

## REVIEW ARTICLE

# Efficacy of micronized purified flavonoid fraction (Daflon®) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials

Stavros K. KAKKOS<sup>1</sup>\*, Andrew N. NICOLAIDES<sup>2,3</sup>

<sup>1</sup>Department of Vascular Surgery, University Hospital of Patras, Greece; <sup>2</sup>Imperial College London, London, UK; <sup>3</sup>University of Nicosia Medical School, Nicosia, Cyprus

\*Corresponding author: Stavros K. Kakkos, Department of Vascular Surgery, University Hospital of Patras, Patras, 26504, Greece. E-mail: [kakkos@upatras.gr](mailto:kakkos@upatras.gr)

## ABSTRACT

**INTRODUCTION:** The use of a venoactive drug is considered an important component of medical treatment of chronic venous disease (CVD), although the efficacy of certain venoactive drugs (VADs) on one or more individual leg symptoms or signs may have not been extensively studied to justify a strong recommendation in guidelines on CVD. The aim of this systematic review and meta-analysis was to study the effectiveness of the micronized purified flavonoid fraction (MPFF, Daflon®) across the spectrum of defined venous symptoms, signs, quality of life (QoL) and treatment assessment by the physician.

**EVIDENCE ACQUISITION:** On September 9, 2017, a systematic review of the databases MEDLINE, Scopus and Cochrane Central was performed, supplemented by hand searching, to identify randomized double-blind placebo-controlled trials on MPFF in patients with CVD.

**EVIDENCE SYNTHESIS:** The main outcome measures were the individual and global symptoms, leg edema and redness, skin changes, QoL and evaluation of the overall effectiveness of the treatment by the physician. The effectiveness of MPFF compared with placebo was expressed as risk ratio (RR) or standardized mean difference (SMD) with 95% confidence interval (CI). Trial quality of evidence was graded using the GRADE system.

**RESULTS:** We identified 7 trials, mostly with low risk of bias, involving 1,692 patients. On qualitative analysis, MPFF significantly improved nine defined leg symptoms, including pain, heaviness, feeling of swelling, cramps, paresthesia, burning sensation, and pruritus (itching), but also functional discomfort compared with placebo, leg redness, skin changes and QoL. On quantitative analysis, MPFF compared with placebo, assessed as a categorical variable, reduced leg pain (RR 0.53, P=0.0001, NNT=4.2), heaviness (RR 0.35, P<0.00001, NNT=2.0), feeling of swelling (RR 0.39, P<0.00001, NNT=3.1), cramps (RR 0.51, P=0.02, NNT=4.8), paresthesia (RR 0.45, P=0.03, NNT=3.5), and functional discomfort (RR 0.41, P=0.0004, NNT=3.0). Similarly, MPFF compared with placebo, assessed as a continuous variable reduced pain (SMD -0.25, 95% CI -0.38 to -0.11), heaviness (SMD -0.80, 95% CI -1.05 to -0.54), feeling of swelling (SMD -0.99, 95% CI -1.25 to -0.73), burning sensation (SMD -0.46, 95% CI -0.78 to -0.14), cramps (SMD -0.46, 95% CI -0.78 to -0.14), and functional discomfort (SMD -0.87, 95% CI -1.13 to -0.61). Regarding objective assessments of leg edema, the use of MPFF compared with placebo reduced ankle circumference (SMD -0.59, 95% CI -1.15 to -0.02), and leg redness (SMD -0.32, 95% CI -0.56 to -0.07, RR 0.50, P=0.03, NNT=3.6), improved skin changes (RR 0.18, P=0.0003, NNT=1.6) and quality of life (SMD -0.21, 95% CI -0.37 to -0.04) and was associated with clinical improvement as assessed by the physician (RR 0.28, P<0.00001, NNT=2.5). Heterogeneity was mostly minimal. The existing evidence where sufficient was mostly of high quality.

**CONCLUSIONS:** Based on high quality evidence, MPFF is highly effective in improving leg symptoms, edema and quality of life in patients with CVD.

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**Key words:** Vascular diseases - Sign and symptoms - Quality of life - Flavonoids.

## Introduction

Venoactive drugs (VADs) are considered an important component of the medical (conservative) treatment of chronic venous disorders (CVDs), not only as a stand-alone modality when compression is contraindicated in patients with peripheral arterial disease or not tolerated because of patient pruritus or high ambient temperature, but also in combination with compression,<sup>1,2</sup> across the entire spectrum of disease severity, CEAP clinical class C0s through C6. Often tested for their efficacy on global symptoms or pain alone, VADs are effective in improving patient symptoms and objectively estimated edema of CVDs. However, the efficacy of individual VADs on one or more symptoms, signs such as skin changes or quality of life (QoL) may have not been studied in detail to confirm a high level of evidence or to justify a high grade of recommendation in guidelines of CVD. At present only pain and swelling have been proposed as an indication to use a VAD in one of them.<sup>2</sup>

The SYM Vein Consensus statement, recently developed under the auspices of the European Venous Forum, emphasized the importance of symptoms in venous disorders and provided a review on the description and definition, pathophysiology, scoring, clinical examination and investigations indicated with respect of venous symptoms.<sup>3</sup>

MPFF is an established VAD, and its marketed formulation (Daflon<sup>®</sup> and other trade names) is a flavonoid-based venoactive drug containing 90% of micronized diosmin and 10% of other active flavonoids (diosmetin, hesperidin, linarin and isorhoifolin) expressed as hesperidin. It has a proven record of effectiveness in improving leg symptoms in patients with CVD and venous edema.

However, the original trials might have been underpowered for some efficacy measures or individual symptoms, which formed the rationale of the present investigation. Therefore, the aim of the present systematic review and meta-analysis was to further study the effectiveness of MPFF across the spectrum of different venous symptoms, signs and QoL.

