




New Perspectives on Micronised Purified Flavonoid Fraction in Chronic Venous Disease: From Microvalves to Clinical Effectiveness

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ABSTRACT

The importance of chronic venous disease (CVD), as a cause of reduced quality of life and increased costs to healthcare systems, is expected to rise in parallel with population aging and the increasing prevalence of obesity. Venoactive drugs (VADs) are frequently used to treat the symptoms and signs of CVD. The most commonly used and widely studied VAD, micronised purified flavonoid fraction (MPFF), is effective at all stages of CVD, and has been shown to significantly reduce leg pain, leg heaviness and swelling, as well as ankle oedema

and functional discomfort, in clinical trials. Recently, experiments employing animal models of CVD have demonstrated that MPFF has anti-inflammatory and venotonic effects at the microvalve level, and a pilot clinical study in patients with CVD has provided support for these findings. Collectively, these results suggest that early initiation of MPFF treatment may have the potential to favourably alter the clinical course of the disease, although further clinical data are required to confirm these findings. International guidelines on CVD management strongly recommend MPFF to reduce symptoms and improve quality of life. Studies are now needed to investigate the impact of long-term treatment on disease progression.

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Key Summary Points

Chronic venous disease (CVD) is a progressive condition with a growing global burden associated with population aging and increasing levels of obesity.

Micronised purified flavonoid fraction (MPFF), a venoactive drug used to reduce leg pain and functional discomfort, has recently demonstrated beneficial effects on the microcirculation in animal models of CVD.

MPFF was found to simultaneously inhibit leukocyte adhesion and improve venous tone resulting in the restoration of valvular competence and vessel wall protection from inflammation in both animal models and patients with CVD.

MPFF is strongly recommended by international guidelines on venoactive drug treatment, but further studies are required to assess the impact of early MPFF initiation and long-term treatment on CVD progression.

DIGITAL FEATURES

This article is published with digital features, including a video, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.20029148>.

INTRODUCTION

Chronic venous disease (CVD) is a progressive condition associated with significant burden for individuals, families, societies and healthcare systems [1, 2]. This burden is projected to increase in the coming decades, in association with population aging and rising levels of obesity [3]. Although symptoms and signs can be present early on, the disease is particularly

debilitating and costly in patients with advanced disease and venous leg ulceration [2]; thus, there is an urgent need for interventions that can prevent or slow the progression of CVD.

The cornerstones of conservative treatment for CVD are compression and venoactive drug (VAD) therapy [4]. Surgical options, including endovascular interventions and sclerotherapy, may be offered as the disease progresses. However, the principal aim of all these interventions is, at present, *reactive*—i.e. to reduce symptoms and signs, resolve functional impairments, improve quality of life (QoL) and promote the healing of established ulcers—as opposed to *proactive* measures that halt or slow disease progression.

Micronised purified flavonoid fraction (MPFF)—consisting of 90% diosmin and 10% concomitant active flavonoids, including hesperidin, linarin and isorhoifolin—is the most widely prescribed VAD for the treatment of CVD in Europe [5], and is also available as an over-the-counter product in several countries. Recent discoveries in animal models and in patients with CVD have suggested that MPFF may have the potential to alter the clinical course of CVD [6–10]. These and other findings were the subject of an industry-sponsored symposium, titled “Chronic or not: a disorder for life?”, which was held virtually on 24 June 2021 as part of the 21st Annual Meeting of the European Venous Forum, and the scientific content of which is summarised in this article. Discussion of other venoactive drugs is beyond the scope of this article. Further, 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.

MPFF IN EXPERIMENTAL ANIMAL MODELS OF VENOUS HYPERTENSION

The pathophysiological hallmarks of CVD are venous hypertension and inflammation. Raised venous pressure is transmitted backwards to the capillary beds, causing an increase in

macromolecular permeability, valve and vessel wall remodelling, valvular reflux, and necrosis of skin capillaries [11, 12]. These changes result in the signs and symptoms of CVD.

