

# Micronized purified flavonoid fraction-based conservative treatment of chronic venous disease in a real-world setting

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**Aims:** To investigate the effectiveness and tolerability of adjunctive micronized purified flavonoid fraction (MPFF) in patients with chronic venous disease (CVD). **Patients & methods:** This observational study included adults ( $\geq 18$  years) with clinical–etiology–anatomy–pathophysiology (CEAP) class C4 CVD for whom MPFF was indicated. Outcomes included changes in subcutaneous adipose thickness, venous clinical severity score, CVD symptoms (using a visual analogue scale) and tolerability. **Results:** Of 381 patients, 365 completed the study. After 6 months, subcutaneous adipose tissue thickness, venous clinical severity score and visual analogue scale scores significantly improved (all  $p < 0.001$  vs baseline). No adverse drug reactions occurred. **Conclusion:** Adjunctive MPFF treatment improves skin and subcutaneous tissue conditions in CVD patients.

**Clinical Trial Registration:** NCT04138576 (ClinicalTrials.gov)

**Plain language summary:** Chronic venous disease (CVD) can cause a range of signs and symptoms that reduce patient quality of life. Micronized purified flavonoid fraction (MPFF) is a type of venoactive drug that is recommended in patients with early and advanced CVD. This study investigated the effectiveness and safety of MPFF when added to conservative treatment in patients with advanced CVD with long-term follow-up. After 6 months of MPFF, we observed significant improvements in the skin and subcutaneous tissue, symptoms and patient quality of life; no adverse drug reactions were reported. Therefore, MPFF-based conservative treatment can effectively and safely treat CVD.

**Tweetable abstract:** Micronized-purified-flavonoid-fraction-based conservative treatment reduced chronic venous disease symptoms and improved quality of life in patients with advanced-stage chronic venous disease.

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**Keywords:** chronic venous disease • conservative treatment • flavonoid • micronized purified flavonoid fraction • real-world study • venoactive drugs

Chronic venous disease (CVD) is a condition of the venous system characterized by a spectrum of morphologic and functional abnormalities, including endothelial activation, leukocyte adhesion, deterioration of the vein walls, increased capillary permeability and reticulocyte infiltration, all of which progressively worsen over time [1–3]. These abnormalities can lead to a range of signs and symptoms that primarily affect the legs, including heaviness, tiredness, telangiectasia, varicose veins, edema, itching, pain, nocturnal cramps, venous eczema, ankle skin hyperpigmentation, atrophie blanche, lipodermatosclerosis and venous ulcers [1,4–6].

The clinical–etiology–anatomy–pathophysiology (CEAP) classification is the most commonly used system to describe the severity of CVD, and ranges from early-stage symptomatic disease (class C0s–C1), to more advanced disease with varicose veins (class C2), chronic edema (class C3), skin and subcutaneous tissue changes (class C4) and to the most severe stages, involving venous leg ulcers (class C5–C6) [7]. CEAP class C4 CVD is characterized by changes to the skin and subcutaneous tissue of the affected limbs [7]. CVD is associated with a reduced quality of life



(QoL) and a substantial economic burden [8–10], which worsens with more advanced disease stages. Furthermore, the high clinical burden of CVD was emphasized in a recent epidemiological study in 12,423 CVD patients (mean follow-up of  $6.4 \pm 1.6$  years) [11]. This study was the first to demonstrate that CVD is associated with an increased risk of cardiovascular diseases and all-cause mortality. This association was reported at each stage of CVD and the risk increased proportionally with higher CEAP classes [11].

The aim of treatment for CVD is to relieve symptoms, reduce visible signs, prevent progression to greater severity and improve patient QoL. Conservative treatments, such as lifestyle modifications (exercise, avoiding long periods of standing or sitting, bodyweight loss and leg elevation), venoactive drugs, compressive leg garments, and wound and skin care are recommended as first-line treatments [12–14]. Interventional therapies can be considered depending on the severity of the disease (i.e., superficial venous incompetence or deep venous pathology) and may include minimally invasive procedures, such as sclerotherapy or endovenous ablation, for telangiectasia and varicose veins *in situ*, as well as surgery in some cases [13,14].

