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REVIEW
VENOUS DISEASE

Pharmacological treatment for chronic venous disease: an umbrella review of systematic reviews

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ABSTRACT

Introduction: Chronic venous disease is a persistent venous drainage alteration caused by valvular incompetence and/or outflow obstruction. Disease management includes a variety of treatments, whose evidence and clinical performance in the mid-long term are variable. The objective of this umbrella review was to summarize efficacy data for pharmacological treatments including venoactive drugs from previously published reviews that included a meta-analytic component.

Evidence acquisition: Systematic database searches were conducted via Ovid SP on 13 August 2019, covering MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. Reviews that included a meta-analytic component of four or more clinical trials or observational studies reporting on the efficacy of systemic or topical pharmacological treatments for adults with chronic venous disease published since 2010 were eligible for inclusion.

Evidence synthesis: Eleven publications were included in this umbrella review. Change in ankle circumference was the most commonly reported outcome. Overall, several systemic treatments had significant effects compared with placebo on multiple efficacy outcomes, including measures of edema and pain. Out of them, Micronized Purified Flavonoid Fraction had the most comprehensive evidence of effectiveness on main symptoms and signs and on improving quality of life throughout chronic venous disease stages.

Conclusions: Systemic pharmacotherapies represent a valuable therapeutic option in CVD management. As a result of this umbrella review, several gaps were identified with respect to research topics that warrant further investigation, particularly in the category of topical medications.

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Key words: Varicose veins; Lower extremity; Edema; Quality of life.

Introduction

Chronic venous disease (CVD), specifically lower limb CVD, is a persistent venous drainage alteration caused by valvular incompetence and/or outflow obstruction.[1] CVD-induced venous hypertension leads to varicose veins, edema, and skin changes up to open wounds, or ulcers. This inflammatory condition is associated with several symptoms such as swelling, feeling of heaviness, achiness, throbbing, and pruritus.

CVD management includes compression therapy, pharmacological therapy, surgical and endovenous treatments, all of which are associated with validated clinical results.[2] However, these treatments do not ensure long term patient satisfaction and functioning or better quality of life (QoL), as recurrence rates are high.[1, 3-5] In addition, there is a global variability in clinicians' awareness of optimal treatments and their compliance with recommended disease management algorithms and pathways.[1, 3, 4]

International treatment guidelines often recommend conservative options such as lifestyle modifications, compression, and medical management particularly with venoactive drugs (VAD) (also known as phlebotonics), as baseline treatment for CVD.[2, 6, 7] Main VADs are listed in Table I.

Despite international efforts to standardize CVD classification, ensure early diagnosis, and deliver optimal treatments, consensus on individualized, effective disease management is under discussion.[8, 9]

Previous systematic literature reviews (SLRs) highlighted the positive impact of VADs on reducing leg symptoms, leg pain, edema, and QoL.[10-13] However, most of the published SLRs were restricted to specific treatments or disease stages and did not provide a broad overview of the benefits of various systemic or topical pharmacological treatment options for patients at different stages of their disease and management. In addition, these SLRs highlighted several limitations across individual studies, including a lack of a clear description of how outcomes were measured and small sample sizes across the included studies.[7, 10, 12, 13]

Table I.—*Main venoactive drugs.*

Group	Main substance
Alpha-benzopyrones	Coumarin
Gamma-benzopyrones (flavonoids)	Diosmin
	Micronized purified flavonoid fraction
	Rutin and rutosides
Saponins	Escin (horse chestnut)
	Ruscus extract
Synthetic products	Calcium dobesilate, naftazone

Modified from CVD international guidelines Int Angiol 2018.[7]

The objective of this umbrella review (*i.e.*, a review of SLRs) was to summarize efficacy data from various systemic and topical pharmacological treatment options for CVD based on previously published SLRs that included a meta-analytic component. To our knowledge, no prior umbrella reviews in CVD have been published.

Evidence acquisition

The topics of interest reported herein were part of a broader SLR focused on the overall burden of CVD, which included literature on the diagnosis, epidemiology, humanistic burden, economic burden, and disease management of CVD as well as clinical efficacy and safety of treatment for CVD. This review was conducted following standards in line with the Cochrane Collaboration[14, 15] and reporting standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] Guidance on conducting an overview of reviews as suggested by the Cochrane Collaboration has been followed.[15]

Eligibility criteria

SLRs that included a meta-analytic component of four or more clinical trials or observational studies reporting on the efficacy of systemic or topical pharmacological treatments (alone or in combination with other therapies) for adults with CVD published since 2010 were eligible for inclusion. No restrictions by language, geography, or disease stage were applied. SLRs of fewer than four studies, or those focusing on compression therapy, topical therapy, surgery, or only interventional procedures, were excluded. The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) criteria are presented in Supplementary Digital Material 1 (Supplementary Table I).