The development of animal models of venous hypertension has increased our knowledge of CVD pathophysiology. However, the models developed to date have featured high blood flow, which does not accurately reflect clinical CVD, and have not allowed extended periods of observation. Recent experiments, using a more accurate and longer-lasting rodent model, have been performed to investigate microcirculation changes and inflammation that result from venous hypertension, and to assess how VADs influence these changes [8].

In one series of experiments, ligations of the right femoral vein, left and right branches of the right femoral vein and of the right iliac vein were used to study haemodynamic and microcirculatory changes over time in male hamsters [8]. Controls underwent the sham procedure, in which matching incisions were made without any vein ligation. Procedures were performed at week 0, with outcomes measured every 2 weeks.

Over 10 weeks, mean jugular and epigastric venous pressures were highly variable in animals with femoral vein ligations [8]. In contrast, animals with iliac vein ligations had relatively stable mean jugular venous pressure over time, while epigastric venous pressure increased steadily over time. The treatment of these animals with MPFF (100 mg/kg/day) was superior to diosmin alone (at the same dosage) and to hesperidin fraction (10 mg/kg/day) in preventing microcirculatory changes associated with the procedures. Vein diameter tended to increase over 6 weeks, relative to sham, in animals treated with vehicle (10% lactose solution). This increase was significantly attenuated by treatment with MPFF ($p < 0.01$), but not by diosmin alone or hesperidin fraction.

Functional capillary density (FCD) is a surrogate marker of tissue perfusion/oxygenation. FCD decreased significantly over 6 weeks in right iliac vein-ligated vehicle-treated animals, relative to sham. Although MPFF, diosmin (100 mg/kg/day) and hesperidin fraction (10 mg/kg/day) all prevented the reduction in FCD, the magnitude of the effect was greater for

MPFF than for either of the other treatments ($p < 0.001$) [8]. In the same study, leukocyte–endothelial interactions were investigated by measuring leukocyte sticking and rolling in the different treatment groups. The number of sticking and rolling leukocytes was significantly increased in vehicle-treated animals compared to sham-operated animals ($p < 0.001$). MPFF, diosmin and hesperidin fraction all attenuated this increase; however, MPFF was significantly more effective than the other treatments ($p < 0.001$), decreasing the sticking and rolling to almost the level observed in sham animals.

In a separate hamster model of ischaemia/reperfusion-induced capillary leakage, orally administered MPFF (30 mg/kg) was found to attenuate macromolecular permeability to a greater extent than any of its individual components (diosmin, hesperidin, linarin and iso-rohoifolin) given at the same dosage [13].

The findings of these two studies independently suggest that MPFF is likely to be more effective than its constituents in reversing the microcirculatory changes associated with CVD. Clinical studies are warranted to confirm these observations in human subjects.

The existence of microvalves and their potential role in the progression of CVD was first discussed by Vincent and co-workers in 2011 [12]. To better understand the mechanisms involved in the initiation of venous insufficiency at the microvalve level, and to explore whether early MPFF treatment can influence these processes, Bouskela and colleagues subsequently investigated microvascular changes in an experimental animal model of acute venous hypertension [9]. Venular diameter was only significantly elevated 2–4 h after common iliac vein ligation, gradually returning to baseline within 5 weeks. Leukocyte adhesion also increased significantly following ligation ($p < 0.0001$), though not as quickly; the peak occurred at around 3 days post-procedure, with subsequent normalisation over the following 2–3 weeks. These observations suggest that acute venous hypertension is associated with rapid activation of inflammatory processes at the microvalve level, and that compensatory blood-shunting mechanisms can reverse initial increases in venous pressure and inflammation.

However, previous research has shown that these compensatory mechanisms are not sustained, and thus may be overwhelmed, leading to valvular reflux and chronic inflammation of both small and large veins [8].

