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Phlebotonics for venous insufficiency (Review)

Martinez-Zapata MJ, Vernooij RWM, Simancas-Racines D, Uriona Tuma SM, Stein AT, Moreno Carriles RMM, Vargas E, Bonfill Cosp X

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[Intervention Review]

Phlebotonics for venous insufficiency

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ABSTRACT

Background

Chronic venous insufficiency (CVI) is a condition in which veins are unable to transport blood unidirectionally towards the heart. CVI usually occurs in the lower limbs. It might result in considerable discomfort, with symptoms such as pain, itchiness and tiredness in the legs. Patients with CVI may also experience swelling and ulcers. Phlebotonics are a class of drugs often used to treat CVI. This is the second update of a review first published in 2005.

Objectives

To assess the efficacy and safety of phlebotonics administered orally or topically for treatment of signs and symptoms of lower extremity CVI.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and the World Health Organization International Clinical Trials Registry Platform and Clinicaltrials.gov trials register up to 12 November 2019. We searched the reference lists of the articles retrieved by electronic searches for additional citations. We also contacted authors of unpublished studies.

Selection criteria

We included randomised, double-blind, placebo-controlled trials (RCTs) assessing the efficacy of phlebotonics (rutosides, hidrosmine, diosmine, calcium dobesilate, chromocarbe, *Centella asiatica*, disodium flavodate, French maritime pine bark extract, grape seed extract and aminaftone) in patients with CVI at any stage of the disease.

Data collection and analysis

Two review authors independently extracted data and assessed the quality of included RCTs. We estimated the effects of treatment by using risk ratios (RRs), mean differences (MDs) and standardized mean differences (SMDs), according to the outcome assessed. We calculated 95% confidence intervals (CIs) and percentage of heterogeneity (I^2). Outcomes of interest were oedema, quality of life (QoL), assessment of CVI and adverse events. We used GRADE criteria to assess the certainty of the evidence.

Main results

We identified three new studies for this update. In total, 69 RCTs of oral phlebotonics were included, but only 56 studies (7690 participants, mean age 50 years) provided quantifiable data for the efficacy analysis. These studies used different phlebotonics (28 on rutosides, 11 on hidrosmine and diosmine, 10 on calcium dobesilate, two on *Centella asiatica*, two on aminaftone, two on French maritime pine bark extract and one on grape seed extract). No studies evaluating topical phlebotonics, chromocarbe, naftazone or disodium flavodate fulfilled the inclusion criteria.

Moderate-certainty evidence suggests that phlebotonics probably reduce oedema slightly in the lower legs, compared with placebo (RR 0.70, 95% CI 0.63 to 0.78; 13 studies; 1245 participants); and probably reduce ankle circumference (MD -4.27 mm, 95% CI -5.61 to -2.93 mm; 15 studies; 2010 participants). Moderate-certainty evidence shows that phlebotonics probably make little or no difference in QoL compared with placebo (SMD -0.06, 95% CI -0.22 to 0.10; five studies; 1639 participants); and similarly, may have little or no effect on ulcer healing (RR 0.94, 95% CI 0.79 to 1.13; six studies; 461 participants; low-certainty evidence). Thirty-seven studies reported on adverse events. Pooled data suggest that phlebotonics probably increase adverse events slightly, compared to placebo (RR 1.14, 95% CI 1.02 to 1.27; 37 studies; 5789 participants; moderate-certainty evidence). Gastrointestinal disorders were the most frequently reported adverse events. We downgraded our certainty in the evidence from 'high' to 'moderate' because of risk of bias concerns, and further to 'low' because of imprecision.

Authors' conclusions

There is moderate-certainty evidence that phlebotonics probably reduce oedema slightly, compared to placebo; moderate-certainty evidence of little or no difference in QoL; and low-certainty evidence that these drugs do not influence ulcer healing. Moderate-certainty evidence suggests that phlebotonics are probably associated with a higher risk of adverse events than placebo. Studies included in this systematic review provided only short-term safety data; therefore, the medium- and long-term safety of phlebotonics could not be estimated. Findings for specific groups of phlebotonics are limited due to small study numbers and heterogeneous results. Additional high-quality RCTs focusing on clinically important outcomes are needed to improve the evidence base.

PLAIN LANGUAGE SUMMARY

Drugs to improve blood flow for people who have poor blood circulation in the veins of their legs

Background

In chronic venous insufficiency, veins of the lower limbs are unable to transport blood towards the heart. It might be caused by genetic factors, may occur after trauma, or may result from a blood clot. Poor movement of blood up the legs may cause swelling and puffiness, feelings of heaviness, tingling, cramps, pain, varicose veins and changes in skin pigmentation. If severe insufficient blood circulation occurs, ulcers and skin wasting can develop. Drugs such as natural flavonoids extracted from plants and similar synthetic products may improve blood circulation. These drugs are known collectively as venoactive drugs or phlebotonics. This review examined evidence from randomised controlled clinical trials comparing these drugs versus inactive treatment (placebo), generally given over one to three months.

Study characteristics and key results

We identified three new studies for this update. In total, 69 studies met the eligibility criteria for this review. However, we could only use 56 studies (7690 participants; mean age 50 years) in further analysis.

We compared the results and summarised the evidence from the studies. After doing so, we assessed how certain the evidence was. To do this, we considered factors such as the way studies were conducted, study sizes, and consistency of findings across studies. Based on our assessments, we categorised the evidence as potentially being of very low, low, moderate or high certainty.

Moderate-certainty evidence from 13 studies (involving 1245 people) suggests that phlebotonics probably slightly reduce puffiness (oedema) compared with placebo. Moderate-certainty evidence suggests that there is little or no difference in quality of life for people taking phlebotonics when compared with placebo. Low-certainty evidence suggests there is little or no difference in the proportion of healed ulcers with phlebotonics, compared with placebo. Moderate-certainty evidence from 37 studies (involving 5789 people) suggests that phlebotonics probably produce more side effects, especially gastrointestinal disorders.

Certainty of the evidence

All evidence was of moderate or low certainty. Starting from an initial assumption of high certainty, we downgraded the certainty of evidence by one level for each outcome because of the high risk of bias, primarily due to selective outcome reporting and incomplete

outcome data. For the outcome of ulcer healing, we downgraded by an additional level due to statistical imprecision (small number of events). With moderate-certainty evidence, we are moderately confident in the effect estimates for these outcomes. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. With low-certainty evidence, our confidence in the effect estimate for that outcome is limited. The true effect may be substantially different from the estimate of the effect.

How-up-to date is this review?

The evidence in this Cochrane Review is current to November 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Do phlebotonics improve signs and symptoms of venous insufficiency when compared with placebo?

Phlebotonics compared with placebo for venous insufficiency

Patient or population: patients with venous insufficiency
Settings: hospital and ambulatory settings
Intervention: phlebotonics
Comparison: placebo

Outcomes	Anticipated absolute effects *		Relative effect (95% CI)	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with phlebotonics				
Oedema in the lower legs (dichotomous variable) Follow-up: 1-6 months	**575 per 1000**	**403 per 1000** (362 to 449)	**RR 0.70** (0.63 to 0.78)	1245 (13 studies)	⊕⊕⊕⊖ **Moderate** [a]	Phebotonics probably slightly reduce oedema in the lower limb compared to placebo
Oedema in the lower legs (ankle circumference, mm) Follow-up: 1-12 months	-	Mean ankle circumference in the lower legs in the phlebotonic groups was **4.27 mm lower** (5.61 to 2.93 lower) than in the placebo groups	-	2010 (15 studies)	⊕⊕⊕⊖ **Moderate** [b]	Phlebotonics probably slightly reduce ankle perimeter circumference compared to placebo
Quality of life (CIVIQ and other questionnaires) Follow-up: mean 2-12 months	-	The QoL in the phlebotonic groups was **0.06 SMD lower** (0.22 lower to 0.1 higher) than in the placebo groups	-	1639 (5 studies)	⊕⊕⊕⊖ **Moderate** [c]	Phebotonics probably make little or no difference to QoL compared with placebo
Ulcer healing (dichotomous variable) Follow-up: 1-12 months	**381 per 1000**	**358 per 1000** (301 to 430)	**RR 0.94** (0.79 to 1.13)	461 (6 studies)	⊕⊕⊖⊖ **Low** [d]	Phlebotonics may make little or no difference to ulcer healing compared to placebo

Adverse events Follow-up: 1-12 months	**158 per 1000**	**180 per 1000** (161 to 200)	**RR 1.14** (1.02 to 1.27)	5789 (37 studies)	⊕⊕⊕⊖ **Moderate** [e]	Phlebotonics probably slightly increase adverse events compared to placebo

*__The risk in the intervention group__ (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; **CIVIQ**: Chronic Venous Insufficiency International Questionnaire; **QoL**: quality of life; **RCT**: randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The certainty of the evidence was downgraded (1 level) to moderate because of overall risk of bias (10 studies had an unclear risk of bias and two had a high risk of bias)
[b]The certainty of the evidence was downgraded (1 level) to moderate because of overall risk of bias (11 studies had an unclear risk of bias and one had a high risk of bias)
[c]The certainty of the evidence was downgraded (1 level) to moderate because of overall risk of bias (one study had an unclear risk of bias and two had a high risk of bias)
[d]The certainty of the evidence was downgraded (2 levels) to low because of overall risk of bias (four studies had an unclear risk of bias and two had a high risk of bias) and imprecision (low number of events)
[e]The certainty of the evidence was downgraded (1 level) to moderate because of overall risk of bias (28 RCTs had unclear risk of bias and four RCTs had high risk of bias)

BACKGROUND

Description of the condition

Chronic venous insufficiency (CVI) is a condition in which veins are unable to transport blood unidirectionally toward the heart with flow adapted to tissue drainage needs, temperature regulation and haemodynamic reserve, regardless of their position and activity. CVI first manifests as an increase in venous tension (venous hypertension, or high blood pressure in the veins) with or without reflux (Kurz 1999). Depending on its cause, CVI can be congenital, primary (with undetermined cause) or secondary (post-thrombotic, post-traumatic or other). Depending on its pathophysiology, CVI can be related to occlusion (blocked veins), reflux or both. Finally, it might depend on superficial or deep venous systems or on perforator anomalies (Porter 1995).

CVI is an important cause of discomfort and inability to work, and many people find it difficult to live with this condition. Its prevalence has not been clearly determined because available studies regarding this subject are few, and those that are available present limitations. Some studies do not cover the whole pathological spectrum and focus only on varicose veins or ulcers; others do not use standardized definitions of the illness and apply a variety of diagnostic criteria (Nicolaides 2000). As a result, prevalence has been estimated at between 1% and 50% (Evans 1999; Stanhope 1975; Van den Oever 1998). The Framingham Study showed an annual incidence of 2.6% among women and 1.9% among men (Brand 1988). In a recent publication of the Edinburgh Vein Study, annual incidence of CVI was reported as 1% among the general population of the UK (Robertson 2014).

Causes of CVI are unknown, although it has been associated with venous dilation, deformity and valvular venous incompetence. Trophic skin disorders and venous ulcers result from severe varicose illness (Carpentier 2000). Varicose veins have a multi-factorial origin related to advanced age and certain lifestyles (sedentary life), pregnancy, hereditary factors and obesity. Risk of ulcers may be increased by trauma and previous episodes of deep venous thrombosis (clinical or subclinical) (Scott 1995).

Clinical manifestations of CVI differ according to stage of the illness and can include feelings of heaviness in the extremities, paraesthesia (tingling), cramps, pain, oedema (swellings), varicose veins, skin pigmentation, varicose sores and signs of skin atrophy (wasting). Symptoms are frequently related to extent of disease. Underlying venous disease (superficial, deep or both, with or without obstruction) has a major impact on both manifestations of the disease and response to treatment. Since 1994, criteria develop by the International Consensus Committee on Chronic Venous Disease have been used to define and classify CVI in a standardized fashion (Porter 1995). According to this Consensus, clinical signs (C), aetiology (E), anatomical distribution (A) and physiological conditions (P) ("Clinical-Etiology-Anatomy-Pathophysiology"; CEAP) are used to classify CVI (Porter 1995). A later revision of the CEAP classification established a means of differentiating between chronic venous disorder (referring to all morphology and functional abnormalities of the venous system) and CVI (reserved for more advanced stages of the disease with oedema, skin changes or venous ulcers) (Eklöf 2004). In parallel, a venous clinical severity score (ranging from none (0) to severe (3)) was established to assess pain, varicose veins, venous oedema, skin pigmentation, inflammation, induration, active ulcer (number, duration and size) and use of compression therapy (Vasquez 2010). Recently, a new version of CEAP classification has been published (Lurie 2020), in which Corona phlebectatica was added as a C4c clinical subclass, the modifier “r” introduced for recurrent varicose veins and recurrent venous ulcers and numeric descriptions of the venous segments replaced by their common abbreviations (Lurie 2020).

Description of the intervention

Surgery, sclerotherapy and mechanical compression are generally the preferred treatments for CVI. However, pharmacological treatments or phlebotonics are often used because they are easy to administer, and because compliance with compressive treatments (such as elastic stockings) is often poor.

Phlebotonics represent a heterogeneous group of medications used to treat CVI. Most of these drugs are natural flavonoids extracted from plants. Synthetic products with flavonoid-like properties are also used to treat venous disorders. In the Anatomical Therapeutic Chemical (ATC) system, phlebotonics are classified as vasoprotective agents (ATC 2015). Within this classification system, active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Phlebotonics are known as venoactive drugs whose mechanism of action is not scientifically well established despite the availability of numerous studies examining their pharmacological and clinical properties. These medications are associated with effects on macrocirculation (e.g. they may improve venous tone) (Tsouderos 1991) and on microcirculatory parameters (e.g. they may decrease capillary hyperpermeability) (Behar 1988).

Why it is important to do this review

Lower limb CVI affects a predominantly adult population and it is a frequent cause for a referral from primary to secondary care (Venous Forum 2011). Although phlebotonics are commercialised in many countries, in others they are not widely available. In some countries, such as Spain, for certain phlebotonics (calcium dobesilate, chromocarbe and naftazone) the CVI indication has been withdrawn, and for several other phlebotonics, such as aminaftone, diosmine, hidrosmine, escin and some rutosides, conditions of use during exacerbations of CVI have been limited to two or three months by the Spanish Ministry of Health (AEM 2002).

Controversy surrounds the clinical relevance of the efficacy and benefit-risk balance of phlebotonics. Case-control studies have found that risk of agranulocytosis (reduced numbers of white blood cells, mainly neutrophils) is associated with some phlebotonics (Ibañez 2000; Ibáñez 2005; Kaufman 1991). As efficacy is not well defined and serious harmful effects have been associated with phlebotonics, an evaluation of available evidence is needed.

OBJECTIVES

To assess the efficacy and safety of phlebotonics administered orally or topically for treatment of signs and symptoms of lower extremity CVI.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, double-blind, controlled trials assessing the efficacy and/or safety of phlebotonics compared with placebo in patients with chronic venous insufficiency (CVI) at any stage of the disease. We did not include studies which were not RCTs or double-blind. We did not choose specific diagnostic classifications of CVI a priori because most of the studies were carried out before 1994, before the international diagnostic consensus of CVI. Therefore, we included RCTs with different diagnostic criteria. We included studies in which use of compression measures (support tights) was similar across groups.

Types of participants

We included both male and female participants who were 18 years of age and older, suffering from any type of CVI. CVI could be diagnosed according to explicit clinical criteria and/or by objective instruments. Participant background, ethnicity and medical co-morbidities at the beginning of the study did not influence the decision to include or exclude the study. We excluded studies that included participants with active thrombophlebitis and those including pregnant women.

Types of interventions

We considered the following interventions to treat CVI acceptable for inclusion: treatments including venoactive drugs or phlebotonics, administered orally or topically, at any dosage and independently of the duration of treatment, compared with placebo. We excluded studies that compared phlebotonics among themselves or with any other therapeutic method (i.e. support tights or surgery).

- Natural products
  - Flavonoids: rutoside, French maritime pine bark extract (also known as pycnogenol), grape seed extract, diosmine and hidrosmine, disodium flavodate
  - Saponosides: *Centella asiatica*
- Synthetic products
  - Calcium dobesilate, naftazone, aminaftone, chromocarbe

We excluded escin (horse chestnut seed extract), as it is covered in another Cochrane Review (Pittler 2012).

Pentoxifylline is classified as a peripheral vasodilator, not as a vasoprotective agent (ATC 2015); therefore, we excluded it from this review.

Types of outcome measures

We included studies that assessed any of the following outcome measures.

Primary outcomes

- Oedema in the lower limb measured by the dichotomous variable 'oedema' and the continuous variables 'ankle perimeter circumference' and 'volume of the leg'
- Specific quality of life (QoL) scales (e.g. Chronic Venous Insufficiency International Questionnaire (CIVIQ))

Secondary outcomes

- Assessment of CVI: objective signs
  - Skin manifestations including venous ulcer healing and trophic alterations (e.g. lipodermatosclerosis (hardening of the skin that may cause red/brown pigmentation and is accompanied by wasting of subcutaneous fat), telangiectasia (tiny blood vessels cause threadlike red lines or patterns on the skin), reticular veins (dilated veins that show as a net-like pattern on the skin), varicose veins (permanently dilated veins)
- Assessment of CVI: subjective symptoms
  - Pain in the lower legs
  - Cramps in the lower legs
  - Restless legs
  - Itching in the lower legs
  - Feeling of heaviness in the lower legs
  - Swelling in the lower legs
  - Paraesthesias (abnormal sensations, such as prickling, burning, tingling) in the lower legs
  - Participant satisfaction
- Adverse events
  - Adverse reactions experienced by participants during the trial, as reported by questionnaire or related by participants and specified within the publication

Search methods for identification of studies

Electronic searches

For this update, the Cochrane Vascular Information Specialist conducted systematic searches of the following databases for randomised controlled trials and controlled clinical trials without language, publication year or publication status restrictions:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched on 12 November 2019);
- the Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Register of Studies Online (CRSO 2019, issue 10);
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) (searched from 1 January 2017 to 12 November 2019);
- Embase Ovid (searched from 1 January 2017 to 12 November 2019);
- CINAHL Ebsco (searched from 1 January 2017 to 12 November 2019); and
- AMED Ovid (searched from 1 January 2017 to 12 November 2019).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. Where appropriate, strategies were combined with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6, Lefebvre 2011). Search strategies for major databases are provided in Appendix 1.

The Information Specialist searched the following trials registries on 12 November 2019:

- the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch);
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

For this update, we searched the reference lists of articles retrieved by electronic searches for additional citations.

Data collection and analysis

Selection of studies

For this update, two review authors (RV and DS) independently assessed the eligibility of new studies identified by the searches. A third review author (MMZ) helped to resolve disagreements by discussion.

Data extraction and management

For this update, two review authors (RV and MMZ) independently extracted data from new studies and entered them to a previously tested standardized form. A consensus between reviewers were reached if any data extraction discrepancies occurred. We collected information including characteristics of study participants, characteristics of intervention and control groups and outcome characteristics of every group of participants. For cross-over studies, we extracted and analyzed only data related to the first period of treatment.

Assessment of risk of bias in included studies

For this update, two review authors (RV and MJMZ) independently assessed the risk of bias of the newly included studies. A consensus between review authors was reached by discussion when there was any disagreement. We specifically assessed the randomisation method (sequence generation and allocation concealment); blinding of participants, caregivers/study researchers and outcome assessors to the intervention; whether outcome data were incomplete; and presence of selection bias. Once this information was gathered, review authors classified each study into one of three levels of risk of bias: low, unclear or high, based on the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We estimated effects of treatment with phlebotonics by using risk ratios (RRs) for dichotomous variables and mean differences (MDs) or standardized mean differences (SMDs) for continuous variables, along with their corresponding 95% confidence intervals (CIs). We calculated SMDs when studies used different instruments to measure the same variable.

Unit of analysis issues

We took the unit of analysis to be the individual participant. For cross-over studies, we extracted and analyzed only data related to the first period of treatment.

Dealing with missing data

We analyzed dichotomous variables by applying the intention-to-treat (ITT) principle to analyze every individual in the randomly assigned treatment group regardless of whether individuals completed treatment or withdrew prematurely from the study. We included in the ITT analysis only studies that provided data from all randomised participants, or that stated the number of participants lost during follow-up. We numerically imputed missing values due to withdrawal of participants or loss to follow-up as therapeutic failures in both comparative groups. For continuous variables, we analyzed data as provided by study authors, either per protocol or as ITT values.

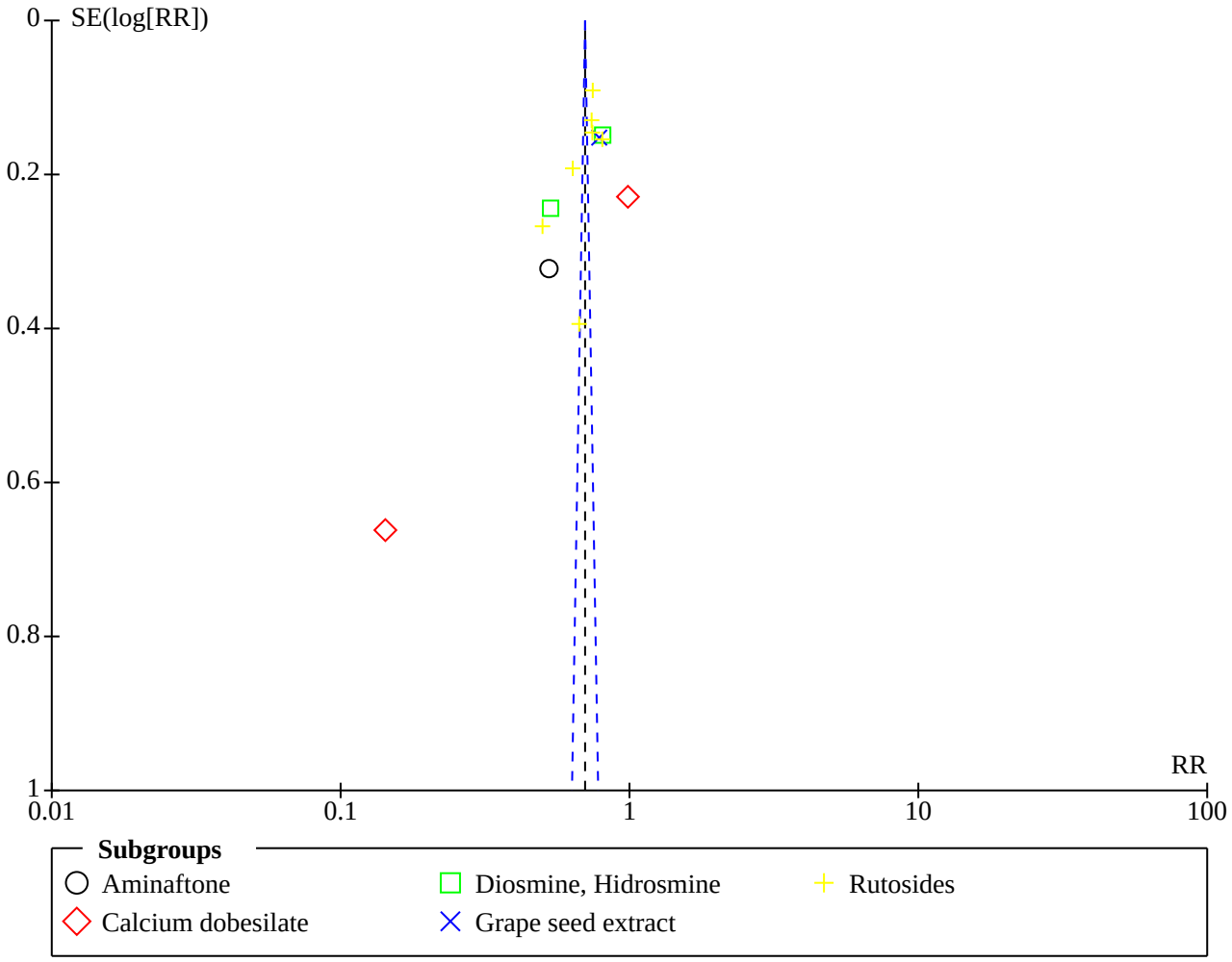
Assessment of heterogeneity

We carried out an analysis to detect the presence of heterogeneity by using the I^2 statistic before obtaining global effect estimators. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than to sampling error (Deeks 2011). When statistical heterogeneity was high (I^2 > 75%), we did not pool studies. For levels of I^2 less than 50%, we applied a fixed-effect model; for levels of I^2 greater than 50% but less than 75%, we applied a random-effects model (DerSimonian 1986).

Assessment of reporting biases

We constructed a funnel plot to assess whether the outcome of oedema (dichotomous variable) was subject to publication bias (Figure 1).

Figure 1. Funnel plot of comparison: 1 Phlebotonics vs placebo, outcome: 1.1 Oedema in the lower legs (dichotomous variable).



Data synthesis

We obtained data from the included studies for variables evaluated at the end of treatment. In addition, we obtained data from measures of change when no significant baseline differences were evident between compared groups. We then pooled these together with other similar continuous outcomes.

We split the outcomes of variables measured by ordinal categorical scales into two groups of response. We considered one group as showing success (no signs or symptoms or mild manifestations) and the other as showing failure (moderate, severe or very severe persistence of signs and symptoms).

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses in addition to the overall analysis of phlebotonics. These included looking at the effects of the following phlebotonics: rutosides, hidrosmine, diosmine, calcium dobesilate, disodium flavodate, grape seed extract, French maritime pine bark extract, chromocarbe and aminaftone.

Sensitivity analysis

We performed sensitivity analyses to assess the influence on data of assumptions and decisions of review authors during the review process. We re-analysed data by:

- excluding studies that used compression measures;
- excluding unpublished studies; and
- excluding studies with high or unclear risk of bias in at least one domain.

Summary of findings and assessment of certainty of the evidence

We created one 'Summary of findings' table to present the main findings for 'Phlebotonics compared with placebo for venous insufficiency' using GRADE profiler software (GRADEpro 2008). See Summary of findings 1. We used the principles of the GRADE system to assess the certainty of the body of evidence associated with the main outcomes listed below. The GRADE approach appraises the certainty of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects

the item being assessed. Evaluation of the certainty of a body of evidence considers within-study risk of bias, indirectness of the evidence, inconsistency (heterogeneity in the data), imprecision (precision of effect estimates) and publication bias (Schünemann 2011).

Two review authors (DS and RV) independently assessed the certainty of the body of evidence for the following outcomes.

- Oedema in the lower legs (dichotomous variable)
- Oedema in the lower legs (circumference mm)
- QoL
- Ulcer healing
- Adverse events

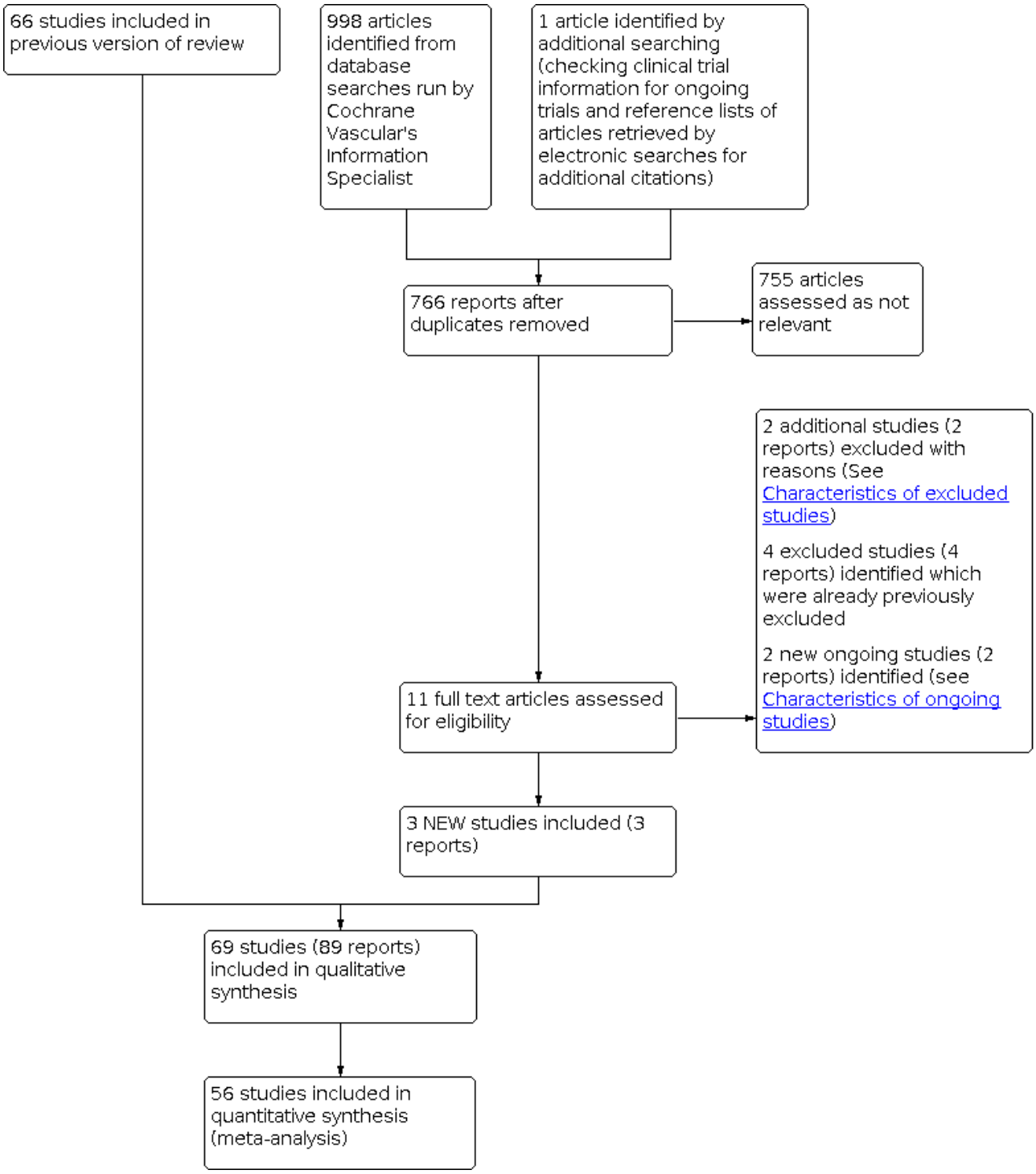
RESULTS

Description of studies

Results of the search

For this update we identified three new included studies (NCT01848210; Rabe 2015; Rabe 2016); two new ongoing studies (Barattini 2019; NCT03833024); and two new studies were excluded (EudraCT2009-014681-25; ISRCTN54360155). See Figure 2. Details of all studies are provided in the Characteristics of included studies, Characteristics of ongoing studies and Characteristics of excluded studies tables.

Figure 2. Study flow diagram.



Included studies

For this update, we identified three new included studies (NCT01848210; Rabe 2015; Rabe 2016). In total with those identified in earlier versions, we included 69 studies. See Characteristics of included studies tables.

Most studies were published in English, but four were published in German (Biland 1982; Kiesewetter 1997; Koscielnny 1996; Pedersen 1992), seven in French (Cauwenberge 1978; Chassignolle 1994; Planchon 1990; Thebaut 1985; Vin 1994; Welch 1985; Zucarelli 1987), four in Spanish (Flota-Cervera 2008; Klüken 1971; Marinello 2002; Serralde 1990), three in Italian (Allegra 1981; Lazzarini 1982; Pecchi 1990), and one in Spanish, French and Dutch (Padrós 1972).

Of the 69 included double-blind, placebo-controlled clinical trials, we did not include 13 studies in the efficacy analysis. Of these, 10 studies corresponded to the rutoside group (Bergqvist 1981;

Cloarec 1994; Jongste 1986; Mann 1981; Nocker 1990; Prerovsky 1972; Renton 1994; Rose 1970; Rudofsky 1989; Sentou 1984), two corresponded to calcium dobesilate (Padrós 1972; Pecchi 1990) and another corresponded to French bark pine extract (Petrassi 2000).

We excluded these studies from the efficacy analysis for the following reasons.

- Only mean data were provided without standard deviations (SDs) or standard errors (SEs) (Sentou 1984).
- Medians were provided instead of means (Renton 1994).
- Outcomes were reported by graph only (Nocker 1990; Rose 1970; Rudofsky 1989).
- First period data were not provided in studies of cross-over design (Padrós 1972; Prerovsky 1972).
- No data were provided for any variable (Bergqvist 1981; Cloarec 1994; Jongste 1986).
- Measured changes were reported when significant differences in baseline were noted between compared groups (Mann 1981; Petrassi 2000).
- A quasi-randomisation method was used in which treatments were alternatively allocated depending on participants' order of arrival (Pecchi 1990).
- At baseline, a significant imbalance in the ulcer area was evident between groups (1130 mm^2 in the rutoside group vs 430 mm^2 in the placebo group; P = 0.039) (Mann 1981).

Of the 56 studies with oral phlebotonics included in the efficacy analysis, studied phlebotonics corresponded to 28 studies of rutosides (Balmer 1980; Burnand 1989; Cloarec 1996; Cauwenberge 1972; Cauwenberge 1978; Cesarone 2002; Cornu-Thenard 1985; Diebschlag 1994; Ihme 1996; Jongste 1986; Jongste 1989; Kiesewetter 1997; Koscielnny 1996; Klüken 1971; Kriner 1985; Languillat 1988; Laurent 1988; MacLennan 1994; NCT01848210; Parrado 1999; Pedersen 1992; Pulvertaft 1983; Schultz-Ehrenburg 1993; Serralde 1990; Unkauf 1996; Vanscheidt 2002a; Vanscheidt 2002b; Vin 1994), 11 of hidrosmine and diosmine (Chassignolle 1994; Danielsson 2002; Dominguez 1992; Fermoso 1992; Gilly 1994; Guilhou 1997; Planchon 1990; Rabe 2015; Thebaut 1985; Welch 1985; Zucarelli 1987), 10 of calcium dobesilate (Casley-Smith 1988; DOBESILATO500/2; Flota-Cervera 2008; Hachen 1982; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Rabe 2016; Widmer 1990), two of *Centella asiatica* (Allegra 1981; Pointel 1986), two of aminaftone (Belczak 2014; Lazzarini 1982), two of French maritime pine bark extract (Arcangeli 2000; Petrassi 2000) and one of grape seed extract (Thebaut 1985). No studies using topical phlebotonics or chromocarbe or naftazone or disodium flavodate fulfilled the inclusion criteria. Length of treatment and participant follow-up ranged from 28 days to four months, except for three studies, in which follow-up lasted six months or more (DOBESILATO500/2; MacLennan 1994; Martinez-Zapata 2008).

Overall, we included 7690 participants in the meta-analysis; 83% were female and 17% were male; mean age was 50 years (range 32 to 62 years). The mean number of participants included per clinical trial was 150 (range 20 to 1137). All participants met the respective CVI criteria of every study, although we noted variation between studies in degree of progression to CVI, as well as in diagnostic classification criteria applied. Only 22% of studies reported the diagnostic classification used. Among studies that did report on the diagnostic classification of CVI, the CEAP classification was used most often (Belczak 2014; Danielsson 2002; DOBESILATO500/2; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Rabe 2015; Rabe 2016; Vanscheidt 2002a; Vanscheidt 2002b), followed by Widmer's classification (Casley-Smith 1988; Cloarec 1996; Koscielnny 1996; Parrado 1999; Unkauf 1996). Wert's was the only other classification used (Kiesewetter 1997).

Differences in severity of disease were observed: some studies were performed with participants at early and symptomatic CVI stages (Cornu-Thenard 1985; Danielsson 2002; Gilly 1994; Hachen 1982; Thebaut 1985), and others included participants at advanced stages because of long progression of the disease or the presence of venous ulcers (Casley-Smith 1988; DOBESILATO500/2; Guilhou 1997; Lazzarini 1982; Marinello 2002; Planchon 1990; Schultz-Ehrenburg 1993; Vanscheidt 2002a). However, most studies included participants at moderate CVI stages with oedema, skin pigmentation, varicose veins and post-thrombotic syndromes.

Ten studies specified that investigators used additional compression therapy (DOBESILATO500/2; Guilhou 1997; Laurent 1988; Lazzarini 1982; Marinello 2002; Martinez-Zapata 2008; Planchon 1990; Rabe 2011; Schultz-Ehrenburg 1993; Zucarelli 1987).

Eleven studies used a visual analogue scale (VAS) to measure subjective variables (Alterkamper 1987; Cesarone 2002; DOBESILATO500/2; Labs 2004; Martinez-Zapata 2008; Rabe 2011; Rabe 2015; Unkauf 1996; Vanscheidt 2002b; Widmer 1990; Zucarelli 1987). Other studies used ordinal categorical scales with a scoring system from -3 to +1 (Hachen 1982), -1 to + 1 (Casley-Smith 1988), 0 to 1 (Ihme 1996), 0 to 2 (Biland 1982; Ihme 1996; Kiesewetter 1997), 0 to 3 (Allegra 1981; Arcangeli 2000; Cloarec 1996; Cornu-Thenard 1985; Danielsson 2002; Diebschlag 1994; Dominguez 1992; Gilly 1994; Jongste 1989; Languillat 1988; Laurent 1988; Lazzarini 1982; Parrado 1999; Planchon 1990; Pointel 1986; Pulvertaft 1983; Serralde 1990; Thebaut 1985; Tsouderos 1989; Welch 1985), 0 to 4 (Balmer 1980; Chassignolle 1994; Fermoso 1992; Flota-Cervera 2008), 0 to 5 (NCT01848210; Rabe 2011), 0 to 7 (Labs 2004) or 0 to 9 (Dominguez 1992). Likewise, some of these scales were used to evaluate signs or objective variables such as oedema or trophic disorders. Methods used to measure oedema included metric tape to measure ankle or calf circumference and plethysmographic values (used in most studies) to determine leg volume.

Excluded studies

For this update, we identified two new studies that were excluded (EudraCT2009-014681-25; ISRCTN54360155). Four previously excluded studies were also identified by the search (Belczak 2014; Kiesewetter 1997; Prerovsky 1972; NCT01532882), making a total of 104 studies excluded for a variety of reasons (see Characteristics of excluded studies for details). We summarise the exclusion details below.

- We excluded 58 studies because the intervention used by researchers was not included in this Cochrane Review (Akbulut 2010; Bacci 2003; Bastide 1976; Batchvarova 1989a; Behar 1993; Bello 1990; Bento 2006; Berson 1978; Bohm 1989; Bolliger 1972; Bosse 1985; Brami 1983; Carstens 1985; Cataldi 2001; Cesarone 2001b; Chiummariello 2009; Cospite 1996; de Parades 1990; Delacroix 1981; Delecluse 1991; Dustmann 1984; Erdlen 1989; Erler 1991; EudraCT2009-014681-25; Henriet 1995; Horvath 1985; Janssens 1999a; Kiesewetter 2000; Koltringer 1993;

Krähenbühl 1975; Krcílek 1973; Languillat 1988b; Marastoni 1982; Monteil-Seurin 1993; Morales 1993; NCT02191163; NCT02191254; NCT02191280; Neumann-Mangoldt 1979; Nill 1970; Ottillinger 2001; Paciaroni 1982; Partsch 1981; Paul 1983; Pauschinger 1987; Pointel 1987b; Pokrovskii 2005; Rabe 2011b; Riccioni 2004; Sanctis 2001; Steiner 1990; Steiner 1992; Topalov 1990; Turio 2000; ISRCTN54360155; Weindorf 1987; Widmer 1972; Zuccarelli 1996).

- We excluded 30 studies because researchers assessed no clinical endpoints or reported only outcomes not included in this Cochrane Review (Androulakis 1989; Auteri 1990; Belcaro 1995; Belcaro 2008; Boisseau 1995; Bort 1995; Cesarone 1992; Cesarone 1994; Cesarone 2001; Cesarone 2001c; Cesarone 2002b; Chant 1973; Clemens 1986; Duchene 1988; Forconi 1977; Gonzalez-Fajardo 1990; Incandela 1995; Incandela 1996; Janssens 1999; Kalus 2004; Kostering 1985; Languillat 1989; Le Dévéhat 1989; Le Dévéhat 1997; Naser-Hijazi 2004; Neumann 1988; Neumann 1990; Questel 1983; Roztocil 1977; Seydewitz 1992).
- We excluded 16 studies because they were not double-blinded (Belcaro 1989; Blume 1996; Cesarone 2001a; Cesarone 2010; De Anna 1989; De Sanctis 2001; Frausini 1985; Glinski 1999; Granger 1995; Incandela 2001; Incandela 2002; Menyhei 1994; NCT01654016; Petruzzellis 2002; Roztocil 2003; Steru 1988).

Ongoing studies

For this update, we identified two new ongoing studies (Barattini 2019; NCT03833024). This brings the total number of ongoing studies included to four (Barattini 2019; ISRCTN18841175; NCT01532882; NCT03833024). Details of these can be found in the Characteristics of ongoing studies table.

Risk of bias in included studies

Overall, only four studies (Labs 2004; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a) were at low risk of bias (see Characteristics of included studies, Figure 3 and Figure 4).

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

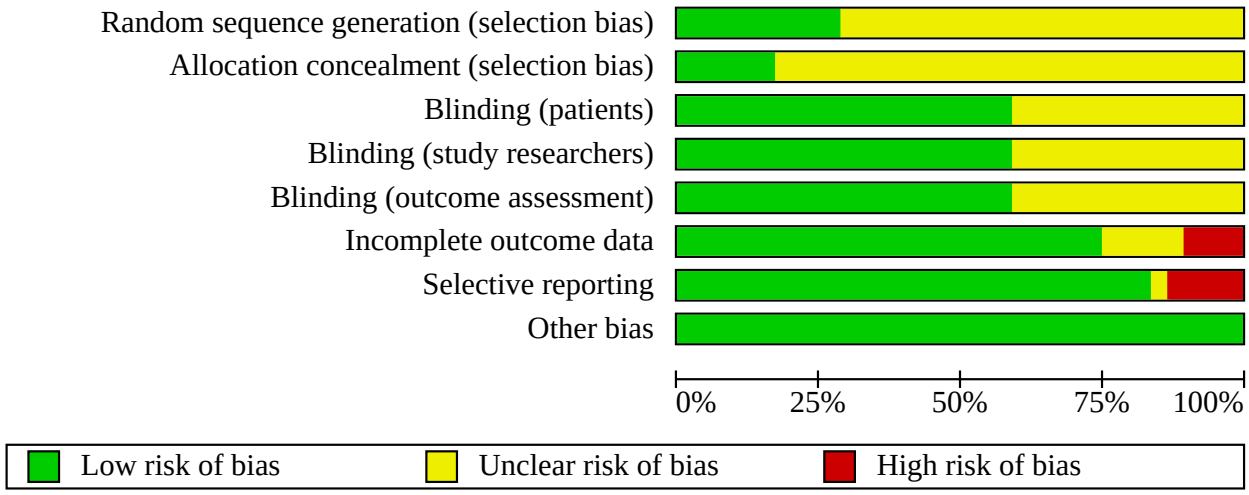


Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

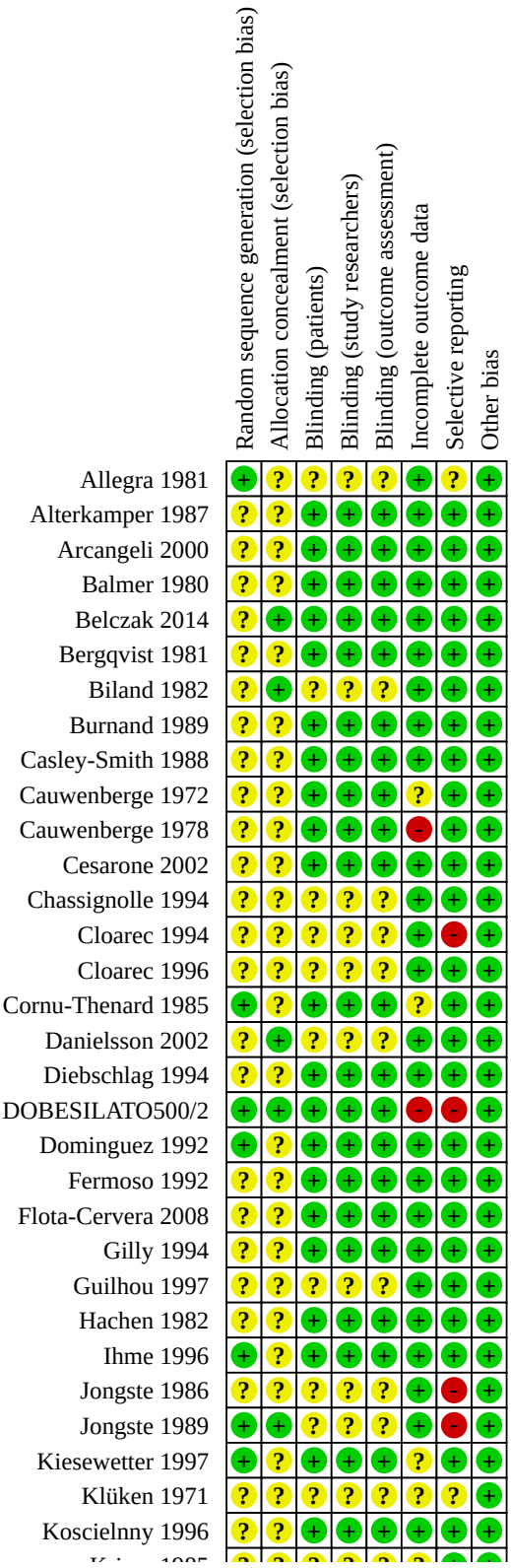
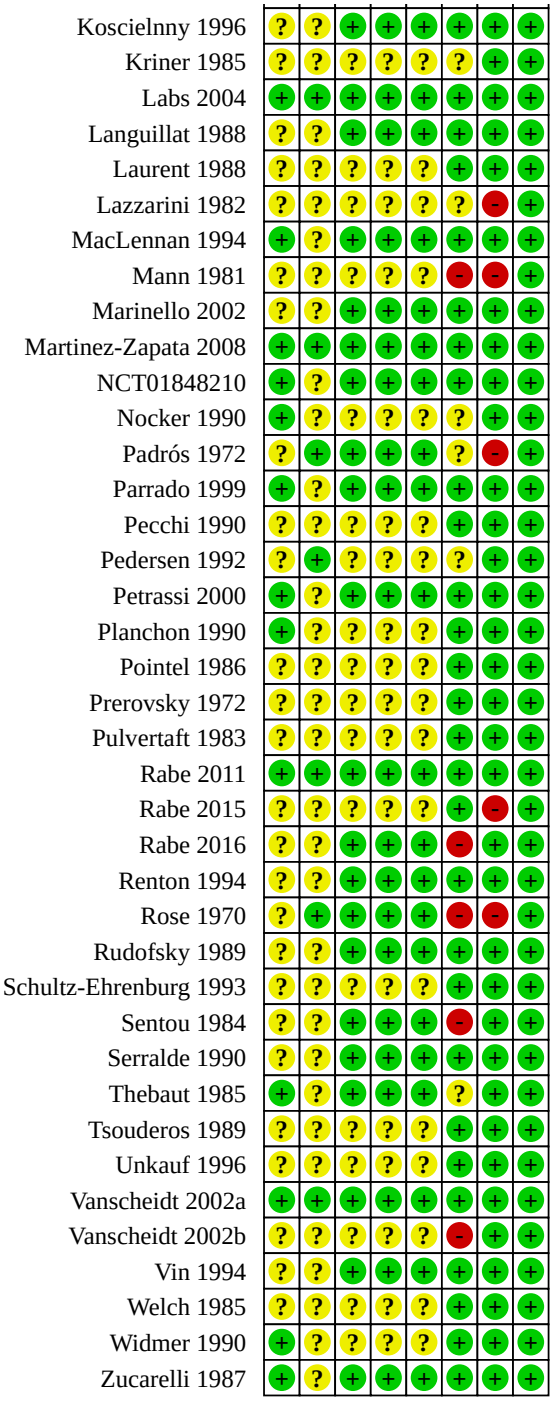


Figure 4. (Continued)



Allocation

Of the 69 studies included, 19 (28%) submitted details on the randomisation process and were assessed as being at low risk (see Figure 4 and Characteristics of included studies). The remaining studies were all judged to be at an unclear risk of bias.

Only 12 (17%) studies provided an accurate explanation of the allocation concealment process. Two used the sealed envelope method (Danielsson 2002; Pedersen 1992), four used indistinguishable number packaging (Biland 1982; Padrós 1972; Rabe 2011; Rose 1970), one used randomised numbered bottles provided by an external investigator (Belczak 2014), two used allocation concealment by direct phone calls (DOBESILATO500/2; Martinez-Zapata 2008), and the remaining three studies used computerised random assignment (Jongste 1989; Labs 2004; Vanscheidt 2002a).

Blinding

Of the 69 studies included, 41 (59%) reported that the placebo used was identical to the active treatment; thus participants, study researchers and outcome assessors were blinded to the intervention and these were judged to have a low risk of bias. The other 28 studies did not mention whether placebo had identical characteristics to those of the active drug and so were at an unclear risk of bias (see Figure 4 and Characteristics of included studies).

Incomplete outcome data

Of the 69 studies included, 52 (75%) reported participant withdrawals, and thus were at low risk of bias. The percentage of withdrawn participants ranged from 0% to 42.5% (see Characteristics of included studies). Only eight (12%) studies included in the efficacy analysis stated that investigators carried out an ITT analysis (Dominguez 1992; Guilhou 1997; Ihme 1996; Martinez-Zapata 2008; Rabe 2011; Rabe 2016; Unkauf 1996; Vanscheidt 2002a). Seven studies had high risk of bias in this domain (Cauwenberge 1978; DOBESILATO500/2; Mann 1981; Rabe 2016; Rose 1970; Sentou 1984; Vanscheidt 2002b): four described an important percentage of losses (42.5% Cauwenberge 1978; 18% Mann 1981; 39% Rose 1970; 34% Vanscheidt 2002b), one interrupted recruitment because financial support was interrupted (DOBESILATO500/2) and one did not specify the number of participants included (Sentou 1984). In the Rabe 2016 study, 14.8% of the randomised participants were lost during follow-up and major protocol violations were reported for 42.4% of the randomised participants. Ten studies were judged to be at unclear risk of bias because the reasons for dropouts (Cauwenberge 1972), or the number of dropouts, were not provided (Cornu-Thenard 1985; Kiesewetter 1997; Klüken 1971; Kriner 1985; Lazzarini 1982; Nocker 1990; Padrós 1972; Pedersen 1992), or the standard deviation was lacking in the results (Thebaut 1985).

Selective reporting

Of the 69 studies included, 57 (84%) reported all outcomes specified in the methods section and were judged as being at low risk of reporting bias. We evaluated seven studies as having high risk of selective reporting bias because we noted differences between outcomes reported in the methods and results sections (Cloarec 1994; Jongste 1986; Jongste 1989; Mann 1981; Rabe 2015), and because data before the cross-over were not reported (Padrós 1972; Rose 1970). One study was interrupted, and results of this study were not published (DOBESILATO500/2). Lazzarini 1982 provided no information about adverse events. Two studies were judged to be at unclear risk of reporting bias because characteristics of participants were not provided ((Allegra 1981) and outcomes were not reported in methods and neither a protocol was published (Klüken 1971).

Figure 1 shows that all studies, except one (Casley-Smith 1988), are located symmetrically around the effect measure at the top of the pyramid, indicating highly precise results (Cauwenberge 1972; Cornu-Thenard 1985; Kiesewetter 1997; Klüken 1971; Kriner 1985; Lazzarini 1982; Nocker 1990; Padrós 1972; Pedersen 1992; Thebaut 1985). Apart from one imprecise study favouring phlebotonics, no small or heterogeneous studies provided results favouring placebo or phlebotonics (Casley-Smith 1988).

Other potential sources of bias

No other potential sources of bias were detected.

Effects of interventions

See: **Summary of findings 1** Do phlebotonics improve signs and symptoms of venous insufficiency when compared with placebo?

See Summary of findings 1 for the main comparison. Results of all analyzed outcomes are specified in an additional Table 1. Results of outcomes analyzed by active agent (aminaftone, calcium dobesilate, *Centella asiatica*, diosmine and hidrosmine, French maritime pine bark extract, grape seed extract and rutosides) are specified in Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; and Table 8, respectively.

Of the 69 included studies, we excluded 13 studies from the efficacy analysis for the reasons explained under Included studies (Bergqvist 1981; Cloarec 1994; Jongste 1986; Mann 1981; Nocker 1990; Padrós 1972; Pecchi 1990; Petrassi 2000; Prerovsky 1972; Renton 1994; Rose 1970; Rudofsky 1989; Sentou 1984). Belczak 2014 compared three different interventions with placebo. For the analysis, we included only the comparison of aminaftone with placebo because the other two interventions were combinations of different drugs (micronised diosmine and hesperidin; coumarin and troxerutin).

Primary outcomes

Oedema in the lower limb (dichotomous variable)

We included 13 trials in the meta-analysis: seven corresponding to rutosides (Cauwenberge 1972; Cauwenberge 1978; Cloarec 1996; Ihme 1996; Kriner 1985; MacLennan 1994; Welch 1985), two to calcium dobesilate (Casley-Smith 1988; Labs 2004), two to hidrosmine and diosmine (Fermoso 1992; Planchon 1990), one to grape seed extract (Thebaut 1985) and one to aminaftone (Lazzarini 1982), with a total of 626 participants in the active treatment group and 619 in the placebo group. The median time to follow-up was 49 days. Phebotonics probably reduce oedema in the lower limb compared to placebo (RR 0.70, 95% CI 0.63 to 0.78; 13 studies; 1245 participants; moderate-certainty evidence; Analysis 1.1). The certainty of the evidence was downgraded by one step to moderate because of overall risk of bias (10 studies had an unclear risk of bias and two had a high risk of bias) (Summary of findings 1). No differences between the subgroups was detected (test for subgroup differences: P = 0.74).

Oedema in the lower limb (continuous variables)

Ankle perimeter circumference

We included 15 studies in the meta-analysis: seven corresponding to rutosides (Cloarec 1996; Cornu-Thenard 1985; Jongste 1989; MacLennan 1994; Parrado 1999; Vin 1994; Welch 1985), five to calcium dobesilate (Flota-Cervera 2008; Labs 2004; Martinez-Zapata 2008; Rabe 2011; Widmer 1990), and three to diosmine (Gilly 1994; Planchon 1990; Tsouderos 1989), with a total of 1001 participants given active treatment and 1009 given placebo. The median time to follow-up was 60 days. Phlebotonics probably slightly reduce ankle perimeter circumference compared to placebo (MD -4.27 mm; 95% CI -5.61 to -2.93; 15 studies; 2010 participants; moderate-certainty evidence; Analysis 1.2). The certainty of the evidence was downgraded by one step to moderate because of overall risk of bias (11 studies had an unclear risk of bias

and one had a high risk of bias). Differences between the subgroups was detected (test for subgroup differences: P = 0.02) due to a larger effect of diosmin-hidrosmin.

Volume of the leg

We included 11 studies in the analysis: six corresponding to rutosides (Burnand 1989; Diebschlag 1994; Ihme 1996; Kiesewetter 1997; NCT01848210; Vanscheidt 2002a), four to calcium dobesilate (Casley-Smith 1988; Rabe 2011;Rabe 2016; Widmer 1990) and one to aminaftone (Belczak 2014), with a total of 686 participants treated with phlebotonics and 706 with placebo. Phlebotonics probably slightly reduce volume of the leg compared to placebo (SMD -0.24 mL; 95% CI -0.33 to -0.15; 11 studies; 2072 participants; moderate-certainty evidence; Analysis 1.3). The certainty of the evidence was downgraded (1 level) to moderate because of overall risk of bias (seven studies had an unclear risk of bias and one had a high risk of bias). Differences between the subgroups was detected (test for subgroup differences: P = 0.04) due to a larger effect of calcium dobesilate.

QoL

Seven studies evaluated QoL (Belczak 2014; Martinez-Zapata 2008; Rabe 2011; Rabe 2015; Rabe 2016; Vanscheidt 2002a; Vanscheidt 2002b). Vanscheidt 2002a and Vanscheidt 2002b assessed QoL by using a questionnaire (EuroQol Measure of Health-Related QoL and Freiburg Life Quality Assessment, respectively) and therefore did not provide quantifiable results. Martinez-Zapata 2008, Rabe 2011, Rabe 2015 and Rabe 2016 evaluated QoL via the Chronic Venous Insufficiency International Questionnaire (CIVIQ). Belczak 2014 used a specific questionnaire for chronic venous disease adapted from Cesarone 2006. Phebotonics probably make little or no difference to QoL compared with placebo (SMD -0.06, 95% CI -0.22 to 0.10; five studies; 1639 participants; moderate-certainty evidence; Analysis 1.4). The certainty of the evidence was downgraded by one step to moderate because of overall risk of bias (one study had an unclear risk of bias and two had a high risk of bias). Differences between the subgroups was detected (test for subgroup differences: P = 0.02) due to a larger effect of aminaftone .

Secondary outcomes

Assessment of CVI by objective signs: skin manifestations

Ulcer healing (dichotomous variable)

We included six trials in the meta-analysis: one on aminaftone (Lazzarini 1982), one on calcium dobesilate (DOBESILATO500/2), two on diosmine (Fermoso 1992; Guilhou 1997) and two on rutoside (MacLennan 1994; Schultz-Ehrenburg 1993), with a total of 230 participants in the active treatment group and 231 in the placebo group. Phlebotonics may make little or no difference to dichotomous variable ulcer cured compared to placebo (RR 0.94; 95% CI 0.79 to 1.13; 6 studies; 461 participants; low-certainty evidence; Analysis 1.5). The certainty of the evidence was downgraded by two levels to low because of overall risk of bias (four studies had an unclear risk of bias and two had a high risk of bias) and imprecision (low number of total events) (Summary of findings 1). No differences between the subgroups was detected (test for subgroup differences: P = 0.21).

Trophic disorders (dichotomous variable)

We included six studies in the meta-analysis: four on hidrosmine and diosmine (Fermoso 1992; Gilly 1994; Laurent 1988; Planchon 1990), one on aminaftone (Lazzarini 1982) and one on rutosides (MacLennan 1994), with a total of 355 participants in the phlebotonics group and 350 in the placebo group. Phlebotonics probably slightly improve trophic disorders compared to placebo (RR 0.87, 95% CI 0.81 to 0.95; 6 studies; 705 participants; moderate-certainty evidence; Analysis 1.6). The certainty of the evidence was downgraded by one level to moderate because of overall risk of bias (five studies had an unclear risk of bias and one had a high risk of bias). No differences between the subgroups was detected (test for subgroup differences: P = 0.80).

Telangiectasia, reticular veins and varicose veins (dichotomous variable)

Included studies did not report data on improvement in skin signs such as telangiectasia, reticular veins and varicose veins. Only Fermoso 1992 reported results regarding varicose veins. Before treatment, 3/16 (18.8%) participants presented varicose veins in the hidrosmine group and 2/12 participants in the placebo group (16.7%). After treatment, one participant from the hidrosmine group was cured of varicose veins, and no participants from the placebo group were cured.

