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Phlebotonics for venous insufficiency (Review)

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TABLE OF CONTENTS

[Intervention Review]

Phlebotonics for venous insufficiency

Maria José Martinez-Zapata[1], Robin WM Vernooij[2], Sonia Maria Uriona Tuma[3], Airton T Stein[4], Rosa M Moreno[5], Emilio Vargas[6], Dolors Capellà[7], Xavier Bonfill Cosp[8]

[1]Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. [2]Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain. [3]Preventive Medicine and Public Health, Vall Hebron University Hospital, Barcelona, Spain. [4]Department of Public Health, Universidade Federal de Ciências da Saúde, Porto Alegre, Brazil. [5]Angiology, Vascular and Endovascular Surgery, Universitary Hospital La Princesa, Madrid, Spain. [6]Hospital Clínico San Carlos. Universidad Complutense de Madrid, Madrid, Spain. [7]Unit of Clinical Pharmacology, TransLab Research Group, Department of Medical Sciences, Faculty of Medicine, Universitat de Girona, Girona, Spain. [8]Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP) - Universitat Autònoma de Barcelona, Barcelona, Spain

Contact address: Maria José Martinez-Zapata, Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Sant Antoni Maria Claret 167, Pavilion 18, Barcelona, Catalunya, 08025, Spain. mmartinezz@santpau.cat.

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ABSTRACT

Background

Chronic venous insufficiency (CVI) is a common condition caused by valvular dysfunction with or without associated obstruction, usually 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 an update of a review first published in 2005.

Objectives

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

Search methods

For this update, the Cochrane Vascular Trials Search Co-ordinator (TSC) searched the Specialised Register (August 2015), as well as the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 7). The reference lists of the articles retrieved by electronic searches were searched for additional citations. We also contacted pharmaceutical companies and searched the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal for ongoing studies (last searched in August 2015).

Selection criteria

Randomised, double-blind, placebo-controlled trials (RCTs) assessing the efficacy of 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 standardised mean differences (SMDs), according to the outcome assessed. We calculated 95% confidence interval (CIs) and percentage of heterogeneity (I^2). Additionally, we performed sensitivity analyses.

Main results

We included 66 RCTs of oral phlebotonics, but only 53 trials provided quantifiable data (involving 6013 participants; mean age 50 years) for the efficacy analysis: 28 for rutosides, 10 hidrosmine and diosmine, nine calcium dobesilate, two Centella asiatica, two aminaftone, two french maritime pine bark extract and one grape seed extract. No studies evaluating topical phlebotonics, chromocarbe, naftazone or disodium flavodate fulfilled the inclusion criteria.

Moderate-quality evidence suggests that phlebotonics reduced oedema in the lower legs compared with placebo. Phlebotonics showed beneficial effects among participants including reduced oedema (RR 0.70, 95% CI 0.63 to 0.78; I^2 = 20%; 1245 participants) and ankle circumference (MD -4.27 mm, 95% CI -5.61 to -2.93 mm; I^2 = 47%; 2010 participants). Low-quality evidence reveals no difference in the proportion of ulcers cured with phlebotonics compared with placebo (RR 0.94, 95% CI 0.79 to 1.13; I^2 = 5%; 461 participants). In addition, phlebotonics showed greater efficacy for trophic disorders, cramps, restless legs, swelling and paraesthesia, when compared with placebo. We identified heterogeneity for the variables of pain, itching, heaviness, quality of life and global assessment by participants. For quality of life, it was not possible to pool the studies because heterogeneity was high. However, high-quality evidence suggests no differences in quality of life for calcium dobesilate compared with placebo (MD -0.60, 95% CI -2.15 to 0.95; I^2 = 40%; 617 participants), and low-quality evidence indicates that in the aminaftone group, quality of life was improved over that reported in the placebo group (MD -10.00, 95% CI -17.01 to - 2.99; 79 participants). Moderate-quality evidence shows that the phlebotonics group had greater risk of non-severe adverse events than the placebo group (RR 1.21, 95% CI 1.05 to 1.41; I^2 = 0; 3975 participants). Gastrointestinal disorders were the most frequently reported adverse events.

Authors' conclusions

Moderate-quality evidence shows that phlebotonics may have beneficial effects on oedema and on some signs and symptoms related to CVI such as trophic disorders, cramps, restless legs, swelling and paraesthesia when compared with placebo but can produce more adverse effects. Phlebotonics showed no differences compared with placebo in ulcer healing. Additional high-quality RCTs focused 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

Insufficient blood circulation in the veins of the legs 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.

Key results

In total, 66 studies (53 with quantifiable data, including 6013 participants; mean age 50 years) met the eligibility criteria for this review (current until August 2015). Moderate-quality evidence from 13 studies (involving 1245 people) suggests that phlebotonics reduce puffiness (oedema) compared with placebo. Low quality evidence suggests there is no difference in the proportion of healed ulcers with phlebotonics compared with placebo. For quality of life, it was not possible to combine all studies because of differences between the studies. However, individual phlebotonic treatments shows high quality evidence there is no difference in quality of life for the phlebotonic calcium dobesilate. Low-quality evidence revealed improvement of quality of life for aminaftone when compared to placebo. Furthermore evidence suggests phlebotonics have beneficial effects on trophic disorders, cramps, restless legs, swelling and tingling. However, the relevance of these findings to the overall clinical state remains unclear. Moderate-quality evidence from 33 studies (involving 3975 people) shows that phlebotonics produce more side effects, especially gastrointestinal disorders.

Quality of the evidence

The quality of evidence was downgraded because of selective reporting for the outcome ulcer healing, for incomplete outcome data for the outcomes ulcer healing, oedema and adverse events and for unclear randomisation and imprecision of the overall results for the outcome quality of life.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Phlebotonics compared with placebo for venous insufficiency

Phlebotonics compared with placebo for venous insufficiency

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

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	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]	Evidence of a positive effect of phlebotonics for patients with CVI regarding oedema in the lower legs with a statistically significant lower risk ratio for the phlebotonics group
Oedema in the lower legs (circumference, mm) Follow-up: 1-12 months		Mean oedema in the lower legs (circumference, mm) in the intervention groups was **4.27 mm lower** (5.61 to 2.93 lower)		2010 (15 studies)	⊕⊕⊕⊖ **Moderate** [b]	Evidence of a positive effect of phlebotonics for patients with CVI regarding oedema in the lower legs with statistically significant lower mean oedema in the lower legs in the intervention group
Ulcer cured 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** [c,d]	No evidence of an effect of phlebotonics for patients with CVI regarding ulcer healing. Differences between phlebotonics and placebo groups were not statistically significant
Quality of life: **aminaftone** Follow-up: mean 6 months		Mean quality of life in the intervention groups was **10 lower** (17.01 to 2.99 lower)		79 (1 study)	⊕⊕⊖⊖ **Low** [e,f]	Evidence of an effect of phlebotonics for patients with CVI regarding quality of life
Quality of life:		Mean quality of life in the intervention groups was		617 (2 studies)	⊕⊕⊕⊕ **High**	No evidence of an effect of phlebotonics for patients with CVI regarding quality of

dobesilate Follow-up: 2-12 months		**0.60 lower** (2.15 lower to 0.95 higher)				life. Differences between phlebotonics and placebo groups were not statistically significant
Adverse events Follow-up: 1-12 months	**126 per 1000**	**153 per 1000** (132 to 177)	**RR 1.21** (1.05 to 1.40)	4054 (34 studies)	⊕⊕⊕⊖ **Moderate** g	Evidence of a greater incidence of adverse events in the phlebotonics group than in the placebo group

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]One study rated as high risk of bias for incomplete outcome data (number of participants excluded after randomisation was important (51/120; 42.5%), no ITT analysis conducted)
[b]Some studies presented unclear risk of bias
[c]One study rated as high risk of bias for incomplete outcome data and selective reporting because this study was not published
[d]One study rated as high risk of bias for selective reporting
[e]The generation of randomisation was unclear
[f]The confidence interval was wide
[g]One study rated as high risk of bias for incomplete outcome data (number of participants who withdrew prematurely was described, but percentage was high (34%), no ITT analysis conducted)

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 standardised 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, 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, International Consensus has been used to define and classify CVI in a standardised fashion (Porter 1995). According to this Consensus, clinical signs (C), aetiology (E), anatomical distribution (A) and physiological conditions (P) (CEAP) are used to classify CVI. 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).

Description of the intervention

Surgery, sclerotherapy and mechanical compression are generally 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

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 (Spanish Min. Health).

Controversy surrounds the clinical relevance of the efficacy and benefit-risk balance of phlebotonics. Case-control studies have found that risk of agranulocytosis 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, evaluation of available evidence is needed.

OBJECTIVES

To assess the efficacy and safety of phlebotonics administered both orally and 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 CVI at any stage of the disease. We excluded from this systematic review (SR) studies that did not meet the above criteria. We did not choose specific diagnostic classifications of CVI a priori because most of the studies were carried out before 1994 - the year of 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

Participants included males and females over 18 years of age suffering from any type of CVI. CVI could be diagnosed according to explicit clinical criteria and/or by objective instruments. Patient 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 patients 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 did not include in this review 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, 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 such as venous ulcers 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 (small red points on the skin caused by permanently opened tiny blood vessels), 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.
  - Satisfaction of participants.
- *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 Trials Search Co-ordinator (TSC) searched the Specialised Register (August 2015), along with the Cochrane Central Register of Controlled Trials (http://www.metaxis.com/CRSWeb/Index.asp) (CENTRAL; 2015, Issue 7). See Appendix 1 for details of the search strategy used to search the CRS. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular module in *The Cochrane Library* (www.cochranelibrary.com).

Searching other resources

For this update, we searched the reference lists of articles retrieved by electronic searches for additional citations. We also contacted authors of unpublished studies.

We searched for ongoing studies in the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch) (last searched August 2015, using the terms "chronic venous" AND "placebo" and the recruitment status "recruiting patients").

Data collection and analysis

Selection of studies

In the first version of this SR, two review authors (MMZ and RV, DC or EV) assessed independently the eligibility of studies identified by the searches. Some disagreements arose about the eligibility assessment; consequently, a third review author (XB) evaluated these studies independently and discussed them with the rest of the team, and a consensus opinion was reached. In the present update, two review authors (RV and SU) assessed independently the eligibility of new studies identified by the searches. A third review author (MMZ) helped to resolve disagreements.

Data extraction and management

In the update of this SR, two review authors (RV and SU) independently extracted data from new studies and entered them on a previously tested standardised form. A third review author

(MMZ) checked the extracted data. Collected information includes 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 analysed only data related to the first period of treatment.

Assessment of risk of bias in included studies

Two review authors (RV and SU) assessed independently the risk of bias of included studies. A third review author (MMZ) helped to resolve disagreements. 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 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).

We also evaluated the quality of the evidence by using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) system and developed a 'Summary of findings' table (Schünemann 2011). We rated the quality (certainty) of the evidence as high, moderate, low or very low while considering several components (risk of bias, consistency, directness, precision and publication bias).

Measures of treatment effect

We estimated effects of treatment with phlebotonics by using risk ratios (RRs) for dichotomous variables and mean differences (MDs) or standardised 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

The unit of analysis was the individual participant.

Dealing with missing data

We analysed dichotomous variables by applying the intention-to-treat (ITT) principle to analyse 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 analysed data as provided by study authors, either per protocol or as ITT values.

Assessment of heterogeneity

Before obtaining global effect estimators, we carried out an analysis to detect the presence of heterogeneity by using the I^2 statistic. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than to sampling error (Higgins 2011b). 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 oedema (dichotomous variable) was subject to publication bias.

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 outcomes of variables measured by ordinal categorical scales in the included studies 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).

Summary of findings

We used the principles of the GRADE system to assess the quality of the body of evidence associated with main outcomes and constructed a 'Summary of findings' (SoF) table using GRADE profiler software (GRADEpro 2008). The GRADE approach appraises the quality 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 quality of a body of evidence considers within-study risk of bias, directness of the evidence, heterogeneity in the data, precision of effect estimates and additional considerations (including risk of publication bias) (Schünemann 2011).

Two review authors (MMZ and RV) independently assessed the quality of the body of evidence on the following outcomes.

- Oedema in the lower legs (dichotomous variable).
- Oedema in the lower legs (circumference mm).
- Quality of life.
- Participants with ulcer cured.
- Participants with adverse events.

Subgroup analysis and investigation of heterogeneity

Apart from the overall analysis of phlebotonics, we carried out subgroup analyses of the active principles. These included looking at the influence on results 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.

RESULTS

Description of studies

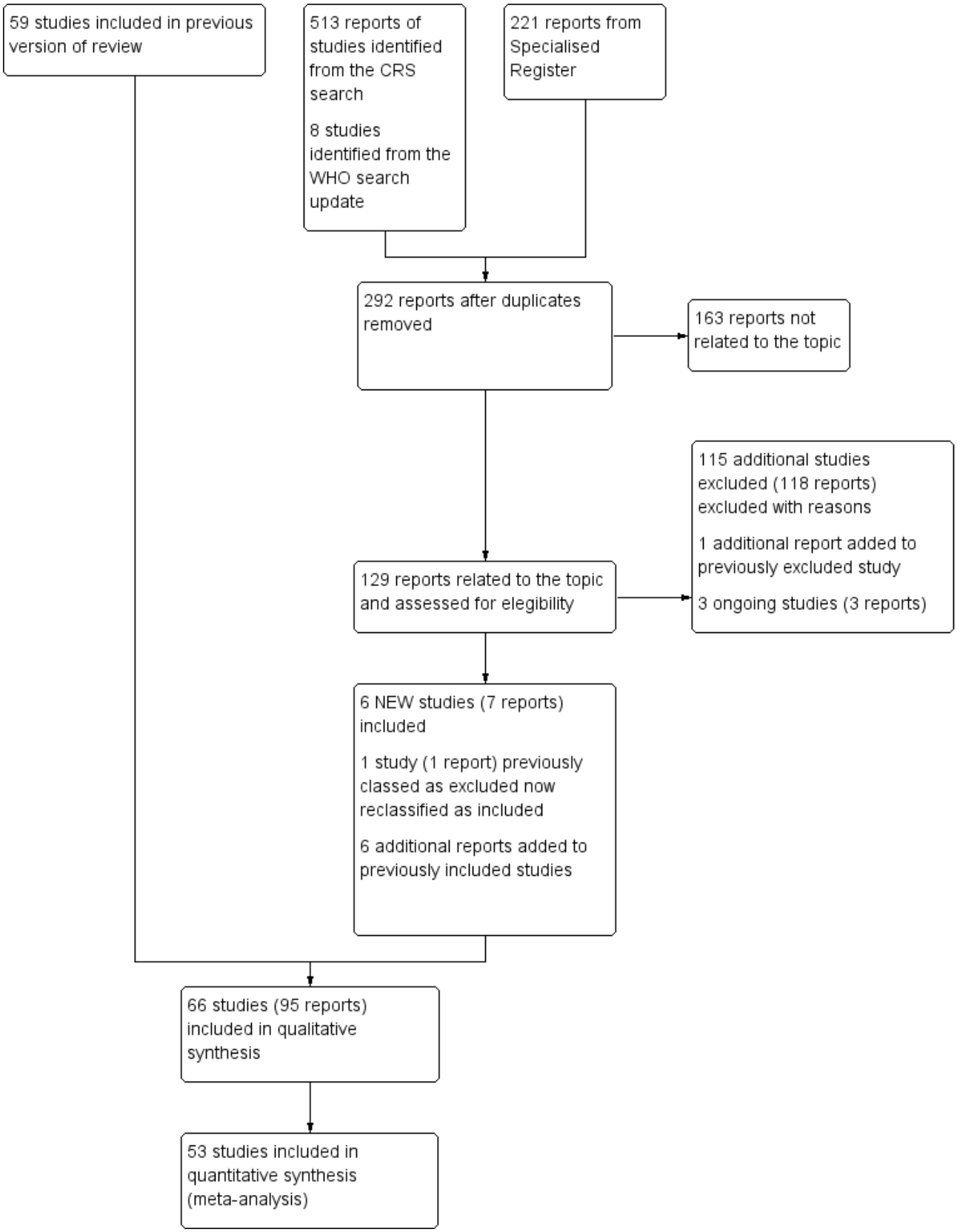
Details of all included studies are provided in the Characteristics of included studies, Characteristics of ongoing studies and Characteristics of excluded studies tables.

We applied no language restrictions.

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

For this update, we identified six new included studies (Belczak 2014; DOBESILATO500/2; Martinez-Zapata 2008; Padros 1972; Rabe 2011; Rose 1970). We reclassified one study that was previously excluded as an included study (Cesarone 2002). We obtained information from researchers about the unpublished and interrupted clinical trial DOBESILATO500/2. In total, we included 66 studies. Of the 66 included double-blind, placebo-controlled clinical trials, we did not include 13 studies in the efficacy analysis; 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 (Padros 1972; Pecchi 1990) and another corresponded to french bark pine extract (Petrassi 2000). Most studies were published in English, but five were published in German (Biland 1982; Kiesewetter 1997; Koscielnny 1996; Padros 1972; Pedersen 1992), eight in French (Cauwenberge 1978; Chassignolle 1994; Padros 1972; Planchon 1990; Thebaut 1985; Vin 1994; Welch 1985; Zucarelli 1987), four in Spanish (Flota-Cervera 2008; Klüken 1971; Marinello 2002; Serralde 1990) and three in Italian (Allegra 1981; Lazzarini 1982; Pecchi 1990).

We excluded these studies from the efficacy analysis for these 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 (Padros 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 value = 0.039) (Mann 1981).

Of the 53 studies with oral phlebotonics included in the efficacy analysis, studied phlebotonics corresponded to 28 studies of rutosides, 10 of hidrosmine and diosmine, nine of calcium dobesilate, two of Centella asiatica, two of aminaftone, one of french maritime pine bark extract and one of grape seed extract. No studies with 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 two studies, in which follow-up lasted six months.

Overall, we included 6013 participants in the meta-analysis; 81% were female and 19% were male; mean age was 50 years (range 32 to 62 years). The mean number of participants included per clinical trial was 113 (range 20 to 660). 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 28% of studies reported the diagnostic classification used. Among studies that did report on the diagnostic classification of CVI, the CEAP classification (Belczak 2014; Danielsson 2002; DOBESILATO500/2; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a; Vanscheidt 2002b) was used most often, 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 (Cornu-Thenard 1985; Danielsson 2002; Gilly 1994; Hachen 1982; Thebaut 1985) were performed with participants at early and symptomatic CVI stages, and others (Casley-Smith 1988; DOBESILATO500/2; Guilhou 1997; Lazzarini 1982; Marinello 2002; Planchon 1990; Schultz-Ehrenburg 1993; Vanscheidt 2002a) included participants at advanced stages because of long progression of the disease or the presence of venous ulcers. 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 compression therapy (DOBESILATO500/2; Guilhou 1997; Laurent 1988; Lazzarini 1982; Marinello 2002; Martinez-Zapata 2008; Planchon 1990; Rabe 2011; Schultz-Ehrenburg 1993; Zucarelli 1987).

Ten studies used a visual analogue scale (VAS) to measure subjective variables (Alterkamper 1987; Cesarone 2002; DOBESILATO500/2; Labs 2004; Martinez-Zapata 2008; Rabe 2011; 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 (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 excluded an additional 115 studies (Akbulut 2010; Allaert 1992; Amato 1994; Androulakis 1989; Avram 1996; Bacci 2003; Bastide 1976; Batchvarova 1989; Batchvarova 1989a; Behar 1993; Belcaro 1986; Belcaro 1995; Belcaro 2002; Belcaro 2003; Belcaro 2008; Belcaro 2008b; Bello 1990; Beltramino 1999; Bento 2006; Berson 1978; Berson 1980; Bohm 1989; Bolliger 1972; Bosse 1985; Brami 1983; Brock 1991; Brock 2001; Carstens 1985; Cesarone 1992; Cesarone 1994; Cesarone 2001b; Cesarone 2001d; Cesarone 2001e; Cesarone 2003; Cesarone 2005; Cesarone 2006; Cesarone 2006a; Cesarone 2006b; Cesarone 2006c; Cesarone 2006d; Cesarone 2010; Chiummariello 2009; Cospite 1989; Cospite 1996; Cospite 1998; Delacroix 1981; Delecluse 1991; de Parades 1990; Dustmann 1984; Erdlen 1989; Erler 1991; Fitzgerald 1967; Glinski 1999; Gonzalez-Fajardo 1990; Henriet 1995; Honorato 1990;

Horvath 1985; Incandela 2001a; Incandela 2001b; Incandela 2002b; ISRCTN5340167; Janssens 1999; Janssens 1999a; Jantet 2000; Kalus 2004; Koch 2002; Koltringer 1993; Kostering 1985; Krähenbühl 1975; Krcílek 1973; Le Dévéhat 1989; Lefebvre 1991; Marastoni 1982; Marastoni 1982a; Monreal 1994; Monreal 1997; Monteil-Seurin 1993; Monteverde 1987; Morales 1993; Muschietti 1978; Naser-Hijazi 2004; NCT01654016; NCT02191163; NCT02191254; NCT02191280; Neumann 1995; Neumann-Mangoldt 1979; Nill 1970; Ottillinger 2001; Paciaroni 1982; Partsch 1981; Paul 1983; Pauschinger 1987; Pecking 1998; Pointel 1987b; Pokrovskii 2005; Questel 1983; Rabe 2011b; Rehn 1993; Rehn 1993b; Riccioni 2004; Roztocil 1977; Roztocil 2003; Sadoun 1993; Sanctis 2001; Schmeck-Lindenau 2003; Stefanini 1996; Steiner 1990; Steiner 1992; Strefezza 2010; Topalov 1990; Tsukanov 2010; Turio 2000; Weindorf 1987; Zuccarelli 1996), making a total of 163 studies excluded for a variety of reasons (see Characteristics of excluded studies for details). In total, we excluded 31 studies because they did not use placebo as a control (Amato 1994; Avram 1996; Belcaro 1986; Belcaro 2002; Beltramino 1999; Berson 1976; Berson 1980; Brock 1991; Brock 2001; Cesarone 2005; Cesarone 2006; Cesarone 2006a; Cesarone 2006b; Cospite 1989; Cospite 1998; Honorato 1990; ISRCTN5340167; Koch 2002; Marastoni 1982a; Monreal 1994; Monteverde 1987; Muschietti 1978; Neumann 1995; Rehn 1993; Rehn 1996; Sadoun 1993; Stefanini 1996; Stegmann 1987; Strefezza 2010; Tsukanov 2010; Zicot 1993), 56 because the intervention used by researchers was not included in this SR (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; 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; Weindorf 1987; Widmer 1972; Zuccarelli 1996), 29 because no clinical endpoints were assessed or only outcomes not included in this SR were reported (Androulakis 1989; Auteri 1990; Belcaro 1995; Belcaro 2008; Boisseau 1995; Bort 1995; Cesarone 1992; Cesarone 1994; Cesarone 2001; Cesarone 2001c; 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), 16 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) and seven because they were not considered RCTs (Batchvarova 1989; Belcaro 2008b; Berson 1978; Cesarone 2006c; Fitzgerald 1967; Jantet 2000; Pollastri 1982). Furthermore, we excluded 24 studies because the study population did not include patients with venous insufficiency (Allaert 1992; Belcaro 2003; Boccalon 1989; Cesarone 2001d; Cesarone 2001e; Cesarone 2002a; Cesarone 2003; Cesarone 2006d; Friederich 1978; Gouny 1999; Incandela 2001a; Incandela 2001b; Incandela 2002b; Kranendonk 1993; Lambelet 1973; Lefebvre 1991; Monreal 1997; Pecking 1998; Petruzzellis 1990; Rehn 1993b; Rish 1972; Schmeck-Lindenau 2003; Steiner 1986; Strauss 1992).

Risk of bias in included studies

Only four studies (Labs 2004; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a) presented low risk of bias (see Characteristics of included studies, Figure 2 and Figure 3).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

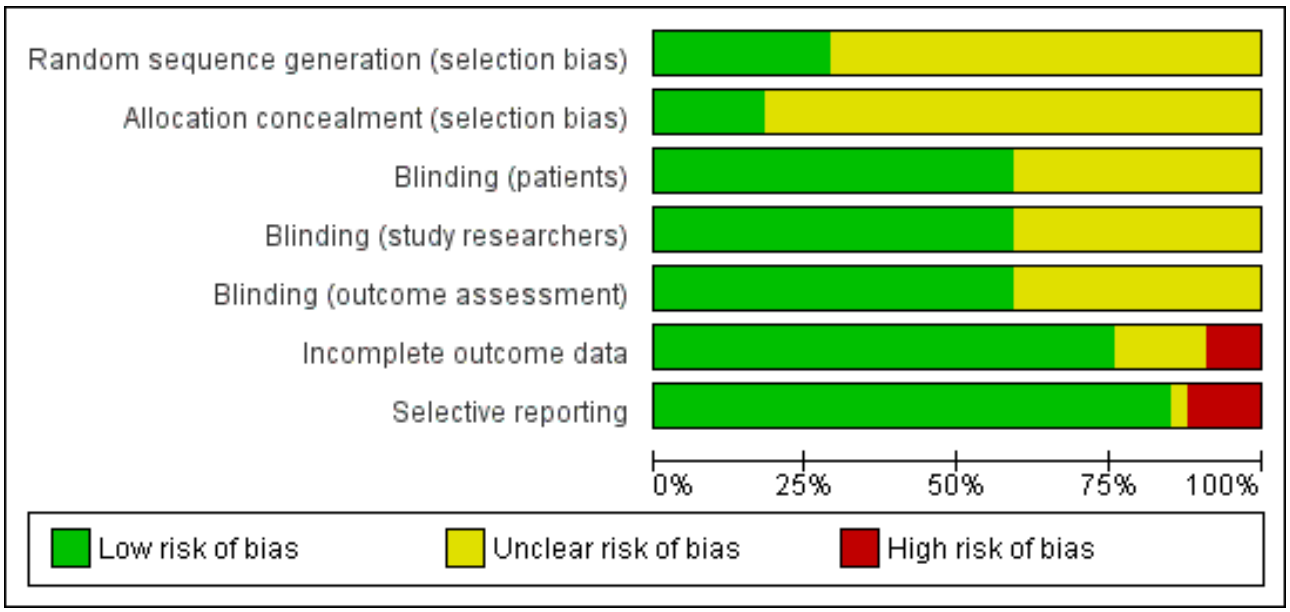


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

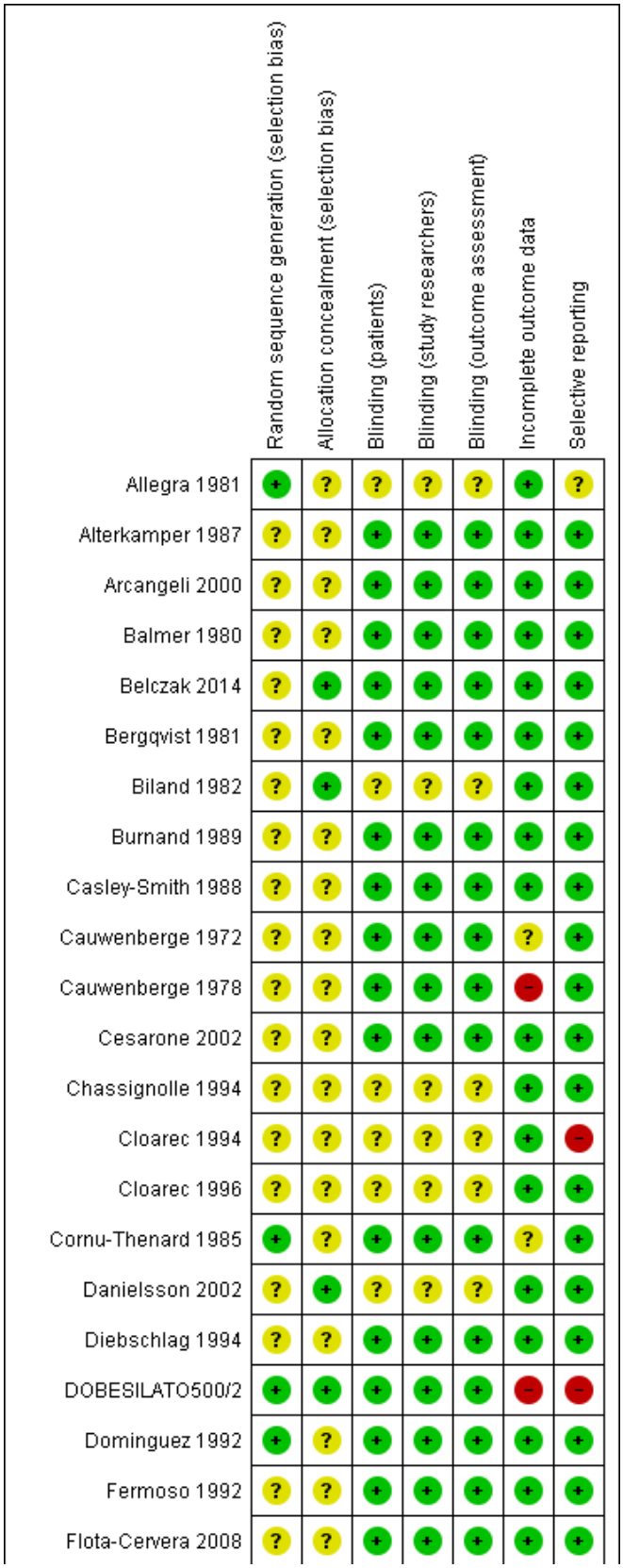


Figure 3. (Continued)

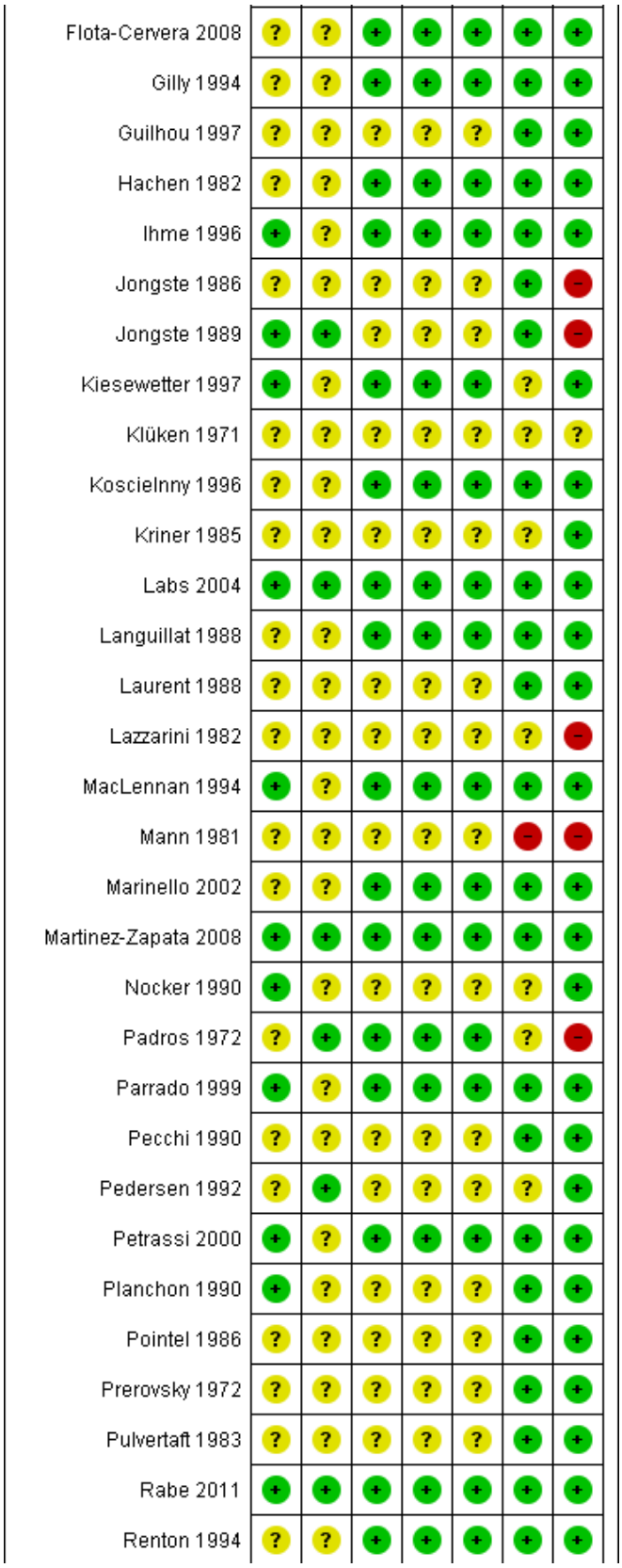
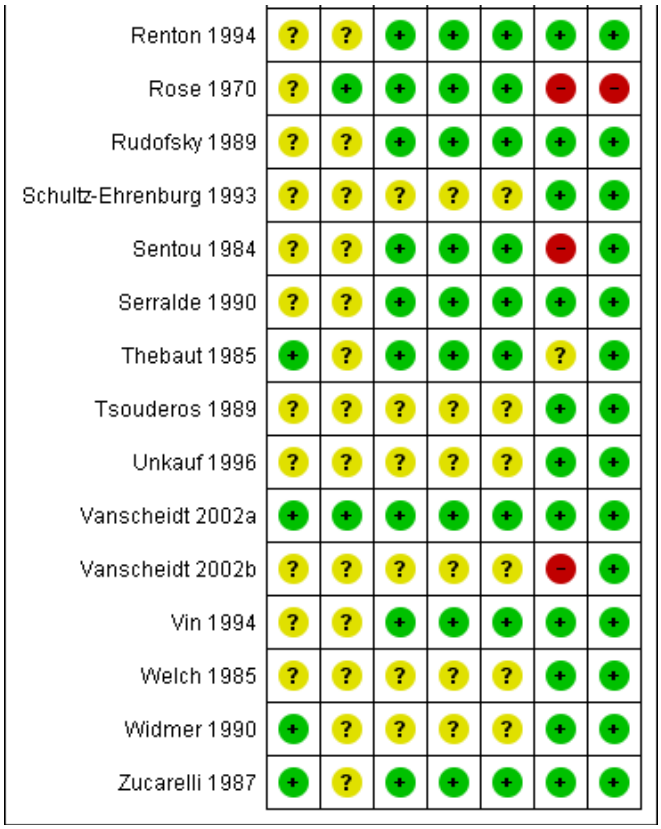


Figure 3. (Continued)



Allocation

Of the 66 studies included, 19 (29%) submitted details on the randomisation process (see Characteristics of included studies).