In a subsequent series of experiments, Bouskela and colleagues randomised 30 hamsters 1:1:1 to have iliac vein ligation plus MPFF (100 mg/kg), ligation plus vehicle (10% lactose solution), or sham ligation [9]. MPFF and vehicle were given daily for 7 days, beginning 2 days before ligation. At day 5 post-ligation, MPFF almost completely abolished the increase in the number of adherent leukocytes observed in vehicle-treated animals (mean \pm standard error of the mean: MPFF, 2.4 ± 0.24 leukocytes per 6 mm^2 ; vehicle, 13.7 ± 0.61 leukocytes per 6 mm^2 ; $p < 0.0001$; see Fig. 1, and Video 1 in the electronic supplementary material). At the same time point, median venular diameter was significantly smaller in MPFF-treated than in vehicle-treated animals ($p < 0.05$). These findings demonstrate that MPFF has anti-inflammatory and venotonic activity at the microvalvular level and suggest that it may have

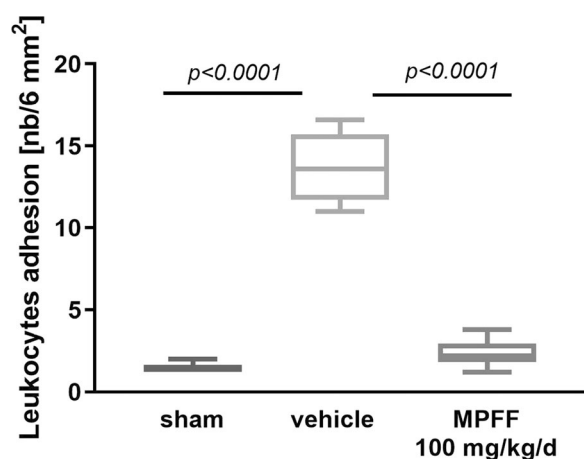


Fig. 1 MPFF treatment significantly attenuated leukocyte adhesion at day 5 post-ligation in a hamster model of venous hypertension, relative to vehicle (10% lactose solution) [9]. Ten hamsters each received either MPFF 100 mg/kg/day per os, vehicle or sham. Treatment was started 2 days before induction of venous hypertension. Comparisons versus vehicle group were post hoc. Horizontal lines indicate median and interquartile range; whiskers indicate minima and maxima. MPFF, micronised purified flavonoid fraction

the potential to slow the progression of venous disease in humans, although specific clinical data are required to confirm this.

MICROVALVULAR EFFECTS OF MPFF IN SYMPTOMATIC CVD

To better understand the features of early-stage CVD at the microcirculatory level, Lugli and colleagues performed haemodynamic studies of small veins in both symptomatic and asymptomatic Clinical-Etiological-Anatomical-Pathophysiological (CEAP) stage C_0 patients ($n = 18$ per group) [7]. Continuous wave Doppler ultrasonography, by means of a dedicated flat adhesive probe, was used to detect flow direction in reticular veins and identify patterns that might suggest microvalvular incompetence. Bidirectional blood flow, indicating the presence of reflux at the microvalvular level, was detected in both symptomatic and asymptomatic C_0 patients, but was significantly more frequent among symptomatic patients ($p = 0.05$).

Based on these findings, an open-label, single-arm pilot study was designed to investigate the haemodynamic effects of 6 months' treatment with MPFF (1000 mg/day) in 30 symptomatic patients at C_0 or C_1 CEAP stage [10]. To be included, patients had to have evidence of microvalvular reflux, but no evidence of reflux on duplex scans of higher-order veins of the saphenous system. MPFF treatment was associated with significant reductions over time in the number of microvalve sites where reflux was detected, from 60 (100%) at baseline to 31 (52%; $p < 0.001$) at 3 months, and 21 (35%; $p < 0.001$) after 6 months of treatment (Fig. 2). Additionally, mean scores for pain, leg heaviness and cramps (measured on a visual analogue scale [VAS]) decreased progressively at each time point, and were statistically significantly lower at 6 months versus baseline (Fig. 3; $p < 0.001$) [10]. Thus, in this study, MPFF treatment of symptomatic patients at C_0 or C_1 CEAP stage appeared to reduce microvalvular reflux and relieved symptoms, presumably owing to reductions in venular diameter and subsequent recovery of microvalvular

