Adv Ther
https://doi.org/10.1007/s12325-023-02657-0

REVIEW

Cardiovascular Insights for the Appropriate Management of Chronic Venous Disease: A Narrative Review of Implications for the Use of Venoactive Drugs

Sergio Gianesini · Leonardo De Luca · Toni Feodor · Wassila Taha · Kursat Bozkurt · Fedor Lurie

Received: July 6, 2023 / Accepted: August 17, 2023

ABSTRACT

Evidence suggests that chronic venous disease (CVD) may be a cardiovascular disorder, as patients with CVD are prone to developing arterial (atherosclerosis) and venous (thromboembolism) diseases. This may be partly explained by shared risk factors. Thus, patients with CVD or cardiovascular disease require careful history-taking and physical assessment to identify coexisting pathologies and risk factors. This article summarises a symposium at the XIX World Congress of the International Union of Phlebology held in Istanbul, Turkey, in September 2022. Common pathophysiological features of CVD and cardiovascular disease are endothelial injury, hypercoagulability and systemic inflammation. In CVD, inflammation primarily affects the microcirculation, with changes in capillary permeability, vein wall and valve remodelling and increase in oxidative stress. Once patients develop symptoms/signs of CVD, they tend to reduce their physical activity,

This article is based on presentations given at a symposium at the XIX World Congress of the International Union of Phlebology held in Istanbul, Turkey in September 2022.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-023-02657-0) contains supplementary material, which is available to authorized users.

S. Gianesini (✉)
Translational Medicine Department, University of Ferrara, Via Porta a Mare 11, 45100 Ferrara, Rovigo, Italy
e-mail: gnssrg@unife.it

L. De Luca
Division of Cardiology, Department of Cardio-Thoracic and Vascular Medicine and Surgery, A.O. San Camillo-Forlanini, Rome, Italy
e-mail: leo.deluca@libero.it

T. Feodor
Medical Center for Diagnosis, Ambulatory Treatment and Medical Prevention, Surgery Clinic 'Sf. Nicolae', Bucharest, Romania
e-mail: feodor.toni14@gmail.com

W. Taha
Non-Invasive Vascular Laboratory, AlSalam Hospital Mohandessin, Cairo, Egypt
e-mail: wassila.taha@gmail.com

K. Bozkurt
Department of Cardiovascular Surgery, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey
e-mail: akbozkurt@yahoo.com

F. Lurie
Jobst Vascular Institute, Toledo, OH, USA

F. Lurie
Division of Vascular Surgery, University of Michigan, Ann Arbor, MI, USA
e-mail: Fedor.Lurie@ProMedica.org

Published online: 28 September 2023

which may contribute to increased risk of cardiovascular disease. Data show that the presence of CVD is associated with an increased risk of cardiovascular disease, including peripheral arterial disease and heart failure (HF), and the risk of adverse cardiovascular events increases with CVD severity. In addition, patients with cardiovascular disease, particularly those with HF, are at increased risk of venous thromboembolism (VTE) and should be assessed for VTE risk if they are hospitalised with cardiovascular disease. Therefore, CVD management must include a multi-specialty approach to assess risk factors associated with both the venous and arterial systems. Ideally, treatment should focus on the resolution of endothelial inflammation to control both CVD and cardiovascular disease. International guidelines recommend various conservative treatments, including venoactive drugs (VADs), to improve the symptoms/signs of CVD. Micronized purified flavonoid fraction (MPFF) is a VAD, with high-quality evidence supporting its use in relieving symptoms/signs of CVD and improving quality of life. Moreover, in large-scale observational studies, MPFF has shown superior effectiveness in real-world populations compared with other VADs.

PLAIN LANGUAGE SUMMARY

Blood vessel disease can affect both arteries and veins; when it affects arteries, it is called cardiovascular disease, and when it affects veins, it is called chronic venous disease (CVD). In most cases, the underlying disease process is similar, irrespective of the type of blood vessels affected, and the risk of both CVD and cardiovascular disease is increased by age, smoking, overweight/obesity and diabetes. If cardiovascular disease affects arteries in the legs, the symptoms can be similar to that of CVD, with pain, feelings of leg heaviness or tiredness and skin changes. CVD and cardiovascular disease are usually treated by different specialists. A symposium was held at the XIX World Congress of the International Union of Phlebology in Istanbul, Turkey, in September 2022, to raise awareness of the relationship between the two conditions. The speakers described the common disease processes in CVD and cardiovascular disease, and how patients with CVD are at increased risk of cardiovascular disease, and vice versa. They reiterated the importance of thoroughly assessing patients with either cardiovascular disease or CVD to see if both arterial and venous disease were present. When patients have CVD, international treatment guidelines recommend various conservative treatments, including venoactive drugs, to improve symptoms and signs. There is high-quality evidence to support the use of the venoactive drug, micronized purified flavonoid fraction (MPFF), to improve quality of life and relieve a broad range of CVD symptoms/signs. Large-scale observational studies support the effectiveness of MPFF in a real-world population of patients with CVD compared with other venoactive drugs.

Keywords: Arterial disease; Cardiovascular disease; Chronic venous disease; Endothelium; Inflammation; Micronized purified flavonoid fraction; Real-world evidence; Venous thromboembolism

Key Summary Points

Arterial and vein diseases affect a single organ (the endothelium) and share common pathophysiological processes and related risk factors.

Patients with chronic venous disease (CVD) must be carefully assessed for visible symptoms as well as vascular inflammation, as it may increase the risk for both major arterial and venous diseases.

Physicians of all specialities need to be aware of these commonalities, and assess both the venous and arterial circulation, without underestimating the potential overlap of both conditions.

Multi-disciplinary action and awareness is needed for both arterial and venous disease management.

Graduated compression therapy and venoactive drugs (VADs) are the pillars of conservative measures for CVD management.

Among VADs, micronized purified flavonoid fraction (MPFF) is the most researched drug, and the weight of evidence from randomised controlled trials and real-world studies favour its use in relieving symptoms/signs and improving quality of life in patients with CVD.

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.23968188.

INTRODUCTION

Naomi Hamburg, in a 2021 editorial in the *European Heart Journal*, noted that "the legs are the pathway to the heart" [1]. The editorial describes the shared risk factors and shared pathophysiology between chronic venous disease (CVD) and cardiovascular disease. In both conditions, obesity, smoking, aging and diabetes contribute to the disease process through endothelial dysfunction, inflammation and thrombosis (Fig. 1) [1]. In addition, the calf muscle acts as a peripheral pump, supporting circulatory function through venous return, and impairment of calf muscle function is an independent risk factor for mortality [2]. Indeed, the Gutenberg Health Study demonstrated that CVD is an independent risk factor for cardiovascular disease [3]; however, the relationship may be under-recognised by physicians in clinical practice [1, 4].

CVD is highly prevalent in the general population, affecting between 38 and 90% of adults around the world, depending on the definition [5]. However, the symptoms can be nonspecific, and may not always have a direct correlation with the severity of the haemodynamic impairment. Common symptoms and signs of CVD are varicose veins, oedema, leg pain and cutaneous changes that may include telangiectasia, dermatitis, pigmentation changes, lipodermatosclerosis and venous ulceration [6, 7]. CVD is categorised on the basis of clinical C), aetiological (E), anatomical (A) and pathophysiological (P) features to derive a CEAP class, with telangiectasia classed as C1, varicose veins as C2, oedema as C3, and CVD with skin changes as C4–C6 [8]. The estimated global prevalence of symptomatic C1 disease is 26% and of C2 is 19% [5]; however, prevalence may vary depending on the population type.