Only 12 (18%) 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; Padros 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 (Jongste 1989; Labs 2004; Vanscheidt 2002a) used computerised random assignment.

Blinding

Of the 66 studies included, 39 (59%) reported that the placebo used was identical to the active treatment; thus participants, study researchers and outcome assessors were blinded to the intervention. The other studies did not mention whether placebo had identical characteristics to those of the active drug (see Characteristics of included studies).

Incomplete outcome data

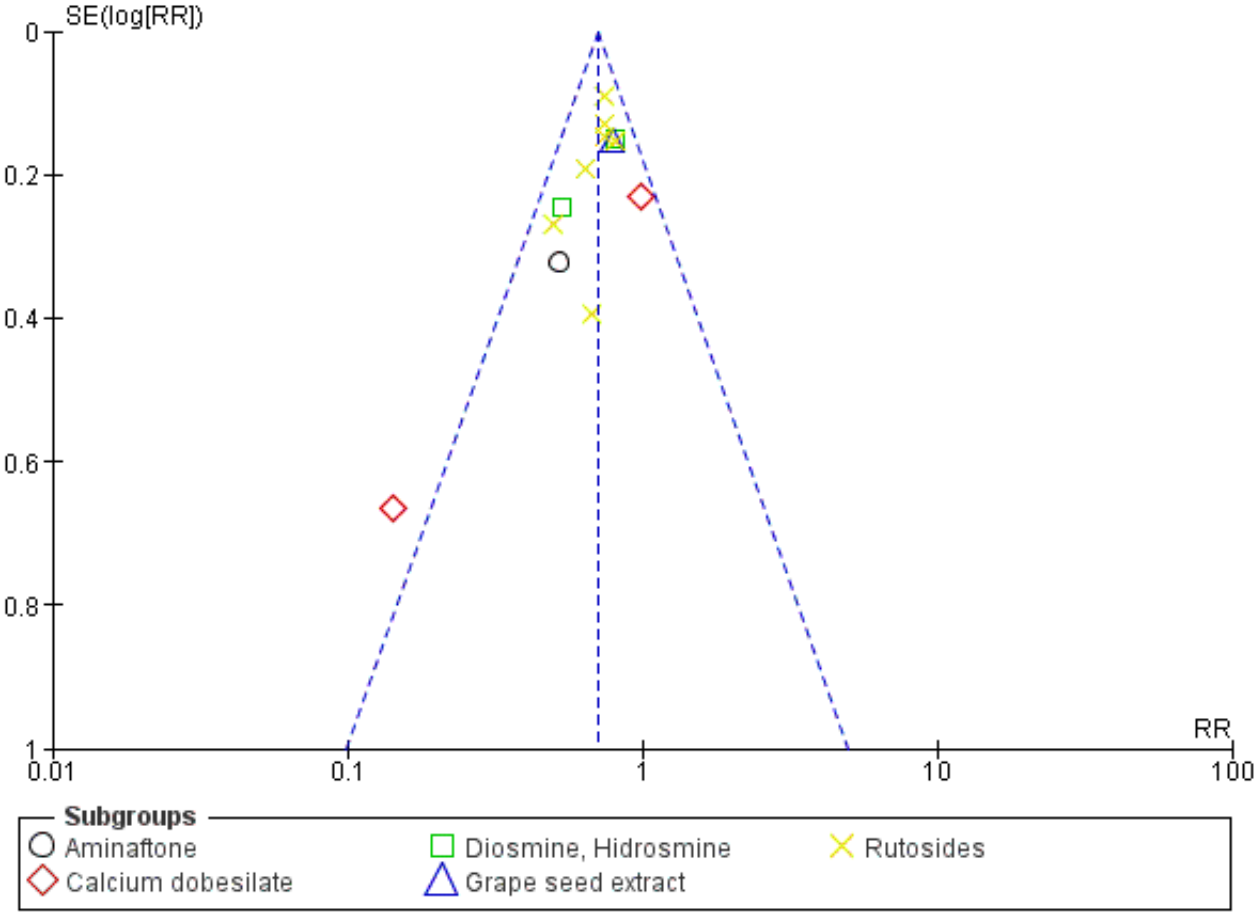
Of the 66 studies included, 51 (77%) reported participant withdrawals. The percentage of withdrawn participants ranged from 0% to 42.5% (see Characteristics of included studies). Only seven (16%) studies included in the efficacy analysis stated that investigators carried out an ITT analysis (Dominguez 1992; Guilhou 1997; Ihme 1996; Martinez-Zapata 2008; Rabe 2011; Unkauf 1996; Vanscheidt 2002a). Six studies had high risk of bias in this domain (Cauwenberge 1978; DOBESILATO500/2; Mann 1981; 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).

Selective reporting

Of the 66 studies included, 56 (85%) reported all outcomes specified in the methods section. We evaluated six 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), and because data before the cross-over were not reported (Padros 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.

Figure 4 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. Apart from one imprecise study favouring phlebotonics (Casley-Smith 1988), no small or heterogeneous studies provided results favouring placebo or phlebotonics.

Figure 4. Funnel plot of comparison: 1 Phlebotonics vs placebo, outcome: 1.1 Oedema in the lower legs (dichotomous variable).



Effects of interventions

See: **Summary of findings for the main comparison** Phlebotonics compared with placebo for venous insufficiency

See Summary of findings for the main comparison for the main comparison. Results of all analysed outcomes are specified in an additional Table 1. Results of outcomes analysed 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 66 included studies, we excluded 13 studies (Bergqvist 1981; Cloarec 1994; Jongste 1986; Mann 1981; Nocker 1990; Padros 1972; Pecchi 1990; Petrassi 2000; Prerovsky 1972; Renton 1994; Rose 1970; Rudofsky 1989; Sentou 1984) from the efficacy analysis for the reasons explained under Included studies. 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).

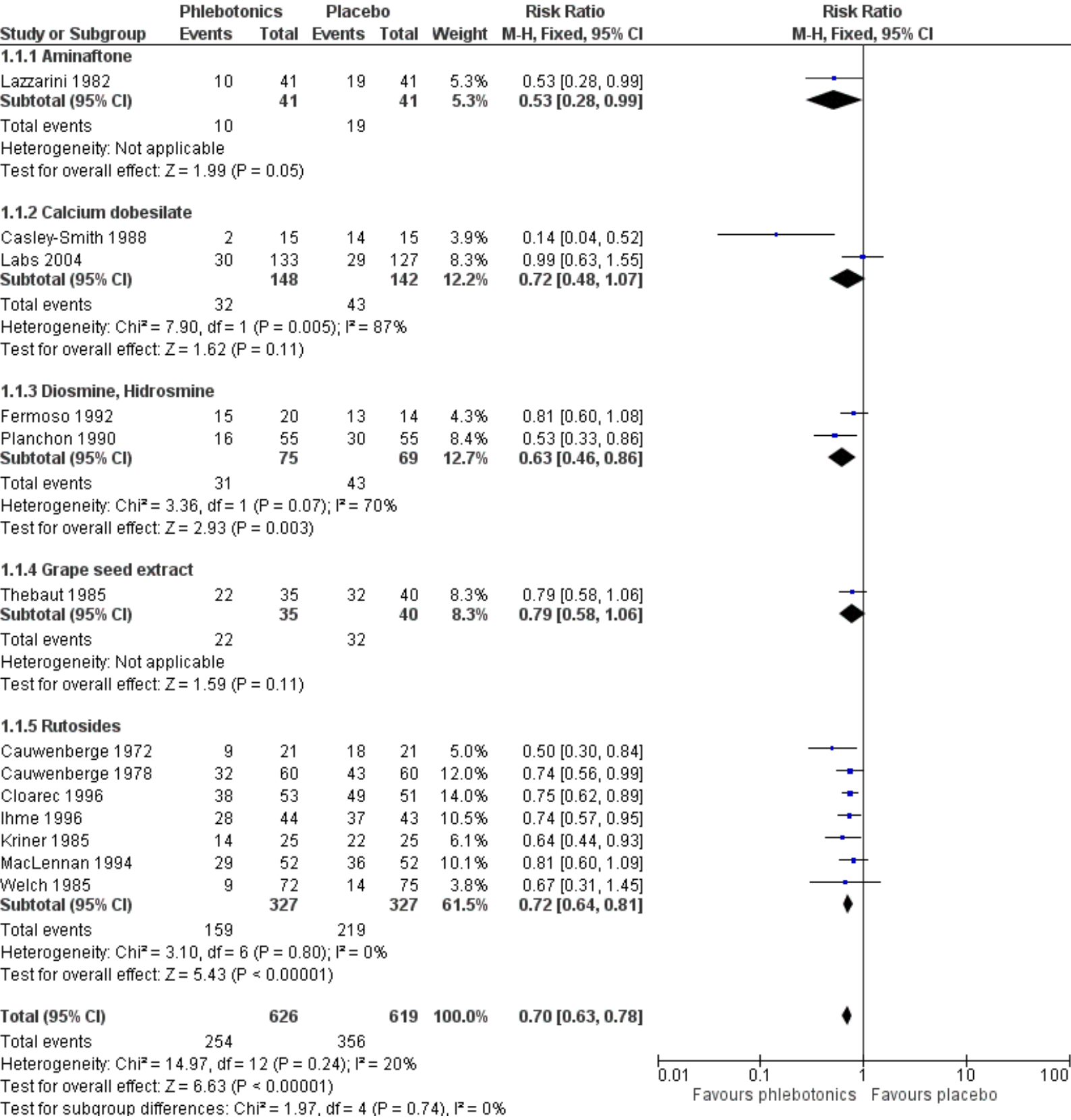
Assessment of CVI: objective signs

Oedema in the lower limb

Dichotomous variable

We included 13 trials in the 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 overall quality of the evidence was moderate because incomplete outcome data for one study led to high risk of bias (Summary of findings for the main comparison). Pooled results were statistically significant and favoured phlebotonics (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.63 to 0.78; I^2 = 20%) (Analysis 1.1) (Figure 5).

Figure 5. Forest plot of comparison: 1 Phlebotonics vs placebo, outcome: 1.1 Oedema in the lower legs (dichotomous variable).



Continuous variables

Ankle perimeter circumference

We included 15 studies in the 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 overall quality of the evidence was moderate because 12 studies had unclear risk of bias. Pooled results significantly favoured phlebotonics (Analysis 1.2) (mean difference (MD) -4.27 mm, 95% CI -5.61 to -2.93; I^2 = 47%).

Volume of the leg

We included nine studies in the analysis: five corresponding to rutosides (Burnand 1989; Diebschlag 1994; Ihme 1996; Kiesewetter 1997; Vanscheidt 2002a), three to calcium dobesilate (Casley-Smith 1988; Rabe 2011; Widmer 1990) and one to aminaftone (Belczak 2014), with a total of 512 participants treated with phlebotonics and 529 with placebo. Pooled results significantly favoured phlebotonics (Analysis 1.3) (standardised mean difference (SMD) -0.38 mL, 95% CI -0.50 to -0.25; I^2 = 11%).

Skin manifestations

Ulcer cured

Dichotomous variable

We included six trials in the 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. Pooled results of these six studies showed no statistically significant differences between phlebotonics and placebo (Analysis 1.4) (RR 0.94; 95% CI 0.79 to 1.13; I^2 = 5%). The quality of the evidence was low (Summary of findings for the main comparison).

Trophic disorders

Dichotomous variable

We included six studies in the 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. Pooled results significantly favoured phlebotonics (Analysis 1.5) (RR 0.87, 95% CI 0.81 to 0.95; I^2 = 0%).

Telangiectasia, reticular veins and varicose veins

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: subjective symptoms

Pain in the lower legs

Dichotomous variable

We included 20 trials in the analysis: 10 on rutosides (Balmer 1980; Cauwenberge 1972; Cauwenberge 1978; Jongste 1989; Klüken 1971; Languillat 1988; Pedersen 1992; Pulvertaft 1983; Vanscheidt 2002a; Welch 1985), four on calcium dobesilate (Casley-Smith 1988; Flota-Cervera 2008; Hachen 1982; 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 1294 participants treated with phlebotonics and 953 with placebo (Analysis 1.6). The analysis showed heterogeneity (I^2 = 78%); therefore, we did not pool the data.

Continuous variable

We included nine studies in the analysis: four on calcium dobesilate (DOBESILATO500/2; Marinello 2002; Martinez-Zapata 2008; Rabe 2011), three on rutosides (Cloarec 1996; Cornu-Thenard 1985; Parrado 1999), one on diosmine (Gilly 1994) and one on french maritime pine bark extract (Arcangeli 2000), with a total of 588 participants assigned to phlebotonics and 597 to placebo (Analysis 1.7). The analysis showed heterogeneity (I^2 = 80%); therefore, we did not pool the data.

Cramps in the lower legs

Dichotomous variable

We included 14 studies in the 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 (Analysis 1.8). Pooled results significantly favoured phlebotonics (RR 0.72, 95% CI 0.58 to 0.89; I^2 = 73%).

Continuous variable

We included four studies in the 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 1.9). The analysis showed heterogeneity (I^2 = 86%); therefore, we did not pool the data.

Restless legs

Dichotomous variable

We included seven studies in the 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 1.10). Pooled results significantly favoured phlebotonics (RR 0.81, 95% CI 0.72 to 0.91; I^2 = 18%).

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 1.11). The analysis showed heterogeneity (I^2 = 92%); therefore, we did not pool the data.

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 1.12). 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 1.13). The analysis showed heterogeneity (I^2 = 80%), and we did not pool the data.

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 1.14). 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 (Analysis 1.15). Pooled results significantly favoured phlebotonics (RR 0.63, 95% CI 0.50 to 0.80; I^2 = 69%).

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 1.16). 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 1.17). Pooled results significantly favoured phlebotonics (RR 0.67, 95% CI 0.50 to 0.88; I^2 = 72%).

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 1.18). Outcomes of the analysis were not statistically significantly different between phlebotonics and placebo (SMD -0.15, 95% CI -0.44 to 0.13; I^2 = 0%).

Global assessment measures

Quality of life

Five studies (Belczak 2014; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a; Vanscheidt 2002b) evaluated quality of life (QoL). 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 and Rabe 2011 evaluated QoLvia the Chronic Venous Insufficiency International Questionnaire (CIVIQ).Belczak 2014 used a specific questionnaire for chronic venous disease adapted from Cesarone 2006b. It was not possible to pool results of these three studies because heterogeneity was assessed at 76% (Analysis 1.19).

The subgroup analysis of aminaftone showed favourable results compared with placebo, but the confidence interval was wide because few participants were included (MD -10.00, 95% CI -17.01 to - 2.99). However, pooled results of the two studies of dobesilate were not statistically significantly different between phlebotonics and placebo (MD -0.60, 95% CI -2.15 to 0.95; I^2 = 40%). The quality of the evidence was low for aminaftone and high for dobesilate (Summary of findings for the main comparison).

Global assessment by the participant

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.

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

Trials considering rutosides (16 trials), hidrosmine-diosmine (eight trials), calcium dobesilate (seven trials), aminaftone (one trial), grape seed extract (one trial) and Centella asiatica (one trial) reported information on adverse events.

Adverse events

We included in the analysis a total of 2080 participants treated with phlebotonics and 1974 with placebo. Pooled results statistically significantly favoured the placebo group (RR 1.21, 95% CI 1.05 to 1.40; I^2 = 0%) (Analysis 1.22) (Figure 6). The quality of the evidence was moderate (Summary of findings for the main comparison).

Figure 6. Forest plot of comparison: 1 Phlebotonics vs placebo, outcome: 1.22 Adverse events.

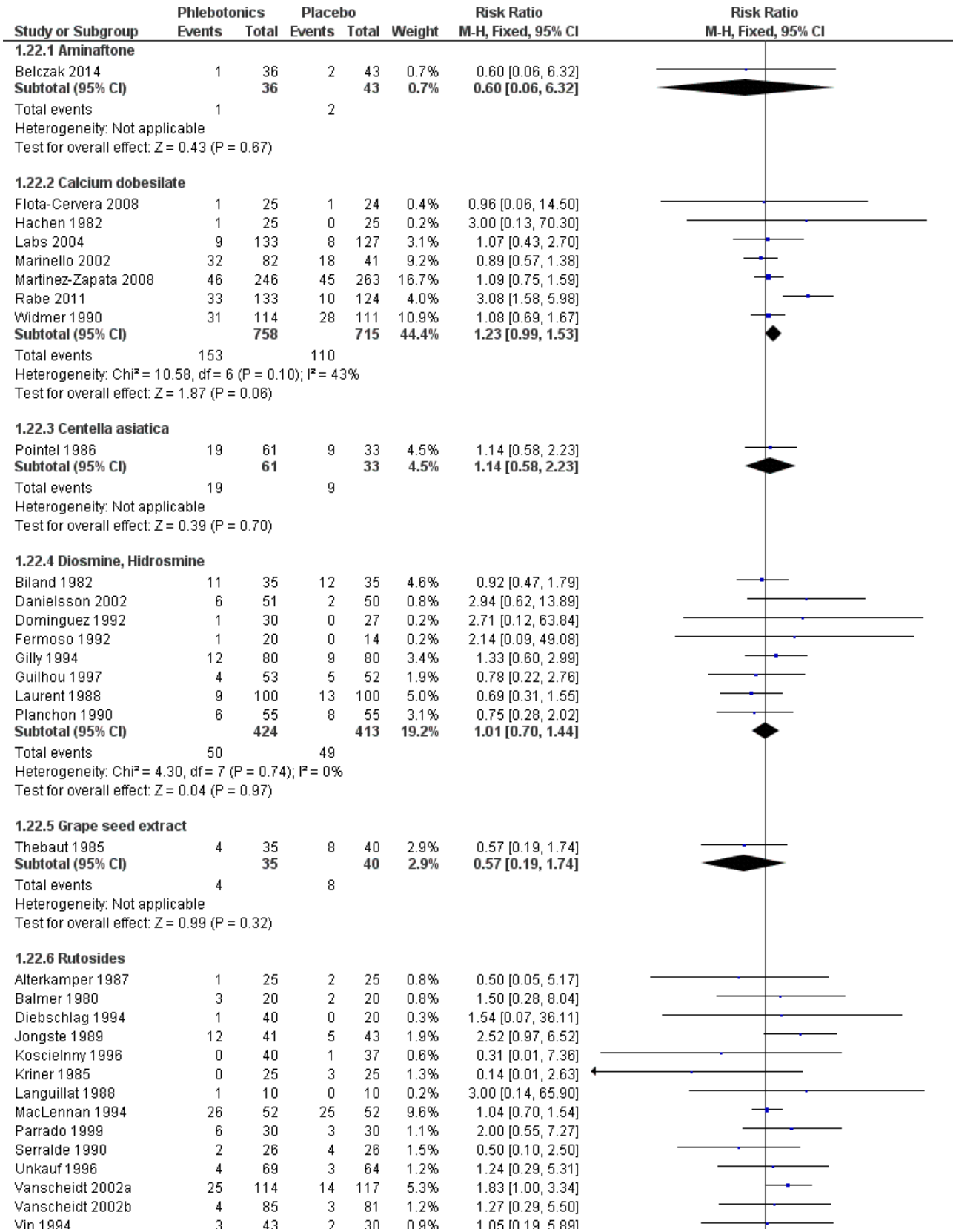
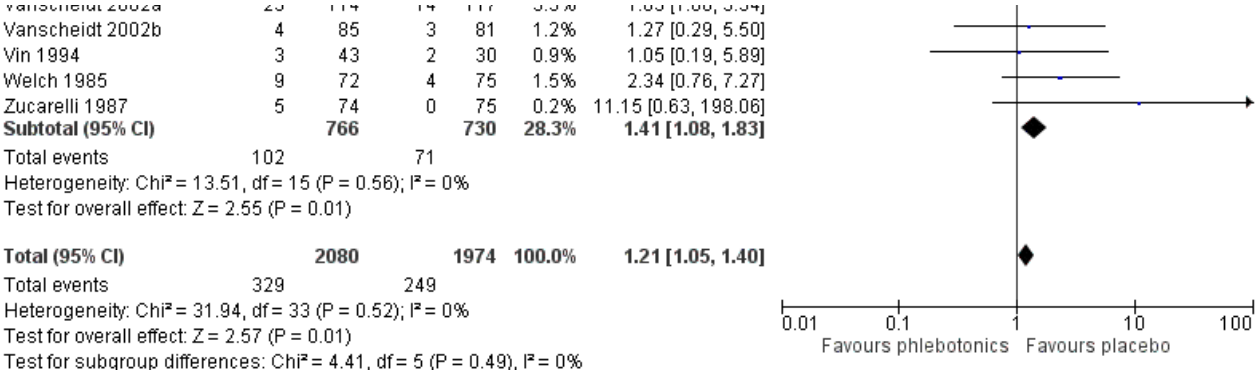


Figure 6. (Continued)



Adverse events analysed 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 (RR 0.60, 95% CI 0.06 to 6.32).

Calcium dobesilate

In total, seven trials evaluated adverse events (Flota-Cervera 2008; Hachen 1982; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Widmer 1990). Twenty per cent of participants in the calcium dobesilate group (153/758) experienced an adverse event and 15.4% (110/715) in the placebo group. Pooled results showed no statistically significant differences between phlebotonics and placebo (RR 1.23, 95% CI 0.99 to 1.53; I^2 = 43%; P value = 0.06). The most common adverse event was a gastrointestinal event (epigastric discomfort, vomiting). No agranulocytosis or white blood cell disorders were identified. Nineteen participants were withdrawn from the calcium dobesilate group and 10 from the placebo group as the result of adverse events.

Centella asiatica

One study reported information on adverse events (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. Comparison between groups showed no statistically significant differences between phlebotonics and placebo (RR 1.14, 95% CI 0.58 to 2.23). 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

Eight 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). Fifty adverse events were identified in the hidrosmine and diosmine group (50/424) and 49 (49/413) in the placebo group. Pooled results showed no statistically significant differences between phlebotonics and placebo (RR 1.01, 95% CI 0.70 to 1.44; I^2 = 0%). Gastrointestinal disorders were the most significant adverse events (heartburn and nausea): 12 cases were reported in the hidrosmine and diosmine group and 11 in the placebo group.

Nine participants withdrew from the hidrosmine group and 11 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. Pooled results showed no statistically significant differences between phlebotonics and placebo (RR 0.57, 95% CI 0.19 to 1.74).

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). Thirteen per cent of participants (102/766) in the rutoside group suffered from adverse events and 9.7% (71/730) in the placebo group. Comparison between groups statistically significantly favoured the placebo group (RR 1.41, 95% CI 1.08 to 1.83; I^2 = 0%). The most common adverse events were gastrointestinal in nature (constipation, dry mouth, epigastric discomfort, vomiting): 90 in the rutoside group and 62 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).

Six participants withdrew from the rutoside group and 13 from the placebo group as the result of adverse events.

Sensitivity analysis

Exclusion of studies using compression measures (elastic stockings)

When we re-analysed 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 general results did not change, except for the following variables.

- Global analysis of the dichotomous variable pain significantly favoured phlebotonics (Analysis 2.6) (RR 0.69, 95% CI 0.57 to 0.82; 1467 participants; 17 studies; I^2 = 67%).
- Global analysis of the continuous variable cramps significantly favoured phlebotonics (Analysis 2.9) (SMD -0.70, 95% CI -1.15 to -0.24; 314 participants; three studies; I^2 = 73%).
- Global analysis of the dichotomous variable global assessment by the participant significantly favoured phlebotonics (Analysis 2.20) (RR 0.69, 95% CI 0.53 to 0.90; 1193 participants; 12 studies; I^2 = 73%).
- Global analysis of the continuous variable quality of life showed favourable results compared with placebo, but the confidence interval was wide because few participants were included (Analysis 2.19) (MD -10.00, 95% CI -17.01 to - 2.99).

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.

Analysis based on studies at low risk of bias

Exclusion of studies at high or unclear risk of bias

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

Results changed only for the following variables.

- Analysis of the dichotomous variable oedema in one study on calcium dobesilate (Labs 2004) was not significantly different between phlebotonics and placebo (Analysis 4.1) (RR 0.99, 95% CI 0.63 to 1.55; 260 participants).
- Global analysis of the continuous variable oedema (measure of ankle circumference in mm) in three studies on calcium dobesilate (Labs 2004; Martinez-Zapata 2008; Rabe 2011) was not significantly different between phlebotonics and placebo (Analysis 4.2) (MD -2.34 mm, 95% CI -8.79 to 4.11; 867 participants; I^2 = 65%).
- Analysis of the continuous variable oedema (measure of leg volume in mL) in two studies (Rabe 2011; Vanscheidt 2002a) favoured phlebotonics (Analysis 4.3) (MD -59.08 mL, 95% CI -84.40 to -33.76; 418 participants; I^2 = 0%).
- Analysis of the dichotomous variable itching in one study on rutoside (Vanscheidt 2002a) favoured phlebotonics (Analysis 4.7) (RR 0.44, 95%CI 0.32 to 0.62; 231 participants).
- Analysis of the continuous variable itching in one study on calcium dobesilate (Martinez-Zapata 2008) was not significantly different (Analysis 4.8) (MD 4.60 cm, 95% CI -5.66 to 14.86; 416 participants).
- Analysis of the dichotomous variable heaviness in one study on rutoside (Vanscheidt 2002a) favoured phlebotonics (Analysis 4.9) (RR 0.62, 95% CI 0.47 to 0.82; 231 participants).
- Analysis of the continuous variable heaviness in one study on calcium dobesilate (Martinez-Zapata 2008) was not significantly different between phlebotonics and placebo (Analysis 4.10) (MD -2.40 cm, 95% CI -7.89 to 3.09; 417 participants).
- Analysis of the continuous variable swelling in one study on calcium dobesilate (Martinez-Zapata 2008) was not significantly different between phlebotonics and placebo (Analysis 4.12) (MD -1.30 cm, 95% CI -6.72 to 4.12; 417 participants).
- Analysis of the dichotomous variable global assessment by the participant in two studies on calcium dobesilate (Labs 2004; Rabe 2011) was not significantly different between phlebotonics and placebo (Analysis 4.14) (RR 1.04, 95% CI 0.81 to 1.32; 476 participants; I^2 = 0%).
- Analysis of the continuous variable global assessment by the participant in one study on calcium dobesilate (Rabe 2011) favoured phlebotonics (Analysis 4.15) (MD -5.64, 95% CI -8.85 to -2.43; 223 participants).
- Analysis of the dichotomous variable adverse events in the four included studies was not significantly different between phlebotonics and placebo (Analysis 4.16) (RR 1.59, 95% CI 0.97 to 2.63; 1257 participants; I^2 = 63%).

DISCUSSION

Summary of main results

We evaluated the efficacy and safety of phlebotonics in the treatment of chronic venous insufficiency (CVI). Only analyses of studies with oral phlebotonics were possible because no identified study of topical phlebotonics met the inclusion criteria of this systematic review (SR). This SR included 66 randomised controlled trials (RCTs) and analysed data from 53 trials involving 6013 participants. Studies included in the review generally provided objective measurement of ankle and calf oedema reduction, as well as subjective assessment of other signs and symptoms of CVI. According to the intention-to-treat (ITT) analysis, studies showed a moderate beneficial effect for the dichotomous variable oedema. Analyses in general point to possible beneficial efficacy of phlebotonics for oedema. In addition, phlebotonics showed possible beneficial effects for trophic disorders, cramps, swelling, paraesthesia and restless legs.

However, regarding results of the dichotomous variable ulcer cured and the continuous variable paraesthesias, we found no differences between phlebotonics and placebo. For quality of life (QoL) the results were heterogeneous; evidence of low quality favoured aminaftone, and high-quality evidence showed no significant differences between calcium dobesilate and placebo. Furthermore, the incidence of adverse events was higher in the phlebotonics group than in the placebo group. Gastrointestinal disorders were the most frequently reported adverse events among studies that provided this information (rutosides, calcium dobesilate, diosmine-hidrosmine). Our SR 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.

One study on aminaftone presented favourable results for the dichotomous variables oedema, pain, cramps, itching and heaviness, although this is an old study that was not replicated

later (Lazzarini 1982). Another more recent study of aminaftone presented favourable results for the continuous variables oedema (volume) and QoL, and non-significant results for adverse events (Belczak 2014). Calcium dobesilate showed favourable results for continuous volume of the leg and global assessment by the participant. Meanwhile, results were not significant for the following continuous variables: ankle perimeter circumference, pain, restless legs, itching, heaviness and QoL. Calcium dobesilate showed favourable results for the following dichotomous variables: cramps, restless legs and swelling. However, it did not present significant differences in the dichotomous variables ulcer cured and paraesthesia. The incidence of adverse events was similar between phlebotonics and placebo groups. Centella asiatica was assessed in two studies. One study showed non-significant results compared with placebo in the dichotomous variable heaviness (Pointel 1986); the other study showed favourable results for Centella asiatica in the dichotomous variable global assessment by the participant (Allegra 1981). The number of participants with adverse events was not significantly different between Centella asiatica and placebo. Diosmine and hidrosmine showed favourable results for the dichotomous variables oedema and trophic disorders. Results of analyses of the dichotomous and continuous variables cramps and swelling favoured the diosmine and hidrosmine group, as did results of analyses of the continuous variables pain, restless, heaviness and global assessment by the participant. Results of analyses of the dichotomous variables ulcer cured, ulcer, pain, restlessness, itching, heaviness and paraesthesia were non-significant. The incidence of adverse events was not significant when we compared diosmine and hidrosmine with placebo. French maritime pine bark extract was assessed in only one study and was favoured in both dichotomous and continuous variables of pain (Arcangeli 2000). Results favoured phlebotonics in the continuous variables heaviness and swelling but were non-significant in the dichotomous variables heaviness and swelling. Grape seed extract was assessed in one study, with non-significant results reported in the dichotomous variable oedema (Thebaut 1985). Rutosides were included in the greatest number of clinical trials, showing favourable results for the dichotomous variables oedema, swelling and paraesthesia, although results were not significant for the corresponding continuous variable. Results of the variables ulcer cured, trophic disorder and restless legs were non-significant when compared with placebo. The incidence of adverse events significantly favoured the placebo group.

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

Overall completeness and applicability of evidence

Several limitations were identified in the included studies. Only 28% of studies specified standard diagnostic criteria for CVI, and different studies applied different criteria. Only nine studies (Belczak 2014; Danielsson 2002; DOBESILATO500/2; Labs 2004; Marinello 2002; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a; Vanscheidt 2002b) used the currently accepted Clinical-Aetiology-Anatomy-Pathophysiology (CEAP) classification (Porter 1995). Therefore, homogeneity in diagnostic criteria is limited, and potential misclassification bias cannot be ruled out. Furthermore, we were unable to perform a subgroup analysis by CVI stage because 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, and investigators failed to find statistically significant differences 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; some were positive, and others were not significant. Only five RCTs assessed the variable QoL using a standardised questionnaire (Belczak 2014; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a; Vanscheidt 2002b), but two studies (Vanscheidt 2002a; Vanscheidt 2002b) did not provide quantifiable information. 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 (DOBESILATO500/2; Fermoso 1992; Guilhou 1997; Lazzarini 1982; MacLennan 1994; Schultz-Ehrenburg 1993) and, when pooled, showed none that yielded a difference in ulcer healing.

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

Most studies provided short-term results (one to three months). 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 standardised. 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 uncertain 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 66 RCTs included in this SR, 38 explained the double-blinding procedure in detail, 18 provided data on randomisation and 10 explained blinding of the randomisation. Furthermore, 13 studies had attrition bias. These issues were not addressed in the remaining included studies, and this adds uncertainty to the quality of evidence. Only four studies (Labs 2004; Martinez-Zapata 2008; Rabe 2011; Vanscheidt 2002a) were graded as having low risk of bias.

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 SR. 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 SR, 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 quality of the body of evidence using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach (Schünemann 2011), which is based on five considerations including 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 quality of the body of evidence for a priori selected outcomes (in our SR, these included the dichotomous variable of oedema in the lower legs and the continuous variables of oedema in the lower legs, quality of life, participants with ulcer cured and participants with adverse events) (Summary of findings for the main comparison).

In this SR, the overall quality of evidence is ranked from low (ulcer cured and QoL for aminaftone) to moderate (dichotomous and continuous outcomes of oedema and adverse events) to high (QoL for calcium dobesilate).

Reasons for rating down the quality of evidence for the outcome ulcer cured include the presence of selective reporting and incomplete outcome data; for the outcome QoL for aminaftone unclear generation of randomisation and imprecision (wide confidence intervals); for the dichotomous variables oedema and adverse events incomplete outcome data and for the continuous variable oedema unclear risk of bias of one trial.

Potential biases in the review process

Sensitivity analyses did not significantly 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.