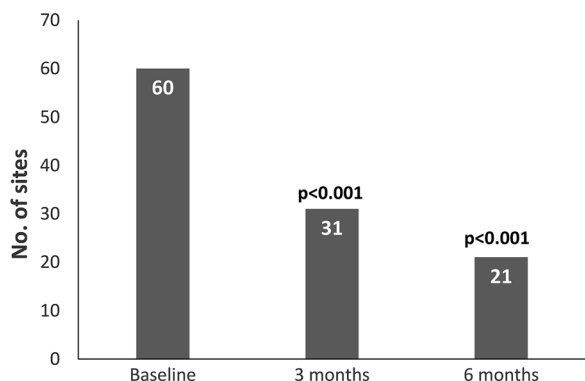


Fig. 2 Number of sites at which microvalvular reflux was detected in small veins of the lower extremities, using continuous wave Doppler ultrasonography, in 30 patients with symptomatic C₀ (9% of patients) or C₁ (81% of patients) CVD who received MPFF 1000 mg/day [10]. The proportion of sites with reflux was compared at each time point versus baseline using the Pearson’s chi-squared test. CVD, chronic venous disease; MPFF, micronised purified flavonoid fraction

competence. This evidence of the effect of MPFF treatment on microvalvular reflux is informative, but should be confirmed in a larger randomised controlled study.

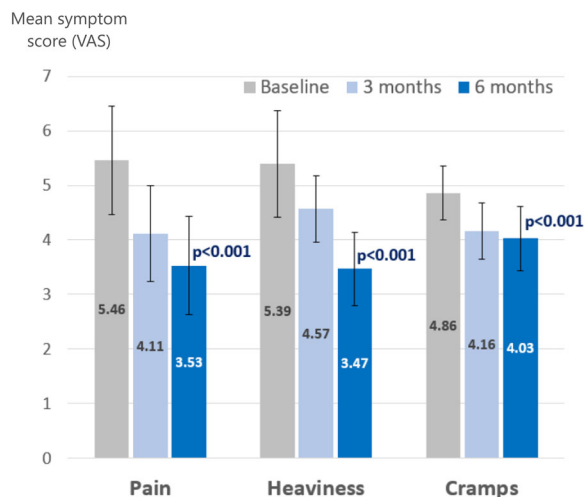


Fig. 3 Mean symptom scores over time in 30 patients with symptomatic C₀ (9% of patients) or C₁ (81% of patients) CVD who received MPFF 1000 mg/day [10]. Bars represent mean values and error bars standard deviation. Paired Student *t* tests were used to compare baseline and 6-month mean symptom scores. CVD, chronic venous disease; MPFF, micronised purified flavonoid fraction

The ability of MPFF to simultaneously inhibit leukocyte adhesion (protecting valves and vessel walls from damage) while improving venous tone (restoring valvular competence and reducing reflux) is likely to explain, at least in part, its clinical efficacy. Moreover, the observation of effects on microvalvular reflux in patients with early-stage CVD supports the hypothesis that longer-term treatment with MPFF (e.g. for 6 months) may delay disease progression.

RECENT CLINICAL STUDIES OF MPFF IN CVD

MPFF has been shown to improve symptoms and signs in all CEAP stages of CVD [5, 14]. A systematic review and meta-analysis was conducted to quantify the effects of MPFF, relative to placebo, on symptoms, oedema, skin changes and QoL in patients at all CEAP stages [15]. The meta-analysis included seven randomised, double-blind trials that were originally published between 1982 and 2015, had a duration of 1–4 months and enrolled a total of 1692 patients. Analysed as categorical variables, most venous symptoms were significantly reduced by MPFF compared with placebo, with risk ratios of 0.53 (95% confidence interval [CI], 0.38–0.73) for leg pain, 0.35 (95% CI 0.24–0.51) for heaviness, and 0.51 (95% CI 0.29–0.92) for cramps. A particularly important finding of this study was the very low ‘number needed to treat’ (NNT) to prevent one negative outcome: 4.2 for pain, 2.9 for heaviness, 3.1 for feeling of swelling, 4.8 for cramps, and 3.5 for paraesthesia. These low NNT values provide robust support for the use of MPFF in CVD regardless of CEAP class. Moreover, pharmacoeconomic analyses have demonstrated the cost-effectiveness of MPFF treatment in patients with venous leg ulcers (CEAP stage C₆) [16, 17], suggesting that MPFF provides robust clinical improvements at an affordable cost.