It must be remembered that the CEAP class is a measure of disease characteristics rather than disease severity, and that there is no overlap between CEAP progression and histopathological changes in the vein wall [9]. Nevertheless, the histopathological changes of CVD worsen with an increasing CEAP class [9], and reduced capillary density (a sign of venous hypertension) and venous reflux may be present even before patients present with symptoms [10, 11].

The association between CVD and cardiovascular disease was the topic of a symposium at the XIX World Congress of the International Union of Phlebology held in Istanbul, Turkey, in September 2022. This article summarises the content of that symposium, describing the association between CVD and cardiovascular disease, and providing new insights into our understanding of CVD management. An in-depth analysis of all current literature on and possible controversial issues related to the topic are outside the scope of this article. Rather, the aim is to provide an overview of the relationship between lower limb CVD and several cardiovascular conditions, based on the literature and as discussed by the speakers at the symposium.

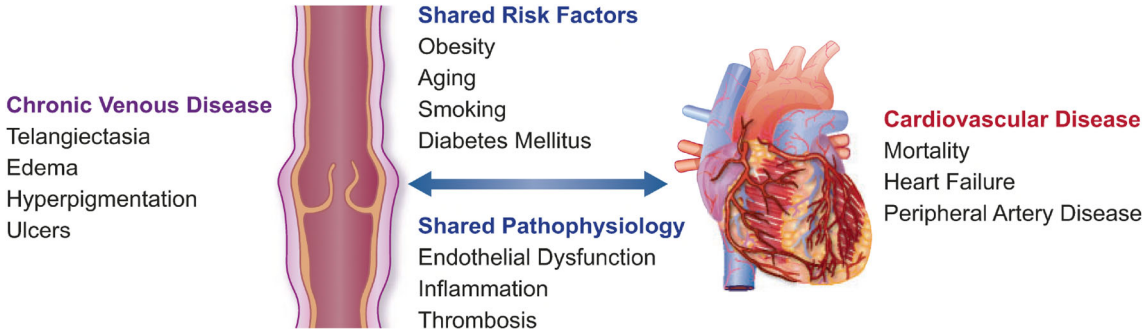

Fig. 1 The interconnected relationship between chronic venous disease and cardiovascular disease [1]. Reproduced from the graphical abstract of Hamburg [1], with permission from Oxford University Press

METHODS

The content of the article is based on the presentations at the symposium. The speakers at the symposium (and authors of this review) conducted literature searches of PubMed for articles on CVD and cardiovascular disease in association with key terms for treatment and real-world evidence (RWE).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

THE RELATIONSHIP BETWEEN CVD AND CARDIOVASCULAR DISEASE

Arterial Disease in Patients with CVD

CVD and cardiovascular disease predominantly affect the venous and arterial vascular beds; however, there is considerable evidence for a relationship between the presence of CVD and cardiovascular events. The Gutenberg Health Study demonstrated a relationship between higher CEAP class and cardiovascular risk [3]. The prevalence of cardiovascular disease increased with higher CEAP class and was significantly increased in those with CEAP classes 3–6, even after adjustment for age, sex and traditional cardiovascular risk factors. Similarly, the 10-year risk of incident cardiovascular disease and all-cause mortality were both progressively greater in patients with increasing CEAP class [3].

Within a CEAP class, the risk of cardiovascular disease may be increased with worsening disease severity. For example, Wu and colleagues reported a two-fold increase in the risk of major adverse cardiovascular events (MACEs)—acute coronary syndrome (ACS), congestive heart failure (CHF), ischaemic stroke, deep vein thrombosis (DVT) and pulmonary embolism (PE)—among patients with versus without varicose veins [hazard ratio (HR) 20.5; 95% confidence interval (CI) 1.89–2.23; $p < 0.0001$] [12]. The risk of MACEs increased with the severity of varicose veins (Fig. 2), with the risk of ACS, CHF, ischaemic stroke and mortality all significantly higher in patients with grade 3 varicose veins than in those without CVD [12].

Further data for the relationship between varicose veins and cardiovascular disease come from a Finnish study, which found that the presence of varicose veins doubles the risk of developing new-onset CHF, even after adjustment for sex, age, body mass index, hypertension and arterial disease [13]. It is noteworthy that the increased risk in this study was independent of arterial disease, since arterial disease is common in patients with varicose veins, and vice versa. For example, in a large case–control study ($n = 425{,}698$), Chang and colleagues found a significant increase in the risk of incident peripheral arterial disease (PAD) in patients with varicose veins (HR 1.72; 95% CI 1.68–1.77) versus controls [14].

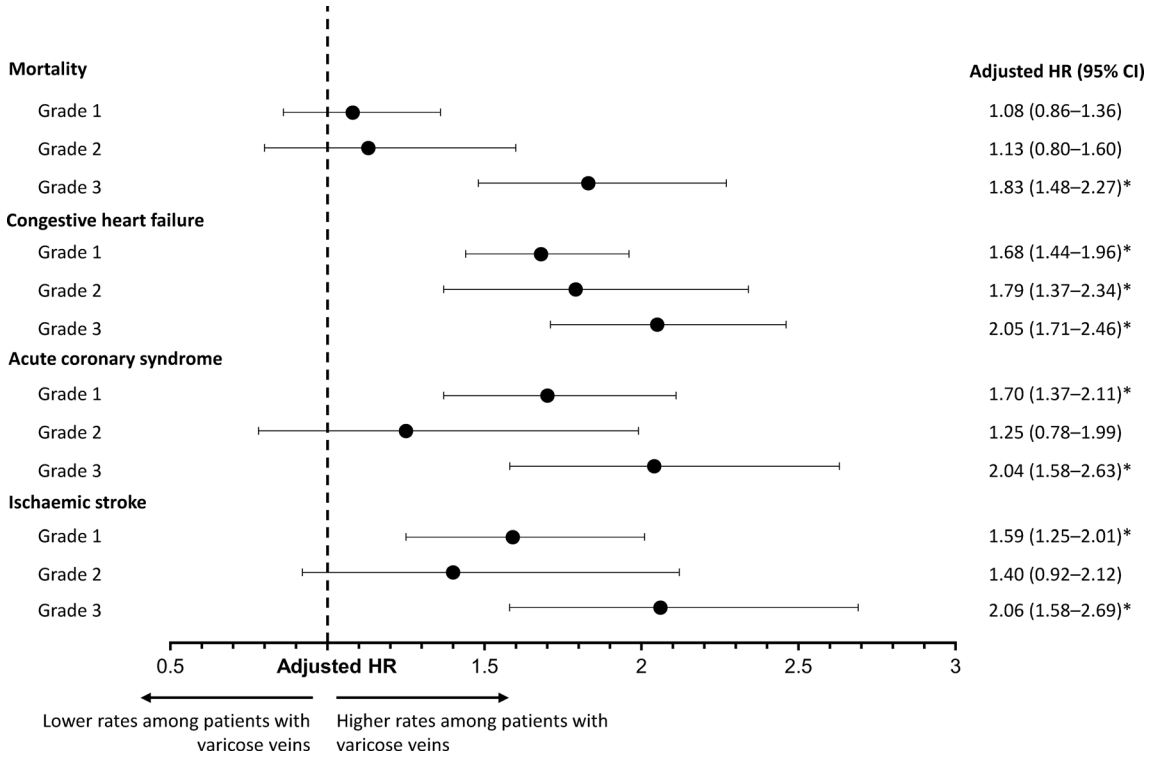

Fig. 2 The risk of all-cause mortality and cardiovascular events in patients with versus without varicose veins, stratified by varicose vein severity grade [12]. *$p < 0.05$ versus patients without varicose veins. *CI* confidence interval, *HR* hazard ratio (adjusted for chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischaemic heart disease and chronic renal insufficiency)