Any SR 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 vs 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 51% 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)). Four reviews pursued data meta-analysis (Aziz 2015; Boada 1999; Ciapponi 2004; Poynard 1994).

One review specifically evaluated hydroxyethylrutosides: 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 analysed rutosides: 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 mentioned no CVI signs (Poynard 1994).

Another review covered 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. However, review authors performed PP rather than ITT analysis and provided no information on individual phlebotonics (Boada 1999).

The review led by Ciapponi analysed calcium dobesilate: 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).

Except for Aziz 2015, the above-cited reviews were published a relatively long time ago and have not been updated. Our SR updates 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). Investigators reported no differences compared with placebo for ulcer healing. Additional high-quality randomised controlled trials (RCTs) are needed to improve the evidence base, with greater attention paid to methodological quality and clinically important outcomes.

Moderate-quality evidence supports the efficacy of phlebotonics in oedema. Low-quality evidence indicates that these drugs do not influence ulcer healing.

Some specific groups of 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.

On the other hand, moderate-quality evidence shows that phlebotonics are associated with higher risk of adverse events than placebo, especially in the rutoside group. Studies included in this systematic review (SR) provided only short-term safety data; therefore, the middle- and long-term safety of phlebotonics could not be estimated.

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 SR have improved methodological aspects and have already considered in a standardised 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 quality of life (QoL) and both ulcers 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

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 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	

Allegra 1981 *(Continued)*

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

Alterkamper 1987

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

Alterkamper 1987 *(Continued)*

	• 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" 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

Arcangeli 2000

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

Arcangeli 2000 *(Continued)*

	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	

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

Balmer 1980

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 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

Balmer 1980 *(Continued)*

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

Belczak 2014

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

Belczak 2014 *(Continued)*

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"
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

Bergqvist 1981

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

Bergqvist 1981 *(Continued)*

Outcomes	Primary • Symptoms - pain, cramps, tired legs, pruritus, swelling, side effects • Signs - plethysmographic values, calf circumference Secondary • Not stated
Notes	

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

Biland 1982

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

Biland 1982 *(Continued)*

	Gender: 7 M:49 F Inclusion criteria: symptoms related to CVI and oedema 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

Burnand 1989

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

Burnand 1989 *(Continued)*

	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
Blinding (outcome assessment)	Low risk	Quote: "This code was not broken until the completion of the study" Comment: outcome assessors blinded

Burnand 1989 *(Continued)*

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

Casley-Smith 1988

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
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"

Casley-Smith 1988 *(Continued)*

		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

Cauwenberge 1972

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 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

Cauwenberge 1972 *(Continued)*

	• 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

Cauwenberge 1978

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'

Cauwenberge 1978 *(Continued)*

	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
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

Cauwenberge 1978 *(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

Cesarone 2002

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
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

Cesarone 2002 *(Continued)*

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

Chassignolle 1994

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 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

Chassignolle 1994 *(Continued)*

- 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

Cloarec 1994

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

Cloarec 1994 *(Continued)*

	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
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)

Cloarec 1996

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: 5/109 (5%) Losses to follow-up: none

Cloarec 1996 *(Continued)*

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 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

Cloarec 1996 *(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

Cornu-Thenard 1985

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 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

Cornu-Thenard 1985 *(Continued)*

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
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

Danielsson 2002

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

Danielsson 2002 *(Continued)*

	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

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

Diebschlag 1994

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: not stated Exclusions post randomisation: none Losses to follow-up: none

Diebschlag 1994 *(Continued)*

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
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

Diebschlag 1994 *(Continued)*

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

DOBESILATO500/2

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

DOBESILATO500/2 *(Continued)*

- 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

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

Dominguez 1992

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

Dominguez 1992 *(Continued)*

	Gender: 5 M:52 F Inclusion criteria: symptomatic CVI and varicose veins and oedema 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

Fermoso 1992

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" Comment: Identical placebo ensures double-blinding

Fermoso 1992 *(Continued)*

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

Flota-Cervera 2008

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

Flota-Cervera 2008 *(Continued)*

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

Gilly 1994

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 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

Gilly 1994 *(Continued)*

	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
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

Guilhou 1997

Methods	Study design: randomised, multi-centre, double-blind, placebo-controlled Method of randomisation: not stated

Guilhou 1997 *(Continued)*

	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 endpoint • Percentage of participants with complete healing at 2 months Secondary endpoint • 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
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

Guilhou 1997 *(Continued)*

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

Hachen 1982

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 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

Hachen 1982 *(Continued)*

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

Ihme 1996

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)

Ihme 1996 *(Continued)*

	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
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

Jongste 1986

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 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

Jongste 1986 *(Continued)*

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

Jongste 1989

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 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

Jongste 1989 *(Continued)*

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
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

Kiesewetter 1997

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

Kiesewetter 1997 *(Continued)*

	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" 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

Klüken 1971

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

Klüken 1971 *(Continued)*

	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 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

Koscielnny 1996

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 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"

Koscielnny 1996 *(Continued)*

		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 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

Kriner 1985

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	

Kriner 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Labs 2004

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

Languillat 1988

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	

Risk of bias

Bias	Authors' judgement	Support for judgement

Languillat 1988 *(Continued)*

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

Laurent 1988

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 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

Laurent 1988 *(Continued)*

	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

Lazzarini 1982

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

Lazzarini 1982 *(Continued)*

	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
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

Lazzarini 1982 *(Continued)*

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

MacLennan 1994

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: 16/104 (15%)
Participants	Country: UK 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 Secondary • Side effects
Notes	
Risk of bias	

MacLennan 1994 *(Continued)*

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

Mann 1981

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 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

Mann 1981 *(Continued)*

	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

Marinello 2002

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%)

Marinello 2002 *(Continued)*

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
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"

Marinello 2002 *(Continued)*

		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

Martinez-Zapata 2008

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 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

Martinez-Zapata 2008 *(Continued)*

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

Nocker 1990

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

Nocker 1990 *(Continued)*

	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 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

Padros 1972

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

Padros 1972 *(Continued)*

	Age: 48 to 51 years Gender: female Inclusion criteria: CVI with signs (oedema, venous ectasia) and symptoms (heaviness, paraesthesias) 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

Parrado 1999

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

Parrado 1999 *(Continued)*

	Losses to follow-up: none
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

Parrado 1999 *(Continued)*

		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
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

Pecchi 1990

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) Secondary

Pecchi 1990 *(Continued)*

- 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

Pedersen 1992

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 Exclusion criteria: diuretic drugs; venotonic drugs; pregnant women
Interventions	Treatment: oxirutoside 900 mg per day Control: placebo

Pedersen 1992 *(Continued)*

	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

Petrassi 2000

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

Petrassi 2000 *(Continued)*

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)" 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)"

Petrassi 2000 *(Continued)*

		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

Planchon 1990

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
	  * 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

Planchon 1990 *(Continued)*

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

Pointel 1986

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 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

Pointel 1986 *(Continued)*

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

Prerovsky 1972

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

Prerovsky 1972 *(Continued)*

	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
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

Pulvertaft 1983

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 • 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

Pulvertaft 1983 *(Continued)*

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

Rabe 2011

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 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

Rabe 2011 *(Continued)*

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 ensureproper 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..." 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

Renton 1994

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

Renton 1994 *(Continued)*

	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 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

Renton 1994 *(Continued)*

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

Rose 1970

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

Rose 1970 *(Continued)*

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"
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

Rudofsky 1989

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

Rudofsky 1989 *(Continued)*

- Side effects

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Schultz-Ehrenburg 1993

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

Schultz-Ehrenburg 1993 *(Continued)*

	Age: 'adults' Gender: not stated 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

Sentou 1984

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
Blinding (study researchers)	Low risk	Quote: "Cyclo 3® and the placebo had an identical appearance"

Sentou 1984 *(Continued)*

		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

Serralde 1990

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 • Side effects • Participants' opinion on efficacy of treatment
Notes	

Risk of bias

Serralde 1990 *(Continued)*

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

Thebaut 1985

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 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

Thebaut 1985 *(Continued)*

	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
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

Tsouderos 1989

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

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

Tsouderos 1989 *(Continued)*

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

Unkauf 1996

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 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

Unkauf 1996 *(Continued)*

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

Vanscheidt 2002a

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 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

Vanscheidt 2002a *(Continued)*

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" 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

Vanscheidt 2002b

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

Vanscheidt 2002b *(Continued)*

	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 • 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

Vanscheidt 2002b *(Continued)*

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

Vin 1994

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 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	

Vin 1994 *(Continued)*

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 addition, 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

Welch 1985

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

Welch 1985 *(Continued)*

	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

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

Widmer 1990

Methods	Study design: randomised, double-blind, placebo-controlled Method of randomisation: randomisation list prepared by statistician Exclusions post randomisation: none

Widmer 1990 *(Continued)*

	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 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

Widmer 1990 *(Continued)*

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

Zucarelli 1987

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

Zucarelli 1987 *(Continued)*

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..." 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

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
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
NSAIDs: non-steroidal anti-inflammatories
QoL: quality of life
tid: 3 times a day
VAS: visual analogue scale

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

Study	Reason for exclusion
Akbulut 2010	This study assessed the combination of calcium dobesilate and oxerutin
Allaert 1992	This study assessed efficacy of drugs for CVI aggravated by oral contraceptives
Amato 1994	Micronised flavonoid and non-micronised diosmine were compared
Androulakis 1989	Principal outcome consists of plethysmographic parameters - a surrogate outcome
Auteri 1990	No clinical endpoints were assessed
Avram 1996	Two flavonoids were compared, and no placebo group was included
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 1989	This is not a randomised study
Batchvarova 1989a	This study assesses a product with escin, which is not included in our review
Behar 1993	This study assesses a product with escin, which is not included in our review
Belcaro 1986	This study compared a rutoside with or without elastic compression and included no placebo group
Belcaro 1989	This was a single-blind study
Belcaro 1995	Outcomes studied were surrogates (laser Doppler and transcutaneous oximetry)
Belcaro 2002	Venoruton was compared with Daflon
Belcaro 2003	Prophylaxis with Venoruton was provided for flight oedema in normal participants
Belcaro 2008	No clinical endpoints were assessed - only microcirculatory parameters
Belcaro 2008b	This controlled clinical trial assessed O-(β-Hydroxyethyl)-rutosides, but the study was not randomised
Bello 1990	Calcium dobesilate was combined with a heparinoid
Beltramino 1999	Two different drugs (Cyclo 3 Fort vs hydroxyethilrutoside) were compared for CVI
Bento 2006	This study assessed a combination of different active products that contain escin
Berson 1976	Comparative group was given a heparinoid rather than placebo
Berson 1978	Two clinical trials are described. One was a non-controlled clinical trial, and in the other, the control group was given naftazone
Berson 1980	Two different drugs given for CVI were compared
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

Study	Reason for exclusion
Boccalon 1989	The purpose of this study was to check effects of active treatment after microcirculatory disturbances caused by heat
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
Brock 1991	No placebo was given to the control group
Brock 2001	No placebo was given to the control group
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 2001d	This study assessed Centella asiatica for flight microangiopathy
Cesarone 2001e	This study assessed Centella asiatica for diabetic microangiopathy
Cesarone 2002a	This study assessed hydroxyrutosides for flight microangiopathy
Cesarone 2002b	This study assessed variations in plasma free radicals in participants with CVI
Cesarone 2003	This study assessed Venoruton for prophylaxis of flight oedema
Cesarone 2005	This study compared 2 drugs for CVI (beta-hydroxirutoside and diosmine plus hesperidin)
Cesarone 2006	This study was not double-blinded
Cesarone 2006a	This study compared 2 drugs for CVI (Venoruton and Daflon)

Study	Reason for exclusion
Cesarone 2006b	This study compared 2 drugs for CVI (Pycnogenol and Daflon)
Cesarone 2006c	This controlled clinical trial was not randomised; it focused on endothelial cells
Cesarone 2006d	This study assessed french maritime pine bark for diabetic microangiopathy
Cesarone 2010	This study was not double-blinded
Chant 1973	Non-clinical criteria were given
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 1989	This study compared 5682 SE (combination of micronised diosmine and hesperidin) vs diosmine
Cospite 1996	This study compared heparan sulphate vs diosmine for CVI
Cospite 1998	This study compared micronised diosmine and hesperidin vs diosmine
De Anna 1989	This was a single-blind study
de Parades 1990	This study compared Cyclo 3 Fort vs diosmine plus hesperidin for CVI
De Sanctis 2001	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
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
Fitzgerald 1967	In this cross-over, not-randomised, study, participants received placebo or troxerutin monthly in an alternative way. The paper does not describe numerical results
Forconi 1977	No clinical endpoints were assessed - only microcirculatory parameters
Frausini 1985	This was a single-blind study
Friederich 1978	Some included patients had thrombophlebitis; these individuals could not be separated out from the patient population
Glinski 1999	This was an open RCT conducted to examine venous ulcers
Gonzalez-Fajardo 1990	The outcome assessed was a surrogate (photoplethysmographic evaluation)
Gouny 1999	This study looked at the efficacy of hydroxyethyl rutosides in the local treatment of symptoms of venous insufficiency during air travel; this topic does not come under the scope of this review

Study	Reason for exclusion
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
Honorato 1990	This study compared the efficacy of hidrosmine vs diosmine
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 2001a	This study assessed escin for diabetic microangiopathy
Incandela 2001b	This study assessed Centella asiatica for diabetic microangiopathy
Incandela 2002	This was a single-blind study
Incandela 2002b	This study assessed a rutoside for diabetic microangiopathy
ISRCTN5340167	This study compared micronised purified flavonoid fraction 1000 mg vs 500 mg
Janssens 1999	No clinical endpoints were assessed - only microcirculatory parameters
Janssens 1999a	This study looked at the effects of Ginkor Fort (ginkgo biloba), which is not included in our review
Jantet 2000	This was not an RCT
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
Koch 2002	This study compared Venostasin and Pycnogenol
Koltringer 1993	This study assessed Ginkgo biloba, which is not included in our review
Kostering 1985	This study assessed microcirculatory parameters
Kranendonk 1993	This study focused on patients who had recently undergone venous surgery. Leg oedema and other symptoms could be attributed to the surgery - not to venous insufficiency
Krcílek 1973	The drug evaluated was escin, which is not included in our review
Krähenbühl 1975	The bencyclan is a drug with cardiovascular depression effects; it is not included in the review
Lambelet 1973	Some included patients had thrombophlebitis; these could not be separated out from the patient population
Languillat 1988b	The drug studied (Veliten) was a combination of rutin, ascorbic acid and alpha-tocopherol. No clinical endpoints were assessed - only microcirculatory parameters

Study	Reason for exclusion
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
Lefebvre 1991	This study assessed troxerutine during pregnancy
Marastoni 1982	This study assessed dihydroergotamine, which is not included in our review
Marastoni 1982a	This study compared Centella asiatica vs tribenoside
Menyhei 1994	No placebo group was included
Monreal 1994	Two active products for CVI were compared
Monreal 1997	Investigators examined prevention of post-thrombotic syndrome with hidrosmine
Monteil-Seurin 1993	This study compared Cyclo 3 Fort vs diosmine
Monteverde 1987	This study compared extract of Centella asiatica vs beta-hydroxiethyl-rutoside
Morales 1993	This RCT assessed escin, which is not included in our review
Muschietti 1978	This study compared natural diosmine, synthetic diosmine and tribenoside
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 1995	No placebo group was included. This study assessed the efficacy of 1 tablet or 500 mg HR twice daily or class II compressive stockings
Neumann-Mangoldt 1979	The drug evaluated contained escin and heparin
Nill 1970	This study assessed escin, which is not included in our review
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

Study	Reason for exclusion
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
Pecking 1998	This study assessed Daflon for lymphoedema associated with breast cancer
Petruzzellis 1990	This study included patients with superficial phlebitis
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
Pollastri 1982	This was a cross-over, double-blind study. The article does not state that this trial was randomised
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)
Rehn 1993	This study compared hidroxirutin vs oxerutin for CVI
Rehn 1993b	This study assessed different dose regimens of O-(beta-hydroxyethyl) rutosides in healthy volunteers
Rehn 1996	This single-blind study looked at the bioequivalence of oxerutins
Riccioni 2004	This study assessed the efficacy of the combination of troxerutin plus french maritime pine bark
Rish 1972	This study included patients with thrombophlebitis
Roztocil 1977	This study assessed microcirculatory parameters (capillary filtration)
Roztocil 2003	This was an RCT that was not blinded
Sadoun 1993	This study compared the efficacy of 2 different doses of chromocarbe diethylamine (800 and 1200 mg/d/3 mo)
Sanctis 2001	This study assessed escin, which is not included in our review
Schmeck-Lindenau 2003	This study assessed the hepatic safety of the combination of coumarin-troxerutin
Seydewitz 1992	Non-clinical parameters were evaluated in this study
Stefanini 1996	The control was not placebo - it was balneotherapy
Stegmann 1987	This trial did not include a placebo group as control
Steiner 1986	This study included 20 voluntary, ambulant patients with a history of pregnancy-related varicosis, with varicosis with CVI or with both

Study	Reason for exclusion
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
Strauss 1992	The aim of this study was to check the effects of active treatment following oedema caused by the orthostatic test
Strefezza 2010	This study compared the effects of different formulations of heperidin and diosmine
Topalov 1990	This study assessed the efficacy of troxesamol (combination of troxerutin, acetylsalicylic acid and dipyridamole)
Tsukanov 2010	This study looked at doses of a phlebotropic therapy
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
Zicot 1993	This trial did not include a placebo group
Zuccarelli 1996	This study assessed GinKor Fort (Ginkgo biloba), which is not included in our review

CVI: chronic venous insufficiency
HR: hidroxy rutoside
PO2: pressure of oxygen in blood
PCO2: pressure of carbon dioxide in blood
RCT: randomised controlled trial

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

ISRCTN18841175

Trial name or title	Effects of micronised purified flavonoic fraction on microcirculation in women suffering from chronic venous disease
Methods	Single-centre double-blind randomised placebo-controlled parallel-group study
Participants	240 females 18 to 30 years old suffering from primary chronic venous disease
Interventions	Micronised purified flavonoic fraction 500 mg over 4 menstrual cycles vs 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 Fisiologicasên-cias Fisiologicas Rua Sao Francisco Xavier 524 - PHLC - Sala 104 - Lab. Presq em Microcirculaçao. Rio de Janeiro. Brazil 20550-013

ISRCTN18841175 *(Continued)*

Notes	Sponsor: Institut de Recherches Internationales Servier (France)

NCT01532882

Trial name or title	Efficacy and safety of diosmine 600 mg vs placebo for painful symptoms in patients with chronic venous disease of lower limbs (EDEN)
Methods	Multi-centre controlled randomised double-blind placebo-controlled parallel-group study
Participants	378 patients with painful symptoms of chronic venous disorder (CVD) of the lower limbs
Interventions	Diosmine 600 mg - DIOVENOR vs placebo (1 tablet per day during 28 days)
Outcomes	Primary outcome measure: Change in visual analogue scale score for assessment of painful venous symptoms
Starting date	January 2012
Contact information	Dr Jean-Jérôme GUEX, Nice, France 06000
Notes	Sponsor: Innotech International

NCT01848210

Trial name or title	Efficacy and safety of coumarin and troxerutin in the symptomatic treatment of chronic venous insufficiency
Methods	Controlled randomised double-blind placebo-controlled parallel-group study
Participants	398 patients with chronic venous insufficiency in the reference leg with the clinical classification C3, or C4a or C4b or C5
Interventions	Coumarin 30 mg, troxerutin 180 mg fixed-dose combination tablets (Venalot), orally, 3 times daily for up to 16 weeks vs placebo
Outcomes	Primary outcome measure: Mean change from baseline in volume of reference leg at week 16
Starting date	May 2013
Contact information	Takeda
Notes	Sponsor: Takeda

DATA AND ANALYSES

Comparison 1. Phlebotonics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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 Aminaftone	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
1.2 Calcium dobesilate	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
1.3 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
1.4 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]
1.5 Rutosides	7	654	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.81]
2 Ankle perimeter circumference (mm)	15	2010	Mean Difference (IV, Fixed, 95% CI)	-4.27 [-5.61, -2.93]
2.1 Calcium dobesilate	5	1122	Mean Difference (IV, Fixed, 95% CI)	-1.69 [-4.84, 1.47]
2.2 Diosmine, Hidrosmine	3	286	Mean Difference (IV, Fixed, 95% CI)	-5.98 [-7.78, -4.18]
2.3 Rutosides	7	602	Mean Difference (IV, Fixed, 95% CI)	-2.45 [-5.06, 0.15]
3 Volume of the leg (mL)	9	1041	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.50, -0.25]
3.1 Aminaftone	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.61, 0.28]
3.2 Calcium dobesilate	3	475	Std. Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.68, -0.31]
3.3 Rutosides	5	487	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.47, -0.11]
4 Ulcer cured	6	461	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.13]
4.1 Aminaftone	1	100	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.18]
4.2 Calcium dobesilate	1	69	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.69, 1.74]
4.3 Diosmine, Hidrosmine	2	133	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.01]
4.4 Rutosides	2	159	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.87, 1.86]
5 Trophic disorders (dichotomous variable)	6	705	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.95]
5.1 Aminaftone	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Diosmine, Hidrosmine	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
5.3 Rutosides	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.25]
6 Pain in the lower legs (dichotomous variable)	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.79]
6.2 Calcium dobesilate	4	354	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.16, 0.93]
6.3 Diosmine, Hidrosmine	4	271	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.08]
6.4 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.48, 0.91]
6.5 Rutosides	10	1485	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.83]
7 Pain in the lower legs (continuous variable)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Calcium dobesilate	4	776	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.35, 0.12]
7.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.67, -0.02]
7.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.39 [-2.09, -0.69]
7.4 Rutosides	3	219	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.23, -0.19]
8 Cramps in the lower legs (dichotomous variable)	14	1793	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.89]
8.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.99]
8.2 Calcium dobesilate	2	255	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
8.3 Diosmine, Hidrosmine	3	214	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
8.4 Rutosides	8	1227	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.02]
9 Cramps in the lower legs (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Calcium dobesilate	1	415	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.29, 0.09]
9.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.78, -0.14]
9.3 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.16]

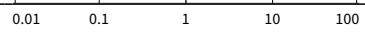
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Restless legs (dichotomous variable)	7	652	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
10.1 Calcium dobesilate	2	255	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.59, 0.91]
10.2 Diosmine, Hidrosmine	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.15]
10.3 Rutosides	4	327	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
11 Itching in the lower legs (dichotomous variable)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
11.2 Diosmine, Hidrosmine	1	34	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.25]
11.3 Rutosides	2	274	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.21, 2.21]
12 Itching in the lower legs (continuous variable)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Calcium dobesilate	1	416	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.11, 0.28]
12.2 Rutosides	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.10, -0.06]
13 Heaviness in the lower legs (dichotomous variable)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.60]
13.2 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
13.3 Centella asiatica	1	63	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
13.4 Diosmine, Hidrosmine	4	241	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.05]
13.5 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
13.6 Rutosides	9	1420	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.74]
14 Heaviness in the lower legs (continuous variable)	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Calcium dobesilate	2	483	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.23, 0.13]
14.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.02, -0.36]
14.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.50 [-2.21, -0.79]

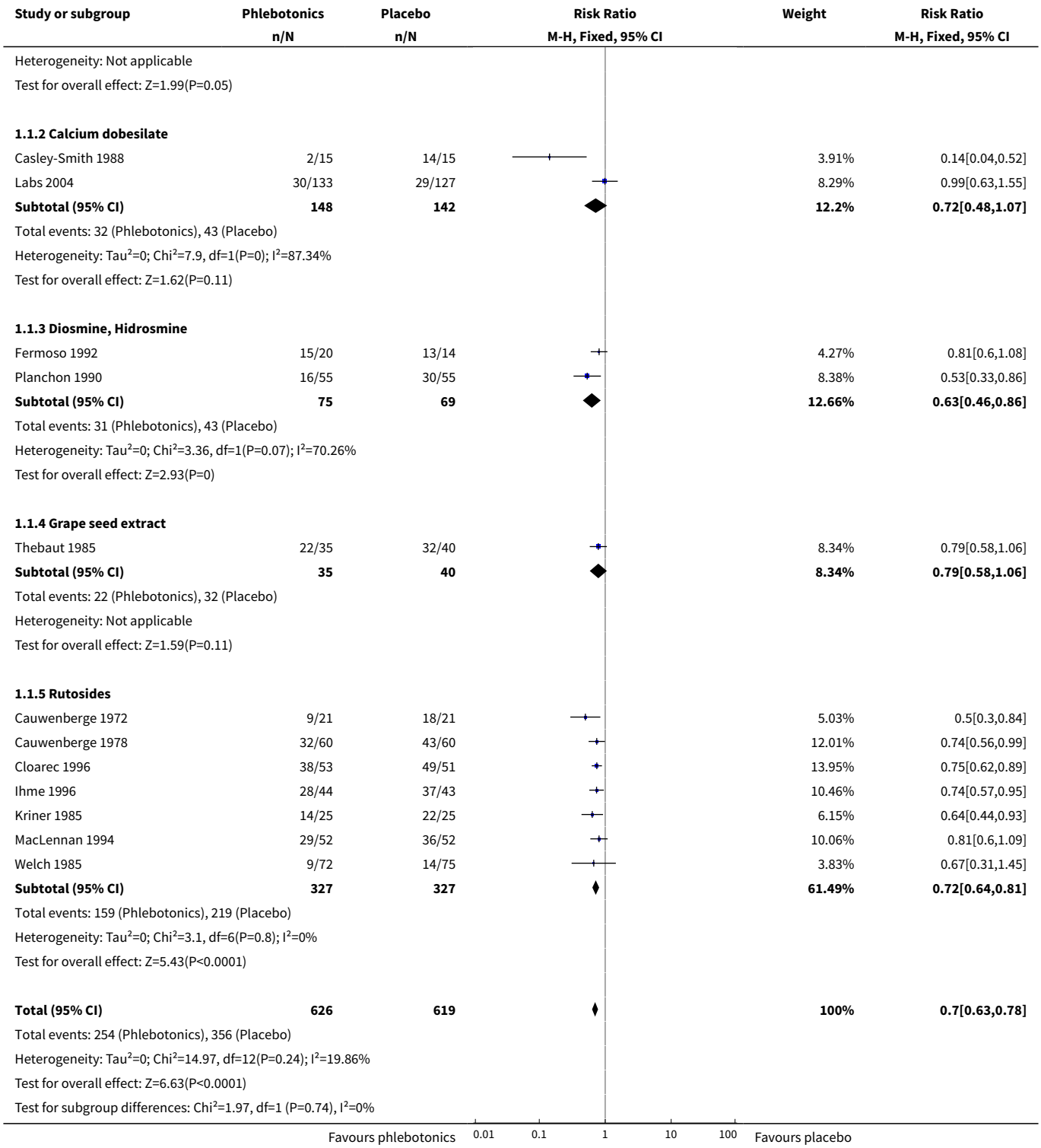
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.4 Rutosides	6	441	Std. Mean Difference (IV, Random, 95% CI)	-1.11 [-1.87, -0.36]
15 Swelling in the lower legs (dichotomous variable)	14	1072	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.50, 0.80]
15.1 Calcium dobesilate	2	80	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.41]
15.2 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.52, 0.94]
15.3 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.02]
15.4 Rutosides	9	848	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.88]
16 Swelling in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Calcium dobesilate	1	417	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.24, 0.15]
16.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.26, -0.58]
16.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.65 [-2.38, -0.92]
16.4 Rutosides	3	264	Std. Mean Difference (IV, Random, 95% CI)	-1.73 [-3.50, 0.04]
17 Paraesthesia in the lower legs (dichotomous variable)	9	1456	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.88]
17.1 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
17.2 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.05]
17.3 Rutosides	4	1007	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.83]
18 Paraesthesia in the lower legs (continuous variable)	2	188	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.44, 0.13]
18.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.44, 0.21]
18.2 Rutosides	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.96, 0.33]
19 Quality of life	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Aminaftone	1	79	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-17.01, -2.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Calcium dobesilate at 3 months of treatment	2	617	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
20 Global assessment by the participant (dichotomous variable)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 Calcium dobesilate	3	506	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.46]
20.2 Diosmine, Hidrosmine	4	451	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.02]
20.3 Centella asiatica	1	80	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.14, 0.57]
20.4 Rutosides	8	1167	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.30, 0.84]
21 Global assessment by the participant (continuous variable)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Calcium dobesilate	2	448	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.71, -0.33]
21.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.14, -0.47]
21.3 Rutosides	4	283	Std. Mean Difference (IV, Random, 95% CI)	-1.18 [-1.96, -0.39]
22 Adverse events	34	4054	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.05, 1.40]
22.1 Aminaftone	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.06, 6.32]
22.2 Calcium dobesilate	7	1473	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.99, 1.53]
22.3 Centella asiatica	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.58, 2.23]
22.4 Diosmine, Hidrosmine	8	837	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.70, 1.44]
22.5 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.19, 1.74]
22.6 Rutosides	16	1496	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.08, 1.83]

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

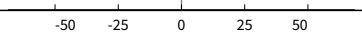
Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Aminaftone					
Lazzarini 1982	10/41	19/41		5.31%	0.53[0.28,0.99]
Subtotal (95% CI)	**41**	**41**		**5.31%**	**0.53[0.28,0.99]**
Total events: 10 (Phlebotonics), 19 (Placebo)					





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

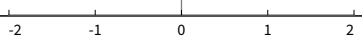
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 Calcium dobesilate							
Flota-Cervera 2008	25	335.6 (38.2)	24	356.2 (38.2)		0.39%	-20.6[-42,0.8]
Labs 2004	124	229.5 (22.7)	123	228.3 (19.6)		6.44%	1.2[-4.09,6.49]
Martinez-Zapata 2008	193	254.9 (43.2)	203	266.8 (53.9)		1.95%	-11.9[-21.5,-2.3]
Rabe 2011	109	240.9 (21.3)	115	240.7 (21.8)		5.65%	0.2[-5.44,5.84]
Widmer 1990	103	230.1 (21.3)	103	232.3 (29.4)		3.65%	-2.2[-9.22,4.82]
Subtotal ***	**554**		**568**			**18.08%**	**-1.69[-4.84,1.47]**
Heterogeneity: Tau^2=0; Chi^2=8.95, df=4(P=0.06); I^2=55.29%							
Test for overall effect: Z=1.05(P=0.29)							
1.2.2 Diosmine, Hidrosmine							
Gilly 1994	76	-7.1 (7)	74	-1.2 (4.3)		52.69%	-5.9[-7.75,-4.05]
Planchon 1990	48	229.1 (30.3)	48	234.8 (31)		1.2%	-5.7[-17.96,6.56]
Tsouderos 1989	20	239.1 (20.6)	20	248.1 (13.7)		1.53%	-9[-19.84,1.84]
Subtotal ***	**144**		**142**			**55.41%**	**-5.98[-7.78,-4.18]**
Heterogeneity: Tau^2=0; Chi^2=0.31, df=2(P=0.86); I^2=0%							
Test for overall effect: Z=6.51(P<0.0001)							
1.2.3 Rutosides							
Cloarec 1996	53	221 (22)	51	225 (19)		2.89%	-4[-11.89,3.89]
Cornu-Thenard 1985	33	226.8 (16.4)	21	224.6 (14)		2.68%	2.2[-6,10.4]
Jongste 1989	40	236 (22)	42	237 (20)		2.17%	-1[-10.11,8.11]
MacLennan 1994	41	258 (40)	45	249 (42)		0.6%	9[-8.33,26.33]
Parrado 1999	30	209 (50)	30	243 (48)		0.29%	-34[-58.8,-9.2]
Vin 1994	34	-3.7 (7.2)	35	-0.8 (7.3)		15.37%	-2.9[-6.32,0.52]
Welch 1985	72	232.5 (27.4)	75	235.7 (24.9)		2.51%	-3.2[-11.67,5.27]
Subtotal ***	**303**		**299**			**26.5%**	**-2.45[-5.06,0.15]**
Heterogeneity: Tau^2=0; Chi^2=9.47, df=6(P=0.15); I^2=36.65%							
Test for overall effect: Z=1.84(P=0.07)							
Total ***	**1001**		**1009**			**100%**	**-4.27[-5.61,-2.93]**
Heterogeneity: Tau^2=0; Chi^2=26.63, df=14(P=0.02); I^2=47.43%							
Test for overall effect: Z=6.24(P<0.0001)							
Test for subgroup differences: Chi^2=7.91, df=1 (P=0.02), I^2=74.71%							