Assessment of CVI by subjective symptoms

Pain in the lower legs (dichotomous variable)

A total of 21 studies reported on this outcome as a dichotomous variable: 10 on rutosides (Balmer 1980; Cauwenberge 1972; Cauwenberge 1978; Jongste 1989; Klüken 1971; Languillat 1988; Pedersen 1992; Pulvertaft 1983; Vanscheidt 2002a; Welch 1985), five on calcium dobesilate (Casley-Smith 1988; Flota-Cervera 2008; Hachen 1982; Rabe 2016; Widmer 1990), four on diosmine and hidrosmine (Biland 1982; Dominguez 1992; Fermoso 1992; Planchon 1990), one on aminaftone (Lazzarini 1982), and one on French maritime pine bark extract (Arcangeli 2000), with a total of 1468 participants treated with phlebotonics and 1130 with placebo (Analysis 1.7). The analysis showed heterogeneity (I^2 = 77%); therefore, we did not pool the data.

Pain in the lower legs (continuous variable)

We included 12 studies in the meta-analysis: five on calcium dobesilate (DOBESILATO500/2; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Rabe 2016), three on rutosides (Cloarec 1996; Cornu-Thenard 1985; Parrado 1999), three on diosmine (Gilly 1994; Planchon 1990; Rabe 2015) and one on French maritime pine bark extract (Arcangeli 2000), with a total of 1110 participants assigned to phlebotonics and 1122 to placebo (Analysis 1.8). Phlebotonics may reduce pain (measured as a continuous variable) in the lower legs compared to placebo (SMD -0.35, 95% CI -0.54 to -0.17; 12 studies; 2232 participants; low-certainty evidence). The certainty of the evidence was downgraded by two levels to low because of overall risk of bias (seven studies had an unclear risk of bias and three had a high risk of bias) and imprecision. We used a random-effects model as heterogeneity was detected (I^2 = 75%). Differences between the subgroups was detected (test for subgroup differences: P = 0.002) due to differences in results between the subgroup of French maritime pine bark extract compared to the other subgroups.

Cramps in the lower legs (dichotomous variable)

We included 14 studies in the meta-analysis: eight on rutosides (Balmer 1980; Cauwenberge 1978; Jongste 1989; Languillat 1988;

Pedersen 1992; Pulvertaft 1983; Vin 1994; Welch 1985), three on diosmine and hidrosmine (Biland 1982; Fermoso 1992; Planchon 1990), two on calcium dobesilate (Casley-Smith 1988; Widmer 1990) and one on aminaftone (Lazzarini 1982), with a total of 1072 participants treated with phlebotonics and 721 with placebo. Phlebotonics probably reduce cramps (measured as a dichotomous variable) compared to placebo (RR 0.72, 95% CI 0.58 to 0.89; 14 studies; 1793 participants; moderate-certainty evidence; Analysis 1.9) The certainty of the evidence was downgraded by one level to moderate because of overall risk of bias (11 studies had an unclear risk of bias and three had a high risk of bias). We used a random-effects model as heterogeneity was detected (I^2 = 73%). No differences between the subgroups was detected (test for subgroup differences: P = 0.28).

Cramps in the lower legs (continuous variable)

We included four studies in the meta-analysis: two on rutosides (Cloarec 1996; Parrado 1999), one on calcium dobesilate (Martinez-Zapata 2008), and one on diosmine (Gilly 1994), with 363 participants treated with phlebotonics and 366 with placebo (Analysis 1.10). The analysis showed heterogeneity (I^2 = 86%); therefore, we did not pool the data.

Restless legs (dichotomous variable)

We included seven studies in the meta-analysis: four on rutosides (Balmer 1980; Cauwenberge 1978; Jongste 1989; Pedersen 1992), two on calcium dobesilate (Casley-Smith 1988; Widmer 1990), and one on diosmine (Biland 1982). A total of 329 participants were treated with phlebotonics and 323 with placebo (Analysis 1.11). Phebotonics probably slightly reduce restless legs (measured as a dichotomous variable) compared to placebo (RR 0.81, 95% CI 0.72 to 0.91; 7 studies; 652 participants; moderate-certainty evidence). The certainty of the evidence was downgraded by one level to moderate because of overall risk of bias (five studies had an unclear risk of bias and two had a high risk of bias). No differences between the subgroups was detected (test for subgroup differences: P = 0.41).

Itching in the lower legs (dichotomous variable)

We included four studies in the analysis: two on rutoside (Pedersen 1992; Vanscheidt 2002a), one on hidrosmine (Fermoso 1992), and one on aminaftone (Lazzarini 1982). A total of 206 participants were included in the active treatment group and 199 in the placebo group (Analysis 1.12). The analysis showed heterogeneity (I^2 = 92%); therefore, we did not pool the data.

Itching in the lower legs (continuous variable)

We included two studies in the analysis: one on calcium dobesilate (Martinez-Zapata 2008), and one on rutosides (Parrado 1999). A total of 234 participants were treated with phlebotonics and 242 with placebo (Analysis 1.13). The analysis showed heterogeneity (I^2 = 82%), and we did not pool the data.

Feeling of heaviness in the lower legs (dichotomous variable)

We included 19 studies in the analysis: nine on rutosides (Cauwenberge 1972; Cauwenberge 1978; Jongste 1989; Languillat 1988; Pedersen 1992; Pulvertaft 1983; Vanscheidt 2002a; Vin 1994; Welch 1985), four on diosmine and hidrosmine (Dominguez 1992; Fermoso 1992; Planchon 1990; Tsouderos 1989), three on calcium dobesilate (Casley-Smith 1988; Hachen 1982; Widmer 1990), one on aminaftone (Lazzarini 1982), one on *Centella asiatica* (Pointel 1986), and one on French maritime pine bark extract (Arcangeli 2000). A total of 1257 participants were included in the active treatment group and 909 in the placebo group (Analysis 1.14). The analysis showed heterogeneity (I^2 = 80%), and we did not pool the data.

Feeling of heaviness in the lower legs (continuous variable)

We included 10 studies in the analysis: six on rutosides (Alterkamper 1987; Cloarec 1996; Cornu-Thenard 1985; Diebschlag 1994; Parrado 1999; Unkauf 1996), two on calcium dobesilate (Marinello 2002; Martinez-Zapata 2008), one on diosmine (Gilly 1994), and one on French maritime pine bark extract (Arcangeli 2000). A total of 557 participants were included in the active treatment group and 557 in the placebo group (Analysis 1.15). The analysis showed heterogeneity (I^2 = 91%); therefore, we did not pool the data.

Swelling in the lower legs (dichotomous variable)

We included 14 studies in the analysis: nine on rutosides (Balmer 1980; Cauwenberge 1978; Jongste 1989; Kriner 1985; Languillat 1988; Pedersen 1992; Vanscheidt 2002a; Vin 1994; Welch 1985), two on calcium dobesilate (Casley-Smith 1988; Hachen 1982), two on diosmine and hidrosmine (Biland 1982; Fermoso 1992), and one on French maritime pine bark extract (Arcangeli 2000), with 544 participants included in the active treatment group and 528 in the placebo group. Phebotonics probably reduce swelling in the lower leg (measured as a dichotomous variable) compared to placebo (RR 0.63, 95% CI 0.50 to 0.80; 14 studies; 1072 participants; moderate-certainty evidence; Analysis 1.16). The certainty of the evidence was downgraded by one level to moderate because of overall risk of bias (11 studies had an unclear risk of bias and two had a high risk of bias). We used a random-effects model as heterogeneity was detected (I^2 = 69%). Differences between the subgroups was detected (test for subgroup differences: P = 0.007) due to a larger effect of calcium dobesilate.

Swelling in the lower legs (continuous variable)

We included six studies in the analysis: three on rutosides (Cloarec 1996; Diebschlag 1994; Unkauf 1996), one on diosmine (Gilly 1994), one on calcium dobesilate (Martinez-Zapata 2008), and one on French maritime pine bark extract (Arcangeli 2000), with 436 participants assigned to active treatment and 435 to placebo (Analysis 1.17). The analysis showed heterogeneity (I^2 = 95%), and we did not pool the data.

Paraesthesia in the lower legs (dichotomous variable)

We included nine studies in the analysis: four on rutosides (Balmer 1980; Cauwenberge 1978; Pulvertaft 1983; Welch 1985), three on calcium dobesilate (Casley-Smith 1988; Hachen 1982; Widmer 1990) and two on diosmine and hidrosmine (Fermoso 1992; Planchon 1990), with 896 participants assigned to active treatment and 560 to placebo (Analysis 1.18). Phlebotonics probably reduce paraesthesia in the lower legs (measured as a dichotomous variable) compared to placebo (RR 0.67, 95% CI 0.50 to 0.88; 9 studies; 1456 participants; moderate-certainty evidence). The certainty of the evidence was downgraded by one level) to moderate because of overall risk of bias (eight studies had an unclear risk of bias and one had a high risk of bias). We used a random-effects model as heterogeneity was detected (I^2 = 72%). No

differences between the subgroups was detected (test for subgroup differences: P = 0.32).

Paraesthesia in the lower legs (continuous variable)

We included two studies in the analysis: one on diosmine (Gilly 1994), and one on rutoside (Cornu-Thenard 1985), with 97 participants assigned to active treatment and 91 to placebo (Analysis 1.19). It is uncertain whether phlebotonics reduce continuous variable paraesthesia because the certainty of this evidence is very low (SMD -0.15, 95% CI -0.44 to 0.13; 2 studies; 188 participants). The certainty of the evidence was downgraded by three levels to very low because of risk of bias (one level) and the sample size was small with a high imprecision in the results (two levels). No differences between the subgroups was detected (test for subgroup differences: P = 0.59).

Participant satisfaction (dichotomous variable)

We included 16 studies in the analysis: eight on rutosides (Burnand 1989; Cloarec 1996; Jongste 1989; Languillat 1988; Parrado 1999; Pedersen 1992; Pulvertaft 1983; Welch 1985), three on calcium dobesilate (Casley-Smith 1988; Labs 2004; Rabe 2011), four on diosmine (Biland 1982; Chassignolle 1994; Danielsson 2002; Laurent 1988), and one on *Centella asiatica* (Allegra 1981), with a total of 1265 participants treated with phlebotonics and 939 with placebo (Analysis 1.20). The analysis showed heterogeneity (I^2 = 86%), and we did not pool the data.

Participant satisfaction (continuous variable)

We included seven studies in the analysis: four on rutosides (Cesarone 2002; Cloarec 1996; Ihme 1996; Kiesewetter 1997), two on calcium dobesilate (Rabe 2011; Widmer 1990), and one on diosmine (Gilly 1994), with 440 participants treated with phlebotonics and 441 with placebo (Analysis 1.21). The analysis showed heterogeneity (I^2 = 85%), and we did not pool the data.

Adverse events

Thirty-seven studies reported on adverse events. These included 17 trials considering rutosides (Alterkamper 1987; Balmer 1980; Diebschlag 1994; Jongste 1989; Koscielnny 1996; Kriner 1985; Languillat 1988; MacLennan 1994; NCT01848210; Parrado 1999; Serralde 1990; Unkauf 1996; Vanscheidt 2002a; Vanscheidt 2002b; Vin 1994; Welch 1985; Zucarelli 1987), nine on hidrosmine-diosmine (Biland 1982; Danielsson 2002; Dominguez 1992; Fermoso 1992; Gilly 1994; Guilhou 1997; Laurent 1988; Planchon 1990; Rabe 2015), eight on calcium dobesilate (Flota-Cervera 2008; Hachen 1982; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Rabe 2016; Widmer 1990), one on aminaftone (Belczak 2014), one on grape seed extract (Thebaut 1985), and one on *Centella asiatica* (Pointel 1986).

We included in the meta-analysis a total of 2944 participants treated with phlebotonics and 2845 with placebo. Phlebotonics probably increase adverse events slightly, compared to placebo (RR 1.14, 95% CI 1.02 to 1.27; 37 studies; 5789 participants; moderate-certainty evidence; Analysis 1.22). The certainty of the evidence was downgraded by one level to moderate because of overall risk of bias (28 RCTs had unclear risk of bias and four RCTs had high risk of bias) (Summary of findings 1). No differences between the subgroups was detected (test for subgroup differences: P = 0.36).

Adverse events analyzed by active agent

Aminaftone

Only one trial reported adverse events (Belczak 2014). One participant presented with headache in the group given Aminaftone, and two in the placebo group dropped out as the result of subjective worsening of leg pain. It is uncertain whether aminaftone reduces adverse events because the certainty of this evidence is very low (RR 0.60, 95% CI 0.06 to 6.32; 79 participants; Analysis 1.22). The certainty of the evidence was downgraded by three levels to very low because Belczak 2014 had unclear risk of bias (one level) and the sample size was very small with a high imprecision in the results (two levels).

Calcium dobesilate

In total, eight trials evaluated adverse events with calcium dobesilate use (Flota-Cervera 2008; Hachen 1982; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Rabe 2016; Widmer 1990). Nineteen per cent of participants in the calcium dobesilate group (179/932) experienced an adverse event and 15% (133/892) in the placebo group. Calcium dobesilate may make little or no difference to adverse events compared with placebo (RR 1.22, 95% CI 1.00 to 1.49; 8 studies 1824 participants; low-certainty evidence). The certainty of the evidence was downgraded by 2 levels to low because of overall risk of bias (four RCTs had unclear risk of bias and one RCT had high risk of bias). The most common adverse event was a gastrointestinal event (epigastric discomfort, vomiting). No agranulocytosis or white blood cell disorders were identified. Twenty-five participants were withdrawn from the calcium dobesilate group and 17 from the placebo group as the result of adverse events.

Centella asiatica

One study reported information on adverse events with *Centalla asiatica* (Pointel 1986). Thirty-one per cent of participants in the *Centella asiatica* group (19/61) suffered from adverse events and 27.3% (9/33) in the placebo group. It is uncertain whether *Centella asiatica* reduces adverse events because the certainty of this evidence is very-low (RR 1.14, 95% CI 0.58 to 2.23; 94 participants). The certainty of the evidence was downgraded by three levels to very low because Pointel 1986 had unclear risk of bias (one level) and the sample size was very small with a high imprecision in the results (two levels). Two participants who took *Centella asiatica* 120 mg withdrew - one because of gastralgia (gastric colic) and the other because of neurological absence (absence of nerve activity). One participant taking placebo discontinued the study because of cyanosis of the extremities (bluish discolouration caused by lack of oxygen in the blood).

Diosmine and hidrosmine

Nine studies reported the number of participants who experienced adverse events (Biland 1982; Danielsson 2002; Dominguez 1992; Fermoso 1992; Gilly 1994; Guilhou 1997; Laurent 1988; Planchon 1990; Rabe 2015). Ninety-nine adverse events occurred in the hidrosmine and diosmine group (99/720) and 106 (106/709) in the placebo group. Diosmine and hidrosmine may make little or no difference to adverse events compared with placebo (RR 0.93, 95% CI 0.72 to 1.19; 9 studies; 1429 participants; low-certainty evidence). The certainty of the evidence was downgraded by two levels to low because of overall risk of bias (eight RCTs had unclear risk of bias and one RCT had high risk of bias).

Gastrointestinal disorders were the most reported adverse events (heartburn and nausea): 14 cases were reported in the hidrosmine and diosmine group and 11 in the placebo group.

Thirteen participants withdrew from the hidrosmine group and 12 from the placebo group as the result of adverse events.

Grape seed extract

One study reported information regarding adverse events (Thebaut 1985). Eleven per cent of participants (4/35) receiving active treatment reported adverse effects (three withdrew): two participants had gastralgia, one participant had a headache and one had an allergic reaction. Twenty per cent of participants in the placebo group (8/40) experienced adverse effects (one withdrew); these included constipation, gastralgia, tiredness, dry mouth and discomfort. It is uncertain whether grape seed extract reduces adverse events because of the certainty of this evidence is very low (RR 0.57, 95% CI 0.19 to 1.74; 75 participants). The certainty of the evidence was downgraded by three levels to very low because of Thebaut 1985 had unclear risk of bias (one level) and the sample size was very small with a high imprecision in the results (two levels).

Rutoside

Sixteen trials reported information regarding the number of participants who experienced adverse events (Alterkamper 1987; Balmer 1980; Diebschlag 1994; Jongste 1989; Koscielnny 1996; Kriner 1985; Languillat 1988; MacLennan 1994; Parrado 1999; Serralde 1990; Unkauf 1996; Vanscheidt 2002a; Vanscheidt 2002b; Vin 1994; Welch 1985; Zucarelli 1987).Twenty per cent of participants (233/1160) in the rutoside group suffered from adverse events and 16% (181/1128) in the placebo group. Rutosids may slightly increase adverse events compared to placebo (RR 1.41, 95% CI 1.08 to 1.83; 16 studies; 2288 participants; low-certainty evidence). The certainty of the evidence was downgraded by two levels to low because of the overall risk of bias (13 RCTs had unclear risk of bias and two had high risk of bias). The most common adverse events were gastrointestinal in nature (constipation, dry mouth, epigastric discomfort, vomiting): 127 in the rutoside group and 81 in the placebo group, followed by headache (23 in the rutoside group, 21 in the placebo group) and tiredness (17 in the rutoside group, nine in the placebo group).

Thirteen participants withdrew from the rutoside group and 22 from the placebo group as the result of adverse events.

Sensitivity analysis

Exclusion of studies using compression measures (elastic stockings)

We carried out sensitivity analysis by re-analysing the data excluding studies that allowed the use of elastic stockings (Balmer 1980; DOBESILATO500/2; Guilhou 1997; Laurent 1988; MacLennan 1994; Martinez-Zapata 2008; Rabe 2011; Schultz-Ehrenburg 1993; Zucarelli 1987). We found that generally, results did not change, except for the following variables.

- Phlebotonics may reduce dichotomous variable pain (RR 0.70, 95% CI 0.60 to 0.82; 18 studies; 1818 participants, low-certainty evidence; Analysis 2.7). The certainty of evidence was downgraded by two levels to low because of overall risk of bias (18 studies had unclear risk of bias and five had high risk of bias). No differences between the subgroups was detected (test for subgroup differences: P = 0.12). In the overall analysis, the results were very heterogeneous, so we did not pool them.
- Phlebotonics may reduce dichotomous variable participant satisfaction (RR 0.69, 95% CI 0.53 to 0.90; 12 studies; 1193 participants; low-certainty evidence; Analysis 2.20). The certainty of evidence was downgraded by two levels to low because of overall risk of bias (10 studies had unclear risk of bias and one had high risk of bias). No differences between the subgroups was detected (test for subgroup differences: P = 0.33). In the overall analysis, the results were very heterogeneous, so we did not pool them.

Exclusion of unpublished data

Only one study, which focused on rutosides, was not published (Welch 1985). When we re-analysed the data while excluding this study, we found results very similar to those of the main analysis for all outcomes.

Exclusion of studies at high or unclear risk of bias

In judging quality levels based on the aforementioned criteria, we identified only four studies with low risk of bias (Labs 2004; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a). Consequently, limited sensitivity analyses for the included variables were possible.

Results changed only for the following variables:

- For the dichotomous variable of oedema, only one study on calcium dobesilate was included with a low risk of bias (Labs 2004). Phlebotonics may make little or no difference in the dichotomous variable oedema compared to placebo (RR 0.99, 95% CI 0.63 to 1.55; 1 study; 260 participants; low-certainty evidence; Analysis 4.1). The certainty of the evidence was downgraded by two levels to low because Labs 2004 had a small sample size and imprecision.
- For the continuous variable of oedema (measure of ankle circumference in mm), three studies on calcium dobesilate were included with a low risk of bias (Labs 2004; Martinez-Zapata 2008; Rabe 2011). Based on their results, phlebotonics probably make little or no difference in the continuous variable oedema (measure of ankle circumference in mm) compared to placebo (MD -2.34 mm, 95% CI -8.79 to 4.11; 3 studies; 867 participants; moderate-certainty evidence; Analysis 4.2). The certainty of the evidence was downgraded by one level for imprecision.
- For the dichotomous variable of itching, only one study on rutoside had a low risk of bias (Vanscheidt 2002a). Phlebotonics probably reduce dichotomous variable itching, compared with placebo (RR 0.44, 95% CI 0.32 to 0.62; 231 participants; moderate-certainty evidence; Analysis 4.7). The certainty of the evidence was downgraded by one level for imprecision.
- For the continuous variable of itching, one study on calcium dobesilate was at low risk of bias (Martinez-Zapata 2008). Phlebotonics probably make little or no difference to the continuous variable itching (MD 4.60 cm, 95% CI -5.66 to 14.86; 416 participants; moderate-certainty evidence; Analysis 4.8). The certainty of the evidence was downgraded by one level by imprecision.
- For the dichotomous variable of heaviness, one study on rutoside was at low risk of bias (Vanscheidt 2002a). Phlebotonics probably reduce the dichotomous variable heaviness compared

to placebo (RR 0.62, 95% CI 0.47 to 0.82; 231 participants; moderate-certainty evidence; Analysis 4.9). The certainty of the evidence was downgraded by one level by imprecision.

- For the continuous variable of heaviness, one study on calcium dobesilate was at low risk of bias (Martinez-Zapata 2008). Phlebotonics probably make little or no difference on the continuous variable heaviness compared with placebo (MD -2.40 cm, 95% CI -7.89 to 3.09; 417 participants; moderate-certainty evidence; Analysis 4.10). The certainty of the evidence was downgraded by one level for imprecision.
- For the continuous variable of swelling, one study on calcium dobesilate was at low risk of bias (Martinez-Zapata 2008). Phlebotonics probably make little or no difference on the continuous variable swelling, compared to placebo (MD -1.30 cm, 95% CI -6.72 to 4.12; 417 participants; moderate-certainty evidence; Analysis 4.12). The certainty of the evidence was downgraded by one level for imprecision.
- For the dichotomous variable of participant satisfaction, two studies on calcium dobesilate were at low risk of bias (Labs 2004; Rabe 2011). Phlebotonics probably make little or no difference on the dichotomous variable participant satisfaction compared to placebo (RR 1.04, 95% CI 0.81 to 1.32; 2 studies; 476 participants; moderate-certainty evidence; Analysis 4.13). The certainty of the evidence was downgraded by one level for imprecision.
- For the continuous variable of participant satisfaction, one study on calcium dobesilate had a low risk of bias (Rabe 2011). Phlebotonics probably improve the continuous variable participant satisfaction (MD -5.64, 95% CI -8.85 to -2.43; 223 participants; moderate- certainty evidence; Analysis 4.14). The certainty of the evidence was downgraded by one level for imprecision.
- For the dichotomous variable of adverse events, four studies were at low risk of bias (Labs 2004; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a). Phlebotonics probably make little or no difference on the dichotomous variable adverse events compared to placebo (RR 1.59, 95% CI 0.97 to 2.63; four studies; 1257 participants; moderate-certainty evidence; Analysis 4.15). The certainty of the evidence was downgraded by one level for imprecision (low number of events). No differences between the subgroups was detected (test for subgroup differences: P = 0.70)

DISCUSSION

Summary of main results

We evaluated the efficacy and safety of phlebotonics in the treatment of CVI. Only analyses of studies using oral phlebotonics were possible because no identified study of topical phlebotonics met the inclusion criteria of this Cochrane Review. This Cochrane Review included 69 RCTs, and analyzed data from 56 trials involving 7690 participants. Studies included in the review generally provided objective measurement of ankle and calf oedema reduction, as well as a subjective assessment of other signs and symptoms of CVI.

According to the ITT analysis, there was moderate-certainty evidence of a probable beneficial effect on the dichotomous variable oedema. Analyses with continuous variables also showed a probable beneficial effect of phlebotonics on oedema (moderate-certainty evidence).

However, there was moderate-certainty evidence of little or no difference in QoL with phlebotonic use compared to placebo; and little or no difference to dichotomous variable ulcer healing (low-certainty evidence).

Phlebotonic use probably slightly improves trophic disorders compared to placebo (moderate-certainty evidence). Data on telangiectasia, reticular veins and varicose veins were very limited. Heterogeneity prevented meta-analysis on dichotomous variable pain but showed phlebotonic use may reduce pain (continuous variable) compared to placebo (low-certainty evidence). Similarly, a possible benefit was seen in cramps (moderate-certainty evidence), restless legs (moderate-certainty evidence); swelling in lower legs (moderate-certainty evidence); and paraesthesia (dichotomous variable) in the lower legs (moderate-certainty evidence). However, based on very low-certainty evidence, it is uncertain whether phlebotonics reduce continuous variable paraesthesia.

Heterogeneity prevented meta-analysis on the outcomes of itching and feeling of heaviness in the lower legs.

There was moderate-certainty evidence that the incidence of adverse events was probably slightly increased in the phlebotonics group compared to placebo group. Gastrointestinal disorders were the most frequently reported adverse events among studies that provided this information (rutosides, calcium dobesilate, diosmine-hidrosmine). Our review did not report agranulocytosis associated with calcium dobesilate, although this adverse effect was described in a previous case-control study that detected potential risk of agranulocytosis, with an incidence rate of 1.21 cases per 10,000 patient-years of treatment (Ibañez 2000; Ibáñez 2005). This could be explained by the small number of participants in the included RCTs and the short period of participant follow-up provided.

The results by type of active drug showed that It is uncertain whether aminaftone reduces dichotomous variables oedema, pain, cramps, itching and heaviness (very low-certainty evidence). There was low-certainty evidence that aminaftone may slightly improve the continuous variables oedema (volume) and QoL, and may make little or no difference to adverse events.

Calcium dobesilate may reduce continuous volume of the leg and may slightly improve continuous variable participant satisfaction (low-certainty evidence); it may reduce dichotomous variable swelling and may slightly reduce the dichotomous variables pain, cramps and restless legs. Meanwhile, based on moderate-certainty evidence, calcium dobesilate probably makes little or no difference on QoL and dichotomous variables assessment by the participant and adverse events. Furthermore, calcium dobesilate may make little or no differences on the continuous variables ankle perimeter circumference, pain and heaviness; and for the dichotomous variables heaviness and paraesthesia (low-certainty evidence). Calcium dobesilate does not have an important effect on the continuous variables swelling, cramps and itching (high-certainty evidence). We do not know if calcium dobesilate improves dichotomous variable oedema and ulcer healing as the certainty of the evidence is very low.

Based on very low-certainty evidence, it is uncertain whether *Centella asiatica* compared to placebo reduces dichotomous variable heaviness (Pointel 1986), improves the dichotomous

variable participant satisfaction (Allegra 1981) or increases adverse events (Pointel 1986).

Diosmine and hidrosmine, based on a moderate-certainty evidence, probably slightly reduces ankle perimeter, trophic disorders and cramps; and, probably make little or no differences in dichotomous variable pain, QoL, dichotomous variable participant satisfaction and adverse events, Additionally, based on low-certainty evidence, they may slightly reduce oedema, cramps, heaviness, swelling and dichotomous variable participant satisfaction. Furthermore, diosmine and hidrosmine, based on low-certainty evidence, may make little or no difference in paraesthesia, ulcer healing, continuous variable pain and dichotomous variable heaviness. We do not know if these drugs improve itching because the certainty of the evidence is very low.

Based on very low-certainty evidence, it is uncertain whether French maritime pine bark extract reduces pain, heaviness and swelling. For grape seed extract it is also uncertain if it reduces the dichotomous variable oedema (very low-certainty evidence).

Rutosides were included in the greatest number of clinical trials. Based on moderate-certainty evidence, rutosides probably improve oedema, volume of the leg and continuous variable pain; and they probably make little or no difference in ankle perimeter and ulcer healing. Based on low-certainty evidence, rutosides may slightly reduce heaviness, participant satisfaction, continuous variables cramps and itching, dichotomous variables pain, and paraesthesia. Furthermore, rutosides may make little or no difference in continuous variables swelling and paraesthesia and dichotomous variables trophic disorders, cramps, restless and itching. Rutosides may slightly increase adverse events (low-certainty evidence).

No evidence was found regarding the efficacy of disodium flavodate, naftazone, chromocarbe or topical phlebotonics.

Sensitivity analyses did not alter the results of this review. Whether elastic stockings were used did not influence pooled results, supporting the view that an appropriate randomisation method results in a homogeneous distribution of the groups under comparison.

Overall completeness and applicability of evidence

Several limitations were identified in the included studies. Only one of five studies specified standard diagnostic criteria for CVI, and different studies applied different criteria. Only eleven studies used the currently accepted CEAP classification (Porter 1995) (Belczak 2014; Danielsson 2002; DOBESILATO500/2; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Rabe 2015; Rabe 2016; Vanscheidt 2002a; Vanscheidt 2002b). Therefore, homogeneity in diagnostic criteria is limited, and potential misclassification bias cannot be ruled out. Furthermore, we were unable to perform subgroup analysis by CVI stage because the severity of CVI was variable.

In most RCTs, the way in which participants were included is heterogeneous, and this may have led to differences in response to treatment. In addition, too few participants were included in the studies with the limitations of imprecision in the results and lack of statistical power to detect a difference between phlebotonics and placebo, when an effect could have occurred (beta error, or type II error). Different instruments were used to measure signs and symptoms, and sometimes results were inconclusive. Only seven RCTs assessed the variable QoL using a standardized questionnaire (Belczak 2014; Martinez-Zapata 2008; Rabe 2011; Rabe 2015; Rabe 2016;Vanscheidt 2002a; Vanscheidt 2002b), but two studies did not provide quantifiable information (Vanscheidt 2002a; Vanscheidt 2002b). Although some studies favoured phlebotonics, the clinical relevance of these findings remains questionable.

Although infrequent, important signs such as venous ulcers have been poorly evaluated. Only six studies included participants with venous ulcers and when pooled, showed none that yielded a difference in ulcer healing (DOBESILATO500/2; Fermoso 1992; Guilhou 1997; Lazzarini 1982; MacLennan 1994; Schultz-Ehrenburg 1993).

Only two studies addressing trophic disorders defined this term (MacLennan 1994; Planchon 1990), and four did not (Fermoso 1992; Gilly 1994; Laurent 1988; Lazzarini 1982). However, in two studies, trophic disorders were assessed subjectively as present or absent (Fermoso 1992; MacLennan 1994), or as reported on semi-quantitative four-item scales (Gilly 1994; Lazzarini 1982; Planchon 1990). Therefore, although data from the examination of trophic alterations were analyzed, these results should be interpreted with caution.

Most studies provided short-term results (one to three months). Specificaly, for the primary outcome 'oedema in the lower limb,' the median time of follow-up was 49 days for oedema measured as a dichotomous outcome and 60 days for oedema measures as a continuous outcome. Given the chronic nature of the disease, more long-term data on the efficacy and safety of phlebotonics are needed (at least one-year follow-up). To achieve homogeneous data collection and to specify evidence on the efficacy of phlebotonics, measurement of signs and symptoms should be standardized. Although we have done a subgroup analysis by drugs, we noted that different doses were involved, and we are unable to comment on which is the optimal dose.

Quality of the evidence

Risk of bias of the included studies is somewhat unclear regarding randomisation and blinding because only a limited number of studies specifically reported details regarding these issues. It is difficult to determine whether this is a result of poor design or publication restrictions. As a result, among the 69 RCTs included in this review, only 39 explained the double-blinding procedure in detail, 18 provided data on randomisation and 10 explained blinding of the randomisation. Furthermore, seven studies had attrition bias and nine selective reporting with high risk of bias. These issues were not addressed in the remaining included studies, and this adds uncertainty to the evidence. Only four studies were graded as having an overall low risk of bias (Labs 2004; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a).

In the clinical area of CVI, results lack reliability if the RCT did not include a placebo group because of seasonal exacerbations (spring and summer) that might be self limiting and highly subjective symptoms. Consequently, an adequate control group is needed, and both randomisation and treatment should be appropriately blinded (preferably double-blinded). For this reason, studies that did not include a control group and single-blinded studies were excluded from the review. Among studies identified as

double-blinded, those with inappropriate blinding of treatments or randomisation were excluded from the meta-analyses.

We adopted a conservative approach in our review, which prioritised the ITT analysis in terms of both treatment losses and failures. On the other hand, we used change measures only if conditions of the compared groups at baseline were the same, to avoid bias in the assessment of results related to participants' baseline differences.

We evaluated the certainty of the body of evidence using the GRADE approach (Schünemann 2011), which is based on five considerations including risk of bias (study limitations), directness of the evidence, heterogeneity in the data, precision of effect estimates and additional considerations (including risk of publication bias) to assess the certainty of the body of evidence for a priori selected outcomes (in our review, these included the dichotomous variable of oedema in the lower legs and the continuous variables of oedema in the lower legs, QoL, participants with ulcer healing and participants with adverse events) (Summary of findings 1).

With this approach, the overall certainty of evidence is ranked from very low (paraesthesia (continuous variable) to moderate (dichotomous and continuous outcomes of oedema and adverse events; cramps, restless legs, swelling and paraesthesia (dichotomous variable).

Reasons for downgrading the certainty of evidence for the outcome ulcer healing include the presence of selective reporting and incomplete outcome data; for the outcome QoL, we downgraded for incomplete outcome data and imprecision (wide confidence intervals); for the dichotomous variables measurement of oedema we downgraded for incomplete outcome data; and for the continuous variable oedema we downgraded for unclear risk of bias of one trial; for the outcome adverse events we downgraded for incomplete outcome data and indirectness (moderate heterogeneity). See Summary of findings 1.

Potential biases in the review process

Any systematic review is influenced by the quality of included studies and reports. In this respect, we classified only four RCTs as having low risk of bias, and we considered most included studies to have moderate risk of potential bias. We excluded RCTs with high risk of bias. Therefore, conclusions about the results of these studies should be interpreted with caution.

The heterogeneity of several analysis variables may be due to the following:

- Different diagnosis classification criteria have been applied; therefore, characteristics of the included population in terms of degree of progression of CVI might vary among studies.
- No standardisation is involved in measuring variables, given the different scales that have been used, some of which are not validated. Although the same criteria were applied to the data dichotomisation (participants without symptoms/signs or with mild symptoms/sign versus participants with moderate to severe symptoms/signs), these may not be equally relevant, as they result from the application of different scales.
- On the other hand, the same subjectivity of collected variables may represent differences among individuals and may influence the variability of results.
- In addition, efficacy of evaluated treatments may not be the same because different active principles were used. This explains observed differences among treatments in the subgroup analysis.

All these considerations limit the validity of included clinical trials and the conclusions of this review. The existence of such heterogeneity restricts the importance of its detection in the process of generating hypotheses (i.e. phlebotonics could be effective for treatment of the pain, cramps, heaviness and swelling of CVI).

Only 54% of included studies reported information on adverse events. However, to adequately assess adverse events related to phlebotonics, it is necessary to include observational study designs that were excluded from our review.

Agreements and disagreements with other studies or reviews

Several reviews have tried to evaluate the clinical benefit of phlebotonics. Some of these used poor methods, which did not include information on search strategies and data collection sources, extraction and statistical treatment (diosmine, escin and rutosides (Diehm 1996b); flavonoids, tribenosides, escin and calcium dobesilate (Markwardt 1996); rutosides (Wadworth 1992); flavonoids (Rabe 2013)). Other reviews are more elaborate and were developed systematically (global phlebotonics (Boada 1999); calcium dobesilate (Ciapponi 2004); escin (Pittler 1998); rutosides (Aziz 2015; Poynard 1994); flavonoids (Kakkos 2018)). Five reviews pursued data meta-analysis (Aziz 2015; Boada 1999; Ciapponi 2004; Kakkos 2018; Poynard 1994).

One review specifically evaluated hydroxyethyl rutosides and the review authors included 15 randomised studies and applied a per-protocol (PP) analysis. They stated that rutosides were better than control for controlling symptoms of pain, cramps and heaviness (Aziz 2015).

Another review analyzed rutosides and the review authors included 12 randomised, double-blind, placebo-controlled studies and applied an ITT analysis. They stated that rutosides were better than placebo for controlling symptoms of pain, cramps, heaviness, swelling and tiredness of affected legs. They did not mention CVI signs (Poynard 1994).

Boada 1999 reviewed all drugs that have been evaluated for CVI through randomised, double-blind, placebo-controlled trials without concomitant compression procedures. These included traditional agents such as hidrosmine, diosmine, escin, rutosides and calcium dobesilate, along with other, less usual ones such as extract of *Centella asiatica*, benzarone, tribenoside, flunarizine, dihydroergotamine mesylate and mucopolysaccharide sulphate. The conclusion of the Boada 1999 review was that phlebotonics might improve leg heaviness in patients with CVI. Review authors presented no conclusive data regarding other signs or symptoms, performed PP rather than ITT analysis and provided no information on individual phlebotonics (Boada 1999).

The review led by Ciapponi 2004 analyzed calcium dobesilate and the review authors included 10 double-blind, randomised, placebo-controlled studies and applied a PP analysis. They stated that calcium dobesilate was better than placebo for controlling cramps and discomfort. Subgroup analysis showed greater efficacy in more severe cases of the disease in terms of improving symptoms (pain, heaviness and swelling) and signs (leg volume). Sensitivity analysis based on the ITT analysis did not influence these results (Ciapponi 2004).

Kakkos 2018 evaluated the efficacy of a micronized purified flavonoid fraction (diosmine) in CVD. The systematic review included seven double-blind, randomised, placebo-controlled studies. Their results showed a significant improvement for diosmine with respect to signs and symptoms related to CVD, QoL and treatment assessment by the physician. Although our review presents some differences because we pooled studies assessing diosmine and hidrosmine, except for QoL, the general results are in agreement with Kakkos 2018.

With the exception of Aziz 2015 and Kakkos 2018, the above-cited reviews were published some time ago and have not been updated. Our review provides an update regarding evidence on phlebotonics in general and by drug group.

AUTHORS' CONCLUSIONS

Implications for practice

Phlebotonics present limited efficacy for oedema and for some signs and symptoms related to chronic venous insufficiency (CVI).

There is moderate-certainty evidence that phlebotonics probably slightly reduce oedema compared to placebo; moderate-certainty evidence of little or no difference in quality of life (QoL); and low-certainty evidence indicates that these drugs do not influence ulcer healing. Moderate-certainty evidence shows that phlebotonics are probably associated with higher risk of adverse events than placebo, especially in the subgroup analysis of rutoside group. Studies included in this Cochrane Review provided only short-term efficacy and safety data; therefore, the middle- and long-term efficacy and safety of phlebotonics could not be estimated. Based on the results of subgroup analysis some phlebotonics were effective for certain symptoms and signs; however, given the limited number of studies and the discordance in their results, these findings are uncertain.

Implications for research

As a result of the importance of phlebotonics and the limitations of current evidence, high-quality RCTs are needed to evaluate the efficacy and adverse effects of this group of drugs in an independent and rigorous manner. However, the new studies included in this review have improved methodological aspects and have already considered in a standardized manner the diagnostic classification of participants, measurement of signs and symptoms, larger sample sizes and longer follow-up, and future trials should continue these recommendations. Additional research regarding QoL and both ulcer healing and trophic disorders is needed, particularly with an accurate definition of the term and the use of objective measurements. More and better assessments of venous ulcers should be made, and QoL surveys specifically validated for CVI should be introduced. Furthermore, currently available data on safety refer to a short administration period; therefore, long-term observational follow-up studies are needed to better define the safety profile of each of the phlebotonics and to outline more clearly the risk/benefit ratio.

When the efficacy of phlebotonics is investigated, restriction criteria are recommended to avoid situations that are more likely to result in adverse effects, including long-term administration, important co-morbidity, leucopenia, ageing and multiple medications. In addition, researchers involved in these trials should make an explicit statement regarding their conflicts of interest.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allegra 1981

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled
	Method of randomisation: table of random numbers
	Exclusions post randomisation: none
	Losses to follow-up: none
Participants	Country: Italy
	Setting: hospital
	Number: 80 patients
	Age: not stated
	Gender: not stated
	Inclusion criteria: patients with postphlebitic syndrome, oedema of the lower limb, phlebolymphoedema, constitutional venous stasis, varices

Allegra 1981 *(Continued)*

	Exclusion criteria: not stated
Interventions	Treatment: 2 × 10 mg Centella tablets 3 × per day Control: placebo Duration: 30 days Follow-up: 30 days
Outcomes	Primary • Symptoms - heavy legs, pain, cramps, global assessment by participant and by physician measured by an ordinal scale (0 to 3) • Signs - leg oedema, venous dilatation and skin trophism measured by an ordinal scale (0 to 3). Venous pressure measured by echo Doppler Secondary • Tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The assignment of patients to one of two treatments, labelled as A or B, was made randomly using a special randomization list" Comment: a randomisation list is generally accepted as a fair method of ensuring a random sequence
Allocation concealment (selection bias)	Unclear risk	Comment: no information given about methods used for allocation concealment
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up
Selective reporting	Unclear risk	Comment: the number of participants in both groups was described. However, a table with important characteristics was lacking; this could lower the generalisability. Adverse events, tolerability and signs of intolerance were presented
Other bias	Low risk	Comment: none detected

Alterkamper 1987

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled

Alterkamper 1987 *(Continued)*

	Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 3/50 (6%)
Participants	Country: France Setting: not stated Number: 50 patients Age: mean 53 ± 9 years Gender: 13 M:37 F Inclusion criteria: symptomatic stage I to II of CVI Exclusion criteria: oedemas requiring compression, post-thrombotic syndrome, lymphoedema; cardiac, renal or hepatic failure; diuretics; pregnancy; severe disease
Interventions	Treatment: 1.86 mg ruscus and 75 mg hesperidin. 2 capsules 3 × per day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Symptoms - tired, heavy legs; pain and swelling measured by a visual analogue scale (VAS) • Signs - venous refilling time by light reflection rheography (LRR) Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In a randomized double-blind study..." Comment: no information given about method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given about allocation concealment
Blinding (patients)	Low risk	Quote: "The Phlebodril and placebo capsules had the same external appearance" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The Phlebodril and placebo capsules had the same external appearance" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The Phlebodril and placebo capsules had the same external appearance"

Alterkamper 1987 *(Continued)*

		Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Quote: "Three patients dropped out for reasons unconnected with this study" Comment: number in each group described, and number of participants who dropped out of the study prematurely presented
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Arcangeli 2000

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Italy Setting: clinical centre Number: 40 patients Age: mean 57.95 ± 12.78 years pycnogenol group; mean 61.40 ± 10.62 years placebo group Gender: 13 M:27 F Inclusion criteria: symptomatic CVI as a consequence of deep venous thrombosis or idiopathic venous lymphatic deficiency Exclusion criteria: cardiovascular, diuretics, analgesic or anti-inflammatory drugs
Interventions	Treatment: French maritime pine bark extract, 100 mg 3 × per day Control: placebo Duration: 69 days Follow-up: 60 days
Outcomes	Primary • Symptoms - heavy legs, pain and swelling measured by means of a semiquantitative scale (0 to 3) ◦ Percentage of participants showing disappearance of each symptom Secondary • Venous blood flow measured by Doppler ultrasound • Tolerability • Global assessment by physicians at the end of the trial
Notes	

Arcangeli 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After the 2-week run-in period, the patients were randomly divided into two groups and assigned to a treatment with Pycnogenol, 100 mg × 3/day or a placebo for a period of 2 months" Comment: no method of randomisation stated
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment stated
Blinding (patients)	Low risk	Quote: "The placebo visually matched the test drug" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The placebo visually matched the test drug" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The placebo visually matched the test drug" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up described
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Balmer 1980

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Switzerland Setting: not stated Number: 40 patients Age: mean 46.2 ± 14.1 years active group; mean 52.3 ± 14.1 years placebo group Gender: 4 M:36 F Inclusion criteria: CVI without venous ulcers

Balmer 1980 *(Continued)*

	Exclusion criteria: varicose ulcers
Interventions	Treatment: oxirutoside 900 mg per day Control: placebo Duration: 28 days Follow-up: 28 days Compression therapy was allowed if participants were unwilling to abandon this support
Outcomes	Primary • Oedema as measured by circumference of ankle and calf (mm) Secondary • Symptoms - pain, cramps, tiredness, pins and needles, swelling, restless legs measured by an ordinal scale (0 to 4) • Clinician's assessment • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The trial was double-blind, randomised, placebo controlled, between patients..." Comment: no information given about method of randomisation used
Allocation concealment (selection bias)	Unclear risk	Comment: no information given about method of treatment allocation used
Blinding (patients)	Low risk	Quote: "Patients receiving respectively the test drug or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Patients receiving respectively the test drug or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Patients receiving respectively the test drug or identical placebo" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Belczak 2014

Study characteristics

Belczak 2014 *(Continued)*

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 9/136 (6.6%)
Participants	Country: Brazil Setting: Department of Vascular Surgery of Sao Camilo Medical School Number: 136 patients Age: mean 52.8 ± 16.4 years active group; mean 50.6 ± 13.1 years placebo group Gender: 33 M:103 F Inclusion criteria: treatment-naïve (no history of pharmacological or compression therapy), CVD (CEAP grades 2 to 5) Exclusion criteria: other conditions that might produce lower extremity-related symptoms
Interventions	Treatments: micronised diosmine (450 mg) + hesperidin (50 mg), aminaftone (75 mg), coumarin (15 mg), troxerutin (90 mg) Control: placebo Duration: 112 days Follow-up: 112 days Compression therapy: not used
Outcomes	Primary • Quality of life • Mean limb volumes • Mean joint range of motion Secondary • Not stated
Notes	Funding: all medications and placebos purchased by the investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into four groups" Comments: no methods of randomisation described
Allocation concealment (selection bias)	Low risk	Quote: "All tablets (active and placebo) were randomly divided into numbered bottles by an external investigator..."
Blinding (patients)	Low risk	Quote: "All tablets (active and placebo) were randomly divided into numbered bottles by an external investigator, and the contents of each bottle were unmasked only at the time of statistical analysis"

Belczak 2014 *(Continued)*

Blinding (study researchers)	Low risk	Quote: "All tablets (active and placebo) were randomly divided into numbered bottles by an external investigator, and the contents of each bottle were unmasked only at the time of statistical analysis"
Blinding (outcome assessment)	Low risk	Quote: "Assessors were blind to the treatment groups"
Incomplete outcome data	Low risk	Comment: very few participants lost to follow-up
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Bergqvist 1981

Study characteristics	
Methods	Study design: randomised, cross-over, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 6/149 (4%)
Participants	Country: Sweden Setting: outpatient clinic and local population Number: 149 patients Age: 'adults' Gender: 33 M:116 F Inclusion criteria: symptoms related to varicose veins and CVI Exclusion criteria: not stated
Interventions	Treatment: oxirutoside 1000 mg intravenous injection followed by 1 tablet of 500 mg per 8 hours Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Symptoms - pain, cramps, tired legs, pruritus, swelling, side effects • Signs - plethysmographic values, calf circumference Secondary • Not stated
Notes	

Bergqvist 1981 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were then randomly allocated to treatment with either HR or identical placebo" Comment: no details of randomisation method provided
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "The placebo regime was identical" and "... or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The placebo regime was identical" and "... or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The placebo regime was identical" and "... or identical placebo" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. Loss to follow-up described along with exclusions after randomisation, including reasons
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Biland 1982

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 14/70 (20%)
Participants	Country: Germany Setting: hospital Number: 70 patients Age: mean 43 ± 13 years diosmine group; mean 39 ± 12.5 years placebo group Gender: 7 M:49 F Inclusion criteria: symptoms related to CVI and oedema

Biland 1982 *(Continued)*

	Exclusion criteria: phlebitis, venous thromboses, post-thrombotic syndrome, ulcus cruris, heart insufficiency, recent sclerotherapy or venous stripping, trauma, neuropathy, arthrosis, pregnancy
Interventions	Treatment: diosmine 450 mg plus hesperidin 50 mg, 2 capsules twice a day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Symptoms - pain, cramps, swelling, restless legs measured by an ordinal scale (0 to 2) ○ Oedema - circumference of ankle and calf Secondary • Clinical assessment by participants and doctors • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was double-blind, randomized, placebo with Daflon" Comment: no method of randomisation stated
Allocation concealment (selection bias)	Low risk	Quote: "Placebo tablets were given in indistinguishable numbered packaging" Comment: Indistinguishable number packaging ensures a fair method of allocation concealment
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: numbers of participants in each group reported, along with participants excluded after randomisation,reasons for exclusion and information on compliance
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Burnand 1989

Study characteristics

Burnand 1989 *(Continued)*

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: UK Setting: hospital Number: 49 patients Age: mean 53 years Gender: 18 M:31 F Inclusion criteria: venous reflux by volumetry, with varicose veins and lipodermatosclerosis Exclusion criteria: patients with ankle-to-arm arterial Doppler pressure ratio < 1.0 (significant arterial disease)
Interventions	Treatment: oxerutin (Paroven) 500 mg per 12 hours Control: placebo Duration: 30 days Follow-up: 30 days
Outcomes	Primary • Signs - oedema (foot volumes) measured by water displacement, transcutaneous oximetry (TCPO2) Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A double-blind controlled trial was undertaken.." and "the two groups of patients were balanced and randomized by trial number so that as far as possible an equal number in each group..." Comment: no details of randomisation method provided
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Low risk	Quote: "Were given Paroven 500 mg bd or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Were given Paroven 500 mg bd or identical placebo" Comment: Identical placebo ensures double-blinding

Burnand 1989 *(Continued)*

Blinding (outcome assessment)	Low risk	Quote: "This code was not broken until the completion of the study" Comment: outcome assessors blinded
Incomplete outcome data	Low risk	Comment: neither exclusions post randomisation nor losses to follow-up described
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Casley-Smith 1988

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Australia Setting: university Number: 60 patients Age: 'adults' Gender: 28 M:32 F Inclusion criteria: 30 normal volunteer participants and 30 patients with CVI grade I to III Widmer (dilated subcutaneous veins, alteration of pigmentation, open or healed crural ulcer) Exclusion criteria: not stated
Interventions	Treatment: calcium dobesilate 1000 mg per day Control: placebo Duration: 42 days Follow-up: 42 days
Outcomes	Primary • Symptoms - tenderness, swelling, tiredness, pain, cramps, restless legs, paraesthesias and general well-being measured by an ordinal scale scored from -1 (deterioration) to +1 (total relief) • Signs - oedema measured by a semiquantitative scale scored from -1 (deterioration) to +1 (total relief). Foot volume and lower limb (measured by standardised water displacement plethysmographic tank) Secondary • Side effects

Casley-Smith 1988 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized, double-blind, placebo-controlled technique was used. Because of carryover effects, a matched-pair technique was used" Comment: no methods of randomisation stated
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment stated
Blinding (patients)	Low risk	Quote: "Calcium dobesilate, or an identical placebo, were administered..." Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Calcium dobesilate, or an identical placebo, were administered..." Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Calcium dobesilate, or an identical placebo, were administered..." Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up described
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Cauwenberge 1972

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 7/44 (16%)
Participants	Country: Belgium Setting: Liège Number: 44 patients Age: 'adults' Exclusion criteria: not stated Gender: not stated

Cauwenberge 1972 *(Continued)*

	Inclusion criteria: varicose veins and postphlebitic syndrome Exclusion criteria: not stated
Interventions	Treatment: O-(beta-hydroxyethyl)-rutoside 900 mg per day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Oedema • Pain • Heaviness Secondary • Not stated
Notes	Description of 2 clinical trials (CTs): One is a parallel CT, and the other is a cross-over CT. Only the parallel CT is included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "44 patients were treated randomly and under double-blind conditions" Comment: no specific methods stated for randomisation of participants
Allocation concealment (selection bias)	Unclear risk	Comment: no specific methods stated for allocation concealment
Blinding (patients)	Low risk	Quote: "In addition, a placebo identical in appearance to the active drug..." Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "In addition, a placebo identical in appearance to the active drug..." Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "In addition, a placebo identical in appearance to the active drug..." Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Unclear risk	Comment: number in each group described, including drop-outs and those excluded after randomisation during follow-up (7/44; 16%); reasons for drop-out not provided
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Cauwenberge 1978

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: 51/120 (42.5%)
Participants	Country: Belgium Setting: Liège Number: 120 patients Age: 'adults' Gender: not stated Inclusion criteria: varicose veins, postphlebitic syndrome Exclusion criteria: symptoms not attributed to CVI
Interventions	Treatment: O-(beta-hydroxyethyl)-rutoside 1200 mg per day Control: placebo Duration: 90 days Follow-up: 90 days
Outcomes	Primary • Oedema • Pain • Cramps • Tiredness • Swelling • Restless legs • Paraesthesia Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients are divided into two series according to the degree of symptoms. Within these two series, patients were distributed randomly into two groups, receiving respectively the active ingredient or placebo" Comment: no method of randomisation stated
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment stated

Cauwenberge 1978 *(Continued)*

Blinding (patients)	Low risk	Quote: "We also used a placebo of identical presentation" Comment: Identical placebo ensure double-blinding
Blinding (study researchers)	Low risk	Quote: "We also used a placebo of identical presentation" Comment: Identical placebo ensure double-blinding
Blinding (outcome assessment)	Low risk	Quote: "We also used a placebo of identical presentation" Comment: Identical placebo ensure double-blinding
Incomplete outcome data	High risk	Comment: number of participants in each group described, but no information given on important characteristics of participants. Number of persons excluded after randomisation was important (51/120; 42.5%). Reasons for exclusion were given
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Cesarone 2002

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Italy Setting: hospital Number: 46 patients and 10 healthy individuals Age: 44 to 45 years Gender: percentages/numbers of men and women not specified Inclusion criteria: severe superficial venous incompetence with a normal deep venous system Exclusion criteria: diabetes, peripheral arterial disease
Interventions	Treatment A: hidroxirutoxide 500 mg tid Treatment B: hidroxirutoxide 1000 mg tid Control (group C): placebo tid Treatment D: hidroxirutoxide 1000 mg/d Duration: 28 days Follow-up: 28 days

Cesarone 2002 *(Continued)*

Outcomes	Primary • Plethysmographic parameters Secondary • CVI symptoms - swelling sensation, restlessness of lower limbs, pain, tiredness, cramps measured by a visual analogue scale (0 to 10). Global evaluation of symptoms (average score of symptoms) • Tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no randomisation methods stated
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment stated
Blinding (patients)	Low risk	Comment: placebo used with the same frequency as in experimental groups
Blinding (study researchers)	Low risk	Comment: placebo used with the same frequency as in experimental groups
Blinding (outcome assessment)	Low risk	Comment: placebo used with the same frequency as in experimental groups
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Chassignolle 1994

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 4/40 (10%)
Participants	Country: France Setting: hospital Number: 40 patients Age: 32.0 (1.3) years active group; 35.6 (1.1) years placebo group

Chassignolle 1994 *(Continued)*

	Gender: female Inclusion criteria: women with functional CVI Exclusion criteria: not stated
Interventions	Treatment: diosmine 1000 mg per day Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Plethysmographic parameters • CVI symptoms - heaviness, pain, tiredness, itching, paraesthesias and cramps measured by an ordinal scale (0 to 4). Global evaluation of symptoms (score functional) • CVI signs - oedema, cyanosis, redness, leg heat and induration measured by an ordinal scale (0 to 4). Global evaluation of signs (score objective) • Tolerance Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to two parallel groups of 20" Comment: no randomisation methods stated
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment stated
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, number of participants who dropped out prematurely stated and reasons for dropping out described
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Cloarec 1994

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: 16/120 (13%) Losses to follow-up: not stated
Participants	Country: France Setting: not stated Number: 120 patients Age: mean 50 years Gender: not stated Inclusion criteria: history of CVI for several years Exclusion criteria: not stated
Interventions	Treatment: O-(beta-hydroxyethyl)-rutoside 2000 mg per day Control: placebo Duration: 56 days Follow-up: 56 days
Outcomes	Primary • Reduction in calf and ankle circumference Secondary • Pain • Cramps • Tiredness • Swelling • Restless legs • Pitting oedema measured by a scale (0 to 3) • Plethysmographic parameters • Transcutaneous oxygen tension
Notes	This clinical trial is published in abstract format; not possible to extract data showing results

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A multicenter double blind randomized clinical trial was designed" Comment: no methods described for randomisation of participants
Allocation concealment (selection bias)	Unclear risk	Comment: no information given about methods used for allocation concealment

Cloarec 1994 *(Continued)*

Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: only 13% drop-out rate (16/120) for violation of study protocol reported
Selective reporting	High risk	Comment: no protocol identified. In the methods section, subjective symptoms identified that were not reported in the results section (pain, heaviness, swelling, restless leg, cramps, presence of pitting oedema)
Other bias	Low risk	Comment: none detected

Cloarec 1996

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: 5/109 (5%) Losses to follow-up: none
Participants	Country: France Setting: outpatient university clinic in a military hospital Number: 109 patients Age: 48 ± 14 years active group; 53.6 ± 13.6 years placebo group Gender: 16 M:88 F Inclusion criteria: CVI (Widmer grade II) and oedema and symptoms Exclusion criteria: elastic stockings, arterial insufficiency, venous ulcers or superficial thrombophlebitis, venous surgery or sclerotherapy in the preceding 6 months, other possible causes of leg oedema, pregnancy, irregular menstrual cycles; therapy with diuretics, steroids, anti-inflammatories or venous drugs
Interventions	Treatment: O-(beta-hydroxyethyl)-rutoside 1000 mg per 12 hours Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Symptoms - pain, cramps, heavy legs, swelling, restless legs measured by a semiquantitative scale (0 to 3) ○ Oedema - pitting present or absent, circumference of ankle and calf; plethysmographic parameters

Cloarec 1996 *(Continued)*

	Secondary • Side effects • Global opinion of investigators and participants
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "For this reason, we undertook a randomized, double-blind, placebo-controlled trial..." Comment: no methods for randomisation of participants described
Allocation concealment (selection bias)	Unclear risk	Comment: no methods for allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: only 5% drop-out rate (5/109) for violation of study protocol. Number in each group provided, along with reasons for exclusion after randomisation and information on compliance
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Cornu-Thenard 1985

Study characteristics

Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: random distribution of numbered batches Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: France Setting: not stated Number: 83 patients Age: 20 to 65 years; mean 43.73 ± 11.92 years active group; mean 43.55 ± 11.42 years placebo group Gender: 6 M:77 F

Cornu-Thenard 1985 *(Continued)*

	Inclusion criteria: symptoms related to CVI Exclusion criteria: severe damage to venous musculature requiring urgent treatment - surgery or sclerosis; surgical operation on venous or deep or superficial vein thrombosis in the past year; sclerosis or heavy support bandages (light support bandages not excluded), major trophic lesions, Raynaud's syndrome, arteritis, lymphoedema, renal or cardiac insufficiency; anti-migraine treatment, analgesic or anti-inflammatory treatment, diuretic treatment, low-sodium diet, treatment for cardiovascular system (except nifedipine)
Interventions	Treatment: extract Ruscus aculeatus 75 mg plus hesperidin 75 mg plus ascorbic acid 50 mg per day (Cyclo 3) Control: placebo Duration: 60 days Follow-up: 60 days Light compression therapy allowed
Outcomes	Primary • Symptoms - pain, cramps, heavy legs, paraesthesia, pins and needles, burning and restless legs measured by a semiquantitative scale (0 to 3) Secondary • Doctor's global assessment • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A double-blind comparative study against placebo, using two groups treated in parallel, after random distribution of numbered batches of the two treatments to be compared" Comment: seems like a fair method of randomisation was conducted
Allocation concealment (selection bias)	Unclear risk	Comment: no information given about methods used for allocation concealment
Blinding (patients)	Low risk	Quote: "The two products to be compared were presented in the form of identical capsules for both Cyclo 3 and placebo" Comment: Identical placebo ensures a fair method used for double-blinding
Blinding (study researchers)	Low risk	Quote: "The two products to be compared were presented in the form of identical capsules for both Cyclo 3 and placebo" Comment: Identical placebo ensures a fair method used for double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The two products to be compared were presented in the form of identical capsules for both Cyclo 3 and placebo" Comment: Identical placebo ensures a fair method used for double-blinding

Cornu-Thenard 1985 *(Continued)*

Incomplete outcome data	Unclear risk	Quote: no information provided about participants who withdrew prematurely from the trial
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Danielsson 2002