## Evidence acquisition

### Search method

On September 9<sup>th</sup>, 2017, we conducted an up-to-date literature search of three electronic databases (Medline,

Scopus and Cochrane Central), which was updated on December 14<sup>th</sup>, 2017, using the following key-words: Daflon or MPFF or diosmin with no language restrictions. Studies in patients with venous ulcers were excluded to avoid confounding due to compression treatment. The aim was to identify placebo-controlled double-blind RCTs investigating the efficacy of MPFF in the treatment of individual symptoms of CVD or venous edema. This was followed by a manual search of the reference list of the relevant articles and known reviews on the topic of VADs to potentially identify additional studies. Studies published in an abstract form or having a cross-over design were not considered. Unpublished data (*e.g.* from the manufacturers and the authors of the included studies) were not sought. The full-text article of each

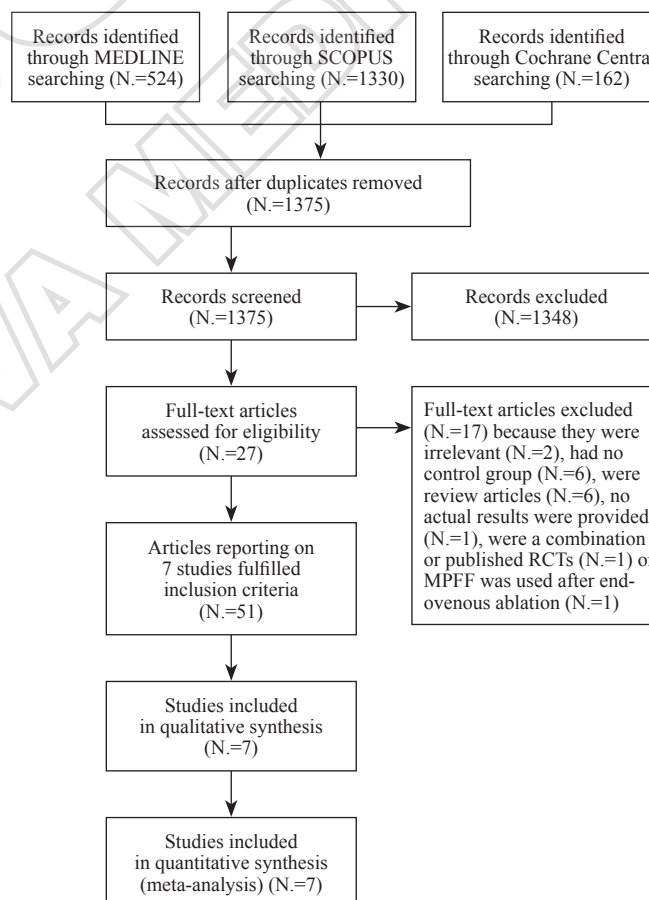


Figure 1.—PRISMA flow diagram showing the selection process of randomized controlled trials for the meta-analysis.

RCT was obtained and translated into English if published in another language. The study selection process (PRISMA flow-diagram) is shown in Figure 1. For each RCT included in the study, raw data (number of patients who developed an endpoint, *i.e.* improvement or symptom-free status, or the mean/standard deviation in case of a continuous variable, and total number of patients in the intervention and control groups) were extracted by the first author and entered into the meta-analysis software Review Manager (RevMan, version 5.3.5 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014); all entries were checked against the original source to identify and correct potential errors.

### *Main outcome measures*

The following information, if provided, was retrieved from each RCT:

1) Venous symptoms, *i.e.* pain or aching, throbbing, tightness, heaviness, fatigue, feeling of swelling, cramps, itching, restless legs, paresthesia (tingling) and heat or burning sensation, as continuous variable when mean ( $\pm$ SD or SEM) and/or categorical when frequency was provided. Secondary symptoms (as described in the SYM Vein Consensus statement, including functional discomfort if provided), global symptoms and quality of life measures were also retrieved.

2) Objective assessment of venous disease in the form of leg redness, edema (ankle circumference or foot or limb volume), skin changes (often described as trophic changes), and evaluation of the overall effectiveness of the treatment by the physician.

### *Methodological assessment of studies*

The risk of bias assessment tool RevMan was used to assess the methodological quality of the included studies, by assessing seven types of bias for each trial separately.

### *Statistical analysis*

Data underwent qualitative and quantitative analysis, the latter to completely assess the studies and provide summary results for potentially underpowered studies, and check for heterogeneity of the evidence. We performed separate analyses for individual symptoms and

venous edema measures (*i.e.* ankle circumference or foot/limb volume). Raw data were entered into RevMan, which performed the meta-analyses, calculated the risk ratio (RR, Mantel-Haenszel method) and standardized mean difference (SMD) and their 95% confidence interval (CI), produced forest plots and provided inconsistency ( $I^2$ ) statistics to evaluate the heterogeneity of the included studies. A non-significant P value for the Cochrane Q statistic indicates that the included studies are homogeneous. An  $I^2$  value of 0% indicates no heterogeneity, while larger values are consistent with increasing heterogeneity. An  $I^2$  over 50% is indicative of substantial heterogeneity. In case of statistically significant heterogeneity ( $P < 0.05$ ) a random effects model was chosen, instead of the fixed effect model. To address possible heterogeneity introduced by pooling studies with different risk of bias we performed sensitivity analyses by excluding studies with a high risk of bias. MedCalc® free statistical calculator (<http://www.medcalc.org>, MedCalc Software bvba, Ostend, Belgium) was used to calculate the number needed to treat (NNT), to prevent one negative outcome (the reciprocal of the difference between the event rate in the two groups, known also as absolute risk reduction) and calculate RR of variables not processed through RevMan. Missing standard deviations were not imputed and such data could not be used. Calculation of a missing standard deviation from the corresponding standard error if provided was performed using formulas published in the Cochrane handbook ([www.handbook.cochrane.org](http://www.handbook.cochrane.org)).<sup>4</sup>

### *Quality of evidence assessment*

The risk of bias assessment tool of Review Manager was used to assess the methodological quality of the included studies. The system developed by the Grading of Recommendation, Assessment, Development and Evaluation Working Group (GRADE working group) was used to grade the quality of evidence as high, moderate, low and very low, based on risk of bias, directness of evidence, heterogeneity, precision of effects estimates, and risk of publication bias. A “summary of findings” table was created using GRADE profiler (version 3.6.1), which included the outcome measures assessed by three or more RCTs. The assumed control intervention risks were calculated from the mean number of events in the control groups of the included studies for each outcome.