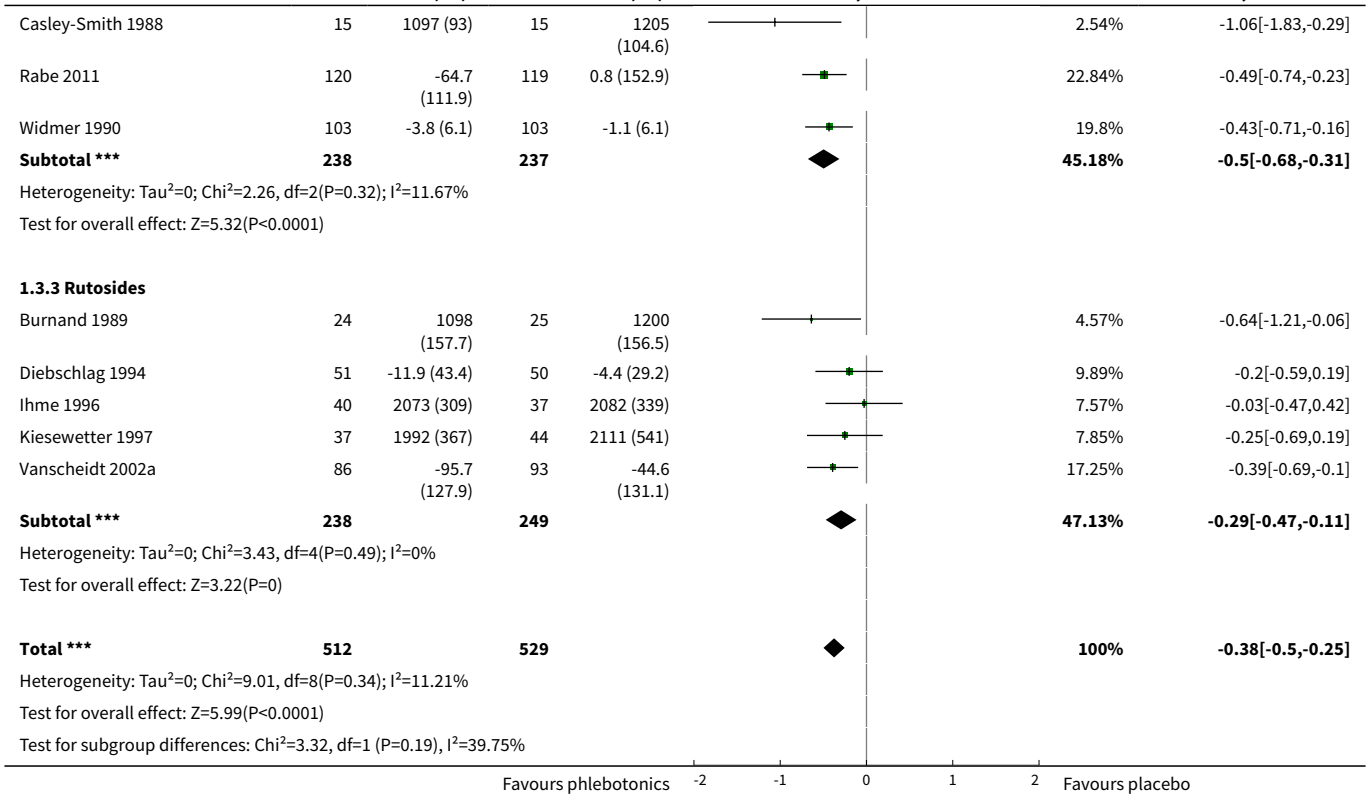
Favours phlebotonics — Favours placebo

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

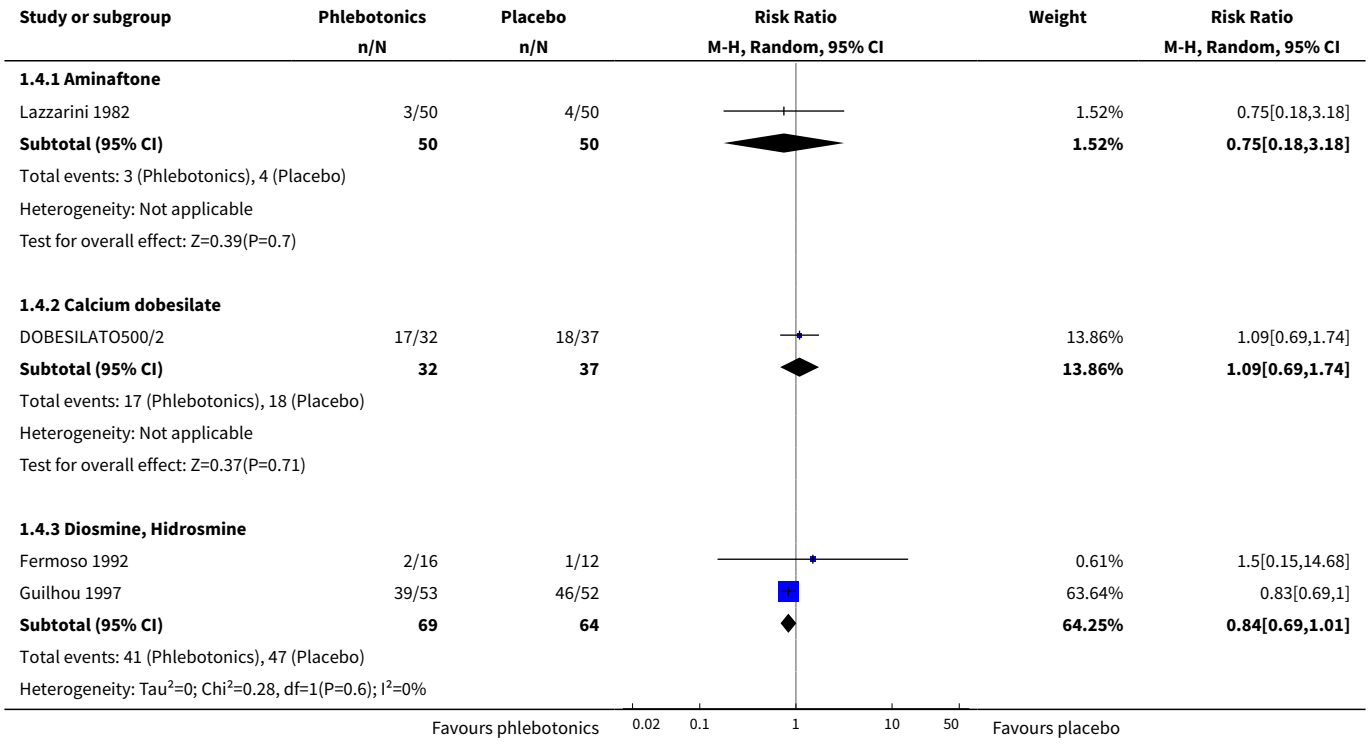
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.3.1 Aminaftone							
Belczak 2014	36	3276.5 (584.6)	43	3391.5 (751.1)		7.69%	-0.17[-0.61,0.28]
Subtotal ***	**36**		**43**			**7.69%**	**-0.17[-0.61,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
1.3.2 Calcium dobesilate							

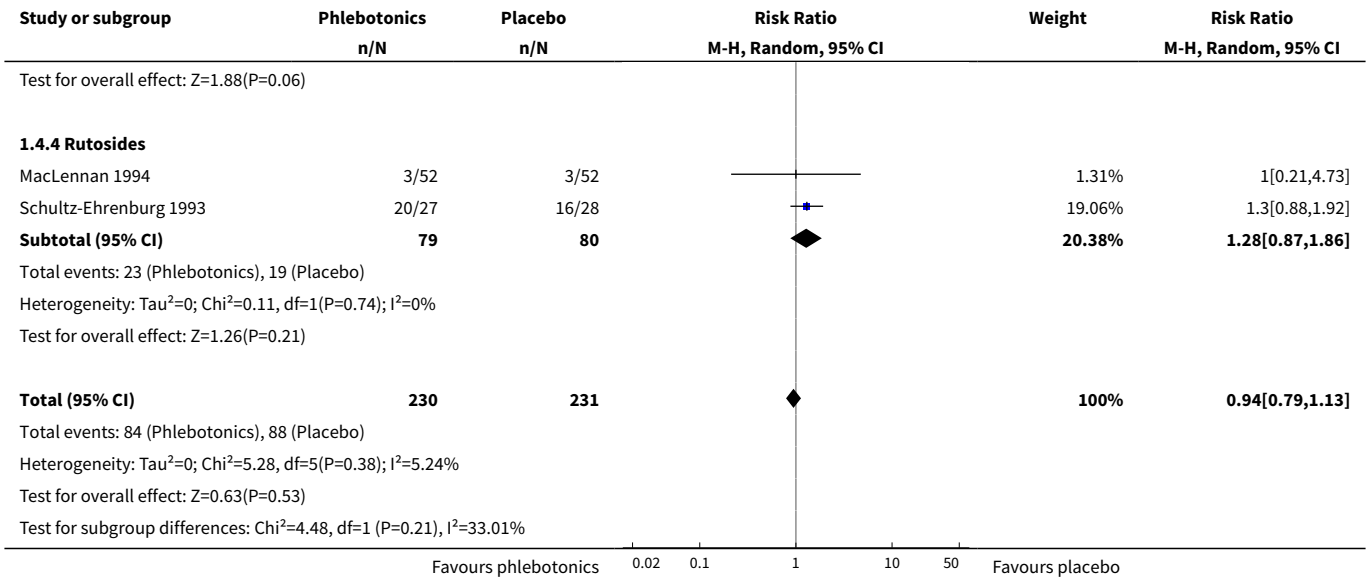


Favours phlebotonics — Favours placebo

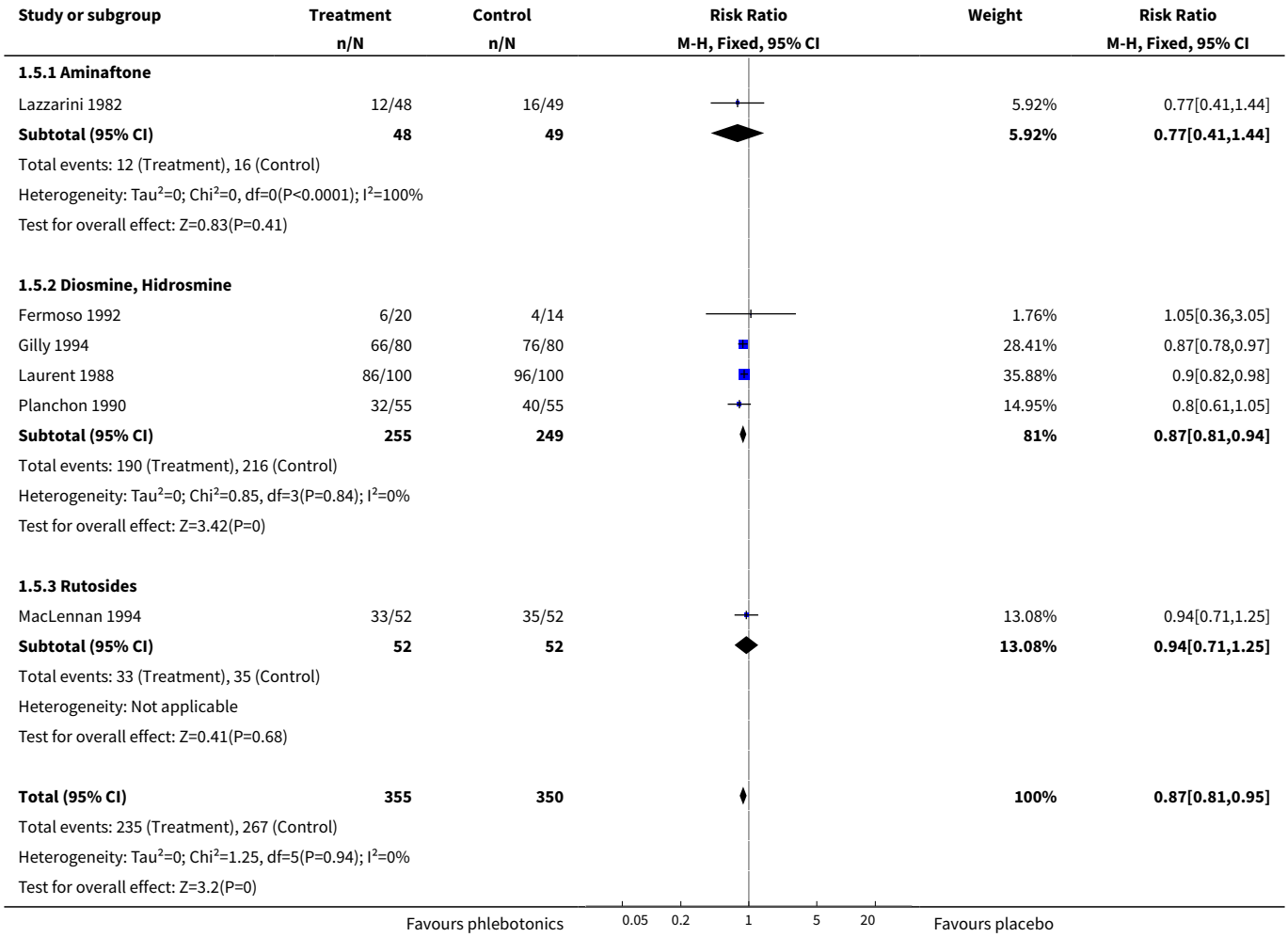


Analysis 1.4. Comparison 1 Phlebotonics versus placebo, Outcome 4 Ulcer cured.





Analysis 1.5. Comparison 1 Phlebotonics versus placebo, Outcome 5 Trophic disorders (dichotomous variable).



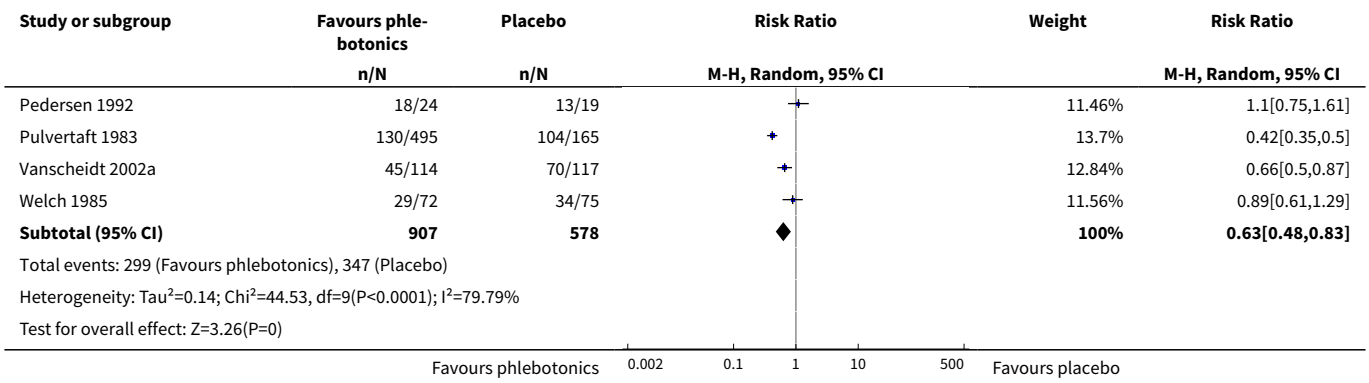
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=0.45, df=1 (P=0.8), I²=0%					

Favours phlebotonics 0.05 0.2 1 5 20 Favours placebo

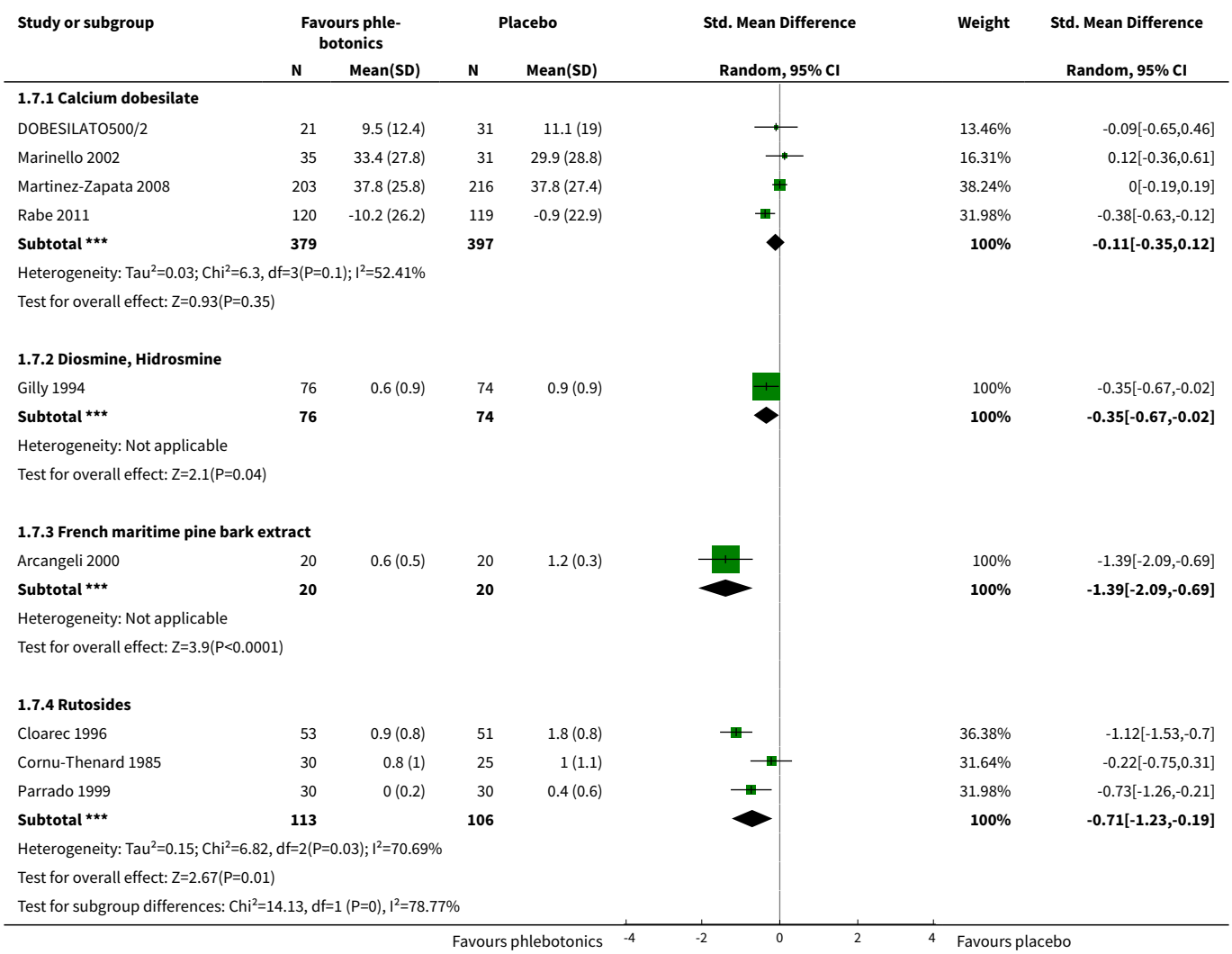
Analysis 1.6. Comparison 1 Phlebotonics versus placebo, Outcome 6 Pain in the lower legs (dichotomous variable).

Study or subgroup	Favours phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Aminaftone					
Lazzarini 1982	10/48	24/49		100%	0.43[0.23,0.79]
Subtotal (95% CI)	**48**	**49**		**100%**	**0.43[0.23,0.79]**
Total events: 10 (Favours phlebotonics), 24 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.7(P=0.01)					
1.6.2 Calcium dobesilate					
Casley-Smith 1988	3/15	14/15		21.49%	0.21[0.08,0.59]
Flota-Cervera 2008	3/25	24/24		22.05%	0.14[0.05,0.36]
Hachen 1982	9/25	15/25		26.52%	0.6[0.33,1.11]
Widmer 1990	62/114	68/111		29.94%	0.89[0.71,1.11]
Subtotal (95% CI)	**179**	**175**		**100%**	**0.39[0.16,0.93]**
Total events: 77 (Favours phlebotonics), 121 (Placebo)					
Heterogeneity: Tau²=0.64; Chi²=23.01, df=3(P<0.0001); I²=86.96%					
Test for overall effect: Z=2.12(P=0.03)					
1.6.3 Diosmine, Hidrosmine					
Biland 1982	26/35	25/35		33.37%	1.04[0.78,1.38]
Dominguez 1992	22/30	23/27		35.11%	0.86[0.66,1.12]
Fermoso 1992	6/20	6/14		7.54%	0.7[0.28,1.73]
Planchon 1990	20/55	34/55		23.99%	0.59[0.39,0.88]
Subtotal (95% CI)	**140**	**131**		**100%**	**0.82[0.63,1.08]**
Total events: 74 (Favours phlebotonics), 88 (Placebo)					
Heterogeneity: Tau²=0.03; Chi²=5.91, df=3(P=0.12); I²=49.2%					
Test for overall effect: Z=1.42(P=0.16)					
1.6.4 French maritime pine bark extract					
Arcangeli 2000	13/20	20/20		100%	0.66[0.48,0.91]
Subtotal (95% CI)	**20**	**20**		**100%**	**0.66[0.48,0.91]**
Total events: 13 (Favours phlebotonics), 20 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.51(P=0.01)					
1.6.5 Rutosides					
Balmer 1980	3/40	18/40		4.25%	0.17[0.05,0.52]
Cauwenberge 1972	7/21	16/21		8.15%	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		12.24%	0.9[0.66,1.25]
Klüken 1971	13/30	23/28		10.67%	0.53[0.34,0.82]
Languillat 1988	2/10	6/10		3.35%	0.33[0.09,1.27]

Favours phlebotonics 0.002 0.1 1 10 500 Favours placebo

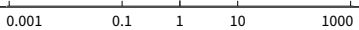


Analysis 1.7. Comparison 1 Phlebotonics versus placebo, Outcome 7 Pain in the lower legs (continuous variable).



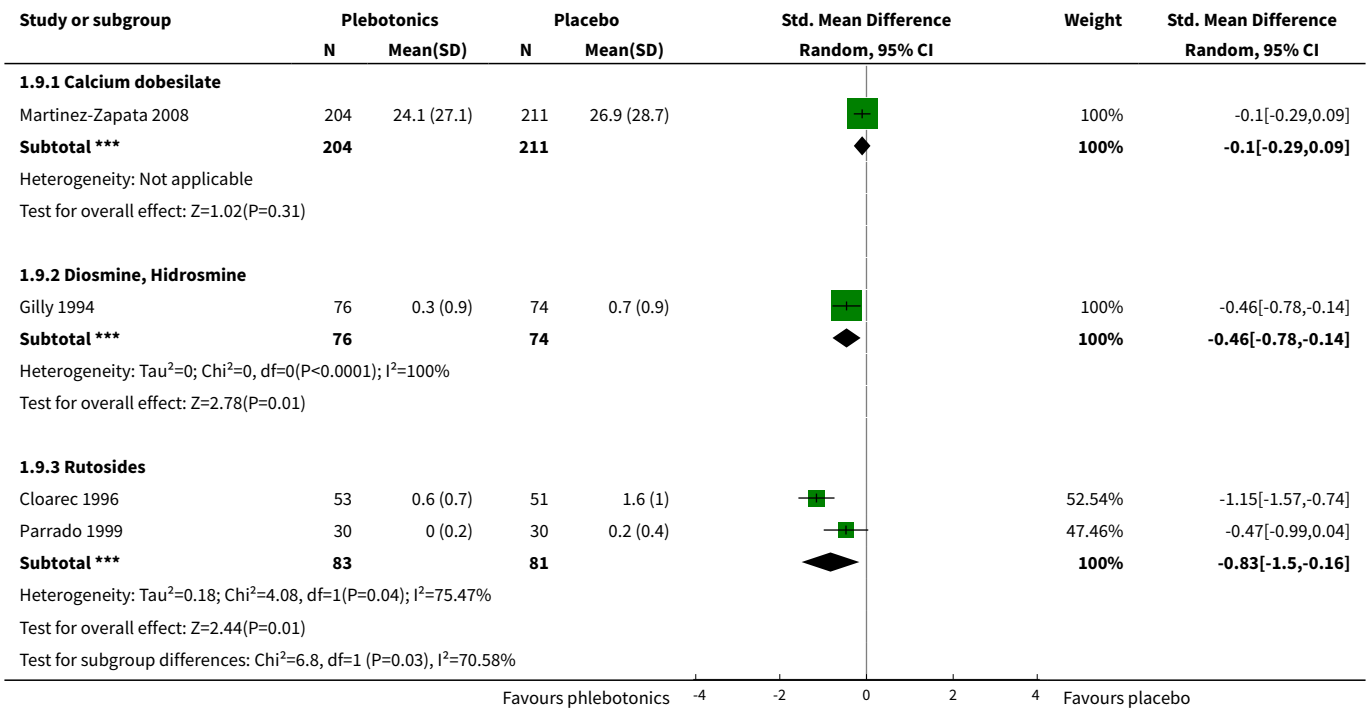
Analysis 1.8. Comparison 1 Phlebotonics versus placebo, Outcome 8 Cramps in the lower legs (dichotomous variable).

Study or subgroup	Favours phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Aminaftone					
Lazzarini 1982	12/48	22/49		6.51%	0.56[0.31,0.99]
Subtotal (95% CI)	**48**	**49**		**6.51%**	**0.56[0.31,0.99]**
Total events: 12 (Favours phlebotonics), 22 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
1.8.2 Calcium dobesilate					
Casley-Smith 1988	8/15	10/15		6.37%	0.8[0.44,1.45]
Widmer 1990	41/114	65/111		10.08%	0.61[0.46,0.82]
Subtotal (95% CI)	**129**	**126**		**16.45%**	**0.65[0.5,0.84]**
Total events: 49 (Favours phlebotonics), 75 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=3.28(P=0)					
1.8.3 Diosmine, Hidrosmine					
Biland 1982	26/35	30/35		10.74%	0.87[0.68,1.1]
Fermoso 1992	5/20	4/14		2.83%	0.88[0.28,2.69]
Planchon 1990	35/55	44/55		10.71%	0.8[0.63,1.01]
Subtotal (95% CI)	**110**	**104**		**24.28%**	**0.83[0.7,0.98]**
Total events: 66 (Favours phlebotonics), 78 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=2(P=0.88); I^2=0%					
Test for overall effect: Z=2.17(P=0.03)					
1.8.4 Rutosides					
Balmer 1980	0/40	8/40		0.56%	0.06[0,0.99]
Cauwenberge 1978	25/60	41/60		9.37%	0.61[0.43,0.86]
Jongste 1989	27/41	28/43		9.82%	1.01[0.74,1.38]
Languillat 1988	0/10	3/10		0.55%	0.14[0.01,2.45]
Pedersen 1992	17/24	11/19		7.88%	1.22[0.77,1.94]
Pulvertaft 1983	120/495	95/165		11.12%	0.42[0.34,0.52]
Vin 1994	21/43	21/30		8.85%	0.7[0.47,1.03]
Welch 1985	10/72	11/75		4.61%	0.95[0.43,2.09]
Subtotal (95% CI)	**785**	**442**		**52.76%**	**0.7[0.47,1.02]**
Total events: 220 (Favours phlebotonics), 218 (Placebo)					
Heterogeneity: Tau^2=0.19; Chi^2=37.93, df=7(P<0.0001); I^2=81.54%					
Test for overall effect: Z=1.84(P=0.07)					
Total (95% CI)	**1072**	**721**		**100%**	**0.72[0.58,0.89]**
Total events: 347 (Favours phlebotonics), 393 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=48.7, df=13(P<0.0001); I^2=73.31%					
Test for overall effect: Z=3.02(P=0)					
Test for subgroup differences: Chi^2=3.87, df=1 (P=0.28), I^2=22.56%					

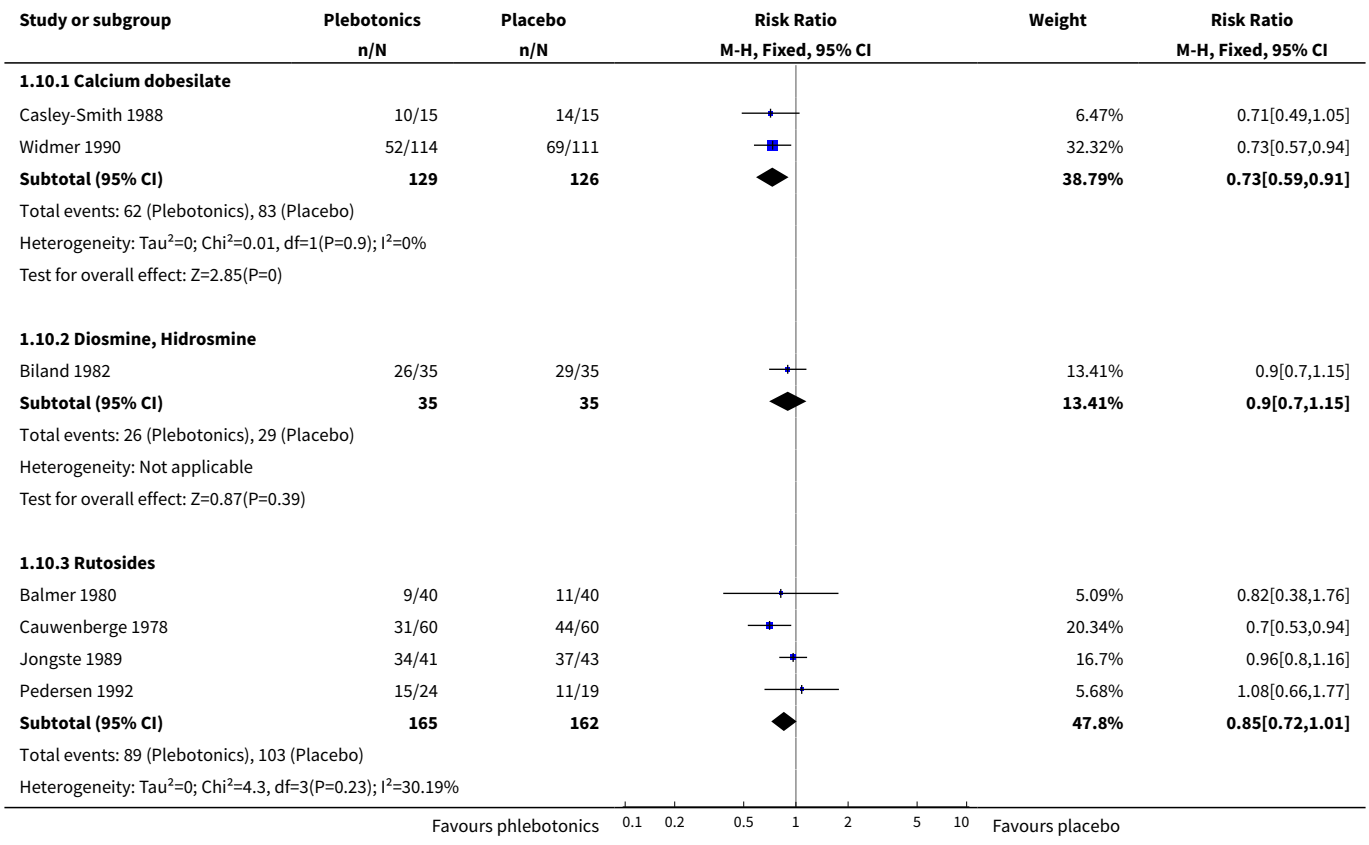


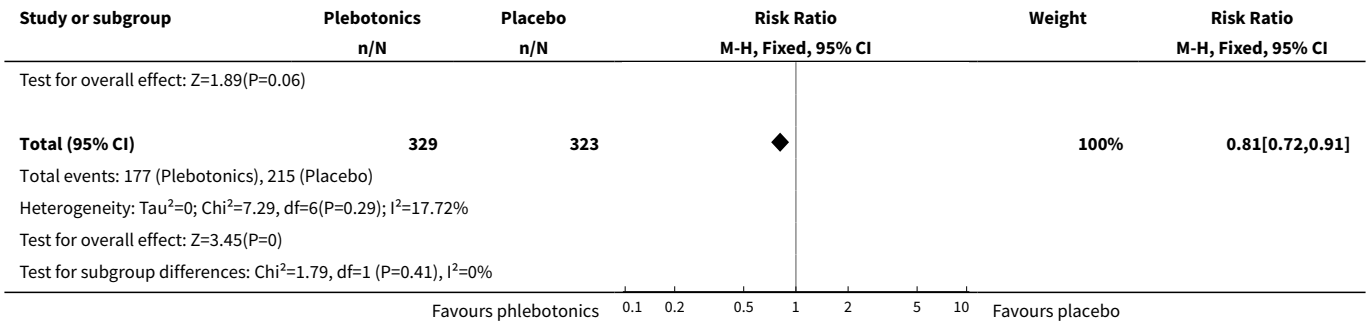
Favours phlebotonics — Favours placebo

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

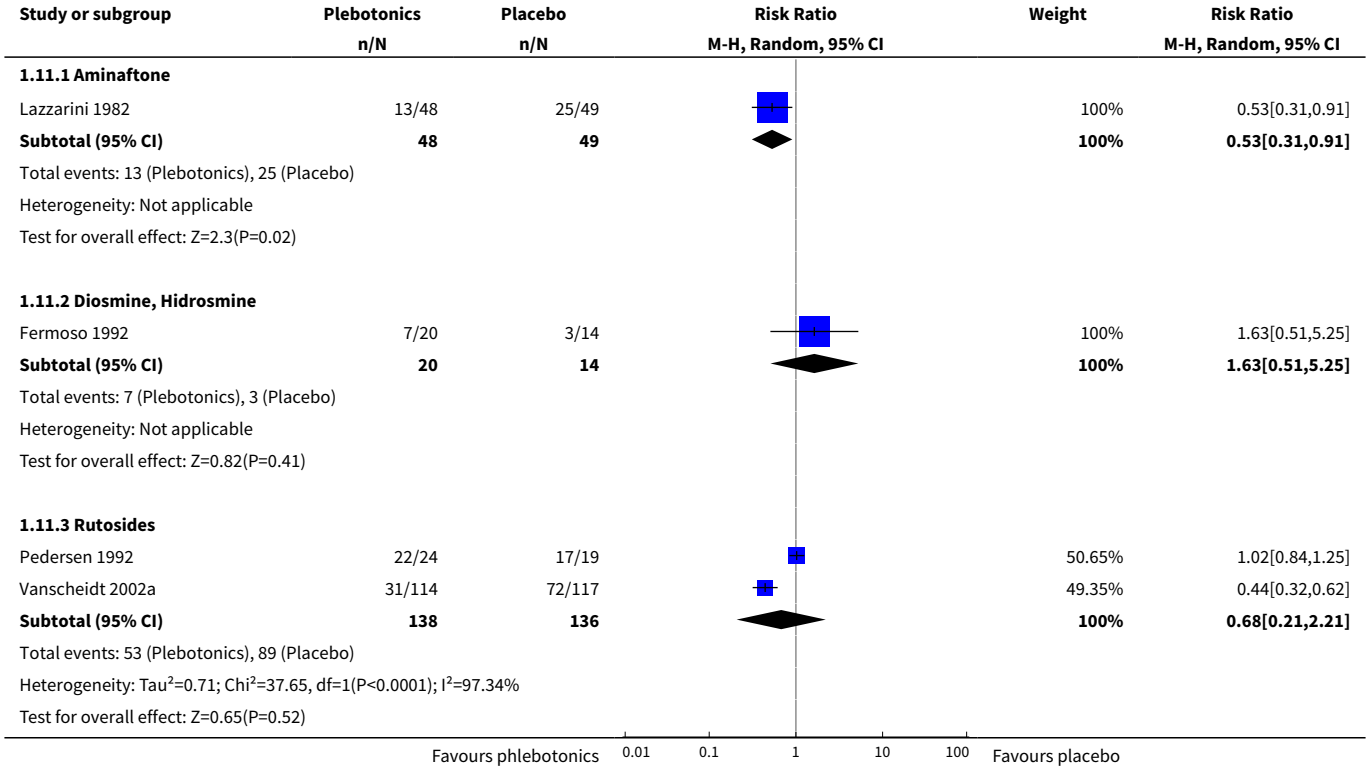


Analysis 1.10. Comparison 1 Phlebotonics versus placebo, Outcome 10 Restless legs (dichotomous variable).