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: sealed envelope principle Exclusions post randomisation: none Losses to follow-up: 4/101 (4%)
Participants	Country: Sweden Setting: hospital Number: 101 patients Age: 18 to 65 years Gender: 28 M:73 F Inclusion criteria: symptomatic CVI with reflux venous, CEAP II classification Exclusion criteria: diabetes; inflammatory, heart, renal, hepatic or peripheral arterial disease. Treatment with diuretics or anti-inflammatory drugs (steroids, NSAIDs). Allergic reactions to venoactive drugs
Interventions	Treatment: micronised purified flavonoid fraction (MPFF) 1000 mg per day Control: placebo Duration: 60 days Follow-up: 60 days

Outcomes	Primary
	• Symptoms - heaviness, tiredness, ankle swelling, pain and cramps measured by an ordinal scale (0 to 3)
	  ○ Oedema - foot volumetry by plethysmography
	  ○ Reflux by Duplex ultrasonography
	  ○ Improvement in global score of symptoms
	Secondary
	• Side effects

Notes	No description of double-blind

Danielsson 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "One hundred and one patients with symptomatic CVD were randomly allocated to treatment with either MPFF (51 patients) or placebo..." Comment: no methods described for randomisation of participants
Allocation concealment (selection bias)	Low risk	Quote: "After informed consent, patients were randomised in a blinded fashion (sealed envelope principle)" Comment: sealed envelope principle considered a good method to ensure allocation concealment
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. In addition, information given about numbers of participants who withdrew prematurely (4/101; 4%)
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Diebschlag 1994

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Germany Setting: not stated Number: 60 postmenopausal females Age: 'adults' Gender: 60 F Inclusion criteria: stage II CVI (oedema and symptoms) Exclusion criteria: not stated

Diebschlag 1994 *(Continued)*

Interventions	Treatment: oxerutin 500 mg per day or 1000 mg per day Control: placebo Duration: 84 days Follow-up period: 112 days
Outcomes	Primary • Symptoms - pain, cramps, heavy legs, swelling, restless legs measured by a semiquantitative scale (0 to 3) ○ Oedema - pitting present or absent, circumference of ankle and calf; plethysmographic parameters Secondary • Side effects • Global opinion of investigators and participants
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study design consisted of a double-blind placebo controlled, randomized parallel group comparison with three treatment groups" Comment: no methods described for randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no methods described for allocation concealment
Blinding (patients)	Low risk	Quote: "All medications appeared to be identical with respect to volume, colour of the bottle and the smell of solution. The difference in taste could be accepted as this type is of solution was not commercially available and, therefore, unknown and unidentifiable to patients" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "All medications appeared to be identical with respect to volume, colour of the bottle and the smell of solution. The difference in taste could be accepted as this type is of solution was not commercially available and, therefore, unknown and unidentifiable to patients" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "All medications appeared to be identical with respect to volume, colour of the bottle and the smell of solution. The difference in taste could be accepted as this type is of solution was not commercially available and, therefore, unknown and unidentifiable to patients" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section

Diebschlag 1994 *(Continued)*

Other bias	Low risk	Comment: none detected

DOBESILATO500/2

Study characteristics	
Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: random list generated by computer Exclusions post randomisation: study interrupted Losses to follow-up: study interrupted
Participants	Country: Spain Setting: hospital Number: 69 patients Age: 60.9 (13.9) years placebo; 63.0 (20.5) years calcium dobesilate Gender: 36 M:33 F Inclusion criteria: adult patients with venous ulcer (CEAP 6) that affected epidermis, dermis and/or subcutaneous tissue, with an area superior to 3 cm^2, an ankle-arm index 0.9 or superior and written informed consent of patients Exclusion criteria: diabetes mellitus I or II. Renal failure and dialysis. Vascular surgery needed Impossibility to use compressive measures on the leg. Use of topical antibiotics, silver dressing, growth factors; plasma-rich platelets, skin graft, pentoxifylline, ultrasound, laser, hyperbaric oxygen, electrical stimulation or vacuum. Pregnancy. Breast feeding. No anti-contraceptive measures. Allergy or intolerance to phlebotonics. Background of neutropenia or leucopenia. Basal leucocytes < 3.500/mL
Interventions	Treatment: calcium dobesilate 500 mg 3× per day (capsules) Control: placebo Duration: 180 days Follow-up period: 365 days
Outcomes	Primary • Healed venous ulcers at 6 months of treatment Secondary • Percentage of re-epithelialisation area (cm^2) • Length of time to ulcer healing • Ulcer recurrence • Ulcer pain • Safety
Notes	Financial support for Laboratories Dr Esteve was withdrawn and the study was interrupted. Register at clinicatrial.gov: NCT00979836 We obtained information from researchers who conducted this unpublished and interrupted clinical trial

DOBESILATO500/2 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation to treatment was randomised, centralised and computer stratified in blocks, by ulcer size and centre" Comment: Random sequence ensured by computer-stratified blocks
Allocation concealment (selection bias)	Low risk	Comment: Treatment allocated by researcher phoning the co-ordinating centre
Blinding (patients)	Low risk	Quote: "... to placebo (inactive capsules of identical appearance and weight) twice a day" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "... to placebo (inactive capsules of identical appearance and weight) twice a day" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "... to placebo (inactive capsules of identical appearance and weight) twice a day" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	High risk	Study was interrupted when only 69 of the 230 necessary participants were included
Selective reporting	High risk	Study was not published
Other bias	Low risk	Comment: none detected

Dominguez 1992

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: computer-generated random number table Exclusions post randomisation: none Losses to follow-up: 7/57 (12%)
Participants	Country: Spain Setting: hospital Number: 57 patients Age: 20 to 65 years Gender: 5 M:52 F Inclusion criteria: symptomatic CVI and varicose veins and oedema

Dominguez 1992 *(Continued)*

	Exclusion criteria: elastic bandages, anti-inflammatory drugs and diuretics not permitted. Surgical operation, thrombophlebitis, pregnancy, diabetes, cardiopathy, hepatopathy, nephropathy, varicose veins secondary to extrinsic compression and varicose ulcers excluded
Interventions	Treatment: hidrosmine 600 mg per day Control: placebo Duration: 45 days Follow-up: 45 days
Outcomes	Primary • Symptoms - heaviness, pain and cramps measured by an ordinal scale (0 to 9); pruritus and cramps measured by a semiquantitative scale (0 to 3); ankle swelling, measure of narrowest section by photogram Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "On entry, patients were assigned to one or other of the two treatment groups according to a computer-generated random number table" Comment: computer-generated random number table considered a fair method to ensure good randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Low risk	Quote: "The medications were supplied in identical capsule form" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The medications were supplied in identical capsule form" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The medications were supplied in identical capsule form" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group reported, along with information on compliance, drop-outs (7/57; 12%), reasons for drop-out and adverse events. ITT analysis conducted
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Fermoso 1992

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 6/34 (18%)
Participants	Country: Spain Setting: hospital Number: 34 patients Age: mean 53 ± 18 (range 21 to 86) years Gender: 20 M:14 F Inclusion criteria: CVI (varicose veins and/or disturbances of venous circulation by Doppler) Exclusion criteria: not stated
Interventions	Treatment: hidrosmine 600 mg per day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Symptoms - local tension, pain, paraesthesia, heaviness, pruritus, cramps measured by a semiquantitative scale (0 to 4) • Signs - oedema, varicose ulcers, trophic disorders and abnormal skin colour as measured by presence or absence ◦ Venous circulation using Doppler Secondary • Side effects
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The 34 patients chosen were randomly assigned to two treatment groups" Comment: no methods of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Low risk	Quote: "And the other group received placebo capsules indistinguishable from the hidrosmin capsules, according to the double-blind technique"

Fermoso 1992 *(Continued)*

		Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "And the other group received placebo capsules indistinguishable from the hidrosmin capsules, according to the double-blind technique" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "And the other group received placebo capsules indistinguishable from the hidrosmin capsules, according to the double-blind technique" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. In addition, number of participants who prematurely withdrew from the study (6/34; 18%) described
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Flota-Cervera 2008

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Mexico Setting: hospital Number: 49 patients (25 in the calcium dobesilate group; 24 in the placebo group) Age: mean 52.20 ± 8.45 years Gender: 5 M:44 F Inclusion criteria: venous oedema Exclusion criteria: not stated
Interventions	Treatment: calcium dobesilate 1500 mg per day Control: placebo Duration: 49 days Follow-up: 49 days
Outcomes	Primary • Signs - oedema; thigh, calf and ankle circumference ○ Overall efficacy assessed by physician; safety

Flota-Cervera 2008 *(Continued)*

	Secondary • Symptoms - pain measured by an ordinal scale of 4 items (from no pain to severe pain) ○ Plethysmographic parameters
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A single center, prospective, randomized double-blind, parallel group, placebo-controlled" Comment: no method of randomisation generation described
Allocation concealment (selection bias)	Unclear risk	Quote: "A single center, prospective, randomized double-blind, parallel group, placebo-controlled" Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Comment: placebo capsules identical to calcium dobesilate capsules
Blinding (study researchers)	Low risk	Comment: placebo capsules identical to calcium dobesilate capsules
Blinding (outcome assessment)	Low risk	Comment: placebo capsules identical to calcium dobesilate capsules
Incomplete outcome data	Low risk	Comment: no exclusions post randomisation and no losses to follow-up
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Gilly 1994

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 10/160 (6%)
Participants	Country: France Setting: hospital Number: 160 patients Age: 'adults' Gender: 26 M:134 F

Gilly 1994 *(Continued)*

	Inclusion criteria: symptomatic disturbances of the veno-lymphatic system Exclusion criteria: other or associated vascular diseases; oedema of cardiac, renal or hepatic origin; symptoms or signs of arterial, metabolic, neurological or orthopaedic origin; pregnancy; recent venous surgery; deep or superficial thrombosis in the past 6 months
Interventions	Treatment: micronised purified flavonoid fraction (MPFF) 1000 mg per day Control: placebo Duration: 42 days Follow-up: 42 days

Outcomes	Primary
	
	• Symptoms - discomfort, pain, swelling, paraesthesia, redness and/or cyanosis, burning, heaviness, tiredness and cramps measured by a semiquantitative scale (0 to 3)
	  ○ Oedema - circumference of calf and ankle
	  ○ Trophic disorders measured by investigator on a verbal scale (disappearance, improvement, stabilisation or aggravation)
	
	Secondary
	
	• Side effects

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eighty patients were randomly allocated to the S 5682 group and eighty patients to the placebo group" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "Patients fulfilling the inclusion criteria were randomly allocated to receive one S 5682 tablet twice daily or matching placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Patients fulfilling the inclusion criteria were randomly allocated to receive one S 5682 tablet twice daily or matching placebo" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Patients fulfilling the inclusion criteria were randomly allocated to receive one S 5682 tablet twice daily or matching placebo" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. In addition, adverse events experienced, number of drop-outs and reasons for drop-outs described. Methods used for imputing missed data not described. Six per cent of participants lost to follow-up

Gilly 1994 *(Continued)*

Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Guilhou 1997

Study characteristics	
Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 6/107 (6%)
Participants	Country: France Setting: hospital Number: 107 patients Age: 'adults' Gender: 30 M:77 F Inclusion criteria: venous ulcers Exclusion criteria: not stated Randomisation of treatment stratified according to ulcer size: < 10 cm or ≥ 10 cm
Interventions	Treatment: diosmine 450 mg plus hesperidin 50 mg per 12 hours plus compression stockings Control: placebo and standard compression stockings Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Percentage of participants with complete healing at 2 months Secondary • Percentage of surface area healed • Aspect of ulcer and peri-ulcerous skin of the reference ulcer • Total number of healed ulcers in cases of multiple ulcers • Evolution of symptoms of CVI • Socioeconomic incidence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Guilhou 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation of treatment was stratified according to the size of the ulcers" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. ITT analysis conducted. Information provided about participants who withdrew prematurely from the study, along with reasons for premature withdrawal
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Hachen 1982

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 2/50 (4%)
Participants	Country: Switzerland Setting: hospital Number: 50 females Age: 10 to 45 years Gender: 50 F Inclusion criteria: recent onset of CVI; no venous surgery, presence of symptoms (heaviness, fatigue, etc.) or aggravation during prolonged sitting or standing or during premenstrual periods Exclusion criteria: pregnancy, diabetes, polyneuropathy, osteo-articular lesions in the legs, arterial peripheral insufficiency, oral contraceptives, poor co-operation
Interventions	Treatment: calcium dobesilate 1000 mg per day Control: placebo Duration: 28 days

Hachen 1982 *(Continued)*

	Follow-up: 28 days
Outcomes	Primary • Plethysmographic parameters • Symptoms - pain, heaviness, swelling and paraesthesia measured by an ordinal scale scored from -3 (total relief) to +1 (deterioration) Secondary • Global score of symptoms • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Fifty female patients with recent onset of venous insufficiency were randomly allocated to two subgroups receiving either calcium dobesilate or a corresponding placebo" Comment: no method of randomisation of participants described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "Fifty female patients with recent onset of venous insufficiency were randomly allocated to two subgroups receiving either calcium dobesilate or a corresponding placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Fifty female patients with recent onset of venous insufficiency were randomly allocated to two subgroups receiving either calcium dobesilate or a corresponding placebo" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Fifty female patients with recent onset of venous insufficiency were randomly allocated to two subgroups receiving either calcium dobesilate or a corresponding placebo" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. Participants who withdrew prematurely from the trial described, along with reasons for withdrawal. Four per cent of participants lost to follow-up
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Ihme 1996

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: Rancode computer software Exclusions post randomisation: none Losses to follow-up: 11/77 (14%)
Participants	Country: Germany Setting: hospital Number: 77 patients Age: mean 57.3 ± 9.6 years active group; mean 59.8 ± 7.3 years placebo group Gender: 24 M:53 F Inclusion criteria: CVI stages I and II (oedema, symptoms, stem varicosis, post-thrombotic syndrome, valvular insufficiency of the deep veins) Exclusion criteria: varicosis with surgical indication; active or healed ulcus cruris; acute thrombosis or venous inflammation; oedema due to cardiac or renal insufficiency; treatment with a diuretic, dihydroergotamine or any other drugs for venous therapy; other severe disorder
Interventions	Treatment: Buckwheat herb tea (rutoside) 270 mg per day Control: placebo Duration: 90 days Follow-up: 112 days
Outcomes	Primary • Signs - oedema, lower leg volume of more seriously affected leg by a Gutmann volumeter and ultrasound Secondary • Symptoms - tenseness, heaviness, swelling by an ordinal scale (0, 1, 2). Pain, paraesthesia, cramps, burning feet, restless legs by an ordinal scale (0, 0.5, 1) ○ Side effects
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was carried out by Rancode computer software (IDV Gauting, Germany)" Comment: Randomisation seems like a fair method to ensure a random sequence of participants
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described

Ihme 1996 *(Continued)*

Blinding (patients)	Low risk	Quote: "A blinded taste test with pharmacists demonstrated that the teas were similar in taste and appearance and hard to distinguish" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "A blinded taste test with pharmacists demonstrated that the teas were similar in taste and appearance and hard to distinguish" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "A blinded taste test with pharmacists demonstrated that the teas were similar in taste and appearance and hard to distinguish" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described. Number of drop-outs and reasons for dropping out of the trial described. ITT analysis conducted
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Jongste 1986

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: The Netherlands Setting: outpatient Number: 80 patients Age: 20 to 75 years Gender: male and female; breakdown not given Inclusion criteria: unilateral post-thrombotic syndrome Exclusion criteria: elastic stockings; diuretics; venoactive drugs; open venous ulcers; paralysis of the leg with post-thrombotic syndrome; arterial disease; oedema of other origin; regular users of anti-inflammatories, corticosteroids or analgesics
Interventions	Treatment: O-(beta-Hydroxyethyl)-rutosides 1200 mg per day Control: placebo Duration: 56 days

Jongste 1986 *(Continued)*

	Follow-up: 56 days

Outcomes	Primary
	• Symptoms (tiredness, pain, heaviness, cramps, swelling feeling, restless legs) measured by an ordinal scale (0 to 3)
	• Signs - pitting oedema, circumference of ankle and calf, pitting oedema, venous pressure
	  ○ Overall efficacy assessed by physician and participant
	  ○ Side effects

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The trial was double blind, randomised, placebo controlled between patients" Comment: no methods of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described.
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Quote: number of participants in each group described. No losses reported
Selective reporting	High risk	Comment: no published protocol identified. In the methods section, outcomes of “restless legs” and “venous pressure” reported, but in the results/conclusion sections, no data regarding these outcomes reported
Other bias	Low risk	Comment: none detected

Jongste 1989

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: computerised random assignment method used Exclusions post randomisation: 17/101 (17%) Losses to follow-up: 3 (0.3%)
Participants	Country: The Netherlands Setting: hospital Number: 101 patients

Jongste 1989 *(Continued)*

	Age: 53 ± 12 years active group; 54 ± 13 years placebo group Gender: 48 M:35 F Inclusion criteria: unilateral post-thrombotic syndrome > 6 months' duration and history of venography with deep vein thrombosis Exclusion criteria: elastic stockings; veno-active drugs within 2 weeks of entry into the trial; active venous ulcer; pregnancy; age > 75 years
Interventions	Treatment: oxirutosides 1200 mg per day Control: placebo Duration: 56 days Follow-up: 56 days
Outcomes	Primary • Symptoms - tiredness, pain, heaviness, swelling feeling, restless legs, cramps, pitting oedema measured by an ordinal scale (0 to 3) • Signs - circumference of calf and ankle Secondary • Side effects • Physicians' and participants' opinions on efficacy of treatment
Notes	Concealment of placebo not explicit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Upon entering the study, patients were randomly assigned to receive either HR or placebo with the use of a computerized random assignment method" Comment: computerised random assignment method generally accepted as a good method to generate a random sequence of participants
Allocation concealment (selection bias)	Low risk	Quote: "A series of coded sealed envelopes for decoding any particular case was supplied to the local hospital pharmacy" Comment: sealed envelopes generally accepted as a good method of allocation concealment
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with number of participants who dropped out and number who experienced adverse events

Jongste 1989 *(Continued)*

Selective reporting	High risk	Comment: no published protocol identified. In the methods section, outcomes of “restless legs” and “venous pressure” reported, but in the results/conclusion sections, no data regarding these outcomes reported
Other bias	Low risk	Comment: none detected

Kiesewetter 1997

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Germany Setting: university Number: 81 patients Age: mean 59 ± 7 years Gender: 26 M:55 F Inclusion criteria: stage I to II of Wert CVI Exclusion criteria: acute thromboses; ulcus cruris; heart insufficiency; recent venous surgery; venoactive drugs
Interventions	Treatment: 500 mg Buckwheat herb and 30 mg troxerutin. 2 tablets 3 × per day Control: placebo Duration: 84 days Follow-up: 112 days
Outcomes	Primary • Lower leg volume determined by ultrasound of the more affected leg Secondary • Symptoms - pain, paraesthesia, cramps, swelling, restless legs, burning feet measured by an ordinal scale (0 to 2)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "For randomization of patients, the program was 'Rancode' of the company IDV data analysis and experimental design, Gauting, used"

Kiesewetter 1997 *(Continued)*

		Comment: computerised generation of a random sequence generally accepted as a fair method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given about methods used for allocation concealment
Blinding (patients)	Low risk	Quote: "The same number of identical-looking placebo tablets consisting of lactose were given" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The same number of identical-looking placebo tablets consisting of lactose were given" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The same number of identical-looking placebo tablets consisting of lactose were given" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Unclear risk	Comment: number of participants in each group described. No information provided about participants who prematurely dropped out of the study
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Klüken 1971

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Germany Setting: hospital Number: 60 patients Age: 'adults' Gender: not stated Inclusion criteria: CVI (varicoses or post-thrombotic syndrome) Exclusion criteria: not stated
Interventions	Treatment: troxerutin 75 mg and coumarin 15 mg per day Control: placebo

Klüken 1971 *(Continued)*

	Duration: 21 days Follow-up: 21 days
Outcomes	Primary • Symptoms - pain, tension measured by a qualitative scale ○ Oedema - circumference of calf and ankle Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Double-blind, randomized, placebo-controlled. In two parallel groups" Comment: information about methods of randomisation not provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information about methods of allocation concealment provided
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Unclear risk	Comment: number of participants in each group described. No information provided about the number of participants who dropped out of the study prematurely or the number who experienced adverse events
Selective reporting	Unclear risk	Comment: no published protocol identified. No outcomes reported in the methods section
Other bias	Low risk	Comment: none detected

Koscielnny 1996

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 6/77 (8%)
Participants	Country: Germany

Koscielnny 1996 *(Continued)*

	Setting: university Number: 94 patients selected; 67 randomised Age: 'adults' Gender: not stated Inclusion criteria: CVI stage I to II Widmer Exclusion criteria: not stated
Interventions	Treatment: Buckwheat herb tea 3 × 1.8 g per day Control: placebo tea Duration: 84 days Follow-up: 112 days
Outcomes	Primary • Oedema, by reduction of leg volume • Symptoms - tenseness, heaviness, swelling, pain, paraesthesia, cramps, burning feet, restless legs, itching Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After a placebo period of two weeks, patients were randomly assigned to active treatment or a placebo group" Comment: no information about methods of randomisation provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information about methods of allocation concealment provided
Blinding (patients)	Low risk	Quote: "Placebo is with taste and appearance indistinguishable from the treatment" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Placebo is with taste and appearance indistinguishable from the treatment" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Placebo is with taste and appearance indistinguishable from the treatment" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in both placebo and treatment groups described, along with the most important participant characteristics, numbers of

Koscielnny 1996 *(Continued)*

		participants who dropped out prematurely, reasons for drop-out, influence of drop-outs and information on compliance
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Kriner 1985

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Germany Setting: hospital Number: 50 patients Age: 'adults' Gender: not stated Inclusion criteria: disturbances of venous blood flow, oedema Exclusion criteria: not stated
Interventions	Treatment: ruscus extract 75 mg and hesperidin 75 mg 2 × 2 capsules per day. rutoside cream once per day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Oedema - circumference of foot, heel and calf • Symptoms - fatigue, tension, heaviness, cramps, burning, itching Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Kriner 1985 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "The two groups were balanced and comparable with respect to age, weight, and type and duration of disturbances" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Unclear risk	Comment: number in each group described, but important characteristics lacking. In addition, number of participants who dropped out prematurely or were excluded after randomisation not described
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Labs 2004

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: computerised random assignment method Exclusions post randomisation: 7/260 (0.3%), protocol violation Losses to follow-up: 21/260 (8%)
Participants	Country: Switzerland Setting: university Number: 260 patients Age: 20 to 70 years Gender: 16 M:201 F Inclusion criteria: CVI class 1 to 4 (CEAP classification), oedema and symptoms Exclusion criteria: CVI class 5 to 6 (CEAP classification); other causes of oedema (cardiac, renal, etc.); hypertension with change in treatment within 6 weeks of study start; obesity; peripheral arterial occlusive disease; venous surgery in the past 12 months or sclerotherapy during the past 6 months; irregular menstrual cycle; elevated transaminases; neutropenia; significant renal insufficiency; gastrointestinal disease; allergy to study medication; pregnant or lactating women; unreliable patient (psychiatric disorders, alcoholism, etc.); compression stockings or bandages; diuretics; venotropic medication; antiphlogistic drugs; corticosteroids; analgesics
Interventions	Treatment: calcium dobesilate 1500 mg per day

Labs 2004 *(Continued)*

	Control: placebo Duration: 28 days Follow-up: 42 days

Outcomes	Primary
	
	• Signs - oedema, reduction in leg volume (≥ 25 mL/litre tissue), circumference of ankle and calf
	
	Secondary
	
	• Symptoms - pain and discomfort measured by a visual analogue scale
	  ○ Discomfort measured as the sum of frequencies of symptoms: heaviness, tingling and itching
	  ○ Pain measured as the sum of frequencies of symptoms: pain and cramps
	  ○ Total symptoms score (discomfort and pain)
	  ○ Overall efficacy assessed by physician and participant on a 7-point scale
	  ○ Side effects

Notes	Reasons for withdrawal unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The corresponding boxes were randomized in balanced blocks and were labelled by the sponsor with the study number, the dosage, the batch numbers, with the patient number and with the note 'for clinical trials only'. The randomization was done by BIOMETRIX S. A., CH-1911 Gland, Switzerland, using appropriate software" Comment: computer-generated list of random numbers accepted as a good method for generating a random sequence of participants
Allocation concealment (selection bias)	Low risk	Quote: "The allocation of the study treatment to each patient was done according to the next available consecutive patient number printed on the prescription card and on the label of the box. This number was recorded on each page of the CRF.¨ and ¨Each investigator was provided with a sealed envelope containing the code for each patients randomisation number" Comment: seems like a fair method of allocation concealment
Blinding (patients)	Low risk	Quote: "For the double-blind treatment period, the boxes, labels, and capsules containing Doxium 500 and placebo were identical in appearance for each drug, to ensure patient and investigator blinding" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "For the double-blind treatment period, the boxes, labels, and capsules containing Doxium 500 and placebo were identical in appearance for each drug, to ensure patient and investigator blinding" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "For the double-blind treatment period, the boxes, labels, and capsules containing Doxium 500 and placebo were identical in appearance for each drug, to ensure patient and investigator blinding" Comment: Identical placebo ensures double-blinding

Labs 2004 *(Continued)*

Incomplete outcome data	Low risk	Comment: number of participants in each group described. Adverse events, participant experience, compliance and number of participants who dropped out prematurely reported (29/260 participants)
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Languillat 1988

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: France Setting: hospital Number: 20 patients Age: 20 and 65 years Gender: 1 M:19 F Inclusion criteria: symptomatic CVI and oedema Exclusion criteria: previous venous sclerosis; surgery or elastic support; trophic disturbances; ulcers or permanent oedema; cardiac, renal, hepatic insufficiency or arterial disease; Raynaud's phenomenon; lymphoedema; pregnancy; venoactive drugs; any significant change in patient lifestyle or work
Interventions	Treatment: extract Ruscus aculeatus 450 mg plus hesperidin 450 mg plus ascorbic acid 300 mg per 12 hours Control: placebo Duration: 28 days Follow-up: 42 days
Outcomes	Primary • Venous circulatory velocity measured by Xenon 133 Secondary • Symptoms - heavy legs, pain, paraesthesias, cramp, restlessness, swelling measured by a semiquantitative scale (0 to 3) • Overall assessment by investigator • Safety
Notes	

Languillat 1988 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a double-blind placebo-controlled trial with two groups of patients treated in parallel" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "The double-blind nature of the trial was guaranteed by the strictly identical appearance of treatment units (capsules) as well as their packaging (bottles and bags of treatment kits)" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The double-blind nature of the trial was guaranteed by the strictly identical appearance of treatment units (capsules) as well as their packaging (bottles and bags of treatment kits)" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The double-blind nature of the trial was guaranteed by the strictly identical appearance of treatment units (capsules) as well as their packaging (bottles and bags of treatment kits)" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with the most important baseline characteristics. No losses reported
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Laurent 1988

Study characteristics	
Methods	Study design: 2 randomised, double-blind, placebo-controlled studies analysed together Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 5/200 (2.5%)
Participants	Country: France Setting: hospital Number: 200 patients Age: mean 49 (range 22 to 82) years

Laurent 1988 *(Continued)*

	Gender: 26 M:174 F Inclusion criteria: One study included patients with functional venous insufficiency (presence of symptoms but not signs); n = 83. The other study included patients with chronic organic venous insufficiency (varicose disease, post-thrombotic syndrome); n = 117 Elastic stockings permitted Exclusion criteria: not exclusively venous symptoms (arterial, neurological or metabolic origin, disorders of static equilibrium); venotropic drugs in the past 3 months; pregnancy; prolonged immobilisation
Interventions	Treatment: diosmine 450 mg plus hesperidin 50 mg per 12 hours Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Symptoms - functional discomfort, evening oedema, redness or cyanosis, heart or burning pain, paraesthesia, heaviness, cramps measured by an ordinal scale (0 to 3). Clinicians' overall assessment by a qualitative scale (results very good, useful or nil) • Signs - oedema measured by circumference of ankle; changes in trophic disorders Secondary • Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized trials were conducted versus placebo using appropriate statistical tests determined a priori" Comment: no methods of sequence generation specified
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group provided, along with inclusion and exclusion criteria and characteristics of participants Number of participants who experienced adverse events presented, along with number who dropped out of the study. Losses 2.5%
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section

Laurent 1988 *(Continued)*

Other bias	Low risk	Comment: none detected

Lazzarini 1982

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Italy Setting: hospital Number: 100 patients Age: 'adults' Gender: 23 M:74 F Inclusion criteria: stratification for participant groups: varicose legs, ulcer, thrombophlebitis, slight CVI Exclusion criteria: not stated
Interventions	Treatment: aminaftone 150 mg per day Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Symptoms - itching, heaviness, cramps and pain measured by an ordinal scale (0 to 3) • Signs - oedema, dystrophy and ulcer measured by an ordinal scale (0 to 3) Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The trial was conducted in 100 patients, informed consent and randomized into two groups of 50 and 50 and double-blind treatment, the first with Capillarema and the second with placebo" Comment: method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described

Lazzarini 1982 *(Continued)*

Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Unclear risk	Comment: number of participants in each group described, but important baseline characteristics lacking. In addition, number of participants who withdrew prematurely not described
Selective reporting	High risk	Comment: no information regarding adverse events provided
Other bias	Low risk	Comment: none detected

MacLennan 1994

Study characteristics	
Methods	Study design: multicenter, international, parallel, randomised, double-blind, placebo-controlled trial Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 16/104 (15%)
Participants	Country: UK, Germany, Netherland and Belgium Setting: hospital Number: 104 patients Age: ≥ 65 years Gender: 24 M:62 F Inclusion criteria: unilateral or bilateral symptoms and signs of CVI. Compression stockings allowed Exclusion criteria: bed-bound or with cardiac or renal or hepatic disease or clinically important obesity; arterial insufficiency of the legs
Interventions	Treatment • Oxirutoside 900 mg per day for 180 days • Oxirutoside 1000 mg per day for 180 days • Oxirutoside 1200 mg per day for 180 days • Placebo for 180 days Follow-up: 180 days Participants who wore elastic support stockings had to continue to wear them throughout the study
Outcomes	Primary • Oedema, by reduction of leg volume • Symptoms - tenseness, heaviness, swelling, pain, paraesthesia, cramps, burning feet, restless legs and itching

MacLennan 1994 *(Continued)*

	Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was made according to a computer-generated randomization list in blocks of 10" Comment: computer-generated randomisation list generally accepted as an appropriate way to generate a random sequence of participants
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment stated
Blinding (patients)	Low risk	Quote: "Patients from each centre in the randomised control group were given placebo capsules identical in appearance" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Patients from each centre in the randomised control group were given placebo capsules identical in appearance" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Patients from each centre in the randomised control group were given placebo capsules identical in appearance" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants described, along with the most important characteristics, number of drop-outs, adverse events and information on compliance
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Mann 1981

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 5/28 (18%)
Participants	Country: UK

Mann 1981 *(Continued)*

	Setting: outpatient Number: 28 patients Age: mean 69 years active treatment; mean 63 years placebo Gender: not stated Inclusion criteria: ≥ 1 venous ulcer Exclusion criteria: not stated
Interventions	Treatment: hidroxirutoside 1000 mg per day Control: placebo Duration: 90 days Follow-up: 90 days Concomitant therapy: topical therapy and an "elastoweb" bandage
Outcomes	Primary • Symptoms - tiredness, pain, heaviness, swelling feeling, restless legs, cramps, pitting oedema measured by an ordinal scale (0 to 3) • Signs - circumference of calf and ankle Secondary • Side effects • Physicians' and participants' opinions on the efficacy of treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided about the method used for randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided about the method used for allocation concealment
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	High risk	Comment: number of participants for each group described, but no information provided about participants lost to follow-up or dropped out. Data were missing from the analysis and adverse events were not described. Losses were reported as 18%
Selective reporting	High risk	Comment: no protocol identified. Differences were noted between methods and results for the following outcomes: tiredness, heaviness, tender legs, distended veins, nights disturbed, daytime cramps

Mann 1981 *(Continued)*

Other bias	Low risk	Comment: none detected

Marinello 2002

Study characteristics	
Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 21/123 (17%)
Participants	Country: Spain Setting: hospital Number: 143 patients Age: mean 52.87 (range 19 to 72) years Gender: 25 M:77 F Inclusion criteria: CVI stage CEAP III, IV and V Exclusion criteria: not stated
Interventions	Treatment: calcium dobesilate 1000 mg per day or calcium dobesilate 2000 mg per day Control: placebo Duration: 84 days Follow-up: 84 days Elastic stockings permitted
Outcomes	Primary • Symptoms - heaviness and pain in the legs • Signs - transcutaneous PO2 and CO2 Secondary • Not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "In total 143 patients 123 were randomized (41 per treatment group)" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described

Marinello 2002 *(Continued)*

Blinding (patients)	Low risk	Quote: "The placebo had the same characteristics which include active treatment. The oral administration was under the same conditions as the active treatment" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The placebo had the same characteristics which include active treatment. The oral administration was under the same conditions as the active treatment" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The placebo had the same characteristics which include active treatment. The oral administration was under the same conditions as the active treatment" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with baseline characteristics. In addition, numbers and information provided about adverse events and participants who withdrew prematurely from the study
Selective reporting	Low risk	Comment: no published protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Martinez-Zapata 2008

Study characteristics	
Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: computer-generated random number table Exclusions post randomisation: none Losses to follow-up: 131/509 (25.7%)
Participants	Country: Spain Setting: hospital Number: 509 patients Age: mean 53.3 ± 13.3 years treatment group; mean 54.7 ± 14.9 years placebo group Gender: 66 M:443 F Inclusion criteria: adults of either gender with CVD, CEAP clinical grades 1 to 6 and able to complete a QoL questionnaire Exclusion criteria: chronic or acute disease that limited compliance with the protocol, scheduled surgery or sclerotherapy in the coming calendar year, pregnant or lactating women, patients with allergies or known intolerance to the study medication, history of neutropoenia or leucopoenia, baseline serum leucocyte count < 3500/mL
Interventions	Treatment: 500 mg capsules of oral calcium dobesilate twice a day for 3 months

Martinez-Zapata 2008 *(Continued)*

	Control: placebo: Inactive capsules of identical appearance and weight Duration: 90 days Follow-up: 365 days
Outcomes	Primary • Symptoms - change in QoL Secondary • Signs - oedema • Symptoms - pain or cramps
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation to treatment was randomised, centralised and computer stratified in blocks of 10 patients, by clinical CEAP classification and centre" Comment: Computer-stratified blocks ensure a random sequence
Allocation concealment (selection bias)	Low risk	Comment: treatment was allocated by researcher phoning the co-ordinating centre
Blinding (patients)	Low risk	Quote: "to placebo (inactive capsules of identical appearance and weight) twice a day" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "to placebo (inactive capsules of identical appearance and weight) twice a day" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "to placebo (inactive capsules of identical appearance and weight) twice a day" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number in each group was described, and those lost to follow-up (25.7%) and participants who prematurely withdrew were described. Important characteristics were described, and inclusion and exclusion criteria were reported. ITT analysis was conducted, and imputation technique was described
Selective reporting	Low risk	Comment: protocol identified and no differences identified between protocol and article
Other bias	Low risk	Comment: none detected

NCT01848210

Study characteristics

NCT01848210 *(Continued)*

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: "by chance, like flipping a coin" Exclusions post randomisation: 166 Losses to follow-up: 36
Participants	Country: Brazil Setting: not specified Number: 829 (411 experimental group and 418 placebo group) included and 711 analysed (383 experimental group and 388 placebo group) Age (mean): 56 (18 to 75 years old) Gender: 83 men and 688 women Inclusion criteria: consent of subject or legal representative. Men or women of any ethnicity, aged between 18 and 75 years, and BMI equal or less than 40. CVI in the reference leg with the clinical classification C3, or C4a or C4b or C5, stable edema. Scoring in "Severity Score of Local Complaints" equal to or higher than 5 total points. Women who are using an effective birth control or who are postmenopausal Exclusion criteria: Deep vein insufficiency or venous obstruction and/or DVT and/or presence of phlebitis in lower limbs during the last 3 months.Surgery at the venous system or sclerotherapy or any treatment for CVI during the last 3 months. History of known or suspected allergy or intolerance to any of the ingredients of the medicinal product under investigation. Serious systemic disease. Hepatitis A, hepatitis B, or C or any liver disease. Use of diuretics. Diabetes insulin-dependent. History of alcoholism, drug abuse, psychological or emotional problems
Interventions	Treatment: Coumarin 30 mg, troxerutin 180 mg fixed-dose combination tablets (Venalot), orally, 3 times daily Control: placebo Duration: 16 weeks Follow-up: 18 weeks
Outcomes	Primary: • Mean change from baseline in volume of reference leg at week 16 using a water plethysmometer Secondary: • Change from baseline in local complaint severity (eight symptoms assessed by a lickert scale) • Overal assessment by the investigator • Number of participants with adverse events
Notes	Sponsor: Takeda. Results published in clinicaltrials.gov

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants will be randomly assigned (by chance, like flipping a coin) to one of the two treatment groups"
Allocation concealment (selection bias)	Unclear risk	Comment: not specified.

NCT01848210 *(Continued)*

Blinding (patients)	Low risk	Quote: "Placebo (dummy inactive pill) - this is a tablet that looks like the study drug but has no active ingredient. All participants will be asked to take two tablets three times a day throughout the study"
Blinding (study researchers)	Low risk	Quote: "Placebo (dummy inactive pill) - this is a tablet that looks like the study drug but has no active ingredient. All participants will be asked to take two tablets three times a day throughout the study"
Blinding (outcome assessment)	Low risk	Quote: "Placebo (dummy inactive pill) - this is a tablet that looks like the study drug but has no active ingredient. All participants will be asked to take two tablets three times a day throughout the study"
Incomplete outcome data	Low risk	Comment: there was a IIT analysis (patient that taken the treatment at least 28 days) and a PP analysis. The total losses were 166 (20%)
Selective reporting	Low risk	Comment: all results are published.
Other bias	Low risk	Comment: none detected

Nocker 1990

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Germany Setting: university Number: 30 Age: 55 to 59 years Gender: menopausal females Inclusion criteria: stage II CVI with symptoms Exclusion criteria: venoactive drugs, anti-inflammatories, corticosteroids or diuretics in the last 8 days before the start of the study; use of compression bandages or elastic stockings
Interventions	Treatment: oxirutoside 600 mg or 900 mg or 1200 mg or 1500 mg per day Control: placebo Duration: 90 days Follow-up: 112 days
Outcomes	Primary • Symptoms - tired and heavy legs, tenseness, tingling measured by means of a visual analogue scale (VAS) • Signs - oedema by volume of leg

Nocker 1990 *(Continued)*

	Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized to one of the five groups, receiving oral solutions of HR in small bottles containing 600, 900, 1200, 1500 mg HR or simply distilled water (controls) with six patients in each group" Comment: no methods described for randomising participants
Allocation concealment (selection bias)	Unclear risk	Comment: no methods for allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Unclear risk	Comment: no data given about drop-outs. Most important characteristics described with inclusion and exclusion criteria
Selective reporting	Low risk	Comment: no protocol identified, but no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Padrós 1972

Study characteristics	
Methods	Study design: randomised, double-blind, cross-over, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Spain Setting: university Number: 30 females Age: 48 to 51 years Gender: female Inclusion criteria: CVI with signs (oedema, venous ectasia) and symptoms (heaviness, paraesthesias)

Padrós 1972 *(Continued)*

	Exclusion criteria: not stated
Interventions	Treatment: calcium dobesilate 250 mg tablet 3 × per day Control: placebo tablet 3 × per day Duration: 21 days Follow-up: 28 days
Outcomes	Primary • Symptoms - heaviness and paraesthesias • Signs - oedema and venous ectasia Secondary • Tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no methods of random sequence generation described
Allocation concealment (selection bias)	Low risk	Comment: each bottle of treatment was identical and was numbered in a random way
Blinding (patients)	Low risk	Comment: each bottle of treatment was identical. Participants did not know the type of treatment administered
Blinding (study researchers)	Low risk	Comment: each bottle of treatment was identical. Researcher did not know the type of treatment administered
Blinding (outcome assessment)	Low risk	Comment: each bottle of treatment was identical. Assessor did not know the type of treatment administered
Incomplete outcome data	Unclear risk	Comment: no information on losses
Selective reporting	High risk	Comment: results before cross-over not reported
Other bias	Low risk	Comment: none detected

Parrado 1999

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: table of random numbers Exclusions post randomisation: none Losses to follow-up: none

Parrado 1999 *(Continued)*

Participants	Country: Argentina Setting: hospital Number: 60 patients Age: 30 to 70 years Gender: 16 M:44 F Inclusion criteria: CVI, stages I to II of the Widmer classification (pigmentation, oedema, varicoses and symptoms) Exclusion criteria: elastic stockings; urgent surgical treatment or venous surgical treatment or sclerotherapy in previous 6 months; cardiac, renal or hepatic insufficiency; anti-migraine drugs; analgesics; NSAIDs; diuretics or cardiovascular drugs; pregnant women or women who had given birth during previous 3 months
Interventions	Treatment: Ruscus aculeatus with hesperidin and vitamin C 300 mg per day Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Symptoms - heaviness, pain, cramps, tiredness, pruritus, tingling sensation, swelling, measured by means of an ordinal scale from 0 to 3 (from no symptoms to severe symptoms) ○ Participants' global assessment by a qualitative scale • Signs - venous inflammation, pigmentation, trophic ulceration and oedema (circumference of ankle measured by a medical ribbon and by the ordinal scale) Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study was double-blind and patients were randomly allocated to be included in one of two parallel groups by using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Low risk	Quote: "Bottles, identical in form and presentation contained dobesilate calcium or placebo, according to a randomization code that was opened until the end of experiment" Comments: Identical presentation of intervention and control groups ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Bottles, identical in form and presentation contained dobesilate calcium or placebo, according to a randomization code that was opened until the end of experiment"; "Neither the patient nor the medical staff did not know the nature of the substance administered, thereby satisfying the conditions of a double-blind trial"

Parrado 1999 *(Continued)*

		Comments: Identical presentation of intervention and control groups ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Bottles, identical in form and presentation contained dobesilate calcium or placebo, according to a randomization code that was opened until the end of experiment"; "Neither the patient nor the medical staff did not know the nature of the substance administered, thereby satisfying the conditions of a double-blind trial" Comments: Identical presentation of intervention and control groups ensures double-blinding
Incomplete outcome data	Low risk	Comment: no losses reported
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Pecchi 1990

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: use of alternation by order of arrival of each participant Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Italy Setting: university Number: 40 patients Age: mean 48.2 ± 15.7 years Gender: 4 M:36 F Inclusion criteria: primary CVI and post-thrombotic syndrome Exclusion criteria: postphlebitic syndrome; severe trophic lesions; no venous oedema; patients taking diuretics, corticosteroids or vasoactive drugs; elastic stockings or bandages
Interventions	Treatment: calcium dobesilate 1000 mg per day Control: placebo Duration: 30 days Follow-up: 30 days
Outcomes	Primary • Symptoms - pain, cramps, heaviness, pruritus, swelling and paraesthesia measured by a semiquantitative scale (0 to 4) • Signs - oedema measured by plethysmographic parameters and circumference of ankle; varicoses in the legs measured by a semiquantitative scale (0 to 4)

Pecchi 1990 *(Continued)*

	Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients admitted to the study were randomly divided into two balanced groups treated respectively with calcium or placebo for one month..." Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Quote: "The allocation to individual patients of either type of treatment was performed according to the access sequence number of the patient" Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: numbers of participants in both groups described. No losses reported. No baseline characteristics of participants provided
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Pedersen 1992

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Denmark Setting: not stated Number: 43 patients Age: 'adults' Gender: 8 M:41 F Inclusion criteria: symptoms of CVI and oedema

Pedersen 1992 *(Continued)*

	Exclusion criteria: diuretic drugs; venotonic drugs; pregnant women
Interventions	Treatment: oxirutoside 900 mg per day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Oedema, circumference of legs • Symptoms - swelling, pain, heaviness, restlessness, itching, cramps measured by a qualitative scale (from 'get worse' to 'improvement') Secondary • Not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "If patients met the inclusion criteria, they were randomised using envelope method, double-blind treatment with Venoruton 300 mg × 3 daily or placebo" Comment: method of randomisation not described
Allocation concealment (selection bias)	Low risk	Quote: "If patients met the inclusion criteria, they were randomised using envelope method, double-blind treatment with Venoruton 300 mg × 3 daily or placebo" Comment: envelope methods generally accepted as a fair method for allocation concealment
Blinding (patients)	Unclear risk	Comment: no methods of blinding described
Blinding (study researchers)	Unclear risk	Comment: no methods of blinding described
Blinding (outcome assessment)	Unclear risk	Comment: no methods of blinding described
Incomplete outcome data	Unclear risk	Comment: number of participants in both groups described, along with the most important characteristics and inclusion and exclusion criteria. Number of participants who withdrew prematurely not described
Selective reporting	Low risk	Comment: no protocol identified, but no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Petrassi 2000

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: computer-elaborated simple randomisation table Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Italy Setting: ambulatory Number: 20 patients Age: 47.7 (3.65) years active group; 36.7 (3.66) placebo group Gender: 3 M:19 F Inclusion criteria: CVI symptoms (heaviness and subcutaneous swelling) and venous pressure > 40 mmHg Exclusion criteria: cardiovascular drugs, diuretic drugs and analgesic or anti-inflammatory compounds
Interventions	Treatment: French bark pine extract capsules 100 mg 3 × per day Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Symptoms - evening oedema, swelling, pain, heaviness, cramps and paraesthesias measured by an ordinal scale (from 0 to 3) • Signs - ambulatory venous leg pressure Secondary • Side effects • Global assessment by the physician
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "They were treated with placebo or Pycnogenol 100mg × 3/day for 2 months according to a computer elaborated simple randomization table" Comment: computerised randomisation table generally accepted as a proper way to randomise participants
Allocation concealment (selection bias)	Unclear risk	Comment: no method described for allocation concealment
Blinding (patients)	Low risk	Quote: "The drugs were prepared in white opaque capsules in order to make the slightly pinkish-coloured Pycnogenol® indistinct from placebo (lactose)"

Petrassi 2000 *(Continued)*

		Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The drugs were prepared in white opaque capsules in order to make the slightly pinkish-coloured Pycnogenol® indistinct from placebo (lactose)" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The drugs were prepared in white opaque capsules in order to make the slightly pinkish-coloured Pycnogenol® indistinct from placebo (lactose)" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants was described in each group, along with the most important characteristics of participants, including inclusion and exclusion criteria. In addition, information was given about drop-outs and adverse events
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Planchon 1990

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 6/110 (5%)
Participants	Country: France Setting: hospital Number: 110 participants Age: mean 50 (range 22 to 79) years Gender: 18 M:92 F Inclusion criteria: symptoms of functional and organic (post-thrombotic syndrome and varices) CVI Exclusion criteria: venous thrombosis; long-term immobilisation; hepatic, renal and cardiac oedema; neurological, arterial and metabolic symptoms
Interventions	Treatment: diosmine 450 mg plus hesperidin 50 mg × 2 capsules per day Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Symptoms of CVI and oedema

Planchon 1990 *(Continued)*

- Symptoms - pain, cramps, heaviness, paraesthesias measured by an ordinal scale (0 to 3)
- Oedema - circumference of ankle
- Cyanosis and redness measured by an ordinal scale (0 to 3)

Secondary

- Side effects

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The award of the therapeutic group membership made by draw lots was ignored until the complete end of the study by both the clinician and the patients" Comment: drawn seems a method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment stated
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, as well as the inclusion and exclusion criteria and the most important characteristics. Numbers of participants who withdrew prematurely were described, including reasons for dropping out, information about compliance and adverse events
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Pointel 1986

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 4 (4%)
Participants	Country: France Setting: hospital Number: 94 patients

Pointel 1986 *(Continued)*

	Age: mean 49 ± 12 years Gender: 8 M:86 F Inclusion criteria: CVI Exclusion criteria: severe varicose veins requiring an elastic strip, postphlebitic patients, those with unilateral venous insufficiency, those treated with a venoactive drug before the start of the study
Interventions	Treatment: Centella asiatica (TECA) 120 mg: two 30 mg capsules twice a day vs Centella asiatica (TECA) 60 mg: one 30 mg capsule twice a day Control: placebo Duration: 56 days Follow-up: 56 days
Outcomes	Primary • Symptoms of CVI (pain, heaviness) and oedema measured by an ordinal scale (0 to 3) Secondary • Venous distensibility measured by plethysmography • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study conducted in four hospitals according to a controlled, randomized, double-blind (double dummy) study performed on three parallel groups for eight weeks" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with inclusion and exclusion criteria and important characteristics for participants. In addition, study author reported the number of adverse events that occurred, the number of participants who withdrew prematurely and reasons for dropping out
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Prerovsky 1972

Study characteristics	
Methods	Study design: 2 independent, randomised, double-blind, cross-over, placebo-controlled trials • In the first trial, outcomes are haemodynamic, so this trial was not included • The second trial is included Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Czechoslovakia Setting: research centre Number: 50 patients Age: 'adults' Gender: not stated Inclusion criteria: signs (oedema, pigmentation, post-thrombotic syndrome) and symptoms of CVI Exclusion criteria: not stated
Interventions	Treatment: oxirutoside 1200 mg per day Control: placebo Duration: 126 days Follow-up: 126 days
Outcomes	Primary • Oedema, leg volume, pitting oedema, cellulitis • Symptoms - heavy legs, fatigue, pain, cramps, swelling scored by a qualitative scale (improvement, without changes, deterioration) Secondary • Not stated
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "... after the administration of 3 capsules of HR (900 mg) or 3 capsules of placebo in a double blind cross-over trial in a randomized-order" Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described

Prerovsky 1972 *(Continued)*

Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants described in each group, along with the most important characteristics. However, inclusion and exclusion criteria were, apart from clinical features, not well described. Adverse events and drop-outs were well described
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Pulvertaft 1983

Study characteristics	
Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: 64/660 (10%)
Participants	Country: UK Setting: general practice Number: 660 patients Age: 54 years Gender: 220 M:440 F Inclusion criteria: symptomatic CVI Exclusion criteria: not stated
Interventions	Treatment: oxirutoside 1000 mg per day Control: placebo Duration: 28 days Follow-up: 28 days Participants who wore elastic support had to continue to wear it throughout the study
Outcomes	Primary • Symptoms - heavy or swelling, pain, restless legs, paraesthesia, cramps assessed on a 3-point scale (none, moderate or severe) Secondary

Pulvertaft 1983 *(Continued)*

- Doctor's global assessment (better, unchanged or worse)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Four patients would receive active treatment with Paroven and one would be randomly and blindly treated with placebo" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, and a table includes the most important characteristics of participants and inclusion and exclusion criteria. In addition, number of participants excluded after randomisation reported
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Rabe 2011

Study characteristics

Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: table of random numbers Exclusions post randomisation: 22 (8%) Losses to follow-up: 32/256 (12.5%)
Participants	Countries: Germany and Switzerland Setting: not stated Number: 256 patients Age: mean 53.2 ± 11.5 years treatment group; mean 53.5 ± 12.1 years placebo group Gender: 38 M:218 F Inclusion criteria: pitting oedema due to CVI (C3-C5 according to CEAP classification) and ≥ 1 of the symptoms such as discomfort and pain

Rabe 2011 *(Continued)*

	Exclusion criteria: disease that imitates symptoms of CVI, cardiac insufficiency, ulceration of the lower leg, diabetes mellitus, hypertension, lymphoedema, sclerotherapy during the past 6 months, lipoedema, obesity (BMI > 30 kg/m^2), disease of the gastrointestinal tract; female patients who were pregnant, lactating or of childbearing potential and not protected from pregnancy by a sufficiently reliable method; malignant disease
Interventions	Treatment: calcium dobesilate 1500 mg per day Control: matching placebo Duration: 56 days Follow-up post treatment: 70 days Elastic stockings permitted
Outcomes	Primary • Signs - relative leg volume change in the most pathological leg assessed by a volumetric measurement with a calibrated tape and calculated by assimilating the lower leg volume to a truncated cone Secondary • Signs - change in leg perimeters • Symptoms - subjective symptoms (pain, discomfort, feeling of tired or heavy legs, tingling, itching and cramps) on a five-point categorical scale. Pain and discomfort were assessed by 100-mm visual analogue scales, and quality of life was assessed by chronic lower limb venous insufficiency (CIVIQ) • Assessment of overall efficacy by participant and investigator
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization with blocks of four was used. The randomization list was produced by an independent person" Comment: Randomisation list ensures a random sequence
Allocation concealment (selection bias)	Low risk	Quote: "The study medication was packed in identical boxes marked with a randomization number each newly randomized patient was given the medication with the lowest randomization number available" Comment: Identical boxes with randomisation provision ensure proper allocation concealment
Blinding (patients)	Low risk	Quote: ".... or a matching placebo ... The study medication was packed in identical boxes..." Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The study medication was packed in identical boxes marked with a randomization number each newly randomized patient was given the medication with the lowest randomization number available" ; ".... or a matching placebo ... The study medication was packed in identical boxes..." Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: ".... or a matching placebo ... The study medication was packed in identical boxes..."