### Evidence synthesis

We identified 1375 records (after removing the duplicates) on literature search (PRISMA flow-diagram, Figure 1). Some 1348 of them were excluded based on their title and abstract, and an additional 17 records after the full text was obtained for a variety of reasons,<sup>5-21</sup> which left 10 publications reporting on 7 RCTs into the search process.<sup>22-31</sup> The included RCTs investigated a total of 1,692 patients. Key characteristics of these trials are shown in Table I. CVD CEAP clinical class ranged between 0-6, with some studies allowing the inclusion of patients with “functional venous insufficiency,” presumably those with C0s CVD, or with post-thrombotic syndrome. Most trials had duration of two months. Use of leg compression was variable. All trials except one assessed at least one subjective symptom,<sup>32</sup> while all of them provided objective evidence of edema in the form of ankle circumference, or leg or foot edema.

Overall there was generally minimal risk of bias in

most of the 7 RCTs, as clearly shown in Figure 2. Selection bias was unclear for most RCTs since randomization methodology was not reported. All studies provided numerical results suitable for inclusion into the quantitative meta-analysis.

On qualitative analysis of changes of CVD symptoms, MPFF was superior to placebo in reducing almost all symptoms, with statistical significance being demonstrated. More specifically, statistically significant results were obtained for the individual leg symptoms of pain,<sup>24, 26, 31</sup> heaviness,<sup>23, 24, 26</sup> fatigue,<sup>23</sup> feeling of swelling,<sup>22, 24, 26</sup> tightness,<sup>22</sup> cramps,<sup>24, 26, 29</sup> paresthesia,<sup>26</sup> burning sensation,<sup>24, 26</sup> pruritus,<sup>23</sup> global symptoms,<sup>22</sup> and functional discomfort.<sup>23, 24, 26</sup> A trend for reduced symptoms of pain,<sup>22, 23, 29</sup> heaviness,<sup>22, 29</sup> fatigue,<sup>29</sup> cramps,<sup>22, 23</sup> feeling of swelling,<sup>23, 29</sup> and paresthesia<sup>23, 24</sup> was not significant by a few studies. One small study on burning sensation did not demonstrate significance.<sup>23</sup> Two studies on global symptoms demonstrated non-significant trends.<sup>23, 29</sup>

TABLE I.—Characteristics of studies included in qualitative and quantitative meta-analysis.

Trial	Number of patients	Study population	Duration of trial	Compression of the leg	Symptoms and other outcome measures assessed
Biland, 1982 <sup>22</sup>	70	Varicose veins with or without mild edema or skin changes	4 weeks	Not stated	Heaviness, pain, cramps, edema, tightness. Global symptoms. Ankle circumference. Overall treatment effectiveness.
Chassignolle, 1987 <sup>23</sup> Tsouderos, 1989 <sup>25</sup>	40	“Functional venous insufficiency”	2 months	Not stated	Heaviness, pain, fatigue, cramps, paresthesia, sensation of swelling, burning sensation, pruritus. Functional discomfort. Global symptoms. Ankle circumference. Leg redness. Overall treatment effectiveness.
Frileux, 1987 <sup>24</sup> Thiollet, 1992 <sup>27</sup> Gilly, 1994 <sup>28</sup>	160	“Functional venous insufficiency”, varicose veins, post-thrombotic syndrome	8 weeks	Allowed	Heaviness, pain, cramps, paresthesia, sensation of swelling, heat/burning sensation. Functional discomfort. Ankle circumference. Leg redness.
Planchon, 1990 <sup>26</sup>	110	“Functional venous insufficiency”, varicose veins, post-thrombotic syndrome	2 months	Allowed if already used	Heaviness, pain, cramps, paresthesia, sensation of swelling, heat/burning sensation. Functional discomfort. Ankle circumference. Overall treatment effectiveness.
Danielsson, 2002 <sup>29</sup>	101	CEAP C1-C6 CVD	2 months	Not stated	Heaviness, pain, cramps, fatigue, edema. Global symptoms. Foot volume.
Belczak, 2014 <sup>30</sup>	74	CEAP C2-C5 CVD	1 month	Compression naïve patients, supposedly not allowed	Quality of life. Limb volume.
Rabe, 2015 <sup>31</sup>	1,137	CEAP C3 or C4A CVD with evening leg edema (≥30ml) and venous reflux >1 sec on Duplex	4 months	Not allowed	Pain/heaviness. Quality of life (CIVIQ). Evening limb volume.
Total	1,692				

CEAP: clinical, etiology, anatomy, pathophysiology; CVD: chronic venous disease.