Data sources and searches

Systematic database searches were conducted via Ovid SP on 13 August 2019, covering MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. All search strategies were designed using a combination of medical subject heading, Emtree, and free-text terms for CVD paired with validated filters to identify studies examining epidemiology, diagnostics, QoL, clinical and economic burden, and disease management. Searches were not limited to specific treatments to allow for a robust pool of evidence. The search strategies are provided in Supplementary Digital Material 2 (Supplementary Table II, Supplementary Table III, Supplementary Table IV).

Study selection

Each title and abstract was reviewed by one investigator to determine its suitability for inclusion in the review according to the defined inclusion and exclusion criteria. A second independent investigator reviewed a random sample of 10% of the abstracts as a quality check. Discrepancies between the first and second reviewers were resolved by a third, senior investigator. For abstracts that were deemed relevant, the corresponding full-text articles were retrieved for further evaluation.

Each full-text article was reviewed by one investigator. All rejected articles were assigned a reason for exclusion. A second, independent investigator validated all excluded articles to ensure that no relevant articles had been missed. Discrepancies between the first and second reviewers were resolved by a third, senior investigator.

Data extraction

Data extraction was conducted independently by one investigator with all extractions validated by a second investigator. Information extracted from selected full-text articles into a predefined data extraction table included study characteristics, population characteristics, treatment characteristics, and outcomes of interest. Select characteristics of the included SLRs are presented in the Supplementary Digital Material 3 (Supplementary Table V).

Risk of bias

The methodological quality of the included SLRs was assessed using the AMSTAR 2 tool.[17] The AMSTAR 2 checklist includes 16 items that assess specific elements of the conduct of SLRs, seven of which are considered critical.

Synthesis of results

Results pertaining to efficacy and QoL were summarized qualitatively. In line with Cochrane guidance, direct comparisons of different treatment strategies across SLRs were avoided, as this could introduce bias given the differences in patient populations and trials across the SLRs and the lack of an indirect treatment comparison of trials from different SLRs. The key findings and limitations of each SLR are presented in supplementary digital materials.

Evidence synthesis

Description of included studies

Systematic searches identified 8296 records from electronic literature databases (Figure 1). After the removal of 1730 duplicates, 6566 records remained for title and abstract screening. Of these, 997 publications were deemed eligible for screening at the full-text level, of which six met the inclusion criteria for the review. An additional five SLRs not identified through the database searches were flagged by clinical experts in this field, resulting in a total of 11 eligible SLRs.[7, 10, 12, 18-25]

The included SLRs were published between 2012 and 2018 (Supplementary Table V). Databases searched within the SLRs included PubMed/MEDLINE (N.=11), the Cochrane Library (N.=8), Embase (N.=7), Cumulative Index