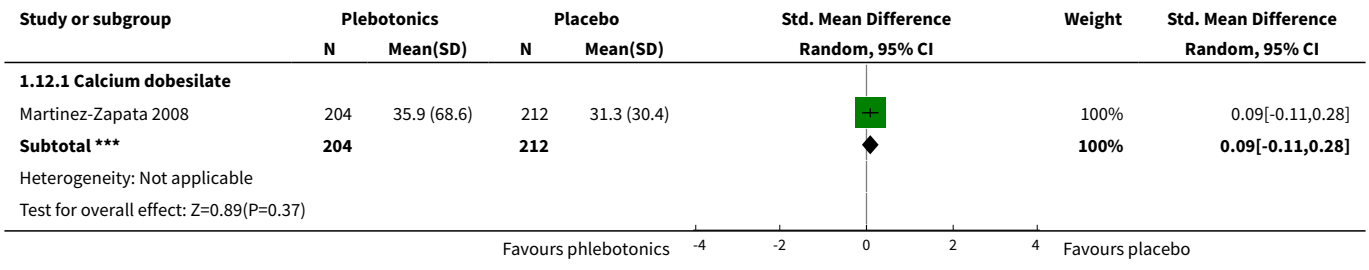




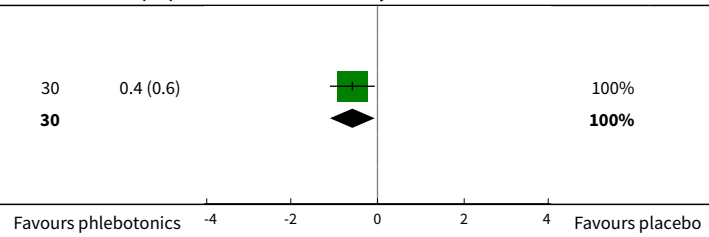
Analysis 1.11. Comparison 1 Phlebotonics versus placebo, Outcome 11 Itching in the lower legs (dichotomous variable).



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

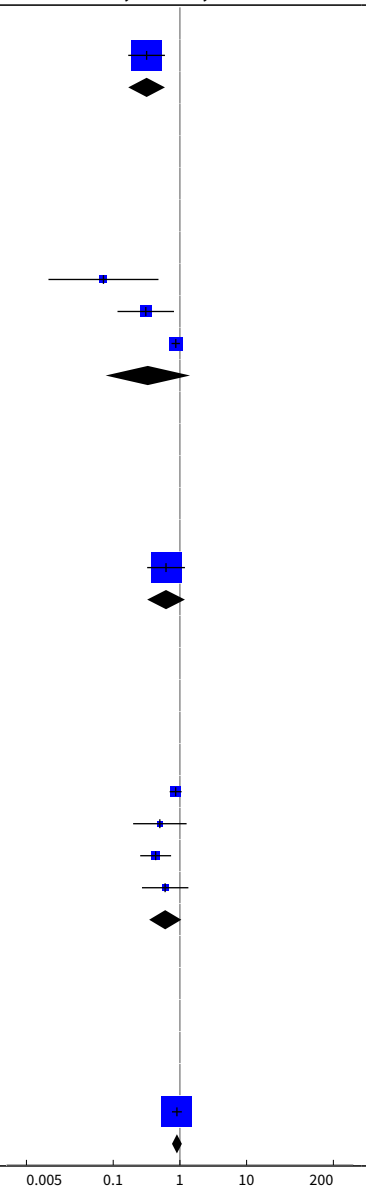


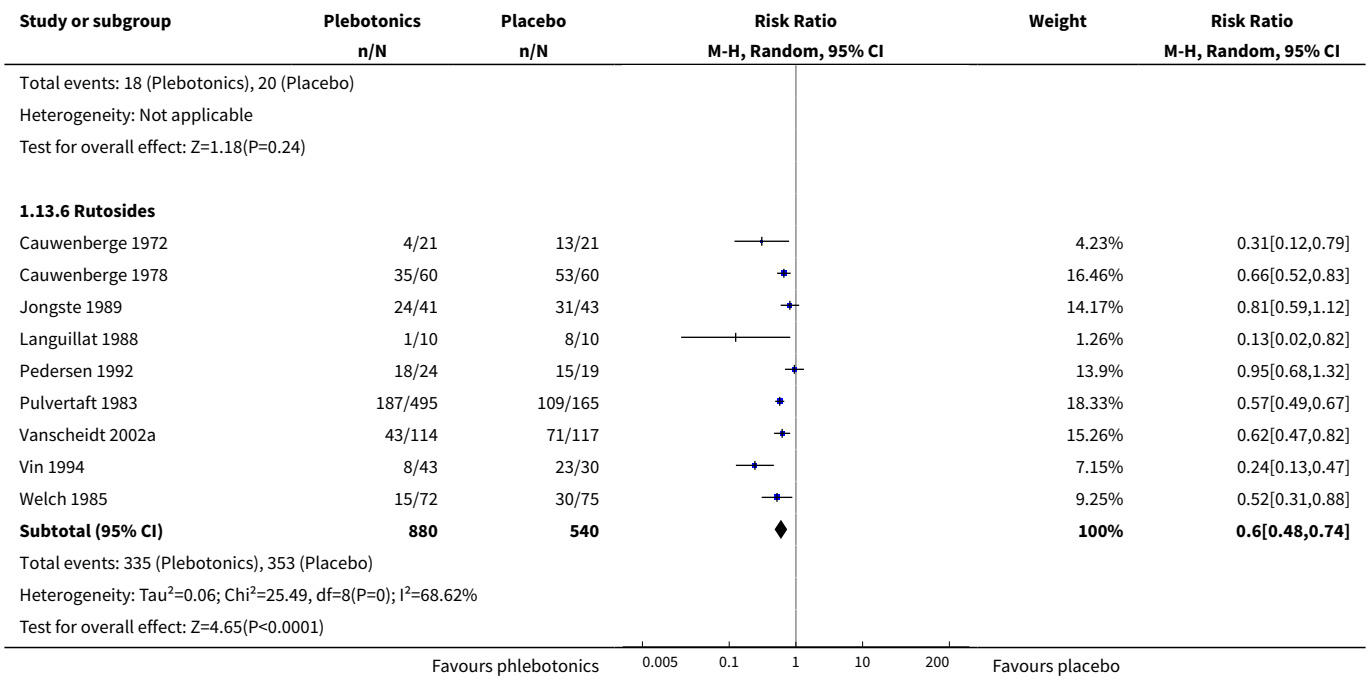
Study or subgroup	Plebotonics N	Plebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.12.2 Rutosides							
Parrado 1999	30	0.1 (0.4)	30	0.4 (0.6)		100%	-0.58[-1.1,-0.06]
Subtotal ***	**30**		**30**			**100%**	**-0.58[-1.1,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.2(P=0.03)							



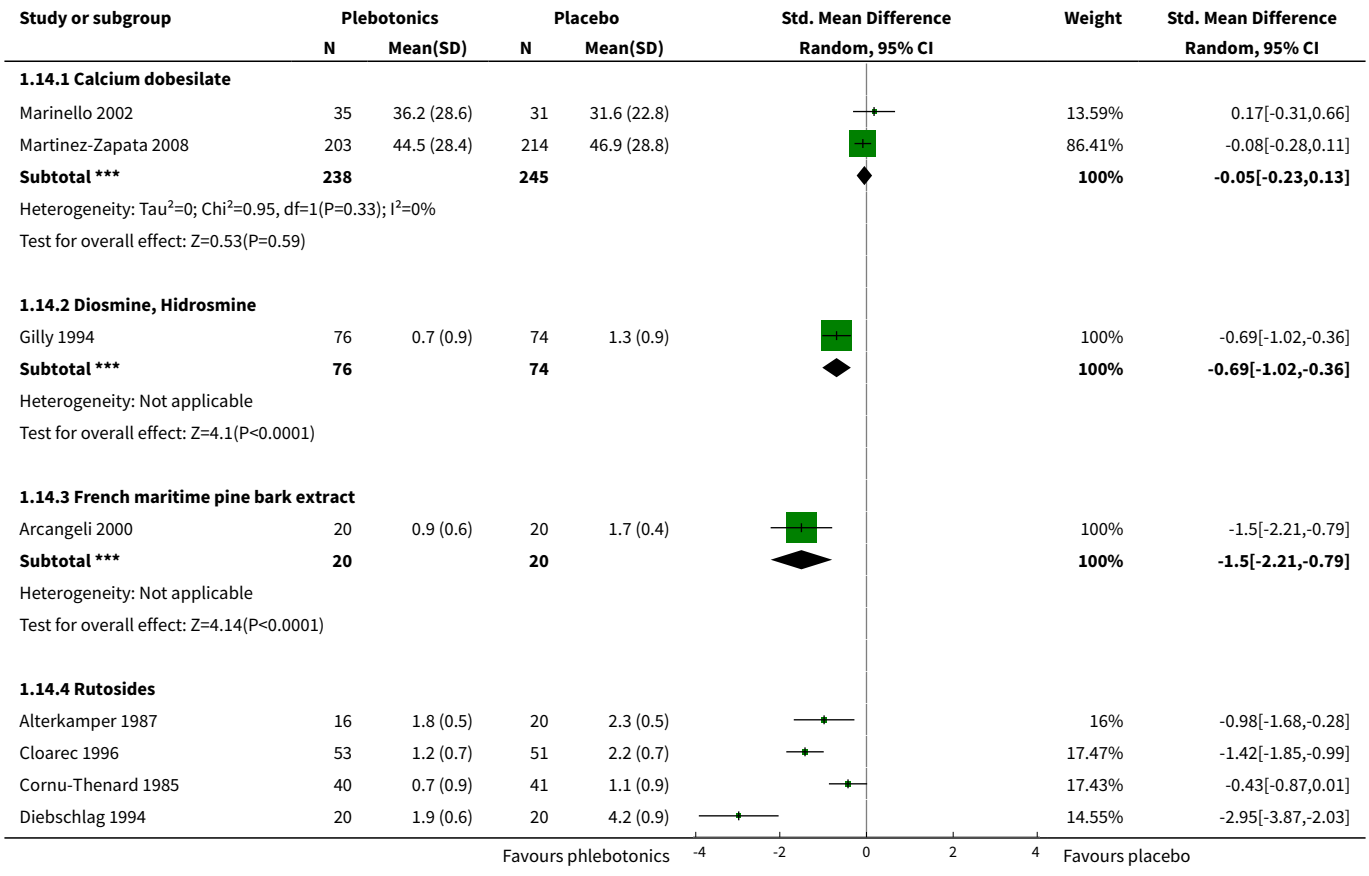
Analysis 1.13. Comparison 1 Phlebotonics versus placebo, Outcome 13 Heaviness in the lower legs (dichotomous variable).

Study or subgroup	Plebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Aminaftone					
Lazzarini 1982	9/48	29/49		100%	0.32[0.17,0.6]
Subtotal (95% CI)	**48**	**49**		**100%**	**0.32[0.17,0.6]**
Total events: 9 (Plebotonics), 29 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.56(P=0)					
1.13.2 Calcium dobesilate					
Casley-Smith 1988	1/15	14/15		24.23%	0.07[0.01,0.48]
Hachen 1982	4/25	13/25		34.77%	0.31[0.12,0.81]
Widmer 1990	81/114	91/111		41%	0.87[0.75,1]
Subtotal (95% CI)	**154**	**151**		**100%**	**0.33[0.08,1.42]**
Total events: 86 (Plebotonics), 118 (Placebo)					
Heterogeneity: Tau^2=1.34; Chi^2=15.42, df=2(P=0); I^2=87.03%					
Test for overall effect: Z=1.49(P=0.14)					
1.13.3 Centella asiatica					
Pointel 1986	9/30	16/33		100%	0.62[0.32,1.19]
Subtotal (95% CI)	**30**	**33**		**100%**	**0.62[0.32,1.19]**
Total events: 9 (Plebotonics), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.45(P=0.15)					
1.13.4 Diosmine, Hidrosmine					
Dominguez 1992	24/30	25/27		34.29%	0.86[0.7,1.06]
Fermoso 1992	5/20	7/14		18.06%	0.5[0.2,1.26]
Planchon 1990	13/55	30/55		27.05%	0.43[0.25,0.74]
Tsouderos 1989	6/20	10/20		20.6%	0.6[0.27,1.34]
Subtotal (95% CI)	**125**	**116**		**100%**	**0.6[0.35,1.05]**
Total events: 48 (Plebotonics), 72 (Placebo)					
Heterogeneity: Tau^2=0.22; Chi^2=12.08, df=3(P=0.01); I^2=75.17%					
Test for overall effect: Z=1.79(P=0.07)					
1.13.5 French maritime pine bark extract					
Arcangeli 2000	18/20	20/20		100%	0.9[0.76,1.07]
Subtotal (95% CI)	**20**	**20**		**100%**	**0.9[0.76,1.07]**





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



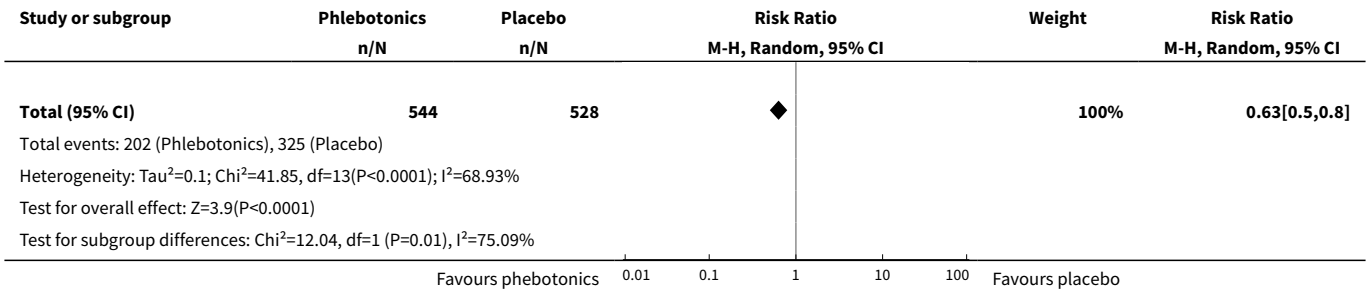
Study or subgroup	Plebotonics N	Plebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Parrado 1999	30	0.1 (0.5)	30	0.8 (0.4)		16.76%	-1.43[-2,-0.86]
Unkauf 1996	64	27 (28)	56	22 (27)		17.78%	0.18[-0.18,0.54]
Subtotal ***	**223**		**218**			**100%**	**-1.11[-1.87,-0.36]**
Heterogeneity: Tau^2=0.81; Chi^2=64.75, df=5(P<0.0001); I^2=92.28%							
Test for overall effect: Z=2.88(P=0)							

Favours phlebotonics -4 -2 0 2 4 Favours placebo

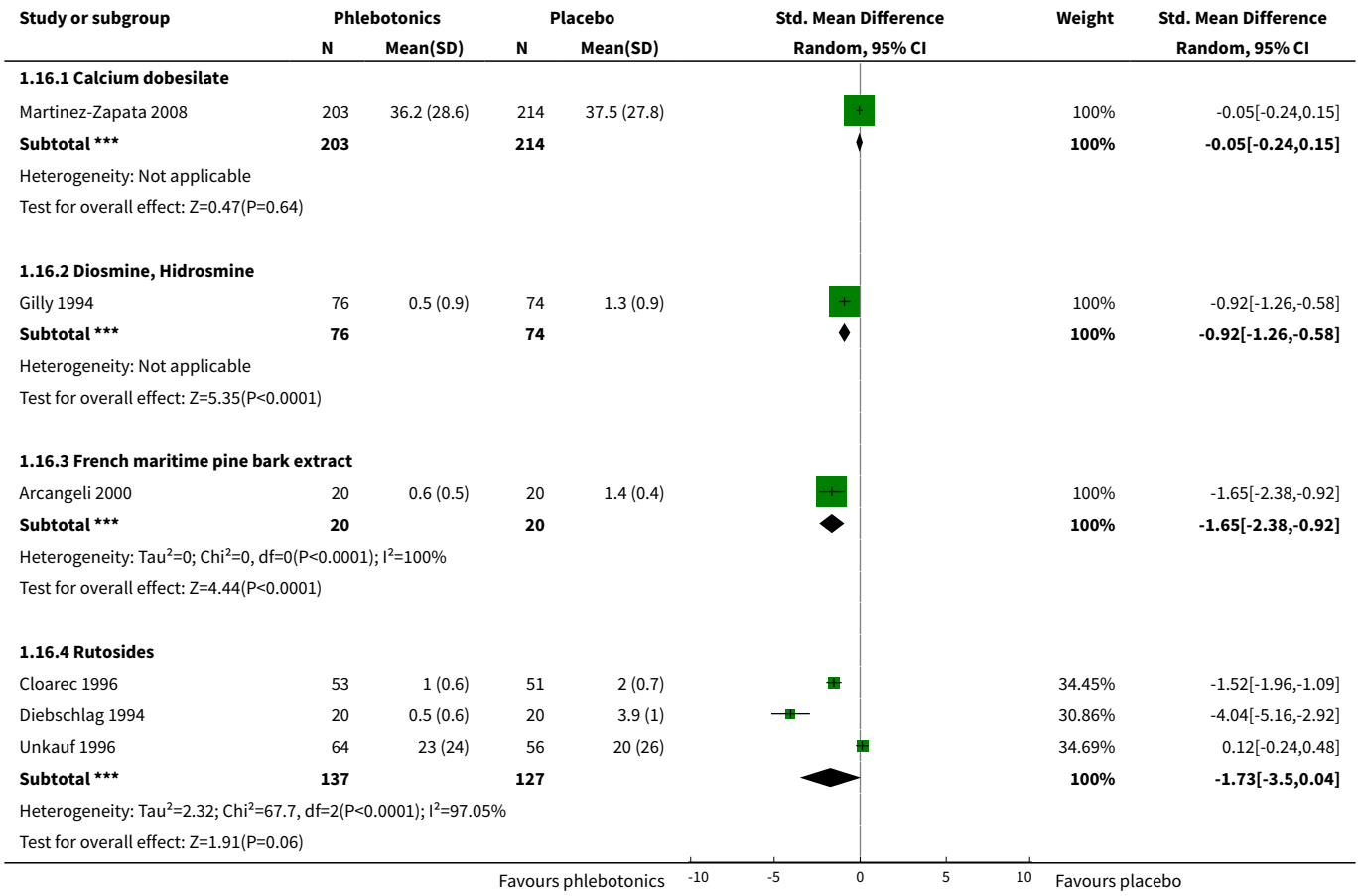
Analysis 1.15. Comparison 1 Phlebotonics versus placebo, Outcome 15 Swelling in the lower legs (dichotomous variable).

Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Calcium dobesilate					
Casley-Smith 1988	2/15	15/15		3.18%	0.16[0.05,0.51]
Hachen 1982	3/25	14/25		3.29%	0.21[0.07,0.65]
Subtotal (95% CI)	**40**	**40**		**6.47%**	**0.19[0.08,0.41]**
Total events: 5 (Phlebotonics), 29 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=4.12(P<0.0001)					
1.15.2 Diosmine, Hidrosmine					
Biland 1982	21/35	30/35		11.24%	0.7[0.52,0.95]
Fermoso 1992	4/20	4/14		2.92%	0.7[0.21,2.34]
Subtotal (95% CI)	**55**	**49**		**14.16%**	**0.7[0.52,0.94]**
Total events: 25 (Phlebotonics), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=2.38(P=0.02)					
1.15.3 French maritime pine bark extract					
Arcangeli 2000	16/20	20/20		12.19%	0.8[0.64,1.02]
Subtotal (95% CI)	**20**	**20**		**12.19%**	**0.8[0.64,1.02]**
Total events: 16 (Phlebotonics), 20 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.82(P=0.07)					
1.15.4 Rutosides					
Balmer 1980	2/40	22/40		2.35%	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		9.95%	0.88[0.6,1.3]
Kriner 1985	1/25	8/25		1.22%	0.13[0.02,0.93]
Languillat 1988	3/10	3/10		2.47%	1[0.26,3.81]
Pedersen 1992	17/24	13/19		9.85%	1.04[0.69,1.54]
Vanscheidt 2002a	42/114	76/117		11.63%	0.57[0.43,0.75]
Vin 1994	27/43	23/30		11.23%	0.82[0.6,1.11]
Welch 1985	11/72	22/75		6.67%	0.52[0.27,1]
Subtotal (95% CI)	**429**	**419**		**67.18%**	**0.67[0.5,0.88]**
Total events: 156 (Phlebotonics), 242 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=24.38, df=8(P=0); I^2=67.19%					
Test for overall effect: Z=2.87(P=0)					

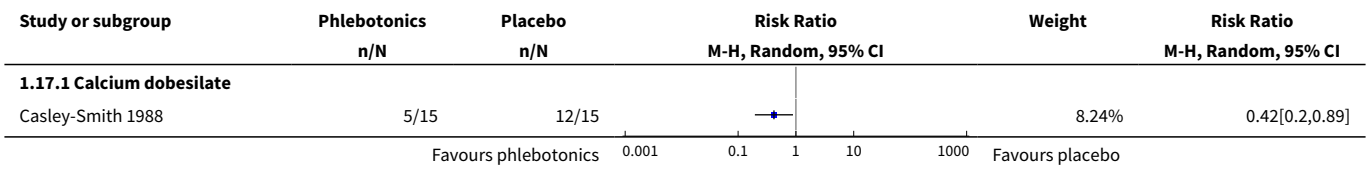
Favours phebotonics 0.01 0.1 1 10 100 Favours placebo

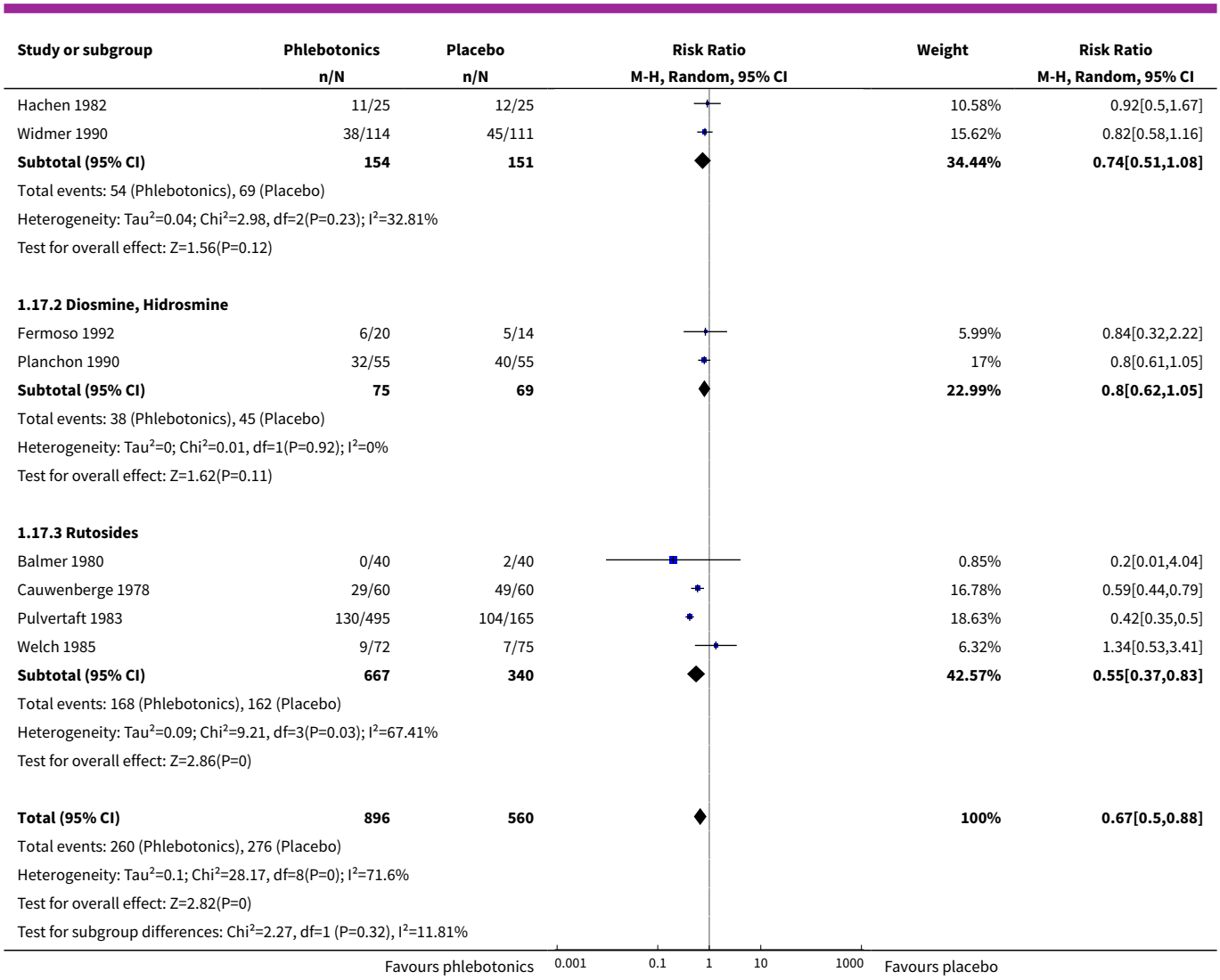


Analysis 1.16. Comparison 1 Phlebotonics versus placebo, Outcome 16 Swelling in the lower legs (continuous variable).

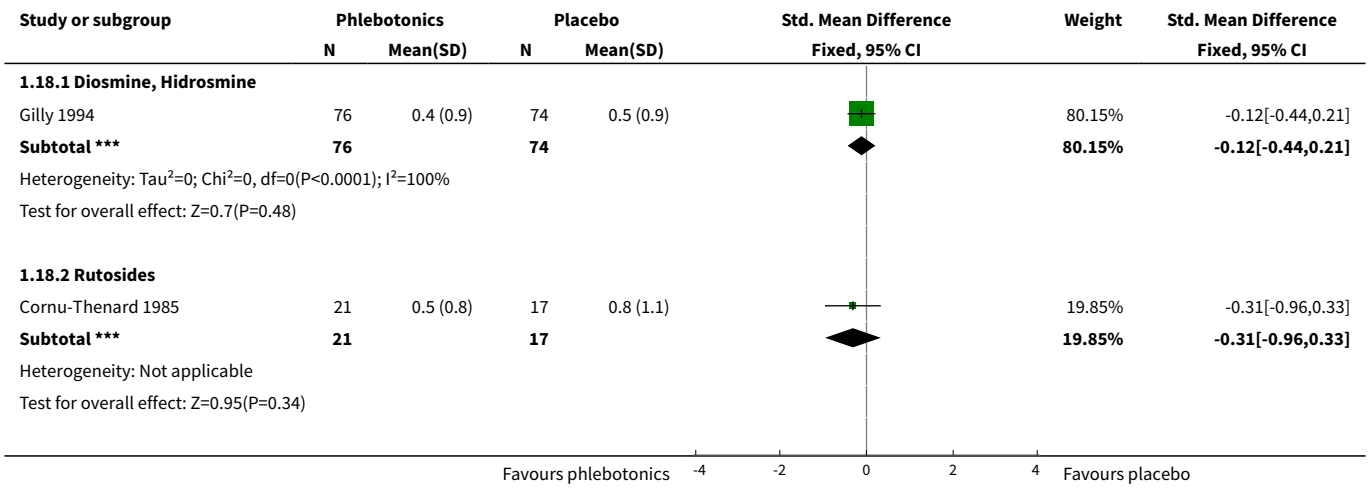


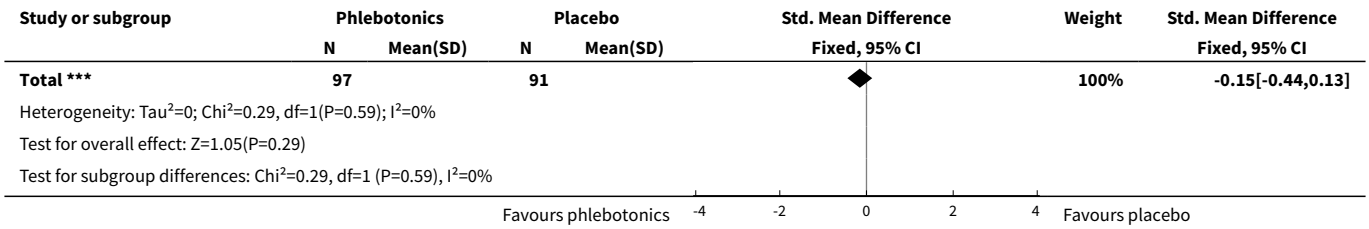
Analysis 1.17. Comparison 1 Phlebotonics versus placebo, Outcome 17 Paraesthesia in the lower legs (dichotomous variable).



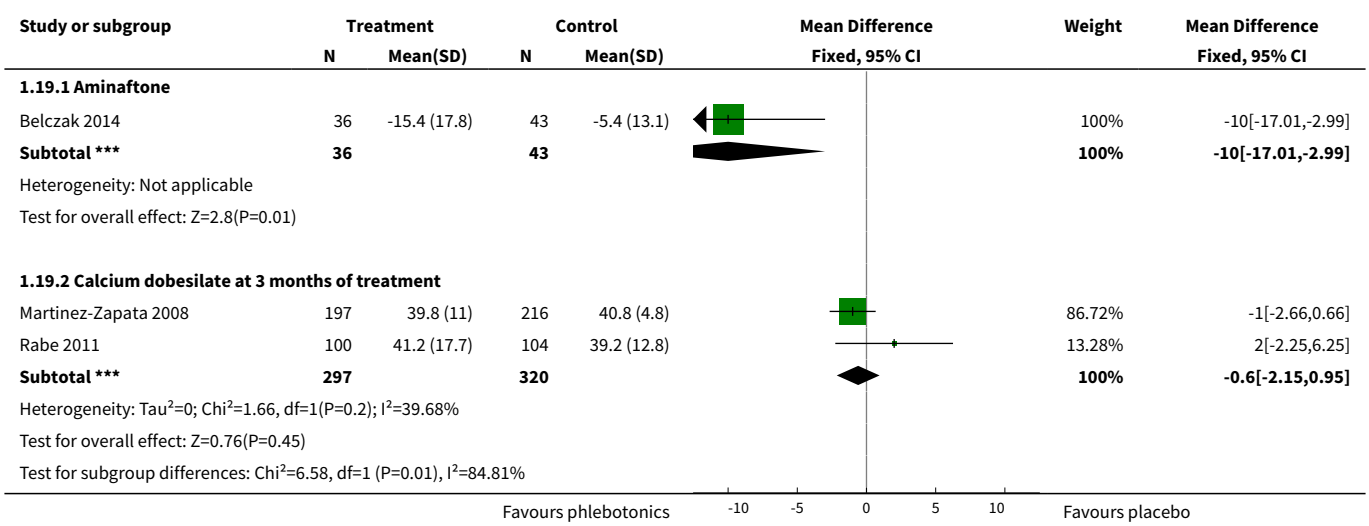


Analysis 1.18. Comparison 1 Phlebotonics versus placebo, Outcome 18 Paraesthesia in the lower legs (continuous variable).