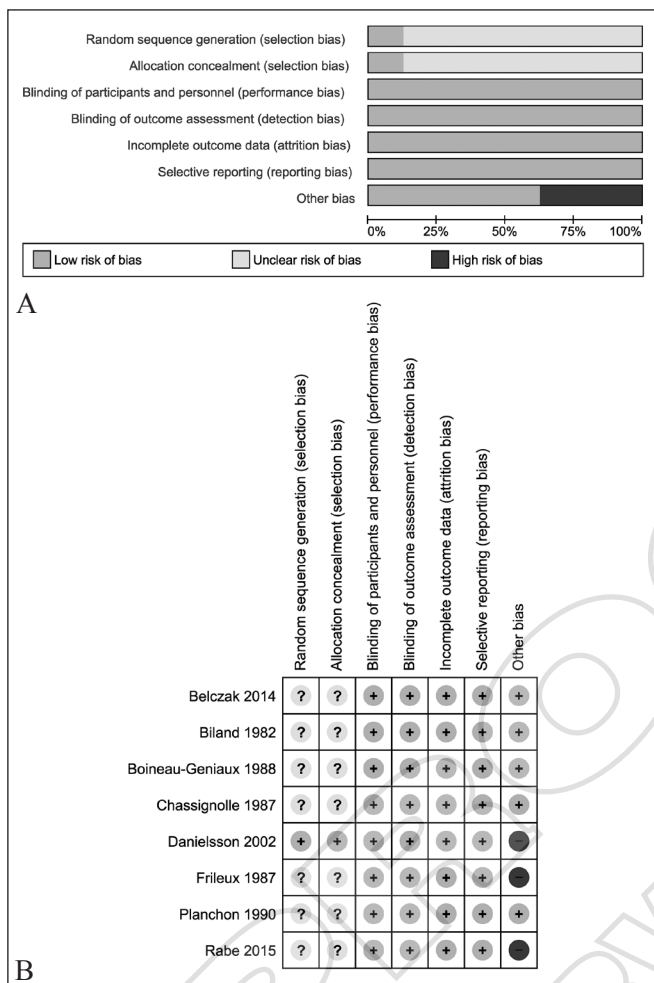


Figure 2.—Risk of bias graph (A) and risk of bias summary (B) demonstrating a mostly uniform low risk of bias.

Leg redness was reduced in three studies.<sup>23, 24, 26</sup> Skin changes were improved in two studies.<sup>24, 26</sup> MPFF was also superior to placebo in significantly reducing ankle circumference in three studies,<sup>24-26</sup> and no effect was reported in another one that included only a few patients with ankle edema.<sup>22</sup> Results for foot or leg volume were either non-significant,<sup>29, 30</sup> or inconclusive.<sup>31</sup> One of these studies that reported a non-significant change in leg volume as a numerical variable,<sup>30</sup> reported that volume reductions >100 mL were observed most frequently in the MPFF group (64.3%) than the placebo group (36.6%), calculated P=0.04, RR 0.56 (95% CI 0.33-0.97). Quality of life was improved in two recent studies.<sup>30, 31</sup> Evaluation of the overall effectiveness of

the treatment by the physician was in favor of MPFF in all three trials that investigated this outcome.<sup>22, 23, 26</sup>

On meta-analysis, quantitative analysis of changes of the CVD symptoms, the following results were obtained:

— pain was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable (SMD -0.25, 95% CI -0.38 to -0.11; participants=839; studies=3; I<sup>2</sup>=0%, Figure 3A)<sup>22-24, 26, 29-31</sup> or a categorical variable (RR 0.53, 95% CI 0.38 to 0.73; participants=271; studies=3; I<sup>2</sup>=0%, Figure 3B). NNT was 4.2 (95% CI 2.8-7.9). One of the included studies reported pain/heaviness as a composite outcome rather than pain.

— Tightness was non-significantly reduced with the use of MPFF compared with placebo in a small study (RR 0.61, 95% CI 0.20 to 1.86; participants=56; studies=1; I<sup>2</sup>=not applicable, Figure 3C).

Heaviness was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.80, 95% CI -1.05 to -0.54; participants=254; studies=2; I<sup>2</sup>=5%, Figure 4A) or a categorical variable (RR

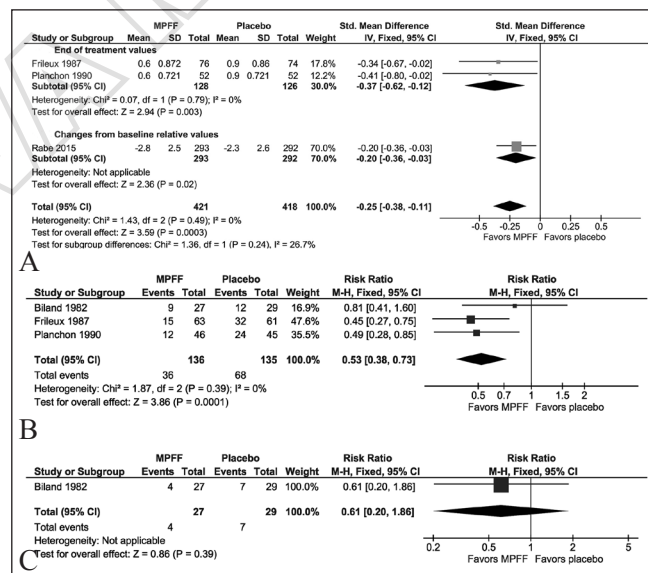


Figure 3.—Pain was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable (SMD -0.25, 839 participants in three studies, panel A) or a categorical variable (RR 0.53, 271 participants in three studies, panel B). One of the included studies reported pain/heaviness as a composite outcome rather than pain.<sup>31</sup> Tightness was non-significantly reduced with the use of MPFF compared with placebo in a small study (RR 0.61, 56 participants, C).

0.35, 95% CI 0.24 to 0.51; participants=283; studies=3;  $I^2=0\%$ , Figure 4B). NNT was 2.9 (95% CI 2.2-4.2).

Fatigue was non-significantly reduced with the use of MPFF compared with placebo when assessed as a categorical variable (RR 0.27, 95% CI 0.07 to 1.09; participants=31; studies=1;  $I^2$ =not applicable, Figure 4C).

Feeling of swelling was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.99, 95% CI -1.25 to -0.73; participants=254; studies=2;  $I^2=0\%$ , Figure 5A) or a categorical variable (RR 0.39, 95% CI 0.27 to 0.56; participants=267; studies=3;  $I^2=0\%$ , Figure 5B). NNT was 3.1 (95% CI 2.3-4.8).