Rabe 2011 *(Continued)*

		Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number in each group described, as were loss to follow-up and participants who prematurely withdrew. Important characteristics and inclusion and exclusion criteria reported. ITT analysis conducted, but no methods used for imputation of missing values described
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Rabe 2015

Study characteristics	
Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: not specified Exclusions post randomisation: 48% of patients (no symptoms) Losses to follow-up: not specified.
Participants	Countries: Argentina, Austria, Czech Republica, France, Germany, Hungary, Italy, Poland, Portugal, Russia, Slovakia, Spain and Switzerland Setting: ambulatory outpatients Number: 1137 (579 to experimental and 558 to placebo group); 592 (52.1%) patients had CVI with symptoms Age: mean 48.9.2 ± 11.1 years old (symptomatic patients) Gender: 87.3% women (symptomatic patients) Inclusion criteria: ambulatory outpatients, adults, with CEAP C3 or C4A, and at least one venous reflux and vesper leg oedema Exclusion criteria: BMI ≥ 30, dermatoliposclerosis, leg ulcer, idiopathic oedema, lymphoedema, a recent (< 1 year) DVT, dermal infection or inflammation of the leg, recent sclerotherapy or surgical treatment of varicose veins. Treatment with anti-inflammatories, calcium channel blockers, diuretics, thymoanaleptics, hormones or venous-active drugs
Interventions	Treatment: micronized purified flavonoid fraction 1000 mg (2 tablets 500 mg) per day Control: matching placebo Duration: 4 months Follow-up post treatment: 2 months Elastic stockings: not specified
Outcomes	Primary • Signs - leg edema measured by water displacement volumetry Secondary

Rabe 2015 *(Continued)*

- Symptoms - subjective symptoms (pain, heaviness assessed by 10-cm visual analogue scale, and quality of life was assessed by CIVIQ
- Tolerance to treatments assessed on recording adverse events and vital signs (blood pressure, heart rate and body weight)

Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The authors did not describe the process of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: The authors did not describe the process of allocation concealment
Blinding (patients)	Unclear risk	Comment: The authors did not describe the placebo characteristics (colour and taste). The patient received two tablets of 500 mg of placebo at lunch time as the experimental group that received micronized purified flavonoid fraction
Blinding (study researchers)	Unclear risk	Comment:The study used placebo
Blinding (outcome assessment)	Unclear risk	Comment: The study used placebo
Incomplete outcome data	Low risk	The baseline characteristics were described only for symptomatic patients (52% of the sample size) and were balanced between groups. Although there is not a flowchart about the total patients included, the authors reported a 4.1% of losses in the overall patients and a 3.6% of losses in the symptomatic subgroup
Selective reporting	High risk	The main outcome "improvement on leg oedema" was not reported adequately. The authors only referred that there were not significant differences between groups when oedema was assessed using water displacement volumetry. This is a posthoc analysis for only symptomatic patients
Other bias	Low risk	Comment: none detected

Rabe 2016

Study characteristics	
Methods	Study design: randomized, double-blind, placebo-controlled, multi-center Phase IV study Method of randomisation: not specified Exclusions post randomisation: the analysis was per ITT but 149 (45.4%) participants presented major protocol violations Losses to follow-up: 52 (14.8%) participants
Participants	Countries: Germany, Italy, Poland, Portugal Setting: ambulatory outpatients

Rabe 2016 *(Continued)*

	Number: 351 (177 calcium dobesilate, 177 placebo) Age: mean 54.9 ± 10.7 years Gender: 280 (79.8%) female Inclusion criteria: participants of both sexes, with moderate CVI, as defined by CEAP classification C3 or C4,3 and assessed by clinical evaluation and duplex sonography. Eligible patients presented with a pitting oedema and at least one of the following: discomfort or pain in at least one leg at both the screening and baseline visits. In addition, all patients had to have chronic but stable edema. Exclusion criteria: participants with diseases that mimicked CVI (such as cardiac, hepatic or renal disease or other causes of leg oedema), those with other vascular system disorders (such as cardiac insufficiency, diabetes mellitus, non-controlled hypertension, recent phlebitis/deep leg vein thrombosis) and those with primary or secondary lymphoedema
Interventions	Treatment: capsules containing 500 mg of calcium dobesilate (Doxium; batch number 23843) Control: placebo Dose: 3 capsules per day of calcium dobesilate or matching placebo Duration: 12 weeks Follow-up post treatment: 12 weeks Elastic stockings: not specified
Outcomes	Primary • Relative volume change in the MPL assessed by WDV between baseline and end of the treatment period Secondary • Relative volume change in the MPL assessed by WDV between baseline and end of study • Absolute volume change of the MPL measured by WDV after the end of the treatment period and after the end of the follow-up period • Relative volume change of the MPL from baseline to the end of treatment and end of study assessed by a volumetric measurement with a calibrated spring metered tape and calculated by assimilating the leg volume to a truncated cone • Change in the score from the CIVIQ tool, comprising 20 questions that were given a score from 1 to 5 (lowest to greatest intensity) from baseline to the end of treatment • Safety
Notes	EudraCT (number 2009-013391-44). clinicaltrialsregister.eu/ctr-search/trial/2009-013391-44/IT. Recruitment between 20 April 2010 and 10 November 2011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "351 were randomized in a 1:1 ratio to treatment with calcium dobesilate or placebo" Comment: There was no information about the generation of the random sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "351 were randomized in a 1:1 ratio to treatment with calcium dobesilate or placebo" Comment: There was no information about the allocation concealment

Rabe 2016 *(Continued)*

Blinding (patients)	Low risk	Quote: "Capsules containing 500 mg of calcium dobesilate (Doxium; batch number 23843) were used. The treatment regimen consisted of three capsules per day of calcium dobesilate or matching placebo" Comment: Placebo were capsules administered at the same posology as Dobesilate
Blinding (study researchers)	Low risk	Quote: "Capsules containing 500 mg of calcium dobesilate (Doxium; batch number 23843) were used. The treatment regimen consisted of three capsules per day of calcium dobesilate or matching placebo" Comment: Placebo were capsules administered at the same posology as Dobesilate
Blinding (outcome assessment)	Low risk	Quote: "Capsules containing 500 mg of calcium dobesilate (Doxium; batch number 23843) were used. The treatment regimen consisted of three capsules per day of calcium dobesilate or matching placebo" Comment: Placebo were capsules administered at the same posology as Dobesilate
Incomplete outcome data	High risk	Comment: 14.8% of the randomised participants were lost during follow-up and major protocol violations were reported for 42.4% of the randomised participants.
Selective reporting	Low risk	Comment: The outcomes specified in the protocol were reported
Other bias	Low risk	Comment: none detected

Renton 1994

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 9/40 (22.5%)
Participants	Country: UK Setting: ambulatory Number: 40 patients Age: 'adults' Gender: not stated Inclusion criteria: ankle oedema due to mild to moderate venous hypertension Exclusion criteria: peripheral arterial disease, diabetes or normal Doppler ultrasound
Interventions	Treatment: hidroxirutoside 500 mg × 2 capsules twice a day Control: placebo Duration: 30 days

Renton 1994 *(Continued)*

	Follow-up: 30 days
Outcomes	Primary • Microcirculatory parameters (resting flux, standing flux, venoarteriolar response measured with a laser Doppler flow meter and transcutaneous PO2 and PCO2) Secondary • Oedema and subjective symptoms (pain, cramps, paraesthesias, restless legs) measured by VAS • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After the final examination, the patients were randomised to receive either...." Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Low risk	Quote: "The patients were randomised to receive either 2 tablets of 500mg HR twice daily or a placebo of identical appearance" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The patients were randomised to receive either 2 tablets of 500mg HR twice daily or a placebo of identical appearance" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The patients were randomised to receive either 2 tablets of 500mg HR twice daily or a placebo of identical appearance" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with information about the most important characteristics and inclusion and exclusion criteria. In addition, study author described the number of participants who experienced adverse events and the number who withdrew prematurely from the study, including reasons for dropping out
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Rose 1970

Study characteristics

Methods	Study design: randomised, double-blind, cross-over, placebo-controlled

Rose 1970 *(Continued)*

	Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: 39% (13/33)
Participants	Country: UK Setting: hospital Number: 33 patients Age: not stated Gender: not stated Inclusion criteria: CVI associate with varicose disorders or postphlebitic syndrome Exclusion criteria: not stated
Interventions	Treatment: hidroxirutoside 1200 mg per day Control: placebo Duration: 180 days Follow-up: 270 days
Outcomes	Primary • Complete relief of CVI symptoms (not specified) Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no methods of random sequence generation described
Allocation concealment (selection bias)	Low risk	Quote: "The active and the placebo material were numbered in randomised order" Comment: Randomised order prevented knowledge of treatment in advance
Blinding (patients)	Low risk	Quote: "The key to the active and placebo capsules was not broken until January of this year, when all the patients had completed treatment for over 6 months"
Blinding (study researchers)	Low risk	Quote: "The key to the active and placebo capsules was not broken until January of this year, when all the patients had completed treatment for over 6 months"
Blinding (outcome assessment)	Low risk	Quote: "The key to the active and placebo capsules was not broken until January of this year, when all the patients had completed treatment for over 6 months"

Rose 1970 *(Continued)*

Incomplete outcome data	High risk	Comment: 39% (13/33) losses; imbalance between groups at the end of follow-up (17 participants received hidroxirutoside; 8 received placebo)
Selective reporting	High risk	Comment: results by symptom before the cross-over not reported
Other bias	Low risk	Comment: none detected

Rudofsky 1989

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: randomisation stratified by centre Exclusions post randomisation: none Losses to follow-up: 10/151 (7%)
Participants	Country: Germany Setting: hospital Number: 151 patients Age: mean 49.7 (range 21 to 73) years Gender: not stated Inclusion criteria: stage I and II CVI, primary varicosis and post-thrombotic symptoms Exclusion criteria: morning oedema (stage I to II CVI); acute thrombosis; leg ulcer; other peripheral arterial occlusive disorders; heart failure; severe cardiac arrhythmia; severe hypertension; diuretics; dihydroergotamine products; pregnancy
Interventions	Treatment: ruscus extract plus hesperidinmethylchalcone × 2 capsules 3 times per day for 4 weeks, then 2 capsules twice per day for 8 weeks Control: placebo Duration: 56 days Follow-up: 56 days
Outcomes	Primary • Reduction in oedema volume of the foot and ankle region measured by a water volumeter Secondary • Oedema - volume • Plethysmographic parameters • Side effects
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Rudofsky 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Following randomisation, stratified by centre, the patients then received daily 3x2 capsules of identical appearance, containing either active drug or placebo" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "Following randomisation, stratified by centre, the patients then received daily 3×2 capsules of identical appearance, containing either active drug or placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Following randomisation, stratified by centre, the patients then received daily 3×2 capsules of identical appearance, containing either active drug or placebo" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Following randomisation, stratified by centre, the patients then received daily 3x2 capsules of identical appearance, containing either active drug or placebo" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with important characteristics and inclusion and exclusion criteria. Number of patients who withdrew prematurely described, but no information on the reasons why participants dropped out
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Schultz-Ehrenburg 1993

Study characteristics	
Methods	Study design: 2 prospective, multi-centre, randomised, double-blind, placebo-controlled trials Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 7/55 (13%)
Participants	Country: France Setting: outpatient Number: 55 patients Age: 'adults' Gender: not stated

Schultz-Ehrenburg 1993 *(Continued)*

	Inclusion criteria: unilateral venous leg ulcers and chronic venous insufficiency (deep or superficial) Exclusion criteria: not stated
Interventions	Treatment • Trial A - O-(beta-hydroxyethyl)-rutoside 1000 mg per day • Trial B - O-(beta-hydroxyethyl)-rutoside 2000 mg per day Control: placebo Duration: 84 days Follow-up: 84 days All participants received pressure bandaging
Outcomes	Primary • Ulcer healed or not • Ulcer surface area recorded in square millimetres by planimetry with transparent foil Secondary • Ulcer healing phase: cleansing, granulating or epithelialising • Oedema: circumference of ankle and calf • Symptoms: ulcer pain and orthostatic complaints • Adverse events
Notes	Data extraction possible only in trial A

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Two prospective, multicentre, double-blind, randomized, parallel, placebo-controlled trial" Comment: no method of randomisation stated
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment stated
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with number of losses, but not reasons
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Sentou 1984

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: 1 participant
Participants	Country: France Setting: ambulatory Number: not stated Age: 34.6 ± 9.18 years active product; 38.2 ± 12.44 years placebo Gender: female Inclusion criteria: slight or moderate varicose disease Exclusion criteria: surgical indication or trophic disorders, other vasoactive drugs
Interventions	Treatment: extract Ruscus aculeatus 450 mg plus hesperidin 450 mg plus ascorbic acid 300 mg per day (Cyclo 3: 3 capsules twice per day) Control: placebo Duration: 28 days Follow-up: 20 days
Outcomes	Primary • Symptoms - heaviness, cramps and paraesthesia by an ordinal scale (0 to +++) • Signs - oedema measured by an ordinal scale (0 to +++) and by circumference of calf and ankle Secondary • Side effects
Notes	Number of included participants not specified

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The allocation of the subjects to the Cyclo 3 and placebo groups was done at random, in a blind manner, according to the order of admission in the study" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "Cyclo 3® and the placebo had an identical appearance" Comment: Identical placebo ensures double-blinding

Sentou 1984 *(Continued)*

Blinding (study researchers)	Low risk	Quote: "Cyclo 3® and the placebo had an identical appearance" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Cyclo 3® and the placebo had an identical appearance" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	High risk	Comment: number of included participants not specified. Only 1 participant did not accomplish the study protocol
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Serralde 1990

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: not stated Exclusions post randomisation: not losses Losses to follow-up: none
Participants	Country: Mexico Setting: hospital Number: 52 patients Age: 42.4 ± 11.6 years active treatment; 42.3 ± 8.4 years placebo Gender: 11 M:41 F Inclusion criteria: CVI and oedema Exclusion criteria: venoactive drugs, diuretics, anti-inflammatories and steroid drugs; elastic stockings or bandages; other causes of oedema; superficial thrombophlebitis; venous ulcer; venous surgery; pregnant women
Interventions	Treatment: oxirutosides 1000 mg per day Control: placebo Duration: 28 days Follow-up: 56 days
Outcomes	Primary • Symptoms - tiredness, pain, heaviness, swelling feeling, restless legs, cramps by an ordinal scale (0 to 3) • Signs - circumference of calf and ankle Secondary

Serralde 1990 *(Continued)*

- Side effects
- Participants' opinion on efficacy of treatment

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The trial was double-blind, randomized, placebo-controlled dose of one tablet of 500 mg twice daily HR or identical placebo" Comment: method of randomisation unclear
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment unclear
Blinding (patients)	Low risk	Quote: "The trial was double-blind, randomized, placebo-controlled dose of one tablet of 500 mg twice daily HR or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "The trial was double-blind, randomized, placebo-controlled dose of one tablet of 500 mg twice daily HR or identical placebo" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "The trial was double-blind, randomized, placebo-controlled dose of one tablet of 500 mg twice daily HR or identical placebo" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in both groups described, along with inclusion and exclusion criteria and the most important characteristics. Adverse events presented. No losses
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Thebaut 1985

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: throwing dice Exclusions post randomisation: not stated Losses to follow-up: 14/92 (15%)
Participants	Country: France Setting: ambulatory Number: 92 patients

Thebaut 1985 *(Continued)*

	Age: 38.9 ± 10.1 years active treatment; 40.7 ± 11.4 years placebo Gender: 8 M:63 F Inclusion criteria: CVI with leg heaviness or paraesthesias (16 to 65 years old) Exclusion criteria: venoactive drugs, elastic stockings or bandages; deep venous insufficiency by echo Doppler, venous complications, postphlebitic syndrome
Interventions	Treatment: grape seed extract tablets 300 mg every 8 hours Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Symptoms - cramps, pain heaviness and subjective oedema. Each item measured by an ordinal scale (0 to 3) and added together. Change in total punctuation (0 to 12) between baseline and final study results analysed • Signs - plethysmographic parameters Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The method chosen was that of a controlled trial conducted a double-blind placebo-controlled with throwing dice assigned treatment" Comment: Throwing dice method seems to be a fair method for generating a random sequence
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment provided
Blinding (patients)	Low risk	Quote: "Two parallel groups were thus formed, the E group received 300mg per day of Endolelon three times daily, P group receiving placebo - in all respects identical to the active pills - and using the same frequency" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Two parallel groups were thus formed, the E group received 300mg per day of Endolelon three times daily, P group receiving placebo - in all respects identical to the active pills - and using the same frequency" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Two parallel groups were thus formed, the E group received 300mg per day of Endolelon three times daily, P group receiving placebo - in all respects identical to the active pills - and using the same frequency" Comment: Identical placebo ensures double-blinding

Thebaut 1985 *(Continued)*

Incomplete outcome data	Unclear risk	Comment: number of participants in each group described, along with inclusion and exclusion criteria and the most important characteristics. Information about participants who withdrew prematurely described. In addition, standard deviation lacking in the results
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Tsouderos 1989

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: 4 participants
Participants	Country: France Setting: hospital Number: 40 patients Age: 'adults' Gender: not stated Inclusion criteria: functional CVI Exclusion criteria: not stated
Interventions	Treatment: diosmine 450 mg plus hesperidin 50 mg per 12 hours Control: placebo Duration: 60 days Follow-up: 60 days
Outcomes	Primary • Plethysmographic parameters (venous tone) • Signs - oedema measured by circumference of ankle • Symptoms - functional discomfort, evening oedema, redness or cyanosis, heart or burning, pain, paraesthesia, heaviness, cramps measured by an ordinal scale (0 to 3). Clinicians' overall assessment by a qualitative scale (results very good, useful or nil) Secondary • Overall assessment by the clinician
Notes	This publication describes 3 clinical trials. Only 1 is included here. The others are phase 2 clinical trials
Risk of bias	

Tsouderos 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All the studies were conducted double blind, according to the methodology of controlled trials" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: 2 participants lost in each group, but reasons not explained
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Unkauf 1996

Study characteristics	
Methods	Study design: randomised, double-blind, parallel, placebo-controlled trial Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 23/133 (17%)
Participants	Country: Germany Setting: outpatients Number: 133 patients Age: mean 58.9 ± 8.6 years active group; mean 60.6 ± 10.0 years placebo group Gender: 133 F Inclusion criteria: CVI grade II (according to Widmer) Exclusion criteria: premenstrual syndrome oedema; acute phlebitis or thrombosis; cardiac insufficiency or peripheral arterial disease; other venotonic drugs, laxatives, theophylline, diuretics, cardiac glycosides, angiotensin-converting enzyme or calcium antagonist within preceding 8 days; changes in postmenopausal hormone therapy within preceding 2 months
Interventions	Treatment: oxerutins 1000 mg per day Control: placebo Duration: 90 days

Unkauf 1996 *(Continued)*

	Follow-up: 90 days All participants received standard compression stockings
Outcomes	Primary • Oedema - leg volume Secondary • Symptoms - tension, tired, heavy legs, tingling measured by a visual analogue scale (cm) • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study had a double-blind, randomised, multi-centered, parallel-group design with two treatment groups" Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with the most important characteristics and inclusion and exclusion criteria. ITT analysis conducted. Information about adverse events, exclusion after randomisation and loss to follow-up given
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Vanscheidt 2002a

Study characteristics

Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 52/231 (22.5%)
Participants	Country: Germany

Vanscheidt 2002a *(Continued)*

	Setting: university Number: 231 patients Age: mean 55.1 (range 23 to 78) years Gender: 48 M:183 F Inclusion criteria: stages 3 to 5 of CEAP Exclusion criteria: surgical treatment of CVI; heart insufficiency; arterial occlusive disease; diabetes mellitus; neuropathy; acute thrombosis; lymphoedema; renal insufficiency or impaired liver function; malignant disease; pregnancy or breast feeding; major surgery; drugs with influence on the veins
Interventions	Treatment: SB-LOT (15 mg coumarin and 90 mg troxerutin) 2 tablets 3 × per day for 16 weeks Control: placebo Duration: 112 days Follow-up: 112 days All participants received standard compression stockings during first 4 weeks
Outcomes	Primary • Differences in lower leg volume after completion of treatment period as compared with baseline, measured by water displacement plethysmometry Secondary • Tired legs, heavy legs, feeling of tension, feeling of swelling, aching, itching, burning, quality of life (EUROQOL), Clinical Global Impression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was generated by the validated PC programme RanCode plus, independently to all study participants. It was based on blocks of 4 patients. All medication was pre-numbered and distributed to the centres" Comment: computer-generated table of random numbers ensures a random sequence of participants
Allocation concealment (selection bias)	Low risk	Quote: "Patients were included in the study by receiving the next consecutive random number. For each patient the study centres were supplied sealed envelopes with the treatment group information" Comment: sealed envelopes and allocation of participants by giving the next consecutive random number ensure fair allocation concealment
Blinding (patients)	Low risk	Quote: "Placebo tablets matched the active tablets in taste, smell and appearance" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Placebo tablets matched the active tablets in taste, smell and appearance"

Vanscheidt 2002a *(Continued)*

		Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Placebo tablets matched the active tablets in taste, smell and appearance" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with the most important characteristics and inclusion and exclusion criteria. In addition, study author stated the number of participants who withdrew from the study prematurely or were excluded after randomisation (22.5%). ITT analysis conducted
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Vanscheidt 2002b

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: computer-generated random number table Exclusions post randomisation: not stated Losses to follow-up: 56/167 (34%)
Participants	Country: Germany Setting: university Number: 167 patients Age: mean 53.2 ± 13.3 years active group; mean 53 ± 10.9 years placebo group Gender: 166 F Inclusion criteria: stages I and II of Widmer or CEAP 3 to 4 Exclusion criteria: other diseases with oedema, compression therapy for the past 6 months before the study; support stockings; patients more than 30% overweight; any concomitant medication that may interfere with study treatment
Interventions	Treatment: Ruscus aculeatus 72 to 75 mg per day Control: placebo Duration: 90 days Follow-up: 90 days
Outcomes	Primary • Oedema - leg volume change measured by water plethysmography Secondary • Oedema - circumference of lower leg and ankle

Vanscheidt 2002b *(Continued)*

- Symptoms - tiredness, heaviness, tension, tingling measured by VAS
- Quality questionnaire: Freiburg Life Quality Assessment (FLQA)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was designed as a multi-center, double-blind, randomized, placebo-controlled trial with women suffering from chronic venous insufficiency..." Comment: no method of randomisation described
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	High risk	Comment: number of participants in each group described, along with important characteristics and inclusion and exclusion criteria. In addition, number of participants who withdrew prematurely described, but percentage was important (34%) and no ITT analysis performed
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Vin 1994

Study characteristics

Methods	Study design: multi-centre, randomised, double-blind, placebo-controlled with a placebo run-in period Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 4/73 (4%)
Participants	Country: France Setting: hospital Number: 73 patients Age: mean 55.7 ± 15.8 years active treatment; mean 53.6 ± 16.7 years placebo Gender: 10 M:59 F

Vin 1994 *(Continued)*

	Inclusion criteria: presence of truncal varicose veins with ostial reflux and subjective symptoms of venous origin Exclusion criteria: occlusive arterial disease; osteoarticular disease; diabetes; acute or chronic inflammatory syndromes; haematological diseases; venoactive drugs; pregnancy; smoking
Interventions	Treatment: troxerutin 3500 mg per day Control: placebo Duration: 60 days Follow-up: 60 days

Outcomes	Primary
	
	• Symptoms - heaviness, aching scored from 0 to 9 by multiplying intensity score (0 to 3) by time of onset (0 to 3)
	  ○ Oedema, swelling scored from 0 to 6 by multiplying intensity score (0 to 3) by time of onset (0 to 2)
	  ○ Atypical pain (cramps, paraesthesia) scored from 0 to 2
	  ○ Venous claudication scored as present (1) or absent (2)
	• Signs - ankle circumference, photoplethysmography, haemorrheological parameters
	
	Secondary
	
	• Not stated

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was controlled, double-blind, randomized, multicentre and with a placebo run-in period" Comment: no method of randomisation stated
Allocation concealment (selection bias)	Unclear risk	Comment: no method of allocation concealment described
Blinding (patients)	Low risk	Quote: "They were then randomly allocated to receive either troxerutin, 3500 mg to be taken in the morning for 2 months, or a placebo with identical appearance and taste" Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "They were then randomly allocated to receive either troxerutin, 3500 mg to be taken in the morning for 2 months, or a placebo with identical appearance and taste" Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "They were then randomly allocated to receive either troxerutin, 3500 mg to be taken in the morning for 2 months, or a placebo with identical appearance and taste" Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with the most important characteristics and inclusion and exclusion criteria. In addi-

Vin 1994 *(Continued)*

		tion, information about participants who withdrew prematurely given, including reasons for dropping out. Adverse events given as well
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Welch 1985

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: 7/147 (5%)
Participants	Country: Belgium Setting: hospital Number: 147 patients Age: mean 44.5 ± 14 years active group; mean 43.6 ± 14 years placebo group Gender: 26 M:119 F Inclusion criteria: CVI with oedema and ≥ 1 related symptom Exclusion criteria: elastic stockings or compressive bandages; leg oedema from another origin; arterial insufficiency; superficial thrombophlebitis; varicose eczema or ulcer; diuretics, analgesics, steroids, NSAIDs or other venous drugs; pregnancy
Interventions	Treatment: O-(beta-hydroxyethyl)-rutoside 1000 mg per day Control: placebo Duration: 28 days Follow-up: 28 days
Outcomes	Primary • Symptoms - pain, cramps, heavy legs, swelling, restlessness, itching and paraesthesia measured by a semiquantitative scale (0 to 3) ◦ Oedema - pitting measured by a semiquantitative scale (0 to 3), circumference of ankle and calf Secondary • Side effects • Global opinion of investigators and participants
Notes	
Risk of bias	

Welch 1985 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not given
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not given
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, and inclusion and exclusion criteria reported as well for the most important characteristics. Number of participants who dropped out prematurely given, along with numbers of and reasons for adverse events
Selective reporting	Low risk	Comment: protocol identified and no differences identified between protocol and article
Other bias	Low risk	Comment: none detected

Widmer 1990

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: randomisation list prepared by statistician Exclusions post randomisation: none Losses to follow-up: 17/225 (7%)
Participants	Country: Switzerland Setting: hospital Number: 225 patients Age: 20 to 70 years Gender: 27 M:181 F Inclusion criteria: CVI grade I to II (alterations in pigmentation, with or without subcutaneous veins, oedema and symptoms of the disease) Exclusion criteria: CVI grade III with open or healed varicose ulcer; venous surgery during past 12 months or sclerotherapy during past 6 months; symptomatic peripheral arterial occlusion; renal or cardiac insufficiency; lymphoedema; diabetes; hypertension; overweight; pregnancy; compression therapy or drugs that might interfere with clinical results (diuretics); intolerance to the active drug of the study
Interventions	Treatment: calcium dobesilate 1500 mg per day

Widmer 1990 *(Continued)*

	Control: placebo Duration: 28 days Follow-up: 28 days

Outcomes	Primary
	
	• Symptoms - pain, cramps, heaviness, paraesthesia and restlessness measured by a visual analogue scale
	• Signs - oedema measured by circumference of ankle
	  ○ Discomfort measured as the sum of frequencies of symptoms: pain, heaviness, paraesthesia and restlessness
	  ○ Total score of all observed symptoms
	
	Secondary
	
	• Overall efficacy assessed by physician and participant
	• Side effects

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were treated for 28 days with either Doxium or placebo at the dosage of 3 capsules daily, according to a randomization list prepared by the statistician" Comment: randomisation list assumed to be a fair method of assuring a random sequence
Allocation concealment (selection bias)	Unclear risk	Comment: no methods described for allocation concealment
Blinding (patients)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (study researchers)	Unclear risk	Comment: no information given about methods used for blinding
Blinding (outcome assessment)	Unclear risk	Comment: no information given about methods used for blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, including most important characteristics and inclusion and exclusion criteria. In addition, reasons for excluding participants after randomisation given, along with number of participants. Number compliant with medication provided, along with adverse events
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

Zucarelli 1987

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: throwing dice Exclusions post randomisation: none Losses to follow-up: 25/149 (16%)
Participants	Country: France Setting: outpatients Number: 149 patients Age: mean 33 ± 9.4 years active treatment; mean 32 ± 8 years placebo Gender: 149 F Inclusion criteria: CVI stage I (functional symptoms and oedema) Participants allowed to wear elastic support Exclusion criteria: chronic venous with trophic alterations; varices; phlebitis; postphlebitic syndrome; lymphoedema; arteriopathy; pregnancy; other phlebotonics; anti-inflammatories; diuretics; anti-platelet or vasculo-protector treatments
Interventions	Treatment: coumarin 10.5 mg per day plus troxerutin 1050 mg per day Control: placebo Duration: 90 days Follow-up: 90 days
Outcomes	Primary • Symptoms - pain, cramps, heavy legs and paraesthesias measured by a visual analogue scale ○ Oedema - measured by circumference of leg Secondary • Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The methodology used was that of a controlled trial against placebo in double-blind perspective with the drawing of lots to constitute two parallel groups" Comment: Drawing of lots seems like a fair method of generating an adequate sequence
Allocation concealment (selection bias)	Unclear risk	Comment: no methods of allocation concealment described
Blinding (patients)	Low risk	Quote: "Ampules of placebo, which are in all respects comparable to those of the active..."

Zucarelli 1987 *(Continued)*

		Comment: Identical placebo ensures double-blinding
Blinding (study researchers)	Low risk	Quote: "Ampules of placebo, which are in all respects comparable to those of the active..." Comment: Identical placebo ensures double-blinding
Blinding (outcome assessment)	Low risk	Quote: "Ampules of placebo, which are in all respects comparable to those of the active..." Comment: Identical placebo ensures double-blinding
Incomplete outcome data	Low risk	Comment: number of participants in each group described, along with inclusion and exclusion criteria and the most important characteristics. In addition, tolerance, adverse events and participants who dropped out prematurely described
Selective reporting	Low risk	Comment: no protocol identified, and no differences between outcomes reported in the methods section and those reported in the results section
Other bias	Low risk	Comment: none detected

BMI: body mass index
CEAP classification (clinical signs (C), aetiology (E), anatomical distribution (A) and physiological conditions (P) of CVI)
CIVIQ: Chronic Venous Insufficiency International Questionnaire
CT: clinical trial
CVD: cardiovascular disease
CVI: chronic venous insufficiency
DVT: deep vein thrombosis
EuroQoL: Descriptive system of health-related quality of life states
FLQA: Freiburg Life Quality Assessment
h: hour
ITT: intention-to-treat
LRR: light reflection rheography
MPL: most pathological leg
NSAIDs: non-steroidal anti-inflammatories
QoL: quality of life
tid: 3 times a day
VAS: visual analogue scale
WDV: water displacement volumetry

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akbulut 2010	This study assessed the combination of calcium dobesilate and oxerutin
Androulakis 1989	Principal outcome consists of plethysmographic parameters - a surrogate outcome
Auteri 1990	No clinical endpoints were assessed
Bacci 2003	This study assessed a combination of different active products
Bastide 1976	This study assessed dihydroergotamine, which is not included in our review
Batchvarova 1989a	This study assesses a product with escin, which is not included in our review

Study	Reason for exclusion
Behar 1993	This study assesses a product with escin, which is not included in our review
Belcaro 1989	This was a single-blind study
Belcaro 1995	Outcomes studied were surrogates (laser Doppler and transcutaneous oximetry)
Belcaro 2008	No clinical endpoints were assessed - only microcirculatory parameters
Bello 1990	Calcium dobesilate was combined with a heparinoid
Bento 2006	This study assessed a combination of different active products that contain escin
Berson 1978	Two clinical trials are described. One was a non-controlled clinical trial, and in the other, the control group was given naftazone
Blume 1996	Inadequate blinding: Initial phase of the trial used 'placebo' that was actually a low concentration of the assessed active drug: coumarin 2 mg and rutoside 100 mg
Bohm 1989	This study assessed the combination of a diuretic and a drug for CVI
Boisseau 1995	Outcomes were not applicable to this review: Biological parameters were measured (erythrocyte aggregation and fibrinolytic activity)
Bolliger 1972	This study assessed the combination of dimethyl sulfoxide and diphenyl butazone with a rutoside
Bort 1995	No clinical endpoints were assessed - only microcirculatory parameters
Bosse 1985	This study compared 2 drugs (Venalot - combination of coumarin and troxerutin - and Benzarone) for CVI
Brami 1983	This study assessed the efficacy of a combination of dyhigroergocriptine mesilate and caffeine for CVI
Carstens 1985	This study assessed the combination of a diuretic and escin (DIU Venostatin)
Cataldi 2001	The drug studied was a combination of several active principles, one of which was rutin
Cesarone 1992	No clinical endpoints were assessed - only microcirculatory parameters
Cesarone 1994	No clinical endpoints were assessed - only microcirculatory parameters
Cesarone 2001	No clinical endpoints were assessed - only microcirculatory parameters
Cesarone 2001a	This was a single-blind study
Cesarone 2001b	This study assessed escin in diabetic microangiopathy
Cesarone 2001c	The study was about microvascular parameters: PO2, PCO2 and volume parameters. This was a single-blind study
Cesarone 2002b	This study assessed variations in plasma free radicals in participants with CVI
Cesarone 2010	This study was not double-blinded
Chant 1973	Non-clinical criteria were given

Study	Reason for exclusion
Chiummariello 2009	The drug evaluated is a combination of different products for CVI. This study was not double-blinded
Clemens 1986	Only haemodynamic venous parameters were assessed by light reflection rheography
Cospite 1996	This study compared heparan sulphate vs diosmine for CVI
De Anna 1989	This was a single-blind study
Delacroix 1981	The drug evaluated was escin, which has been excluded from our review
Delecluse 1991	This study compared Diovenor versus a combination of flavonoids
de Parades 1990	This study compared Cyclo 3 Fort vs diosmine plus hesperidin for CVI
De Sanctis 2001	This was a single-blind study
Duchene 1988	Only haemodynamic venous parameters were assessed by plethysmography
Dustmann 1984	The drug evaluated was escin, which has been excluded from our review
Erdlen 1989	Venostasin contains escin, which has been excluded from our review
Erler 1991	This study assessed escin, which has been excluded from our review
EudraCT2009-014681-25	The outcome (reflux) is not included in our review. The comparison are different doses of Ruscus aculeatus (150 mg), hesperidin methyl chalcone (150 mg) and ascorbic acid (100 mg)
Forconi 1977	No clinical endpoints were assessed - only microcirculatory parameters
Frausini 1985	This was a single-blind study
Glinski 1999	This was an open RCT conducted to examine venous ulcers
Gonzalez-Fajardo 1990	The outcome assessed was a surrogate (photoplethysmographic evaluation)
Granger 1995	It is not specified that the trial was double-blind
Henriet 1995	This study compared the efficacy of Diovenor (diosmine) vs a combination of different flavonoids
Horvath 1985	This study assessed the efficacy of dyhidroergotamine, which is not included in our review
Incandela 1995	No clinical endpoints were assessed - only microcirculatory parameters
Incandela 1996	This study looked at the effects of troxerutin on microcirculatory parameters
Incandela 2001	This was a single-blind study
Incandela 2002	This was a single-blind study
ISRCTN54360155	Different drugs combinations (acetyl salicylic acid, asiaticoside and acemannan) and there is not a placebo group.
Janssens 1999	No clinical endpoints were assessed - only microcirculatory parameters

Study	Reason for exclusion
Janssens 1999a	This study looked at the effects of Ginkor Fort (ginkgo biloba), which is not included in our review
Kalus 2004	No clinical endpoints were assessed - only microcirculatory parameters (cutaneous microcirculation and oxygen supply)
Kiesewetter 2000	This study evaluated red vine leaf extract, an herbal medicine containing several flavonoids that are not included in our review
Koltringer 1993	This study assessed Ginkgo biloba, which is not included in our review
Kostering 1985	This study assessed microcirculatory parameters
Krähenbühl 1975	The bencyclan is a drug with cardiovascular depression effects; it is not included in the review
Krcílek 1973	The drug evaluated was escin, which is not included in our review
Languillat 1988b	The drug studied (Veliten) was a combination of rutin, ascorbic acid and alpha-tocopherol. No clinical endpoints were assessed - only microcirculatory parameters
Languillat 1989	No clinical endpoints were assessed - only microcirculatory parameters
Le Dévéhat 1989	Outcomes were not applicable to this review: microcirculatory and haemorrheological parameters
Le Dévéhat 1997	This study assessed troxerutine for CVI: microcirculatory and haemorrheological parameters
Marastoni 1982	This study assessed dihydroergotamine, which is not included in our review
Menyhei 1994	No placebo group was included
Monteil-Seurin 1993	This study compared Cyclo 3 Fort vs diosmine
Morales 1993	This RCT assessed escin, which is not included in our review
Naser-Hijazi 2004	This RCT assessed the combination of coumarin and troxerutin (SB-LOT) in CVI. The objective of this study was to assess effects of SB-LOT on blood coagulation
NCT01654016	This is an ongoing single-blinded (outcome assessor) clinical trial about Daflon
NCT02191163	This study assessed the efficacy of the red-vine-leaf extract, which is not included in our review (Antistax)
NCT02191254	This study assessed the efficacy of the red-vine-leaf extract, which is not included in our review (Antistax)
NCT02191280	This study assessed the efficacy of the red-vine-leaf extract, which is not included in our review (Antistax)
Neumann 1988	No clinical endpoints were assessed - only microcirculatory parameters
Neumann 1990	Only haemodynamic venous parameters were assessed by light reflection rheography and transcutaneous oxygen tension measurement (TcPO2)
Neumann-Mangoldt 1979	The drug evaluated contained escin and heparin
Nill 1970	This study assessed escin, which is not included in our review

Study	Reason for exclusion
Ottillinger 2001	This study assessed escin, which is not included in our review
Paciaroni 1982	The drug evaluated was escin, which is not included in our review
Partsch 1981	This study assessed oral dyhidroergotamine, which is not included in our review
Paul 1983	The drug evaluated was benzarone, which is not included in our review
Pauschinger 1987	The drug evaluated was escin, which is not included in our review
Petruzzellis 2002	This study included 3 comparative groups (2 of different doses of oxirutoside and 1 of placebo), but treatment concealment was incorrect or was not explained correctly
Pointel 1987b	This study assessed vitamin C combined with Ruscus aculeatus and anthocyanosides from Ribes nigrum (helps to maintain the integrity of capillaries)
Pokrovskii 2005	This study assessed Ginkgo biloba, which is not included in our review
Questel 1983	No clinical endpoints were assessed - only microcirculatory parameters
Rabe 2011b	This study assessed the efficacy of the red-vine-leaf extract, which is not included in our review (Antistax)
Riccioni 2004	This study assessed the efficacy of the combination of troxerutin plus French maritime pine bark
Roztocil 1977	This study assessed microcirculatory parameters (capillary filtration)
Roztocil 2003	This was an RCT that was not blinded
Sanctis 2001	This study assessed escin, which is not included in our review
Seydewitz 1992	Non-clinical parameters were evaluated in this study
Steiner 1990	This study assessed the drug escin, which is not included in our review
Steiner 1992	This study assessed the drug escin, which is not included in our review
Steru 1988	It is not specified whether this trial was double-blind
Topalov 1990	This study assessed the efficacy of troxesamol (combination of troxerutin, acetylsalicylic acid and dipyridamole)
Turio 2000	This study assessed the efficacy of a combination of vitamin PP (niacin), vitamin C and phyto-therapeutic extracts titrated in escin, bromelain and anthocyanosides
Weindorf 1987	This study assessed the efficacy of the combination of Ruscus aculeatus and trimethylhespiridin-chalcone
Widmer 1972	The active treatment in this study was phlebolan composed of rutin and several anti-inflammatory agents such as prednisolone and diphenylbutazone
Zuccarelli 1996	This study assessed GinKor Fort (Ginkgo biloba), which is not included in our review

CVI: chronic venous insufficiency
HR: hidroxy rutoside PO_2: pressure of oxygen in blood

PCO_2: pressure of carbon dioxide in blood
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Barattini 2019

Study name	Clinical trial to assess the efficacy of µSmin® Plus (dietary supplement)
Methods	Multicentre, randomised, double-blind, parallel, placebo-controlled trial
Participants	68 participants adults with CVI between C2-C4 on the CEAP classification system
Interventions	1 tablet of µSMIN® Plus (corresponding to 450 mg of micronized diosmine) or placebo per day during 8 weeks
Outcomes	QoL (CIVIQ-20 questionnaire), VAS pain scale, CVI symptomatology, and change in the circumference of the affected leg at calf level, investigators and patient global assessment, percentage of subjects who would want to continue with the treatment, treatment compliance and safety
Starting date	24 September 2019
Contact information	Contact: Dionisio Franco Barattini, MD Contact: Dumitru-Emanuel Dogaru, PM
Notes	

ISRCTN18841175

Study name	Effects of micronised purified flavonoid fraction on microcirculation in women suffering from CVD
Methods	Single-centre double-blind randomised placebo-controlled parallel-group study
Participants	240 females 18 to 30 years old suffering from primary CVD
Interventions	Micronised purified flavonoid fraction 500 mg over 4 menstrual cycles versus placebo
Outcomes	Effects on microcirculatory and biological parameters over 4 menstrual cycles
Starting date	July 2009
Contact information	Prof Eliete Bouskela. Instituto de Biologia Roberto Alcantara Gomes Dept Ciências Fisiologicasências. Rio de Janeiro. Brazil
Notes	Sponsor: Institut de Recherches Internationales Servier (France)

NCT01532882

Study name	Efficacy and safety of diosmine 600 mg versus placebo for painful symptoms in patients with CVD of lower limbs (EDEN)
Methods	Multi-centre controlled randomised double-blind placebo-controlled parallel-group study
Participants	378 patients with painful symptoms of CVD of the lower limbs

NCT01532882 *(Continued)*

Interventions	Diosmine 600 mg - DIOVENOR versus placebo (1 tablet per day during 28 days)
Outcomes	Primary outcome measure: Change in VAS score for assessment of painful venous symptoms
Starting date	January 2012
Contact information	Dr Jean-Jérôme GUEX, Nice, France
Notes	Sponsor: Innotech International

NCT03833024

Study name	The MUFFIN-PTS Trial
Methods	Multicentre, randomised, double-blind placebo-controlled trial
Participants	86 participants adults with PTS; Villalta score > 4 with at least two of the following four PTS manifestations (daily heaviness, cramps, pain, and objective oedema) in the leg ipsilateral to a previous objectively diagnosed DVT, or DVT of unknown date but with presence of residual proximal or distal venous obstruction on ultrasound
Interventions	Micronized Purified Flavonoid Fraction (MPFF) or placebo for 6 months MPFF 500 mg, bid (morning and evening) for 6 months in addition to their usual treatment (i.e. ECS and/or anticoagulation).
Outcomes	Symptoms and signs of PTS and QoL (EQ-5D-5L and EQ VAS) measured at 3, 6 and 9 months follow-up Primary outcome: Change in PTS (6 months). Improvement will be defined as a decrease of at least 30% in the Villalta score or a Villalta score < 5 in the PTS-affected leg
Starting date	1 December 2019
Contact information	Dr. Susan Kahn, Sir Mortimer B. Davis - Jewish General Hospital, Montreal, Canada
Notes	

bid: twice daily
CEAP: Clinical-Etiology-Anatomy-Pathophysiology
CVD: chronic venous disease
CVI: chronic venous insufficiency
DVT: deep vein thrombosis
ECS: elastic compression stockings
mg: milligrams
QoL: quality of life
PTS: postthrombotic syndrome
VAS: visual analogue scale

DATA AND ANALYSES

Comparison 1. Phlebotonics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Oedema in the lower legs (dichotomous variable)	13	1245	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.63, 0.78]
1.1.1 Aminaftone	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
1.1.2 Calcium dobesilate	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
1.1.3 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
1.1.4 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]
1.1.5 Rutosides	7	654	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.81]
1.2 Ankle perimeter circumference (mm)	15	2010	Mean Difference (IV, Fixed, 95% CI)	-4.27 [-5.61, -2.93]
1.2.1 Calcium dobesilate	5	1122	Mean Difference (IV, Fixed, 95% CI)	-1.69 [-4.84, 1.47]
1.2.2 Diosmine, Hidrosmine	3	286	Mean Difference (IV, Fixed, 95% CI)	-5.98 [-7.78, -4.18]
1.2.3 Rutosides	7	602	Mean Difference (IV, Fixed, 95% CI)	-2.45 [-5.06, 0.15]
1.3 Volume of the leg (mL)	11	2072	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.33, -0.15]
1.3.1 Aminaftone	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.61, 0.28]
1.3.2 Calcium dobesilate	4	826	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.51, -0.24]
1.3.3 Rutosides	6	1167	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.26, -0.03]
1.4 Quality of life	5	1639	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.22, 0.10]
1.4.1 Aminaftone	1	79	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.10, -0.19]
1.4.2 Calcium dobesilate at 3 months of treatment	3	968	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.16, 0.10]
1.4.3 Diosmine, Hidrosmine	1	592	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.12, 0.20]
1.5 Ulcer healing	6	461	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.13]
1.5.1 Aminaftone	1	100	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.18]
1.5.2 Calcium dobesilate	1	69	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.69, 1.74]
1.5.3 Diosmine, Hidrosmine	2	133	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.4 Rutosides	2	159	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.87, 1.86]
1.6 Trophic disorders (dichotomous variable)	6	705	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.95]
1.6.1 Aminaftone	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.44]
1.6.2 Diosmine, Hidrosmine	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
1.6.3 Rutosides	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.25]
1.7 Pain in the lower legs (dichotomous variable)	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.79]
1.7.2 Calcium dobesilate	5	705	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.82]
1.7.3 Diosmine, Hidrosmine	4	271	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.08]
1.7.4 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.48, 0.91]
1.7.5 Rutosides	10	1485	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.83]
1.8 Pain in the lower legs (continuous variable)	12	2232	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.54, -0.17]
1.8.1 Calcium dobesilate	5	1127	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.31, 0.03]
1.8.2 Diosmine, Hidrosmine	3	846	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.41, -0.05]
1.8.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.39 [-2.09, -0.69]
1.8.4 Rutosides	3	219	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.23, -0.19]
1.9 Cramps in the lower legs (dichotomous variable)	14	1793	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.89]
1.9.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.99]
1.9.2 Calcium dobesilate	2	255	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
1.9.3 Diosmine, Hidrosmine	3	214	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
1.9.4 Rutosides	8	1227	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.02]
1.10 Cramps in the lower legs (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

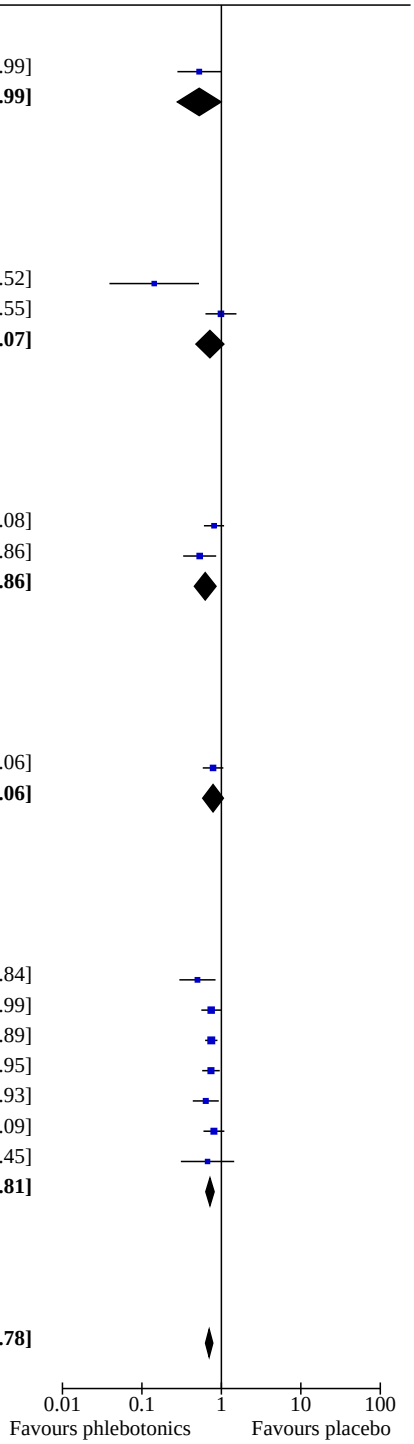
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.1 Calcium dobesilate	1	415	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.29, 0.09]
1.10.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.78, -0.14]
1.10.3 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.16]
1.11 Restless legs (dichotomous variable)	7	652	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
1.11.1 Calcium dobesilate	2	255	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.59, 0.91]
1.11.2 Diosmine, Hidrosmine	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.15]
1.11.3 Rutosides	4	327	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
1.12 Itching in the lower legs (dichotomous variable)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.12.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
1.12.2 Diosmine, Hidrosmine	1	34	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.25]
1.12.3 Rutosides	2	274	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.21, 2.21]
1.13 Itching in the lower legs (continuous variable)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 Calcium dobesilate	1	416	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.11, 0.28]
1.13.2 Rutosides	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.10, -0.06]
1.14 Heaviness in the lower legs (dichotomous variable)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.14.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.60]
1.14.2 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
1.14.3 Centella asiatica	1	63	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
1.14.4 Diosmine, Hidrosmine	4	241	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.05]
1.14.5 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
1.14.6 Rutosides	9	1420	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.74]
1.15 Heaviness in the lower legs (continuous variable)	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.15.1 Calcium dobesilate	2	483	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.23, 0.13]
1.15.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.02, -0.36]
1.15.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.50 [-2.21, -0.79]
1.15.4 Rutosides	6	441	Std. Mean Difference (IV, Random, 95% CI)	-1.11 [-1.87, -0.36]
1.16 Swelling in the lower legs (dichotomous variable)	14	1072	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.50, 0.80]
1.16.1 Calcium dobesilate	2	80	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.41]
1.16.2 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
1.16.3 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.02]
1.16.4 Rutosides	9	848	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.88]
1.17 Swelling in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.17.1 Calcium dobesilate	1	417	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.24, 0.15]
1.17.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.26, -0.58]
1.17.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.65 [-2.38, -0.92]
1.17.4 Rutosides	3	264	Std. Mean Difference (IV, Random, 95% CI)	-1.73 [-3.50, 0.04]
1.18 Paraesthesia in the lower legs (dichotomous variable)	9	1456	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.88]
1.18.1 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
1.18.2 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.05]
1.18.3 Rutosides	4	1007	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.83]
1.19 Paraesthesia in the lower legs (continuous variable)	2	188	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.44, 0.13]
1.19.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.44, 0.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.19.2 Rutosides	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.96, 0.33]
1.20 Participant satisfaction (dichotomous variable)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.20.1 Calcium dobesilate	3	506	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.46]
1.20.2 Diosmine, Hidrosmine	4	451	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.02]
1.20.3 Centella asiatica	1	80	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.14, 0.57]
1.20.4 Rutosides	8	1167	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.30, 0.84]
1.21 Participant satisfaction (continuous variable)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.21.1 Calcium dobesilate	2	448	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.71, -0.33]
1.21.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.14, -0.47]
1.21.3 Rutosides	4	283	Std. Mean Difference (IV, Random, 95% CI)	-1.18 [-1.96, -0.39]
1.22 Adverse events	37	5789	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.02, 1.27]
1.22.1 Aminaftone	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.06, 6.32]
1.22.2 Calcium dobesilate	8	1824	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.00, 1.49]
1.22.3 Centella asiatica	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.58, 2.23]
1.22.4 Diosmine, Hidrosmine	9	1429	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.19]
1.22.5 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.19, 1.74]
1.22.6 Rutosides	17	2288	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.04, 1.43]

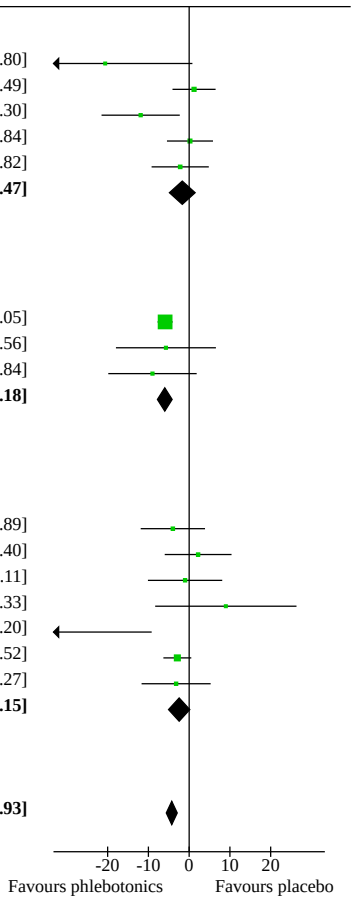
Analysis 1.1. Comparison 1: Phlebotonics versus placebo, Outcome 1: Oedema in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Aminaftone						
Lazzarini 1982	10	41	19	41	5.3%	0.53 [0.28 , 0.99]
Subtotal (95% CI)		**41**		**41**	**5.3%**	**0.53 [0.28 , 0.99]**
Total events:	10		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.1.2 Calcium dobesilate						
Casley-Smith 1988	2	15	14	15	3.9%	0.14 [0.04 , 0.52]
Labs 2004	30	133	29	127	8.3%	0.99 [0.63 , 1.55]
Subtotal (95% CI)		**148**		**142**	**12.2%**	**0.72 [0.48 , 1.07]**
Total events:	32		43			
Heterogeneity: Chi² = 7.90, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 1.62 (P = 0.11)						
1.1.3 Diosmine, Hidrosmine						
Fermoso 1992	15	20	13	14	4.3%	0.81 [0.60 , 1.08]
Planchon 1990	16	55	30	55	8.4%	0.53 [0.33 , 0.86]
Subtotal (95% CI)		**75**		**69**	**12.7%**	**0.63 [0.46 , 0.86]**
Total events:	31		43			
Heterogeneity: Chi² = 3.36, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 2.93 (P = 0.003)						
1.1.4 Grape seed extract						
Thebaut 1985	22	35	32	40	8.3%	0.79 [0.58 , 1.06]
Subtotal (95% CI)		**35**		**40**	**8.3%**	**0.79 [0.58 , 1.06]**
Total events:	22		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
1.1.5 Rutosides						
Cauwenberge 1972	9	21	18	21	5.0%	0.50 [0.30 , 0.84]
Cauwenberge 1978	32	60	43	60	12.0%	0.74 [0.56 , 0.99]
Cloarec 1996	38	53	49	51	14.0%	0.75 [0.62 , 0.89]
Ihme 1996	28	44	37	43	10.5%	0.74 [0.57 , 0.95]
Kriner 1985	14	25	22	25	6.1%	0.64 [0.44 , 0.93]
MacLennan 1994	29	52	36	52	10.1%	0.81 [0.60 , 1.09]
Welch 1985	9	72	14	75	3.8%	0.67 [0.31 , 1.45]
Subtotal (95% CI)		**327**		**327**	**61.5%**	**0.72 [0.64 , 0.81]**
Total events:	159		219			
Heterogeneity: Chi² = 3.10, df = 6 (P = 0.80); I² = 0%						
Test for overall effect: Z = 5.43 (P < 0.00001)						
Total (95% CI)		**626**		**619**	**100.0%**	**0.70 [0.63 , 0.78]**
Total events:	254		356			
Heterogeneity: Chi² = 14.97, df = 12 (P = 0.24); I² = 20%						
Test for overall effect: Z = 6.63 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.97, df = 4 (P = 0.74), I² = 0%						



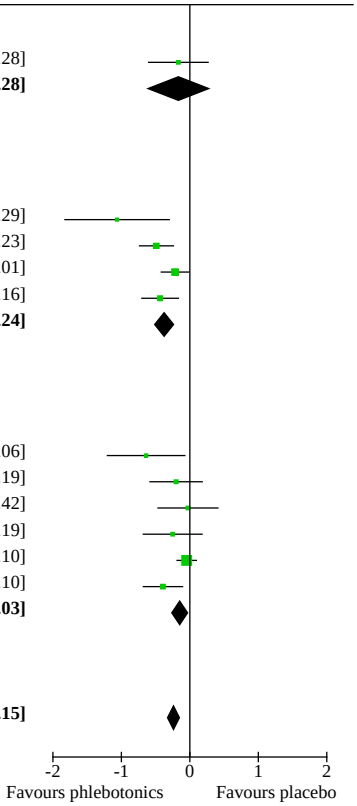
Analysis 1.2. Comparison 1: Phlebotonics versus placebo, Outcome 2: Ankle perimeter circumference (mm)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Calcium dobesilate								
Flota-Cervera 2008	335.6	38.2	25	356.2	38.2	24	0.4%	-20.60 [-42.00 , 0.80]
Labs 2004	229.5	22.7	124	228.3	19.6	123	6.4%	1.20 [-4.09 , 6.49]
Martinez-Zapata 2008	254.9	43.2	193	266.8	53.9	203	2.0%	-11.90 [-21.50 , -2.30]
Rabe 2011	240.9	21.3	109	240.7	21.8	115	5.6%	0.20 [-5.44 , 5.84]
Widmer 1990	230.1	21.31	103	232.3	29.43	103	3.7%	-2.20 [-9.22 , 4.82]
Subtotal (95% CI)			**554**			**568**	**18.1%**	**-1.69 [-4.84 , 1.47]**
Heterogeneity: Chi² = 8.95, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 1.05 (P = 0.29)								
1.2.2 Diosmine, Hidrosmine								
Gilly 1994	-7.1	6.97	76	-1.2	4.3	74	52.7%	-5.90 [-7.75 , -4.05]
Planchon 1990	229.1	30.3	48	234.8	31	48	1.2%	-5.70 [-17.96 , 6.56]
Tsouderos 1989	239.1	20.6	20	248.1	13.7	20	1.5%	-9.00 [-19.84 , 1.84]
Subtotal (95% CI)			**144**			**142**	**55.4%**	**-5.98 [-7.78 , -4.18]**
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 6.51 (P < 0.00001)								
1.2.3 Rutosides								
Cloarec 1996	221	22	53	225	19	51	2.9%	-4.00 [-11.89 , 3.89]
Cornu-Thenard 1985	226.8	16.4	33	224.6	14	21	2.7%	2.20 [-6.00 , 10.40]
Jongste 1989	236	22	40	237	20	42	2.2%	-1.00 [-10.11 , 8.11]
MacLennan 1994	258	40	41	249	42	45	0.6%	9.00 [-8.33 , 26.33]
Parrado 1999	209	50	30	243	48	30	0.3%	-34.00 [-58.80 , -9.20]
Vin 1994	-3.7	7.2	34	-0.8	7.3	35	15.4%	-2.90 [-6.32 , 0.52]
Welch 1985	232.5	27.4	72	235.7	24.9	75	2.5%	-3.20 [-11.67 , 5.27]
Subtotal (95% CI)			**303**			**299**	**26.5%**	**-2.45 [-5.06 , 0.15]**
Heterogeneity: Chi² = 9.47, df = 6 (P = 0.15); I² = 37%								
Test for overall effect: Z = 1.84 (P = 0.07)								
Total (95% CI)			**1001**			**1009**	**100.0%**	**-4.27 [-5.61 , -2.93]**
Heterogeneity: Chi² = 26.63, df = 14 (P = 0.02); I² = 47%								
Test for overall effect: Z = 6.24 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.91, df = 2 (P = 0.02), I² = 74.7%								



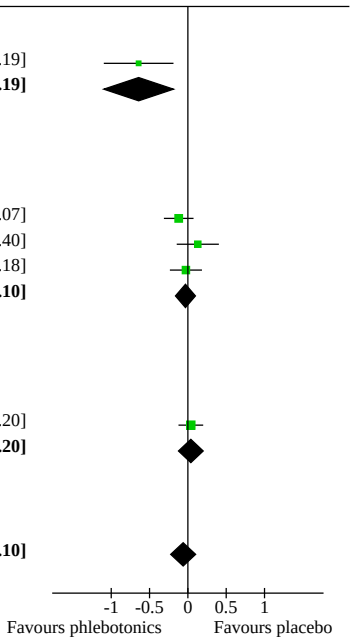
Analysis 1.3. Comparison 1: Phlebotonics versus placebo, Outcome 3: Volume of the leg (mL)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.3.1 Aminaftone								
Belczak 2014	3276.5	584.6	36	3391.5	751.1	43	3.8%	-0.17 [-0.61 , 0.28]
Subtotal (95% CI)			**36**			**43**	**3.8%**	**-0.17 [-0.61 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
1.3.2 Calcium dobesilate								
Casley-Smith 1988	1097	92.95	15	1205	104.57	15	1.3%	-1.06 [-1.83 , -0.29]
Rabe 2011	-64.72	111.9	120	0.76	152.9	119	11.3%	-0.49 [-0.74 , -0.23]
Rabe 2016	-25.68	127.44	174	-1.88	88.33	177	17.1%	-0.22 [-0.43 , -0.01]
Widmer 1990	-3.8	6.08	103	-1.15	6.08	103	9.8%	-0.43 [-0.71 , -0.16]
Subtotal (95% CI)			**412**			**414**	**39.5%**	**-0.38 [-0.51 , -0.24]**
Heterogeneity: Chi² = 6.14, df = 3 (P = 0.11); I² = 51%								
Test for overall effect: Z = 5.34 (P < 0.00001)								
1.3.3 Rutosides								
Burnand 1989	1098	157.74	24	1200	156.5	25	2.3%	-0.64 [-1.21 , -0.06]
Diebschlag 1994	-11.9	43.4	51	-4.4	29.2	50	4.9%	-0.20 [-0.59 , 0.19]
Ihme 1996	2073	309	40	2082	339	37	3.8%	-0.03 [-0.47 , 0.42]
Kiesewetter 1997	1992	367	37	2111	541	44	3.9%	-0.25 [-0.69 , 0.19]
NCT01848210	1.13	93.67	333	5.78	107.26	347	33.2%	-0.05 [-0.20 , 0.10]
Vanscheidt 2002a	-95.7	127.9	86	-44.6	131.1	93	8.6%	-0.39 [-0.69 , -0.10]
Subtotal (95% CI)			**571**			**596**	**56.7%**	**-0.15 [-0.26 , -0.03]**
Heterogeneity: Chi² = 7.74, df = 5 (P = 0.17); I² = 35%								
Test for overall effect: Z = 2.53 (P = 0.01)								
Total (95% CI)			**1019**			**1053**	**100.0%**	**-0.24 [-0.33 , -0.15]**
Heterogeneity: Chi² = 20.13, df = 10 (P = 0.03); I² = 50%								
Test for overall effect: Z = 5.40 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.25, df = 2 (P = 0.04), I² = 68.0%								

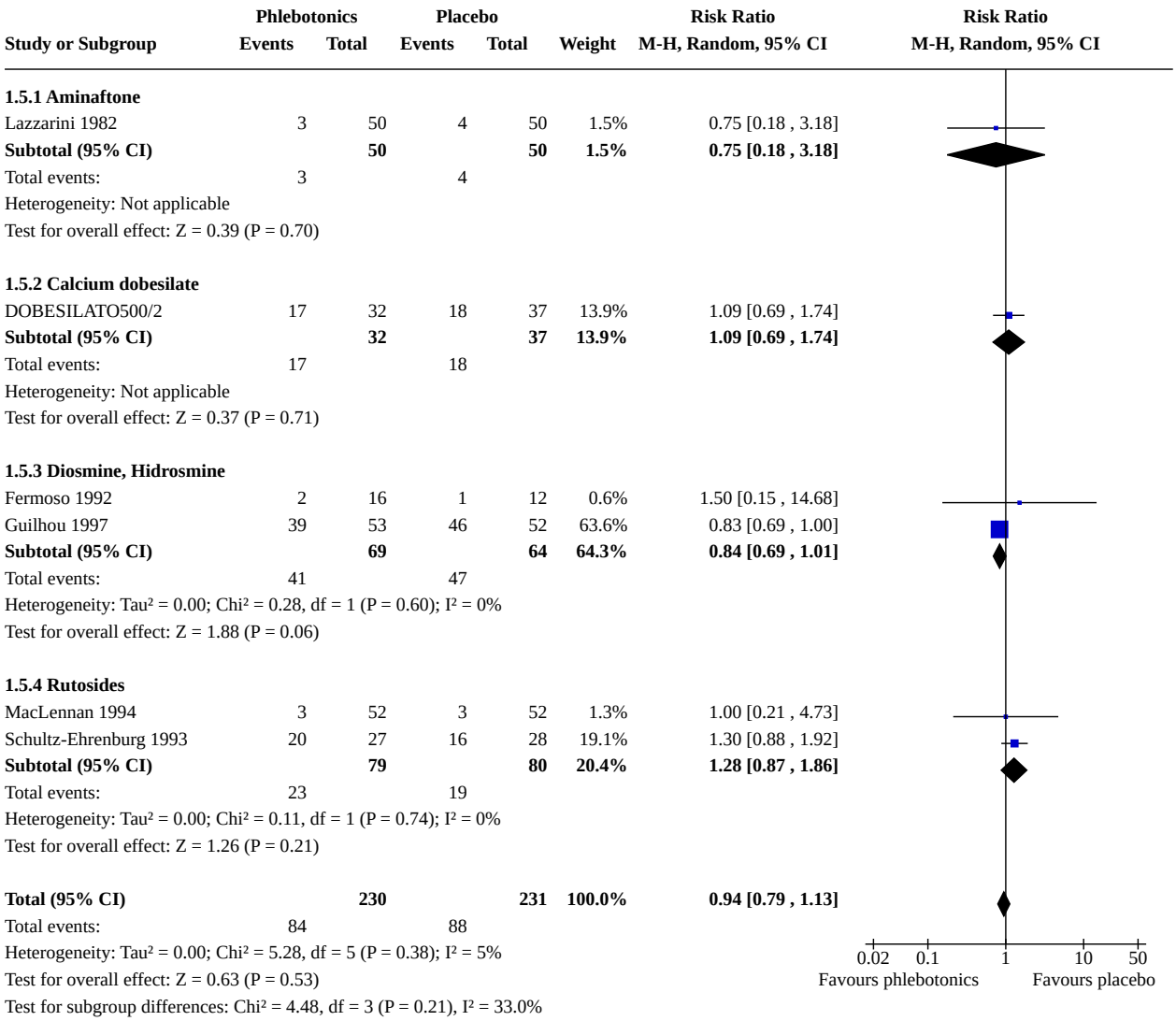


Analysis 1.4. Comparison 1: Phlebotonics versus placebo, Outcome 4: Quality of life