Venous Thromboembolism in Patients with Cardiovascular Diseases

Multiple studies have demonstrated that patients with cardiovascular disease are at increased risk of venous thromboembolism (VTE), and that VTE is a significant cause of morbidity and mortality among patients with cardiovascular disease [15–19]. In 47,611 patients with a history of myocardial infarction, ischaemic stroke or PAD, who were participating in the TRA2P-TIMI 50 or PEGASUS-TIMI 54 trials, the risk of VTE was approximately 0.3% per year [15]. However, the risk of VTE increased with the number of vascular beds affected by atherosclerosis (Fig. 3) [15], and polyvascular disease (i.e., presence of atherosclerosis in ≥ 1 arterial bed) was a significant independent risk factor for VTE, along with age, body mass index, history of chronic obstructive pulmonary disease and history of atrial fibrillation or flutter [15]. Moreover, the risk of MACEs was significantly higher in individuals with versus without VTE [15].

The risk of VTE appears to be particularly high in patients with heart failure (HF). The Atherosclerosis Risk in Communities study demonstrated that the risk of VTE was more than three times higher in patients who were hospitalised with incident HF during 22 years of follow-up than in patients who were not (HR 3.13; 95% CI 2.58–3.80) [17]. Patients with prevalent HF were excluded from this analysis [17]. An autopsy study of patients who died from HF showed that thromboembolism was a direct cause in 25% of deaths and a contributing cause in another 42% [16]. The most common type of VTE was PE, which was the cause of 36% of deaths among HF patients [16].

In the MAGELLAN study, hospitalised HF patients with levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the highest

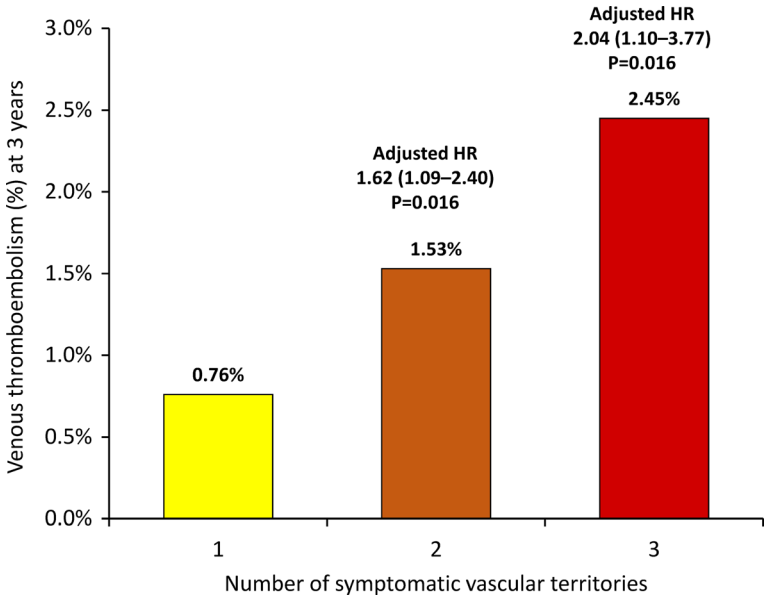

Fig. 3 The adjusted risk of venous thromboembolism in patients with symptomatic atherosclerosis stratified by the number of vascular territories affected by atherosclerosis (coronary, cerebrovascular or peripheral) [15]. *HR* hazard ratio. Reproduced from Fig. 2 of Cavallari et al. [15], with permission from Wolters Kluwer Health, Inc.

quartile were at significantly increased risk of developing VTE compared with patients whose NT-proBNP levels were lower [19].

These data highlight the importance of assessing VTE risk among hospitalised patients with cardiovascular disease, especially those with HF. Using a risk assessment model, such as the Caprini score [20], which incorporates multiple risk factors, including cardiovascular diseases and varicose veins, may be of additional value in assessing VTE risk and planning the appropriate prophylactic measures. This reliable model is freely available as a smartphone application (v-WIN Caprini score, https://v-winapp.com). In the future, additional biomarkers and genomic risk factors are likely to become increasingly important in identifying patients with cardiovascular disease at high risk of VTE.

Recognising CVD and Cardiovascular Disease When They Coexist

In a German study by Ammermann and colleagues, approximately one in five patients with PAD had concomitant CVD as demonstrated by magnetic resonance angiography, yet only 18% of the patients with CVD had been diagnosed [4]. This is likely because of the non-specificity of the symptoms and signs of venous disease, which include pain, aching, tightness, heaviness, muscle cramps, fatigue and an impression of swelling [21]. Since many of these symptoms are also shared by PAD, it is important for clinicians to determine when both venous and non-venous pathology are present [21]. For this reason, it is useful to assess the ankle-brachial index (ABI) or cardio-ankle vascular index (CAVI) in patients with CVD, as these are often abnormal (decreased or increased, respectively) in patients with CVD, indicating the presence of arterial and venous disease [22–25]. The American Heart Association is raising awareness of the link between PAD and heart attack/stroke with their "Take your socks off" campaign, to encourage more active investigation of patients' legs for symptoms and signs of CVD as a marker of cardiovascular health. Key features that can distinguish venous from arterial disease are the sensation of heavy or swollen legs associated with restlessness, itching or pain, and which are worsened by a hot environment and improved

by a cold one [26]. On the other hand, arterial symptoms tend to worsen with walking (claudication), whereas venous ones do not [26], although venous claudication can occur in individuals with outflow obstruction.

Once patients develop symptoms and signs of CVD, they tend to modify their lifestyle by reducing physical activity and time spent standing, which may contribute to increased risk of cardiovascular disease, although this relationship requires further investigation.

Patients with cardiovascular disease or CVD require careful history-taking and physical assessment to identify coexisting pathologies and risk factors. Ideally, they should be managed by a multidisciplinary team of experts in cardiology, vascular surgery and medicine, internal medicine, lymphology, gynaecology, proctology, physiatry, rehabilitation, sport medicine and nutrition.

THE SHARED PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE AND CVD

Endothelial injury and related hypercoagulability are features of CVD and cardiovascular disease, and contribute to thrombus formation and inflammation in both vascular beds [27, 28]. Both conditions are associated with the biological response (i.e. activation of a cascade of inflammatory factors) to the mechanical stress caused by turbulent blood flow, such as venous reflux or arterial stenosis [29]. As pointed out by Dardi and colleagues, changes in venous capacitance and compliance following venous endothelial dysfunction can lead to haemodynamic arterial impairment in conditions such as hypertension and HF [30]. Moreover, normalisation of the venous endothelium has been demonstrated to lead to normalisation of the levels of several inflammatory biomarkers, including platelet-derived growth factor, an effect that may also reduce the likelihood of thrombo-embolic formations [31].