Micronized purified flavonoid fraction (MPFF) is a venoactive agent for oral use consisting of 90% micronized diosmin and 10% other active flavonoids (hesperidin, diosmetin, linarin and isorhoifolin), which all contribute to its pharmacological effects [15,16]. MPFF is an extensively studied venoactive drug with proven anti-inflammatory properties that increases capillary resistance and integrity and reduces endothelial cell activation and leukocyte adhesion [6]. The efficacy of MPFF has been evaluated in several studies of patients with trophic skin disorders, including patients with CEAP class C4 CVD [17–24]. In these studies, MPFF provided rapid reduction in the vein-specific signs and symptoms of CVD (i.e., pain, feeling of heaviness, burning, edema and skin changes), improved venous tone and QoL, and promoted ulcer healing [17–24]. For example, in two studies [17,18], MPFF was associated with significant skin changes compared with placebo, with a risk ratio of 0.18 (95% CI: 0.07–0.46) and a number-needed-to-treat of 1.6 (95% CI: 1.2–2.2) [24]. International guidelines from the European Society for Vascular Surgery (2022) [14], the European Venous Forum/International Union of Angiology/Cardiovascular Disease Educational and Research Trust/Union Internationale de Phlébologie (2018) [5], and the Society for Vascular Surgery and the American Venous Forum (2011) [25] strongly recommend the use of MPFF to reduce the symptoms and signs of CVD and for the healing of venous ulcers as an adjunct to compression therapy. However, studies focusing particularly on the use of MPFF-based conservative treatment specifically in patients with CEAP class C4 disease are scarce.

In this prospective, observational study, we hypothesize that MPFF-based conservative treatment improves symptoms – and, therefore, QoL – effectively and safely in patients with CEAP class C4 CVD in a real-world clinical setting.

## Materials & methods

### Study design

This prospective, observational study (ClinicalTrials.gov identifier, NCT04138576) was conducted in Russia between December 2019 and September 2020. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964 and its later amendments, and the study protocol and subsequent amendments were approved by the Interuniversity Ethics Committee. Written informed consent was collected from all participants before initiating the trial.

### Eligibility criteria

The study enrolled adults ( $\geq 18$  years old) with CVD of CEAP class C4 (a or b) severity whose physicians recommended the initiation of MPFF (1000 mg/day) in addition to conservative treatment according to routine clinical practice, and for whom surgical intervention for their CVD was not currently planned. Patients were excluded from the study if they had CVD that met CEAP class C0–C3 or class C5–C6 criteria only, or if they had arterial disease (ankle–brachial index  $< 0.9$ ), including peripheral arterial disease, lymphatic edema of the lower extremities, secondary varicose veins, angiodyplasia or neoplasia, or an infection in the 6 weeks prior to the screening visit; patients treated with venoactive drugs during the 4 weeks prior to study initiation were also excluded.

### Study procedures

After enrolment, each patient attended three study visits at 2 weeks (visit 1), 3 months (visit 2) and 6 months (visit 3) after study inclusion. All visits were initially conducted in person; however, due to the coronavirus disease 2019



(COVID-19) pandemic, the study protocol was amended so that visit 2 was replaced by a phone call for some patients.

### Outcome measures

The primary outcome of this study was the effectiveness of MPFF use as part of conservative treatment in routine clinical practice. This was assessed by measuring changes in subcutaneous adipose thickness (assessed by ultrasound), changes in overall venous clinical severity score (VCSS) and its components [26] as well as CEAP class, and evolution of symptoms characteristic of CEAP class C4 disease (i.e., skin tightening, burning, skin itching, pain and exudation) using a traditional 10-cm visual analogue scale (VAS). The 10-cm VAS measured the distance between “no symptom” (0 cm) and “the worst symptom imaginable” (10 cm) for each symptom [27].

Secondary outcomes included changes in QoL, assessed using the Chronic Venous Insufficiency Quality of Life questionnaire (CIVIQ-14) [28,29] and tolerability, assessed by monitoring adverse drugs reactions (ADRs) (defined as a response that was noxious and unintended), over the 6-month study period. Skin changes were assessed by curvimetry (measurement of affected skin area) and durometry (measurement of skin density) at selected centers where these techniques were used routinely. A curvimeter is a device used in cartography to measure the length of a curved line. In our study, we measured the length of the border of the zone of the trophic disorder, which is directly proportional to the area of trophic disorder in the skin. That is, a decrease in the length of the border indicated a decrease in the area of trophic skin disorder. A durometer is an instrument used in the production of soft coatings and rubber to measure the hardness of a product. In our study, we measured the hardness (elasticity) of the skin in the area of impaired trophism. A decrease in skin hardness indicated a decrease in trophic disorders. Both curvimetry and durometry were conducted while the patient was lying down at approximately the same time of the day, and measurements were repeated at least three-times for curvimetry or at least five-times for durometry. Repeated measurements were also taken by the investigator during the study visits for patients who were unable to visit the clinic due to the COVID-19 pandemic.