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Aminaftone								
Belczak 2014	-15.4	17.8	36	-5.4	13.1	43	9.4%	-0.64 [-1.10 , -0.19]
Subtotal (95% CI)			**36**			**43**	**9.4%**	**-0.64 [-1.10 , -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.77 (P = 0.006)								
1.4.2 Calcium dobesilate at 3 months of treatment								
Martinez-Zapata 2008	39.8	11	197	40.8	4.8	216	23.8%	-0.12 [-0.31 , 0.07]
Rabe 2011	41.2	17.7	100	39.2	12.8	104	17.7%	0.13 [-0.15 , 0.40]
Rabe 2016	39.9	14.9	174	40.3	16.4	177	22.5%	-0.03 [-0.23 , 0.18]
Subtotal (95% CI)			**471**			**497**	**64.0%**	**-0.03 [-0.16 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 2 (P = 0.35); I² = 6%								
Test for overall effect: Z = 0.48 (P = 0.63)								
1.4.3 Diosmine, Hidrosmine								
Rabe 2015	69.9	20.6	296	69.1	20.6	296	26.5%	0.04 [-0.12 , 0.20]
Subtotal (95% CI)			**296**			**296**	**26.5%**	**0.04 [-0.12 , 0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**803**			**836**	**100.0%**	**-0.06 [-0.22 , 0.10]**
Heterogeneity: Tau² = 0.02; Chi² = 9.78, df = 4 (P = 0.04); I² = 59%								
Test for overall effect: Z = 0.74 (P = 0.46)								
Test for subgroup differences: Chi² = 7.67, df = 2 (P = 0.02), I² = 73.9%								

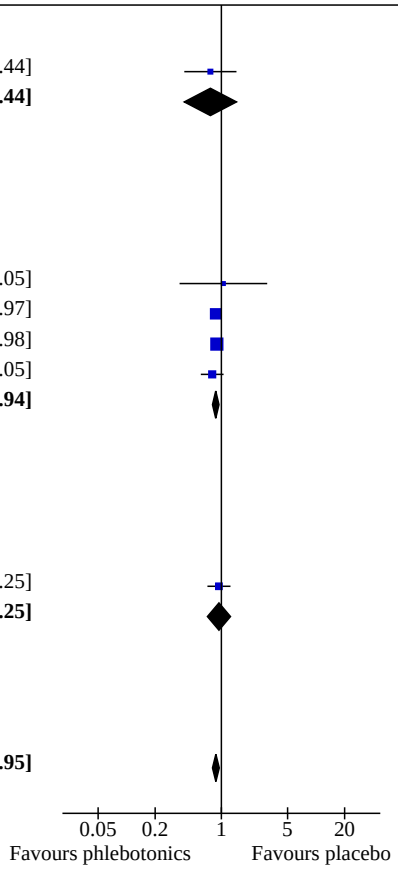


Analysis 1.5. Comparison 1: Phlebotonics versus placebo, Outcome 5: Ulcer healing



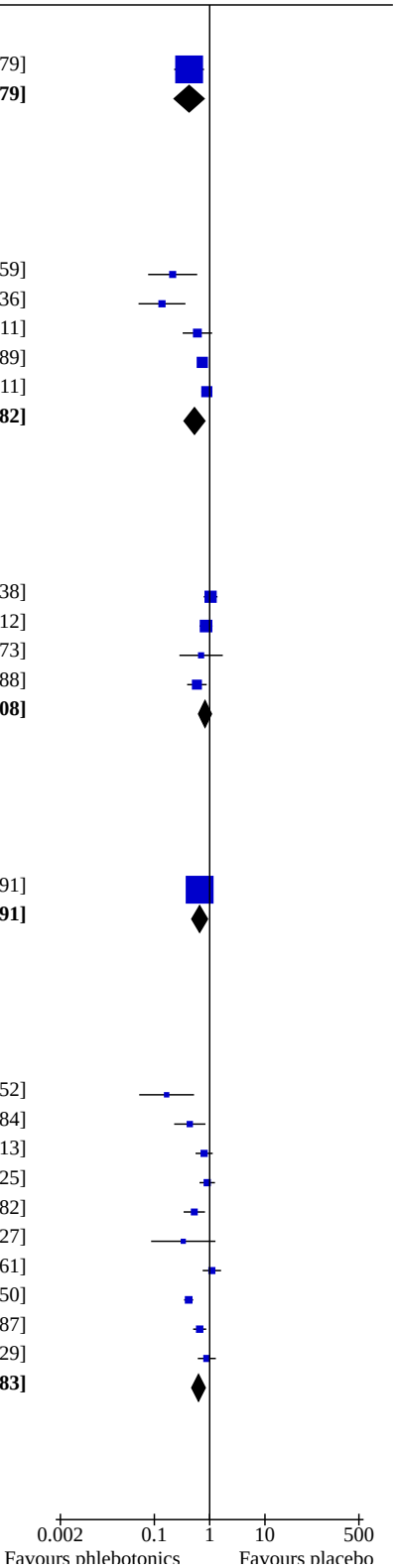
Analysis 1.6. Comparison 1: Phlebotonics versus placebo, Outcome 6: Trophic disorders (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Aminaftone						
Lazzarini 1982	12	48	16	49	5.9%	0.77 [0.41 , 1.44]
Subtotal (95% CI)		**48**		**49**	**5.9%**	**0.77 [0.41 , 1.44]**
Total events:	12		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.6.2 Diosmine, Hidrosmine						
Fermoso 1992	6	20	4	14	1.8%	1.05 [0.36 , 3.05]
Gilly 1994	66	80	76	80	28.4%	0.87 [0.78 , 0.97]
Laurent 1988	86	100	96	100	35.9%	0.90 [0.82 , 0.98]
Planchon 1990	32	55	40	55	15.0%	0.80 [0.61 , 1.05]
Subtotal (95% CI)		**255**		**249**	**81.0%**	**0.87 [0.81 , 0.94]**
Total events:	190		216			
Heterogeneity: $Chi^2 = 0.85$, df = 3 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 3.42 (P = 0.0006)						
1.6.3 Rutosides						
MacLennan 1994	33	52	35	52	13.1%	0.94 [0.71 , 1.25]
Subtotal (95% CI)		**52**		**52**	**13.1%**	**0.94 [0.71 , 1.25]**
Total events:	33		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**355**		**350**	**100.0%**	**0.87 [0.81 , 0.95]**
Total events:	235		267			
Heterogeneity: $Chi^2 = 1.25$, df = 5 (P = 0.94); $I^2 = 0\%$						
Test for overall effect: Z = 3.20 (P = 0.001)						
Test for subgroup differences: $Chi^2 = 0.45$, df = 2 (P = 0.80), $I^2 = 0\%$						

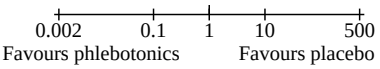


Analysis 1.7. Comparison 1: Phlebotonics versus placebo, Outcome 7: Pain in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Aminaftone						
Lazzarini 1982	10	48	24	49	100.0%	0.43 [0.23 , 0.79]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.43 [0.23 , 0.79]**
Total events:	10		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.70 (P = 0.007)						
1.7.2 Calcium dobesilate						
Casley-Smith 1988	3	15	14	15	11.3%	0.21 [0.08 , 0.59]
Flota-Cervera 2008	3	25	24	24	12.0%	0.14 [0.05 , 0.36]
Hachen 1982	9	25	15	25	19.0%	0.60 [0.33 , 1.11]
Rabe 2016	81	174	112	177	29.1%	0.74 [0.61 , 0.89]
Widmer 1990	62	114	68	111	28.6%	0.89 [0.71 , 1.11]
Subtotal (95% CI)		**353**		**352**	**100.0%**	**0.53 [0.35 , 0.82]**
Total events:	158		233			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 21.62$, df = 4 (P = 0.0002); $I^2 = 82\%$						
Test for overall effect: Z = 2.88 (P = 0.004)						
1.7.3 Diosmine, Hidrosmine						
Biland 1982	26	35	25	35	33.4%	1.04 [0.78 , 1.38]
Dominguez 1992	22	30	23	27	35.1%	0.86 [0.66 , 1.12]
Fermoso 1992	6	20	6	14	7.5%	0.70 [0.28 , 1.73]
Planchon 1990	20	55	34	55	24.0%	0.59 [0.39 , 0.88]
Subtotal (95% CI)		**140**		**131**	**100.0%**	**0.82 [0.63 , 1.08]**
Total events:	74		88			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.91$, df = 3 (P = 0.12); $I^2 = 49\%$						
Test for overall effect: Z = 1.42 (P = 0.16)						
1.7.4 French maritime pine bark extract						
Arcangeli 2000	13	20	20	20	100.0%	0.66 [0.48 , 0.91]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.66 [0.48 , 0.91]**
Total events:	13		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
1.7.5 Rutosides						
Balmer 1980	3	40	18	40	4.2%	0.17 [0.05 , 0.52]
Cauwenberge 1972	7	21	16	21	8.1%	0.44 [0.23 , 0.84]
Cauwenberge 1978	27	60	34	60	11.8%	0.79 [0.56 , 1.13]
Jongste 1989	25	41	29	43	12.2%	0.90 [0.66 , 1.25]
Klüken 1971	13	30	23	28	10.7%	0.53 [0.34 , 0.82]
Languillat 1988	2	10	6	10	3.4%	0.33 [0.09 , 1.27]
Pedersen 1992	18	24	13	19	11.5%	1.10 [0.75 , 1.61]
Pulvertaft 1983	130	495	104	165	13.7%	0.42 [0.35 , 0.50]
Vanscheidt 2002a	45	114	70	117	12.8%	0.66 [0.50 , 0.87]
Welch 1985	29	72	34	75	11.6%	0.89 [0.61 , 1.29]
Subtotal (95% CI)		**907**		**578**	**100.0%**	**0.63 [0.48 , 0.83]**
Total events:	299		347			
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 44.53$, df = 9 (P < 0.00001); $I^2 = 80\%$						
Test for overall effect: Z = 3.26 (P = 0.001)						

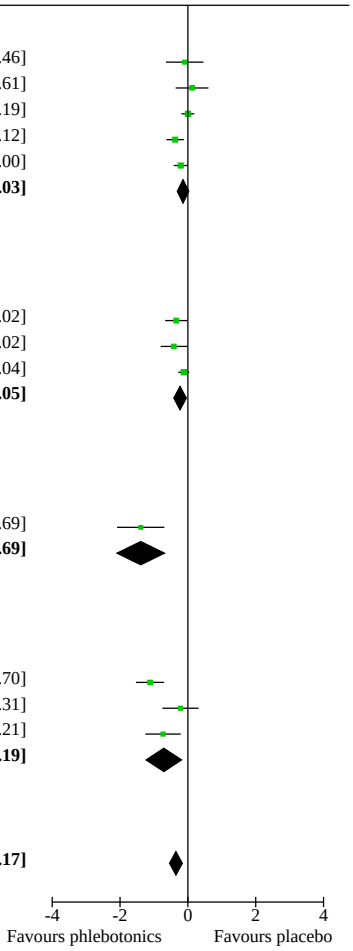


Analysis 1.7. (Continued)



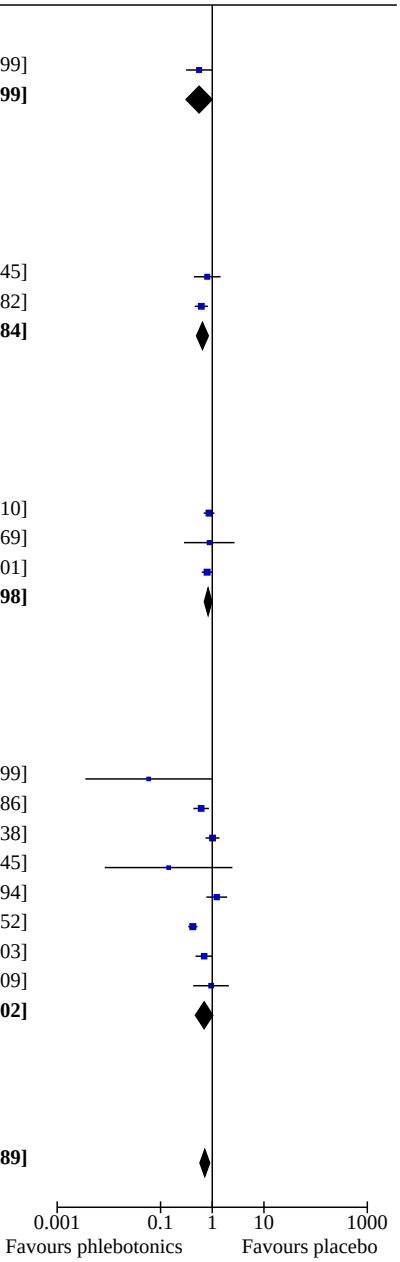
Analysis 1.8. Comparison 1: Phlebotonics versus placebo, Outcome 8: Pain in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.8.1 Calcium dobesilate								
DOBESILATO500/2	9.5	12.4	21	11.1	19	31	6.0%	-0.09 [-0.65 , 0.46]
Marinello 2002	33.4	27.8	35	29.9	28.8	31	6.9%	0.12 [-0.36 , 0.61]
Martinez-Zapata 2008	37.8	25.8	203	37.8	27.4	216	11.3%	0.00 [-0.19 , 0.19]
Rabe 2011	-10.2	26.2	120	-0.92	22.9	119	10.3%	-0.38 [-0.63 , -0.12]
Rabe 2016	2.1	0.9	174	2.3	1	177	11.0%	-0.21 [-0.42 , 0.00]
Subtotal (95% CI)			**553**			**574**	**45.6%**	**-0.14 [-0.31 , 0.03]**
Heterogeneity: Tau² = 0.01; Chi² = 6.89, df = 4 (P = 0.14); I² = 42%								
Test for overall effect: Z = 1.66 (P = 0.10)								
1.8.2 Diosmine, Hidrosmine								
Gilly 1994	0.6	0.87	76	0.9	0.86	74	9.3%	-0.35 [-0.67 , -0.02]
Planchon 1990	0.6	0.72	52	0.9	0.72	52	8.3%	-0.41 [-0.80 , -0.02]
Rabe 2015	34	24	296	37	25	296	11.7%	-0.12 [-0.28 , 0.04]
Subtotal (95% CI)			**424**			**422**	**29.2%**	**-0.23 [-0.41 , -0.05]**
Heterogeneity: Tau² = 0.01; Chi² = 2.83, df = 2 (P = 0.24); I² = 29%								
Test for overall effect: Z = 2.46 (P = 0.01)								
1.8.3 French maritime pine bark extract								
Arcangeli 2000	0.58	0.48	20	1.17	0.34	20	4.6%	-1.39 [-2.09 , -0.69]
Subtotal (95% CI)			**20**			**20**	**4.6%**	**-1.39 [-2.09 , -0.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.90 (P < 0.0001)								
1.8.4 Rutosides								
Cloarec 1996	0.9	0.8	53	1.8	0.8	51	7.9%	-1.12 [-1.53 , -0.70]
Cornu-Thenard 1985	0.8	1.03	30	1.04	1.14	25	6.3%	-0.22 [-0.75 , 0.31]
Parrado 1999	0.04	0.19	30	0.35	0.56	30	6.4%	-0.73 [-1.26 , -0.21]
Subtotal (95% CI)			**113**			**106**	**20.6%**	**-0.71 [-1.23 , -0.19]**
Heterogeneity: Tau² = 0.15; Chi² = 6.82, df = 2 (P = 0.03); I² = 71%								
Test for overall effect: Z = 2.67 (P = 0.008)								
Total (95% CI)			**1110**			**1122**	**100.0%**	**-0.35 [-0.54 , -0.17]**
Heterogeneity: Tau² = 0.07; Chi² = 43.85, df = 11 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 3.69 (P = 0.0002)								
Test for subgroup differences: Chi² = 14.84, df = 3 (P = 0.002), I² = 79.8%								



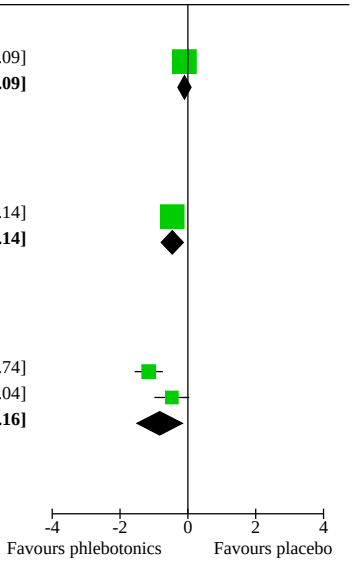
Analysis 1.9. Comparison 1: Phlebotonics versus placebo, Outcome 9: Cramps in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Aminaftone						
Lazzarini 1982	12	48	22	49	6.5%	0.56 [0.31 , 0.99]
Subtotal (95% CI)		**48**		**49**	**6.5%**	**0.56 [0.31 , 0.99]**
Total events:	12		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.98 (P = 0.05)						
1.9.2 Calcium dobesilate						
Casley-Smith 1988	8	15	10	15	6.4%	0.80 [0.44 , 1.45]
Widmer 1990	41	114	65	111	10.1%	0.61 [0.46 , 0.82]
Subtotal (95% CI)		**129**		**126**	**16.4%**	**0.65 [0.50 , 0.84]**
Total events:	49		75			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
1.9.3 Diosmine, Hidrosmine						
Biland 1982	26	35	30	35	10.7%	0.87 [0.68 , 1.10]
Fermoso 1992	5	20	4	14	2.8%	0.88 [0.28 , 2.69]
Planchon 1990	35	55	44	55	10.7%	0.80 [0.63 , 1.01]
Subtotal (95% CI)		**110**		**104**	**24.3%**	**0.83 [0.70 , 0.98]**
Total events:	66		78			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.17 (P = 0.03)						
1.9.4 Rutosides						
Balmer 1980	0	40	8	40	0.6%	0.06 [0.00 , 0.99]
Cauwenberge 1978	25	60	41	60	9.4%	0.61 [0.43 , 0.86]
Jongste 1989	27	41	28	43	9.8%	1.01 [0.74 , 1.38]
Languillat 1988	0	10	3	10	0.5%	0.14 [0.01 , 2.45]
Pedersen 1992	17	24	11	19	7.9%	1.22 [0.77 , 1.94]
Pulvertaft 1983	120	495	95	165	11.1%	0.42 [0.34 , 0.52]
Vin 1994	21	43	21	30	8.8%	0.70 [0.47 , 1.03]
Welch 1985	10	72	11	75	4.6%	0.95 [0.43 , 2.09]
Subtotal (95% CI)		**785**		**442**	**52.8%**	**0.70 [0.47 , 1.02]**
Total events:	220		218			
Heterogeneity: Tau² = 0.19; Chi² = 37.93, df = 7 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Total (95% CI)		**1072**		**721**	**100.0%**	**0.72 [0.58 , 0.89]**
Total events:	347		393			
Heterogeneity: Tau² = 0.10; Chi² = 48.70, df = 13 (P < 0.00001); I² = 73%						
Test for overall effect: Z = 3.02 (P = 0.003)						
Test for subgroup differences: Chi² = 3.87, df = 3 (P = 0.28), I² = 22.6%						



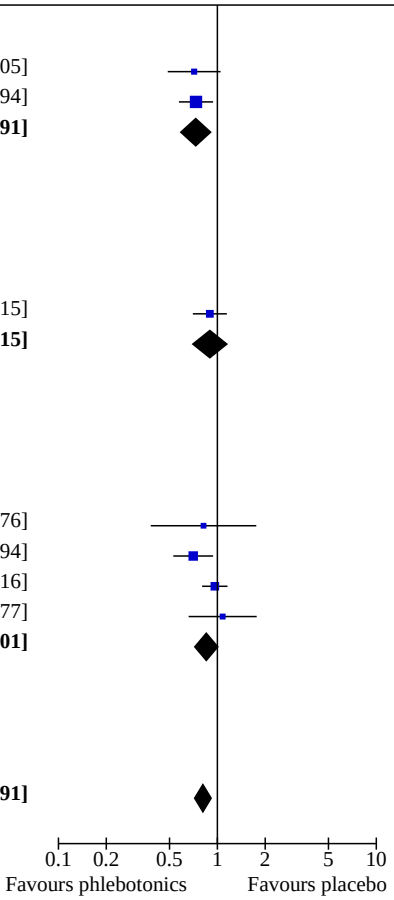
Analysis 1.10. Comparison 1: Phlebotonics versus placebo, Outcome 10: Cramps in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.10.1 Calcium dobesilate								
Martinez-Zapata 2008	24.1	27.1	204	26.9	28.7	211	100.0%	-0.10 [-0.29 , 0.09]
Subtotal (95% CI)			**204**			**211**	**100.0%**	**-0.10 [-0.29 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								
1.10.2 Diosmine, Hidrosmine								
Gilly 1994	0.3	0.87	76	0.7	0.86	74	100.0%	-0.46 [-0.78 , -0.14]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.46 [-0.78 , -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.78 (P = 0.005)								
1.10.3 Rutosides								
Cloarec 1996	0.6	0.7	53	1.6	1	51	52.5%	-1.15 [-1.57 , -0.74]
Parrado 1999	0.04	0.19	30	0.19	0.4	30	47.5%	-0.47 [-0.99 , 0.04]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**-0.83 [-1.50 , -0.16]**
Heterogeneity: Tau² = 0.18; Chi² = 4.08, df = 1 (P = 0.04); I² = 75%								
Test for overall effect: Z = 2.44 (P = 0.01)								



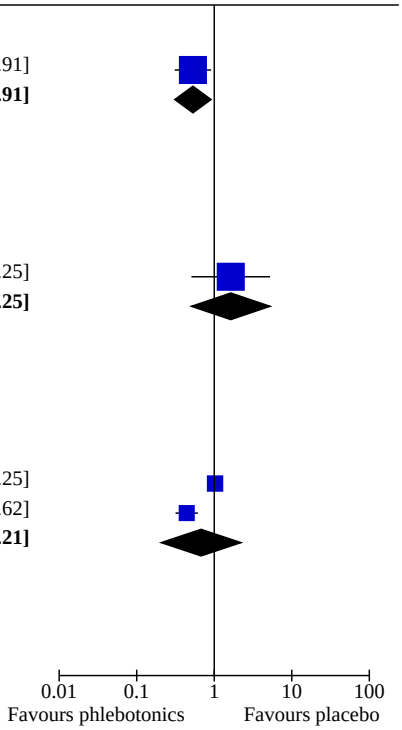
Analysis 1.11. Comparison 1: Phlebotonics versus placebo, Outcome 11: Restless legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Calcium dobesilate						
Casley-Smith 1988	10	15	14	15	6.5%	0.71 [0.49 , 1.05]
Widmer 1990	52	114	69	111	32.3%	0.73 [0.57 , 0.94]
Subtotal (95% CI)		**129**		**126**	**38.8%**	**0.73 [0.59 , 0.91]**
Total events:	62		83			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.85 (P = 0.004)						
1.11.2 Diosmine, Hidrosmine						
Biland 1982	26	35	29	35	13.4%	0.90 [0.70 , 1.15]
Subtotal (95% CI)		**35**		**35**	**13.4%**	**0.90 [0.70 , 1.15]**
Total events:	26		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
1.11.3 Rutosides						
Balmer 1980	9	40	11	40	5.1%	0.82 [0.38 , 1.76]
Cauwenberge 1978	31	60	44	60	20.3%	0.70 [0.53 , 0.94]
Jongste 1989	34	41	37	43	16.7%	0.96 [0.80 , 1.16]
Pedersen 1992	15	24	11	19	5.7%	1.08 [0.66 , 1.77]
Subtotal (95% CI)		**165**		**162**	**47.8%**	**0.85 [0.72 , 1.01]**
Total events:	89		103			
Heterogeneity: Chi² = 4.30, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Total (95% CI)		**329**		**323**	**100.0%**	**0.81 [0.72 , 0.91]**
Total events:	177		215			
Heterogeneity: Chi² = 7.29, df = 6 (P = 0.29); I² = 18%						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Test for subgroup differences: Chi² = 1.79, df = 2 (P = 0.41), I² = 0%						



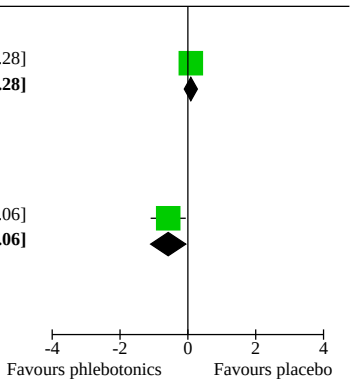
Analysis 1.12. Comparison 1: Phlebotonics versus placebo, Outcome 12: Itching in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Aminaftone						
Lazzarini 1982	13	48	25	49	100.0%	0.53 [0.31 , 0.91]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.53 [0.31 , 0.91]**
Total events:	13		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
1.12.2 Diosmine, Hidrosmine						
Fermoso 1992	7	20	3	14	100.0%	1.63 [0.51 , 5.25]
Subtotal (95% CI)		**20**		**14**	**100.0%**	**1.63 [0.51 , 5.25]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.12.3 Rutosides						
Pedersen 1992	22	24	17	19	50.6%	1.02 [0.84 , 1.25]
Vanscheidt 2002a	31	114	72	117	49.4%	0.44 [0.32 , 0.62]
Subtotal (95% CI)		**138**		**136**	**100.0%**	**0.68 [0.21 , 2.21]**
Total events:	53		89			
Heterogeneity: Tau² = 0.71; Chi² = 37.65, df = 1 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 0.65 (P = 0.52)						



Analysis 1.13. Comparison 1: Phlebotonics versus placebo, Outcome 13: Itching in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Calcium dobesilate								
Martinez-Zapata 2008	35.9	68.6	204	31.3	30.4	212	100.0%	0.09 [-0.11 , 0.28]
Subtotal (95% CI)			**204**			**212**	**100.0%**	**0.09 [-0.11 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.89 (P = 0.37)								
1.13.2 Rutosides								
Parrado 1999	0.14	0.36	30	0.42	0.57	30	100.0%	-0.58 [-1.10 , -0.06]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.58 [-1.10 , -0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.20 (P = 0.03)								



Analysis 1.14. Comparison 1: Phlebotonics versus placebo, Outcome 14: Heaviness in the lower legs (dichotomous variable)

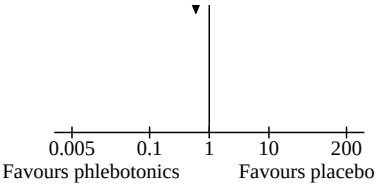
Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Aminaftone						
Lazzarini 1982	9	48	29	49	100.0%	0.32 [0.17 , 0.60]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.32 [0.17 , 0.60]**
Total events:	9		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.56 (P = 0.0004)						
1.14.2 Calcium dobesilate						
Casley-Smith 1988	1	15	14	15	24.2%	0.07 [0.01 , 0.48]
Hachen 1982	4	25	13	25	34.8%	0.31 [0.12 , 0.81]
Widmer 1990	81	114	91	111	41.0%	0.87 [0.75 , 1.00]
Subtotal (95% CI)		**154**		**151**	**100.0%**	**0.33 [0.08 , 1.42]**
Total events:	86		118			
Heterogeneity: Tau² = 1.34; Chi² = 15.42, df = 2 (P = 0.0004); I² = 87%						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.14.3 Centella asiatica						
Pointel 1986	9	30	16	33	100.0%	0.62 [0.32 , 1.19]
Subtotal (95% CI)		**30**		**33**	**100.0%**	**0.62 [0.32 , 1.19]**
Total events:	9		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.14.4 Diosmine, Hidrosmine						
Dominguez 1992	24	30	25	27	34.3%	0.86 [0.70 , 1.06]
Fermoso 1992	5	20	7	14	18.1%	0.50 [0.20 , 1.26]
Planchon 1990	13	55	30	55	27.0%	0.43 [0.25 , 0.74]
Tsouderos 1989	6	20	10	20	20.6%	0.60 [0.27 , 1.34]
Subtotal (95% CI)		**125**		**116**	**100.0%**	**0.60 [0.35 , 1.05]**
Total events:	48		72			
Heterogeneity: Tau² = 0.22; Chi² = 12.08, df = 3 (P = 0.007); I² = 75%						
Test for overall effect: Z = 1.79 (P = 0.07)						
1.14.5 French maritime pine bark extract						
Arcangeli 2000	18	20	20	20	100.0%	0.90 [0.76 , 1.07]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.90 [0.76 , 1.07]**
Total events:	18		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.14.6 Rutosides						
Cauwenberge 1972	4	21	13	21	4.2%	0.31 [0.12 , 0.79]
Cauwenberge 1978	35	60	53	60	16.5%	0.66 [0.52 , 0.83]
Jongste 1989	24	41	31	43	14.2%	0.81 [0.59 , 1.12]
Languillat 1988	1	10	8	10	1.3%	0.13 [0.02 , 0.82]
Pedersen 1992	18	24	15	19	13.9%	0.95 [0.68 , 1.32]
Pulvertaft 1983	187	495	109	165	18.3%	0.57 [0.49 , 0.67]
Vanscheidt 2002a	43	114	71	117	15.3%	0.62 [0.47 , 0.82]
Vin 1994	8	43	23	30	7.2%	0.24 [0.13 , 0.47]
Welch 1985	15	72	30	75	9.2%	0.52 [0.31 , 0.88]
Subtotal (95% CI)		**880**		**540**	**100.0%**	**0.60 [0.48 , 0.74]**
Total events:	335		353			
Heterogeneity: Tau² = 0.06; Chi² = 25.49, df = 8 (P = 0.001); I² = 69%						

Analysis 1.14. (Continued)

Total events:	335	353

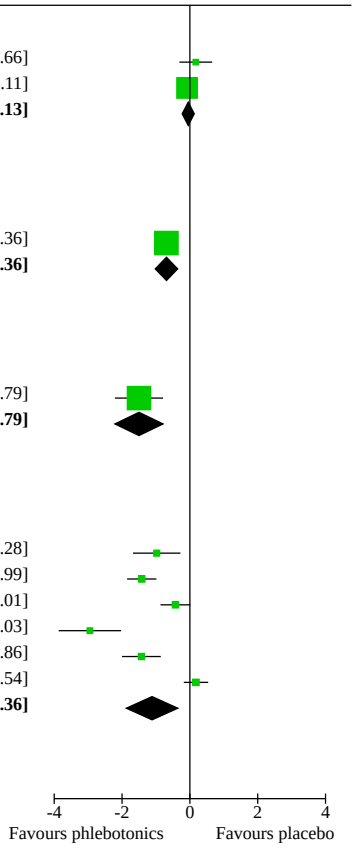
Heterogeneity: Tau² = 0.06; Chi² = 25.49, df = 8 (P = 0.001); I² = 69%

Test for overall effect: Z = 4.65 (P < 0.00001)



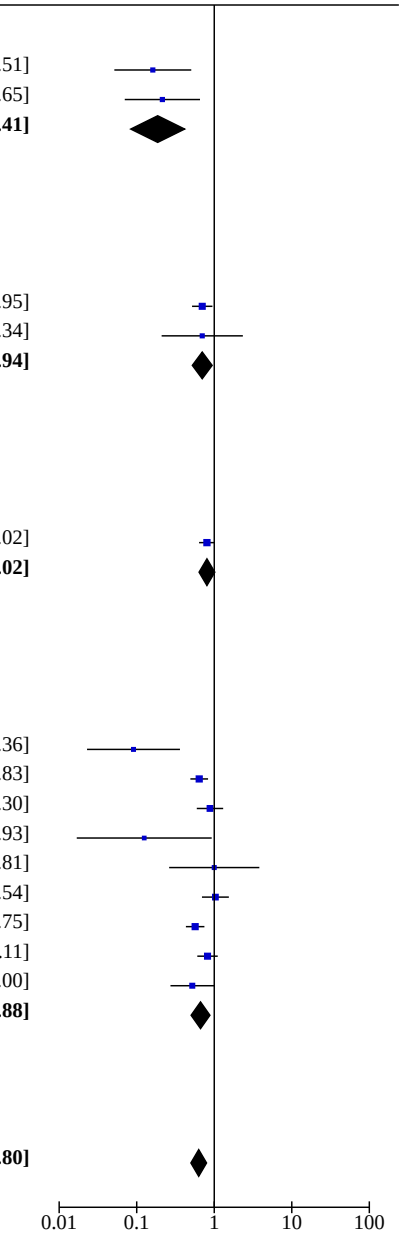
Analysis 1.15. Comparison 1: Phlebotonics versus placebo, Outcome 15: Heaviness in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.15.1 Calcium dobesilate								
Marinello 2002	36.22	28.61	35	31.61	22.82	31	13.6%	0.17 [-0.31 , 0.66]
Martinez-Zapata 2008	44.5	28.4	203	46.9	28.8	214	86.4%	-0.08 [-0.28 , 0.11]
Subtotal (95% CI)			**238**			**245**	**100.0%**	**-0.05 [-0.23 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%								
Test for overall effect: Z = 0.53 (P = 0.59)								
1.15.2 Diosmine, Hidrosmine								
Gilly 1994	0.7	0.87	76	1.3	0.86	74	100.0%	-0.69 [-1.02 , -0.36]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.69 [-1.02 , -0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.10 (P < 0.0001)								
1.15.3 French maritime pine bark extract								
Arcangeli 2000	0.94	0.55	20	1.67	0.39	20	100.0%	-1.50 [-2.21 , -0.79]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.50 [-2.21 , -0.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.14 (P < 0.0001)								
1.15.4 Rutosides								
Alterkamper 1987	1.8	0.5	16	2.3	0.5	20	16.0%	-0.98 [-1.68 , -0.28]
Cloarec 1996	1.2	0.7	53	2.2	0.7	51	17.5%	-1.42 [-1.85 , -0.99]
Cornu-Thenard 1985	0.7	0.94	40	1.1	0.92	41	17.4%	-0.43 [-0.87 , 0.01]
Diebschlag 1994	1.9	0.6	20	4.2	0.9	20	14.6%	-2.95 [-3.87 , -2.03]
Parrado 1999	0.14	0.45	30	0.77	0.42	30	16.8%	-1.43 [-2.00 , -0.86]
Unkauf 1996	27	28	64	22	27	56	17.8%	0.18 [-0.18 , 0.54]
Subtotal (95% CI)			**223**			**218**	**100.0%**	**-1.11 [-1.87 , -0.36]**
Heterogeneity: Tau² = 0.81; Chi² = 64.75, df = 5 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.88 (P = 0.004)								



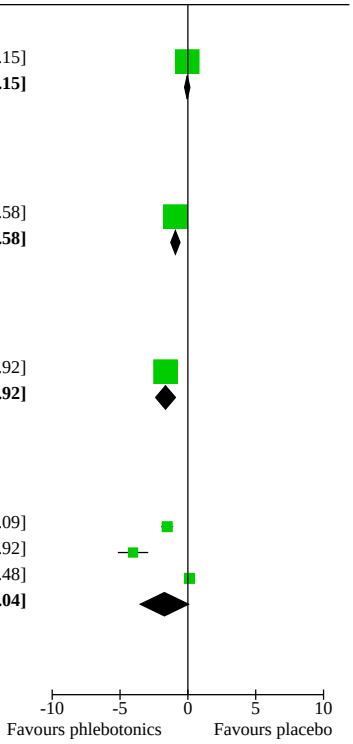
Analysis 1.16. Comparison 1: Phlebotonics versus placebo, Outcome 16: Swelling in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Calcium dobesilate						
Casley-Smith 1988	2	15	15	15	3.2%	0.16 [0.05 , 0.51]
Hachen 1982	3	25	14	25	3.3%	0.21 [0.07 , 0.65]
Subtotal (95% CI)		**40**		**40**	**6.5%**	**0.19 [0.08 , 0.41]**
Total events:	5		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
1.16.2 Diosmine, Hidrosmine						
Biland 1982	21	35	30	35	11.2%	0.70 [0.52 , 0.95]
Fermoso 1992	4	20	4	14	2.9%	0.70 [0.21 , 2.34]
Subtotal (95% CI)		**55**		**49**	**14.2%**	**0.70 [0.52 , 0.94]**
Total events:	25		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.38 (P = 0.02)						
1.16.3 French maritime pine bark extract						
Arcangeli 2000	16	20	20	20	12.2%	0.80 [0.64 , 1.02]
Subtotal (95% CI)		**20**		**20**	**12.2%**	**0.80 [0.64 , 1.02]**
Total events:	16		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
1.16.4 Rutosides						
Balmer 1980	2	40	22	40	2.3%	0.09 [0.02 , 0.36]
Cauwenberge 1978	32	60	50	60	11.8%	0.64 [0.49 , 0.83]
Jongste 1989	21	41	25	43	10.0%	0.88 [0.60 , 1.30]
Kriner 1985	1	25	8	25	1.2%	0.13 [0.02 , 0.93]
Languillat 1988	3	10	3	10	2.5%	1.00 [0.26 , 3.81]
Pedersen 1992	17	24	13	19	9.8%	1.04 [0.69 , 1.54]
Vanscheidt 2002a	42	114	76	117	11.6%	0.57 [0.43 , 0.75]
Vin 1994	27	43	23	30	11.2%	0.82 [0.60 , 1.11]
Welch 1985	11	72	22	75	6.7%	0.52 [0.27 , 1.00]
Subtotal (95% CI)		**429**		**419**	**67.2%**	**0.67 [0.50 , 0.88]**
Total events:	156		242			
Heterogeneity: Tau² = 0.10; Chi² = 24.38, df = 8 (P = 0.002); I² = 67%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Total (95% CI)		**544**		**528**	**100.0%**	**0.63 [0.50 , 0.80]**
Total events:	202		325			
Heterogeneity: Tau² = 0.10; Chi² = 41.85, df = 13 (P < 0.0001); I² = 69%						
Test for overall effect: Z = 3.90 (P < 0.0001)						
Test for subgroup differences: Chi² = 12.04, df = 3 (P = 0.007), I² = 75.1%						



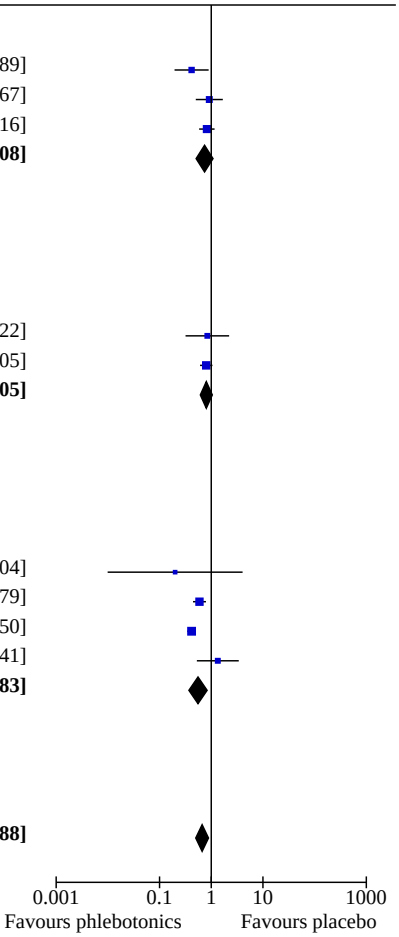
Analysis 1.17. Comparison 1: Phlebotonics versus placebo, Outcome 17: Swelling in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.17.1 Calcium dobesilate								
Martinez-Zapata 2008	36.2	28.6	203	37.5	27.8	214	100.0%	-0.05 [-0.24 , 0.15]
Subtotal (95% CI)			**203**			**214**	**100.0%**	**-0.05 [-0.24 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
1.17.2 Diosmine, Hidrosmine								
Gilly 1994	0.5	0.87	76	1.3	0.86	74	100.0%	-0.92 [-1.26 , -0.58]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.92 [-1.26 , -0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.35 (P < 0.00001)								
1.17.3 French maritime pine bark extract								
Arcangeli 2000	0.6	0.53	20	1.39	0.4	20	100.0%	-1.65 [-2.38 , -0.92]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.65 [-2.38 , -0.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.44 (P < 0.00001)								
1.17.4 Rutosides								
Cloarec 1996	1	0.6	53	2	0.7	51	34.5%	-1.52 [-1.96 , -1.09]
Diebschlag 1994	0.5	0.6	20	3.9	1	20	30.9%	-4.04 [-5.16 , -2.92]
Unkauf 1996	23	24	64	20	26	56	34.7%	0.12 [-0.24 , 0.48]
Subtotal (95% CI)			**137**			**127**	**100.0%**	**-1.73 [-3.50 , 0.04]**
Heterogeneity: Tau² = 2.32; Chi² = 67.70, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.91 (P = 0.06)								



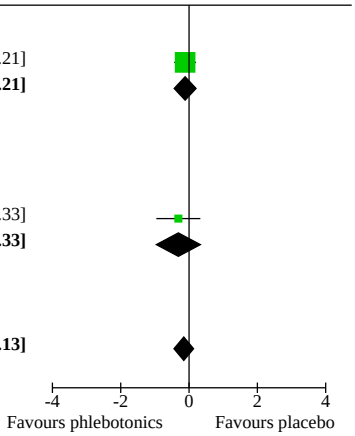
Analysis 1.18. Comparison 1: Phlebotonics versus placebo, Outcome 18: Paraesthesia in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Calcium dobesilate						
Casley-Smith 1988	5	15	12	15	8.2%	0.42 [0.20 , 0.89]
Hachen 1982	11	25	12	25	10.6%	0.92 [0.50 , 1.67]
Widmer 1990	38	114	45	111	15.6%	0.82 [0.58 , 1.16]
Subtotal (95% CI)		**154**		**151**	**34.4%**	**0.74 [0.51 , 1.08]**
Total events:	54		69			
Heterogeneity: Tau² = 0.04; Chi² = 2.98, df = 2 (P = 0.23); I² = 33%						
Test for overall effect: Z = 1.56 (P = 0.12)						
1.18.2 Diosmine, Hidrosmine						
Fermoso 1992	6	20	5	14	6.0%	0.84 [0.32 , 2.22]
Planchon 1990	32	55	40	55	17.0%	0.80 [0.61 , 1.05]
Subtotal (95% CI)		**75**		**69**	**23.0%**	**0.80 [0.62 , 1.05]**
Total events:	38		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.11)						
1.18.3 Rutosides						
Balmer 1980	0	40	2	40	0.8%	0.20 [0.01 , 4.04]
Cauwenberge 1978	29	60	49	60	16.8%	0.59 [0.44 , 0.79]
Pulvertaft 1983	130	495	104	165	18.6%	0.42 [0.35 , 0.50]
Welch 1985	9	72	7	75	6.3%	1.34 [0.53 , 3.41]
Subtotal (95% CI)		**667**		**340**	**42.6%**	**0.55 [0.37 , 0.83]**
Total events:	168		162			
Heterogeneity: Tau² = 0.09; Chi² = 9.21, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 2.86 (P = 0.004)						
Total (95% CI)		**896**		**560**	**100.0%**	**0.67 [0.50 , 0.88]**
Total events:	260		276			
Heterogeneity: Tau² = 0.10; Chi² = 28.17, df = 8 (P = 0.0004); I² = 72%						
Test for overall effect: Z = 2.82 (P = 0.005)						
Test for subgroup differences: Chi² = 2.27, df = 2 (P = 0.32), I² = 11.8%						

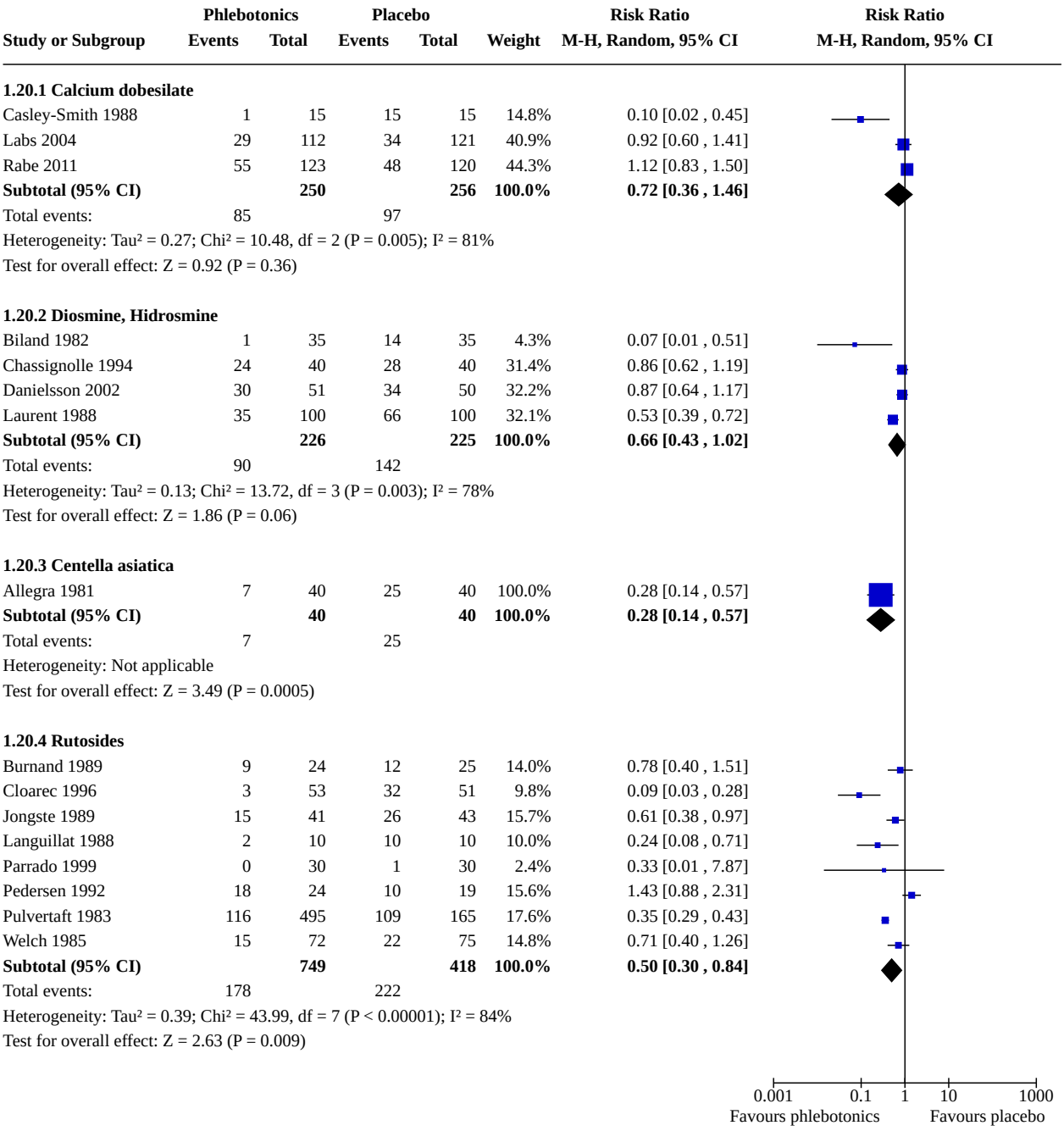


Analysis 1.19. Comparison 1: Phlebotonics versus placebo, Outcome 19: Paraesthesia in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.19.1 Diosmine, Hidrosmine								
Gilly 1994	0.4	0.87	76	0.5	0.86	74	80.2%	-0.12 [-0.44 , 0.21]
Subtotal (95% CI)			**76**			**74**	**80.2%**	**-0.12 [-0.44 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.19.2 Rutosides								
Cornu-Thenard 1985	0.52	0.75	21	0.82	1.13	17	19.8%	-0.31 [-0.96 , 0.33]
Subtotal (95% CI)			**21**			**17**	**19.8%**	**-0.31 [-0.96 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.95 (P = 0.34)								
Total (95% CI)			**97**			**91**	**100.0%**	**-0.15 [-0.44 , 0.13]**
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%								
Test for overall effect: Z = 1.05 (P = 0.29)								
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%								

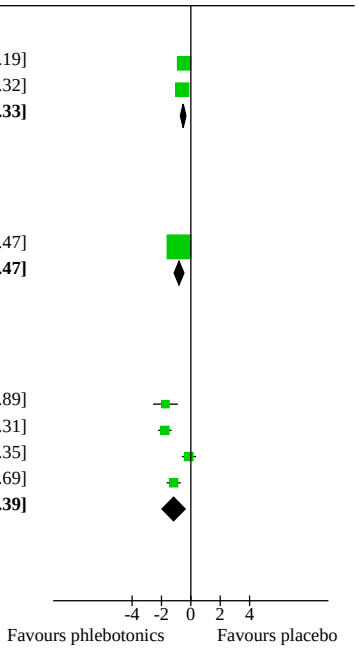


Analysis 1.20. Comparison 1: Phlebotonics versus placebo, Outcome 20: Participant satisfaction (dichotomous variable)



Analysis 1.21. Comparison 1: Phlebotonics versus placebo, Outcome 21: Participant satisfaction (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.21.1 Calcium dobesilate								
Rabe 2011	15.19	12.49	108	20.83	11.91	115	50.2%	-0.46 [-0.73 , -0.19]
Widmer 1990	4.4	4.4	114	7.39	5.7	111	49.8%	-0.59 [-0.85 , -0.32]
Subtotal (95% CI)			**222**			**226**	**100.0%**	**-0.52 [-0.71 , -0.33]**
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 5.44 (P < 0.00001)								
1.21.2 Diosmine, Hidrosmine								
Gilly 1994	0.5	0.87	76	1.2	0.86	74	100.0%	-0.81 [-1.14 , -0.47]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.81 [-1.14 , -0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.74 (P < 0.00001)								
1.21.3 Rutosides								
Cesarone 2002	3.1	1.2	16	6	2	15	21.7%	-1.73 [-2.57 , -0.89]
Cloarec 1996	4.3	2.5	53	9.5	3.3	51	26.3%	-1.77 [-2.22 , -1.31]
Ihme 1996	2.2	1.4	36	2.4	1.7	31	26.0%	-0.13 [-0.61 , 0.35]
Kiesewetter 1997	1.5	1.1	37	3	1.4	44	26.1%	-1.17 [-1.64 , -0.69]
Subtotal (95% CI)			**142**			**141**	**100.0%**	**-1.18 [-1.96 , -0.39]**
Heterogeneity: Tau² = 0.56; Chi² = 26.15, df = 3 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.93 (P = 0.003)								

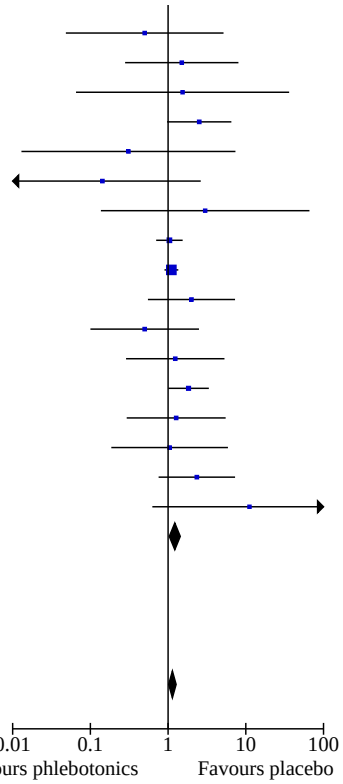


Analysis 1.22. Comparison 1: Phlebotonics versus placebo, Outcome 22: Adverse events

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 Aminaftone						
Belczak 2014	1	36	2	43	0.4%	0.60 [0.06 , 6.32]
Subtotal (95% CI)		**36**		**43**	**0.4%**	**0.60 [0.06 , 6.32]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.22.2 Calcium dobesilate						
Flota-Cervera 2008	1	25	1	24	0.2%	0.96 [0.06 , 14.50]
Hachen 1982	1	25	0	25	0.1%	3.00 [0.13 , 70.30]
Labs 2004	9	133	8	127	1.8%	1.07 [0.43 , 2.70]
Marinello 2002	32	82	18	41	5.2%	0.89 [0.57 , 1.38]
Martinez-Zapata 2008	46	246	45	263	9.5%	1.09 [0.75 , 1.59]
Rabe 2011	33	133	10	124	2.2%	3.08 [1.58 , 5.98]
Rabe 2016	26	174	23	177	5.0%	1.15 [0.68 , 1.94]
Widmer 1990	31	114	28	111	6.2%	1.08 [0.69 , 1.67]
Subtotal (95% CI)		**932**		**892**	**30.1%**	**1.22 [1.00 , 1.49]**
Total events:	179		133			
Heterogeneity: Chi^2 = 10.53, df = 7 (P = 0.16); I^2 = 34%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.22.3 Centella asiatica						
Pointel 1986	19	61	9	33	2.5%	1.14 [0.58 , 2.23]
Subtotal (95% CI)		**61**		**33**	**2.5%**	**1.14 [0.58 , 2.23]**
Total events:	19		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
1.22.4 Diosmine, Hidrosmine						
Biland 1982	11	35	12	35	2.6%	0.92 [0.47 , 1.79]
Danielsson 2002	6	51	2	50	0.4%	2.94 [0.62 , 13.89]
Dominguez 1992	1	30	0	27	0.1%	2.71 [0.12 , 63.84]
Fermoso 1992	1	20	0	14	0.1%	2.14 [0.09 , 49.08]
Gilly 1994	12	80	9	80	2.0%	1.33 [0.60 , 2.99]
Guilhou 1997	4	53	5	52	1.1%	0.78 [0.22 , 2.76]
Laurent 1988	9	100	13	100	2.8%	0.69 [0.31 , 1.55]
Planchon 1990	6	55	8	55	1.7%	0.75 [0.28 , 2.02]
Rabe 2015	49	296	57	296	12.4%	0.86 [0.61 , 1.22]
Subtotal (95% CI)		**720**		**709**	**23.3%**	**0.93 [0.72 , 1.19]**
Total events:	99		106			
Heterogeneity: Chi^2 = 4.56, df = 8 (P = 0.80); I^2 = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.22.5 Grape seed extract						
Thebaut 1985	4	35	8	40	1.6%	0.57 [0.19 , 1.74]
Subtotal (95% CI)		**35**		**40**	**1.6%**	**0.57 [0.19 , 1.74]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.22.6 Rutosides						
Alterkamper 1987	1	25	2	25	0.4%	0.50 [0.05 , 5.17]
Balmer 1980	3	20	2	20	0.4%	1.50 [0.28 , 8.04]

Analysis 1.22. (Continued)

Alterkamper 1987	1	25	2	25	0.4%	0.50 [0.05 , 5.17]
Balmer 1980	3	20	2	20	0.4%	1.50 [0.28 , 8.04]
Diebschlag 1994	1	40	0	20	0.1%	1.54 [0.07 , 36.11]
Jongste 1989	12	41	5	43	1.1%	2.52 [0.97 , 6.52]
Koscielnny 1996	0	40	1	37	0.3%	0.31 [0.01 , 7.36]
Kriner 1985	0	25	3	25	0.8%	0.14 [0.01 , 2.63]
Languillat 1988	1	10	0	10	0.1%	3.00 [0.14 , 65.90]
MacLennan 1994	26	52	25	52	5.4%	1.04 [0.70 , 1.54]
NCT01848210	131	394	120	398	25.9%	1.10 [0.90 , 1.35]
Parrado 1999	6	30	3	30	0.7%	2.00 [0.55 , 7.27]
Serralde 1990	2	26	4	26	0.9%	0.50 [0.10 , 2.50]
Unkauf 1996	4	69	3	64	0.7%	1.24 [0.29 , 5.31]
Vanscheidt 2002a	25	114	14	117	3.0%	1.83 [1.00 , 3.34]
Vanscheidt 2002b	4	85	3	81	0.7%	1.27 [0.29 , 5.50]
Vin 1994	3	43	2	30	0.5%	1.05 [0.19 , 5.89]
Welch 1985	9	72	4	75	0.9%	2.34 [0.76 , 7.27]
Zucarelli 1987	5	74	0	75	0.1%	11.15 [0.63 , 198.06]
Subtotal (95% CI)		**1160**		**1128**	**42.0%**	**1.22 [1.04 , 1.43]**
Total events:	233		191			
Heterogeneity: Chi² = 14.65, df = 16 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Total (95% CI)		**2944**		**2845**	**100.0%**	**1.14 [1.02 , 1.27]**
Total events:	535		449			
Heterogeneity: Chi² = 34.25, df = 36 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.27 (P = 0.02)						
Test for subgroup differences: Chi² = 5.44, df = 5 (P = 0.36), I² = 8.0%						



Comparison 2. Sensitivity analysis excluding studies that allowed the use of elastic stockings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Oedema in the lower legs (dichotomous variable)	12	1131	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.76]
2.1.1 Aminaftone	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
2.1.2 Calcium dobesilate	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
2.1.3 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
2.1.4 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]
2.1.5 Rutosides	6	540	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.78]
2.2 Ankle perimeter circumference (mm)	10	1212	Mean Difference (IV, Fixed, 95% CI)	-4.59 [-6.02, -3.16]
2.2.1 Calcium dobesilate	3	502	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-4.95, 3.34]
2.2.2 Diosmine, Hidrosmine	2	246	Mean Difference (IV, Fixed, 95% CI)	-5.90 [-7.72, -4.07]
2.2.3 Rutosides	5	464	Mean Difference (IV, Fixed, 95% CI)	-3.28 [-6.06, -0.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Volume of the leg (mL)	9	1153	Std. Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.42, -0.19]
2.3.1 Aminaftone	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.61, 0.28]
2.3.2 Calcium dobesilate	3	587	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.49, -0.17]
2.3.3 Rutosides	5	487	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.47, -0.11]
2.4 Quality of life	3	1022	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
2.4.1 Aminaftone	1	79	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.10, -0.19]
2.4.2 Calcium dobesilate	1	351	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.23, 0.18]
2.4.3 Diosmine, Hidrosmine	1	592	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.12, 0.20]
2.5 Ulcer healing	2	128	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.27, 3.10]
2.5.1 Aminaftone	1	100	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.18]
2.5.2 Diosmine, Hidrosmine	1	28	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.15, 14.68]
2.6 Trophic disorders (dichotomous variable)	5	601	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.94]
2.6.1 Aminaftone	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.44]
2.6.2 Diosmine, Hidrosmine	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
2.7 Pain in the lower legs (dichotomous variable)	18	1818	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.82]
2.7.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.79]
2.7.2 Calcium dobesilate	5	705	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.82]
2.7.3 Diosmine, Hidrosmine	4	271	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.08]
2.7.4 Rutosides	8	745	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.91]
2.8 Pain in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8.1 Calcium dobesilate	1	351	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.42, 0.00]