Several studies have provided evidence for systemic inflammation in CVD. For example, Sansilvestri-Morel and colleagues demonstrated that the collagen dysregulation seen in the venous smooth muscle of patients with varicose veins is also present in the skin of these patients [32]. Similarly, the dermal microcirculation of patients with CVD shows inflammatory changes. T cell infiltration is increased in the dermis and epidermis of affected skin in patients with venous disease [33], and even areas of the skin that are unaffected by CVD show increased macrophage infiltration and enlarged lymphatic vessels [34].

Systemic inflammation primarily affects haemodynamics through the microcirculation or small vessels, with changes in capillary permeability, vein wall and valve remodelling, and reflux in microvalves [29]. Data from animal studies indicate that leukocyte adhesion on microvalves in venules is present from the earliest stages of CVD development [35], but these changes can be reversed by treatment with micronized purified flavonoid fraction (MPFF) [35, 36].

Studying microcirculatory changes is more difficult, but Lugli and colleagues noted that reflux was detectable in the non-axial veins, and there was a significantly higher bidirectional flow in symptomatic ($C0_S$) versus asymptomatic ($C0_A$) patients with no visible or palpable signs of venous disease [37]. This observation provides a new perspective on the pathophysiology of microcirculatory change and on the management of patients with $C0_S$ CVD [38]. In 30 patients with $C0_S$ ($n = 3$) or $C1_S$ ($n = 27$) who received MPFF 1000 mg/day, there was a significant decrease in microvessel reflux compared with baseline at 6 months ($p < 0.001$) [38]. This was accompanied by significant reductions in symptoms such as pain, cramps and heaviness (all $p < 0.001$ vs. baseline) [38], suggesting that MPFF improves CVD symptoms by reducing reflux in the microvasculature.

While reflux does contribute to the development of varicose veins, other factors are at play in the development in CVD, as demonstrated in the Edinburgh Vein study [39]. This longitudinal study compared patients with and without venous reflux at baseline and found that, while more of those with reflux developed varicose veins, the proportion who developed CVD after 13 years of follow-up was similar in the two groups (11% of those with reflux and

10% of those without) [39]. Inflammation may explain this difference. Badier-Commander and colleagues conducted a histopathological study of longitudinal sections of varicose veins and control veins to assess changes along their length [40]. Varicose veins showed heterogeneous changes along their length, with sections of vessel wall hypertrophy and atrophy; the hypertrophic segments showed migration and proliferation of smooth muscle cells, overproduction of components of the extracellular matrix and angiogenesis, similar to a 'wound healing response' and stimulated by local cytokines [40].

The association of diabetes mellitus with micro- and macrovascular complications leading to cardiovascular events is well established [41]. However, the observed hypercoagulability and inflammation in individuals with diabetes, which are also pathophysiological features of CVD, suggests that a possible link between these disorders may exist. Further investigation into this association and its therapeutic implications is warranted.

EFFECTS OF CVD TREATMENT

Guideline Recommendations

Despite similarities and controversies among the different guidelines around the world [42], a general global agreement exists on the fundamental role of certified graduated compression therapy and the pivotal role of validated venoactive drugs (VADs) in conservative CVD management.

Both the 2015 and 2022 ESVS guidelines recommend VADs "based on the available evidence for each individual drug" to improve the symptoms and signs of CVD, noting that there is randomised controlled trial (RCT) evidence to support their value in reducing symptoms (Class IIa recommendation with grade A supporting evidence) [25, 43]. For patients with active venous ulceration, the 2022 guidelines recommend MPFF, oxerutins, pentoxifylline or sulodexide, with compression therapy and local wound care (Class IIa recommendation with grade A supporting evidence) [25]. For CVD patients without ulcers, the 2022 recommendations state: "For patients with symptomatic chronic venous disease, who are not undergoing interventional treatment, are awaiting intervention, or have persisting symptoms and/or oedema after intervention, medical treatment with venoactive drugs should be considered to reduce venous symptoms and oedema, based on the available evidence for each individual drug" (Class IIa recommendation with grade A supporting evidence) [25].

The 2018 guidelines from the European Venous Forum, International Union of Angiology, UK Cardiovascular Disease and Research Trust, and the international Union of Phlebology include a detailed analysis of the evidence for each individual VAD (Table 1) [44]. At a roundtable discussion at the Winter international meeting in Phlebology, Lymphology and Aesthetics held in Italy in 2009, phlebo-lymphology experts suggested that it is important to always specify the specific drug indication rather than the VAD category, as VAD definitions vary significantly in the available literature, which makes it difficult to compare their efficacy [42]. Furthermore, international scientific groups should work together to produce the most consistent and uniform recommendations possible. Regardless of the heterogeneity in VADs, MPFF remains the most investigated and validated VAD, with the highest number of grade A or B evidence to support its use in improving most of the symptoms and signs of CVD (Table 1) [44].

The quantity and quality of scientific research is of paramount importance to properly guide healthcare professionals in their treatment decisions, and increase patient awareness on best practices and treatment appropriateness, particularly in an era where some drugs sold over-the-counter may not have been extensively studied and validated [45].

Real-World Evidence

While RCTs are the gold standard to proving treatment efficacy, and have high internal statistical validity, the controlled conditions of these studies do not reflect real-world clinical

Table 1 Grade of evidence quality supporting the use of various venoactive drugs for the symptoms and signs of CVD and for patient QoL, according to the 2018 and 2020 guidelines from the European Venous Forum, International Union of Angiology, UK Cardiovascular Disease and Research Trust, and the Union Internationale de Phlébologie [44, 57]

Parameter	MPFF	Ruscus + HMC + AA	Oxerutins	HCSE	Calcium dobesilate
Pain	A	A	B	A	B
Heaviness	A	A	B	–	A
Feeling of swelling	A	A	–	–	–
Functional discomfort	A	–	–	–	B
Leg fatigue	NS	B	–	–	–
Cramps	B	B/C	B	–	–
Paraesthesia	B/C	A	–	–	B
Burning	B/C	NS	–	–	–
Pruritus	–	B/C	–	A	–
Tightness	NS	–	–	–	–
Restless legs	NS	–	–	–	–
Leg redness	B	–	–	–	–
Skin changes	A	–	–	–	–
Ankle circumference	B	A	NS	A	–
Foot or leg volume	NS	A	NS	A	A
QoL	A	–	–	–	NS

Grade A—RCTs with large sample sizes; meta-analyses combining homogeneous results
Grade B—RCTs with small sample sizes; single randomised trial only
Grade C—other poorly designed controlled trials or non-RCTs
AA ascorbic acid, *CVD* chronic venous disease, *HMC* hesperidin methyl chalcone, *HSCE* horse chestnut seed extract, *MPPF* micronized purified flavonoid fraction, *NS* not significant, *QoL* quality of life, *RCTs* randomised controlled trials

practice, and these studies may have limited external validity and generalisability to a heterogeneous clinical practice population [46]. RWE may include observational studies as well as analyses of health databases (electronic medical records or prescription databases), and the rapid incorporation of digital technologies and tools into clinical practice provides a growing number of opportunities to assess RWE. As a result, RWE is increasingly recognised by regulatory authorities around the world as having a role in the pre- and post-approval of treatments, although the regulatory framework relating to RWE varies considerably from country to country [47].