Cramps were significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.46, 95% CI -0.78 to -0.14; participants=150; studies=1;  $I^2$ =not applicable, Figure 6A) or a categorical variable (RR 0.51, 95% CI 0.29 to 0.92; participants=119; studies=2;  $I^2=0\%$ , Figure 6B). NNT was 4.8 (95% CI 2.7-22.9).

Restless legs symptoms were non-significantly reduced with the use of MPFF compared with placebo when assessed as a categorical variable in a small study (RR 0.36, 95% CI 0.11 to 1.19; participants=56; studies=1;  $I^2$ =not applicable, Figure 6C).

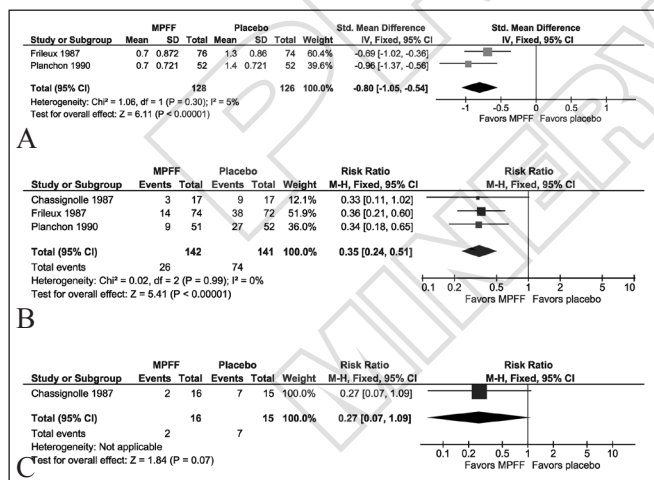


Figure 4.—Heaviness was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.80, 254 participants in three studies, A) or a categorical variable (RR 0.35, 283 participants in three studies, B). Fatigue was non-significantly reduced with the use of MPFF compared with placebo when assessed as a categorical variable (RR 0.27, 31 participants in one study, C).

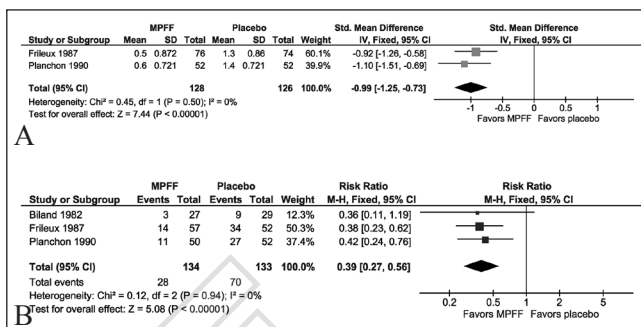


Figure 5.—Feeling of swelling was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.99, 254 participants in two studies, A) or a categorical variable (RR 0.39, 267 participants in three studies, B).

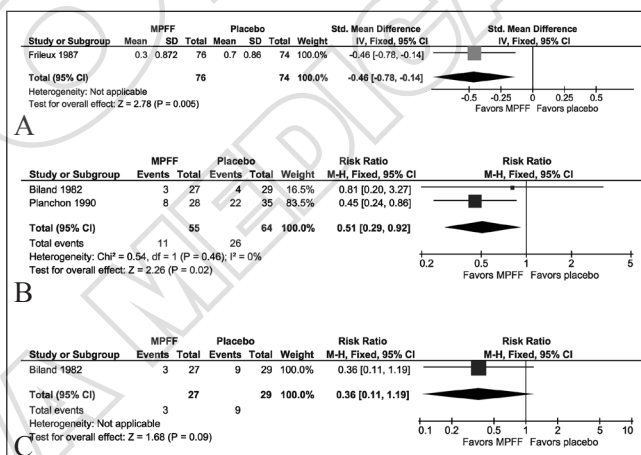


Figure 6.—Cramps were significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.46, 150 participants in one study, A) or a categorical variable (RR 0.51, 119 participants in two studies, B). Restless legs symptoms were non-significantly reduced with the use of MPFF compared with placebo when assessed as a categorical variable in a small study (RR 0.36, 56 participants, C).

Paresthesia was non-significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.11, 95% CI -0.44 to 0.21; participants=150; studies=1;  $I^2$ =not applicable, Figure 7A) but the difference was significant when assessed as a categorical variable (RR 0.45, 95% CI 0.22 to 0.94; participants=61; studies=1;  $I^2$ =not applicable, Figure 7B). NNT was 3.5 (95% CI 1.9-20).

Burning sensation was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD

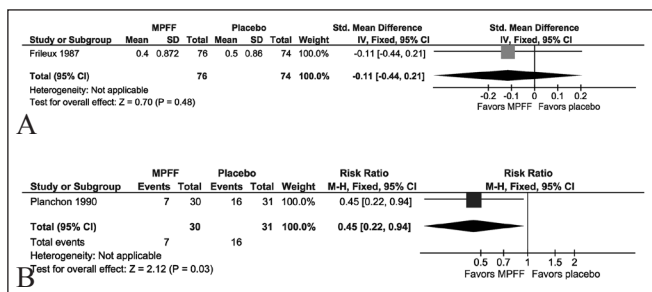


Figure 7.—Paresthesia was non-significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.11, 150 participants in one study, A) but the difference was significant when assessed as a categorical variable (RR 0.45, 61 participants in one study, B).

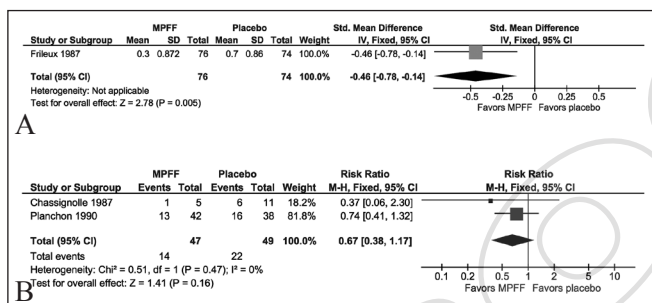


Figure 8.—Burning sensation was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.46, 150 participants in one study), but the difference was not significant when it was assessed as a categorical variable (RR 0.67, 96 participants in two studies, B).