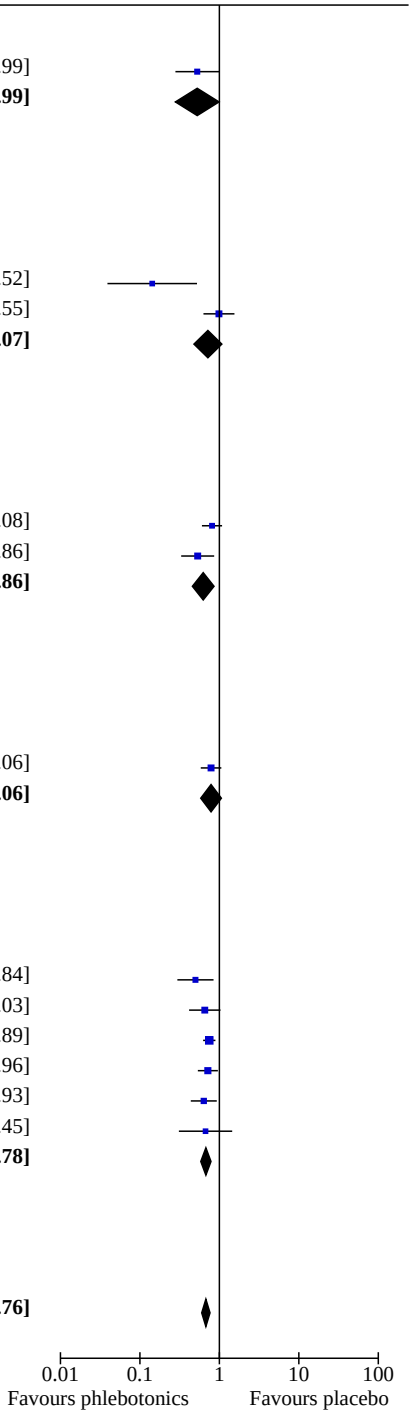
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8.2 Diosmine, Hidrosmine	3	846	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.41, -0.05]
2.8.3 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.33, -0.59]
2.9 Cramps in the lower legs (dichotomous variable)	12	1603	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.57, 0.91]
2.9.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.99]
2.9.2 Calcium dobesilate	2	255	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
2.9.3 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.09]
2.9.4 Rutosides	7	1147	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.06]
2.10 Cramps in the lower legs (continuous variable)	3	314	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.15, -0.24]
2.10.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.78, -0.14]
2.10.2 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.16]
2.11 Restless legs (dichotomous variable)	6	572	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
2.11.1 Calcium dobesilate	2	255	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.59, 0.91]
2.11.2 Diosmine, Hidrosmine	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.15]
2.11.3 Rutosides	3	247	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.01]
2.12 Itching in the lower legs (dichotomous variable)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.12.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
2.12.2 Diosmine, Hidrosmine	1	34	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.25]
2.12.3 Rutosides	2	274	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.21, 2.21]
2.13 Itching in the lower legs (continuous variable)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.13.1 Rutosides	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.14 Heaviness in the lower legs (dichotomous variable)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.14.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.14.2 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
2.14.3 Centella asiatica	1	63	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
2.14.4 Diosmine, Hidrosmine	3	201	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.29, 1.22]
2.14.5 Rutosides	8	531	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.38, 0.80]
2.15 Heaviness in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.15.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.02, -0.36]
2.15.2 Rutosides	5	360	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-2.22, -0.32]
2.16 Swelling in the lower legs (dichotomous variable)	12	952	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.82]
2.16.1 Calcium dobesilate	2	80	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.41]
2.16.2 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
2.16.3 Rutosides	8	768	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.89]
2.17 Swelling in the lower legs (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.17.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.26, -0.58]
2.17.2 Rutosides	3	264	Std. Mean Difference (IV, Random, 95% CI)	-1.73 [-3.50, 0.04]
2.18 Paraesthesias in the lower legs (dichotomous variable)	7	716	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.64, 0.88]
2.18.1 Calcium dobesilate	3	305	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.01]
2.18.2 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.06]
2.18.3 Rutosides	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.91]
2.19 Paraesthesias in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.19.1 Diosmine, Hidrosmine	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.20 Participant satisfaction (dichotomous variable)	12	1193	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.53, 0.90]
2.20.1 Calcium dobesilate	3	515	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.43, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.20.2 Diosmine, Hidrosmine	2	171	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.68, 1.04]
2.20.3 Rutosides	7	507	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.98]
2.21 Participant satisfaction (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.21.1 Diosmine, Hidrosmine	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.21.2 Rutosides	3		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2.22 Adverse events	27	3433	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.95, 1.33]
2.22.1 Aminaftone	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.06, 6.32]
2.22.2 Calcium dobesilate	5	935	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.82, 1.53]
2.22.3 Centella asiatica	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.58, 2.23]
2.22.4 Diosmine, Hidrosmine	7	1124	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.27]
2.22.5 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.19, 1.74]
2.22.6 Rutosides	12	1126	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.08, 2.19]

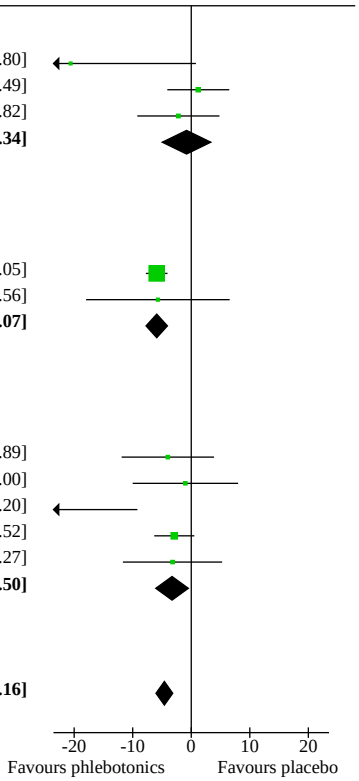
Analysis 2.1. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 1: Oedema in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Aminaftone						
Lazzarini 1982	10	41	19	41	6.3%	0.53 [0.28 , 0.99]
Subtotal (95% CI)		**41**		**41**	**6.3%**	**0.53 [0.28 , 0.99]**
Total events:	10		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
2.1.2 Calcium dobesilate						
Casley-Smith 1988	2	15	14	15	4.6%	0.14 [0.04 , 0.52]
Labs 2004	30	133	29	127	9.8%	0.99 [0.63 , 1.55]
Subtotal (95% CI)		**148**		**142**	**14.4%**	**0.72 [0.48 , 1.07]**
Total events:	32		43			
Heterogeneity: Chi² = 7.90, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 1.62 (P = 0.11)						
2.1.3 Diosmine, Hidrosmine						
Fermoso 1992	15	20	13	14	5.1%	0.81 [0.60 , 1.08]
Planchon 1990	16	55	30	55	9.9%	0.53 [0.33 , 0.86]
Subtotal (95% CI)		**75**		**69**	**15.0%**	**0.63 [0.46 , 0.86]**
Total events:	31		43			
Heterogeneity: Chi² = 3.36, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 2.93 (P = 0.003)						
2.1.4 Grape seed extract						
Thebaut 1985	22	35	32	40	9.9%	0.79 [0.58 , 1.06]
Subtotal (95% CI)		**35**		**40**	**9.9%**	**0.79 [0.58 , 1.06]**
Total events:	22		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
2.1.5 Rutosides						
Cauwenberge 1972	9	21	18	21	5.9%	0.50 [0.30 , 0.84]
Cauwenberge 1978	19	60	29	60	9.6%	0.66 [0.42 , 1.03]
Cloarec 1996	38	53	49	51	16.5%	0.75 [0.62 , 0.89]
Ihme 1996	24	40	31	37	10.6%	0.72 [0.54 , 0.96]
Kriner 1985	14	25	22	25	7.3%	0.64 [0.44 , 0.93]
Welch 1985	9	72	14	75	4.5%	0.67 [0.31 , 1.45]
Subtotal (95% CI)		**271**		**269**	**54.5%**	**0.68 [0.58 , 0.78]**
Total events:	113		163			
Heterogeneity: Chi² = 2.72, df = 5 (P = 0.74); I² = 0%						
Test for overall effect: Z = 5.20 (P < 0.00001)						
Total (95% CI)		**570**		**561**	**100.0%**	**0.68 [0.60 , 0.76]**
Total events:	208		300			
Heterogeneity: Chi² = 14.94, df = 11 (P = 0.19); I² = 26%						
Test for overall effect: Z = 6.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.87, df = 4 (P = 0.76), I² = 0%						



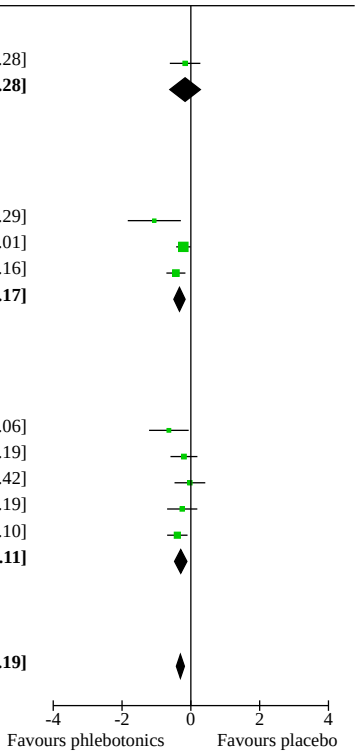
Analysis 2.2. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 2: Ankle perimeter circumference (mm)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 Calcium dobesilate								
Flota-Cervera 2008	335.6	38.2	25	356.2	38.2	24	0.4%	-20.60 [-42.00 , 0.80]
Labs 2004	229.5	22.73	124	228.3	19.59	123	7.3%	1.20 [-4.09 , 6.49]
Widmer 1990	230.1	21.31	103	232.3	29.43	103	4.2%	-2.20 [-9.22 , 4.82]
Subtotal (95% CI)			**252**			**250**	**12.0%**	**-0.80 [-4.95 , 3.34]**
Heterogeneity: Chi² = 3.99, df = 2 (P = 0.14); I² = 50%								
Test for overall effect: Z = 0.38 (P = 0.70)								
2.2.2 Diosmine, Hidrosmine								
Gilly 1994	-7.1	6.97	76	-1.2	4.3	74	60.1%	-5.90 [-7.75 , -4.05]
Planchon 1990	229.1	30.3	48	234.8	31	48	1.4%	-5.70 [-17.96 , 6.56]
Subtotal (95% CI)			**124**			**122**	**61.5%**	**-5.90 [-7.72 , -4.07]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%								
Test for overall effect: Z = 6.32 (P < 0.00001)								
2.2.3 Rutosides								
Cloarec 1996	221	22	53	225	19	51	3.3%	-4.00 [-11.89 , 3.89]
Jongste 1989	236	22	41	237	20	43	2.5%	-1.00 [-10.00 , 8.00]
Parrado 1999	209	50	30	243	48	30	0.3%	-34.00 [-58.80 , -9.20]
Vin 1994	-3.7	7.2	34	-0.8	7.3	35	17.5%	-2.90 [-6.32 , 0.52]
Welch 1985	232.5	27.4	72	235.7	24.9	75	2.9%	-3.20 [-11.67 , 5.27]
Subtotal (95% CI)			**230**			**234**	**26.6%**	**-3.28 [-6.06 , -0.50]**
Heterogeneity: Chi² = 6.22, df = 4 (P = 0.18); I² = 36%								
Test for overall effect: Z = 2.31 (P = 0.02)								
Total (95% CI)			**606**			**606**	**100.0%**	**-4.59 [-6.02 , -3.16]**
Heterogeneity: Chi² = 16.23, df = 9 (P = 0.06); I² = 45%								
Test for overall effect: Z = 6.28 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.02, df = 2 (P = 0.05), I² = 66.8%								



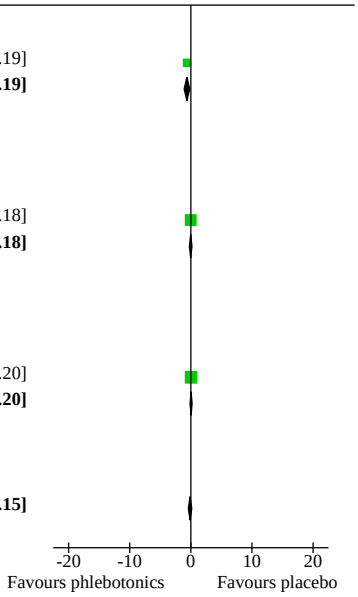
Analysis 2.3. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 3: Volume of the leg (mL)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
2.3.1 Aminaftone								
Belczak 2014	3276.5	584.6	36	3391.5	751.1	43	6.9%	-0.17 [-0.61 , 0.28]
Subtotal (95% CI)			**36**			**43**	**6.9%**	**-0.17 [-0.61 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
2.3.2 Calcium dobesilate								
Casley-Smith 1988	1097	92.95	15	1205	104.57	15	2.3%	-1.06 [-1.83 , -0.29]
Rabe 2016	-25.68	127.44	174	-1.88	88.33	177	30.8%	-0.22 [-0.43 , -0.01]
Widmer 1990	-3.8	6.08	103	-1.15	6.08	103	17.8%	-0.43 [-0.71 , -0.16]
Subtotal (95% CI)			**292**			**295**	**50.8%**	**-0.33 [-0.49 , -0.17]**
Heterogeneity: Chi² = 5.12, df = 2 (P = 0.08); I² = 61%								
Test for overall effect: Z = 3.97 (P < 0.0001)								
2.3.3 Rutosides								
Burnand 1989	1098	157.74	24	1200	156.5	25	4.1%	-0.64 [-1.21 , -0.06]
Diebschlag 1994	-11.9	43.4	51	-4.4	29.2	50	8.9%	-0.20 [-0.59 , 0.19]
Ihme 1996	2073	309	40	2082	339	37	6.8%	-0.03 [-0.47 , 0.42]
Kiesewetter 1997	1992	367	37	2111	541	44	7.0%	-0.25 [-0.69 , 0.19]
Vanscheidt 2002a	-95.7	127.9	86	-44.6	131.1	93	15.5%	-0.39 [-0.69 , -0.10]
Subtotal (95% CI)			**238**			**249**	**42.3%**	**-0.29 [-0.47 , -0.11]**
Heterogeneity: Chi² = 3.43, df = 4 (P = 0.49); I² = 0%								
Test for overall effect: Z = 3.22 (P = 0.001)								
Total (95% CI)			**566**			**587**	**100.0%**	**-0.30 [-0.42 , -0.19]**
Heterogeneity: Chi² = 9.03, df = 8 (P = 0.34); I² = 11%								
Test for overall effect: Z = 5.12 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.48, df = 2 (P = 0.79), I² = 0%								



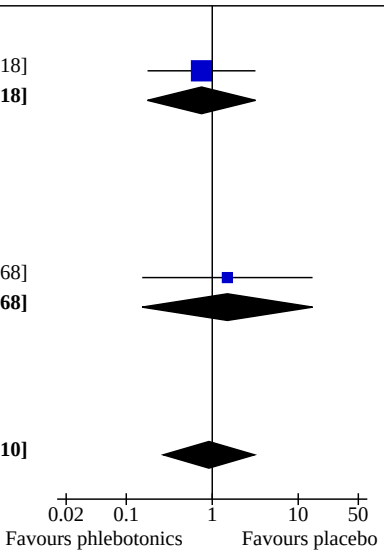
Analysis 2.4. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 4: Quality of life

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.4.1 Aminaftone								
Belczak 2014	-15.4	17.8	36	-5.4	13.1	43	20.9%	-0.64 [-1.10 , -0.19]
Subtotal (95% CI)			**36**			**43**	**20.9%**	**-0.64 [-1.10 , -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.77 (P = 0.006)								
2.4.2 Calcium dobesilate								
Rabe 2016	39.9	14.9	174	40.3	16.4	177	37.7%	-0.03 [-0.23 , 0.18]
Subtotal (95% CI)			**174**			**177**	**37.7%**	**-0.03 [-0.23 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
2.4.3 Diosmine, Hidrosmine								
Rabe 2015	69.9	20.6	296	69.1	20.6	296	41.3%	0.04 [-0.12 , 0.20]
Subtotal (95% CI)			**296**			**296**	**41.3%**	**0.04 [-0.12 , 0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**506**			**516**	**100.0%**	**-0.13 [-0.41 , 0.15]**
Heterogeneity: Tau² = 0.04; Chi² = 7.67, df = 2 (P = 0.02); I² = 74%								
Test for overall effect: Z = 0.91 (P = 0.36)								
Test for subgroup differences: Chi² = 7.67, df = 2 (P = 0.02), I² = 73.9%								



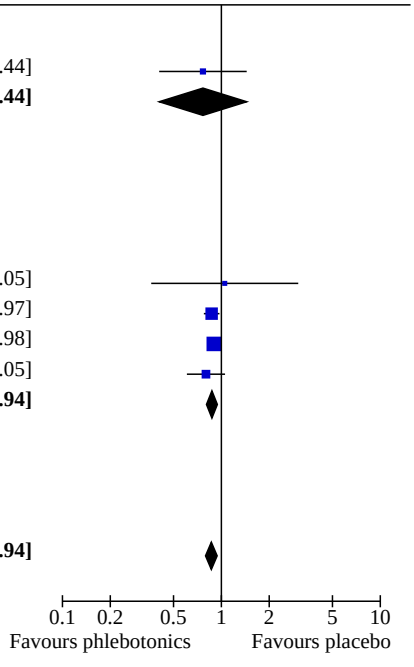
Analysis 2.5. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 5: Ulcer healing

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Aminaftone						
Lazzarini 1982	3	50	4	50	71.4%	0.75 [0.18 , 3.18]
Subtotal (95% CI)		**50**		**50**	**71.4%**	**0.75 [0.18 , 3.18]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
2.5.2 Diosmine, Hidrosmine						
Fermoso 1992	2	16	1	12	28.6%	1.50 [0.15 , 14.68]
Subtotal (95% CI)		**16**		**12**	**28.6%**	**1.50 [0.15 , 14.68]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**66**		**62**	**100.0%**	**0.91 [0.27 , 3.10]**
Total events:	5		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.61), I² = 0%						



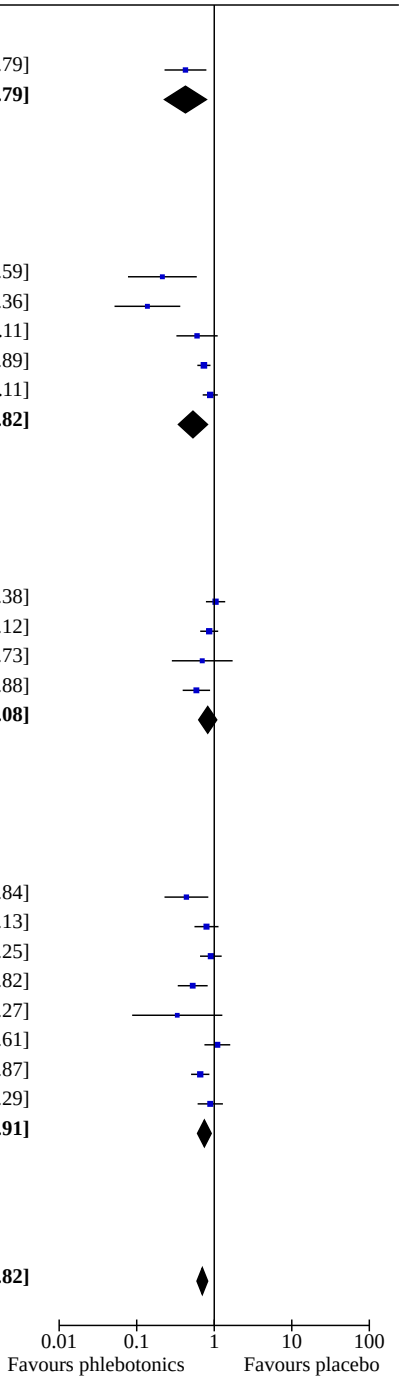
Analysis 2.6. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 6: Trophic disorders (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Aminaftone						
Lazzarini 1982	12	48	16	49	6.8%	0.77 [0.41 , 1.44]
Subtotal (95% CI)		**48**		**49**	**6.8%**	**0.77 [0.41 , 1.44]**
Total events:	12		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
2.6.2 Diosmine, Hidrosmine						
Fermoso 1992	6	20	4	14	2.0%	1.05 [0.36 , 3.05]
Gilly 1994	66	80	76	80	32.7%	0.87 [0.78 , 0.97]
Laurent 1988	86	100	96	100	41.3%	0.90 [0.82 , 0.98]
Planchon 1990	32	55	40	55	17.2%	0.80 [0.61 , 1.05]
Subtotal (95% CI)		**255**		**249**	**93.2%**	**0.87 [0.81 , 0.94]**
Total events:	190		216			
Heterogeneity: Chi² = 0.85, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
Total (95% CI)		**303**		**298**	**100.0%**	**0.86 [0.79 , 0.94]**
Total events:	202		232			
Heterogeneity: Chi² = 1.19, df = 4 (P = 0.88); I² = 0%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						



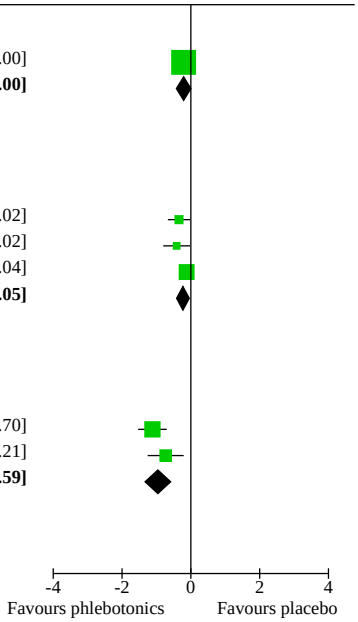
Analysis 2.7. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 7: Pain in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Aminaftone						
Lazzarini 1982	10	48	24	49	4.0%	0.43 [0.23 , 0.79]
Subtotal (95% CI)		**48**		**49**	**4.0%**	**0.43 [0.23 , 0.79]**
Total events:	10		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.70 (P = 0.007)						
2.7.2 Calcium dobesilate						
Casley-Smith 1988	3	15	14	15	1.9%	0.21 [0.08 , 0.59]
Flota-Cervera 2008	3	25	24	24	2.1%	0.14 [0.05 , 0.36]
Hachen 1982	9	25	15	25	4.1%	0.60 [0.33 , 1.11]
Rabe 2016	81	174	112	177	9.0%	0.74 [0.61 , 0.89]
Widmer 1990	62	114	68	111	8.6%	0.89 [0.71 , 1.11]
Subtotal (95% CI)		**353**		**352**	**25.8%**	**0.53 [0.35 , 0.82]**
Total events:	158		233			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 21.62$, df = 4 (P = 0.0002); $I^2 = 82\%$						
Test for overall effect: Z = 2.88 (P = 0.004)						
2.7.3 Diosmine, Hidrosmine						
Biland 1982	26	35	25	35	7.8%	1.04 [0.78 , 1.38]
Dominguez 1992	22	30	23	27	8.0%	0.86 [0.66 , 1.12]
Fermoso 1992	6	20	6	14	2.4%	0.70 [0.28 , 1.73]
Planchon 1990	20	55	34	55	6.2%	0.59 [0.39 , 0.88]
Subtotal (95% CI)		**140**		**131**	**24.4%**	**0.82 [0.63 , 1.08]**
Total events:	74		88			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.91$, df = 3 (P = 0.12); $I^2 = 49\%$						
Test for overall effect: Z = 1.42 (P = 0.16)						
2.7.4 Rutosides						
Cauwenberge 1972	7	21	16	21	3.8%	0.44 [0.23 , 0.84]
Cauwenberge 1978	27	60	34	60	6.8%	0.79 [0.56 , 1.13]
Jongste 1989	25	41	29	43	7.3%	0.90 [0.66 , 1.25]
Klüken 1971	13	30	23	28	5.7%	0.53 [0.34 , 0.82]
Languillat 1988	2	10	6	10	1.2%	0.33 [0.09 , 1.27]
Pedersen 1992	18	24	13	19	6.5%	1.10 [0.75 , 1.61]
Vanscheidt 2002b	45	114	70	117	8.0%	0.66 [0.50 , 0.87]
Welch 1985	29	72	34	75	6.6%	0.89 [0.61 , 1.29]
Subtotal (95% CI)		**372**		**373**	**45.9%**	**0.75 [0.61 , 0.91]**
Total events:	166		225			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 13.49$, df = 7 (P = 0.06); $I^2 = 48\%$						
Test for overall effect: Z = 2.83 (P = 0.005)						
Total (95% CI)		**913**		**905**	**100.0%**	**0.70 [0.60 , 0.82]**
Total events:	408		570			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 47.18$, df = 17 (P = 0.0001); $I^2 = 64\%$						
Test for overall effect: Z = 4.39 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 5.76$, df = 3 (P = 0.12), $I^2 = 47.9\%$						



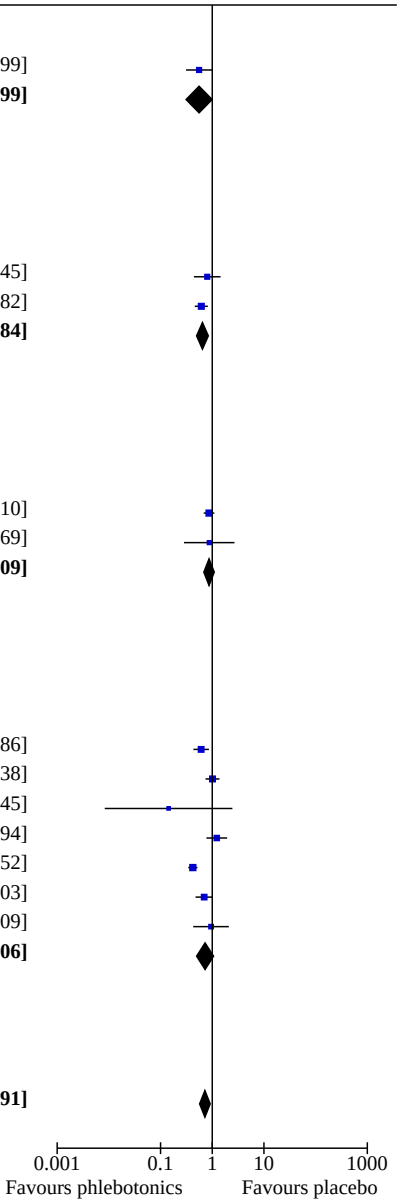
Analysis 2.8. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 8: Pain in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.8.1 Calcium dobesilate								
Rabe 2016	2.1	0.9	174	2.3	1	177	100.0%	-0.21 [-0.42 , 0.00]
Subtotal (95% CI)			**174**			**177**	**100.0%**	**-0.21 [-0.42 , 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.96 (P = 0.05)								
2.8.2 Diosmine, Hidrosmine								
Gilly 1994	0.6	0.87	76	0.9	0.86	74	24.6%	-0.35 [-0.67 , -0.02]
Planchon 1990	0.6	0.72	52	0.9	0.72	52	18.3%	-0.41 [-0.80 , -0.02]
Rabe 2015	34	24	296	37	25	296	57.1%	-0.12 [-0.28 , 0.04]
Subtotal (95% CI)			**424**			**422**	**100.0%**	**-0.23 [-0.41 , -0.05]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.83$, df = 2 (P = 0.24); $I^2 = 29\%$								
Test for overall effect: Z = 2.46 (P = 0.01)								
2.8.3 Rutosides								
Cloarec 1996	0.9	0.8	53	1.8	0.8	51	59.0%	-1.12 [-1.53 , -0.70]
Parrado 1999	0.04	0.19	30	0.35	0.56	30	41.0%	-0.73 [-1.26 , -0.21]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**-0.96 [-1.33 , -0.59]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.28$, df = 1 (P = 0.26); $I^2 = 22\%$								
Test for overall effect: Z = 5.06 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 13.35$, df = 2 (P = 0.001), $I^2 = 85.0\%$								



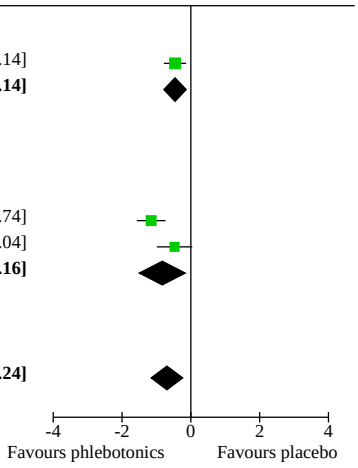
Analysis 2.9. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 9: Cramps in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Aminaftone						
Lazzarini 1982	12	48	22	49	7.4%	0.56 [0.31 , 0.99]
Subtotal (95% CI)		**48**		**49**	**7.4%**	**0.56 [0.31 , 0.99]**
Total events:	12		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.98 (P = 0.05)						
2.9.2 Calcium dobesilate						
Casley-Smith 1988	8	15	10	15	7.3%	0.80 [0.44 , 1.45]
Widmer 1990	41	114	65	111	11.3%	0.61 [0.46 , 0.82]
Subtotal (95% CI)		**129**		**126**	**18.6%**	**0.65 [0.50 , 0.84]**
Total events:	49		75			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
2.9.3 Diosmine, Hidrosmine						
Biland 1982	26	35	30	35	11.9%	0.87 [0.68 , 1.10]
Fermoso 1992	5	20	4	14	3.3%	0.88 [0.28 , 2.69]
Subtotal (95% CI)		**55**		**49**	**15.3%**	**0.87 [0.69 , 1.09]**
Total events:	31		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
2.9.4 Rutosides						
Cauwenberge 1978	25	60	41	60	10.5%	0.61 [0.43 , 0.86]
Jongste 1989	27	41	28	43	11.0%	1.01 [0.74 , 1.38]
Languillat 1988	0	10	3	10	0.7%	0.14 [0.01 , 2.45]
Pedersen 1992	17	24	11	19	8.9%	1.22 [0.77 , 1.94]
Pulvertaft 1983	120	495	95	165	12.3%	0.42 [0.34 , 0.52]
Vin 1994	21	43	21	30	10.0%	0.70 [0.47 , 1.03]
Welch 1985	10	72	11	75	5.3%	0.95 [0.43 , 2.09]
Subtotal (95% CI)		**745**		**402**	**58.7%**	**0.73 [0.50 , 1.06]**
Total events:	220		210			
Heterogeneity: Tau² = 0.18; Chi² = 34.68, df = 6 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**977**		**626**	**100.0%**	**0.72 [0.57 , 0.91]**
Total events:	312		341			
Heterogeneity: Tau² = 0.11; Chi² = 42.77, df = 11 (P < 0.0001); I² = 74%						
Test for overall effect: Z = 2.73 (P = 0.006)						
Test for subgroup differences: Chi² = 3.75, df = 3 (P = 0.29), I² = 20.1%						



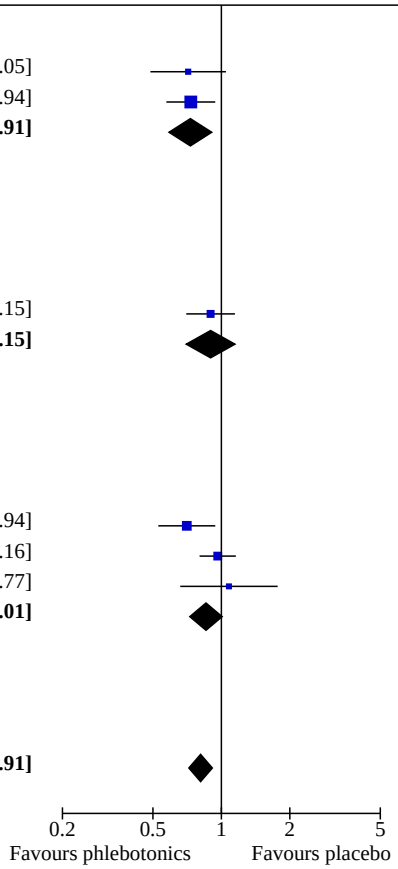
Analysis 2.10. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 10: Cramps in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.10.1 Diosmine, Hidrosmine								
Gilly 1994	0.3	0.87	76	0.7	0.86	74	37.4%	-0.46 [-0.78 , -0.14]
Subtotal (95% CI)			**76**			**74**	**37.4%**	**-0.46 [-0.78 , -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.78 (P = 0.005)								
2.10.2 Rutosides								
Cloarec 1996	0.6	0.7	53	1.6	1	51	33.4%	-1.15 [-1.57 , -0.74]
Parrado 1999	0.04	0.19	30	0.19	0.4	30	29.2%	-0.47 [-0.99 , 0.04]
Subtotal (95% CI)			**83**			**81**	**62.6%**	**-0.83 [-1.50 , -0.16]**
Heterogeneity: Tau² = 0.18; Chi² = 4.08, df = 1 (P = 0.04); I² = 75%								
Test for overall effect: Z = 2.44 (P = 0.01)								
Total (95% CI)			**159**			**155**	**100.0%**	**-0.70 [-1.15 , -0.24]**
Heterogeneity: Tau² = 0.12; Chi² = 7.36, df = 2 (P = 0.03); I² = 73%								
Test for overall effect: Z = 2.98 (P = 0.003)								
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%								



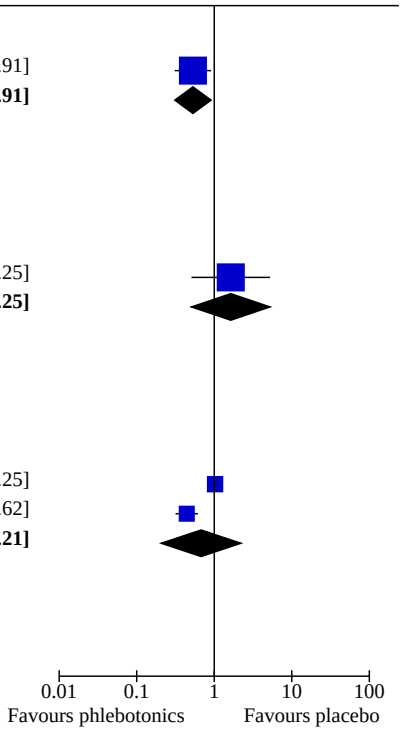
Analysis 2.11. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 11: Restless legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 Calcium dobesilate						
Casley-Smith 1988	10	15	14	15	6.8%	0.71 [0.49 , 1.05]
Widmer 1990	52	114	69	111	34.1%	0.73 [0.57 , 0.94]
Subtotal (95% CI)		**129**		**126**	**40.9%**	**0.73 [0.59 , 0.91]**
Total events:	62		83			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.85 (P = 0.004)						
2.11.2 Diosmine, Hidrosmine						
Biland 1982	26	35	29	35	14.1%	0.90 [0.70 , 1.15]
Subtotal (95% CI)		**35**		**35**	**14.1%**	**0.90 [0.70 , 1.15]**
Total events:	26		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
2.11.3 Rutosides						
Cauwenberge 1978	31	60	44	60	21.4%	0.70 [0.53 , 0.94]
Jongste 1989	34	41	37	43	17.6%	0.96 [0.80 , 1.16]
Pedersen 1992	15	24	11	19	6.0%	1.08 [0.66 , 1.77]
Subtotal (95% CI)		**125**		**122**	**45.0%**	**0.86 [0.73 , 1.01]**
Total events:	80		92			
Heterogeneity: Chi² = 4.21, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Total (95% CI)		**289**		**283**	**100.0%**	**0.81 [0.72 , 0.91]**
Total events:	168		204			
Heterogeneity: Chi² = 7.31, df = 5 (P = 0.20); I² = 32%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
Test for subgroup differences: Chi² = 1.85, df = 2 (P = 0.40), I² = 0%						



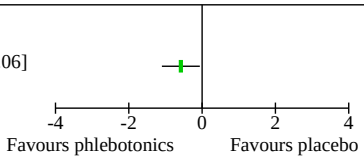
Analysis 2.12. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 12: Itching in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 Aminaftone						
Lazzarini 1982	13	48	25	49	100.0%	0.53 [0.31 , 0.91]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.53 [0.31 , 0.91]**
Total events:	13		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
2.12.2 Diosmine, Hidrosmine						
Fermoso 1992	7	20	3	14	100.0%	1.63 [0.51 , 5.25]
Subtotal (95% CI)		**20**		**14**	**100.0%**	**1.63 [0.51 , 5.25]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
2.12.3 Rutosides						
Pedersen 1992	22	24	17	19	50.6%	1.02 [0.84 , 1.25]
Vanscheidt 2002a	31	114	72	117	49.4%	0.44 [0.32 , 0.62]
Subtotal (95% CI)		**138**		**136**	**100.0%**	**0.68 [0.21 , 2.21]**
Total events:	53		89			
Heterogeneity: Tau² = 0.71; Chi² = 37.65, df = 1 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 0.65 (P = 0.52)						



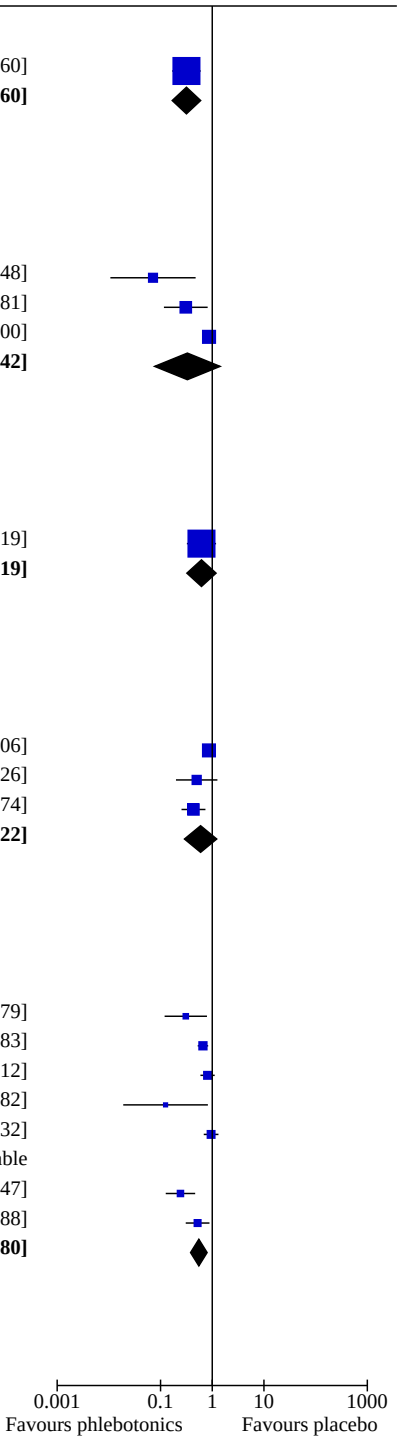
Analysis 2.13. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 13: Itching in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Std. Mean Difference IV, Fixed, 95% CI
2.13.1 Rutosides							
Parrado 1999	0.14	0.36	30	0.42	0.57	30	-0.58 [-1.10 , -0.06]



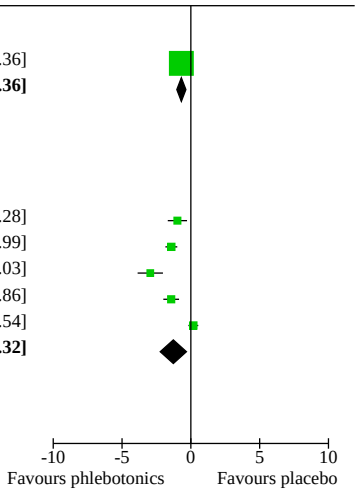
Analysis 2.14. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 14: Heaviness in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 Aminaftone						
Lazzarini 1982	9	48	29	49	100.0%	0.32 [0.17 , 0.60]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.32 [0.17 , 0.60]**
Total events:	9		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.56 (P = 0.0004)						
2.14.2 Calcium dobesilate						
Casley-Smith 1988	1	15	14	15	24.2%	0.07 [0.01 , 0.48]
Hachen 1982	4	25	13	25	34.8%	0.31 [0.12 , 0.81]
Widmer 1990	81	114	91	111	41.0%	0.87 [0.75 , 1.00]
Subtotal (95% CI)		**154**		**151**	**100.0%**	**0.33 [0.08 , 1.42]**
Total events:	86		118			
Heterogeneity: Tau² = 1.34; Chi² = 15.42, df = 2 (P = 0.0004); I² = 87%						
Test for overall effect: Z = 1.49 (P = 0.14)						
2.14.3 Centella asiatica						
Pointel 1986	9	30	16	33	100.0%	0.62 [0.32 , 1.19]
Subtotal (95% CI)		**30**		**33**	**100.0%**	**0.62 [0.32 , 1.19]**
Total events:	9		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
2.14.4 Diosmine, Hidrosmine						
Dominguez 1992	24	30	25	27	40.8%	0.86 [0.70 , 1.06]
Fermoso 1992	5	20	7	14	24.9%	0.50 [0.20 , 1.26]
Planchon 1990	13	55	30	55	34.3%	0.43 [0.25 , 0.74]
Subtotal (95% CI)		**105**		**96**	**100.0%**	**0.60 [0.29 , 1.22]**
Total events:	42		62			
Heterogeneity: Tau² = 0.32; Chi² = 11.89, df = 2 (P = 0.003); I² = 83%						
Test for overall effect: Z = 1.42 (P = 0.16)						
2.14.5 Rutosides						
Cauwenberge 1972	4	21	13	21	9.1%	0.31 [0.12 , 0.79]
Cauwenberge 1978	35	60	53	60	20.7%	0.66 [0.52 , 0.83]
Jongste 1989	24	41	31	43	19.3%	0.81 [0.59 , 1.12]
Languillat 1988	1	10	8	10	3.3%	0.13 [0.02 , 0.82]
Pedersen 1992	18	24	15	19	19.1%	0.95 [0.68 , 1.32]
Vanscheidt 2002a	0	1	0	1		Not estimable
Vin 1994	8	43	23	30	13.1%	0.24 [0.13 , 0.47]
Welch 1985	15	72	30	75	15.4%	0.52 [0.31 , 0.88]
Subtotal (95% CI)		**272**		**259**	**100.0%**	**0.55 [0.38 , 0.80]**
Total events:	105		173			
Heterogeneity: Tau² = 0.16; Chi² = 25.75, df = 6 (P = 0.0002); I² = 77%						
Test for overall effect: Z = 3.18 (P = 0.001)						



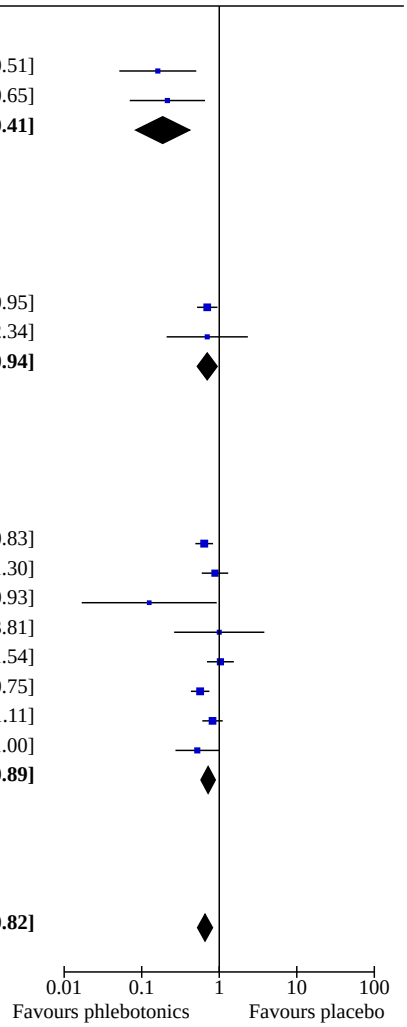
Analysis 2.15. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 15: Heaviness in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.15.1 Diosmine, Hidrosmine								
Gilly 1994	0.7	0.87	76	1.3	0.86	74	100.0%	-0.69 [-1.02 , -0.36]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.69 [-1.02 , -0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.10 (P < 0.0001)								
2.15.2 Rutosides								
Alterkamper 1987	1.8	0.5	16	2.3	0.5	20	19.5%	-0.98 [-1.68 , -0.28]
Cloarec 1996	1.2	0.7	53	2.2	0.7	51	20.9%	-1.42 [-1.85 , -0.99]
Diebschlag 1994	1.9	0.6	20	4.2	0.9	20	18.1%	-2.95 [-3.87 , -2.03]
Parrado 1999	0.14	0.45	30	0.77	0.42	30	20.2%	-1.43 [-2.00 , -0.86]
Unkauf 1996	27	28	64	22	27	56	21.2%	0.18 [-0.18 , 0.54]
Subtotal (95% CI)			**183**			**177**	**100.0%**	**-1.27 [-2.22 , -0.32]**
Heterogeneity: Tau² = 1.08; Chi² = 62.22, df = 4 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 2.62 (P = 0.009)								



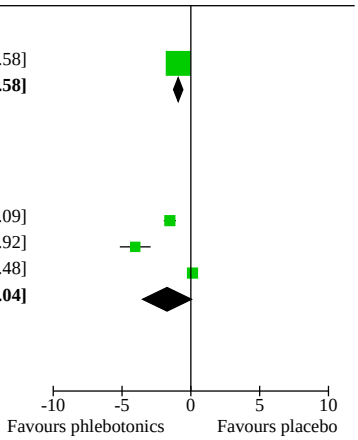
Analysis 2.16. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 16: Swelling in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.16.1 Calcium dobesilate						
Casley-Smith 1988	2	15	15	15	3.1%	0.16 [0.05 , 0.51]
Hachen 1982	3	25	14	25	3.2%	0.21 [0.07 , 0.65]
Subtotal (95% CI)		**40**		**40**	**6.3%**	**0.19 [0.08 , 0.41]**
Total events:	5		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
2.16.2 Diosmine, Hidrosmine						
Biland 1982	21	35	30	35	13.8%	0.70 [0.52 , 0.95]
Fermoso 1992	4	20	4	14	2.8%	0.70 [0.21 , 2.34]
Subtotal (95% CI)		**55**		**49**	**16.7%**	**0.70 [0.52 , 0.94]**
Total events:	25		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.38 (P = 0.02)						
2.16.3 Rutosides						
Cauwenberge 1978	32	60	50	60	14.8%	0.64 [0.49 , 0.83]
Jongste 1989	21	41	25	43	11.7%	0.88 [0.60 , 1.30]
Kriner 1985	1	25	8	25	1.1%	0.13 [0.02 , 0.93]
Languillat 1988	3	10	3	10	2.4%	1.00 [0.26 , 3.81]
Pedersen 1992	17	24	13	19	11.6%	1.04 [0.69 , 1.54]
Vanscheidt 2002a	42	114	76	117	14.5%	0.57 [0.43 , 0.75]
Vin 1994	27	43	23	30	13.8%	0.82 [0.60 , 1.11]
Welch 1985	11	72	22	75	7.1%	0.52 [0.27 , 1.00]
Subtotal (95% CI)		**389**		**379**	**77.0%**	**0.72 [0.58 , 0.89]**
Total events:	154		220			
Heterogeneity: Tau² = 0.04; Chi² = 13.50, df = 7 (P = 0.06); I² = 48%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Total (95% CI)		**484**		**468**	**100.0%**	**0.66 [0.53 , 0.82]**
Total events:	184		283			
Heterogeneity: Tau² = 0.07; Chi² = 25.87, df = 11 (P = 0.007); I² = 57%						
Test for overall effect: Z = 3.76 (P = 0.0002)						
Test for subgroup differences: Chi² = 10.36, df = 2 (P = 0.006), I² = 80.7%						



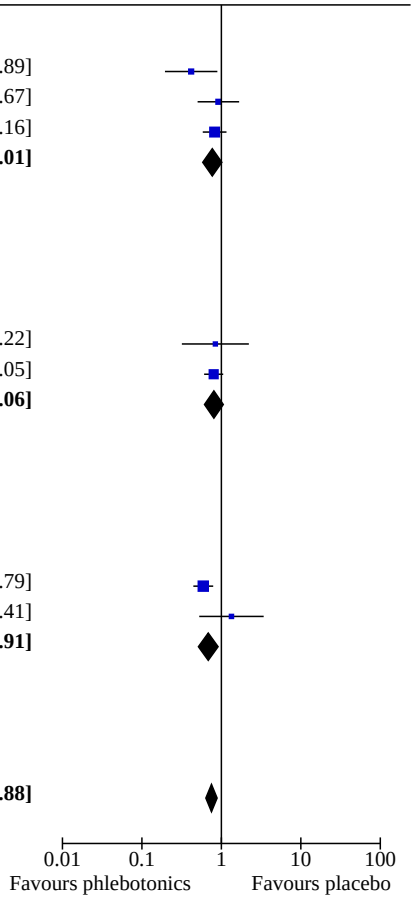
Analysis 2.17. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 17: Swelling in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.17.1 Diosmine, Hidrosmine								
Gilly 1994	0.5	0.87	76	1.3	0.86	74	100.0%	-0.92 [-1.26 , -0.58]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.92 [-1.26 , -0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.35 (P < 0.00001)								
2.17.2 Rutosides								
Cloarec 1996	1	0.6	53	2	0.7	51	34.5%	-1.52 [-1.96 , -1.09]
Diebschlag 1994	0.5	0.6	20	3.9	1	20	30.9%	-4.04 [-5.16 , -2.92]
Unkauf 1996	23	24	64	20	26	56	34.7%	0.12 [-0.24 , 0.48]
Subtotal (95% CI)			**137**			**127**	**100.0%**	**-1.73 [-3.50 , 0.04]**
Heterogeneity: Tau² = 2.32; Chi² = 67.70, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.91 (P = 0.06)								



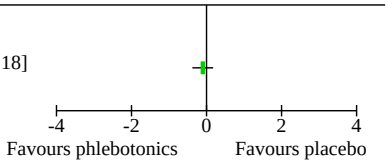
Analysis 2.18. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 18: Paraesthesias in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.18.1 Calcium dobesilate						
Casley-Smith 1988	5	15	12	15	7.0%	0.42 [0.20 , 0.89]
Hachen 1982	11	25	12	25	7.0%	0.92 [0.50 , 1.67]
Widmer 1990	38	114	45	111	26.6%	0.82 [0.58 , 1.16]
Subtotal (95% CI)		**154**		**151**	**40.6%**	**0.77 [0.58 , 1.01]**
Total events:	54		69			
Heterogeneity: Chi² = 2.98, df = 2 (P = 0.23); I² = 33%						
Test for overall effect: Z = 1.87 (P = 0.06)						
2.18.2 Diosmine, Hidrosmine						
Fermoso 1992	6	20	5	14	3.4%	0.84 [0.32 , 2.22]
Planchon 1990	32	55	40	55	23.3%	0.80 [0.61 , 1.05]
Subtotal (95% CI)		**75**		**69**	**26.8%**	**0.81 [0.61 , 1.06]**
Total events:	38		45			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
2.18.3 Rutosides						
Cauwenberge 1978	29	60	49	60	28.6%	0.59 [0.44 , 0.79]
Welch 1985	9	72	7	75	4.0%	1.34 [0.53 , 3.41]
Subtotal (95% CI)		**132**		**135**	**32.6%**	**0.68 [0.51 , 0.91]**
Total events:	38		56			
Heterogeneity: Chi² = 2.96, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 2.62 (P = 0.009)						
Total (95% CI)		**361**		**355**	**100.0%**	**0.75 [0.64 , 0.88]**
Total events:	130		170			
Heterogeneity: Chi² = 7.36, df = 6 (P = 0.29); I² = 18%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
Test for subgroup differences: Chi² = 0.70, df = 2 (P = 0.71), I² = 0%						



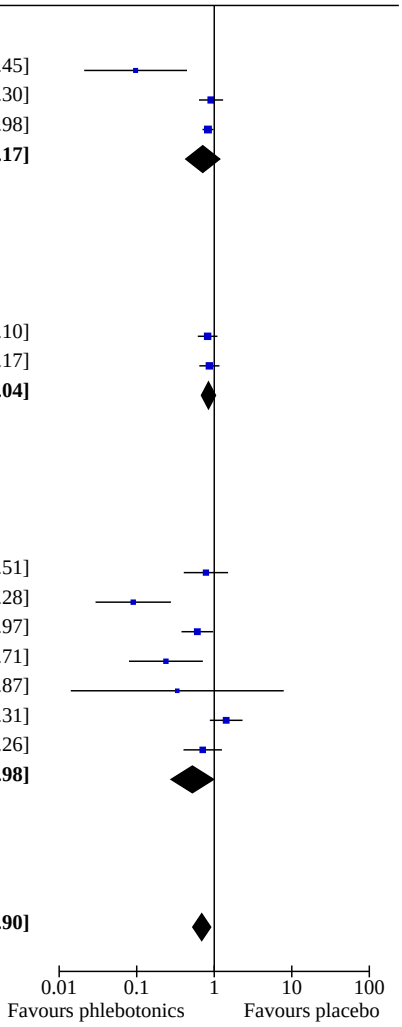
Analysis 2.19. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 19: Paraesthesias in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
2.19.1 Diosmine, Hidrosmine							
Gilly 1994	0.4	0.87	76	0.5	0.86	74	-0.10 [-0.38 , 0.18]



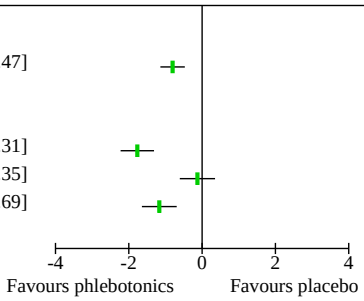
Analysis 2.20. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 20: Participant satisfaction (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.20.1 Calcium dobesilate						
Casley-Smith 1988	1	15	15	15	2.5%	0.10 [0.02 , 0.45]
Labs 2004	40	133	42	127	11.8%	0.91 [0.64 , 1.30]
Widmer 1990	75	114	88	111	14.3%	0.83 [0.71 , 0.98]
Subtotal (95% CI)		**262**		**253**	**28.6%**	**0.71 [0.43 , 1.17]**
Total events:	116		145			
Heterogeneity: Tau² = 0.13; Chi² = 8.55, df = 2 (P = 0.01); I² = 77%						
Test for overall effect: Z = 1.33 (P = 0.18)						
2.20.2 Diosmine, Hidrosmine						
Biland 1982	23	35	28	35	12.8%	0.82 [0.61 , 1.10]
Danielsson 2002	30	51	34	50	12.7%	0.87 [0.64 , 1.17]
Subtotal (95% CI)		**86**		**85**	**25.4%**	**0.84 [0.68 , 1.04]**
Total events:	53		62			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
2.20.3 Rutosides						
Burnand 1989	9	24	12	25	7.8%	0.78 [0.40 , 1.51]
Cloarec 1996	3	53	32	51	4.1%	0.09 [0.03 , 0.28]
Jongste 1989	15	41	26	43	10.2%	0.61 [0.38 , 0.97]
Languillat 1988	2	10	10	10	4.2%	0.24 [0.08 , 0.71]
Parrado 1999	0	30	1	30	0.7%	0.33 [0.01 , 7.87]
Pedersen 1992	18	24	10	19	10.0%	1.43 [0.88 , 2.31]
Welch 1985	15	72	22	75	8.9%	0.71 [0.40 , 1.26]
Subtotal (95% CI)		**254**		**253**	**45.9%**	**0.52 [0.28 , 0.98]**
Total events:	62		113			
Heterogeneity: Tau² = 0.50; Chi² = 29.80, df = 6 (P < 0.0001); I² = 80%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**602**		**591**	**100.0%**	**0.69 [0.53 , 0.90]**
Total events:	231		320			
Heterogeneity: Tau² = 0.12; Chi² = 40.59, df = 11 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 2.75 (P = 0.006)						
Test for subgroup differences: Chi² = 2.20, df = 2 (P = 0.33), I² = 8.9%						



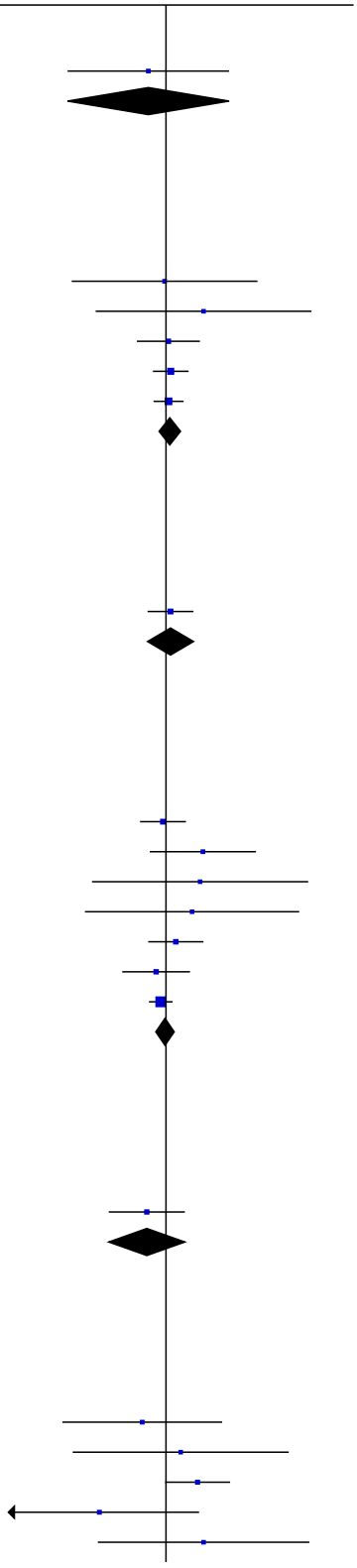
Analysis 2.21. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 21: Participant satisfaction (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Std. Mean Difference IV, Random, 95% CI
2.21.1 Diosmine, Hidrosmine							
Gilly 1994	0.5	0.87	76	1.2	0.86	74	-0.81 [-1.14 , -0.47]
2.21.2 Rutosides							
Cloarec 1996	4.3	2.5	53	9.5	3.3	51	-1.77 [-2.22 , -1.31]
Ihme 1996	2.2	1.4	36	2.4	1.7	31	-0.13 [-0.61 , 0.35]
Kiesewetter 1997	1.5	1.1	37	3	1.4	44	-1.17 [-1.64 , -0.69]



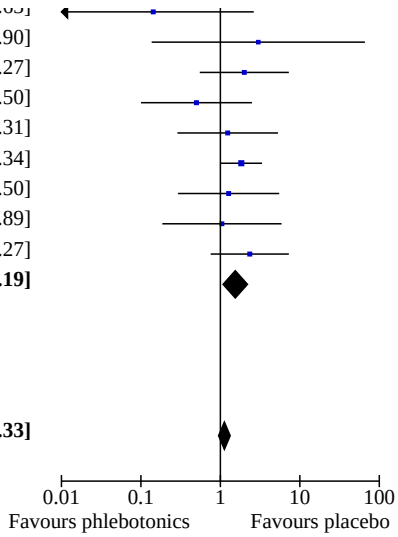
Analysis 2.22. Comparison 2: Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 22: Adverse events