A number of large-scale, real-world studies have investigated the effectiveness of VADs in patients with CVD (Table 2) [48–54]. These studies (described in more detail below) consistently show improvements in symptom severity with VAD treatment. The most studied VAD is MPFF, with considerably more effectiveness data for this agent [48, 51, 52, 54] than for diosmin [53, 54], Ruscus extract [50, 54], or sulodexide [49].

MPFF

The Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids (RELIEF) study was an international observational study conducted in 23 countries in Europe, Africa, America and Asia [51]. Overall, 4527 patients with symptomatic CVD of CEAP class C0–C4 received MPFF 1000 mg/day for 6 months. Of these, 43% of patients had venous reflux on Doppler examination, most commonly in the long saphenous vein, and 57% did not. Compared with the group without reflux, patients with reflux had more severe leg pain and sensations of swelling, a higher CEAP grade (60% had C3 or C4 disease), and worse quality of life (QoL) as measured using the Chronic Venous Insufficiency Questionnaire (CIVIQ). Treatment with MPFF for 6 months was associated with a significant reduction in the severity of oedema (leg circumference), and in symptoms of leg heaviness, swelling sensation, cramps, and pain compared with baseline ($p = 0.0001$) and the improvement was significant in both those with or without venous reflux. In addition, the proportion of patients with C3 or C4 CVD decreased significantly in both groups ($p \leq 0.001$ for both; Fig. 4), and all parameters of QoL significantly improved from baseline after 6 months of treatment with MPFF, with a significantly greater improvement in the pain dimension among those without reflux than those with reflux ($p = 0.005$) [51].

The DECIDE [52], VEIN ACT [48], and VEIN STEP [54] observational studies did not specify which treatments physicians should prescribe for CVD, but MPFF was by far the most commonly used agent, prescribed in between 74 and 93% of patients in these studies.

In the French DECIDE study, 13,131 untreated patients with symptoms of CVD were assessed in general practice using a symptom checklist [52]. The primary aim of the study was to evaluate the symptom checklist for identifying patients with CVD, and it proved to be an effective diagnostic aid. A secondary objective was to assess changes in symptoms and QoL (using the CIVIQ) among CVD patients after 3–6 months of treatment (median 63 days). The most prescribed treatment was MPFF 500 mg/day, which was used in 89% of patients. The prevalence of symptoms decreased significantly compared with baseline in treated patients, and the magnitude of the change was significantly greater with MPFF than with other VADs ($p < 0.001$). There was also a significant improvement in QoL scores across all dimensions, but most notably pain, and the magnitude of the overall improvement in QoL was significantly greater among patients receiving MPFF compared with other treatments ($p < 0.001$).

The VEIN ACT program enrolled 7987 patients with CVD symptoms in Europe (Austria, Romania, Russia, and Spain), Central and South America, and the West Indies [48]. This study is noteworthy because it included patients of all CEAP classes from $C0_S$ to C6, although the most represented class was C3 (32.0%). None of the patients were receiving CVD treatment, and one goal of the study was to investigate the effectiveness of treatment according to the physician's usual prescribing practice. Overall, 99.4% of patients were prescribed VADs, most commonly MPFF (in 92.5%) or diosmin (in 6.1%). Only one-third of patients received VAD alone; the others received VAD in combination with compression therapy ± analgesics. The duration of treatment varied from 4 weeks to more than 12 weeks, but most patients received VADs for ≥ 8 weeks. VAD treatment, which was mostly MPPF, significantly reduced the prevalence of CVD symptoms such as heaviness, pain, swelling and cramps (all $p < 0.0001$ vs. baseline). Symptom severity, measured using a visual analogue scale (VAS), also decreased with VAD treatment, and approximately 94% of treated patients reported high satisfaction with treatment [48].

The VEIN STEP program is similar to VEIN ACT in that treatment choices were at the discretion of the participating physician [54]. VEIN STEP is a large-scale, international, observational study from real-life settings being conducted in nine countries (China, Costa Rica, Dominican Republic, Honduras, Mexico, Morocco, Panama, Romania, and Ukraine); to date, preliminary results from Morocco, China and Romania are available [55]. The key objectives were to assess CVD characteristics and conservative management, including both patient-

Table 2 Large-scale, real-world studies of vasoactive drugs in patients with chronic venous disease

Study, year	Design	Patients	*n*	Treatment	Follow-up	Key findings
Diosmin						
STATUS study, 2020 [53]	Multicentre, prospective, observational	CEAP C1–C3	2013	Diosmin 600 mg OD (98%) or BID (2%)	2 months	Symptom improvement and high satisfaction with treatment
MPFF						
RELIEF study, 2002 [51]	Multicentre (23 countries), prospective, observational	CEAP C0–C4	4527	MPFF 1000 mg/day	6 months	Significant reduction in symptom severity Significant decrease in number of patients with C3 or C4 class CVD Significant improvement in QoL
DECIDE survey, 2011 [52]	Multicentre (1323 centres in France), prospective, observational	Symptoms of CVD[a]	9954[b]	MPFF 500 mg/day (89%) Other VAD (5%) No treatment (2%) No information (4%)	63 days	Significant decrease in number of symptoms with MPFF Significant improvement in symptoms by physician global impression score Significantly greater improvement in QoL with MPFF vs. other VADs
VEIN ACT Program, 2019 [48]	Multicentre (567 centres in Austria, Central America, Colombia, Romania, Russia, and Spain), prospective, observational	CEAP C0–C6	7397	MPFF (93%), diosmin (6%)	4 to > 12 weeks	Number and severity of symptoms decreased with treatment 97% of patients reported symptom relief with treatment

Table 2 continued

Study, year	Design	Patients	*n*	Treatment	Follow-up	Key findings
VEIN STEP Program, 2022 [55]	Multicentre, (Morocco, China and Romania[c]), prospective, observational	Symptomatic CVD (CEAP C0–C6)	4718	MPFF (74%), diosmin (20%)	4 weeks	Treatment with VADs, primarily MPFF, was associated with an improvement in symptoms, signs and QoL in patients with CVD
Ruscus extract						
Guex et al., 2008 [50]	Multicentre (149 centres in Argentina), prospective, observational	CEAP C0–C3	1036	Ruscus[d] 150 mg TID	12 weeks	Significant improvements in QoL Significant reduction in oedema (ankle volume) Symptoms improved in 53.1–76.9% of patients
Sulodexide						
ACVEDUCT Program, 2020 [49]	Multicentre (205 centres in Russia), prospective, observational	CEAP C1–C6	2263	Sulodexide 600–1200 LSU/day as IV or IM injection and/or 250–1000 LSU/day as capsules	Mean 46.8 months	Significant reduction in the number and severity of symptoms with treatment

BID twice daily, *CEAP* Clinical, Etiological, Anatomical, Pathological (score), *CVD* chronic venous disease, *IM* intramuscular, *IV* intravenous, *LSU* lipasaemic units or lipoprotein lipase-releasing units, *MPFF* micronized purified flavonoid fraction, *OD* once daily, *QOL* quality of life, *TID* thrice daily, *VAD* venoactive drug

[a]CEAP class not assessed in this study, but all patients were symptomatic and class C0–C3

[b]Patients with baseline and follow-up results (a total of 13,131 patients with CVD were enrolled and completed baseline assessments)

[c]The VEIN STEP program is being conducted in nine countries, but only data from Morocco, China and Romania have been published to date

[d]Each capsule contained Ruscus 150 mg, hesperidin 150 mg, and ascorbic acid 100 mg; patients took 3 capsules per day