-0.46, 95% CI -0.78 to -0.14; participants=150; studies=1; I<sup>2</sup>=not applicable, Figure 8A), but the difference was not significant when it was assessed as a categorical variable (RR 0.67, 95% CI 0.38 to 1.17; participants=96; studies=2; I<sup>2</sup>=0%, Figure 8B).

Global symptoms assessed by patients were non-significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.48, 95% CI -1.14 to 0.19; participants=36; studies=1; I<sup>2</sup>=not applicable, Figure 9A) or a categorical variable (RR 0.36, 95% CI 0.09 to 1.53; participants=189; studies=3; I<sup>2</sup>=76%, Figure 9B).

Functional discomfort was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.87, 95% CI -1.13 to -0.61; participants=254; studies=2; I<sup>2</sup>=0%, Figure 10A) or a categorical variable (RR 0.41, 95% CI 0.25 to 0.67; participants=134; studies=2; I<sup>2</sup>=0%, Figure 10B). NNT was 3.0 (95% CI 2.1-5.8).

The use of MPFF compared with placebo reduced ankle circumference (SMD -0.59, 95% CI -1.15 to -0.02; participants=282; studies=3; I<sup>2</sup>=79%, Figure 11A), but not leg or foot volume (SMD 0.03, 95% CI -0.28 to 0.33; participants=166; studies=2; I<sup>2</sup>=45%, Figure 11B).

Leg redness was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.32, 95% CI -0.56 to -0.07; participants=254; studies=2; I<sup>2</sup>=0%, Figure 12A) or a categorical variable (RR 0.50, 95% CI 0.27 to 0.94; participants=66; studies=1; I<sup>2</sup>=not applicable, Figure 12B). NNT was 3.6 (95% CI 2.0-20.6).

Skin changes were significantly improved with the use of MPFF compared with placebo when assessed as a categorical variable (RR 0.18, 95% CI 0.07 to 0.46; participants=61; studies=2; I<sup>2</sup>=0%, Figure 13). NNT was 1.6 (95% CI 1.2-2.2).

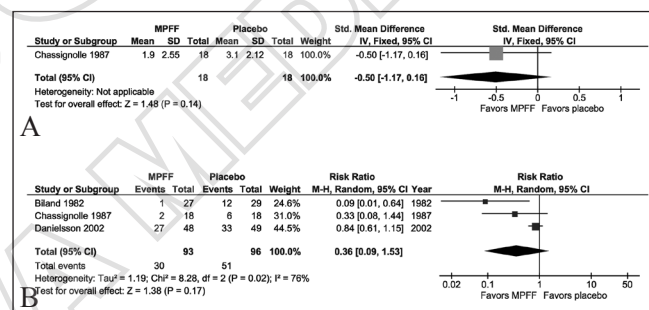


Figure 9.—Global symptoms were non-significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.48, 36 participants in one study, A) or a categorical variable (RR 0.36, 189 participants in three studies, B).

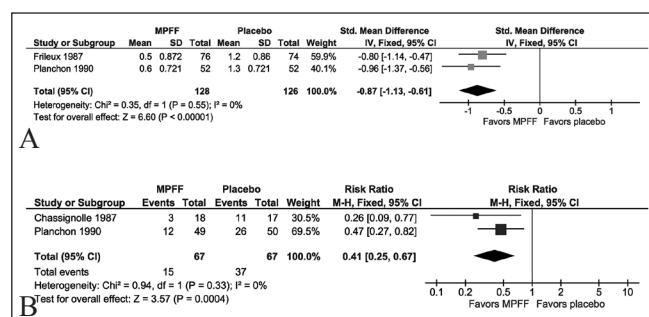


Figure 10.—Functional discomfort was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.87, 154 participants in two studies, A) or a categorical variable (RR 0.41, 134 participants in two studies).

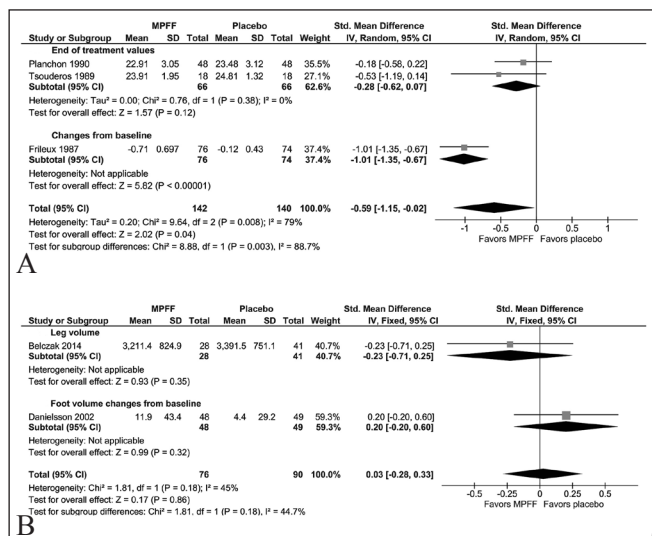


Figure 11.—The use of MPFF compared with placebo reduced ankle circumference, in mm, (SMD -0.59, 282 participants in three studies, A), but not leg or foot volume, in ml, (SMD 0.03, 166 participants in two studies, B).