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.22.1 Aminaftone						
Belczak 2014	1	36	2	43	0.8%	0.60 [0.06 , 6.32]
Subtotal (95% CI)		**36**		**43**	**0.8%**	**0.60 [0.06 , 6.32]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
2.22.2 Calcium dobesilate						
Flota-Cervera 2008	1	25	1	24	0.5%	0.96 [0.06 , 14.50]
Hachen 1982	1	25	0	25	0.2%	3.00 [0.13 , 70.30]
Labs 2004	9	133	8	127	3.8%	1.07 [0.43 , 2.70]
Rabe 2016	26	174	23	177	10.6%	1.15 [0.68 , 1.94]
Widmer 1990	31	114	28	111	13.1%	1.08 [0.69 , 1.67]
Subtotal (95% CI)		**471**		**464**	**28.2%**	**1.12 [0.82 , 1.53]**
Total events:	68		60			
Heterogeneity: Chi² = 0.43, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
2.22.3 Centella asiatica						
Pointel 1986	19	61	9	33	5.4%	1.14 [0.58 , 2.23]
Subtotal (95% CI)		**61**		**33**	**5.4%**	**1.14 [0.58 , 2.23]**
Total events:	19		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
2.22.4 Diosmine, Hidrosmine						
Biland 1982	11	35	12	35	5.6%	0.92 [0.47 , 1.79]
Danielsson 2002	6	51	2	50	0.9%	2.94 [0.62 , 13.89]
Dominguez 1992	1	30	0	27	0.2%	2.71 [0.12 , 63.84]
Fermoso 1992	1	20	0	14	0.3%	2.14 [0.09 , 49.08]
Gilly 1994	12	80	9	80	4.2%	1.33 [0.60 , 2.99]
Planchon 1990	6	55	8	55	3.7%	0.75 [0.28 , 2.02]
Rabe 2015	49	296	57	296	26.4%	0.86 [0.61 , 1.22]
Subtotal (95% CI)		**567**		**557**	**41.3%**	**0.97 [0.74 , 1.27]**
Total events:	86		88			
Heterogeneity: Chi² = 3.97, df = 6 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
2.22.5 Grape seed extract						
Thebaut 1985	4	35	8	40	3.5%	0.57 [0.19 , 1.74]
Subtotal (95% CI)		**35**		**40**	**3.5%**	**0.57 [0.19 , 1.74]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
2.22.6 Rutosides						
Alterkamper 1987	1	25	2	25	0.9%	0.50 [0.05 , 5.17]
Diebschlag 1994	1	40	0	20	0.3%	1.54 [0.07 , 36.11]
Jongste 1989	12	41	5	43	2.3%	2.52 [0.97 , 6.52]
Kriner 1985	0	25	3	25	1.6%	0.14 [0.01 , 2.63]
Languillat 1988	1	10	0	10	0.2%	3.00 [0.14 , 65.90]



Analysis 2.22. (Continued)

Languillat 1988	1	10	0	10	0.2%	3.00 [0.14 , 65.90]
Parrado 1999	6	30	3	30	1.4%	2.00 [0.55 , 7.27]
Serralde 1990	2	26	4	26	1.9%	0.50 [0.10 , 2.50]
Unkauf 1996	4	69	3	64	1.4%	1.24 [0.29 , 5.31]
Vanscheidt 2002a	25	114	14	117	6.4%	1.83 [1.00 , 3.34]
Vanscheidt 2002b	4	85	3	81	1.4%	1.27 [0.29 , 5.50]
Vin 1994	3	43	2	30	1.1%	1.05 [0.19 , 5.89]
Welch 1985	9	72	4	75	1.8%	2.34 [0.76 , 7.27]
Subtotal (95% CI)		**580**		**546**	**20.8%**	**1.54 [1.08 , 2.19]**
Total events:	68		43			
Heterogeneity: Chi² = 7.89, df = 11 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Total (95% CI)		**1750**		**1683**	**100.0%**	**1.12 [0.95 , 1.33]**
Total events:	246		210			
Heterogeneity: Chi² = 19.07, df = 26 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.17)						
Test for subgroup differences: Chi² = 5.89, df = 5 (P = 0.32), I² = 15.1%						



Comparison 3. Sensitivity analysis of published studies only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Oedema in the lower legs (dichotomous variable)	12	1088	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.63, 0.78]
3.1.1 Aminaftone	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
3.1.2 Calcium dobesilate	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
3.1.3 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
3.1.4 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]
3.1.5 Rutosides	6	497	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.81]
3.2 Ankle perimeter circumference (mm)	13	1796	Mean Difference (IV, Random, 95% CI)	-3.61 [-6.77, -0.45]
3.2.1 Calcium dobesilate	5	1122	Mean Difference (IV, Random, 95% CI)	-3.17 [-8.37, 2.02]
3.2.2 Diosmine, Hidrosmine	3	286	Mean Difference (IV, Random, 95% CI)	-5.98 [-7.78, -4.18]
3.2.3 Rutosides	5	388	Mean Difference (IV, Random, 95% CI)	-2.18 [-9.79, 5.43]
3.3 Volume of the leg (mL)	10	1392	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.44, -0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 Aminaftone	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.61, 0.28]
3.3.2 Calcium dobesilate	4	826	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.51, -0.24]
3.3.3 Rutosides	5	487	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.47, -0.11]
3.4 Quality of life	5	1639	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.22, 0.10]
3.4.1 Aminaftone	1	79	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.10, -0.19]
3.4.2 Calcium dobesilate	3	968	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.16, 0.10]
3.4.3 Diosmine, Hidrosmine	1	592	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.12, 0.20]
3.5 Patients with ulcer (dichotomous variable)	5	392	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.15]
3.5.1 Aminaftone	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.18]
3.5.2 Diosmine, Hidrosmine	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.03]
3.5.3 Rutosides	2	159	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.84, 1.87]
3.6 Trophic disorders (dichotomous variable)	6	705	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.95]
3.6.1 Aminaftone	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.44]
3.6.2 Diosmine, Hidrosmine	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
3.6.3 Rutosides	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.25]
3.7 Pain in the lower legs (dichotomous variable)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.7.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.79]
3.7.2 Calcium dobesilate	5	705	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.82]
3.7.3 Diosmine, Hidrosmine	4	271	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.08]
3.7.4 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.48, 0.91]
3.7.5 Rutosides	8	1318	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.84]
3.8 Pain in the lower legs (continuous variable)	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8.1 Calcium dobesilate	4	1075	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.34, 0.05]
3.8.2 Diosmine, Hidrosmine	3	846	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.41, -0.05]
3.8.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.39 [-2.09, -0.69]
3.8.4 Rutosides	3	219	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.23, -0.19]
3.9 Cramps in the lower legs (dichotomous variable)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.9.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.99]
3.9.2 Calcium dobesilate	2	255	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
3.9.3 Diosmine, Hidrosmine	3	214	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
3.9.4 Rutosides	6	1060	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.45, 1.05]
3.10 Cramps in the lower legs (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.10.1 Calcium dobesilate	1	415	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.29, 0.09]
3.10.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.78, -0.14]
3.10.3 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.16]
3.11 Restless legs (dichotomous variable)	7	652	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
3.11.1 Calcium dobesilate	2	255	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.59, 0.91]
3.11.2 Diosmine, Hidrosmine	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.15]
3.11.3 Rutosides	4	327	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
3.12 Itching in the lower legs (dichotomous variable)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.12.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
3.12.2 Diosmine, Hidrosmine	1	34	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.25]
3.12.3 Rutosides	2	274	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.21, 2.21]
3.13 Itching in the lower legs (continuous variable)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

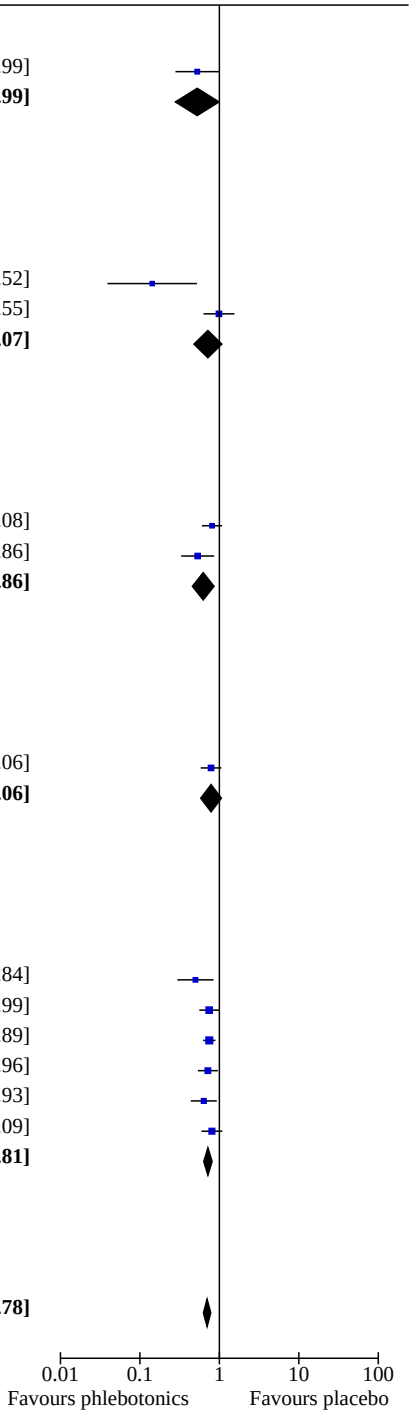
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.13.1 Calccium dobesilate	1	416	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.11, 0.28]
3.13.2 Rutosides	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.10, -0.06]
3.14 Heaviness in the lower legs (dichotomous variable)	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.14.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.60]
3.14.2 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
3.14.3 Centella asiatica	1	63	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
3.14.4 Diosmine, Hidrosmine	4	241	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.05]
3.14.5 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
3.14.6 Rutosides	7	1253	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.49, 0.78]
3.15 Heaviness in the lower legs (continuous variable)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.15.1 Calcium dobesilate	2	483	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.23, 0.13]
3.15.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.02, -0.36]
3.15.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.50 [-2.21, -0.79]
3.15.4 Rutosides	5	360	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-2.22, -0.32]
3.16 Swelling in the lower legs (dichotomous variable)	12	905	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.81]
3.16.1 Calcium dobesilate	2	80	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.41]
3.16.2 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
3.16.3 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.02]
3.16.4 Rutosides	7	681	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.49, 0.91]
3.17 Swelling in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.17.1 Calcium dobesilate	1	417	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.24, 0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.17.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-1.15 [-1.50, -0.80]
3.17.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.65 [-2.38, -0.92]
3.17.4 Rutosides	3	264	Std. Mean Difference (IV, Random, 95% CI)	-1.73 [-3.50, 0.04]
3.18 Paraesthesias in the lower legs (dichotomous variable)	8	1309	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.84]
3.18.1 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
3.18.2 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.05]
3.18.3 Rutosides	3	860	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.35, 0.66]
3.19 Paraesthesias in the lower legs (continuous variable)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.19.1 Diosmine, Hidrosmine	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.20 Participant satisfaction (dichotomous variable)	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.20.1 Calcium dobesilate	4	758	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.61, 1.19]
3.20.2 Centella asiatica	1	80	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.14, 0.57]
3.20.3 Diosmine, Hidrosmine	4	451	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.96]
3.20.4 Rutosides	6	1000	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.97]
3.21 Participant satisfaction (continuous variable)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.21.1 Calcium dobesilate	2	448	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.71, -0.33]
3.21.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.14, -0.47]
3.21.3 Rutosides	4	283	Std. Mean Difference (IV, Random, 95% CI)	-1.18 [-1.96, -0.39]
3.22 Adverse events	34	4830	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.99, 1.29]
3.22.1 Aminaftone	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.06, 6.32]
3.22.2 Calcium dobesilate	8	1824	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.00, 1.49]
3.22.3 Centella asiatica	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.58, 2.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.22.4 Diosmine, Hidrosmine	9	1429	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.19]
3.22.5 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.19, 1.74]
3.22.6 Rutosides	14	1329	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.02, 1.76]

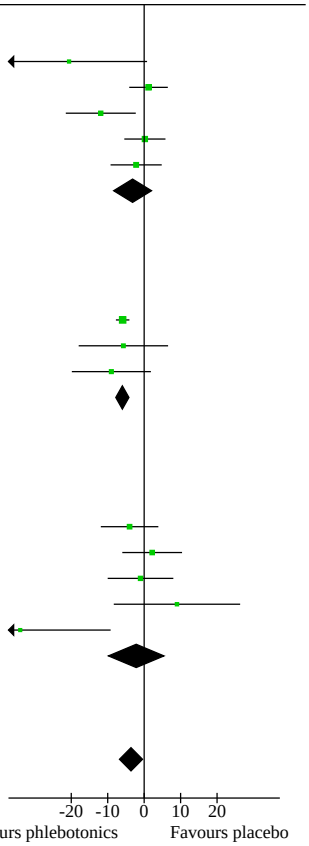
Analysis 3.1. Comparison 3: Sensitivity analysis of published studies only, Outcome 1: Oedema in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Aminaftone						
Lazzarini 1982	10	41	19	41	5.6%	0.53 [0.28 , 0.99]
Subtotal (95% CI)		**41**		**41**	**5.6%**	**0.53 [0.28 , 0.99]**
Total events:	10		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
3.1.2 Calcium dobesilate						
Casley-Smith 1988	2	15	14	15	4.1%	0.14 [0.04 , 0.52]
Labs 2004	30	133	29	127	8.8%	0.99 [0.63 , 1.55]
Subtotal (95% CI)		**148**		**142**	**12.9%**	**0.72 [0.48 , 1.07]**
Total events:	32		43			
Heterogeneity: Chi² = 7.90, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 1.62 (P = 0.11)						
3.1.3 Diosmine, Hidrosmine						
Fermoso 1992	15	20	13	14	4.5%	0.81 [0.60 , 1.08]
Planchon 1990	16	55	30	55	8.9%	0.53 [0.33 , 0.86]
Subtotal (95% CI)		**75**		**69**	**13.4%**	**0.63 [0.46 , 0.86]**
Total events:	31		43			
Heterogeneity: Chi² = 3.36, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 2.93 (P = 0.003)						
3.1.4 Grape seed extract						
Thebaut 1985	22	35	32	40	8.8%	0.79 [0.58 , 1.06]
Subtotal (95% CI)		**35**		**40**	**8.8%**	**0.79 [0.58 , 1.06]**
Total events:	22		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
3.1.5 Rutosides						
Cauwenberge 1972	9	21	18	21	5.3%	0.50 [0.30 , 0.84]
Cauwenberge 1978	32	60	43	60	12.7%	0.74 [0.56 , 0.99]
Cloarec 1996	38	53	49	51	14.7%	0.75 [0.62 , 0.89]
Ihme 1996	24	40	31	37	9.5%	0.72 [0.54 , 0.96]
Kriner 1985	14	25	22	25	6.5%	0.64 [0.44 , 0.93]
MacLennan 1994	29	52	36	52	10.6%	0.81 [0.60 , 1.09]
Subtotal (95% CI)		**251**		**246**	**59.3%**	**0.72 [0.64 , 0.81]**
Total events:	146		199			
Heterogeneity: Chi² = 3.03, df = 5 (P = 0.70); I² = 0%						
Test for overall effect: Z = 5.43 (P < 0.00001)						
Total (95% CI)		**550**		**538**	**100.0%**	**0.70 [0.63 , 0.78]**
Total events:	241		336			
Heterogeneity: Chi² = 14.89, df = 11 (P = 0.19); I² = 26%						
Test for overall effect: Z = 6.59 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.96, df = 4 (P = 0.74), I² = 0%						



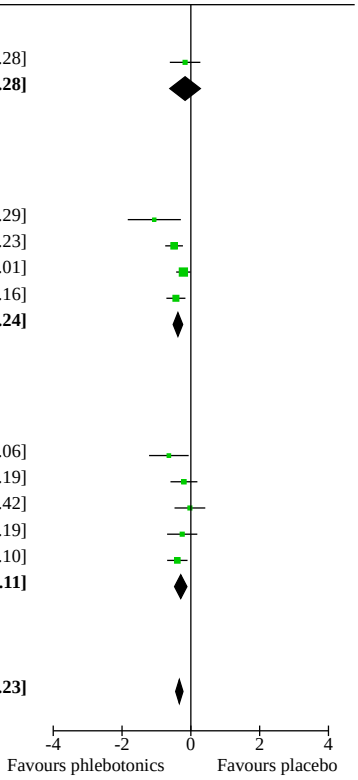
Analysis 3.2. Comparison 3: Sensitivity analysis of published studies only, Outcome 2: Ankle perimeter circumference (mm)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 Calcium dobesilate								
Flota-Cervera 2008	335.6	38.2	25	356.2	38.2	24	2.0%	-20.60 [-42.00 , 0.80]
Labs 2004	229.5	22.7	124	228.3	19.6	123	12.3%	1.20 [-4.09 , 6.49]
Martinez-Zapata 2008	254.9	43.2	193	266.8	53.9	203	6.9%	-11.90 [-21.50 , -2.30]
Rabe 2011	240.9	21.3	109	240.7	21.8	115	11.8%	0.20 [-5.44 , 5.84]
Widmer 1990	230.1	21.31	103	232.3	29.43	103	9.8%	-2.20 [-9.22 , 4.82]
Subtotal (95% CI)			**554**			**568**	**42.7%**	**-3.17 [-8.37 , 2.02]**
Heterogeneity: Tau² = 17.72; Chi² = 8.95, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 1.20 (P = 0.23)								
3.2.2 Diosmine, Hidrosmine								
Gilly 1994	-7.1	6.97	76	-1.2	4.3	74	17.7%	-5.90 [-7.75 , -4.05]
Planchon 1990	229.1	30.3	48	234.8	31	48	4.9%	-5.70 [-17.96 , 6.56]
Tsouderos 1989	239.1	20.6	20	248.1	13.7	20	5.9%	-9.00 [-19.84 , 1.84]
Subtotal (95% CI)			**144**			**142**	**28.5%**	**-5.98 [-7.78 , -4.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 6.51 (P < 0.00001)								
3.2.3 Rutosides								
Cloarec 1996	221	22	53	225	19	51	8.7%	-4.00 [-11.89 , 3.89]
Cornu-Thenard 1985	226.8	16.4	33	224.6	14	21	8.3%	2.20 [-6.00 , 10.40]
Jongste 1989	236	22	41	237	20	43	7.5%	-1.00 [-10.00 , 8.00]
MacLennan 1994	258	40	41	249	42	45	2.8%	9.00 [-8.33 , 26.33]
Parrado 1999	209	50	30	243	48	30	1.5%	-34.00 [-58.80 , -9.20]
Subtotal (95% CI)			**198**			**190**	**28.8%**	**-2.18 [-9.79 , 5.43]**
Heterogeneity: Tau² = 38.73; Chi² = 9.19, df = 4 (P = 0.06); I² = 56%								
Test for overall effect: Z = 0.56 (P = 0.57)								
Total (95% CI)			**896**			**900**	**100.0%**	**-3.61 [-6.77 , -0.45]**
Heterogeneity: Tau² = 13.78; Chi² = 25.82, df = 12 (P = 0.01); I² = 54%								
Test for overall effect: Z = 2.24 (P = 0.03)								
Test for subgroup differences: Chi² = 1.78, df = 2 (P = 0.41), I² = 0%								



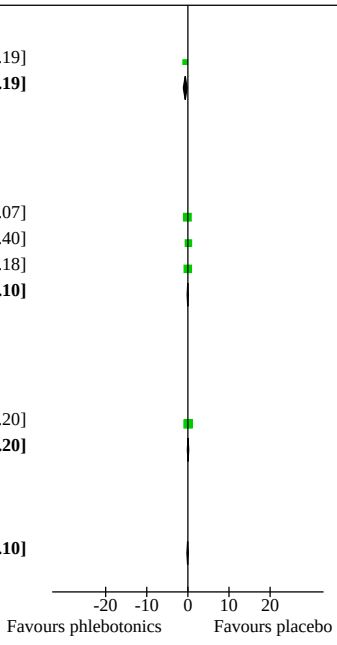
Analysis 3.3. Comparison 3: Sensitivity analysis of published studies only, Outcome 3: Volume of the leg (mL)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.3.1 Aminaftone								
Belczak 2014	3276.5	584.6	36	3391.5	751.1	43	5.7%	-0.17 [-0.61 , 0.28]
Subtotal (95% CI)			**36**			**43**	**5.7%**	**-0.17 [-0.61 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
3.3.2 Calcium dobesilate								
Casley-Smith 1988	1097	92.95	15	1205	104.57	15	1.9%	-1.06 [-1.83 , -0.29]
Rabe 2011	-64.72	111.9	120	0.76	152.9	119	17.0%	-0.49 [-0.74 , -0.23]
Rabe 2016	-25.68	127.44	174	-1.88	88.33	177	25.6%	-0.22 [-0.43 , -0.01]
Widmer 1990	-3.8	6.08	103	-1.15	6.08	103	14.7%	-0.43 [-0.71 , -0.16]
Subtotal (95% CI)			**412**			**414**	**59.2%**	**-0.38 [-0.51 , -0.24]**
Heterogeneity: Chi² = 6.14, df = 3 (P = 0.11); I² = 51%								
Test for overall effect: Z = 5.34 (P < 0.00001)								
3.3.3 Rutosides								
Burnand 1989	1098	157.74	24	1200	156.5	25	3.4%	-0.64 [-1.21 , -0.06]
Diebschlag 1994	-11.9	43.4	51	-4.4	29.2	50	7.4%	-0.20 [-0.59 , 0.19]
Ihme 1996	2073	309	40	2082	339	37	5.6%	-0.03 [-0.47 , 0.42]
Kiesewetter 1997	1992	367	37	2111	541	44	5.8%	-0.25 [-0.69 , 0.19]
Vanscheidt 2002a	-95.7	127.9	86	-44.6	131.1	93	12.8%	-0.39 [-0.69 , -0.10]
Subtotal (95% CI)			**238**			**249**	**35.1%**	**-0.29 [-0.47 , -0.11]**
Heterogeneity: Chi² = 3.43, df = 4 (P = 0.49); I² = 0%								
Test for overall effect: Z = 3.22 (P = 0.001)								
Total (95% CI)			**686**			**706**	**100.0%**	**-0.34 [-0.44 , -0.23]**
Heterogeneity: Chi² = 10.65, df = 9 (P = 0.30); I² = 15%								
Test for overall effect: Z = 6.19 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.08, df = 2 (P = 0.58), I² = 0%								



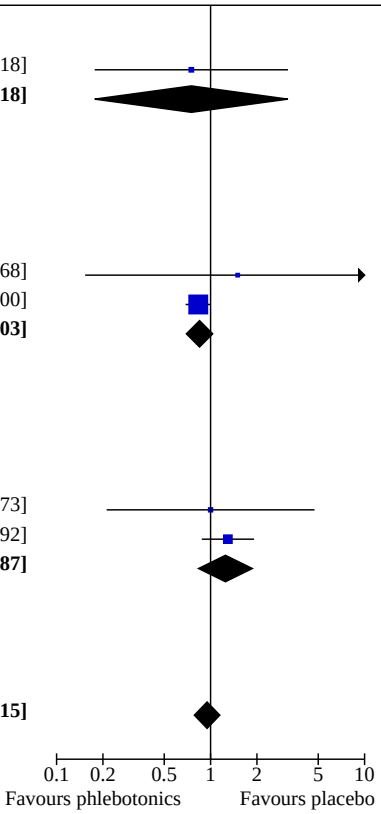
Analysis 3.4. Comparison 3: Sensitivity analysis of published studies only, Outcome 4: Quality of life

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.4.1 Aminaftone								
Belczak 2014	-15.4	17.8	36	-5.4	13.1	43	9.4%	-0.64 [-1.10 , -0.19]
Subtotal (95% CI)			**36**			**43**	**9.4%**	**-0.64 [-1.10 , -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.77 (P = 0.006)								
3.4.2 Calcium dobesilate								
Martinez-Zapata 2008	39.8	11	197	40.8	4.8	216	23.8%	-0.12 [-0.31 , 0.07]
Rabe 2011	41.2	17.7	100	39.2	12.8	104	17.7%	0.13 [-0.15 , 0.40]
Rabe 2016	39.9	14.9	174	40.3	16.4	177	22.5%	-0.03 [-0.23 , 0.18]
Subtotal (95% CI)			**471**			**497**	**64.0%**	**-0.03 [-0.16 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 2 (P = 0.35); I² = 6%								
Test for overall effect: Z = 0.48 (P = 0.63)								
3.4.3 Diosmine, Hidrosmine								
Rabe 2015	69.9	20.6	296	69.1	20.6	296	26.5%	0.04 [-0.12 , 0.20]
Subtotal (95% CI)			**296**			**296**	**26.5%**	**0.04 [-0.12 , 0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**803**			**836**	**100.0%**	**-0.06 [-0.22 , 0.10]**
Heterogeneity: Tau² = 0.02; Chi² = 9.78, df = 4 (P = 0.04); I² = 59%								
Test for overall effect: Z = 0.74 (P = 0.46)								
Test for subgroup differences: Chi² = 7.67, df = 2 (P = 0.02), I² = 73.9%								



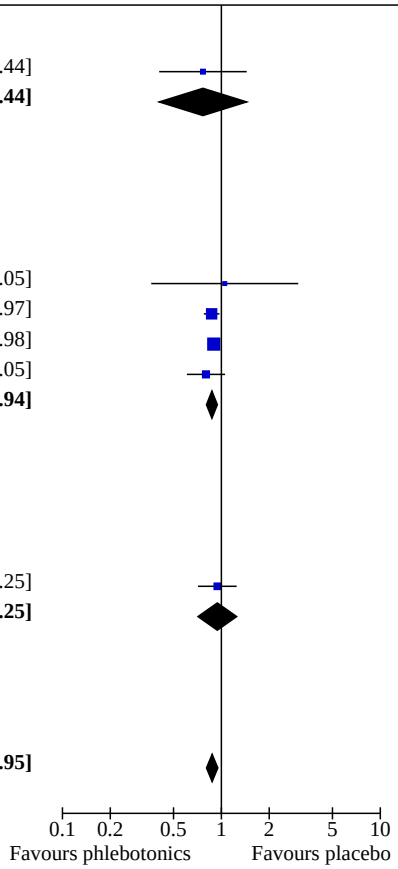
Analysis 3.5. Comparison 3: Sensitivity analysis of published studies only, Outcome 5: Patients with ulcer (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Aminaftone						
Lazzarini 1982	3	50	4	50	5.7%	0.75 [0.18 , 3.18]
Subtotal (95% CI)		**50**		**50**	**5.7%**	**0.75 [0.18 , 3.18]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
3.5.2 Diosmine, Hidrosmine						
Fermoso 1992	2	16	1	12	1.6%	1.50 [0.15 , 14.68]
Guilhou 1997	39	53	46	52	66.1%	0.83 [0.69 , 1.00]
Subtotal (95% CI)		**69**		**64**	**67.7%**	**0.85 [0.70 , 1.03]**
Total events:	41		47			
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
3.5.3 Rutosides						
MacLennan 1994	3	52	3	52	4.3%	1.00 [0.21 , 4.73]
Schultz-Ehrenburg 1993	20	27	16	28	22.3%	1.30 [0.88 , 1.92]
Subtotal (95% CI)		**79**		**80**	**26.6%**	**1.25 [0.84 , 1.87]**
Total events:	23		19			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**198**		**194**	**100.0%**	**0.95 [0.78 , 1.15]**
Total events:	67		70			
Heterogeneity: Chi² = 4.58, df = 4 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 2.95, df = 2 (P = 0.23), I² = 32.2%						



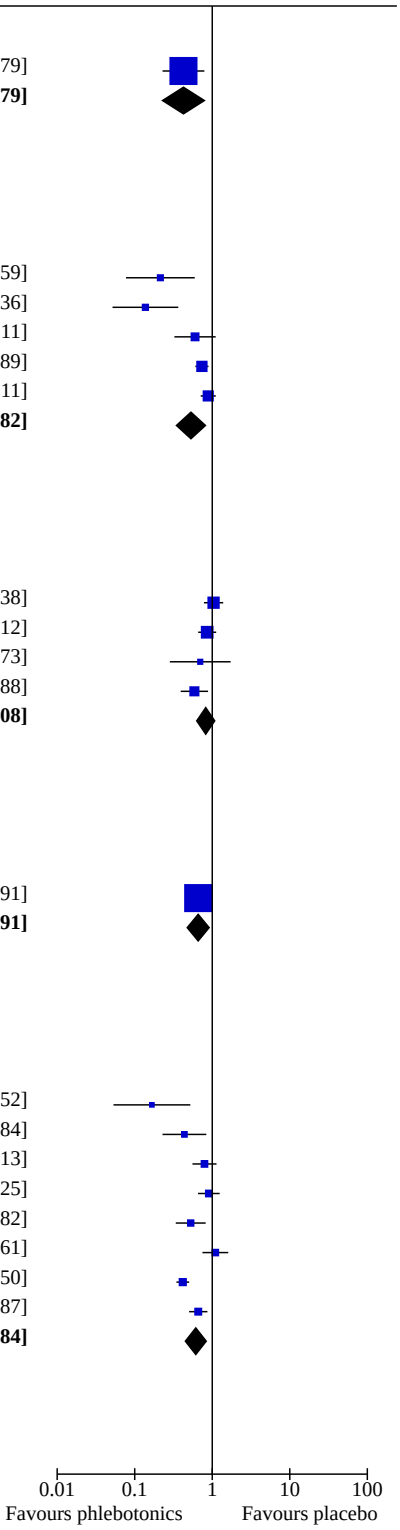
Analysis 3.6. Comparison 3: Sensitivity analysis of published studies only, Outcome 6: Trophic disorders (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Aminaftone						
Lazzarini 1982	12	48	16	49	5.9%	0.77 [0.41 , 1.44]
Subtotal (95% CI)		**48**		**49**	**5.9%**	**0.77 [0.41 , 1.44]**
Total events:	12		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
3.6.2 Diosmine, Hidrosmine						
Fermoso 1992	6	20	4	14	1.8%	1.05 [0.36 , 3.05]
Gilly 1994	66	80	76	80	28.4%	0.87 [0.78 , 0.97]
Laurent 1988	86	100	96	100	35.9%	0.90 [0.82 , 0.98]
Planchon 1990	32	55	40	55	15.0%	0.80 [0.61 , 1.05]
Subtotal (95% CI)		**255**		**249**	**81.0%**	**0.87 [0.81 , 0.94]**
Total events:	190		216			
Heterogeneity: $Chi^2 = 0.85$, df = 3 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 3.42 (P = 0.0006)						
3.6.3 Rutosides						
MacLennan 1994	33	52	35	52	13.1%	0.94 [0.71 , 1.25]
Subtotal (95% CI)		**52**		**52**	**13.1%**	**0.94 [0.71 , 1.25]**
Total events:	33		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**355**		**350**	**100.0%**	**0.87 [0.81 , 0.95]**
Total events:	235		267			
Heterogeneity: $Chi^2 = 1.25$, df = 5 (P = 0.94); $I^2 = 0\%$						
Test for overall effect: Z = 3.20 (P = 0.001)						
Test for subgroup differences: $Chi^2 = 0.45$, df = 2 (P = 0.80), $I^2 = 0\%$						



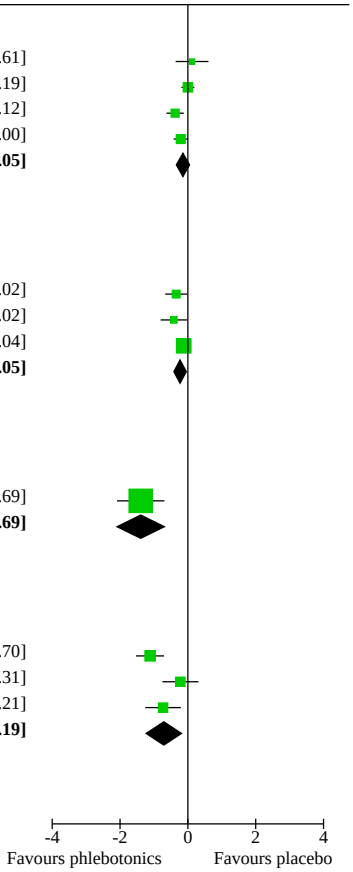
Analysis 3.7. Comparison 3: Sensitivity analysis of published studies only, Outcome 7: Pain in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Aminaftone						
Lazzarini 1982	10	48	24	49	100.0%	0.43 [0.23 , 0.79]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.43 [0.23 , 0.79]**
Total events:	10		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.70 (P = 0.007)						
3.7.2 Calcium dobesilate						
Casley-Smith 1988	3	15	14	15	11.3%	0.21 [0.08 , 0.59]
Flota-Cervera 2008	3	25	24	24	12.0%	0.14 [0.05 , 0.36]
Hachen 1982	9	25	15	25	19.0%	0.60 [0.33 , 1.11]
Rabe 2016	81	174	112	177	29.1%	0.74 [0.61 , 0.89]
Widmer 1990	62	114	68	111	28.6%	0.89 [0.71 , 1.11]
Subtotal (95% CI)		**353**		**352**	**100.0%**	**0.53 [0.35 , 0.82]**
Total events:	158		233			
Heterogeneity: Tau² = 0.16; Chi² = 21.62, df = 4 (P = 0.0002); I² = 82%						
Test for overall effect: Z = 2.88 (P = 0.004)						
3.7.3 Diosmine, Hidrosmine						
Biland 1982	26	35	25	35	33.4%	1.04 [0.78 , 1.38]
Dominguez 1992	22	30	23	27	35.1%	0.86 [0.66 , 1.12]
Fermoso 1992	6	20	6	14	7.5%	0.70 [0.28 , 1.73]
Planchon 1990	20	55	34	55	24.0%	0.59 [0.39 , 0.88]
Subtotal (95% CI)		**140**		**131**	**100.0%**	**0.82 [0.63 , 1.08]**
Total events:	74		88			
Heterogeneity: Tau² = 0.03; Chi² = 5.91, df = 3 (P = 0.12); I² = 49%						
Test for overall effect: Z = 1.42 (P = 0.16)						
3.7.4 French maritime pine bark extract						
Arcangeli 2000	13	20	20	20	100.0%	0.66 [0.48 , 0.91]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.66 [0.48 , 0.91]**
Total events:	13		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
3.7.5 Rutosides						
Balmer 1980	3	40	18	40	5.1%	0.17 [0.05 , 0.52]
Cauwenberge 1972	7	21	16	21	9.7%	0.44 [0.23 , 0.84]
Cauwenberge 1978	27	60	34	60	13.8%	0.79 [0.56 , 1.13]
Jongste 1989	25	41	29	43	14.3%	0.90 [0.66 , 1.25]
Klüken 1971	13	30	23	28	12.6%	0.53 [0.34 , 0.82]
Pedersen 1992	18	24	13	19	13.5%	1.10 [0.75 , 1.61]
Pulvertaft 1983	130	495	104	165	16.0%	0.42 [0.35 , 0.50]
Vanscheidt 2002a	45	114	70	117	15.0%	0.66 [0.50 , 0.87]
Subtotal (95% CI)		**825**		**493**	**100.0%**	**0.61 [0.45 , 0.84]**
Total events:	268		307			
Heterogeneity: Tau² = 0.15; Chi² = 39.85, df = 7 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 3.09 (P = 0.002)						
Test for subgroup differences: Chi² = 5.76, df = 4 (P = 0.22), I² = 30.6%						



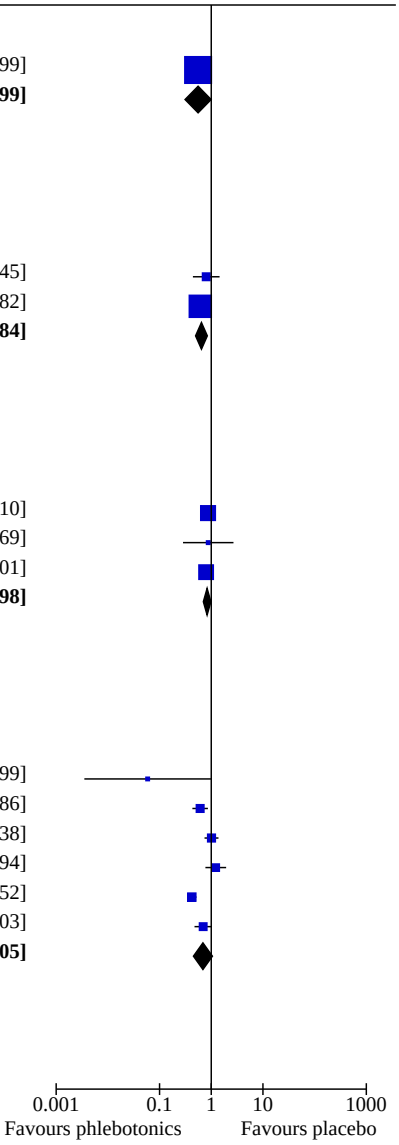
Analysis 3.8. Comparison 3: Sensitivity analysis of published studies only, Outcome 8: Pain in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.8.1 Calcium dobesilate								
Marinello 2002	33.42	27.85	35	29.9	28.77	31	12.0%	0.12 [-0.36 , 0.61]
Martinez-Zapata 2008	37.8	25.8	203	37.8	27.4	216	32.1%	0.00 [-0.19 , 0.19]
Rabe 2011	-10.2	26.2	120	-0.92	22.9	119	25.8%	-0.38 [-0.63 , -0.12]
Rabe 2016	2.1	0.9	174	2.3	1	177	30.2%	-0.21 [-0.42 , 0.00]
Subtotal (95% CI)			**532**			**543**	**100.0%**	**-0.15 [-0.34 , 0.05]**
Heterogeneity: Tau² = 0.02; Chi² = 6.87, df = 3 (P = 0.08); I² = 56%								
Test for overall effect: Z = 1.47 (P = 0.14)								
3.8.2 Diosmine, Hidrosmine								
Gilly 1994	0.6	0.87	76	0.9	0.86	74	24.6%	-0.35 [-0.67 , -0.02]
Planchon 1990	0.6	0.72	52	0.9	0.72	52	18.3%	-0.41 [-0.80 , -0.02]
Rabe 2015	34	24	296	37	25	296	57.1%	-0.12 [-0.28 , 0.04]
Subtotal (95% CI)			**424**			**422**	**100.0%**	**-0.23 [-0.41 , -0.05]**
Heterogeneity: Tau² = 0.01; Chi² = 2.83, df = 2 (P = 0.24); I² = 29%								
Test for overall effect: Z = 2.46 (P = 0.01)								
3.8.3 French maritime pine bark extract								
Arcangeli 2000	0.58	0.48	20	1.17	0.34	20	100.0%	-1.39 [-2.09 , -0.69]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.39 [-2.09 , -0.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.90 (P < 0.0001)								
3.8.4 Rutosides								
Cloarec 1996	0.9	0.8	53	1.8	0.8	51	36.4%	-1.12 [-1.53 , -0.70]
Cornu-Thenard 1985	0.8	1.03	30	1.04	1.14	25	31.6%	-0.22 [-0.75 , 0.31]
Parrado 1999	0.04	0.19	30	0.35	0.56	30	32.0%	-0.73 [-1.26 , -0.21]
Subtotal (95% CI)			**113**			**106**	**100.0%**	**-0.71 [-1.23 , -0.19]**
Heterogeneity: Tau² = 0.15; Chi² = 6.82, df = 2 (P = 0.03); I² = 71%								
Test for overall effect: Z = 2.67 (P = 0.008)								
Test for subgroup differences: Chi² = 14.37, df = 3 (P = 0.002), I² = 79.1%								



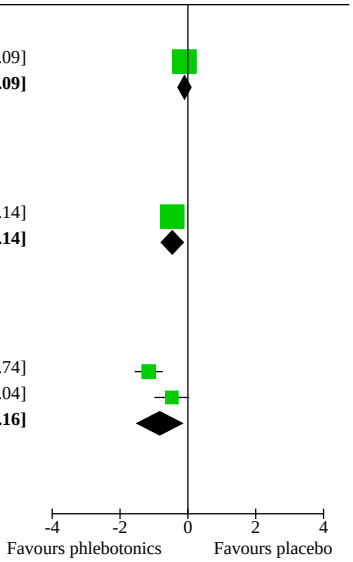
Analysis 3.9. Comparison 3: Sensitivity analysis of published studies only, Outcome 9: Cramps in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Aminaftone						
Lazzarini 1982	12	48	22	49	100.0%	0.56 [0.31 , 0.99]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.56 [0.31 , 0.99]**
Total events:	12		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.98 (P = 0.05)						
3.9.2 Calcium dobesilate						
Casley-Smith 1988	8	15	10	15	19.4%	0.80 [0.44 , 1.45]
Widmer 1990	41	114	65	111	80.6%	0.61 [0.46 , 0.82]
Subtotal (95% CI)		**129**		**126**	**100.0%**	**0.65 [0.50 , 0.84]**
Total events:	49		75			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
3.9.3 Diosmine, Hidrosmine						
Biland 1982	26	35	30	35	49.4%	0.87 [0.68 , 1.10]
Fermoso 1992	5	20	4	14	2.2%	0.88 [0.28 , 2.69]
Planchon 1990	35	55	44	55	48.4%	0.80 [0.63 , 1.01]
Subtotal (95% CI)		**110**		**104**	**100.0%**	**0.83 [0.70 , 0.98]**
Total events:	66		78			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.17 (P = 0.03)						
3.9.4 Rutosides						
Balmer 1980	0	40	8	40	2.0%	0.06 [0.00 , 0.99]
Cauwenberge 1978	25	60	41	60	19.6%	0.61 [0.43 , 0.86]
Jongste 1989	27	41	28	43	20.1%	1.01 [0.74 , 1.38]
Pedersen 1992	17	24	11	19	17.8%	1.22 [0.77 , 1.94]
Pulvertaft 1983	120	495	95	165	21.5%	0.42 [0.34 , 0.52]
Vin 1994	21	43	21	30	19.0%	0.70 [0.47 , 1.03]
Subtotal (95% CI)		**703**		**357**	**100.0%**	**0.69 [0.45 , 1.05]**
Total events:	210		204			
Heterogeneity: Tau² = 0.21; Chi² = 35.97, df = 5 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 3.88, df = 3 (P = 0.27), I² = 22.7%						



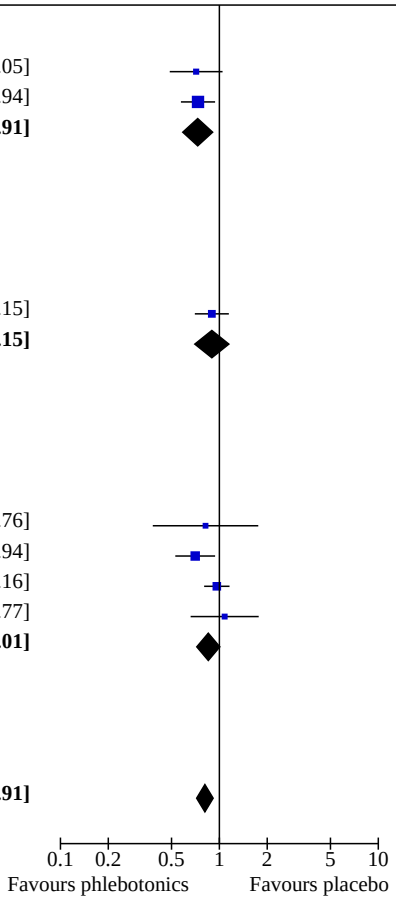
Analysis 3.10. Comparison 3: Sensitivity analysis of published studies only, Outcome 10: Cramps in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.10.1 Calcium dobesilate								
Martinez-Zapata 2008	24.1	27.1	204	26.9	28.7	211	100.0%	-0.10 [-0.29 , 0.09]
Subtotal (95% CI)			**204**			**211**	**100.0%**	**-0.10 [-0.29 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.02 (P = 0.31)								
3.10.2 Diosmine, Hidrosmine								
Gilly 1994	0.3	0.87	76	0.7	0.86	74	100.0%	-0.46 [-0.78 , -0.14]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.46 [-0.78 , -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.78 (P = 0.005)								
3.10.3 Rutosides								
Cloarec 1996	0.6	0.7	53	1.6	1	51	52.5%	-1.15 [-1.57 , -0.74]
Parrado 1999	0.04	0.19	30	0.19	0.4	30	47.5%	-0.47 [-0.99 , 0.04]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**-0.83 [-1.50 , -0.16]**
Heterogeneity: Tau² = 0.18; Chi² = 4.08, df = 1 (P = 0.04); I² = 75%								
Test for overall effect: Z = 2.44 (P = 0.01)								



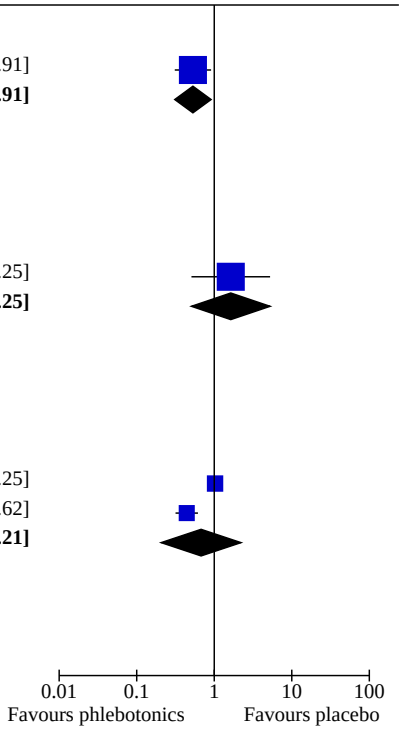
Analysis 3.11. Comparison 3: Sensitivity analysis of published studies only, Outcome 11: Restless legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.11.1 Calcium dobesilate						
Casley-Smith 1988	10	15	14	15	6.5%	0.71 [0.49 , 1.05]
Widmer 1990	52	114	69	111	32.3%	0.73 [0.57 , 0.94]
Subtotal (95% CI)		**129**		**126**	**38.8%**	**0.73 [0.59 , 0.91]**
Total events:	62		83			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.85 (P = 0.004)						
3.11.2 Diosmine, Hidrosmine						
Biland 1982	26	35	29	35	13.4%	0.90 [0.70 , 1.15]
Subtotal (95% CI)		**35**		**35**	**13.4%**	**0.90 [0.70 , 1.15]**
Total events:	26		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
3.11.3 Rutosides						
Balmer 1980	9	40	11	40	5.1%	0.82 [0.38 , 1.76]
Cauwenberge 1978	31	60	44	60	20.3%	0.70 [0.53 , 0.94]
Jongste 1989	34	41	37	43	16.7%	0.96 [0.80 , 1.16]
Pedersen 1992	15	24	11	19	5.7%	1.08 [0.66 , 1.77]
Subtotal (95% CI)		**165**		**162**	**47.8%**	**0.85 [0.72 , 1.01]**
Total events:	89		103			
Heterogeneity: Chi² = 4.30, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Total (95% CI)		**329**		**323**	**100.0%**	**0.81 [0.72 , 0.91]**
Total events:	177		215			
Heterogeneity: Chi² = 7.29, df = 6 (P = 0.29); I² = 18%						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Test for subgroup differences: Chi² = 1.79, df = 2 (P = 0.41), I² = 0%						



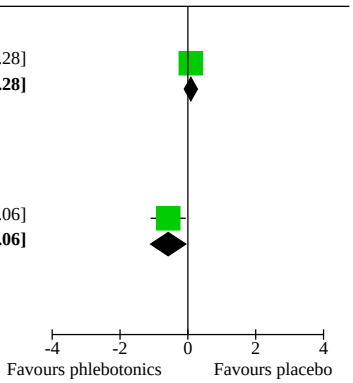
Analysis 3.12. Comparison 3: Sensitivity analysis of published studies only, Outcome 12: Itching in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.12.1 Aminaftone						
Lazzarini 1982	13	48	25	49	100.0%	0.53 [0.31 , 0.91]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.53 [0.31 , 0.91]**
Total events:	13		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
3.12.2 Diosmine, Hidrosmine						
Fermoso 1992	7	20	3	14	100.0%	1.63 [0.51 , 5.25]
Subtotal (95% CI)		**20**		**14**	**100.0%**	**1.63 [0.51 , 5.25]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.12.3 Rutosides						
Pedersen 1992	22	24	17	19	50.6%	1.02 [0.84 , 1.25]
Vanscheidt 2002a	31	114	72	117	49.4%	0.44 [0.32 , 0.62]
Subtotal (95% CI)		**138**		**136**	**100.0%**	**0.68 [0.21 , 2.21]**
Total events:	53		89			
Heterogeneity: Tau² = 0.71; Chi² = 37.65, df = 1 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 0.65 (P = 0.52)						



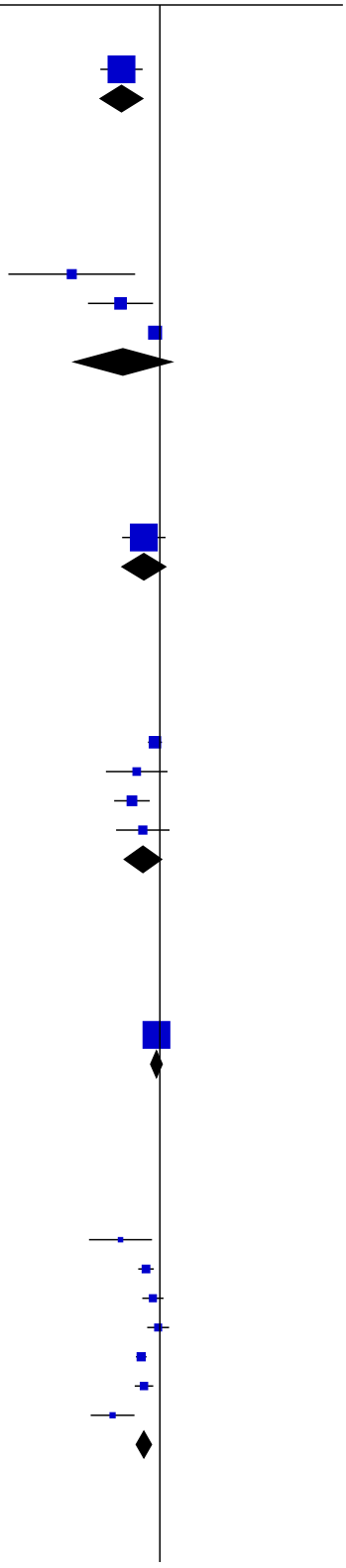
Analysis 3.13. Comparison 3: Sensitivity analysis of published studies only, Outcome 13: Itching in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.13.1 Calccium dobesilate								
Martinez-Zapata 2008	35.9	68.6	204	31.3	30.4	212	100.0%	0.09 [-0.11 , 0.28]
Subtotal (95% CI)			**204**			**212**	**100.0%**	**0.09 [-0.11 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.89 (P = 0.37)								
3.13.2 Rutosides								
Parrado 1999	0.14	0.36	30	0.42	0.57	30	100.0%	-0.58 [-1.10 , -0.06]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.58 [-1.10 , -0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.20 (P = 0.03)								



Analysis 3.14. Comparison 3: Sensitivity analysis of published studies only, Outcome 14: Heaviness in the lower legs (dichotomous variable)

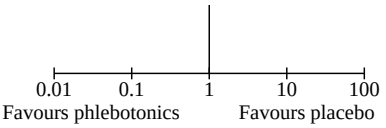
Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 Aminaftone						
Lazzarini 1982	9	48	29	49	100.0%	0.32 [0.17 , 0.60]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**0.32 [0.17 , 0.60]**
Total events:	9		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.56 (P = 0.0004)						
3.14.2 Calcium dobesilate						
Casley-Smith 1988	1	15	14	15	24.2%	0.07 [0.01 , 0.48]
Hachen 1982	4	25	13	25	34.8%	0.31 [0.12 , 0.81]
Widmer 1990	81	114	91	111	41.0%	0.87 [0.75 , 1.00]
Subtotal (95% CI)		**154**		**151**	**100.0%**	**0.33 [0.08 , 1.42]**
Total events:	86		118			
Heterogeneity: Tau² = 1.34; Chi² = 15.42, df = 2 (P = 0.0004); I² = 87%						
Test for overall effect: Z = 1.49 (P = 0.14)						
3.14.3 Centella asiatica						
Pointel 1986	9	30	16	33	100.0%	0.62 [0.32 , 1.19]
Subtotal (95% CI)		**30**		**33**	**100.0%**	**0.62 [0.32 , 1.19]**
Total events:	9		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
3.14.4 Diosmine, Hidrosmine						
Dominguez 1992	24	30	25	27	34.3%	0.86 [0.70 , 1.06]
Fermoso 1992	5	20	7	14	18.1%	0.50 [0.20 , 1.26]
Planchon 1990	13	55	30	55	27.0%	0.43 [0.25 , 0.74]
Tsouderos 1989	6	20	10	20	20.6%	0.60 [0.27 , 1.34]
Subtotal (95% CI)		**125**		**116**	**100.0%**	**0.60 [0.35 , 1.05]**
Total events:	48		72			
Heterogeneity: Tau² = 0.22; Chi² = 12.08, df = 3 (P = 0.007); I² = 75%						
Test for overall effect: Z = 1.79 (P = 0.07)						
3.14.5 French maritime pine bark extract						
Arcangeli 2000	18	20	20	20	100.0%	0.90 [0.76 , 1.07]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.90 [0.76 , 1.07]**
Total events:	18		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
3.14.6 Rutosides						
Cauwenberge 1972	4	21	13	21	4.6%	0.31 [0.12 , 0.79]
Cauwenberge 1978	35	60	53	60	18.5%	0.66 [0.52 , 0.83]
Jongste 1989	24	41	31	43	15.8%	0.81 [0.59 , 1.12]
Pedersen 1992	18	24	15	19	15.5%	0.95 [0.68 , 1.32]
Pulvertaft 1983	187	495	109	165	20.7%	0.57 [0.49 , 0.67]
Vanscheidt 2002a	43	114	71	117	17.1%	0.62 [0.47 , 0.82]
Vin 1994	8	43	23	30	7.8%	0.24 [0.13 , 0.47]
Subtotal (95% CI)		**798**		**455**	**100.0%**	**0.62 [0.49 , 0.78]**
Total events:	319		315			
Heterogeneity: Tau² = 0.06; Chi² = 21.55, df = 6 (P = 0.001); I² = 72%						
Test for overall effect: Z = 4.16 (P < 0.0001)						



Analysis 3.14. (Continued)

Test for overall effect: Z = 4.16 (P < 0.0001)

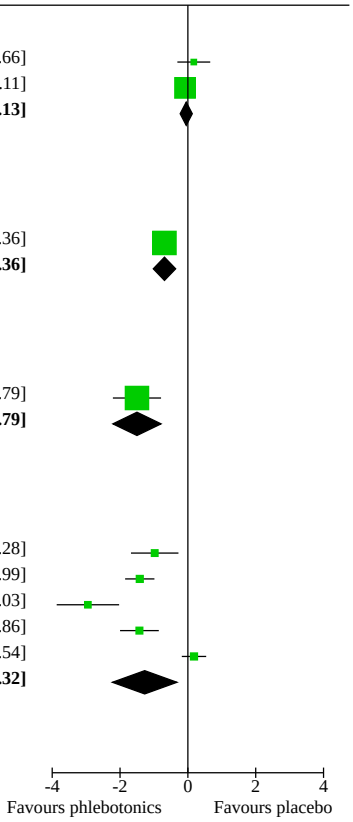
Test for subgroup differences: Chi² = 16.47, df = 5 (P = 0.006), I² = 69.6%



Analysis 3.15. Comparison 3: Sensitivity analysis of published studies only, Outcome 15: Heaviness in the lower legs (continuous variable)

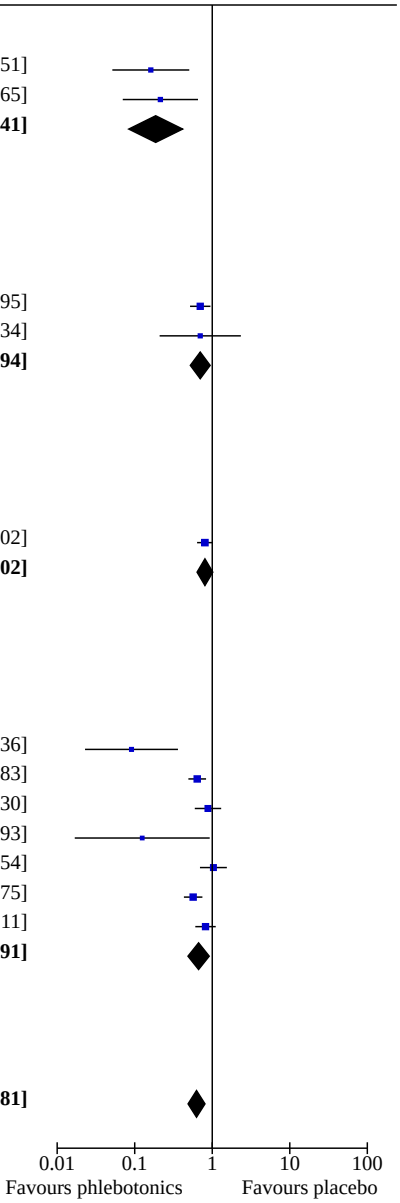
Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.15.1 Calcium dobesilate								
Marinello 2002	36.22	28.61	35	31.61	22.82	31	13.6%	0.17 [-0.31 , 0.66]
Martinez-Zapata 2008	44.5	28.4	203	46.9	28.8	214	86.4%	-0.08 [-0.28 , 0.11]
Subtotal (95% CI)			**238**			**245**	**100.0%**	**-0.05 [-0.23 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%								
Test for overall effect: Z = 0.53 (P = 0.59)								
3.15.2 Diosmine, Hidrosmine								
Gilly 1994	0.7	0.87	76	1.3	0.86	74	100.0%	-0.69 [-1.02 , -0.36]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.69 [-1.02 , -0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.10 (P < 0.0001)								
3.15.3 French maritime pine bark extract								
Arcangeli 2000	0.94	0.55	20	1.67	0.39	20	100.0%	-1.50 [-2.21 , -0.79]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.50 [-2.21 , -0.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.14 (P < 0.0001)								
3.15.4 Rutosides								
Alterkamper 1987	1.8	0.5	16	2.3	0.5	20	19.5%	-0.98 [-1.68 , -0.28]
Cloarec 1996	1.2	0.7	53	2.2	0.7	51	20.9%	-1.42 [-1.85 , -0.99]
Diebschlag 1994	1.9	0.6	20	4.2	0.9	20	18.1%	-2.95 [-3.87 , -2.03]
Parrado 1999	0.14	0.45	30	0.77	0.42	30	20.2%	-1.43 [-2.00 , -0.86]
Unkauf 1996	27	28	64	22	27	56	21.2%	0.18 [-0.18 , 0.54]
Subtotal (95% CI)			**183**			**177**	**100.0%**	**-1.27 [-2.22 , -0.32]**
Heterogeneity: Tau² = 1.08; Chi² = 62.22, df = 4 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 2.62 (P = 0.009)								