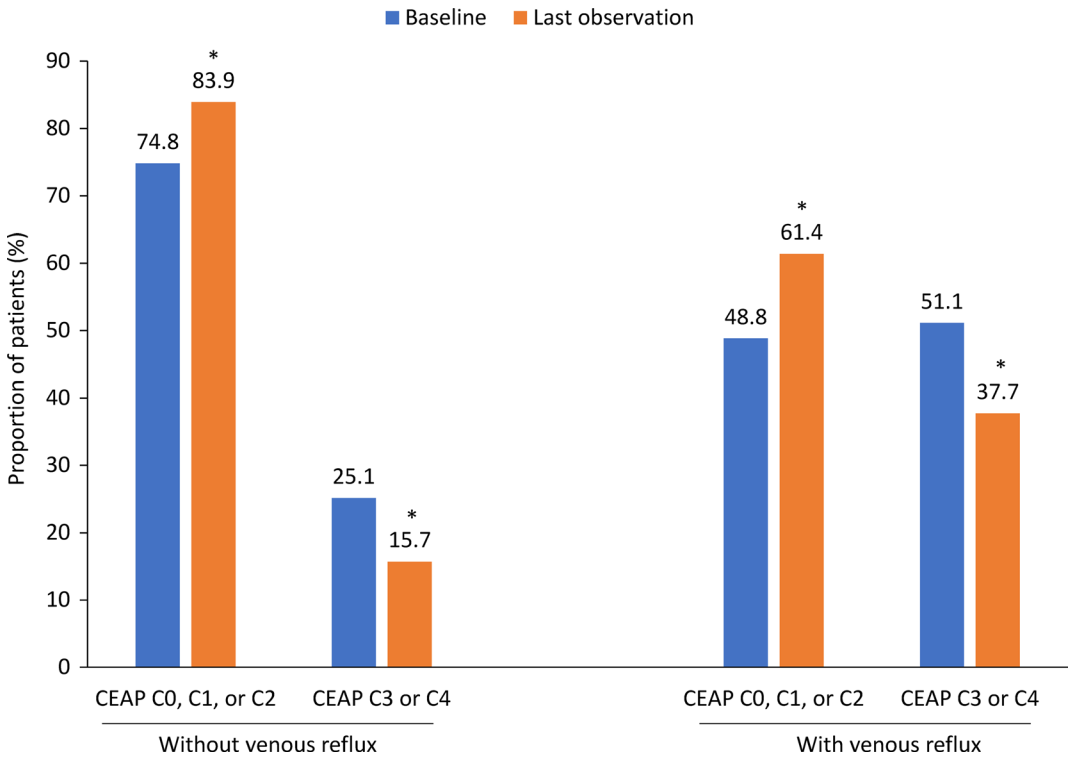

Fig. 4 Clinical, Etiological, Anatomical, Pathological (CEAP) class at baseline and at the last observation in the prospective observational RELIEF study in which patients ($n = 4527$) received micronized purified flavonoid fraction for 6 months [51]. *$p \leq 0.001$ vs. baseline. Recreated from Figs. 2 and 3 of Jantet et al. [51], with permission from SAGE publications

reported outcomes and physician assessments, which focused on the effectiveness of different treatments in chronic venous disease. Patients were assessed in person at baseline (visit 0) and after 4 weeks (visit 2), with phone calls at week 2 (visit 1) and week 8 (visit 3), although the 8-week visit was optional.

While patients with any CEAP class were eligible for inclusion, most patients in the Moroccan, Chinese and Romanian cohorts ($n = 4718$) had C2 (30.6%) or C3 (33.7%) disease [55]. Oral VADs (MPFF: 74.4%; diosmin: 20.1%) alone or in combination were the most prescribed treatments (in 95.7% of patients); compression (45.4%) and topical (34.0%) treatments were also prescribed. Global symptom intensity (as assessed by a VAS) and disease severity [assessed using the Venous Clinical Severity Score (VCSS)] decreased significantly at week 4 with all VADs, used alone or in combination ($p < 0.001$, paired comparisons). Similarly, symptom intensity for pain, heaviness, cramps and swelling decreased significantly from baseline to week 4 with all VADs across all disease severity groups, when used alone or in combination ($p < 0.001$, paired comparisons). Treatment with VADs for 4 weeks was also associated with a significant improvement in QoL ($p < 0.001$), as measured with the CIVIQ, and patient global impression of change (an improvement was reported by 98.1% of patients). When patients treated only with MPFF ($n = 998$) or diosmin ($n = 183$) were considered, there was a significantly greater decrease in median [Q1; Q3] global symptoms intensity with MPFF versus diosmin [− 2.2 (− 3.5; − 1.0) vs. − 2.0 (− 3.0; − 0.5); $p < 0.001$] [55]. The reduction in individual symptom intensity was significantly more marked with MPFF than with diosmin ($p < 0.001$ for pain,

heaviness, cramps and swelling). Moreover, MPFF was associated with a significantly greater reduction in VCSS [− 2.0 (− 4.0; − 1.0) vs. − 1.0 (− 2.0; 0); $p < 0.001$] and a greater improvement in CIVIQ [− 10.0 (− 14.0; 5.0) vs. − 5.0 (− 9.0; − 1.0); $p < 0.001$] compared with diosmin. Thus, the pooled results from Morocco, China and Romania suggest that treatment with VADs, mainly MPFF, improves symptoms and signs and QoL in patients with CVD [55].

Diosmin

A prospective Russian study evaluated the effectiveness of diosmin in 2013 patients with symptomatic C1–C3 CVD. Diosmin was prescribed for between 4 and 18 weeks (median 8 weeks), with 97.6% of patients taking diosmin 600 mg/day (1 tablet) and 2.4% taking 1200 mg/day (2 tablets). Treatment was associated with a marked reduction in all symptoms, and both compliance and satisfaction with treatment were high [53].

Ruscus Extract

A prospective observational study conducted at 149 centres in Argentina examined the relationship between objective changes in leg oedema and symptom severity and QoL in patients with CVD [50]. The study enrolled 1036 patients with symptoms and signs of CVD, who were in CEAP class C0 (2.8%), C1 (24.5%), C2 (36.2%) or C3 (36.6%). Patients were asked to take three capsules a day for 12 weeks, with each capsule containing 150 mg of Ruscus, 150 mg of hesperidin and 100 mg of ascorbic acid. Between 53.1 and 76.9% of patients reported an improvement in symptoms during treatment, with the greatest improvements seen in heaviness (76.9% of patients) and leg pain (76.5%), and the least in paraesthesia (53.1%). Ankle circumference decreased significantly by a mean of 21 mm (or 3.5%) during treatment, and there was a significant correlation between the change in ankle circumference and improvement in leg heaviness ($p = 0.02$) in the overall group, and between ankle circumference and each measured symptom in the group with C2 or C3 CVD ($p \leq 0.005$). QoL, as measured by the CIVIQ, also showed significant improvement during treatment, as did the mental and physical components of QoL as measured by the Short Form 12 [50].

Sulodexide

The ACVEDUCT study with sulodexide was conducted among 2263 patients with CVD being treated with sulodexide at 205 centres in the Russian Federation [49]. Patients received sulodexide as an intravenous or intramuscular injection once a day, or as capsules once or twice a day, with most patients (88%) receiving a combination of oral and parenteral formulations. Patients were followed up for 3–5 visits (mean 3.6) over a mean of 46.8 months.