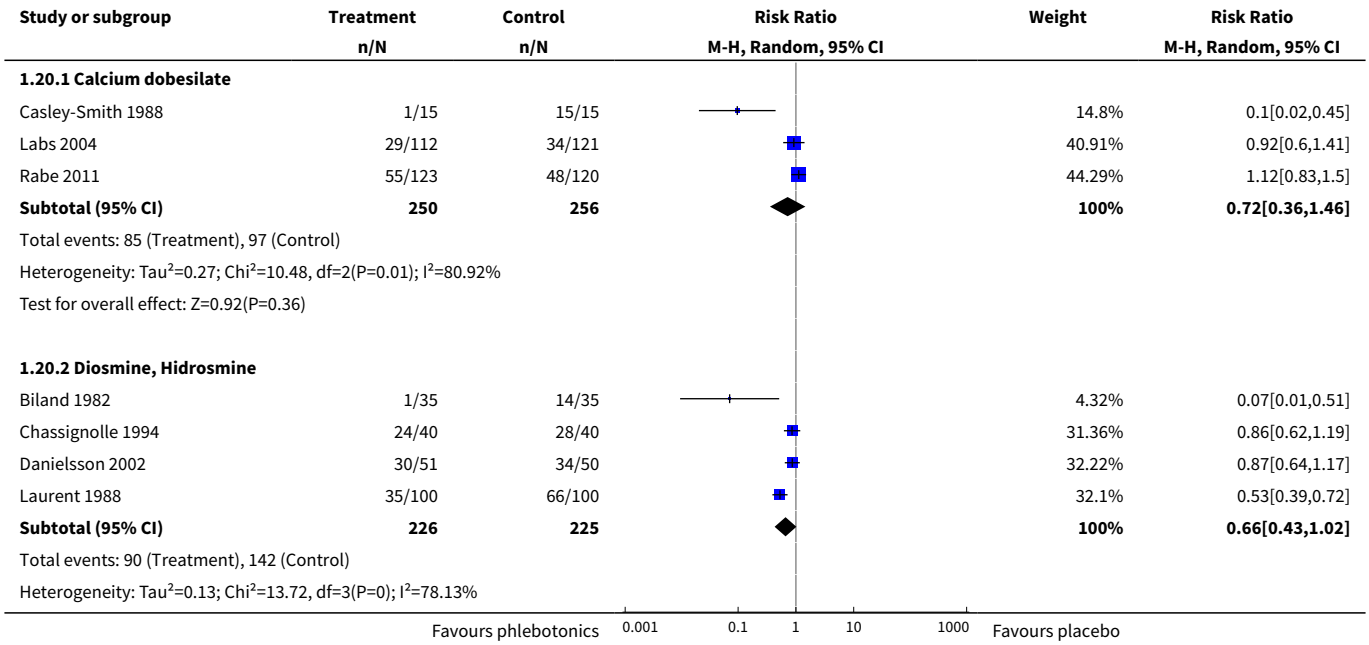


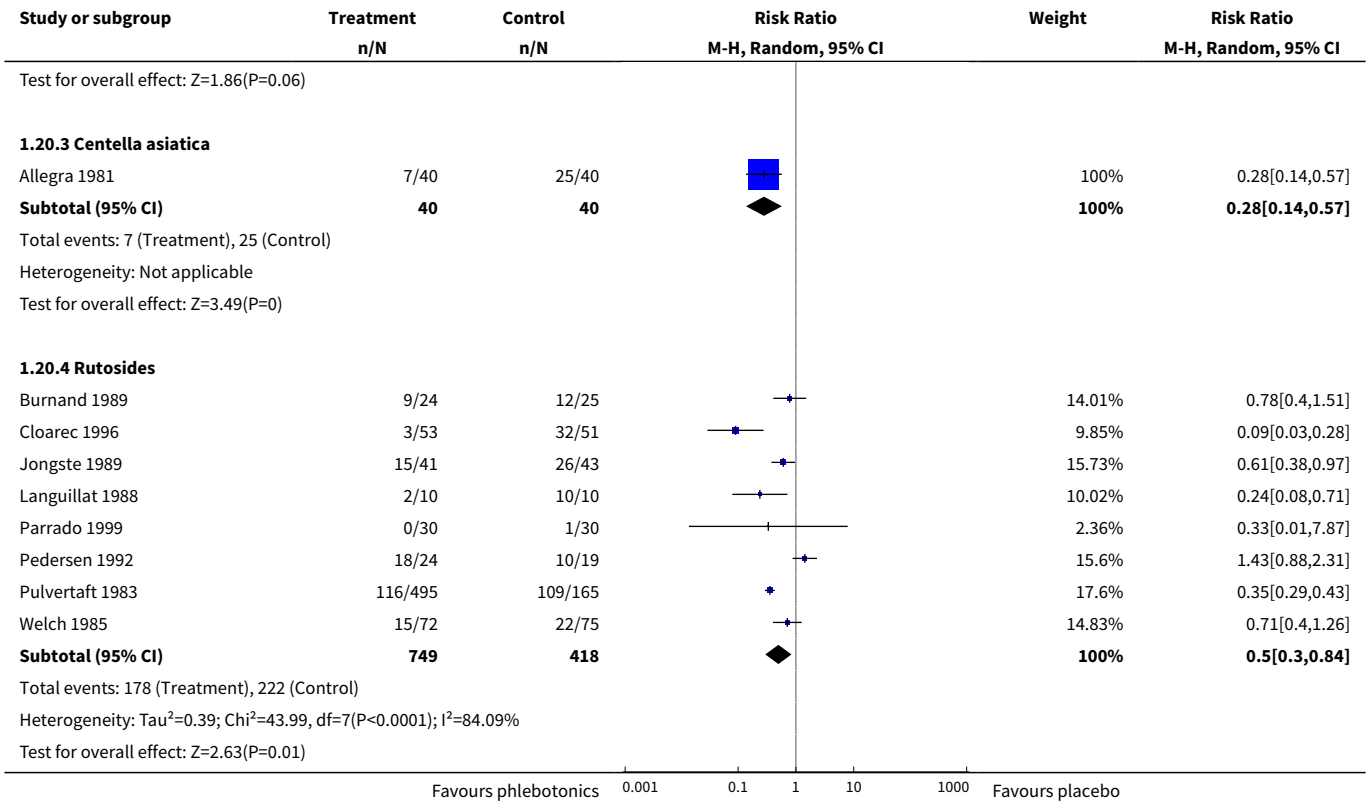


Analysis 1.19. Comparison 1 Phlebotonics versus placebo, Outcome 19 Quality of life.

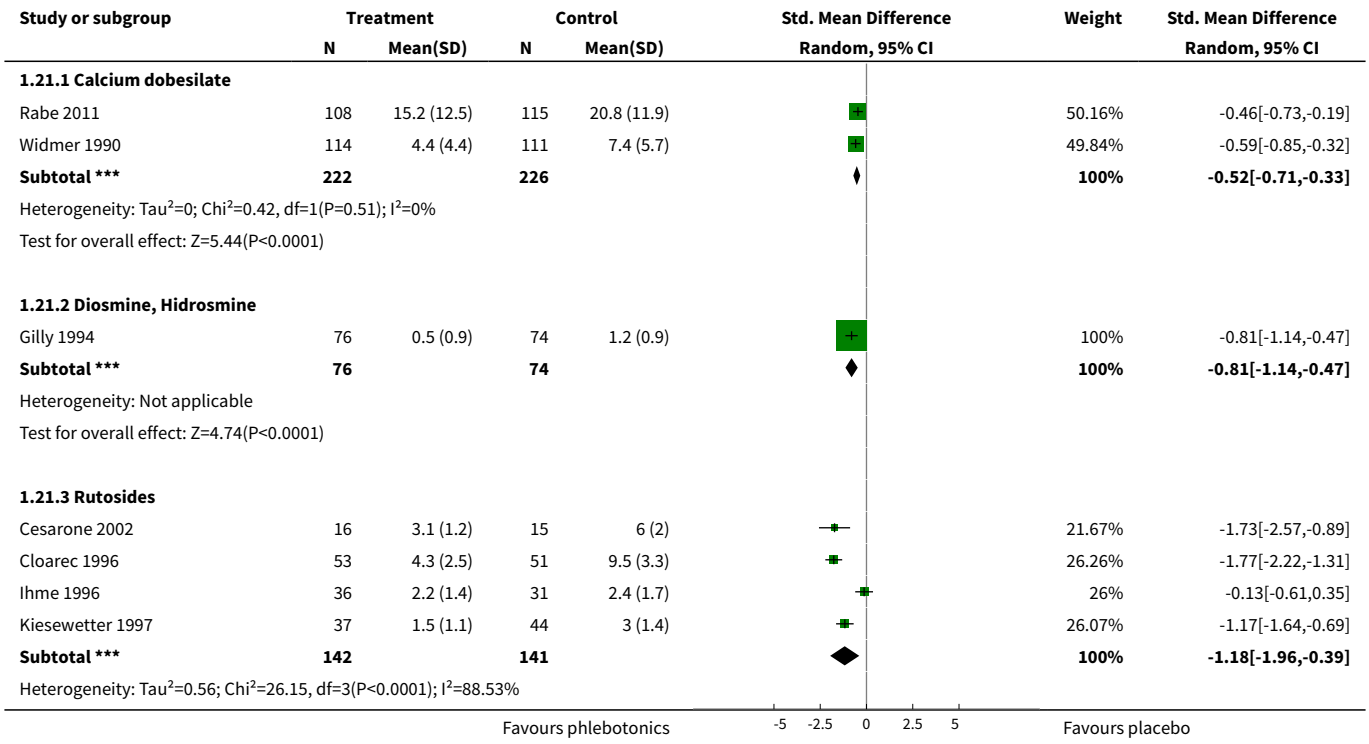


Analysis 1.20. Comparison 1 Phlebotonics versus placebo, Outcome 20 Global assessment by the participant (dichotomous variable).





Analysis 1.21. Comparison 1 Phlebotonics versus placebo, Outcome 21 Global assessment by the participant (continuous variable).

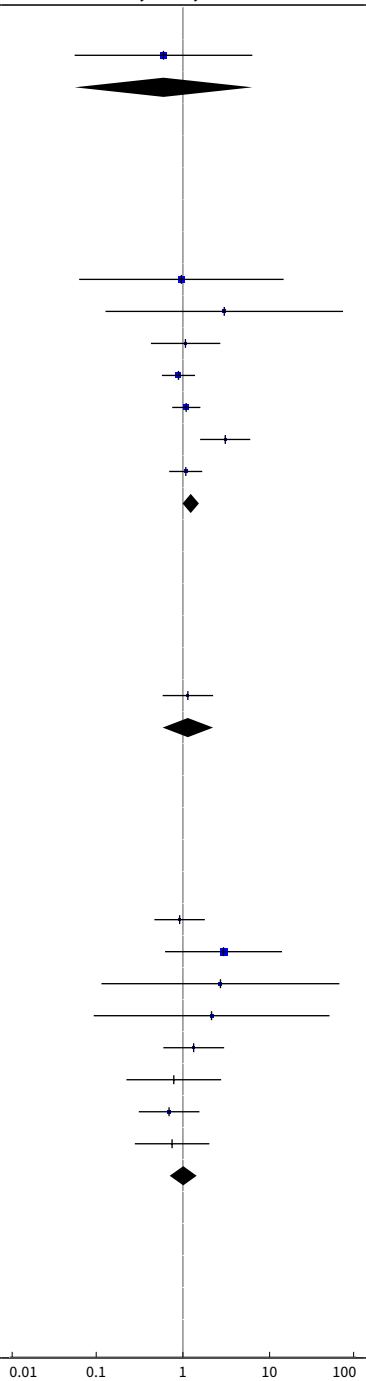


Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Test for overall effect: Z=2.93(P=0)							

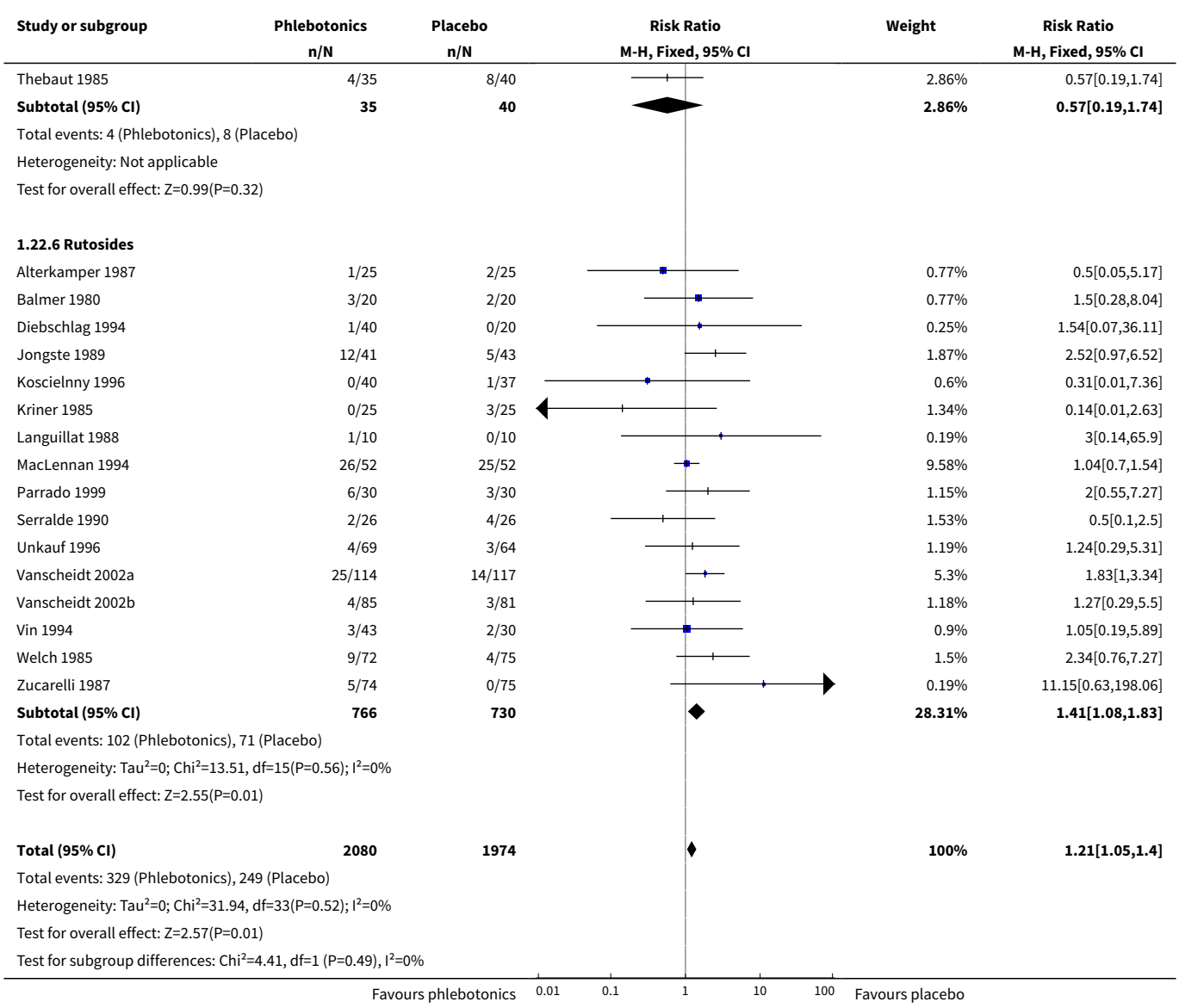
Favours phlebotonics | Favours placebo

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

Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 Aminaftone					
Belczak 2014	1/36	2/43		0.7%	0.6[0.06,6.32]
Subtotal (95% CI)	**36**	**43**		**0.7%**	**0.6[0.06,6.32]**
Total events: 1 (Phlebotonics), 2 (Placebo)					
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		0.39%	0.96[0.06,14.5]
Hachen 1982	1/25	0/25		0.19%	3[0.13,70.3]
Labs 2004	9/133	8/127		3.14%	1.07[0.43,2.7]
Marinello 2002	32/82	18/41		9.2%	0.89[0.57,1.38]
Martinez-Zapata 2008	46/246	45/263		16.67%	1.09[0.75,1.59]
Rabe 2011	33/133	10/124		3.97%	3.08[1.58,5.98]
Widmer 1990	31/114	28/111		10.87%	1.08[0.69,1.67]
Subtotal (95% CI)	**758**	**715**		**44.43%**	**1.23[0.99,1.53]**
Total events: 153 (Phlebotonics), 110 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.58, df=6(P=0.1); I^2=43.3%					
Test for overall effect: Z=1.87(P=0.06)					
1.22.3 Centella asiatica					
Pointel 1986	19/61	9/33		4.48%	1.14[0.58,2.23]
Subtotal (95% CI)	**61**	**33**		**4.48%**	**1.14[0.58,2.23]**
Total events: 19 (Phlebotonics), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
1.22.4 Diosmine, Hidrosmine					
Biland 1982	11/35	12/35		4.6%	0.92[0.47,1.79]
Danielsson 2002	6/51	2/50		0.77%	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		0.22%	2.14[0.09,49.08]
Gilly 1994	12/80	9/80		3.45%	1.33[0.6,2.99]
Guilhou 1997	4/53	5/52		1.93%	0.78[0.22,2.76]
Laurent 1988	9/100	13/100		4.98%	0.69[0.31,1.55]
Planchon 1990	6/55	8/55		3.07%	0.75[0.28,2.02]
Subtotal (95% CI)	**424**	**413**		**19.23%**	**1.01[0.7,1.44]**
Total events: 50 (Phlebotonics), 49 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.3, df=7(P=0.74); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					
1.22.5 Grape seed extract					



Favours phlebotonics | Favours placebo



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
1 Oedema in the lower legs (dichotomous variable)	12	1131	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.60, 0.76]
1.1 Aminaftone	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
1.2 Calcium dobesilate	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
1.3 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
1.4 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Rutosides	6	540	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.78]
2 Ankle perimeter circumference (mm)	10	1212	Mean Difference (IV, Fixed, 95% CI)	-4.59 [-6.02, -3.16]
2.1 Calcium dobesilate	3	502	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-4.95, 3.34]
2.2 Diosmine, Hidrosmine	2	246	Mean Difference (IV, Fixed, 95% CI)	-5.90 [-7.72, -4.07]
2.3 Rutosides	5	464	Mean Difference (IV, Fixed, 95% CI)	-3.28 [-6.06, -0.50]
3 Volume of the leg (mL)	8	802	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.48, -0.20]
3.1 Aminaftone	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.61, 0.28]
3.2 Calcium dobesilate	2	236	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.77, -0.25]
3.3 Rutosides	5	487	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.47, -0.11]
4 Ulcer cured	2	128	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.27, 3.10]
4.1 Aminaftone	1	100	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.18]
4.2 Diosmine, Hidrosmine	1	28	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.15, 14.68]
5 Trophic disorders (dichotomous variable)	5	601	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.94]
5.1 Aminaftone	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.44]
5.2 Diosmine, Hidrosmine	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
6 Pain in the lower legs (dichotomous variable)	17	1467	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.57, 0.82]
6.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.79]
6.2 Calcium dobesilate	4	354	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.16, 0.93]
6.3 Diosmine, Hidrosmine	4	271	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.08]
6.4 Rutosides	8	745	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.91]
7 Pain in the lower legs (continuous variable)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

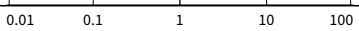
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.67, -0.02]
7.2 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.33, -0.59]
8 Cramps in the lower legs (dichotomous variable)	12	1603	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.57, 0.91]
8.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.99]
8.2 Calcium dobesilate	2	255	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
8.3 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.09]
8.4 Rutosides	7	1147	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.06]
9 Cramps in the lower legs (continuous variable)	3	314	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.15, -0.24]
9.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.78, -0.14]
9.2 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.16]
10 Restless legs (dichotomous variable)	6	572	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
10.1 Calcium dobesilate	2	255	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.59, 0.91]
10.2 Diosmine, Hidrosmine	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.15]
10.3 Rutosides	3	247	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.01]
11 Itching in the lower legs (dichotomous variable)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
11.2 Diosmine, Hidrosmine	1	34	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.25]
11.3 Rutosides	2	274	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.21, 2.21]
12 Itching in the lower legs (continuous variable)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Rutosides	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Heaviness in the lower legs (dichotomous variable)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 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
13.2 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
13.3 Centella asiatica	1	63	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
13.4 Diosmine, Hidrosmine	3	201	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.29, 1.22]
13.5 Rutosides	8	531	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.38, 0.80]
14 Heaviness in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.02, -0.36]
14.2 Rutosides	5	360	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-2.22, -0.32]
15 Swelling in the lower legs (dichotomous variable)	12	952	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.82]
15.1 Calcium dobesilate	2	80	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.41]
15.2 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.52, 0.94]
15.3 Rutosides	8	768	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.89]
16 Swelling in the lower legs (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.26, -0.58]
16.2 Rutosides	3	264	Std. Mean Difference (IV, Random, 95% CI)	-1.73 [-3.50, 0.04]
17 Paraesthesias in the lower legs (dichotomous variable)	7	716	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.64, 0.88]
17.1 Calcium dobesilate	3	305	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.58, 1.01]
17.2 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.06]
17.3 Rutosides	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.91]
18 Paraesthesias in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Diosmine, Hidrosmine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
19.1 Aminaftone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20 Global assessment by the participant (dichotomous variable)	12	1193	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.53, 0.90]
20.1 Calcium dobesilate	3	515	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.43, 1.17]
20.2 Diosmine, Hidrosmine	2	171	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.68, 1.04]
20.3 Rutosides	7	507	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.98]
21 Global assessment by the participant (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.14, -0.47]
21.2 Rutosides	3	252	Std. Mean Difference (IV, Random, 95% CI)	-1.02 [-1.96, -0.09]
22 Adverse events	25	2490	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.00, 1.51]
22.1 Aminaftone	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.06, 6.32]
22.2 Calcium dobesilate	4	584	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.74, 1.62]
22.3 Centella asiatica	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.58, 2.23]
22.4 Diosmine, Hidrosmine	6	532	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.76, 1.79]
22.5 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.19, 1.74]
22.6 Rutosides	12	1126	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.08, 2.19]

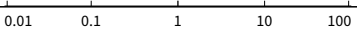
Analysis 2.1. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 1 Oedema in the lower legs (dichotomous variable).

Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Aminaftone					
Lazzarini 1982	10/41	19/41		6.28%	0.53[0.28,0.99]
Subtotal (95% CI)	**41**	**41**		**6.28%**	**0.53[0.28,0.99]**
Total events: 10 (Phlebotonics), 19 (Placebo)					
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		4.63%	0.14[0.04,0.52]



Favours phlebotonics — Favours placebo

Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Labs 2004	30/133	29/127		9.8%	0.99[0.63,1.55]
Subtotal (95% CI)	**148**	**142**		**14.43%**	**0.72[0.48,1.07]**
Total events: 32 (Phlebotonics), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.9, df=1(P=0); I^2=87.34%					
Test for overall effect: Z=1.62(P=0.11)					
2.1.3 Diosmine, Hidrosmine					
Fermoso 1992	15/20	13/14		5.05%	0.81[0.6,1.08]
Planchon 1990	16/55	30/55		9.91%	0.53[0.33,0.86]
Subtotal (95% CI)	**75**	**69**		**14.96%**	**0.63[0.46,0.86]**
Total events: 31 (Phlebotonics), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.36, df=1(P=0.07); I^2=70.26%					
Test for overall effect: Z=2.93(P=0)					
2.1.4 Grape seed extract					
Thebaut 1985	22/35	32/40		9.87%	0.79[0.58,1.06]
Subtotal (95% CI)	**35**	**40**		**9.87%**	**0.79[0.58,1.06]**
Total events: 22 (Phlebotonics), 32 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.59(P=0.11)					
2.1.5 Rutosides					
Cauwenberge 1972	9/21	18/21		5.95%	0.5[0.3,0.84]
Cauwenberge 1978	19/60	29/60		9.58%	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		10.64%	0.72[0.54,0.96]
Kriner 1985	14/25	22/25		7.27%	0.64[0.44,0.93]
Welch 1985	9/72	14/75		4.53%	0.67[0.31,1.45]
Subtotal (95% CI)	**271**	**269**		**54.47%**	**0.68[0.58,0.78]**
Total events: 113 (Phlebotonics), 163 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.72, df=5(P=0.74); I^2=0%					
Test for overall effect: Z=5.2(P<0.0001)					
Total (95% CI)	**570**	**561**		**100%**	**0.68[0.6,0.76]**
Total events: 208 (Phlebotonics), 300 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=14.94, df=11(P=0.19); I^2=26.36%					
Test for overall effect: Z=6.42(P<0.0001)					
Test for subgroup differences: Chi^2=1.87, df=1 (P=0.76), I^2=0%					



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

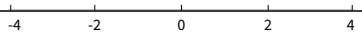
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.2.1 Calcium dobesilate							
Flota-Cervera 2008	25	335.6 (38.2)	24	356.2 (38.2)		0.45%	-20.6[-42,0.8]
Labs 2004	124	229.5 (22.7)	123	228.3 (19.6)		7.34%	1.2[-4.09,6.49]
Widmer 1990	103	230.1 (21.3)	103	232.3 (29.4)		4.17%	-2.2[-9.22,4.82]

Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Subtotal ***	**252**		**250**			**11.95%**	**-0.8[-4.95,3.34]**
Heterogeneity: Tau²=0; Chi²=3.99, df=2(P=0.14); I²=49.89%							
Test for overall effect: Z=0.38(P=0.7)							
2.2.2 Diosmine, Hidrosmine							
Gilly 1994	76	-7.1 (7)	74	-1.2 (4.3)		60.12%	-5.9[-7.75,-4.05]
Planchon 1990	48	229.1 (30.3)	48	234.8 (31)		1.37%	-5.7[-17.96,6.56]
Subtotal ***	**124**		**122**			**61.48%**	**-5.9[-7.72,-4.07]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.97); I²=0%							
Test for overall effect: Z=6.32(P<0.0001)							
2.2.3 Rutosides							
Cloarec 1996	53	221 (22)	51	225 (19)		3.3%	-4[-11.89,3.89]
Jongste 1989	41	236 (22)	43	237 (20)		2.53%	-1[-10,8]
Parrado 1999	30	209 (50)	30	243 (48)		0.33%	-34[-58.8,-9.2]
Vin 1994	34	-3.7 (7.2)	35	-0.8 (7.3)		17.54%	-2.9[-6.32,0.52]
Welch 1985	72	232.5 (27.4)	75	235.7 (24.9)		2.86%	-3.2[-11.67,5.27]
Subtotal ***	**230**		**234**			**26.56%**	**-3.28[-6.06,-0.5]**
Heterogeneity: Tau²=0; Chi²=6.22, df=4(P=0.18); I²=35.68%							
Test for overall effect: Z=2.31(P=0.02)							
Total ***	**606**		**606**			**100%**	**-4.59[-6.02,-3.16]**
Heterogeneity: Tau²=0; Chi²=16.23, df=9(P=0.06); I²=44.56%							
Test for overall effect: Z=6.28(P<0.0001)							
Test for subgroup differences: Chi²=6.02, df=1 (P=0.05), I²=66.78%							

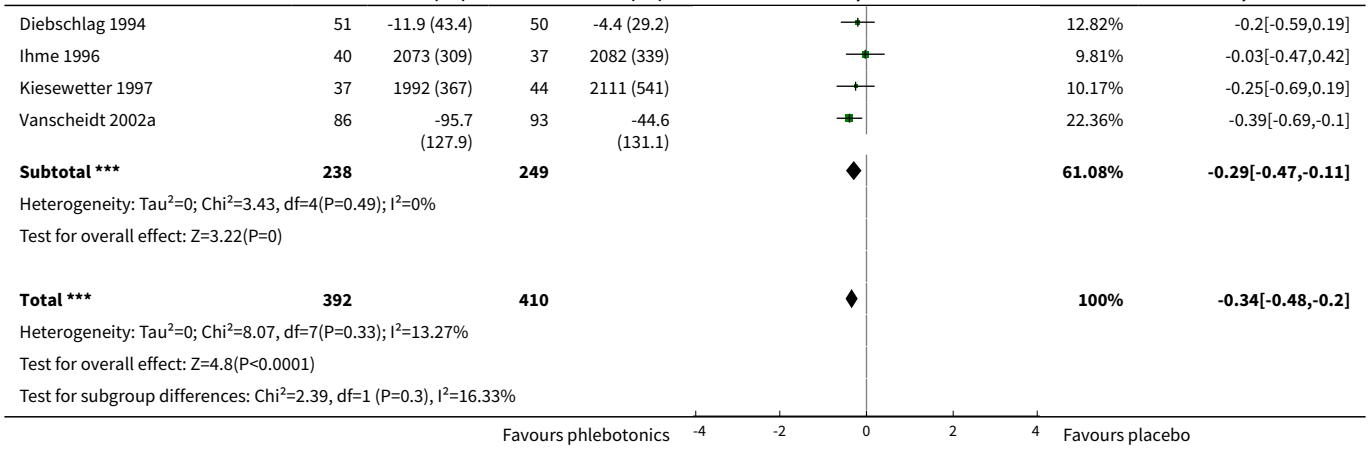
Favours phlebotonics — Favours placebo

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

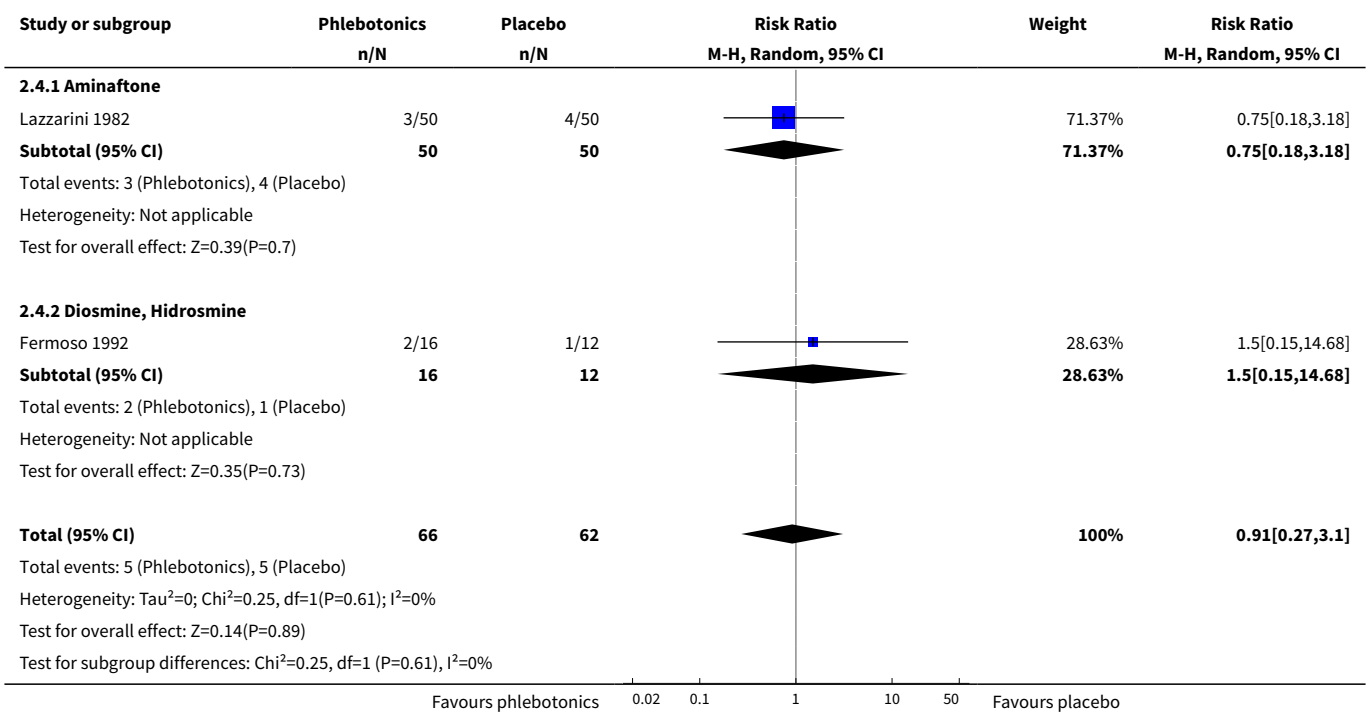
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.3.1 Aminaftone							
Belczak 2014	36	3276.5 (584.6)	43	3391.5 (751.1)		9.96%	-0.17[-0.61,0.28]
Subtotal ***	**36**		**43**			**9.96%**	**-0.17[-0.61,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
2.3.2 Calcium dobesilate							
Casley-Smith 1988	15	1097 (93)	15	1205 (104.6)		3.29%	-1.06[-1.83,-0.29]
Widmer 1990	103	-3.8 (6.1)	103	-1.1 (6.1)		25.66%	-0.43[-0.71,-0.16]
Subtotal ***	**118**		**118**			**28.96%**	**-0.51[-0.77,-0.25]**
Heterogeneity: Tau²=0; Chi²=2.25, df=1(P=0.13); I²=55.65%							
Test for overall effect: Z=3.81(P=0)							
2.3.3 Rutosides							
Burnand 1989	24	1098 (157.7)	25	1200 (156.5)		5.92%	-0.64[-1.21,-0.06]



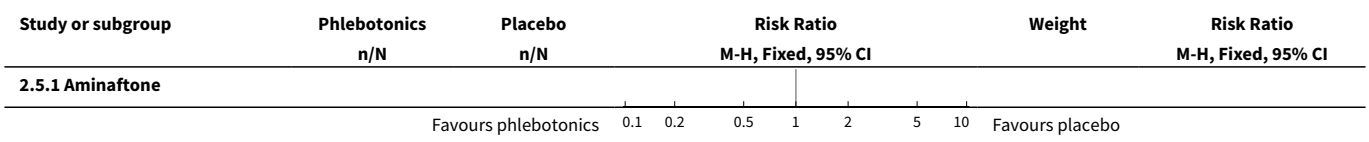
Favours phlebotonics — Favours placebo

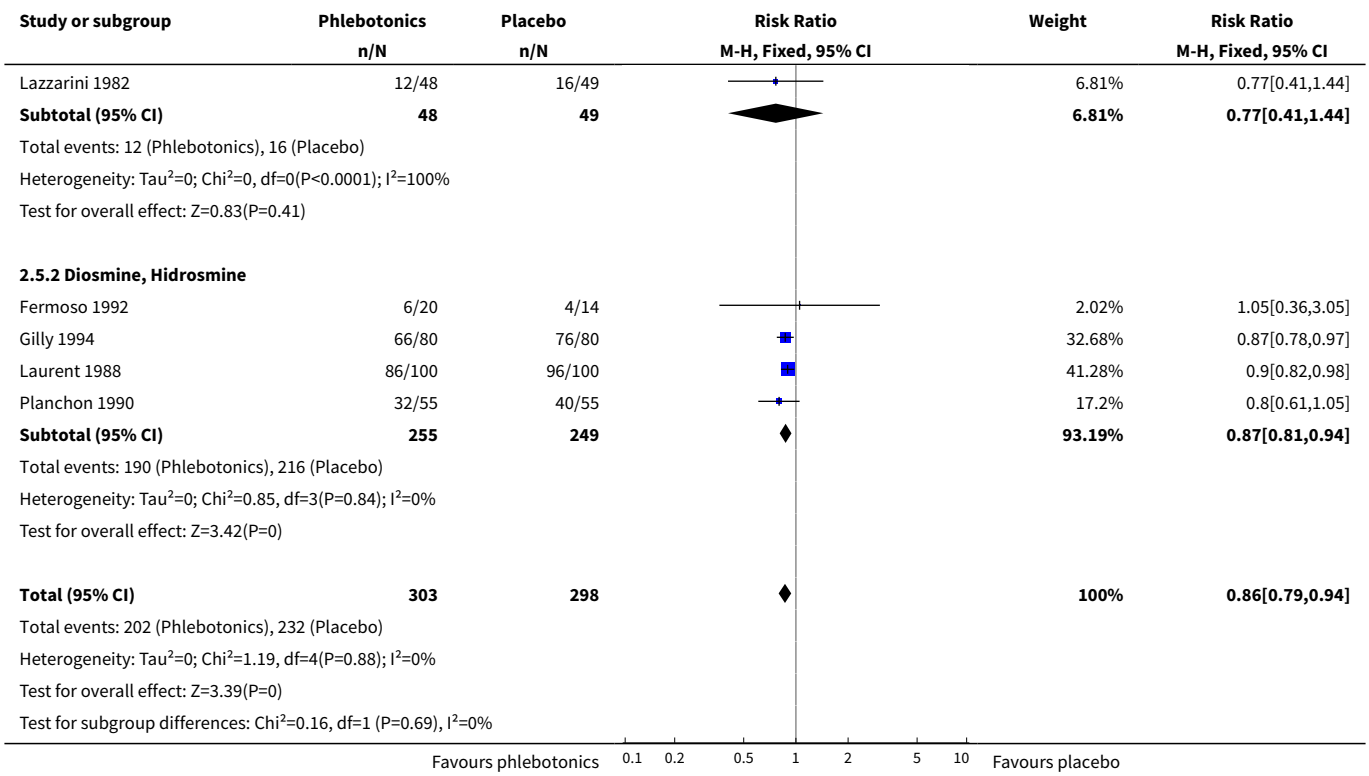


Analysis 2.4. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 4 Ulcer cured.

