:257-63.
164. Stegmann WAE, Deichmann B, Hubner K. Therapeutic effect of hydroxyethylrutosides (HR) in venous ulcer treatment. A controlled multicentre trial. Phlebology 1986;1:617-20.
165. Incandela L, Belcaro G, Renton S, DeSanctis MT, Cesarone MR, Bavera P, *et al*. HR (Paroven, Venoruton; 0-(beta-hydroxyethyl)-rutosides) in venous hypertensive microangiopathy: a prospective, placebo-controlled, randomized trial. J Cardiovasc Pharmacol Ther 2002;7(Suppl 1):S7-S10.
166. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63:834-40.
167. Cloarec M. Study on the effect of a new vasoprotective Venostasin administered over a period of 2 months in chronic venous insufficiency of the lower limb (data from1992). Data on file (quoted by Pittler and Ernst Ref 110 above).
168. Friederich HC, Vogelsberg H, Neiss A. [Evaluation of internally effective venous drugs]. Z Hautkr 1978;53:369-74.
169. Lohr E, Garanin G, Jesau P, Fischer H. [Anti-edemic treatment in chronic venous nsufficiency with tendency to formation of oedema]. MMW Munch Med Wochenschr 1986;128:579-81.
170. Morales Paris CA, Barros Soares RM. Efficacy and safety on use of dried horse chestnut extract in the treatment of chronic venous insufficiency of the limbs. Revista Brasileira de Medicina 1993;50:1563-5.
171. Neiss A, Böhm C. [Demonstration of the effectiveness of horse chestnut seed extract in the varicose syndrome complex]. MMW Munch Med Wochenschr 1976;118:213-6.
172. Rudofsky G, Neiss A, Otto K, Seibel K. [Oedema-protective effect and clinical efficacy of horse chestnut seed extract in a double blind study]. Phlebologie und Proktologie 1986;15:47-54.
173. Steiner M. Investigation into the oedema reducingand oedema protective effects of horse chestnut seed extract [Untersuchungen zur ödemvermindernden und ödemprotektiven Wirkung von Roßkastaniensamenextrakt]. Phlebologie und Proktologie 1990;19:239-42.
174. Steiner M, Hillemanns HG.[Tests for anti-oedema action of a venous therapy]. MMW Munch Med Wochenschr 1986;128:551-2.
175. Diehm C, Schmidt C. Venostasin retard gegen Plazebo und Kompression bei Patienten mit CVI II/IIIA. Final Study Report. Munich: Klinge Pharma GmbH; 2000.
176. Diehm C, Vollbrecht D, Amendt K, Comberg HU. Medical edema protection - Clinical benefit in patients with chronic deep vein incompetence. VASA 1992;21:188-92.
177. Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet 1996;347:292-4.
178. Chiapponi A, Laffaire E, Roque M. Calcium dobesilate for chronic venous insufficiency: a systematic review. Angiology 2004;55:147-54.
179. Hachen HJ, Lorenz P. Double-blind clinical and ple-

thysmographic study of calcium dobesilate in patients with peripheral microvascular disorders. Angiology 1982;33:480-8.
180. Widmer L, Biland L, Barras JP. Doxium 500 in chronic venous insufficiency: a double-blind placebo-controlled multicentre study. Int Angiol 1990;9:105-10.
181. Marinello 2002: Ensayo clinic multicentric, doble ciego, aleatorizado, controlado con placebo sobre la effecta del dobesilato de calico en el tratamiento de la hypertension venosa en patients afectos de insuficienta venosa cronica de extremidades inferiors. ESCLIN-004/99 (Quoted by Ciapponi 2004 in ref 180 above).
182. Casley-Smith JR. A double-blind trial of calcium dobesilate in chronic venous insufficiency. Angiology 1988;39:853-7.
183. Flora LF. Estudio clinic prospective aleatorizado doble ciego, con control placebo, para evaluar la eficacia en la resolucion del edema de origin linfatico, del dobesilato de calico en pacientes con enfermedad varicose. No de Proyec. Knoll-mex-02-99. No de Proyec. 003/MEX/99, 1999
184. DX-1994. Efficacy and safety of Doxium 500 in chronic venous insufficiency. A double-blind placebo-controlled multicentre study. The clinical study report. Study number DX-1994/2:1-114; 2000.