Test for subgroup differences: Chi² = 27.93, df = 3 (P < 0.00001), I² = 89.3%



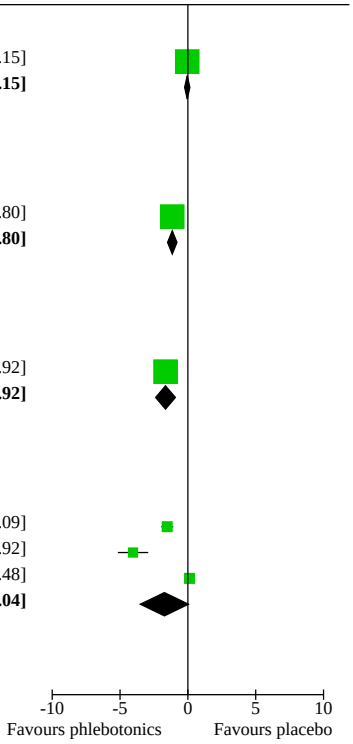
Analysis 3.16. Comparison 3: Sensitivity analysis of published studies only, Outcome 16: Swelling in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.16.1 Calcium dobesilate						
Casley-Smith 1988	2	15	15	15	3.6%	0.16 [0.05 , 0.51]
Hachen 1982	3	25	14	25	3.8%	0.21 [0.07 , 0.65]
Subtotal (95% CI)		**40**		**40**	**7.4%**	**0.19 [0.08 , 0.41]**
Total events:	5		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
3.16.2 Diosmine, Hidrosmine						
Biland 1982	21	35	30	35	12.3%	0.70 [0.52 , 0.95]
Fermoso 1992	4	20	4	14	3.3%	0.70 [0.21 , 2.34]
Subtotal (95% CI)		**55**		**49**	**15.6%**	**0.70 [0.52 , 0.94]**
Total events:	25		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.38 (P = 0.02)						
3.16.3 French maritime pine bark extract						
Arcangeli 2000	16	20	20	20	13.2%	0.80 [0.64 , 1.02]
Subtotal (95% CI)		**20**		**20**	**13.2%**	**0.80 [0.64 , 1.02]**
Total events:	16		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
3.16.4 Rutosides						
Balmer 1980	2	40	22	40	2.7%	0.09 [0.02 , 0.36]
Cauwenberge 1978	32	60	50	60	12.9%	0.64 [0.49 , 0.83]
Jongste 1989	21	41	25	43	11.0%	0.88 [0.60 , 1.30]
Kriner 1985	1	25	8	25	1.4%	0.13 [0.02 , 0.93]
Pedersen 1992	17	24	13	19	10.8%	1.04 [0.69 , 1.54]
Vanscheidt 2002a	42	114	76	117	12.7%	0.57 [0.43 , 0.75]
Vin 1994	27	43	23	30	12.3%	0.82 [0.60 , 1.11]
Subtotal (95% CI)		**347**		**334**	**63.7%**	**0.67 [0.49 , 0.91]**
Total events:	142		217			
Heterogeneity: Tau² = 0.11; Chi² = 23.31, df = 6 (P = 0.0007); I² = 74%						
Test for overall effect: Z = 2.53 (P = 0.01)						
Total (95% CI)		**462**		**443**	**100.0%**	**0.63 [0.49 , 0.81]**
Total events:	188		300			
Heterogeneity: Tau² = 0.11; Chi² = 40.87, df = 11 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Test for subgroup differences: Chi² = 12.01, df = 3 (P = 0.007), I² = 75.0%						



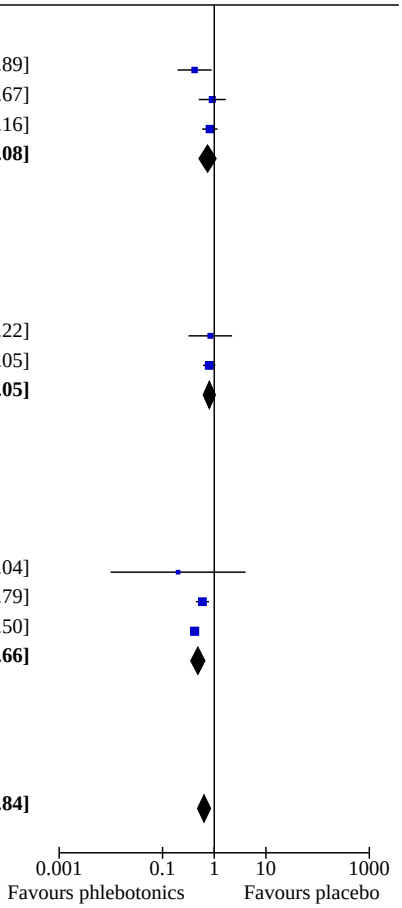
Analysis 3.17. Comparison 3: Sensitivity analysis of published studies only, Outcome 17: Swelling in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.17.1 Calcium dobesilate								
Martinez-Zapata 2008	36.2	28.6	203	37.5	27.8	214	100.0%	-0.05 [-0.24 , 0.15]
Subtotal (95% CI)			**203**			**214**	**100.0%**	**-0.05 [-0.24 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
3.17.2 Diosmine, Hidrosmine								
Gilly 1994	0.5	0.87	76	1.5	0.86	74	100.0%	-1.15 [-1.50 , -0.80]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-1.15 [-1.50 , -0.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.51 (P < 0.00001)								
3.17.3 French maritime pine bark extract								
Arcangeli 2000	0.6	0.53	20	1.39	0.4	20	100.0%	-1.65 [-2.38 , -0.92]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.65 [-2.38 , -0.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.44 (P < 0.00001)								
3.17.4 Rutosides								
Cloarec 1996	1	0.6	53	2	0.7	51	34.5%	-1.52 [-1.96 , -1.09]
Diebschlag 1994	0.5	0.6	20	3.9	1	20	30.9%	-4.04 [-5.16 , -2.92]
Unkauf 1996	23	24	64	20	26	56	34.7%	0.12 [-0.24 , 0.48]
Subtotal (95% CI)			**137**			**127**	**100.0%**	**-1.73 [-3.50 , 0.04]**
Heterogeneity: Tau² = 2.32; Chi² = 67.70, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.91 (P = 0.06)								



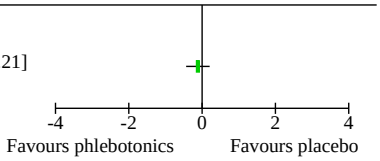
Analysis 3.18. Comparison 3: Sensitivity analysis of published studies only, Outcome 18: Paraesthesias in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.18.1 Calcium dobesilate						
Casley-Smith 1988	5	15	12	15	8.6%	0.42 [0.20 , 0.89]
Hachen 1982	11	25	12	25	11.1%	0.92 [0.50 , 1.67]
Widmer 1990	38	114	45	111	16.7%	0.82 [0.58 , 1.16]
Subtotal (95% CI)		**154**		**151**	**36.4%**	**0.74 [0.51 , 1.08]**
Total events:	54		69			
Heterogeneity: Tau² = 0.04; Chi² = 2.98, df = 2 (P = 0.23); I² = 33%						
Test for overall effect: Z = 1.56 (P = 0.12)						
3.18.2 Diosmine, Hidrosmine						
Fermoso 1992	6	20	5	14	6.2%	0.84 [0.32 , 2.22]
Planchon 1990	32	55	40	55	18.3%	0.80 [0.61 , 1.05]
Subtotal (95% CI)		**75**		**69**	**24.5%**	**0.80 [0.62 , 1.05]**
Total events:	38		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.11)						
3.18.3 Rutosides						
Balmer 1980	0	40	2	40	0.9%	0.20 [0.01 , 4.04]
Cauwenberge 1978	29	60	49	60	18.1%	0.59 [0.44 , 0.79]
Pulvertaft 1983	130	495	104	165	20.2%	0.42 [0.35 , 0.50]
Subtotal (95% CI)		**595**		**265**	**39.1%**	**0.48 [0.35 , 0.66]**
Total events:	159		155			
Heterogeneity: Tau² = 0.04; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Total (95% CI)		**824**		**485**	**100.0%**	**0.63 [0.48 , 0.84]**
Total events:	251		269			
Heterogeneity: Tau² = 0.09; Chi² = 24.98, df = 7 (P = 0.0008); I² = 72%						
Test for overall effect: Z = 3.15 (P = 0.002)						
Test for subgroup differences: Chi² = 6.45, df = 2 (P = 0.04), I² = 69.0%						



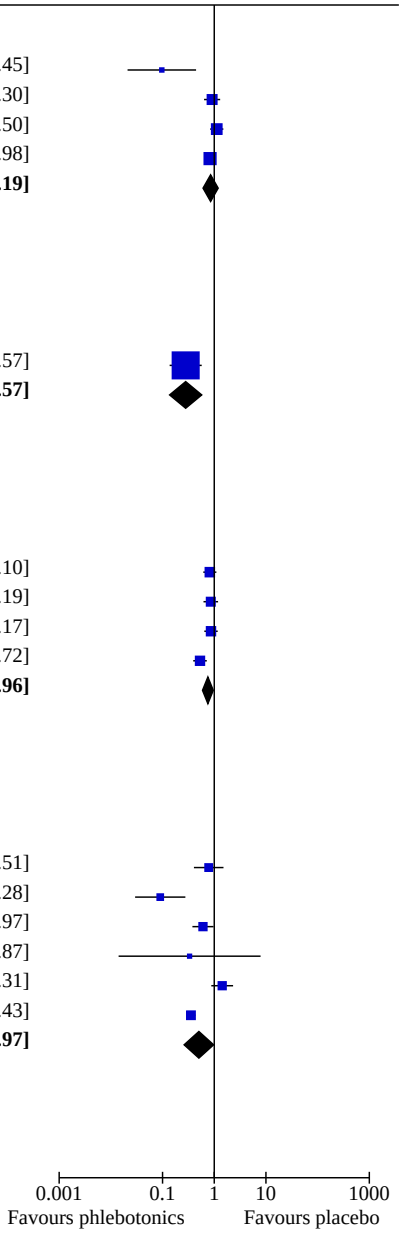
Analysis 3.19. Comparison 3: Sensitivity analysis of published studies only, Outcome 19: Paraesthesias in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Std. Mean Difference IV, Fixed, 95% CI
3.19.1 Diosmine, Hidrosmine							
Gilly 1994	0.4	0.87	76	0.5	0.86	74	-0.12 [-0.44 , 0.21]



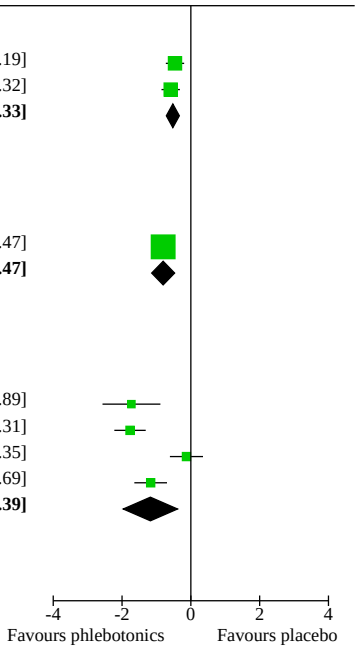
Analysis 3.20. Comparison 3: Sensitivity analysis of published studies only, Outcome 20: Participant satisfaction (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.20.1 Calcium dobesilate						
Casley-Smith 1988	1	15	15	15	4.3%	0.10 [0.02 , 0.45]
Labs 2004	40	133	42	127	27.8%	0.91 [0.64 , 1.30]
Rabe 2011	55	123	48	120	30.9%	1.12 [0.83 , 1.50]
Widmer 1990	75	114	88	111	37.0%	0.83 [0.71 , 0.98]
Subtotal (95% CI)		**385**		**373**	**100.0%**	**0.85 [0.61 , 1.19]**
Total events:	171		193			
Heterogeneity: Tau² = 0.07; Chi² = 11.19, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 0.95 (P = 0.34)						
3.20.2 Centella asiatica						
Allegra 1981	7	40	25	40	100.0%	0.28 [0.14 , 0.57]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.28 [0.14 , 0.57]**
Total events:	7		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.49 (P = 0.0005)						
3.20.3 Diosmine, Hidrosmine						
Biland 1982	23	35	28	35	25.9%	0.82 [0.61 , 1.10]
Chassignolle 1994	24	40	28	40	23.7%	0.86 [0.62 , 1.19]
Danielsson 2002	30	51	34	50	25.4%	0.87 [0.64 , 1.17]
Laurent 1988	35	100	66	100	25.1%	0.53 [0.39 , 0.72]
Subtotal (95% CI)		**226**		**225**	**100.0%**	**0.75 [0.59 , 0.96]**
Total events:	112		156			
Heterogeneity: Tau² = 0.04; Chi² = 7.42, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 2.33 (P = 0.02)						
3.20.4 Rutosides						
Burnand 1989	9	24	12	25	18.7%	0.78 [0.40 , 1.51]
Cloarec 1996	3	53	32	51	13.8%	0.09 [0.03 , 0.28]
Jongste 1989	15	41	26	43	20.7%	0.61 [0.38 , 0.97]
Parrado 1999	0	30	1	30	3.6%	0.33 [0.01 , 7.87]
Pedersen 1992	18	24	10	19	20.5%	1.43 [0.88 , 2.31]
Pulvertaft 1983	116	495	109	165	22.7%	0.35 [0.29 , 0.43]
Subtotal (95% CI)		**667**		**333**	**100.0%**	**0.50 [0.26 , 0.97]**
Total events:	161		190			
Heterogeneity: Tau² = 0.48; Chi² = 40.60, df = 5 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 8.90, df = 3 (P = 0.03), I² = 66.3%						



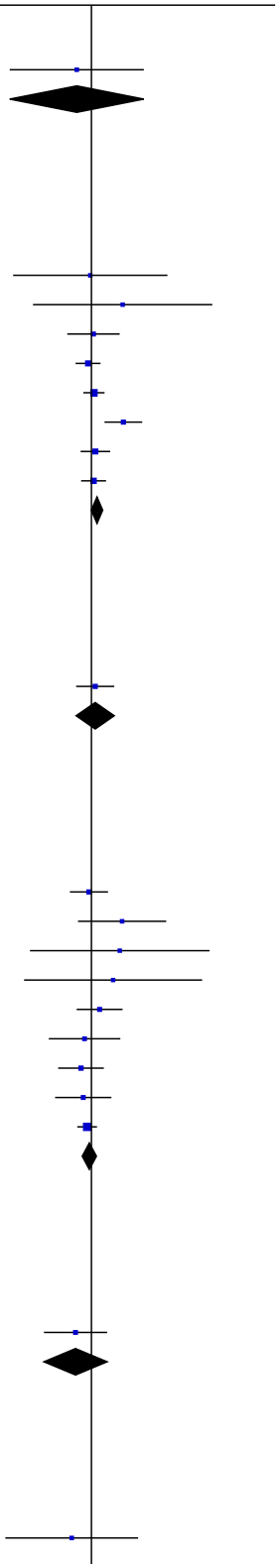
Analysis 3.21. Comparison 3: Sensitivity analysis of published studies only, Outcome 21: Participant satisfaction (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.21.1 Calcium dobesilate								
Rabe 2011	15.19	12.49	108	20.83	11.91	115	50.2%	-0.46 [-0.73 , -0.19]
Widmer 1990	4.4	4.4	114	7.39	5.7	111	49.8%	-0.59 [-0.85 , -0.32]
Subtotal (95% CI)			**222**			**226**	**100.0%**	**-0.52 [-0.71 , -0.33]**
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 5.44 (P < 0.00001)								
3.21.2 Diosmine, Hidrosmine								
Gilly 1994	0.5	0.87	76	1.2	0.86	74	100.0%	-0.81 [-1.14 , -0.47]
Subtotal (95% CI)			**76**			**74**	**100.0%**	**-0.81 [-1.14 , -0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.74 (P < 0.00001)								
3.21.3 Rutosides								
Cesarone 2002	3.1	1.2	16	6	2	15	21.7%	-1.73 [-2.57 , -0.89]
Cloarec 1996	4.3	2.5	53	9.5	3.3	51	26.3%	-1.77 [-2.22 , -1.31]
Ihme 1996	2.2	1.4	36	2.4	1.7	31	26.0%	-0.13 [-0.61 , 0.35]
Kiesewetter 1997	1.5	1.1	37	3	1.4	44	26.1%	-1.17 [-1.64 , -0.69]
Subtotal (95% CI)			**142**			**141**	**100.0%**	**-1.18 [-1.96 , -0.39]**
Heterogeneity: Tau² = 0.56; Chi² = 26.15, df = 3 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.93 (P = 0.003)								
Test for subgroup differences: Chi² = 4.11, df = 2 (P = 0.13), I² = 51.3%								



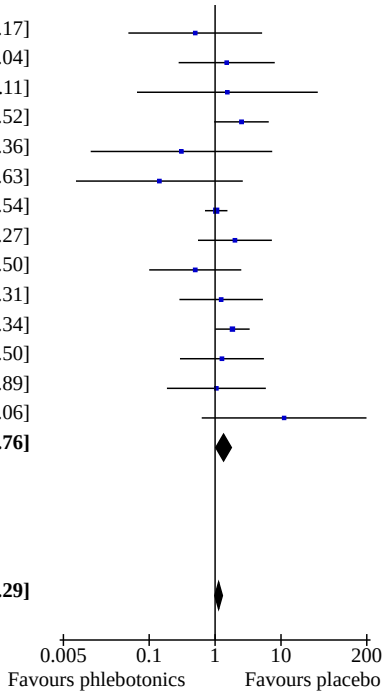
Analysis 3.22. Comparison 3: Sensitivity analysis of published studies only, Outcome 22: Adverse events

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.22.1 Aminaftone						
Belczak 2014	1	36	2	43	0.5%	0.60 [0.06 , 6.32]
Subtotal (95% CI)		**36**		**43**	**0.5%**	**0.60 [0.06 , 6.32]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
3.22.2 Calcium dobesilate						
Flota-Cervera 2008	1	25	1	24	0.3%	0.96 [0.06 , 14.50]
Hachen 1982	1	25	0	25	0.1%	3.00 [0.13 , 70.30]
Labs 2004	9	133	8	127	2.4%	1.07 [0.43 , 2.70]
Marinello 2002	32	82	18	41	7.1%	0.89 [0.57 , 1.38]
Martinez-Zapata 2008	46	246	45	263	12.9%	1.09 [0.75 , 1.59]
Rabe 2011	33	133	10	124	3.1%	3.08 [1.58 , 5.98]
Rabe 2016	26	174	23	177	6.8%	1.15 [0.68 , 1.94]
Widmer 1990	31	114	28	111	8.4%	1.08 [0.69 , 1.67]
Subtotal (95% CI)		**932**		**892**	**41.2%**	**1.22 [1.00 , 1.49]**
Total events:	179		133			
Heterogeneity: Chi^2 = 10.53, df = 7 (P = 0.16); I^2 = 34%						
Test for overall effect: Z = 1.92 (P = 0.05)						
3.22.3 Centella asiatica						
Pointel 1986	19	61	9	33	3.5%	1.14 [0.58 , 2.23]
Subtotal (95% CI)		**61**		**33**	**3.5%**	**1.14 [0.58 , 2.23]**
Total events:	19		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
3.22.4 Diosmine, Hidrosmine						
Biland 1982	11	35	12	35	3.6%	0.92 [0.47 , 1.79]
Danielsson 2002	6	51	2	50	0.6%	2.94 [0.62 , 13.89]
Dominguez 1992	1	30	0	27	0.2%	2.71 [0.12 , 63.84]
Fermoso 1992	1	20	0	14	0.2%	2.14 [0.09 , 49.08]
Gilly 1994	12	80	9	80	2.7%	1.33 [0.60 , 2.99]
Guilhou 1997	4	53	5	52	1.5%	0.78 [0.22 , 2.76]
Laurent 1988	9	100	13	100	3.9%	0.69 [0.31 , 1.55]
Planchon 1990	6	55	8	55	2.4%	0.75 [0.28 , 2.02]
Rabe 2015	49	296	57	296	16.9%	0.86 [0.61 , 1.22]
Subtotal (95% CI)		**720**		**709**	**31.9%**	**0.93 [0.72 , 1.19]**
Total events:	99		106			
Heterogeneity: Chi^2 = 4.56, df = 8 (P = 0.80); I^2 = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
3.22.5 Grape seed extract						
Thebaut 1985	4	35	8	40	2.2%	0.57 [0.19 , 1.74]
Subtotal (95% CI)		**35**		**40**	**2.2%**	**0.57 [0.19 , 1.74]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
3.22.6 Rutosides						
Alterkamper 1987	1	25	2	25	0.6%	0.50 [0.05 , 5.17]
Balmer 1980	3	20	2	20	0.6%	1.50 [0.28 , 8.04]



Analysis 3.22. (Continued)

Alterkamper 1987	1	25	2	25	0.6%	0.50 [0.05 , 5.17]
Balmer 1980	3	20	2	20	0.6%	1.50 [0.28 , 8.04]
Diebschlag 1994	1	40	0	20	0.2%	1.54 [0.07 , 36.11]
Jongste 1989	12	41	5	43	1.5%	2.52 [0.97 , 6.52]
Koscielnny 1996	0	40	1	37	0.5%	0.31 [0.01 , 7.36]
Kriner 1985	0	25	3	25	1.0%	0.14 [0.01 , 2.63]
MacLennan 1994	26	52	25	52	7.4%	1.04 [0.70 , 1.54]
Parrado 1999	6	30	3	30	0.9%	2.00 [0.55 , 7.27]
Serralde 1990	2	26	4	26	1.2%	0.50 [0.10 , 2.50]
Unkauf 1996	4	69	3	64	0.9%	1.24 [0.29 , 5.31]
Vanscheidt 2002a	25	114	14	117	4.1%	1.83 [1.00 , 3.34]
Vanscheidt 2002b	4	85	3	81	0.9%	1.27 [0.29 , 5.50]
Vin 1994	3	43	2	30	0.7%	1.05 [0.19 , 5.89]
Zucarelli 1987	5	74	0	75	0.1%	11.15 [0.63 , 198.06]
Subtotal (95% CI)		**684**		**645**	**20.7%**	**1.34 [1.02 , 1.76]**
Total events:	92		67			
Heterogeneity: Chi² = 12.14, df = 13 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
Total (95% CI)		**2468**		**2362**	**100.0%**	**1.13 [0.99 , 1.29]**
Total events:	394		325			
Heterogeneity: Chi² = 32.15, df = 33 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Chi² = 6.18, df = 5 (P = 0.29), I² = 19.1%						



Comparison 4. Sensitivity analysis based on low risk of bias

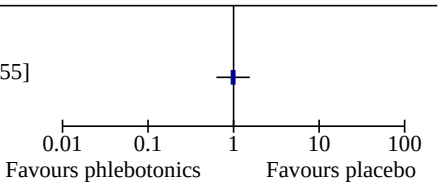
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Oedema in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.1 Calcium dobesilate	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2 Ankle perimeter circumference (mm)	3	867	Mean Difference (IV, Random, 95% CI)	-2.34 [-8.79, 4.11]
4.2.1 Calcium dobesilate	3	867	Mean Difference (IV, Random, 95% CI)	-2.34 [-8.79, 4.11]
4.3 Quality of life	2	617	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
4.3.1 Calcium dobesilate at 3 months of treatment	2	617	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
4.4 Pain in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.4.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5 Pain in the lower legs (continuous variable)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5.1 Calcium dobesilate	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.6 Cramps in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7 Itching in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.8 Itching in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9 Heaviness in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.9.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.10 Heaviness in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.10.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.11 Swelling in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.11.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.12 Swelling in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.12.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.13 Participant satisfaction (dichotomous variable)	2	476	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.32]
4.13.1 Calcium dobesilate	2	476	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.32]
4.14 Participant satisfaction (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.14.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.15 Adverse events	4	1257	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.97, 2.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.15.1 Calcium dobesilate	3	1026	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.76, 3.09]
4.15.2 Rutosides	1	231	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.00, 3.34]

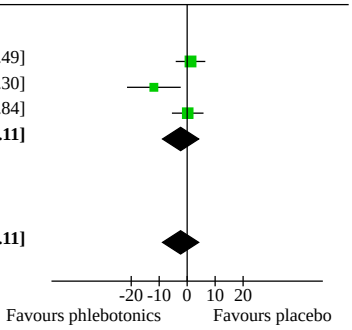
Analysis 4.1. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 1: Oedema in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Calcium dobesilate					
Labs 2004	30	133	29	127	0.99 [0.63 , 1.55]



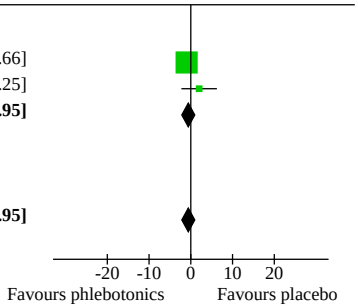
Analysis 4.2. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 2: Ankle perimeter circumference (mm)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
4.2.1 Calcium dobesilate								
Labs 2004	229.5	22.7	124	228.3	19.6	123	38.6%	1.20 [-4.09 , 6.49]
Martinez-Zapata 2008	254.9	43.2	193	266.8	53.9	203	24.2%	-11.90 [-21.50 , -2.30]
Rabe 2011	240.9	21.3	109	240.7	21.8	115	37.2%	0.20 [-5.44 , 5.84]
Subtotal (95% CI)			**426**			**441**	**100.0%**	**-2.34 [-8.79 , 4.11]**
Heterogeneity: Tau² = 20.80; Chi² = 5.79, df = 2 (P = 0.06); I² = 65%								
Test for overall effect: Z = 0.71 (P = 0.48)								
Total (95% CI)			**426**			**441**	**100.0%**	**-2.34 [-8.79 , 4.11]**
Heterogeneity: Tau² = 20.80; Chi² = 5.79, df = 2 (P = 0.06); I² = 65%								
Test for overall effect: Z = 0.71 (P = 0.48)								
Test for subgroup differences: Not applicable								



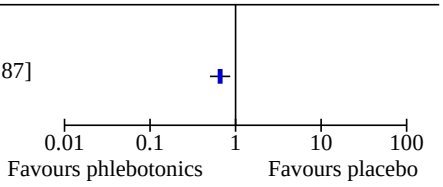
Analysis 4.3. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 3: Quality of life

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.3.1 Calcium dobesilate at 3 months of treatment								
Martinez-Zapata 2008	39.8	11	197	40.8	4.8	216	86.7%	-1.00 [-2.66 , 0.66]
Rabe 2011	41.2	17.7	100	39.2	12.8	104	13.3%	2.00 [-2.25 , 6.25]
Subtotal (95% CI)			**297**			**320**	**100.0%**	**-0.60 [-2.15 , 0.95]**
Heterogeneity: Chi² = 1.66, df = 1 (P = 0.20); I² = 40%								
Test for overall effect: Z = 0.76 (P = 0.45)								
Total (95% CI)			**297**			**320**	**100.0%**	**-0.60 [-2.15 , 0.95]**
Heterogeneity: Chi² = 1.66, df = 1 (P = 0.20); I² = 40%								
Test for overall effect: Z = 0.76 (P = 0.45)								
Test for subgroup differences: Not applicable								



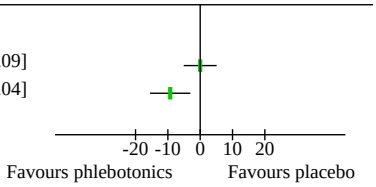
Analysis 4.4. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 4: Pain in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Rutosides					
Vanscheidt 2002a	45	114	70	117	0.66 [0.50 , 0.87]



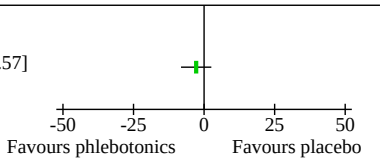
Analysis 4.5. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 5: Pain in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
4.5.1 Calcium dobesilate							
Martinez-Zapata 2008	37.8	25.8	203	37.8	27.4	216	0.00 [-5.09 , 5.09]
Rabe 2011	-10.2	26.2	120	-0.92	22.9	119	-9.28 [-15.52 , -3.04]



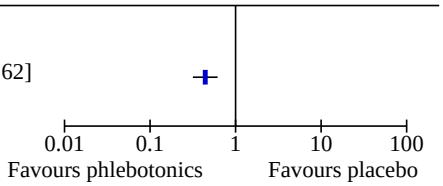
Analysis 4.6. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 6: Cramps in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.6.1 Calcium dobesilate							
Martinez-Zapata 2008	24.1	27.1	204	26.9	28.7	211	-2.80 [-8.17 , 2.57]



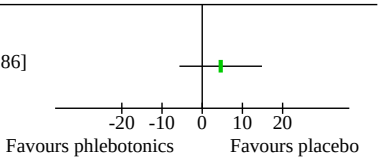
Analysis 4.7. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 7: Itching in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Rutosides					
Vanscheidt 2002a	31	114	72	117	0.44 [0.32 , 0.62]



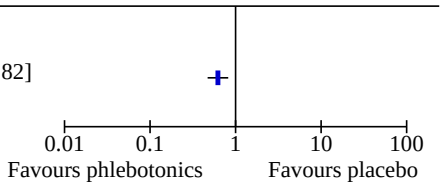
Analysis 4.8. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 8: Itching in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.8.1 Calcium dobesilate							
Martinez-Zapata 2008	35.9	68.6	204	31.3	30.4	212	4.60 [-5.66 , 14.86]



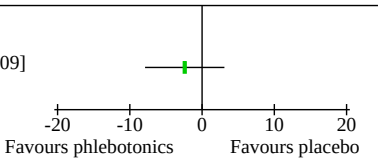
Analysis 4.9. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 9: Heaviness in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
4.9.1 Rutosides					
Vanscheidt 2002a	43	114	71	117	0.62 [0.47 , 0.82]



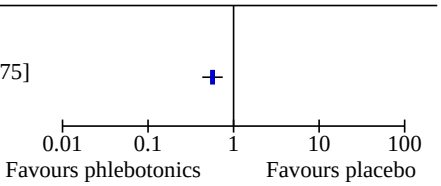
Analysis 4.10. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 10: Heaviness in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.10.1 Calcium dobesilate							
Martinez-Zapata 2008	44.5	28.4	203	46.9	28.8	214	-2.40 [-7.89 , 3.09]



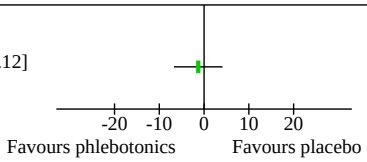
Analysis 4.11. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 11: Swelling in the lower legs (dichotomous variable)

Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
4.11.1 Rutosides					
Vanscheidt 2002a	42	114	76	117	0.57 [0.43 , 0.75]



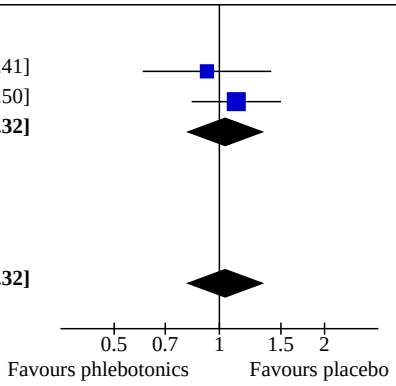
Analysis 4.12. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 12: Swelling in the lower legs (continuous variable)

Study or Subgroup	Phlebotonics Mean	Phlebotonics SD	Phlebotonics Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.12.1 Calcium dobesilate							
Martinez-Zapata 2008	36.2	28.6	203	37.5	27.8	214	-1.30 [-6.72 , 4.12]

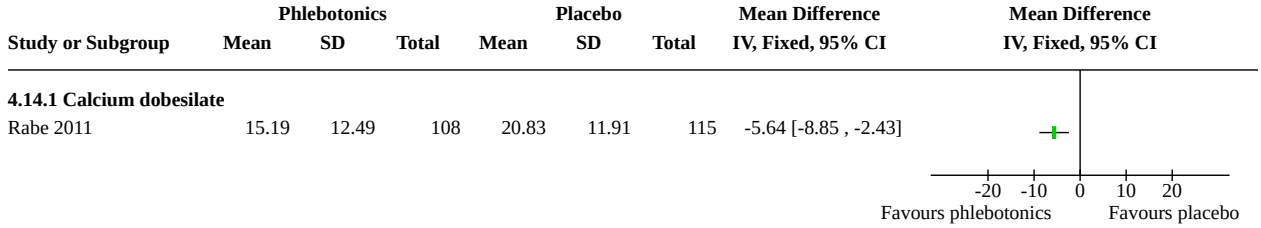


Analysis 4.13. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 13: Participant satisfaction (dichotomous variable)

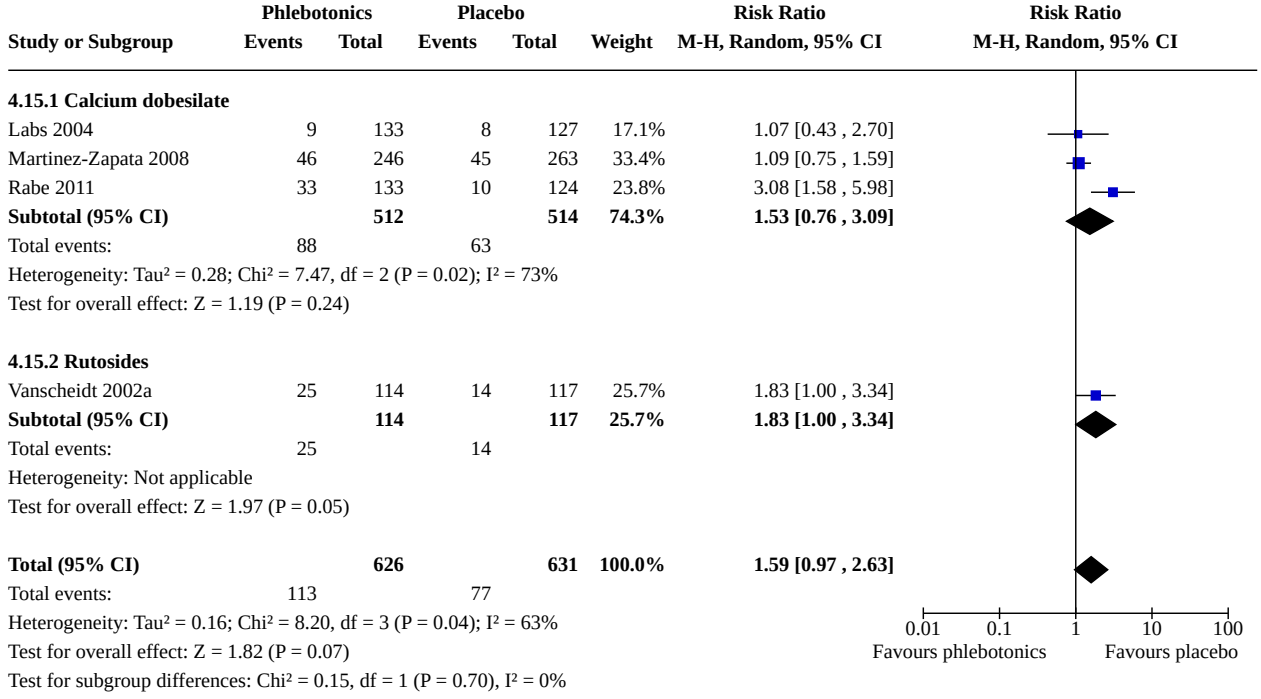
Study or Subgroup	Phlebotonics Events	Phlebotonics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.13.1 Calcium dobesilate						
Labs 2004	29	112	34	121	40.2%	0.92 [0.60 , 1.41]
Rabe 2011	55	123	48	120	59.8%	1.12 [0.83 , 1.50]
Subtotal (95% CI)		**235**		**241**	**100.0%**	**1.04 [0.81 , 1.32]**
Total events:	84		82			
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**235**		**241**	**100.0%**	**1.04 [0.81 , 1.32]**
Total events:	84		82			
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Not applicable						



Analysis 4.14. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 14: Participant satisfaction (continuous variable)



Analysis 4.15. Comparison 4: Sensitivity analysis based on low risk of bias, Outcome 15: Adverse events



ADDITIONAL TABLES

Table 1. Results of all outcomes analysed (all phlebotonics)

Variables	Dichotomous	Continuous
Oedema	RR 0.70 (0.63 to 0.78)	-
Oedema (mm)	-	MD -4.27 (-5.61 to -2.93)
Oedema (volume)	-	SMD -0.24 (-0.33 to -0.15)
Ulcer cured	NS	-
Trophic disorders	RR 0.87 (0.81 to 0.95)	-
Pain	-	SMD -0.35 (-0.54, -0.17)

Table 1. Results of all outcomes analysed (all phlebotonics) *(Continued)*

Cramps	RR 0.72 (0.58 to 0.89)	-
Restless legs	RR 0.81 (0.72 to 0.91)	-
Itching	-	-
Heaviness	-	-
Swelling	RR 0.63 (0.50 to 0.80)	-
Paraesthesia	RR 0.67 (0.50 to 0.88)	NS
Quality of life	-	NS
Global assessment by the participant	-	-
Adverse events	RR 1.14 (1.02 to 1.27)	-
Note: No measures of effect are specified when I^2 was > 75% for the subgroup		

RR: risk ratio
MD: mean difference
NS: non-significant
RR: risk ratio
SMD: standardized mean difference

Table 2. Results by pharmacological group: aminaftone

Variables	Dichotomous	Continous
Oedema	RR 0.53 (0.28 to 0.99)	SMD -0.17 (-0.61 to 0.28)
Ulcer cured	NS	-
Trophic disorder	NS	-
Pain	RR 0.43 (0.23 to 0.79)	-
Cramps	RR 0.56 (0.31 to 0.99)	-
Itching	RR 0.53 (0.31 to 0.91)	-
Heaviness	RR 0.32 (0.17 to 0.60)	-
Quality of live	-	MD -10.00 (-17.01 to -2.99)
Adverse events	NS	-
Note: Only 1 study was analyzed		

MD: mean difference
NS: non-significant
RR: risk ratio
SMD: standardized mean difference

Table 3. Results by pharmacological group: calcium dobesilate

Variables	Dichotomous	Continuous
Oedema	-	-
Oedema (mm)	-	NS
Oedema (volume)	-	SMD -0.38 (-0.51 to -0.24)
Ulcer cured	NS	-
Pain	RR 0.53 (0.35 to 0.82)	NS
Cramps	RR 0.65 (0.50 to 0.84)	-
Restless legs	RR 0.73 (0.59 to 0.91)	NS
Itching	-	NS
Heaviness	NS	NS
Swelling	RR 0.19 (0.08 to 0.41)	NS
Paraesthesia	NS	-
Quality of life	-	NS
Global assessment by the participant	-	SMD -0.52 (-0.71 to -0.33)
Adverse events	RR 1.22 (1.0 to 1.49)	-
Note: No measures of effect are specified when I^2 was > 75% for the subgroup		

NS: non-significant
RR: risk ratio
SMD: standardized mean difference

Table 4. Results by pharmacological group: *Centella asiatica*

Variables	Dichotomous	Continuous
Heaviness	NS	-
Global assessment by the participant	RR 0.28 (0.14 to 0.57)	-
Adverse events	NS	-
Note: Only 1 study was analyzed		

NS: non-significant
RR: risk ratio

Table 5. Results by pharmacological group: diosmine, hidrosmine

Variables	Dichotomous	Continuous
Oedema	RR 0.63 (0.46 to 0.86)	-
Oedema (mm)	-	MD -5.98 (-7.78 to -4.18)
Ulcer cured	NS	-
Trophic disorder	RR 0.87 (0.81 to 0.94)	-
Pain	NS	SMD -0.23 (-0.41 to -0.05)
Cramps	RR 0.83 (0.70 to 0.98)	SMD -0.46 (-0.78 to -0.14)
Restless legs	NS	-
Itching	NS	-
Heaviness	NS	SMD -0.69 (-1.02 to -0.36)
Swelling	RR 0.70 (0.52 to 0.94)	SMD -0.92 (-1.26 to -0.58)
Paraesthesia	NS	NS
Quality of life	-	NS
Global assessment by the participant	-	SMD -0.81 (-1.14 to -0.47)
Adverse events	NS	-
Note: No measures of effect are specified when I^2 was > 75% for the subgroup		

MD: mean difference
NS: non-significant
RR: risk ratio
SMD: standardized mean difference

Table 6. Results by pharmacological group: French maritime pine bark extract

Variables	Dichotomous	Continuous
Pain	RR 0.66 (0.48 to 0.91)	SMD -1.39 (-2.09 to -0.69)
Heaviness	NS	SMD -1.50 (-2.21 to -0.79)
Swelling	NS	SMD -1.65 (-2.38 to -0.92)
Note: Only 1 study was analyzed		

NS: non-significant
RR: risk ratio
SMD: standardized mean difference

Table 7. Results by pharmacological group: grape seed extract

Variables	Dichotomous	Continuous
Oedema	NS	-
Adverse events	NS	NS
Note: Only 1 study was analyzed		

NS: non-significant

Table 8. Results by pharmacological group: rutosides

Variables	Dichotomous	Continuous
Oedema	RR 0.72 (0.64 to 0.81)	-
Oedema (mm)	-	NS
Oedema (volume)	-	SMD -0.15 (-0.16 to -0.03)
Ulcer cured	NS	-
Trophic disorder	NS	-
Pain	-	SMD -0.71 (-1.23 to -0.19)
Cramps	RR -0.83 (-1.50 to -0.16)	NS
Restless legs	NS	-
Itching	-	SMD -0.58 (-1.10 to -0.06)
Heaviness	RR 0.60 (0.48 to 0.74)	-
Swelling	RR 0.67 (0.50 to 0.88)	NS
Paraesthesias	RR 0.55 (0.37 to 0.83)	NS
Global assessment by the participant	-	-
Adverse events	RR 1.22 (1.04 to 1.43)	-
Note: No measures of effect are specified when I^2 was > 75%		

NS: non-significant
RR: risk ratio
SMD: standardized mean difference

APPENDICES

Appendix 1. Database search strategies

Source	Search strategy	Hits retrieved
CENTRAL	#1 MESH DESCRIPTOR Venous Insufficiency EXPLODE ALL TREES 533	182
	#2 ((insuffic* or insufic* or CVI or isch* or incompet* or chronic) and (saphenous or vein* or veno*)):TI,AB,KY 6291	
	#3 (Chronic venous disease):TI,AB,KY 128	
	#4 CVD:TI,AB,KY 4543	
	#5 (chronic venous disorder*):TI,AB,KY 28	
	#6 CEAP:TI,AB,KY 256	
	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 10884	
	#8 MESH DESCRIPTOR 4-Aminobenzoic Acid EXPLODE ALL TREES 35	
	#9 MESH DESCRIPTOR Calcium Dobesilate EXPLODE ALL TREES 51	
	#10 MESH DESCRIPTOR Centella EXPLODE ALL TREES 17	
	#11 MESH DESCRIPTOR Coumarins EXPLODE ALL TREES 2108	
	#12 MESH DESCRIPTOR Diosmin EXPLODE ALL TREES 71	
	#13 MESH DESCRIPTOR Flavonoids EXPLODE ALL TREES 2521	
	#14 MESH DESCRIPTOR Hemostatics EXPLODE ALL TREES 5173	
	#15 MESH DESCRIPTOR Hesperidin EXPLODE ALL TREES 67	
	#16 MESH DESCRIPTOR Hydroxyethylrutoside EXPLODE ALL TREES 97	
	#17 MESH DESCRIPTOR Pinus EXPLODE ALL TREES 36	
	#18 MESH DESCRIPTOR Phytotherapy EXPLODE ALL TREES 3950	
	#19 MESH DESCRIPTOR Plant Extracts EXPLODE ALL TREES 7693	
	#20 MESH DESCRIPTOR Rutin EXPLODE ALL TREES 171	
	#21 MESH DESCRIPTOR Saponins EXPLODE ALL TREES 184	
	#22 aminaftone*:TI,AB,KY 6	
	#23 aminaphthone:TI,AB,KY 3	
	#24 aminaphtone*:TI,AB,KY 8	
	#25 bioflavonoid*:TI,AB,KY 79	
	#26 (calcium dobesilate):TI,AB,KY 131	
	#27 centella:TI,AB,KY 101	
	#28 chromocarbe*:TI,AB,KY 3	
	#29 Coumarin*:TI,AB,KY 326	
	#30 daflon:TI,AB,KY 90	
	#31 diosmin:TI,AB,KY 147	
	#32 diosmine:TI,AB,KY 10	

(Continued)

	#33 diosmiplex:TI,AB,KY 1 #34 (disodium flavodate):TI,AB,KY 3 #35 doxium:TI,AB,KY 42 #36 flavonoids:TI,AB,KY 1083 #37 (french maritime pine):TI,AB,KY 38 #38 (grape seed):TI,AB,KY 184 #39 hesperidin:TI,AB,KY 171 #40 hidrosmin*:TI,AB,KY 7 #41 (horse chestnut):TI,AB,KY 50 #42 hydroxyethylrutoside:TI,AB,KY 98 #43 naftazone*:TI,AB,KY 9 #44 para-aminobenzoates:TI,AB,KY 37 #45 phlebotonics:TI,AB,KY 6 #46 (plant extract*):TI,AB,KY 4598 #47 pycnogenol*:TI,AB,KY 122 #48 rutin*:TI,AB,KY 219 #49 rutoside*:TI,AB,KY 144 #50 saponin*:TI,AB,KY 255 #51 saponosides:TI,AB,KY 0 #52 troxerutin:TI,AB,KY 72 #53 (vasoprotective agents):TI,AB,KY 0 #54 (venoactive drug*):TI,AB,KY 16 #55 (veno-active drug*):TI,AB,KY 4 #56 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 20104 #57 #7 AND #56 559 #58 01/01/2015 TO 12/11/2019:CD 761936 #59 #57 AND #58 182	
Clinicaltrials.gov	Venous Insufficiency OR Chronic venous disease OR chronic venous disorder OR CEAP | 4-Aminobenzoic Acid OR Calcium Dobesilate OR Centella OR Coumarins OR Diosmin OR Flavonoids OR Hemostatics OR Hesperidin OR Hydroxyethylrutoside OR Pinus OR Phytotherapy OR Plant Extracts OR Rutin OR Saponins	7
ICTRP Search Portal		6

(Continued)

Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present	1 exp Venous Insufficiency/	275
	2 ((insuffic* or insufic* or CVI or isch* or incompet* or chronic) and (saphenous or vein* or veno*)).ti,ab.	
	3 "Chronic venous disease".ti,ab.	
	4 CVD.ti,ab.	
	5 " chronic venous disorder*".ti,ab.	
	6 CEAP.ti,ab.	
	7 or/1-6	
	8 4-Aminobenzoic Acid/	
	9 exp Calcium Dobesilate/	
	10 Centella/	
	11 exp Coumarins/	
	12 Diosmin/	
	13 exp Flavonoids/	
	14 Hemostatics/	
	15 Hesperidin/	
	16 Hydroxyethylrutoside/	
	17 Phytotherapy/	
	18 Pinus/	
	19 Plant Extracts/	
	20 exp Rutin/	
	21 exp Saponins/	
	22 aminaftone*.ti,ab.	
	23 aminaphthone.ti,ab.	
	24 aminaphtone*.ti,ab.	
	25 bioflavonoid*.ti,ab.	
	26 "calcium dobesilate".ti,ab.	
	27 centella.ti,ab.	
	28 chromocarbe*.ti,ab.	
	29 Coumarin*.ti,ab.	
	30 daflon.ti,ab.	
	31 diosmin.ti,ab.	
	32 diosmine.ti,ab.	
	33 diosmiplex.ti,ab.	

(Continued)

34 "disodium flavodate".ti,ab.

35 doxium.ti,ab.

36 flavonoids.ti,ab.

37 "french maritime pine".ti,ab.

38 "grape seed".ti,ab.

39 hesperidin.ti,ab.

40 hidrosmin*.ti,ab.

41 "horse ADJ3 (chestnut or chest-nut)".ti,ab.

42 "horse chestnut".ti,ab.

43 hydroxyethylrutoside.ti,ab.

44 naftazone*.ti,ab.

45 para-aminobenzoates.ti,ab.

46 phlebotonics.ti,ab.

47 "plant extract*".ti,ab.

48 pycnogenol*.ti,ab.

49 rutin*.ti,ab.

50 rutoside*.ti,ab.

51 saponin*.ti,ab.

52 saponosides.ti,ab.

53 troxerutin.ti,ab.

54 "vasoprotective agents".ti,ab.

55 "venoactive drug*".ti,ab.

56 "veno-active drug*".ti,ab.

57 or/8-56

58 7 and 57

59 randomized controlled trial.pt.

60 controlled clinical trial.pt.

61 randomized.ab.

62 placebo.ab.

63 drug therapy.fs.

64 randomly.ab.

65 trial.ab.

66 groups.ab.

67 or/59-66

(Continued)

	68 exp animals/ not humans.sh.	
	69 67 not 68	
	70 58 and 69	
Embase 1974 to present	1 exp vein insufficiency/	443
	2 ((insuffic* or insufic* or CVI or isch* or incompet* or chronic) and (saphenous or vein* or veno*)).ti,ab.	
	3 "Chronic venous disease".ti,ab.	
	4 CVD.ti,ab.	
	5 "chronic venous disorder*".ti,ab.	
	6 CEAP.ti,ab.	
	7 or/1-6	
	8 4 aminobenzoic acid/	
	9 exp dobesilate calcium/	
	10 Centella/	
	11 exp coumarin derivative/	
	12 diosmin/	
	13 exp flavonoid/	
	14 hemostatic agent/	
	15 hesperidin/	
	16 monoxerutin/	
	17 phytotherapy/	
	18 pine/	
	19 plant extract/	
	20 exp rutoside/	
	21 exp saponin/	
	22 aminaftone*.ti,ab.	
	23 aminaphthone.ti,ab.	
	24 aminaphtone*.ti,ab.	
	25 bioflavonoid*.ti,ab.	
	26 "calcium dobesilate".ti,ab.	
	27 centella.ti,ab.	
	28 chromocarbe*.ti,ab.	
	29 Coumarin*.ti,ab.	
	30 daflon.ti,ab.	

(Continued)

31 diosmin.ti,ab.

32 diosmine.ti,ab.

33 diosmiplex.ti,ab.

34 "disodium flavodate".ti,ab.

35 doxium.ti,ab.

36 flavonoids.ti,ab.

37 "french maritime pine".ti,ab.

38 "grape seed".ti,ab.

39 hesperidin.ti,ab.

40 hidrosmin*.ti,ab.

41 "horse chestnut".ti,ab.

42 hydroxyethylrutoside.ti,ab.

43 naftazone*.ti,ab.

44 para-aminobenzoates.ti,ab.

45 phlebotonics.ti,ab.

46 "plant extract*".ti,ab.

47 pycnogenol*.ti,ab.

48 rutin*.ti,ab.

49 rutoside*.ti,ab.

50 saponin*.ti,ab.

51 saponosides.ti,ab.

52 troxerutin.ti,ab.

53 "vasoprotective agents".ti,ab.

54 "venoactive drug*".ti,ab.

55 "veno-active drug*".ti,ab.

56 or/8-55

57 7 and 56

58 randomized controlled trial/

59 controlled clinical trial/

60 random$.ti,ab.

61 randomization/

62 intermethod comparison/

63 placebo.ti,ab.

64 (compare or compared or comparison).ti.

(Continued)

	65 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 66 (open adj label).ti,ab. 67 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 68 double blind procedure/ 69 parallel group$1.ti,ab. 70 (crossover or cross over).ti,ab. 71 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 72 (assigned or allocated).ti,ab. 73 (controlled adj7 (study or design or trial)).ti,ab. 74 (volunteer or volunteers).ti,ab. 75 trial.ti. 76 or/58-75 77 57 and 76	
CINAHL	S64 S48 AND S63 S63 S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 S62 MH "Random Assignment" S61 MH "Triple-Blind Studies" S60 MH "Double-Blind Studies" S59 MH "Single-Blind Studies" S58 MH "Crossover Design" S57 MH "Factorial Design" S56 MH "Placebos" S55 MH "Clinical Trials" S54 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" S53 TX crossover OR "cross-over" S52 AB placebo* S51 TX random* S50 TX trial* S49 TX "latin square" S48 S7 AND S47 S47 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR	57

(Continued)

S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46

S46 TX veno-active drug*

S45 TX venoactive drug*

S44 TX vasoprotective agents

S43 TX troxerutin

S42 TX saponosides

S41 TX saponin*

S40 TX rutoside*

S39 TX rutin*

S38 TX pycnogenol*

S37 TX plant extract*

S36 TX phlebotonics

S35 TX para-aminobenzoates

S34 TX naftazone*

S33 TX hydroxyethylrutoside

S32 TX horse chestnut

S31 TX hidrosmin*

S30 TX hesperidin

S29 TX grape seed

S28 TX french maritime pine

S27 TX flavonoids

S26 TX doxium

S25 TX disodium flavodate

S24 TX diosmiplex

S23 TX diosmine

S22 TX diosmin

S21 TX daflon

S20 TX Coumarin*

S19 TX chromocarbe*

S18 TX centella

S17 TX calcium dobesilate

S16 TX bioflavonoid*

S15 TX aminaphtone*

S14 TX aminaphthone

(Continued)

	S13 TX aminaftone*	
	S12 (MH "Rutin")	
	S11 (MH "Plant Extracts+")	
	S10 (MH "Medicine, Herbal+")	
	S9 (MH "Hemostatics+")	
	S8 Flavonoids	
	S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6	
	S6 TX CEAP	
	S5 TX chronic venous disorder*	
	S4 TX CVD	
	S3 TX Chronic venous disease	
	S2 TX ((insuffic* or insufic* or CVI or isch* or incompet* or chronic) and (saphenous or vein* or veno*))	
	S1 (MH "Venous Insufficiency+")	
AMED (Allied and Complementary Medicine) 1985 to present	1 exp Venous insufficiency/	17
	2 ((insuffic* or insufic* or CVI or isch* or incompet* or chronic) and (saphenous or vein* or veno*)).ti,ab.	
	3 "Chronic venous disease".ti,ab.	
	4 CVD.ti,ab.	
	5 "chronic venous disorder*".ti,ab.	
	6 CEAP.ti,ab.	
	7 or/1-6	
	8 exp CLINICAL TRIALS/	
	9 RANDOM ALLOCATION/	
	10 DOUBLE BLIND METHOD/	
	11 Clinical trial.pt.	
	12 (clinic* adj trial*).tw.	
	13 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw.	
	14 PLACEBOS/	
	15 placebo*.tw.	
	16 random*.tw.	
	17 PROSPECTIVE STUDIES/	
	18 or/8-17	
	19 7 and 18	

Appendix 2. Glossary

Agranulocytosis	also known as agranulosis or granulopenia, is an acute condition involving a severe and dangerous leukopenia (lowered white blood cell count), most commonly of neutrophils, and thus causing a neutropenia in the circulating blood
Anatomical Therapeutic Chemical (ATC) Classification System	drug classification system that classifies the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties
Capillary hyperpermeability	the capacity of a blood vessel wall to allow for the flow of small molecules (drugs, nutrients, water, ions) or even whole cells (lymphocytes on their way to the site of inflammation) in and out of the vessel
Chronic venous insufficiency (CVI)	a condition in which veins are unable to transport blood unidirectionally toward the heart, usually occurs in the lower limbs
Corona phlebectatica	cutaneous sign of chronic venous insufficiency, characterised by abnormally dilated veins around the ankle
Exacerbations	the process of making a problem, bad situation, or negative feeling worse
Lipodermatosclerosis	hardening of the skin that may cause red/brown pigmentation and is accompanied by wasting of subcutaneous fat
Paraesthesias	abnormal sensations, such as prickling, burning, tingling) in the lower legs
Pathophysiology	the disordered physiological processes associated with disease or injury
Reticular veins	dilated veins that show as a net-like pattern on the skin
Telangiectasia	condition in which widened venules (tiny blood vessels) cause threadlike red lines or patterns on the skin
Thrombosis	formation of a blood clot, known as a thrombus, within a blood vessel. It prevents blood from flowing normally through the circulatory system
Varicose veins	permanently dilated veins
Vasoprotective drug	medication which acts to alleviate or prevent conditions or diseases which affect the blood vessels

WHAT'S NEW

Date	Event	Description
27 May 2020	New citation required but conclusions have not changed	Searches rerun; three new studies included, two new studies excluded and two new ongoing studies identified. A new author joined the review team. Review text updated according to current Cochrane reporting guidelines.
27 May 2020	New search has been performed	Searches rerun; three new studies included, two new studies excluded and two new ongoing studies identified.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 3, 2005

Date	Event	Description
21 August 2015	New citation required and conclusions have changed	Searches rerun, 6 new studies included, 1 study reclassified as an included study, 115 new studies excluded and 3 new ongoing studies identified. New authors have joined the review team. Risk of bias assessed for all included studies and 'Summary of findings' table added. Review updated according to current Cochrane reporting guidelines
21 August 2015	New search has been performed	Searches rerun, 6 new studies included, 2 publications added to already included studies and 1 study reclassified as an included study, 115 new studies excluded and 3 new ongoing studies identified
8 July 2008	Amended	Converted to new review format
14 November 2006	Amended	Edited update. CDSR citations updated

CONTRIBUTIONS OF AUTHORS

- MJM: assessed the risk of bias and extracted data for the new studies of this update; responsible for statistical and methodological aspects and for overall compiling of this review; responsible for manuscript development and revision of this review;
- RWMV: screened the search of this update; assessed the risk of bias, GRADE and extracted data for the new studies of this update; responsible for manuscript development and revision of this review
- DS: screened the search of this update; assessed the risk of bias, GRADE and responsible for manuscript development and revision of this SR
- SMU: responsible for manuscript development and revision of this review
- ATS: responsible for manuscript development and revision of this review
- RMM: provided clinical experience and insight on the protocol and review reports
- EV: responsible for manuscript development and revision of this review
- XBC: responsible for manuscript development and revision of this review

DECLARATIONS OF INTEREST

- MJM: none known
- RWMV: none known
- DS: none known
- SMU: none known
- ATS: none known
- RMM: none known
- EV: none known
- XBC: none known

Dr RM Moreno, Dr X Bonfill Cosp and Dr MJ Martínez-Zapata were authors of a published double-blind, placebo-controlled clinical trial (Martinez-Zapata 2008) that is included in this review. This study was supported by Laboratorios Dr Esteve, which markets calcium dobesilate (Doxium). Laboratorios Dr Esteve signed a written commitment to fully respect the researchers' independence and to allow dissemination of results, whatever they could be. Furthermore, Dr RM Moreno, Dr X Bonfill Cosp and Dr MJ Martínez-Zapata were researchers in the included clinical trial DOBESILATO500/2, which was prematurely interrupted because of lack of funding. Dr RM Moreno, Dr X Bonfill Cosp and Dr MJ Martínez-Zapata have not been involved in study selection, data analysis, ROB and GRADE assessment of these cited clinical trials.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2020 version:

- We reviewed all previously excluded studies. In keeping with recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), where these meet the definition of 'not relevant,' we removed them and re-classified them as excluded studies.

2016 version:

- In the protocol, we established different assumptions to examine adverse events. In this current review, we simplified the analyses. We calculated the risk of adverse events by considering the number of participants with adverse events reported in the papers as the numerator and the number of participants randomised by group as the denominator.
- In the protocol, we considered the Jadad scale (Jadad 1996) and the Cochrane criteria (Clarke 2003) to assess the risk of bias of included RCTs. In this current review, we used only the current Cochrane criteria to assess risk of bias (Higgins 2011).
- In the protocol, we considered statistical heterogeneity of $P < 0.1$ as a reason for not pooling results of the studies. In this current review, we used the I^2 statistic and considered $I^2 > 75\%$ a reason for not pooling the results of RCTs.
- In the protocol, we specified to use a random-effects statistical model in all analyses. In this current review, however, we used this model only when I^2 was between 50% and 75%.
- In the protocol, we performed a sensitivity analysis by level of quality of studies according to the Cochrane criteria (Clarke 2003). In this current review, we performed a sensitivity analysis that included only studies with low risk of bias according to the Cochrane risk of bias (Higgins 2011).
- In the protocol, assessment of publication bias was not specified. In this current review, we constructed a funnel plot to explore publication bias.
- In the protocol, the quality of evidence was assessed by the Cochrane criteria. In this current review, we applied GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) (Schünemann 2011) criteria and presented a 'Summary of findings' table (Summary of findings 1).

INDEX TERMS

Medical Subject Headings (MeSH)

4-Aminobenzoic Acid [therapeutic use]; Angioedemas, Hereditary [drug therapy]; Calcium Dobesilate [therapeutic use]; Centella; Chronic Disease; Diosmin [analogs & derivatives] [therapeutic use]; Edema [drug therapy]; Hematologic Agents [*therapeutic use]; Leg; Leg Ulcer [drug therapy]; para-Aminobenzoates [therapeutic use]; Phytotherapy [methods]; Pinus; Plant Extracts [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Rutin [therapeutic use]; Venous Insufficiency [*drug therapy]

MeSH check words

Humans; Middle Aged