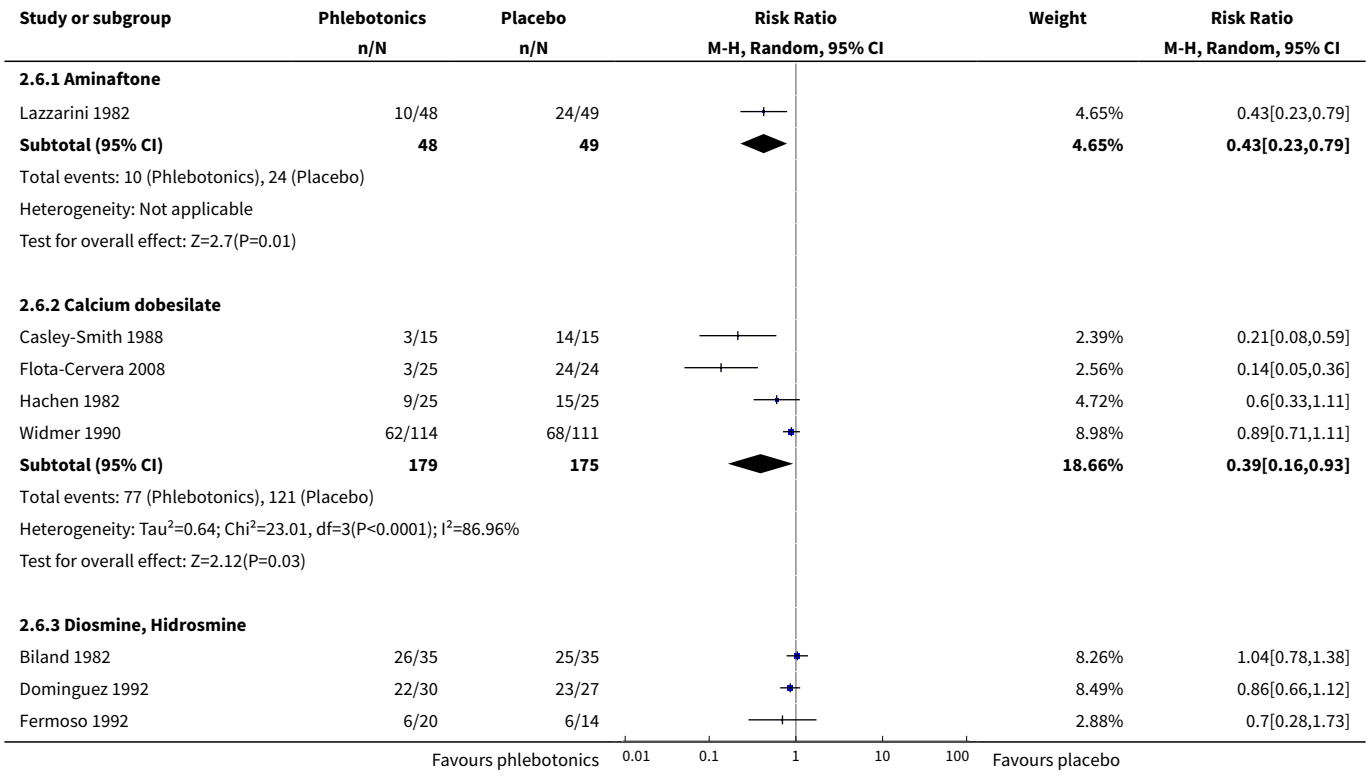


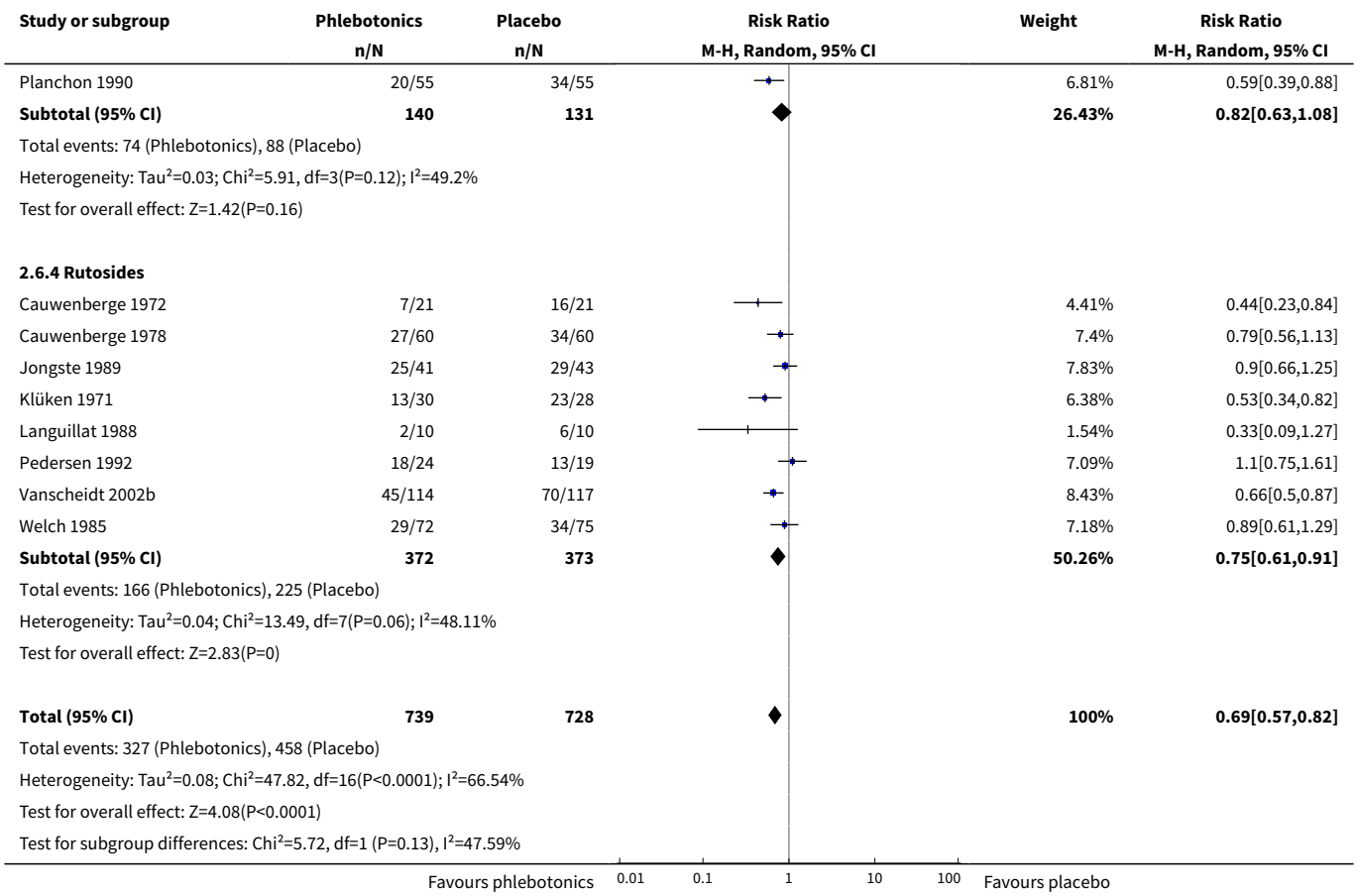
Analysis 2.5. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 5 Trophic disorders (dichotomous variable).



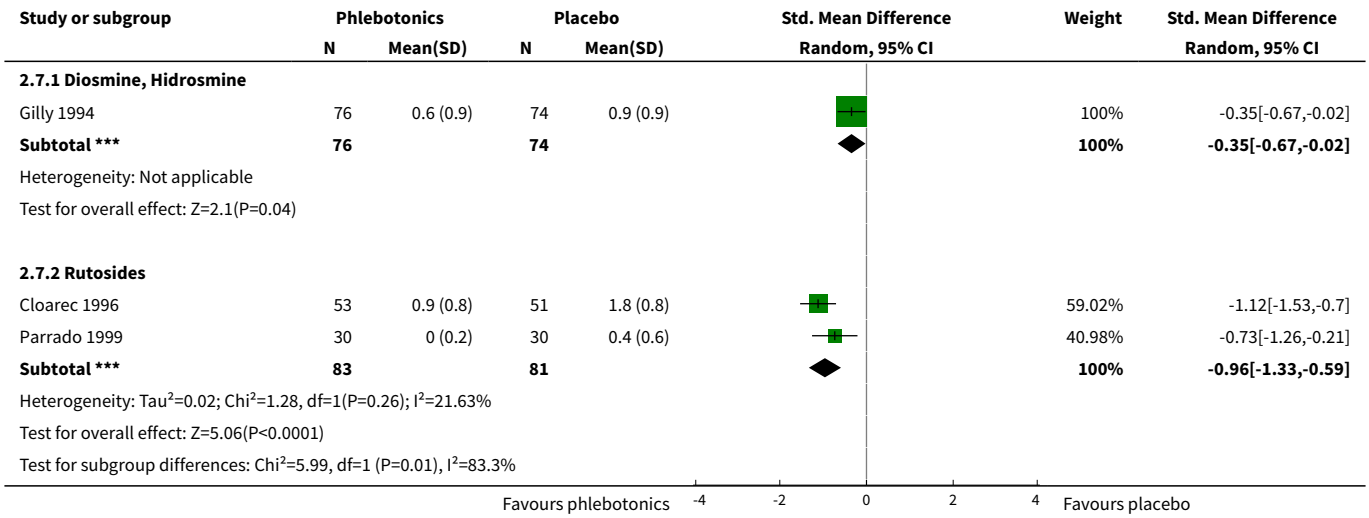


Analysis 2.6. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 6 Pain in the lower legs (dichotomous variable).



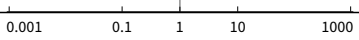


Analysis 2.7. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 7 Pain in the lower legs (continuous variable).



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

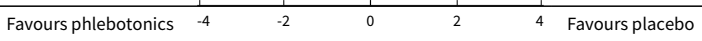
Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Aminaftone					
Lazzarini 1982	12/48	22/49		7.45%	0.56[0.31,0.99]
Subtotal (95% CI)	**48**	**49**		**7.45%**	**0.56[0.31,0.99]**
Total events: 12 (Phlebotonics), 22 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
2.8.2 Calcium dobesilate					
Casley-Smith 1988	8/15	10/15		7.29%	0.8[0.44,1.45]
Widmer 1990	41/114	65/111		11.26%	0.61[0.46,0.82]
Subtotal (95% CI)	**129**	**126**		**18.55%**	**0.65[0.5,0.84]**
Total events: 49 (Phlebotonics), 75 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=3.28(P=0)					
2.8.3 Diosmine, Hidrosmine					
Biland 1982	26/35	30/35		11.95%	0.87[0.68,1.1]
Fermoso 1992	5/20	4/14		3.31%	0.88[0.28,2.69]
Subtotal (95% CI)	**55**	**49**		**15.26%**	**0.87[0.69,1.09]**
Total events: 31 (Phlebotonics), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=1.2(P=0.23)					
2.8.4 Rutosides					
Cauwenberge 1978	25/60	41/60		10.52%	0.61[0.43,0.86]
Jongste 1989	27/41	28/43		10.99%	1.01[0.74,1.38]
Languillat 1988	0/10	3/10		0.65%	0.14[0.01,2.45]
Pedersen 1992	17/24	11/19		8.93%	1.22[0.77,1.94]
Pulvertaft 1983	120/495	95/165		12.34%	0.42[0.34,0.52]
Vin 1994	21/43	21/30		9.96%	0.7[0.47,1.03]
Welch 1985	10/72	11/75		5.34%	0.95[0.43,2.09]
Subtotal (95% CI)	**745**	**402**		**58.74%**	**0.73[0.5,1.06]**
Total events: 220 (Phlebotonics), 210 (Placebo)					
Heterogeneity: Tau^2=0.18; Chi^2=34.68, df=6(P<0.0001); I^2=82.7%					
Test for overall effect: Z=1.65(P=0.1)					
Total (95% CI)	**977**	**626**		**100%**	**0.72[0.57,0.91]**
Total events: 312 (Phlebotonics), 341 (Placebo)					
Heterogeneity: Tau^2=0.11; Chi^2=42.77, df=11(P<0.0001); I^2=74.28%					
Test for overall effect: Z=2.73(P=0.01)					
Test for subgroup differences: Chi^2=3.75, df=1 (P=0.29), I^2=20.06%					



Favours phlebotonics | Favours placebo

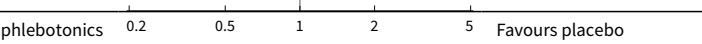
Analysis 2.9. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 9 Cramps in the lower legs (continuous variable).

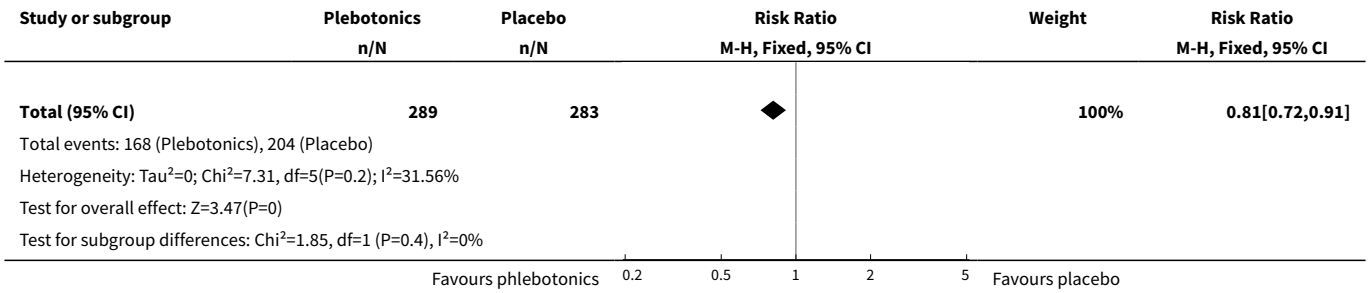
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.9.1 Diosmine, Hidrosmine							
Gilly 1994	76	0.3 (0.9)	74	0.7 (0.9)		37.45%	-0.46[-0.78,-0.14]
Subtotal ***	**76**		**74**			**37.45%**	**-0.46[-0.78,-0.14]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=2.78(P=0.01)							
2.9.2 Rutosides							
Cloarec 1996	53	0.6 (0.7)	51	1.6 (1)		33.38%	-1.15[-1.57,-0.74]
Parrado 1999	30	0 (0.2)	30	0.2 (0.4)		29.17%	-0.47[-0.99,0.04]
Subtotal ***	**83**		**81**			**62.55%**	**-0.83[-1.5,-0.16]**
Heterogeneity: Tau^2=0.18; Chi^2=4.08, df=1(P=0.04); I^2=75.47%							
Test for overall effect: Z=2.44(P=0.01)							
Total ***	**159**		**155**			**100%**	**-0.7[-1.15,-0.24]**
Heterogeneity: Tau^2=0.12; Chi^2=7.36, df=2(P=0.03); I^2=72.84%							
Test for overall effect: Z=2.98(P=0)							
Test for subgroup differences: Chi^2=0.96, df=1 (P=0.33), I^2=0%							



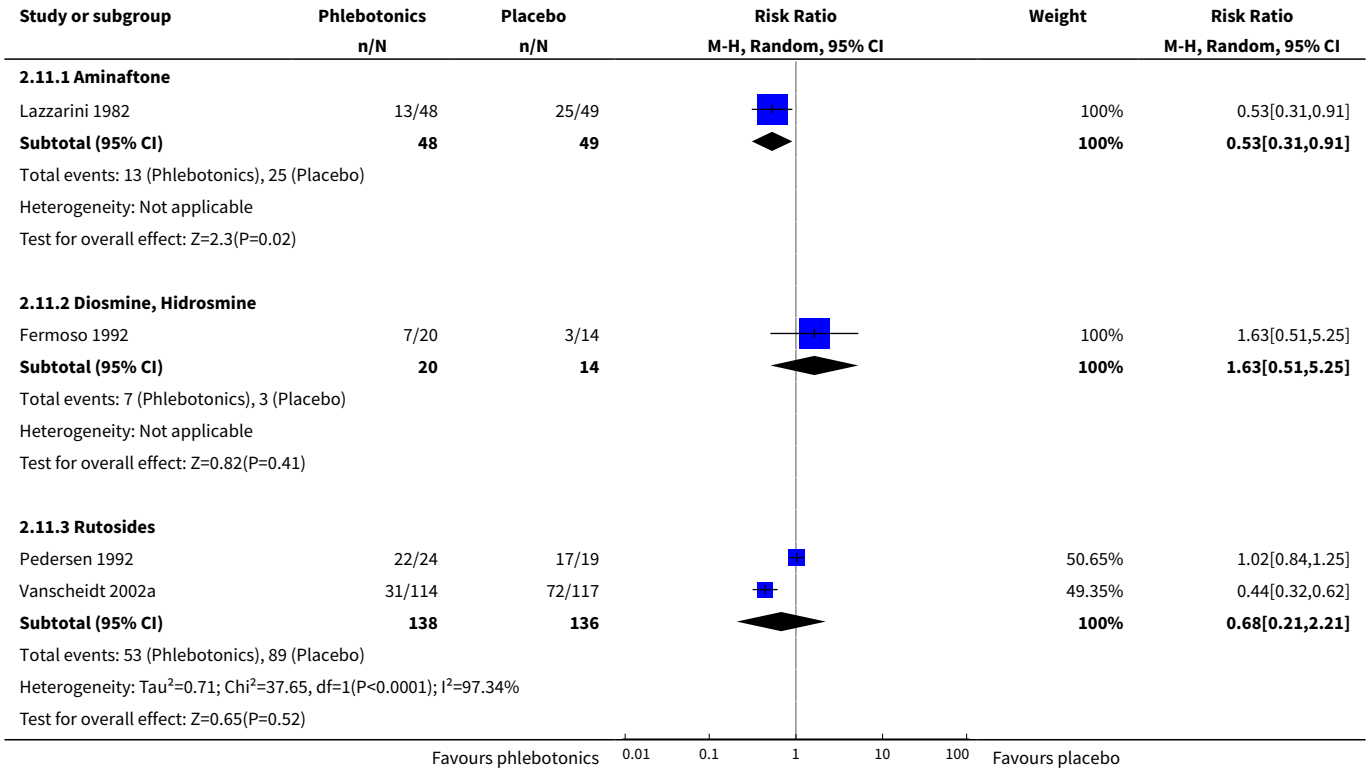
Analysis 2.10. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 10 Restless legs (dichotomous variable).

Study or subgroup	Plebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 Calcium dobesilate					
Casley-Smith 1988	10/15	14/15		6.82%	0.71[0.49,1.05]
Widmer 1990	52/114	69/111		34.05%	0.73[0.57,0.94]
Subtotal (95% CI)	**129**	**126**		**40.87%**	**0.73[0.59,0.91]**
Total events: 62 (Plebotonics), 83 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=2.85(P=0)					
2.10.2 Diosmine, Hidrosmine					
Biland 1982	26/35	29/35		14.12%	0.9[0.7,1.15]
Subtotal (95% CI)	**35**	**35**		**14.12%**	**0.9[0.7,1.15]**
Total events: 26 (Plebotonics), 29 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.39)					
2.10.3 Rutosides					
Cauwenberge 1978	31/60	44/60		21.43%	0.7[0.53,0.94]
Jongste 1989	34/41	37/43		17.59%	0.96[0.8,1.16]
Pedersen 1992	15/24	11/19		5.98%	1.08[0.66,1.77]
Subtotal (95% CI)	**125**	**122**		**45%**	**0.86[0.73,1.01]**
Total events: 80 (Plebotonics), 92 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.21, df=2(P=0.12); I^2=52.45%					
Test for overall effect: Z=1.87(P=0.06)					

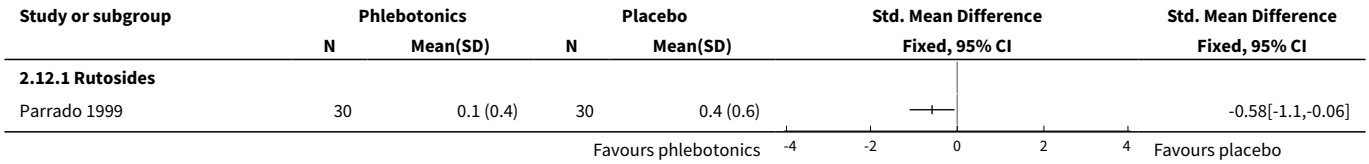




Analysis 2.11. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 11 Itching in the lower legs (dichotomous variable).

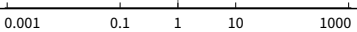


Analysis 2.12. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 12 Itching in the lower legs (continuous variable).



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

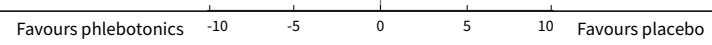
Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Aminaftone					
Lazzarini 1982	9/48	29/49		100%	0.32[0.17,0.6]
Subtotal (95% CI)	**48**	**49**		**100%**	**0.32[0.17,0.6]**
Total events: 9 (Phlebotonics), 29 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.56(P=0)					
2.13.2 Calcium dobesilate					
Casley-Smith 1988	1/15	14/15		24.23%	0.07[0.01,0.48]
Hachen 1982	4/25	13/25		34.77%	0.31[0.12,0.81]
Widmer 1990	81/114	91/111		41%	0.87[0.75,1]
Subtotal (95% CI)	**154**	**151**		**100%**	**0.33[0.08,1.42]**
Total events: 86 (Phlebotonics), 118 (Placebo)					
Heterogeneity: Tau^2=1.34; Chi^2=15.42, df=2(P=0); I^2=87.03%					
Test for overall effect: Z=1.49(P=0.14)					
2.13.3 Centella asiatica					
Pointel 1986	9/30	16/33		100%	0.62[0.32,1.19]
Subtotal (95% CI)	**30**	**33**		**100%**	**0.62[0.32,1.19]**
Total events: 9 (Phlebotonics), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.45(P=0.15)					
2.13.4 Diosmine, Hidrosmine					
Dominguez 1992	24/30	25/27		40.81%	0.86[0.7,1.06]
Fermoso 1992	5/20	7/14		24.91%	0.5[0.2,1.26]
Planchon 1990	13/55	30/55		34.29%	0.43[0.25,0.74]
Subtotal (95% CI)	**105**	**96**		**100%**	**0.6[0.29,1.22]**
Total events: 42 (Phlebotonics), 62 (Placebo)					
Heterogeneity: Tau^2=0.32; Chi^2=11.89, df=2(P=0); I^2=83.18%					
Test for overall effect: Z=1.42(P=0.16)					
2.13.5 Rutosides					
Cauwenberge 1972	4/21	13/21		9.09%	0.31[0.12,0.79]
Cauwenberge 1978	35/60	53/60		20.68%	0.66[0.52,0.83]
Jongste 1989	24/41	31/43		19.31%	0.81[0.59,1.12]
Languillat 1988	1/10	8/10		3.26%	0.13[0.02,0.82]
Pedersen 1992	18/24	15/19		19.13%	0.95[0.68,1.32]
Vanscheidt 2002a	0/1	0/1			Not estimable
Vin 1994	8/43	23/30		13.14%	0.24[0.13,0.47]
Welch 1985	15/72	30/75		15.39%	0.52[0.31,0.88]
Subtotal (95% CI)	**272**	**259**		**100%**	**0.55[0.38,0.8]**
Total events: 105 (Phlebotonics), 173 (Placebo)					
Heterogeneity: Tau^2=0.16; Chi^2=25.75, df=6(P=0); I^2=76.7%					
Test for overall effect: Z=3.18(P=0)					



Favours phlebotonics | Favours placebo

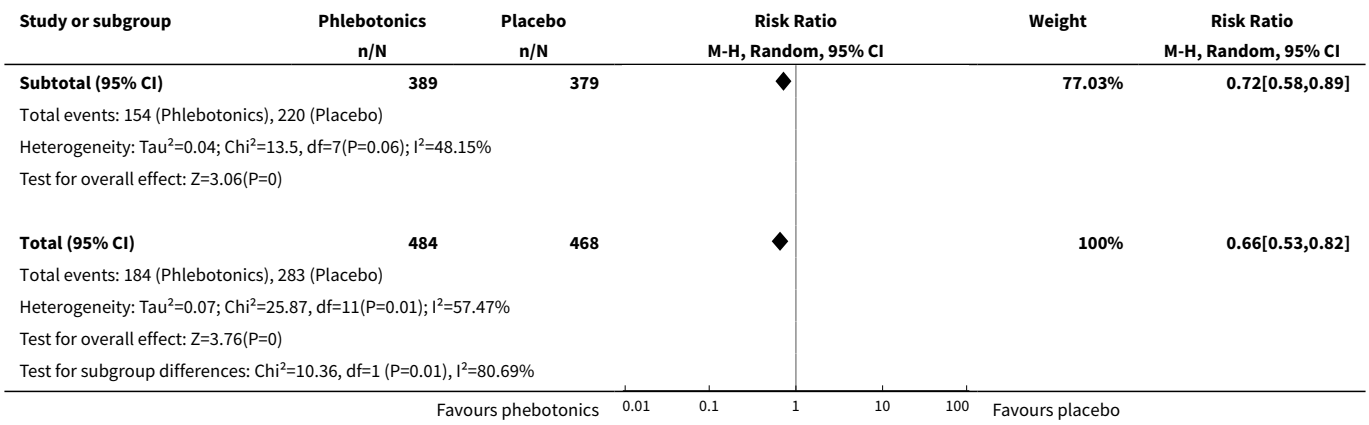
Analysis 2.14. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 14 Heaviness in the lower legs (continuous variable).

Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.14.1 Diosmine, Hidrosmine							
Gilly 1994	76	0.7 (0.9)	74	1.3 (0.9)		100%	-0.69[-1.02,-0.36]
Subtotal ***	**76**		**74**			**100%**	**-0.69[-1.02,-0.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.1(P<0.0001)							
2.14.2 Rutosides							
Alterkamper 1987	16	1.8 (0.5)	20	2.3 (0.5)		19.53%	-0.98[-1.68,-0.28]
Cloarec 1996	53	1.2 (0.7)	51	2.2 (0.7)		20.9%	-1.42[-1.85,-0.99]
Diebschlag 1994	20	1.9 (0.6)	20	4.2 (0.9)		18.13%	-2.95[-3.87,-2.03]
Parrado 1999	30	0.1 (0.5)	30	0.8 (0.4)		20.25%	-1.43[-2,-0.86]
Unkauf 1996	64	27 (28)	56	22 (27)		21.18%	0.18[-0.18,0.54]
Subtotal ***	**183**		**177**			**100%**	**-1.27[-2.22,-0.32]**
Heterogeneity: Tau^2=1.08; Chi^2=62.22, df=4(P<0.0001); I^2=93.57%							
Test for overall effect: Z=2.62(P=0.01)							

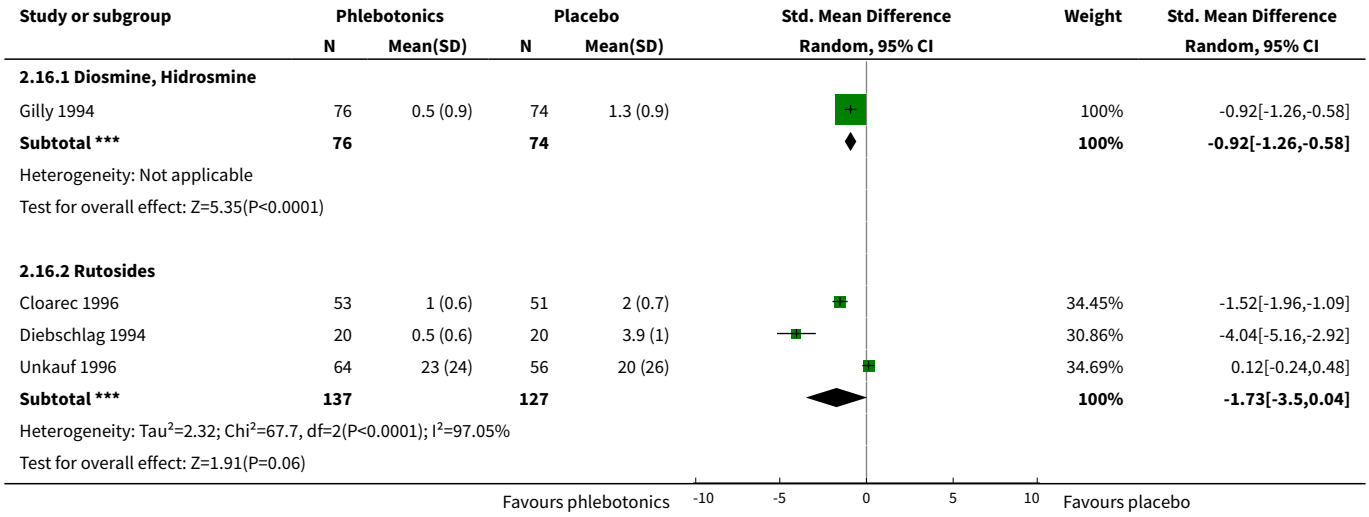


Analysis 2.15. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 15 Swelling in the lower legs (dichotomous variable).