By the third visit, 68.9% of patients showed a reduction in symptom severity and 28.1% had a reduction in the number of symptoms present. Most patients ($n = 1417$; 63%) stopped sulodexide treatment after the third visit, but patients who stayed on treatment continued to show a reduction in the number and severity of symptoms. Overall, < 1% of patients showed no change in their condition with sulodexide [49].

Shared Decision-Making

Current guidelines for the management of CVD include many options for physicians, and this, along with differences in reimbursement policies, may help to explain why there is marked variation in CVD management approaches around the world [56]. An important step in determining the most appropriate treatment is to ask the patient what bothers them most about their condition. Is it the risk of adverse outcomes (e.g. venous ulceration, cardiovascular disease events), the symptoms (e.g. pain, itching) or the aesthetic appearance of their legs (e.g. skin changes, varicose veins)? Once the patient's concerns have been determined, physicians and patients can determine together the best management approach based on the goals of treatment and the evidence to support the efficacy and effectiveness of treatment, considering the patient's overall risk of future events (both venous and arterial), their

comorbidities, their likely compliance/adherence, and the affordability of treatment.

As described earlier, patients with cardiovascular disease or CVD often have a complex medical history and comorbidities, so management of these conditions should be undertaken in a multidisciplinary context, with involvement of, or referral to, other specialists and integration of allied health professionals (e.g. dietician, physiotherapist, vascular/wound care nurse) as needed. Each patient with CVD should be assessed for thrombotic risk, especially those who are at an increased risk of this complication. This has become particularly important after the endothelial thrombo-inflammation evidenced during the COVID period. Therefore, it is crucial to manage inflammation at an early stage, especially since patients rarely achieve $C0_A$ or revert to permanent venous physiological pressure after a vein procedure.

CONCLUSIONS

While cardiovascular disease and CVD are typically considered as separate entities affecting different vascular beds, they both affect a single organ—the vascular endothelium—and are characterised by possible systemic inflammation. As a result, they share many pathophysiological features and risk factors. Therefore, it is unsurprising that arterial patients present vein issues and vice versa.

Physicians of all specialties need to be aware of these commonalities and assess both the venous and arterial circulation in patients with cardiovascular disease or CVD. Whenever CVD is present, it should be actively managed using a shared decision-making model that takes account of the patient's specific risk factors, key symptoms and signs, concerns, financial situation and likely compliance. Guideline recommendations support the use of conservative treatment with VADs in CVD patients to relieve symptoms and signs and improve QoL. Given that MPFF is the most investigated and validated drug in the CVD clinical spectrum, with evidence from both RCTs and real-world studies, clinicians should consider including MPFF in their therapeutic armamentarium.

Medical Writing/Editorial Assistance Editorial assistance for the preparation of this article was provided by Catherine Rees who wrote the first draft of this manuscript on behalf of Springer Healthcare Communications. Support for this assistance was funded by Servier.

Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors (Sergio Gianesini, Leonardo De Luca, Toni Feodor, Wassila Taha, Kursat Bozkurt, and Fedor Lurie) were responsible for the literature search, critically reviewing and revising all drafts, and approving the final version of the manuscript.

Funding. Sponsorship for the symposium, medical writing assistance, as well as the cost of the submission and the Rapid Service and Open Access Fees were provided by Servier. The authors received no honoraria related to the development of this publication.

Data Availability. Data sharing is not applicable to this article as no new datasets were generated or analysed during the current study.

Declarations

Conflict of Interest. Toni Feodor has received honoraria for speaking engagements from Servier, Medtronic and Alfasigma. Wassila Taha has received honoraria for speaking engagements from Servier and for executive committee/advisory board engagements from ECoP. All authors (Sergio Gianesini, Leonardo De Luca, Toni Feodor, Wassila Taha, Kursat Bozkurt, and Fedor Lurie) received an honorarium from Servier, France, for their participation in the symposium.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Hamburg NM. The legs are a pathway to the heart: connections between chronic venous insufficiency and cardiovascular disease. Eur Heart J. 2021;42:4166–8.

2. Halkar M, Medina Inojosa J, Liedl D, et al. Calf muscle pump function as a predictor of all-cause mortality. Vasc Med. 2020;25:519–26.

3. Prochaska JH, Arnold N, Falcke A, et al. Chronic venous insufficiency, cardiovascular disease, and mortality: a population study. Eur Heart J. 2021;42:4157–65.

4. Ammermann F, Meinel FG, Beller E, et al. Concomitant chronic venous insufficiency in patients with peripheral artery disease: insights from MR angiography. Eur Radiol. 2020;30:3908–14.

5. Salim S, Machin M, Patterson BO, Onida S, Davies AH. Global epidemiology of chronic venous disease: a systematic review with pooled prevalence analysis. Ann Surg. 2021;274:971–6.

6. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2014;130:333–46.

7. Kılınç F, Akbaş A, Şener S, Hayran Y, Aktaş A. Cutaneous findings in patients with chronic venous insufficiency. J Cosmet Dermatol. 2022;21:2106–12.

8. Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards. J Vasc Surg Venous Lymphat Disord. 2020;8:342–52.

9. Mironiuc A, Palcau L, Rogojan L, Micula S, Gherman C. Is there a correlation between the CEAP score and the histopathological findings in varicose disease? Rom J Morphol Embryol. 2011;52:117–21.

10. Jünger M, Steins A, Hahn M, Häfner H-M. Microcirculatory dysfunction in chronic venous insufficiency (CVI). Microcirculation. 2010;7:S3–12.

11. Evans CJ, Allan PL, Lee AJ, Bradbury AW, Ruckley CV, Fowkes FG. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh Vein Study. J Vasc Surg. 1998;28:767–76.

12. Wu NC, Chen ZC, Feng IJ, et al. Severe varicose veins and the risk of mortality: a nationwide population-based cohort study. BMJ Open. 2020;10:e034245.

13. Mäkivaara LA, Ahti TM, Luukkaala T, Hakama M, Laurikka JO. The risk of congestive heart failure is increased in persons with varicose veins. Int Angiol. 2009;28:452–7.

14. Chang SL, Huang YL, Lee MC, et al. Association of varicose veins with incident venous thromboembolism and peripheral artery disease. JAMA. 2018;319:807–17.

15. Cavallari I, Morrow DA, Creager MA, et al. Frequency, predictors, and impact of combined antiplatelet therapy on venous thromboembolism in patients with symptomatic atherosclerosis. Circulation. 2018;137:684–92.

16. de Macedo IS, Dinardi LFL, Pereira TV, et al. Thromboembolic findings in patients with heart failure at autopsy. Cardiovasc Pathol. 2018;35:23–8.

17. Fanola CL, Norby FL, Shah AM, et al. Incident heart failure and long-term risk for venous thromboembolism. J Am Coll Cardiol. 2020;75:148–58.

18. Hess CN, Szarek M, Anand SS, et al. Rivaroxaban and risk of venous thromboembolism in patients with symptomatic peripheral artery disease after lower extremity revascularization. JAMA Netw Open. 2022;5: e2215580.

19. Mebazaa A, Spiro TE, Büller HR, et al. Predicting the risk of venous thromboembolism in patients hospitalized with heart failure. Circulation. 2014;130:410–8.