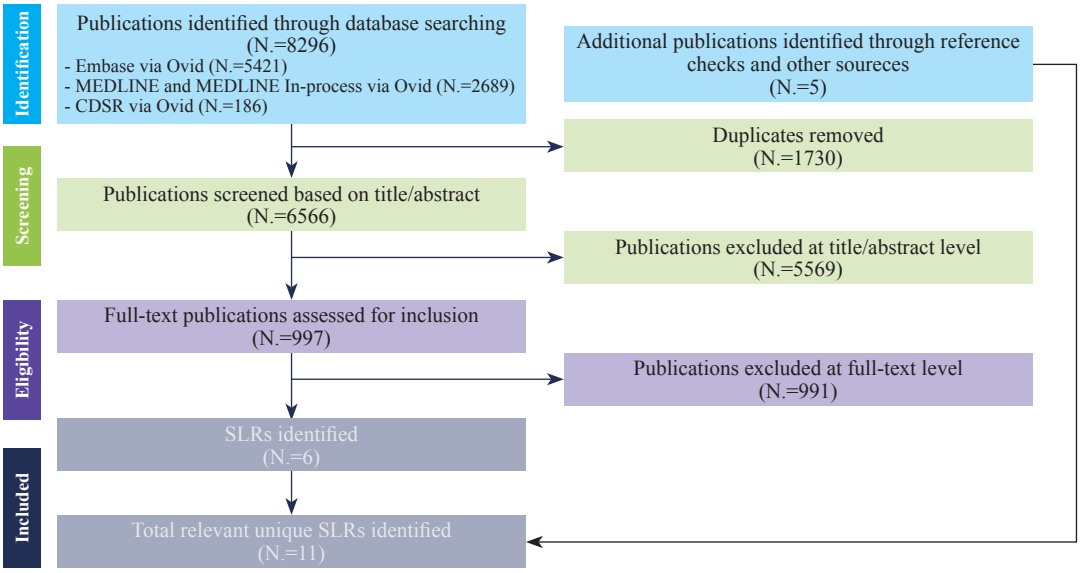

Figure 1.—PRISMA diagram.
CDSR: Cochrane Database of Systematic Reviews; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

to Nursing and Allied Health Literature (CINAHL; N.=8), and the Cochrane Wounds Specialised Register (N.=3). Three SLRs included the Scopus database as a literature source, and one SLR included Chinese databases. All but one SLR included randomized controlled trials (RCTs) only; one SLR evaluated RCTs and non-randomized trials. None of the included SLRs considered real-world evidence. Of the 11 SLRs identified, AMSTAR 2 criteria indicate that the results of three studies are to be viewed with low confidence, the results of seven are to be viewed with critically low confidence, and one is to be viewed with moderate confidence. Most (10 of 11) SLRs failed to assess the impact of publication bias on their results (AMSTAR 2 criterion 15), and six of 11 failed to account for the risk of bias (AMSTAR 2 criterion 13).[17]

The number of included studies within each SLR varied from four to 53, and the number of patients in each SLR ranged from 463 to 6,023. In total, 186 primary studies were included across the 11 SLRs. Of the 186 primary studies, 43 were included in more than one SLR. The most commonly reported studies are listed in the Supplementary Digital Material 4 (Supplementary Table VI), appearing in three of the 11 SLRs each.

Five SLRs focused on venous leg ulcers (VLUs),[19,21,23-25] five SLRs were in patients with chronic venous disorders,[7, 12, 18, 20, 22] and one SLR particularly focused on venous edema.[10]

Change in ankle circumference was the most commonly reported outcome across the 11 SLRs (N.=6), followed by pain and the number of ulcers healed (N.=5 each). Five SLRs reported on a variety of other symptoms, such as skin changes, restless leg symptoms, cramps, and paresthesia (Figure 2). The SLRs often reported more than one outcome. Treatments evaluated are reported in Supplementary Table V and mainly included VAD such as micronized purified flavonoid fraction (MPFF), Ruscus extract, hydroxyethylrutosides, diosmin, horse chestnut seed extract, sulodexide or other treatments such as antibiotics, antiseptics, and medicinal plants.

Clinical efficacy/effectiveness

Edema

All six SLRs with edema as an outcome compared active treatment with placebo,[7, 10, 12, 18, 20, 22] with only one comparing different active treatments with each other.[10] Four SLRs compared a single active treatment or treatment category (MPFF, Ruscus extracts, phlebotonics in general) with placebo only. One SLR evaluated various treatments (MPFF, Ruscus extracts, hydroxyethylrutosides, and placebo), and one compared horse chestnut seed extract with placebo, compression, or hydroxyethylrutosides. The SLRs included different outcomes to describe the impact of these treatments on leg or foot edema: ankle circumference (N.=6), leg/foot volume (N.=4), and edema reduction (N.=2). Three of the SLRs included clinical trials irrespective of disease stage,[7, 12, 18] while one SLR focused on early stages only (1-2).[22] The remaining two SLRs included trials primarily in patients with venous edema.[10, 20]

All six SLRs reported on a change in ankle circumference, expressed as a reduction (*i.e.*, change from baseline)