### Statistical analysis

Baseline characteristics, effectiveness and tolerability were summarized using descriptive statistics. Continuous data were summarized for each treatment group using mean and standard deviation (SD), while categorical data were summarized using the number and percentage of patients. Multiple comparisons included adjustments for continuity. Changes in the quantitative parameters during the follow-up period were evaluated using the two-sided Student's *t*-test for paired samples or the Wilcoxon test. *P*-values <0.05 were considered statistically significant. Potential sources of bias were addressed through a focus on private healthcare clinics where dropout rates were expected to be lower and the evaluation tools to assess skin diseases would be more modern and objective (e.g., curvimetry and durometry).

Data analysis was performed using the SPSS 12.0 software package (SPSS Inc., USA).

## Results

### Patient characteristics

Of the 381 patients enrolled by 77 phlebologists, located mainly in specialist centers but also hospitals, four doctors and their patients (*n* = 16) were withdrawn from the study due to the effects of the COVID-19 pandemic on physicians' availability. As such, 365 patients completed the study and were included in the effectiveness and safety analysis populations.

Patient baseline characteristics are summarized in Table 1. The study population comprised 239 women and 126 men with a mean  $\pm$  SD age of  $56.7 \pm 11.2$  years; just over one-quarter of patients were  $\geq 65$  years old. Mean  $\pm$  SD BMI was  $28.2 \pm 4.1$  kg/m<sup>2</sup>; 49.0% of patients were overweight and 31.0% were obese. The majority of patients (61%) had a family history of CVD, with 12% of patients having leg vein thrombosis prior to study inclusion.

### Treatment

Of 365 patients included in the analysis, 362 (99.2%) were prescribed MPFF at the baseline visit. The proportions of patients at each subsequent study visit who received MPFF treatment were 98.6% (*n* = 360) at visit 1 (at 2 weeks), 77.0% (*n* = 281) at visit 2 (at 3 months) and 67.7% (*n* = 247) at visit 3 (at 6 months) (Table 2). Compression therapy (with below-the-knee CCL 2 RAL standard compression stockings) was recommended for 351 patients (96.2%) at study inclusion, with 349 (95.6%), 336 (92.1%) and 335 (91.8%) patients receiving



Table 1. Baseline characteristics.

Characteristic	n = 365
Age (years), mean $\pm$ SD	56.7 $\pm$ 11.2
$\geq 65$ years, n (%)	95 (26.0)
Male, n (%)	126 (34.5)
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	28.2 $\pm$ 4.1
Weight category, <sup>†</sup> n (%)	
Underweight (<18.5 kg/m <sup>2</sup> )	3 (0.8)
Normal (18.5–24.9 kg/m <sup>2</sup> )	70 (19.2)
Overweight (25.0–29.9 kg/m <sup>2</sup> )	179 (49.0)
Obese ( $>30.2$ kg/m <sup>2</sup> )	113 (31.0)
Family history of CVD, n (%)	221 (60.6)
Thrombosis of leg veins, n (%)	42 (11.5)
Ultrasonography findings, n (%)	
Superficial vein reflux	221 (60.5)
Perforating vein reflux	87 (23.8)
Deep vein reflux	21 (5.8)
Prior treatment for CVD of lower extremities, n (%)	247 (67.7)
VAD	228 (62.5)
Compression therapy	186 (51.0)
Liquid sclerotherapy	35 (9.6)
Foam sclerotherapy	16 (4.4)
Open surgery	53 (14.5)
Endovenous procedure	16 (4.4)
Other	46 (12.6)

<sup>†</sup>BMI ranges are based on data provided by the WHO (<https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi>).  
CVD: Chronic venous disease; SD: Standard deviation; VAD: Venoactive drug.

Table 2. Treatments received during the study.