20. Cronin M, Dengler N, Krauss ES, et al. Completion of the updated Caprini Risk Assessment Model

(2013 Version). Clin Appl Thromb Hemost. 2019;25:1076029619838052.

21. Perrin M, Eklöf B, Rij AV, et al. Venous symptoms: the SYM Vein Consensus statement developed under the auspices of the European Venous Forum. Int Angiol. 2016;35:374–98.

22. Aykan AÇ, Menteşe S, Doğan E, et al. Assessment of arterial stiffness in patients with chronic lower extremity venous disease: an observational study. Phlebology. 2016;31:349–55.

23. Matic M, Matic A, Djuran V, Gajinov Z, Prcic S, Golusin Z. Frequency of peripheral arterial disease in patients with chronic venous insufficiency. Iran Red Crescent Med J. 2016;18: e20781.

24. O'Donnell TF, Passman MA, Marston WA, 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: 3S-59S.

25. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's Choice—European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the management of chronic venous disease of the lower limbs. Eur J Vasc Endovasc Surg. 2022;63: 184–267.

26. Carpentier PH, Poulain C, Fabry R, et al. Ascribing leg symptoms to chronic venous disorders: the construction of a diagnostic score. J Vasc Surg. 2007;46:991–6.

27. Goldhaber SZ. Venous thromboembolism in heart failure patients: pathophysiology, predictability, prevention. J Am Coll Cardiol. 2020;75:159–62.

28. Prandoni P. Links between arterial and venous disease. J Intern Med. 2007;262:341–50.

29. Mansilha A, Sousa J. Pathophysiological mechanisms of chronic venous disease and implications for venoactive drug therapy. Int J Mol Sci. 2018;19: 1669.

30. Dardi P, Dos Reis Costa DEF, Assuncao HCR, Rossoni LV. Venous endothelial function in cardiovascular disease. 2022. Biosci Rep. https://doi.org/10.1042/BSR20220285.

31. Tisato V, Zauli G, Gianesini S, et al. Modulation of circulating cytokine-chemokine profile in patients affected by chronic venous insufficiency undergoing surgical hemodynamic correction. J Immunol Res. 2014;2014: 473765.

32. Sansilvestri-Morel P, Rupin A, Jaisson S, Fabiani JN, Verbeuren TJ, Vanhoutte PM. Synthesis of collagen is dysregulated in cultured fibroblasts derived from skin of subjects with varicose veins as it is in venous smooth muscle cells. Circulation. 2002;106:479–83.

33. Wilkinson LS, Bunker C, Edwards JC, Scurr JH, Smith PD. Leukocytes: their role in the etiopathogenesis of skin damage in venous disease. J Vasc Surg. 1993;17:669–75.

34. Pappas PJ, DeFouw DO, Venezio LM, et al. Morphometric assessment of the dermal microcirculation in patients with chronic venous insufficiency. J Vasc Surg. 1997;26:784–95.

35. Cyrino FZ, Blanc-Guillemaud V, Bouskela E. Time course of microvalve pathophysiology in high pressure low flow model of venous insufficiency and the role of micronized purified flavonoid fraction. Int Angiol. 2021;40:388–94.

36. das Graças C de Souza M, Cyrino FZ, de Carvalho JJ, Blanc-Guillemaud V, Bouskela E. Protective effects of micronized purified flavonoid fraction (MPFF) on a novel experimental model of chronic venous hypertension. Eur J Vasc Endovasc Surg. 2018;55: 694–702.

37. Lugli M, Maleti O, Iabichella ML, Perrin M. Investigation of non-saphenous veins in C0S patients. Int Angiol. 2018;37:169–75.

38. Lugli M, Longhi M, Guerzoni S, Maleti O. Effect of micronized purified flavonoid fraction treatment on microscopic venous valves reflux in C0s and C1s patients with chronic venous disease. In: 21st Annual Meeting of the European Venous Forum; 2021.

39. Robertson LA, Evans CJ, Lee AJ, Allan PL, Ruckley CV, Fowkes FG. Incidence and risk factors for venous reflux in the general population: Edinburgh Vein Study. Eur J Vasc Endovasc Surg. 2014;48: 208–14.

40. Badier-Commander C, Couvelard A, Henin D, Verbeuren T, Michel JB, Jacob MP. Smooth muscle cell modulation and cytokine overproduction in varicose veins. An in situ study. J Pathol. 2001;193: 398–407.

41. Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab. 2013;17:20–33.

42. Gianesini S, Obi A, Onida S, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease: narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics, 23–25 January 2019. Phlebology. 2019;34: 4–66.

43. Wittens C, Davies AH, Bækgaard N, et al. Editor's Choice—management of chronic venous disease: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2015;49:678–737.

44. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines according to scientific evidence. Part I. Int Angiol. 2018;37:181–254.

45. Cooper RJ. Over-the-counter medicine abuse—a review of the literature. J Subst Use. 2013;18: 82–107.

46. Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatology (Oxford). 2018;57:vii54–8.

47. Burns L, Roux NL, Kalesnik-Orszulak R, et al. Real-world evidence for regulatory decision-making: guidance from around the world. Clin Ther. 2022;44:420–37.

48. Bogachev V, Jiménez Arribas JM, Baila S, et al. Management and evaluation of treatment adherence and effectiveness in chronic venous disorders: results of the international study VEIN Act Program. Drugs Ther Perspect. 2019;35:396–404.

49. Chupin AV, Katorkin SE, Katelnitsky II, et al. Sulodexide in the treatment of chronic venous insufficiency: results of the all-Russian multicenter ACVEDUCT program. Adv Ther. 2020;37:2071–82.

50. Guex JJ, Enrici E, Boussetta S, Avril L, Lis C, Taieb C. Correlations between ankle circumference, symptoms, and quality of life demonstrate the clinical relevance of minimal leg swelling reduction: results of a study in 1,036 Argentinean patients. Dermatol Surg. 2008;34:1666–75.

51. Jantet G, RELIEF Study Group. Chronic venous insufficiency: worldwide results of the RELIEF study. Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids. Angiology. 2002;53:245–56.

52. Pitsch F. Results of the DECIDE survey: appraisal of the predictive value for chronic venous disease of a symptom checklist. Phlebolymphology. 2011;18: 140–8.

53. Stoyko YM, Tsyplyashchuk AV, Kryzhanovsky SM. Diosmin therapy for chronic vein diseases in outpatient settings: results of non-intervention STATUS study. Flebologiya. 2020;14:230–6.

54. Zoubida TM, Ulloa JH. VEIN STEP: chronic VEnous dIsorders maNagement and treatment effectiveness evaluation in chronic venous disease, an international observational prospective study. Results from Morocco. Phlebolymphology. 2021;28:68–78.

55. Mezalek ZT, Chen Z, Feodor T. VEINSTEP: chronic venous disorders management and treatment effectiveness evaluation in chronic venous disease, an international observational prospective study. Results from Morocco, China and Romania (Abstract and oral presentation for the UIP XIX World Congress of Phlebology, 12–16 September 2022, Istanbul, Turkey). Phlebology. 2022;37: 3–276.

56. van der Velden SK, Pichot O, van den Bos RR, Nijsten TE, De Maeseneer MG. Management strategies for patients with varicose veins (C2–C6): results of a worldwide survey. Eur J Vasc Endovasc Surg. 2015;49:213–20.

57. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part II. Int Angiol. 2020;39:175–240.