Cohort studies have demonstrated the haemodynamic and clinical benefits of MPFF, given at a dosage of 1000 mg/day for 2 or 3 months, across the spectrum of CVD disease [18–20]. In a study of 40 symptomatic women at

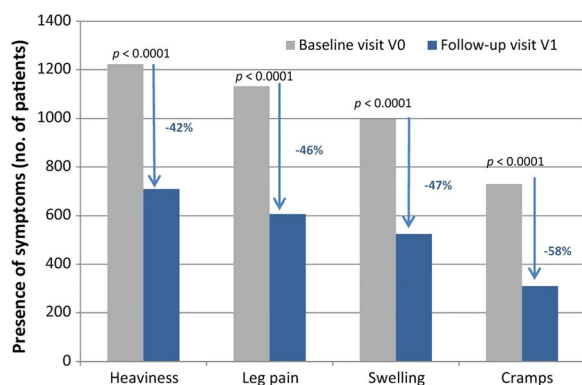


Fig. 4 Number of patients with CVD symptoms at baseline (V0) and at follow-up (V1) among those prescribed MPFF in the observational VEIN Act Program [24]. CVD, chronic venous disease; MPFF, micronised purified flavonoid fraction. Reprinted by permission from Springer Nature. Drugs and Therapy Perspectives, Management and evaluation of treatment adherence and effectiveness in chronic venous disorders: results of the international study VEIN Act Program. Bogachev V, Arribas JM, Baila S, Dominguez JU, Walter J, Maharaj D, et al. © 2019 Drugs & Therapy Perspectives

C₀ CEAP stage, reported by Tsukanov and colleagues, a 2-month treatment with MPFF 1000 mg/day normalised the diameter of the great saphenous vein and abolished afternoon reflux, decreasing the intensity of leg pain (measured using a VAS) and improving QoL (assessed using the Chronic Venous Insufficiency Quality of life Questionnaire [CIVIQ]-20) [18]. Subsequently, this research group investigated MPFF 1000 mg/day in 53 symptomatic women at C₁ CEAP stage who experienced transient evening reflux [19]. After 3 months of treatment, transient reflux had disappeared in 49 women (92.5%), and leg pain was reported by none of the 15 patients with this symptom at baseline. All patients had leg heaviness at baseline, compared with only six patients after 3 months [19]. The mean (95% CI) CIVIQ-20 score decreased significantly, from 42 (28–56) at baseline to 30 (15–22) at 3 months, indicating clinically meaningful improvement in QoL. In a larger cohort of 294 patients with symptomatic CVD, among whom 63.9% (*n* = 188) were C₂ CEAP stage, a 3-month MPFF treatment was

associated with marked reductions in evening reflux, night cramps, evening heaviness, pain, and mean CIVIQ-20 score [20].

The combination of MPFF with low-pressure (15–20 mmHg) compression stockings was studied recently in 112 patients with varicose veins and saphenofemoral junction (SFJ) reflux [21]. Mean (\pm standard deviation [SD]) SFJ diameter was significantly decreased, from 6.3 ± 2.9 mm at baseline to 5.7 ± 1.8 mm, after a mean of 5.3 months of treatment (*p* = 0.033). SFJ reflux was abolished in 55 of the 99 patients (55.6%) who completed the study, and the number of symptomatic patients decreased from 63 at baseline to 16 after treatment [21].

In the VEIN Act Prolonged (VAP)-C3 study [22], the effects of MPFF on oedema, symptoms and QoL (measured using CIVIQ-14) were investigated in a large observational cohort of C₃ CEAP stage patients (*n* = 708). Results were analysed according to whether or not patients also underwent surgery for CVD. After 4 weeks of treatment, MPFF was associated with statistically significant reductions in ankle volume and CIVIQ-14 score (indicating improved QoL), as well as in mean symptom scores (measured on a VAS) for leg heaviness, pain, and swelling. In patients receiving MPFF, although surgery was not associated with additional reductions in ankle volume, it was associated with additional improvements in QoL [22].