	Week 2	Month 3	Month 6
MPFF, n (%)	360 (98.6)	281 (77.0)	247 (67.7)
Compression therapy, n (%)	349 (95.6)	336 (92.1)	335 (91.8)
Duration of compression therapy (weeks), mean $\pm$ SD	11.4 $\pm$ 10.5	12.0 $\pm$ 7.3	15.4 $\pm$ 9.5
	At any time during treatment		
Topical treatment, n (%):			
Corticosteroids	72 (19.7)		
NSAIDs	63 (17.3)		
Heparins	91 (24.9)		
Emollients	87 (23.8)		
Antibiotics	19 (5.2)		
Other	27 (7.4)		

MPFF: Micronized purified flavonoid fraction; SD: Standard deviation.

compression therapy at visits 1, 2 and 3, respectively. A total of 13 patients treated with MPFF did not receive compression therapy. During the study, patients also received one or more topical treatments, including heparins (n = 91; 24.9%), emollients (n = 87; 23.8%), corticosteroids (n = 72; 19.7%), non-steroidal anti-inflammatory drugs (n = 63; 17.3%), antibiotics (n = 19; 5.2%) or others (n = 27; 7.4%; Table 2).

The majority of patients included in the study were candidates for surgery; however, in these cases conservative treatment was administered in order to improve the condition of the skin of the lower leg and improve the QoL of these patients while waiting for surgical intervention, which, in some cases, had been delayed or suspended due to COVID-19.



**Table 3. Changes in efficacy outcomes and quality of life with adjunctive micronized purified flavonoid fraction treatment after 6 months (n = 365).**

	Baseline	Month 6	$\Delta^{\dagger}$	p-value vs baseline
Subcutaneous adipose tissue thickness (mm)	12.4 $\pm$ 8.4	9.9 $\pm$ 7.1	-2.5 $\pm$ 4.5	< 0.001
VCSS component scores				
Pain	1.52 $\pm$ 0.65	0.78 $\pm$ 0.58	-0.74 $\pm$ 0.69	< 0.001
Varicose veins	1.78 $\pm$ 0.77	1.38 $\pm$ 0.90	-0.40 $\pm$ 0.76	< 0.001
Venous edema	1.40 $\pm$ 0.70	0.64 $\pm$ 0.65	-0.76 $\pm$ 0.75	< 0.001
Hyperpigmentation	1.43 $\pm$ 0.72	0.94 $\pm$ 0.72	-0.49 $\pm$ 0.74	< 0.001
Inflammation	0.56 $\pm$ 0.75	0.10 $\pm$ 0.35	-0.46 $\pm$ 0.75	< 0.001
Induration of skin and subcutaneous tissue	0.95 $\pm$ 0.87	0.59 $\pm$ 0.73	-0.36 $\pm$ 0.72	< 0.001
Compression therapy	0.78 $\pm$ 0.58	1.29 $\pm$ 1.11	0.48 $\pm$ 1.09	< 0.001
Total VCSS	8.67 $\pm$ 3.12	5.81 $\pm$ 3.07	-2.97 $\pm$ 3.26	< 0.001
Intensity of CVD symptoms by VAS				
Skin tightening	3.52 $\pm$ 2.73	0.89 $\pm$ 1.36	-2.63 $\pm$ 2.41	< 0.001
Burning	3.10 $\pm$ 2.67	0.70 $\pm$ 1.34	-2.40 $\pm$ 2.44	< 0.001
Skin itching	3.27 $\pm$ 2.69	0.61 $\pm$ 1.23	-2.66 $\pm$ 2.42	< 0.001
Pain	3.89 $\pm$ 2.58	0.99 $\pm$ 1.34	-2.90 $\pm$ 2.33	< 0.001
Exudation	0.55 $\pm$ 1.54	0.07 $\pm$ 0.47	-0.48 $\pm$ 1.45	< 0.001
Lesion area (cm) <sup>‡</sup>	30.3 $\pm$ 19.7	23.4 $\pm$ 17.7	-6.9 $\pm$ 13.4	< 0.001
Skin density (units) <sup>§</sup>	15.8 $\pm$ 12.1	12.5 $\pm$ 8.1	-3.9 $\pm$ 9.3	0.002
CIVIQ-14 dimension scores (%)				
Pain	46.5 $\pm$ 19.7	20.2 $\pm$ 14.4	-26.4 $\pm$ 18.7	< 0.001
Physical	42.7 $\pm$ 24.7	21.2 $\pm$ 18.1	-21.5 $\pm$ 18.7	< 0.001
Psychological	37.7 $\pm$ 23.7	18.4 $\pm$ 16.0	-19.3 $\pm$ 18.8	< 0.001
CIVIQ-14 GIS score (%)	42.3 $\pm$ 20.5	19.9 $\pm$ 14.2	-22.4 $\pm$ 16.5	< 0.001

Values are presented as mean  $\pm$  standard deviation.