185. Rabe E, Ballarini S, Lehr L. A randomized, double-blind, placebo-contrlled, clinical study on the efficacy and safety of calcium dobesilate in the treatment of chronic venous insufficiency. Phlebology 2016;31:264-74.
186. Hammerschmidt DE1, Kotasek D, McCarthy T, Huh PW, Freyburger G, Vercellotti GM. Pentoxifylline inhibits granulocyte and platelet function, including granulocyte priming by platelet activating factor. J Lab Clin Med 1988;112:254-63.
187. Cocceri S, Mannello F. Development and use of sulodexide in vascular diseases: implications for treatment. Drug Des Devel Ther 2013;8:49-65.
188. Wu B, Lu J, Yang M, Xu T. Sulodexide for treating venous leg ulcers. Cochrane Database of Systematic Reviews 2016, issue 6. Art. No :CD010694
189. Cocceri S, Bignamini AA. Pharmacological adjuncts for chronic venous ulcer healing. Phlebology 2016;31:366-7.
190. Zuccarelli F, Taccoen A, Coget JM. Treatment of venous ulcers with troxerutin: a randomized double-blind, controlled study. Int Angiol 1987;15:53-8.
191. Nicolaides AN, Kakkos S, Eklof B, Perrin M, Nelzen O, Neglen P, *et al.* Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. Chapter 8: Venoactive Drugs. Int Angiol 2014;33:126-39.
192. Perrin M, Eklof B, van Rij A, Labropoulos N, Vasquez M, Nicolaides A, *et al.* Venous symptoms: the SYMvein Consensus statement developed under the auspices of the European Venous Forum. Int Angiol 2016;35:374-98.
193. Lee BB, Nicolaides AN, Myers K, Meissner M, Kalodiki E, Allegra C, *et al.* Venous hemodynamic changes in lower limb venous disease: the UIP consensus according to scientific evidence. Int Angiol 2016;35:236-352.
194. de Souza MGC, Cyrino FZ, Mayal MR, Virgini-Magalhaes CE, Sicuro FL, de Carvalho JJ, *et al.* Beneficial effects of the micronized purified flavonoid fraction (MPFF, Daflon 500 mg) on microvascular damage elicited by sclerotherapy. Phlebology 2016;31:50-6.
195. Bogachev VY, Golovanova OV, Kuznetsov AN, Sheokyan AO; the DECISION investigators group. Can micronized purified flavonoid fraction (MPFF) improve outcomes of lower extremity varicose vein endovenous treatment? First results from DECISION study. Phlebolymphology 2013;20:181-7.
196. Bogachev VY, Boldin BV, Lobanov VN. Benefits of micronized purified flavonoid fraction as adjuvant therapy on the inflammatory response after sclerotherapy. Int Angiol 2018;37:71-8.
197. Pitsch F. Benefit of Daflon 500 mg in combination with sclerotherapy of telangiectasias of the lower limbs: results from the SYNERGY and SATISFY surveys. Phlebolymphology 2011;19:182-7.
198. Saveljev VS, Pokrovsky AV, Kirienko AI, Bogachev VY, Zolotukhin IA, Sapelkin SV. Stripping of the great saphenous vein under micronized purified flavonoid fraction (MPFF) protection (results of the Russian multicentre controlled trial DEANCE). Phlebolymphology 2008;15:45-51.
199. Verenkova L, Kalac J, Jedlicka V, Wechsler J. Analysis of the various procedures used in great saphenous vein surgery in the Chech Republic and benefit of Daflon 500 mg to postoperative symptoms. Phlebolymphology 2006;13:193-9.
200. Mazzaccaro D, Muzzarelli L, Modafferi A, Righini PC, Settembrini M, Nano G. Use of venoactive drugs after surgery for varicose veins: a preliminary study. Int Angiol 2018;37:79-84.
201. Raffetto JD, Eberhardt RT, Dean SM, Ligi D, Mannello F. Pharmacologic treatment to improve venous leg ulcer healing. J Vasc Surg Ven and Lym Dis 2016;4:371-4.
202. Marcelon G, Pouget G, Tisné-Versailles J. Effect of Ruscus on the adenoreceptors of the canine lymphatic thoracic duct. Phlebology 1988;3(S1):109-12.
203. Le Devehat F. The effect of Cyclo 3 Fort treatment on hemorheological disturbances during a provoked venous stasis in patients with chronic venous insufficiency. Clinical hemorheology 1994;14(S1):53-63.