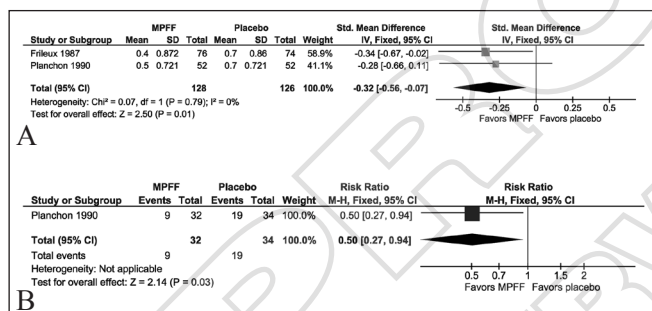


Figure 12.—Leg redness was significantly reduced with the use of MPFF compared with placebo when assessed as a continuous variable of end of treatment values (SMD -0.32, 254 participants in two studies, A) or a categorical variable (RR 0.50, 66 participants in one study).

QoL measures were improved with the use of MPFF compared to placebo when assessed as a continuous variable of changes from baseline (SMD -0.21, 95% CI -0.37 to -0.04; participants=601; studies=2; I<sup>2</sup>=27%, Figure 14).

Objective improvement as assessed by the physician was significantly better with the use of MPFF compared with placebo when assessed as a categorical variable (RR 0.28, 95% CI 0.19 to 0.41; participants=348; studies=4; I<sup>2</sup>=0%, Figure 15). NNT was 2.5 (95% CI 2.1-3.3).

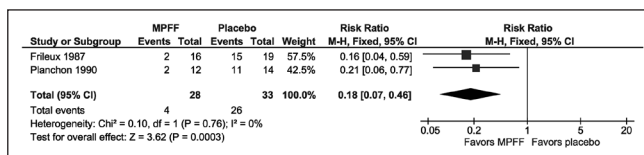


Figure 13.—Skin changes were significantly improved with the use of MPFF compared with placebo when assessed as a categorical variable (RR 0.18, 61 participants in two studies).

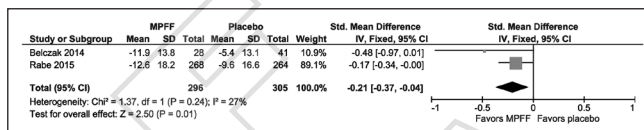


Figure 14.—QoL measures were improved with the use of MPFF compared to placebo when assessed as a continuous variable of changes from baseline (SMD -0.21, 601 participants in two studies).

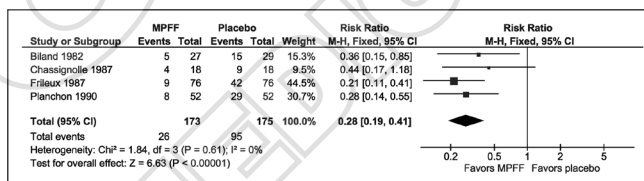


Figure 15.—Objective improvement as assessed by the physician was significantly better with the use of MPFF compared with placebo when assessed as a categorical variable (RR 0.28, 348 participants in four studies).

Sensitivity analysis

This was performed for the categorical variable of global symptoms, where the exclusion of two studies with a bias attribute of high risk<sup>23, 29</sup> left into the analysis a single albeit significant RCT, and the outcome of ankle circumference, where the exclusion of one high risk study<sup>24</sup> completely eliminated heterogeneity (I<sup>2</sup>=0%) but eliminated statistical significance.

Quality of the evidence per GRADE system

A detailed assessment of study outcomes where three or more studies were available appears in Table II. There was high quality of evidence for the outcomes of pain, heaviness and feeling of swelling.

Discussion

Based on mostly high-quality evidence, our meta-analysis of RCTs has demonstrated that MPFF is highly



effective in reducing a large number of venous symptoms, including pain, heaviness, feeling of swelling, cramps, paresthesia, and burning sensation, but also the secondary symptom of functional discomfort in patients with CVD. Objectively measured ankle circumference, leg redness, skin changes, clinical improvement assessed by physician and QoL were also positively affected. Most outcomes were assessed as continuous and categorical variables with concordant results, increasing thus the validity of our results.

We have included only double-blind placebo-controlled RCTs in our meta-analysis to avoid issues related to bias, which can involve certain domains. Indeed, this reduced the overall risk of bias of the 7 RCTs we identified on literature search. In the presence of subjective outcome measures, like those in patients with CVD, only RCTs with a double-blind design that use

a placebo can lead to reliable results. Therefore, consistent results for most outcome measures of this meta-analysis were obtained, with mostly a small amount of or no heterogeneity for most symptoms, and QoL. In combination with the often-large effect size, these parameters permitted us to award high quality of evidence per GRADE system for some of the symptoms shown in Table II; equally important was the fact that our assessment was consistent for the continuous and categorical expression of the symptoms irrespectively if they were expressed as a categorical or continuous variable.

Our meta-analysis has shown that leg symptoms attributed to CVD, including pain, heaviness, feeling of swelling, etc. were significantly reduced in patients treated with MPFF compared with placebo on quantitative analysis. Effect size varied approximately between

TABLE II.—Summary of findings table per GRADE methodology.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Symptoms				
Pain (continuous variable)		The mean pain (continuous variable) in the intervention groups was 0.25 standard deviations lower (0.38 to 0.11 lower)		839 (3 studies)	⊕⊕⊕⊕ high	SMD -0.25 (-0.38 to -0.11)
Pain (categorical variable)	504 per 1000	267 per 1000 (191 to 368)	RR 0.53 (0.38 to 0.73)	271 (3 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
Heaviness (categorical variable)	525 per 1000	184 per 1000 (126 to 268)	RR 0.35 (0.24 to 0.51)	283 (3 studies)	⊕⊕⊕⊕ high <sup>1,2</sup>	
Feeling of swelling (categorical variable)	526 per 1000	205 per 1000 (142 to 295)	RR 0.39 (0.27 to 0.56)	267 (3 studies)	⊕⊕⊕⊕ high <sup>1,2</sup>	
Global symptoms (categorical variable)	531 per 1000	191 per 1000 (48 to 813)	RR 0.36 (0.09 to 1.53)	189 (3 studies)	⊕⊕⊕⊖ moderate <sup>1,2</sup>	
Ankle circumference (mm)		The mean ankle circumference (mm) in the intervention groups was 0.59 standard deviations lower (1.15 to 0.02 lower)		282 (3 studies)	⊕⊕⊕⊖ moderate <sup>4</sup>	SMD -0.59 (-1.15 to -0.02)
Objective improvement	517 per 1000	160 per 1000 (98 to 253)	RR 0.31 (0.19 to 0.49)	231 (4 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence  
 High quality: Further research is very unlikely to change our confidence in the estimate of effect.  
 Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
 Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
 Very low quality: We are very uncertain about the estimate.  
<sup>1</sup> Total number of events is less than 300  
<sup>2</sup> Large effect size  
<sup>3</sup> Presence of significant heterogeneity  
<sup>4</sup> Total population size is less than 400