<sup>†</sup> $\Delta$  = change from baseline at month 6.

<sup>‡</sup>Measured by curvometry at centers where this technique was used routinely (n = 60).

<sup>§</sup>Measured by durometry at centers where this technique was used routinely (n = 55).

CIVIQ-14: Chronic Venous Insufficiency Quality of Life questionnaire; CVD: Chronic venous disease; GIS: Global index score; VAS: Visual analogue scale; VCSS: Venous clinical severity score.

## Effectiveness

After 6 months of MPFF-based conservative treatment, subcutaneous adipose tissue thickness was significantly improved from baseline ( $p < 0.001$ ; Table 3). Significant improvements in total VCSS were also seen after 6 months of treatment with MPFF ( $p < 0.001$ ; Table 3). This improvement in total VCSS was driven by significant reductions in the individual component scores for pain, varicose veins, venous edema, hyperpigmentation, inflammation and induration of skin and subcutaneous tissue (all  $p < 0.001$  vs baseline).

CVD symptom intensity measured by VAS scores in symptomatic patients was significantly improved with MPFF-based treatment at 6 months versus baseline for all measured components (skin tightening, burning, itching, pain and exudation: all  $p < 0.001$  vs baseline; Table 3).

After 6 months of treatment, significant reductions from baseline were seen in lesion area ( $p < 0.001$ ) and skin density ( $p = 0.002$ ; Table 3), as measured by curvometry and durometry, respectively. QoL was also significantly improved, with a mean  $\pm$  SD reduction in the CIVIQ-14 global index score of  $-22.4 \pm 16.5\%$  from baseline to 6 months ( $p < 0.001$ ; Table 3).

## Safety

No ADRs were reported with adjunctive MPFF treatment over the 6-month study period.

## Discussion

This observational, prospective study showed that conservative treatment based on MFPP was associated with a significant improvement in the condition of the skin and subcutaneous tissue in patients with CEAP class C4 CVD and was well tolerated. After 6 months, there was a significant reduction in the objective measures of subcutaneous



adipose tissue thickness, lesion area and skin density, and improved subjective measures of the disease, such as total VCSS and its individual components, ratings of symptom intensity (including skin tightening, burning, itching, pain and exudation) and QoL scores. No ADRs were reported during the treatment period.

This is the first study to use the objective measures of ultrasound, curvimetry and durometry to assess the effectiveness of MPFF-based treatment on the skin and subcutaneous tissue symptoms in patients with CEAP class C4 CVD. The results of this study are also consistent with those of previous studies that demonstrate the efficacy of MPFF with regard to improving the signs and symptoms of CVD [20–22]. A randomized placebo-controlled study of 1137 patients with CEAP class C3 or C4 CVD showed significantly greater reductions in leg pain/heaviness and improvements in QoL with once-daily MPFF treatment over 4 months compared with placebo [20]. In a randomized study of 174 patients with CEAP class C0–C4 disease, once-daily MPFF 500 mg or 1000 mg for 8 weeks significantly improved VAS-reported leg pain compared with baseline and was well tolerated [21]. Likewise, a larger randomized study of 1076 patients with CEAP class C0–C4 disease found that MPFF 500 mg or 1000 mg once daily for 8 weeks significantly reduced the symptoms of lower limb discomfort, leg pain and leg heaviness, and improved QoL [22]. The efficacy and safety of MPFF for the treatment of the signs and symptoms of CVD were also supported by a meta-analysis of seven randomized clinical trials of 1692 patients [24], which indicated that MPFF substantially and significantly reduced pain, heaviness, feeling of swelling, cramps and functional discomfort, and improved QoL and objective signs of edema and leg redness compared with placebo. In addition, observational real-world studies have demonstrated improvements in CVD symptoms and QoL with MPFF 1000 mg once daily or 500 mg twice daily [30,31], although these studies did not include patients with CEAP class C4 disease.

No new safety concerns with MPFF were identified in this study. MPFF is generally well tolerated [32]; the most common adverse events reported with MPFF in clinical trials are gastrointestinal in nature [21,22,33], and the rates of these do not differ from those reported with placebo [34,35]. The long-term safety of MPFF was demonstrated in the RELIEF study, which enrolled 5052 patients from 23 countries with grade C0–C4 CVD who received MPFF for 6 months [36,37].