The effects of VAD therapy on ankle oedema were also studied in a meta-analysis of 10 randomised placebo- or active-controlled trials (total *n* = 1010) in which changes in ankle circumference were measured [23]. Among the VADs included in the analysis, the mean \pm SD reduction in ankle circumference was significantly greater with MPFF (0.80 ± 0.53 cm) than with hydroxyethylrutoside (0.58 ± 0.31 cm), *Ruscus* extracts (0.58 ± 0.47 cm) or diosmin (0.20 ± 0.5 cm) [*p* < 0.0001 for all comparisons between MPFF and other VADs].

Many clinical trials and real-world studies evaluating CVD treatments have focused on patients at specific CEAP stages. However, the VEIN Act Program, a large, international observational study, enrolled patients across a wide spectrum of CVD, from C₀-C₆ stages, with data analysed according to stage at baseline [24].

Table 1 Level of evidence from randomised placebo controlled trials and meta-analyses that merits grade A (strong) or grade B (weak) recommendations based on magnitude of effects on individual symptoms or signs, versus side effects, for the main venoactive drugs as published in 2018 international guidelines [4, 14]

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

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AA ascorbic acid, HMC hesperidine methyl chalcone, HSCE horse chestnut seed extract, MPFF micronised purified flavonoid fraction, NNT number needed to treat to benefit one patient, NS not significant, QoL quality of life, SMD standardised mean difference

Patients presenting with lower leg pain, and/or other symptoms consistent with a diagnosis of CVD, were entered into the study, and received conservative treatment, including VADs, compression therapy and lifestyle modification, accordance with the physician's usual practice. Of the 7397 patients in the analysis set, most ($n = 4806$) had stage C₃ or higher CVD [24]. Almost all patients (92.5%) were prescribed MPFF, and the majority (67.6%) were prescribed compression therapy. MPFF treatment was associated with significant reductions (of 42% to 58%, depending on symptom) in the number of patients with leg heaviness, leg pain, swelling and cramps at the follow-up visit (Fig. 4). In addition, adherence was higher with MPFF than with compression therapy: 87.8% of those prescribed MPFF had taken it as directed, whereas 29.1% of patients prescribed compression therapy had fully complied with instructions. Overall, persistence with MPFF was 65.9%; in comparison, persistence with compression was lower and declined with age, from 34.5% in patients aged 18–34 years to 27.0% in patients aged over 65 years. Non-persistence with compression therapy was frequently related to discomfort, difficulty of use and concerns about appearance.

Overall, the evidence base that supports the clinical use of MPFF in CVD is both more comprehensive (i.e. demonstrating benefits in a wider range of signs and symptoms) and more robust than the evidence for other VADs such as *Ruscus* and oxerutins [4]. Additionally, MPFF has been shown to significantly improve QoL. Consequently, the most recent guidelines on the use of VADs strongly endorse MPFF for the treatment of most signs and symptoms of CVD (Table 1).

CONCLUSIONS

MPFF has a number of well-established mechanisms of action that make it an effective treatment for various symptoms associated with all stages of CVD; as a result it is strongly recommended by international guidelines on VAD treatment [4]. Recent evidence has shown that its beneficial effects may be mediated, at least in

part, via inhibition of leukocyte adhesion, improvements in venous tone and valvular competence, and reductions in reflux. These findings suggest that, in addition to alleviating symptoms and improving QoL, MPFF could potentially slow CVD progression. In the future, studies assessing early initiation of, and long-term treatment with, MPFF to prevent CVD, delay downstream events (e.g. venous leg ulceration and surgery) and/or improve socioeconomic outcomes (e.g. employment, productivity, social functioning and QoL) will generate valuable new insights.

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Compliance with Ethics Guidelines. 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.

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

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