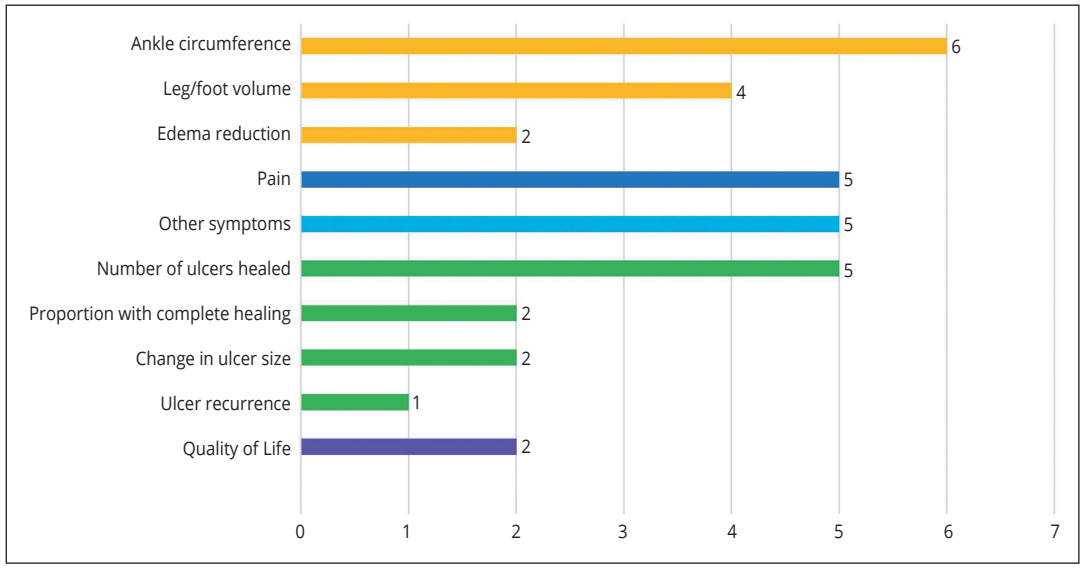

Figure 2.—Number of SLRs contributing to each outcome group. Yellow bars: edema; blue bars: symptoms; green bars: ulcer healing; purple bars: quality of life.

within a treatment arm or a mean difference between treatment arms.[7, 10, 12, 18, 20, 22] MPFF,[7, 10] Ruscus extracts,[10, 20] and horse chestnut seed extract[22] were found to be statistically significantly superior to placebo in reducing ankle circumference.

In one SLR of patients with venous edema, the impact of four phlebotonics (MPFF, hydroxyethylrutosides, Ruscus extract and diosmin) was assessed as the decrease in ankle circumference.[10] All four drugs achieved reduction in ankle circumference that was superior to placebo. This was statistically significant for MPFF (-0.80±0.53 cm), hydroxyethylrutosides (-0.58±0.31 cm), Ruscus extract (-0.58±0.47 cm) (P<0.0001 in each case) but not for simple diosmin (-0.20±0.5 cm, P value not reported). For comparisons between drugs, MPFF was superior to hydroxyethylrutosides and Ruscus extract, although there was no statistically significant difference in change in ankle circumference between the latter two. In a second SLR, MPFF was also superior to placebo in reducing ankle circumference (standardized mean difference [SMD] -0.59; 95% confidence interval [CI] -1.15 to -0.02]).[7]

The evidence is conflicting regarding the superiority of hydroxyethylrutosides over placebo for ankle circumference: one SLR in patients with venous edema found a statistically significant difference compared with placebo (P<0.0001),[10] while a second SLR in patients with chronic vein insufficiency (CVI) in general (comprising all CVD stages) did not (mean difference [MD] -3.63; 95% CI: -9.4 to 2.15).[18] Two SLRs, one in patients with venous edema and one in patients with C3-5, found Ruscus extract to be superior to placebo.[10, 20] In patients with CVI, phlebotonics in general (risk ratio [RR] 0.70; 95% CI: 0.63 to 0.78) and horse chestnut seed extract were found to be superior to placebo in one SLR each.[12, 22]

Four SLRs also reported on leg and/or foot volume: one SLR concerning phlebotonics in general demonstrated superior efficacy compared with placebo in reducing leg or foot volume (MD -0.38 mL; 95% CI: -0.50 to -0.25]).[12] Another SLR evaluating MPFF reported inconclusive evidence (SMD 0.03; 95% CI: -0.28 to 0.33) but demonstrated that volume reductions >100 mL were observed statistically significantly more often in the MPFF group (64.3%) than the placebo group (36.6%) (P=0.04, RR 0.56; 95% CI: 0.33 to 0.97).[7]

In other SLRs, horse chestnut seed extract (SMD 0.34; 95% CI: 0.15 to 0.52)[22] and Ruscus extract (SMD -0.61; 95% CI: -0.91 to -0.31)[20] were more efficacious in reducing leg volume than placebo.