0.27 and 0.67 for categorical variables, indicating a large effect of MPFF in ameliorating venous symptoms. The symptoms of pain, heaviness, feeling of swelling may well be intercorrelated and the result of venous incompetence leading to hypertension and fluid extravasation.<sup>3</sup> This is further supported by the similar RRs, *i.e.* around 0.4, obtained for these three symptoms. On the other hand, cramps, paresthesia and burning sensation were also reduced, although there was no agreement between categorical and continuous assessment for the last two variables; this may have been the result of the small sample sizes for these variables (prompting for larger studies) or a smaller effect size (ranging between 0.45 and 0.67) compared with the symptoms of pain, heaviness and feeling of swelling. Paresthesia is thought to be the result of peripheral neuropathy due to venous hypertension as previously described,<sup>33, 34</sup> although a similar pathophysiology for cramps and burning sensation may exist.<sup>3</sup> Future studies could investigate for such potential associations between the various symptom types. Nevertheless, the common effect of all symptoms may be the symptom of fatigue,<sup>3</sup> and also secondary symptoms (*i.e.* functional discomfort) and impaired QoL. This may explain the large effect size observed for these two symptoms (RR 0.27 and 0.41, respectively). Nevertheless, the large effect size for most symptoms tested by the RCTs included herein accounts for the corresponding very small NNT, around 3, calculated for most symptoms. These observations strongly support the use of MPFF in patients with CVD and call for formal cost-effectiveness analyses, taking also into account the improvement for QoL observed in two recent studies.<sup>30, 31</sup>

Apart from the subjective outcome measures of CVD symptoms, MPFF reduced ankle circumference; the observation of significant heterogeneity leading to moderate quality of evidence was abolished on sensitivity analysis, prompting for further assessment using more vigorous criteria. For example one study with seemingly negative results included only a handful of patients with leg edema, potentially introducing heterogeneity because of the apparent lack of effect.<sup>22</sup> Nevertheless, this observation indicates that there is a measurable effect on venous hemodynamics, which may contribute to the improvement of symptoms after using MPFF. On the other hand, effect of MPFF on the objective measures of leg or foot volume could not be demonstrated by the

current meta-analysis, consistent with the inconclusive results of a recent RCT, which claimed methodological issues to be responsible.<sup>31</sup>

The pharmacological effects of MPFF and its anti-inflammatory effects in particular have been extensively documented.<sup>35-38</sup> The mechanism of action of MPFF includes a beneficial hemorheological effect, resolving the stasis with an increase in red blood cell velocity,<sup>39</sup> inhibition of the synthesis of prostaglandins and free radicals and a decrease in bradykinin-induced microvascular leakage, which may act favorably to inhibit leukocyte activation, trapping, and migration,<sup>40</sup> improvement of the microvascular reactivity and functional capillary density with a protective effect against leakage of macromolecules after application of permeability-increasing substances and a suppression of leukocyte adhesion in animal models of ischemia/reperfusion.<sup>35, 41-43</sup> Additionally, MPFF treatment decreases the levels of some plasma markers of endothelial activation,<sup>44, 45</sup> and also the surface expression of CD62L by neutrophils and by monocytes.<sup>46</sup> Moreover, in a chronic rodent model of hind limb venous hypertension associated with low blood flow, MPFF completely prevented microcirculatory dysfunction and prevented the initiation of the venous inflammatory cascade more effectively than diosmin by additional beneficial effects of concomitant active flavonoids of MPFF.<sup>47</sup> Finally, MPFF improves venous tone in COs patients.<sup>48</sup> These mechanisms of actions may explain the effectiveness of MPFF on several venous symptoms and signs as found by the present meta-analysis.

Quality of evidence assessment for the outcomes supported by at least three RCTs, revealed high quality evidence for the outcomes of pain, heaviness, and feeling of swelling, which reflects the absence of bias and the large effect size. Systematic reviews comparing MPFF with placebo are scarce.<sup>49-52</sup> Assessment of individual symptoms was performed in the 2005 Cochrane meta-analysis, some 13 years ago.<sup>49</sup> Although we came into similar conclusions, the current study included additional studies, investigated more outcome measures, and used the most up-to-date methodology to assess the quality of the RCTs and also the evidence produced by the meta-analysis. Furthermore, we have assessed skin changes and objective improvement as a result of treatment and awarded a high level of evidence for both outcomes.

### Limitations of the study

Our meta-analysis has some limitations; we have not assessed hemodynamic changes after using MPFF. Inherent with the RCTs, the small number of patients that improved in most outcomes limits somewhat our assessment, particularly for the symptoms of cramps, burning sensation and paresthesia. Future work in our opinion should also focus on these symptoms. Given the large effectiveness for some of the symptoms and the high quality of evidence we suggest that consensus and guideline documents on CVD should upgrade their recommendations with the presented evidence for MPFF.<sup>1, 2, 53</sup>

### Conclusions

In conclusion, based on high quality evidence, MPFF is highly effective in improving leg symptoms, edema and quality of life in patients with CVD.

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