The results of this real-life study are in line with international guidelines, which strongly recommend MPFF treatment [5,14,25], particularly for reduction in pain, heaviness, and feeling of swelling and discomfort, and improvement of skin changes and QoL [5]. Moreover, a recent epidemiological study found a clear association between CVD and an increased risk of cardiovascular disease and all-cause mortality [11], highlighting the significant health burden of CVD beyond cosmetic issues and the importance of ensuring effective management of patients. However, it is important to note that, to our knowledge, there are no data on what happens to this increased risk of cardiovascular disease with MPFF treatment. Further research is warranted.

### Limitations

This study has some limitations, which include the biases that are typically associated with observational study designs and the absence of a control arm. Therefore, these effectiveness and safety data may be affected by confounding factors, such as the inability to objectively evaluate adherence to treatment and the potential for incomplete data reporting. In particular, as patients were selected for this study based on having C4 disease (i.e., were enrolled based on one part [the clinical “C” class] of the 4-part CEAP classification system), there was no requirement in the objectives of the study to collect the E, A and P classification details of the patients enrolled, so this information is not available. These other classifications may influence the results of the study (for example, patients with deep venous obstruction [class Ad; Po] are clinically very different from patients with superficial reflux [class As; Pr], and patients with primary disease [class Ep] are different from those with secondary diseases [class Es]) and, therefore, must be taken into consideration when interpreting the results. Moreover, as patients received MPFF as an adjunct to other conservative therapy, including compression therapy or topical treatments, it is not possible to assess the effect of each treatment independently. In addition, this analysis was conducted in a population of Russian individuals, so the data may not be generalizable to individuals of other ethnicities with CVD or those who live in other countries with different clinical practices. In particular, in Russian clinical practice, phlebotropic drugs are used in various forms and stages of CVD, and MPFF is the most popular phlebotropic drug. Furthermore, sample bias may exist, as we were unable to determine whether management practices at participating sites reflected those practiced at a national level. Finally, during the time this study was conducted, an update to the applicability of these results in clinical practice may be limited. Although further studies with a controlled design and a larger sample size are required to determine the



treatment efficacy, these results may have implications for the treatment of a wide range of patients with CVD in clinical practice.

## Conclusion

In conclusion, this study showed that conservative treatment based on MPFF improves the symptoms, QoL, and condition of the skin and subcutaneous tissue in patients with CEAP class C4 CVD. These results suggest that this treatment approach can be effectively and safely implemented to treat patients with CVD in routine clinical practice.

### Summary points

- Chronic venous disease (CVD) is a condition of the venous system that reduces quality of life and is associated with an increased risk of cardiovascular disease and mortality.
- International guidelines recommend the use of micronized purified flavonoid fraction (MPFF) to reduce the symptoms and signs of CVD.
- There are limited studies on the use of MPFF-based conservative treatment specifically in patients with class C4 CVD.
- The aim of this real-world, prospective, observational study was to investigate the effectiveness, safety and tolerability of MPFF-based conservative treatment in patients with class C4 CVD.
- The study enrolled 381 patients with class C4 CVD for whom initiation of MPFF was indicated; of these, 365 completed the study and were included in the analysis.
- After 6 months of MPFF-based treatment, patients experienced significantly improved skin and subcutaneous tissue condition compared with baseline.
- The treatment also provided significant reductions from baseline in skin lesion area and skin density, and QoL was significantly improved.
- No adverse drug reactions were reported during MPFF treatment.
- In conclusion, MPFF-based conservative treatment improved symptoms, quality of life, and the condition of the skin and subcutaneous tissue in patients with class C4 CVD.

### Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by V Bogachev and P Turkin. All authors read and approved the final manuscript.

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## Ethical conduct of research

The authors state that the study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 and its later amendments, and the study protocol and subsequent amendments were approved by the Interuniversity Ethics Committee. Written informed consent was collected from all participants before initiating the trial.

## Data sharing statement

The authors acknowledge that this manuscript presents original data from clinical trials. Raw Clinical Report Form data may be made available upon reasonable request via email [vadim.bogachev63@gmail.com](mailto:vadim.bogachev63@gmail.com) at any time required. The study protocol is available at Clinical Trial.gov NCT04138576.

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