Leg pain

Five SLRs reported on leg pain, evaluating MPFF,[7] Ruscus extract,[20] horse chestnut seed extract,[22] hydroxyethylrutosides,[18] or phlebotonics in general,[12] all compared with placebo. In one SLR including 1,210 CVD patients, MPFF demonstrated a statistically significant reduction in pain when compared with placebo when assessed as a continuous variable (SMD -0.25; 95% CI: -0.38 to -0.11) or a categorical variable (RR 0.53; 95% CI: 0.38 to 0.73).[7]

Similarly, Ruscus extract resulted in a statistically significant reduction in pain from baseline to the end of treatment compared to placebo (SMD -0.73 [95% CI: -1.26 to -0.21]). These findings were based on a single study of 60 patients.[20] Also in one SLR including 418 patients with CVD, the odds of experiencing an improvement in leg pain when treated with horse chestnut seed extract were statistically significantly higher than those for placebo (odds ratio [OR]: 2.22; 95% CI: 1.5 to 3.29).[22] At the same time, one SLR in patients with CVD across all Clinical-Etiological-Anatomical-Pathophysiological (CEAP) stages did not find a significant difference between phlebotonics in general and placebo in pain improvements.[12] Inconsistent evidence was found for hydroxyethylrutosides in one SLR where there was no statistically significant difference in proportion with pain improvement compared with placebo.[18]

Other symptoms and signs

Five SLRs reported on a variety of other symptoms, including cramps, restless leg symptoms or heavy legs, swelling sensation, pruritus, and skin changes, with one SLR each for treatment with MPFF,[7] Ruscus extract,[20] horse chestnut seed extract,[22] hydroxyethylrutosides,[18] or phlebotonics in general[12] *vs*. placebo.[18] Results were generally variable across treatments and symptoms. Compared with placebo, MPFF statistically significantly reduced cramps (SMD -0.46; 95% CI: -0.78 to -0.14 and RR 0.51; 95% CI: 0.29 to 0.92), feeling of swelling (SMD -0.89; 95% CI: -1.25 to -0.73 and RR 0.39; 95% CI: 0.27 to 0.56), leg heaviness (SMD -0.80; 95% CI: -1.05 to -0.54 and RR 0.35; 95% CI: 0.24 to 0.51), and skin changes (RR 0.18; 95% CI: 0.07 to 0.46).[7] MPFF was statistically superior to placebo for burning sensation when measured as a reduction in score (SMD -0.46; 95% CI: -0.78 to -0.14). Similar findings were reported for a reduction in functional discomfort, with a decrease in score from baseline being statistically significant (SMD -0.87; 95% CI: -1.13 to -0.61). Also, MPFF resulted in a statistically significantly higher likelihood than placebo of reducing paresthesia (RR 0.45;

95% CI: 0.22 to 0.94). For Ruscus extract[20] compared with placebo, significant differences were found mainly for leg heaviness (SMD -1.23; 95% CI: -1.60 to -0.86), feeling of swelling (SMD -2.27; 95% CI: -3.83 to -0.70), and paresthesia (SMD -0.86; 95% CI: -1.59 to -0.21). Another SLR with hydroxyethylrutosides,[18] reported significant results on leg heaviness (SMD -1.00; 95% CI: -1.27 to -0.73) and cramps (SMD -1.07; 95% CI: -1.45 to -0.69) compared with placebo, but there was no significant difference for pruritus (OR 1.29; 95% CI: 0.17 to 10.15) and feeling of swelling (OR 0.60, 95% CI: 0.25 to 1.46). For horse chestnut seed extract,[22] SLR outcomes indicated a statistically significant reduction of pruritus compared to placebo (P<0.05; 95% CI: 3.3 to 36.3). Lastly, an SLR comparing phlebotonics in general with placebo significantly favored phlebotonics on the improvement of trophic disorders (RR 0.87; 95% CI: 0.81 to 0.95), cramps in the lower legs (RR 0.72; 95% CI: 0.58 to 0.89), feeling of swelling (RR 0.63; 95% CI: 0.50 to 0.80), and paresthesia (RR 0.67; 95% CI: 0.50 to 0.88).

Ulcer healing

Three SLRs assessed ulcer healing with phlebotonics in combination with compression and/or topical therapy compared with compression and/or topical therapy only.[12, 18, 23] In one of these SLRs, the addition of MPFF (RR 1.36; 95% CI: 1.07 to 1.74]) or hydroxyethylrutosides (RR 1.7; 95% CI: 1.24 to 2.34) to compression and topical therapy resulted in a statistically significantly higher likelihood of ulcer healing).[23] Another SLR did not find any difference between the combination of hydroxyethylrutosides and compression and compression therapy only.[18] The third SLR including phlebotonics in general reported no significant difference compared with placebo (RR 0.94; 95% CI: 0.79 to 1.13).[12] Concerning other treatments, one SLR found sulodexide and topical therapy to be superior to topical therapy only (RR 1.66; 95% CI: 1.3 to 2.12),[24] whereas findings of another SLR assessing the effects of topical medicinal plants on venous ulcer healing could not be interpreted due to the heterogeneity of the results.[19] In an SLR including systemic and topical nutritional supplements for venous ulcers, the data showed significant benefits when comparing topical nutritional supplementation with placebo (RR: 1.44; 95% CI: 1.31 to 1.59).[25] Lastly in another SLR, the role of systemic and topical antibiotics and topical antiseptics in managing VLUs remained poorly understood because of inconsistent results and limitations of the included studies.[21]

Quality of life

Two SLRs were found to assess the quality of life in patients with CVD. In the first SLR where the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) tool was used, MPFF statistically significantly improved QoL compared with placebo (SMD -0.21; 95% CI: -0.37 to -0.04).[7] In the second SLR, which assessed the effects of phlebotonics in general for QoL, it was not possible to pool the studies because heterogeneity was high. However, high-quality evidence suggested no differences in quality of life for calcium dobesilate compared with placebo (MD -0.60; 95% CI: -2.15 to 0.95), and low-quality evidence indicated that in the aminaftone group, QoL was improved over that reported in the placebo group (MD -10.00; 95% CI: -17.01 to -2.99).[12]

Discussion

This umbrella SLR provides a summary of efficacy data from various systemic and topical pharmacological treatments as assessed by multiple previously published SLRs. Overall, several systemic phlebotonics such as MPFF, Ruscus extract, hydroxyethylrutosides, and horse chestnut seed extract had significant effects compared with placebo on multiple efficacy outcomes for CVD, including measures of edema and pain. Nevertheless, the literature search did not reveal any randomized controlled studies on the efficacy of sulodexide for CVD symptoms. Only one SLR investigating the effects of sulodexide on VLUs was identified. Also, studies included in the SLRs and investigating the effectiveness of topical treatments were limited to VLU patient populations; their role remained poorly understood because of the inconsistent results and limitations of the studies.

Systemic VADs generally resulted in statistically significantly higher reductions concerning leg edema when compared with placebo, particularly in ankle circumference, with MPFF also showing superiority over other phlebotonics such as hydroxyethylrutosides, Ruscus extract, and diosmin in one of the SLRs.[10]

On the other hand, the available evidence across SLRs was more variable and inconclusive for the efficacy of active treatment *vs*. placebo for other CVD symptoms and signs, such as leg pain, cramps, restless leg symptoms or heavy legs, swelling sensation, pruritus, and skin changes. Among VADs, Ruscus extract and hydroxyethylrutosides showed effectiveness in relieving leg pain and heaviness. Ruscus extract was shown also to improve the feeling of swelling and paresthesia, while hydroxyethylrutosides and horse chestnut seed extract were found to reduce cramps and pruritus, respectively.

MPFF had beneficial effects covering the main CVD symptoms and signs, with significant reduction in leg pain, leg heaviness, functional discomfort, cramps, skin changes, and the feeling of swelling. These findings were consistent with recommendations made by a recent international guideline on CVD management produced by the Cardiovascular Disease Educational and Research Trust, the European Venous Forum, the International Union of Phlebology, and the International Union of Angiology, which provided the highest number of strong recommendations with Grade A and Grade B evidence for MPFF in improving symptoms and signs of CVD compared with other venoactive drugs.[7]

In patients with VLUs, the addition of MPFF, hydroxyethylrutosides, or sulodexide to compression and/or topical therapy resulted in statistically significantly better ulcer healing results than compression and/or topical therapy only. These results reinforce the importance of pharmacotherapy to promote healing by reducing the inflammatory reaction initiated by venous hypertension.

Data on the impact of treatment on QoL in patients with CVD were limited. One SLR reported a significant improvement of QoL for patients treated with MPFF compared with placebo, which was again coherent with recommendations of international CVD guidelines that indicated MPFF as the only VAD with the highest level of recommendation (Grade A evidence) for the improvement of QoL.[7]

Although the assessment of treatments' safety was not in the scope of this review, a brief analysis of the 11 SLRs indicated that four reported on safety outcomes. Three included studies of patients with VLU,[21, 23, 24] with the remaining study focused on CVI in general.[12] Overall, systemic pharmacological treatments were generally well-tolerated when used in patients with CVD with few reporting mild to moderate adverse events such as gastrointestinal complaints and skin reactions. The exception being calcium dobesilate, which has been suspected of inducing rare cases of agranulocytosis.[26, 27]

This umbrella review identified CVD research topics that warrant further investigation. Few primary studies examined QoL, therefore, a focus of future SLRs and primary publications could be to evaluate QoL in patients with CVD. The clinical course of CVD starts early with venous hypertension and progresses to additional complications such as varicose veins or ulcers. The ability to slow the progression of CVD starting at the earliest stages has not been extensively researched and is further complicated by the plethora of preventable and non-preventable factors involved. None of the included SLRs were designed to explore specific disease severities or stages. Primary studies on the integration of VAD for controlling clinical expression of CVD starting at the earliest stages of the disease would be considered valuable.

Additionally, long-term analyses were lacking across individual studies and adherence to treatment was not compared across treatments. CVD studies that examine extended follow-up would address this research gap, particularly if these studies assessed treatment duration and adherence during long-term treatment. Furthermore, data on dosing and duration of VAD treatments in different patient profiles are scarce. Lastly, data on patient subgroups such as demographic or specific patient categories (*e.g.* BMI or lifestyle), comorbid subgroups, and treatment outcomes by specific CEAP severity groups are lacking in the literature. A future SLR/network meta-analysis (NMA) aimed at disease management in these specific subgroups would be useful to identify any (comparative) trends in treatment efficacy/effectiveness.

Limitations of the study

This umbrella review has several limitations. First, the review is limited by the availability of information and comprehensiveness of the included primary publications reported in the included SLRs. Second, differences across the included SLRs such as inclusion and exclusion criteria, treatments evaluated, and reporting of outcomes limit the comparability of results across SLRs. Third, although a mapping of primary studies across the included SLRs was undertaken in line with Cochrane guidance, it is anticipated that individual trials contributed multiple times to the interpretation of pooled results. Avoiding this 'double counting' would require a summary of primary studies themselves. Finally, this umbrella SLR is limited by the quality of the SLRs it includes. Only one of the SLRs included met the AMSTAR 2 criteria to have its results viewed with moderate confidence, although many were published before the AMSTAR 2 criteria were developed.[17] Better reporting in the literature and wider adoption of these criteria will increase confidence in the results of umbrella reviews such as this one.

Despite the limitations mentioned above, this umbrella review brings added value with several strengths. First, the search strategy used for this umbrella review was paired with additional grey literature searches to ensure all relevant evidence was identified. Though only 11 SLRs were included, they represented 186 individual publications covering subsets of CVD and a broad range of severities.

Secondly, most included SLRs were also focused on clinical trial data, ensuring a high level of evidence. Third, the umbrella review was conducted in alignment with guidance by the Cochrane Collaboration. Fourth, certain gaps were identified to provide direction for future research. Lastly, though outcomes lacked standardization across the included SLRs, outcome categories were similar, allowing the synthesis of information over a wide network of primary publications. In summary, this umbrella review provides a broad overview of the benefits of various systemic or topical pharmacological treatment options for patients at different stages of CVD.

Conclusions

Based on published SLRs, systemic pharmacotherapies appeared to be an effective management strategy for patients with CVD across disease stages including VLU. Among these treatments, MPFF in particular has been extensively researched and found to be effective in reducing main symptoms and signs of CVD and in improving patients' QoL.

As a result of this umbrella review, several gaps were identified with respect to CVD research topics that warrant further investigation. Additional research on QoL, long term effectiveness and adherence, and studies by specific severity or patient subgroups are needed.

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