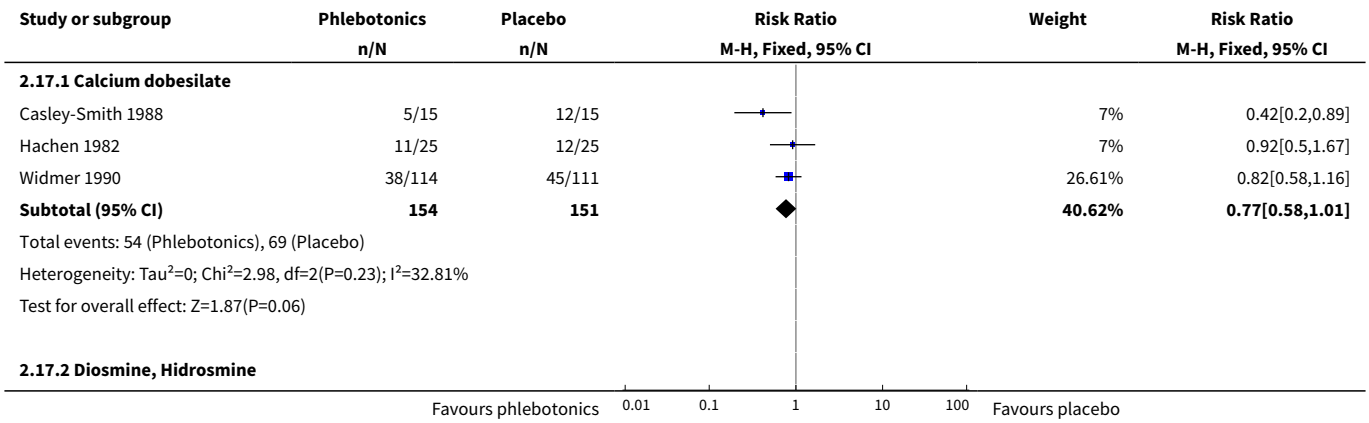
Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 Calcium dobesilate					
Casley-Smith 1988	2/15	15/15		3.1%	0.16[0.05,0.51]
Hachen 1982	3/25	14/25		3.22%	0.21[0.07,0.65]
Subtotal (95% CI)	**40**	**40**		**6.32%**	**0.19[0.08,0.41]**
Total events: 5 (Phlebotonics), 29 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=4.12(P<0.0001)					
2.15.2 Diosmine, Hidrosmine					
Biland 1982	21/35	30/35		13.82%	0.7[0.52,0.95]
Fermoso 1992	4/20	4/14		2.83%	0.7[0.21,2.34]
Subtotal (95% CI)	**55**	**49**		**16.65%**	**0.7[0.52,0.94]**
Total events: 25 (Phlebotonics), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=2.38(P=0.02)					
2.15.3 Rutosides					
Cauwenberge 1978	32/60	50/60		14.77%	0.64[0.49,0.83]
Jongste 1989	21/41	25/43		11.74%	0.88[0.6,1.3]
Kriner 1985	1/25	8/25		1.13%	0.13[0.02,0.93]
Languillat 1988	3/10	3/10		2.36%	1[0.26,3.81]
Pedersen 1992	17/24	13/19		11.58%	1.04[0.69,1.54]
Vanscheidt 2002a	42/114	76/117		14.48%	0.57[0.43,0.75]
Vin 1994	27/43	23/30		13.8%	0.82[0.6,1.11]
Welch 1985	11/72	22/75		7.15%	0.52[0.27,1]

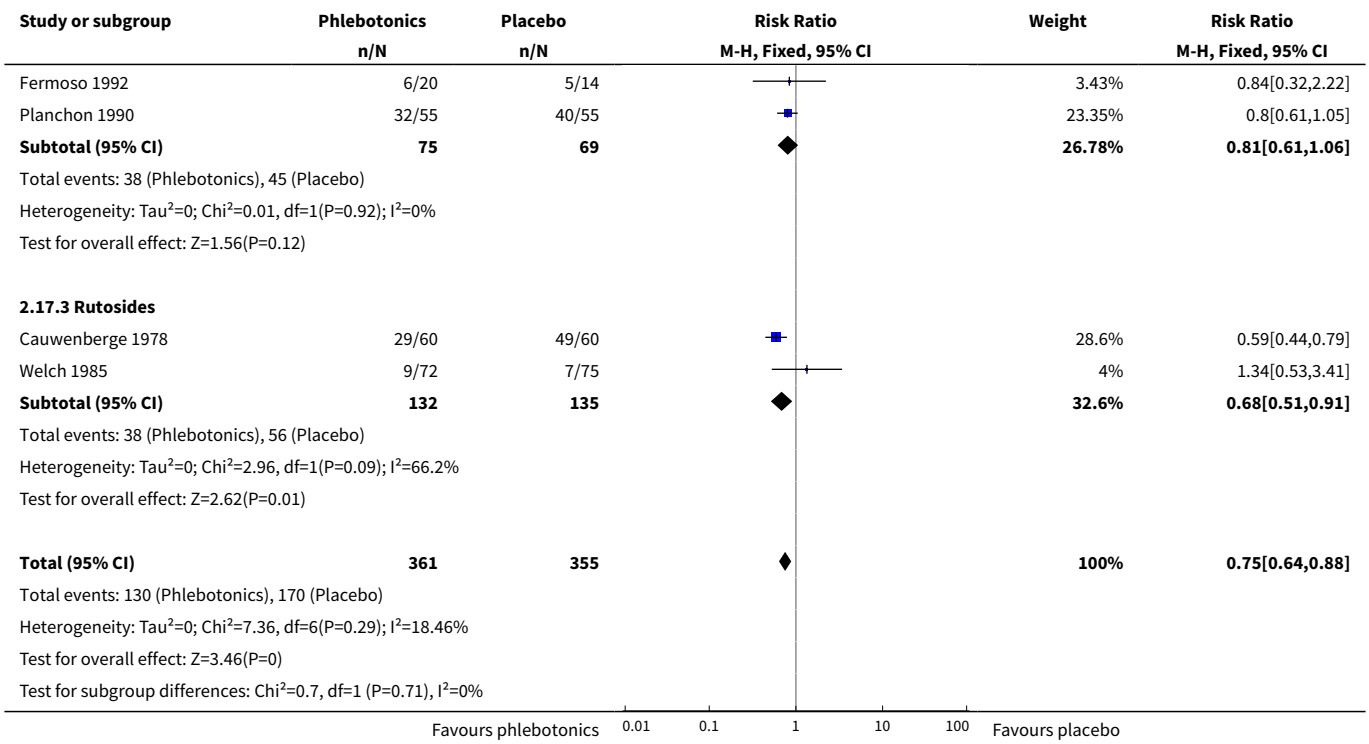


Analysis 2.16. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 16 Swelling in the lower legs (continuous variable).

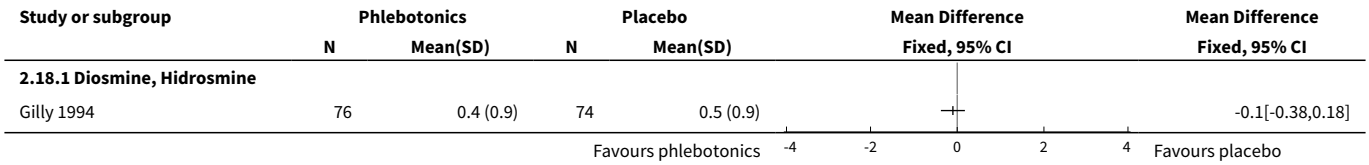


Analysis 2.17. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 17 Paraesthesias in the lower legs (dichotomous variable).

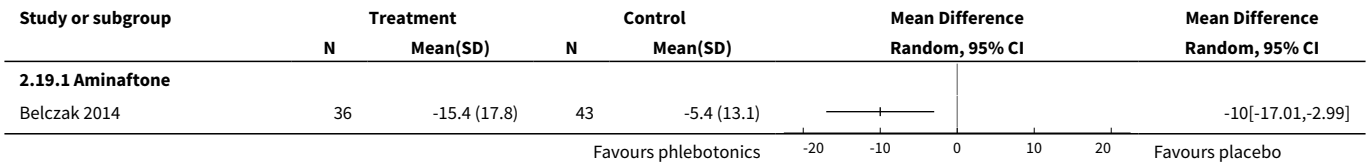




Analysis 2.18. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 18 Paraesthesias in the lower legs (continuous variable).

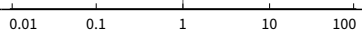


Analysis 2.19. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 19 Quality of life.



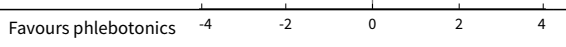
Analysis 2.20. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 20 Global assessment by the participant (dichotomous variable).

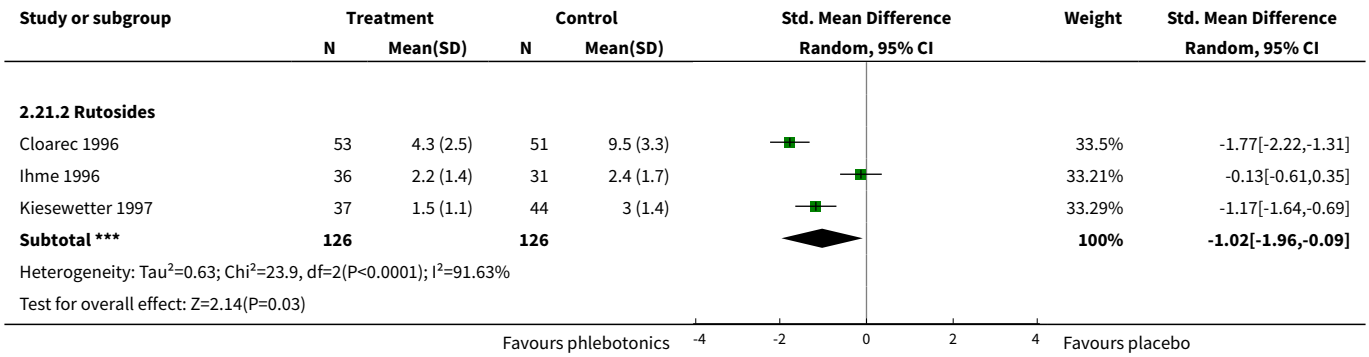
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.20.1 Calcium dobesilate					
Casley-Smith 1988	1/15	15/15		2.51%	0.1[0.02,0.45]
Labs 2004	40/133	42/127		11.83%	0.91[0.64,1.3]
Widmer 1990	75/114	88/111		14.28%	0.83[0.71,0.98]
Subtotal (95% CI)	**262**	**253**		**28.63%**	**0.71[0.43,1.17]**
Total events: 116 (Treatment), 145 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=8.55, df=2(P=0.01); I^2=76.61%					
Test for overall effect: Z=1.33(P=0.18)					
2.20.2 Diosmine, Hidrosmine					
Biland 1982	23/35	28/35		12.77%	0.82[0.61,1.1]
Danielsson 2002	30/51	34/50		12.68%	0.87[0.64,1.17]
Subtotal (95% CI)	**86**	**85**		**25.45%**	**0.84[0.68,1.04]**
Total events: 53 (Treatment), 62 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					
2.20.3 Rutosides					
Burnand 1989	9/24	12/25		7.82%	0.78[0.4,1.51]
Cloarec 1996	3/53	32/51		4.09%	0.09[0.03,0.28]
Jongste 1989	15/41	26/43		10.24%	0.61[0.38,0.97]
Languillat 1988	2/10	10/10		4.21%	0.24[0.08,0.71]
Parrado 1999	0/30	1/30		0.67%	0.33[0.01,7.87]
Pedersen 1992	18/24	10/19		10.03%	1.43[0.88,2.31]
Welch 1985	15/72	22/75		8.88%	0.71[0.4,1.26]
Subtotal (95% CI)	**254**	**253**		**45.93%**	**0.52[0.28,0.98]**
Total events: 62 (Treatment), 113 (Control)					
Heterogeneity: Tau^2=0.5; Chi^2=29.8, df=6(P<0.0001); I^2=79.86%					
Test for overall effect: Z=2.02(P=0.04)					
Total (95% CI)	**602**	**591**		**100%**	**0.69[0.53,0.9]**
Total events: 231 (Treatment), 320 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=40.59, df=11(P<0.0001); I^2=72.9%					
Test for overall effect: Z=2.75(P=0.01)					
Test for subgroup differences: Chi^2=2.2, df=1 (P=0.33), I^2=8.95%					



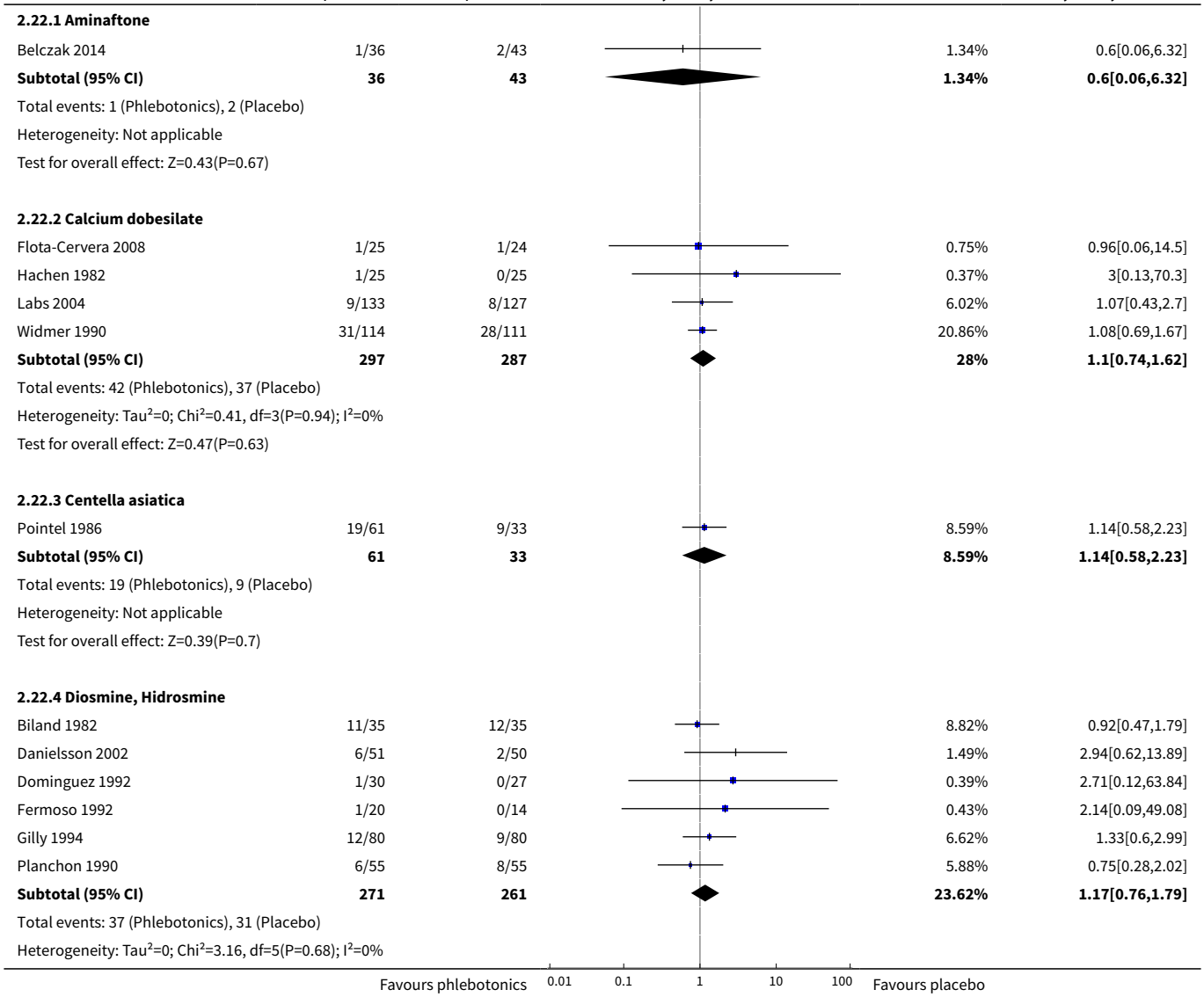
Analysis 2.21. Comparison 2 Sensitivity analysis excluding studies that allowed the use of elastic stockings, Outcome 21 Global assessment by the participant (continuous variable).

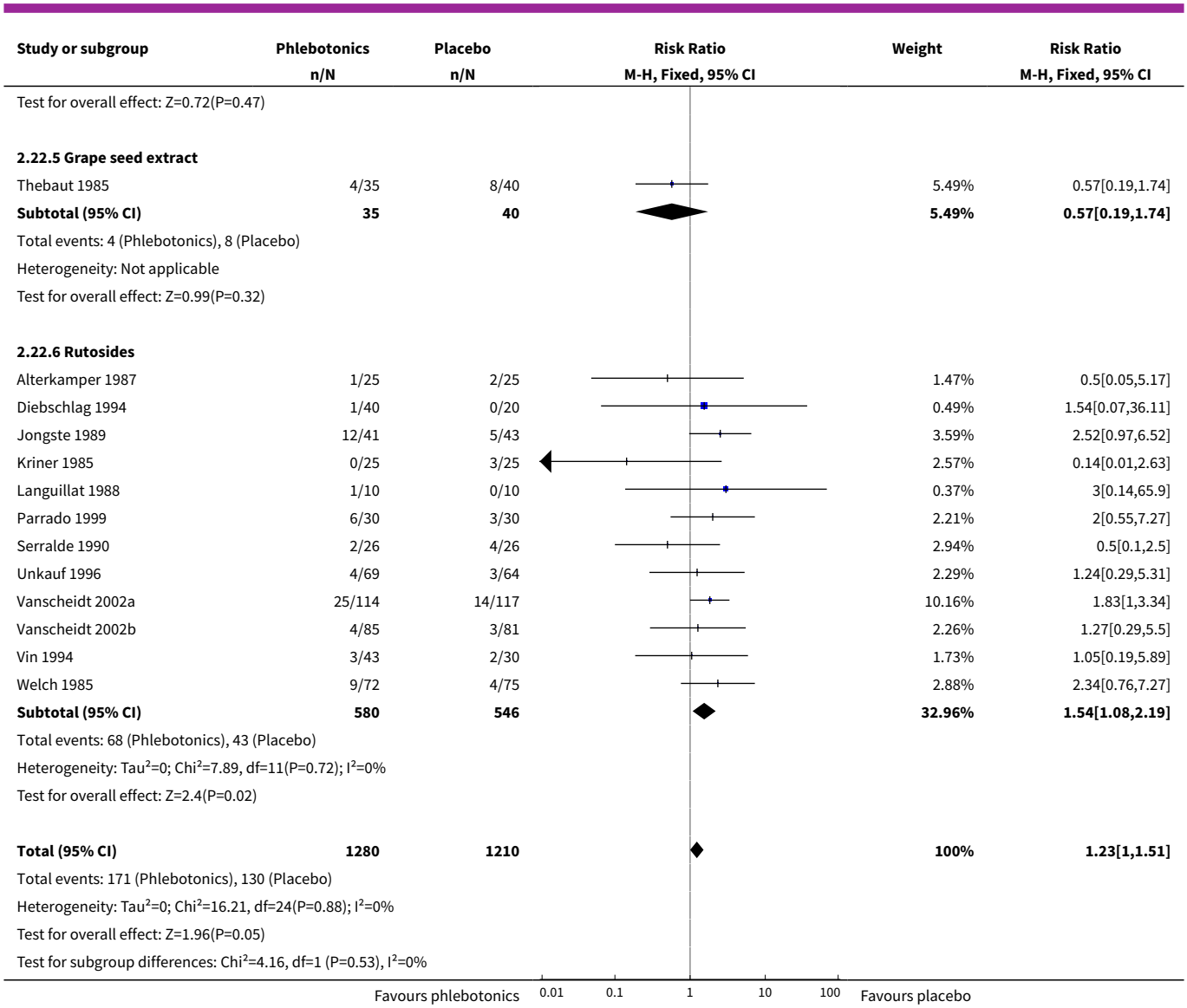
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.21.1 Diosmine, Hidrosmine							
Gilly 1994	76	0.5 (0.9)	74	1.2 (0.9)		100%	-0.81[-1.14,-0.47]
Subtotal ***	**76**		**74**			**100%**	**-0.81[-1.14,-0.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.74(P<0.0001)							





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





Comparison 3. Sensitivity analysis of published studies only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oedema in the lower legs (dichotomous variable)	12	1088	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.63, 0.78]
1.1 Aminaftone	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 0.99]
1.2 Calcium dobesilate	2	290	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.07]
1.3 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
1.4 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Rutosides	6	497	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.64, 0.81]
2 Ankle perimeter circumference (mm)	13	1796	Mean Difference (IV, Random, 95% CI)	-3.61 [-6.77, -0.45]
2.1 Calcium dobesilate	5	1122	Mean Difference (IV, Random, 95% CI)	-3.17 [-8.37, 2.02]
2.2 Diosmine, Hidrosmine	3	286	Mean Difference (IV, Random, 95% CI)	-5.98 [-7.78, -4.18]
2.3 Rutosides	5	388	Mean Difference (IV, Random, 95% CI)	-2.18 [-9.79, 5.43]
3 Volume of the leg (mL)	9	1041	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.50, -0.25]
3.1 Aminaftone	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.61, 0.28]
3.2 Calcium dobesilate	3	475	Std. Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.68, -0.31]
3.3 Rutosides	5	487	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.47, -0.11]
4 Patients with ulcer (dichotomous variable)	5	392	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.15]
4.1 Aminaftone	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.18]
4.2 Diosmine, Hidrosmine	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.03]
4.3 Rutosides	2	159	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.84, 1.87]
5 Trophic disorders (dichotomous variable)	6	705	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.95]
5.1 Aminaftone	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.44]
5.2 Diosmine, Hidrosmine	4	504	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
5.3 Rutosides	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.25]
6 Pain in the lower legs (dichotomous variable)	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.23, 0.79]
6.2 Calcium dobesilate	4	354	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.16, 0.93]
6.3 Diosmine, Hidrosmine	4	271	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.08]
6.4 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.48, 0.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.5 Rutosides	8	1318	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.45, 0.84]
7 Pain in the lower legs (continuous variable)	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Calcium dobesilate	3	724	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.41, 0.18]
7.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.67, -0.02]
7.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.39 [-2.09, -0.69]
7.4 Rutosides	3	219	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.23, -0.19]
8 Cramps in the lower legs (dichotomous variable)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.99]
8.2 Calcium dobesilate	2	255	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
8.3 Diosmine, Hidrosmine	3	214	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
8.4 Rutosides	6	1060	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.45, 1.05]
9 Cramps in the lower legs (continuous variable)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Calcium dobesilate	1	415	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.29, 0.09]
9.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.78, -0.14]
9.3 Rutosides	2	164	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.50, -0.16]
10 Restless legs (dichotomous variable)	7	652	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
10.1 Calcium dobesilate	2	255	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.59, 0.91]
10.2 Diosmine, Hidrosmine	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.15]
10.3 Rutosides	4	327	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
11 Itching in the lower legs (dichotomous variable)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
11.2 Diosmine, Hidrosmine	1	34	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.25]

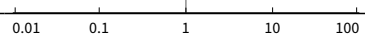
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Rutosides	2	274	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.21, 2.21]
12 Itching in the lower legs (continuous variable)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Calccium dobesilate	1	416	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.11, 0.28]
12.2 Rutosides	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.10, -0.06]
13 Heaviness in the lower legs (dichotomous variable)	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Aminaftone	1	97	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.60]
13.2 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.42]
13.3 Centella asiatica	1	63	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
13.4 Diosmine, Hidrosmine	4	241	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.05]
13.5 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
13.6 Rutosides	7	1253	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.49, 0.78]
14 Heaviness in the lower legs (continuous variable)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Calcium dobesilate	2	483	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.23, 0.13]
14.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.02, -0.36]
14.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.50 [-2.21, -0.79]
14.4 Rutosides	5	360	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-2.22, -0.32]
15 Swelling in the lower legs (dichotomous variable)	12	905	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.81]
15.1 Calcium dobesilate	2	80	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.41]
15.2 Diosmine, Hidrosmine	2	104	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.52, 0.94]
15.3 French maritime pine bark extract	1	40	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.02]
15.4 Rutosides	7	681	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.49, 0.91]
16 Swelling in the lower legs (continuous variable)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Calcium dobesilate	1	417	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.24, 0.15]
16.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-1.15 [-1.50, -0.80]
16.3 French maritime pine bark extract	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.65 [-2.38, -0.92]
16.4 Rutosides	3	264	Std. Mean Difference (IV, Random, 95% CI)	-1.73 [-3.50, 0.04]
17 Paraesthesias in the lower legs (dichotomous variable)	8	1309	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.84]
17.1 Calcium dobesilate	3	305	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
17.2 Diosmine, Hidrosmine	2	144	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.05]
17.3 Rutosides	3	860	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.35, 0.66]
18 Paraesthesias in the lower legs (continuous variable)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Diosmine, Hidrosmine	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Quality of life	3	696	Mean Difference (IV, Fixed, 95% CI)	-1.04 [-2.55, 0.47]
19.1 Aminaftone	1	79	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-17.01, -2.99]
19.2 Calcium dobesilate at 3 months of treatment	2	617	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
20 Global assessment by the participant (dichotomous variable)	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 Calcium dobesilate	4	758	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.61, 1.19]
20.2 Centella asiatica	1	80	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.14, 0.57]
20.3 Diosmine, Hidrosmine	4	451	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.96]
20.4 Rutosides	6	1000	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.97]
21 Global assessment by the participant (continuous variable)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Calcium dobesilate	2	448	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.71, -0.33]

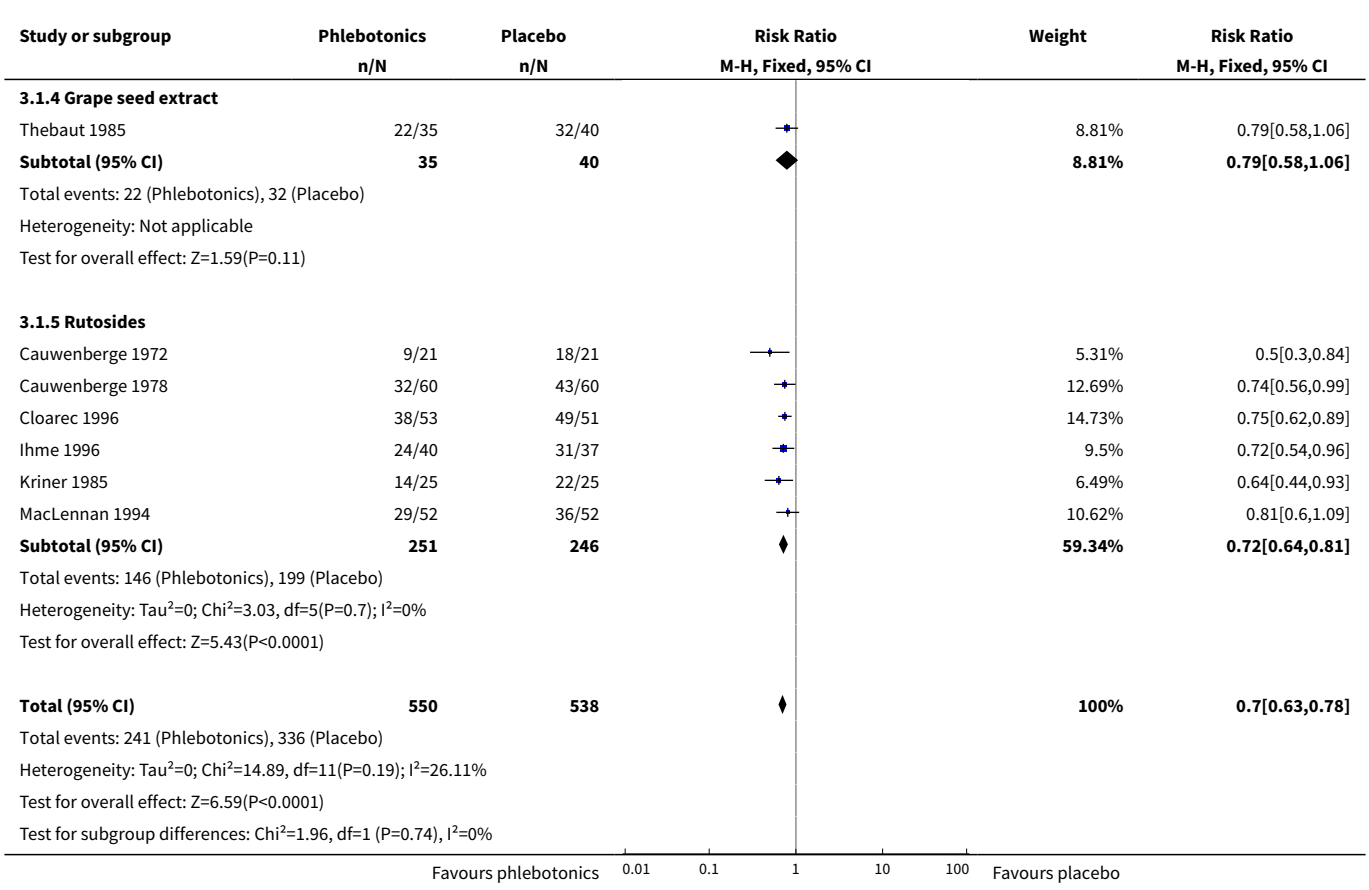
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
21.2 Diosmine, Hidrosmine	1	150	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.14, -0.47]
21.3 Rutosides	4	283	Std. Mean Difference (IV, Random, 95% CI)	-1.18 [-1.96, -0.39]
22 Adverse events	32	3887	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.03, 1.38]
22.1 Aminaftone	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.06, 6.32]
22.2 Calcium dobesilate	7	1473	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.99, 1.53]
22.3 Centella asiatica	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.58, 2.23]
22.4 Diosmine, Hidrosmine	8	837	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.70, 1.44]
22.5 Grape seed extract	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.19, 1.74]
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).

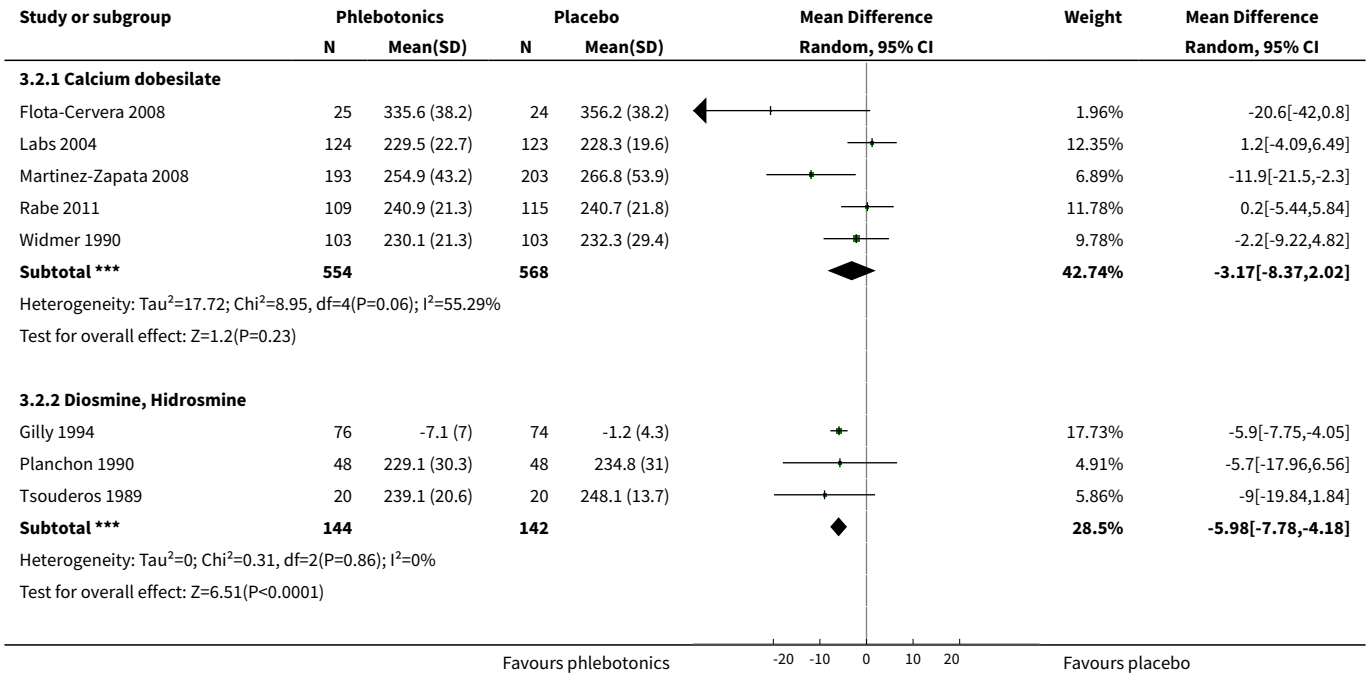
Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Aminaftone					
Lazzarini 1982	10/41	19/41		5.61%	0.53[0.28,0.99]
Subtotal (95% CI)	**41**	**41**		**5.61%**	**0.53[0.28,0.99]**
Total events: 10 (Phlebotonics), 19 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.99(P=0.05)					
3.1.2 Calcium dobesilate					
Casley-Smith 1988	2/15	14/15		4.13%	0.14[0.04,0.52]
Labs 2004	30/133	29/127		8.75%	0.99[0.63,1.55]
Subtotal (95% CI)	**148**	**142**		**12.88%**	**0.72[0.48,1.07]**
Total events: 32 (Phlebotonics), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.9, df=1(P=0); I^2=87.34%					
Test for overall effect: Z=1.62(P=0.11)					
3.1.3 Diosmine, Hidrosmine					
Fermoso 1992	15/20	13/14		4.51%	0.81[0.6,1.08]
Planchon 1990	16/55	30/55		8.85%	0.53[0.33,0.86]
Subtotal (95% CI)	**75**	**69**		**13.36%**	**0.63[0.46,0.86]**
Total events: 31 (Phlebotonics), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.36, df=1(P=0.07); I^2=70.26%					
Test for overall effect: Z=2.93(P=0)					



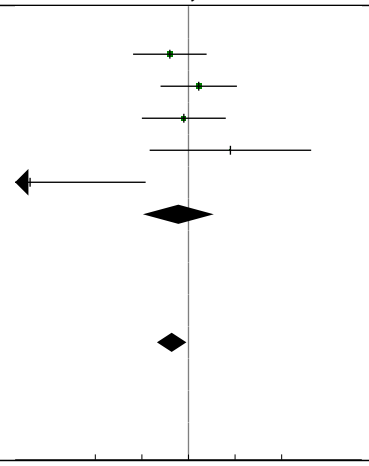
Favours phlebotonics Favours placebo



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

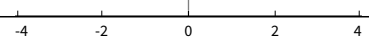


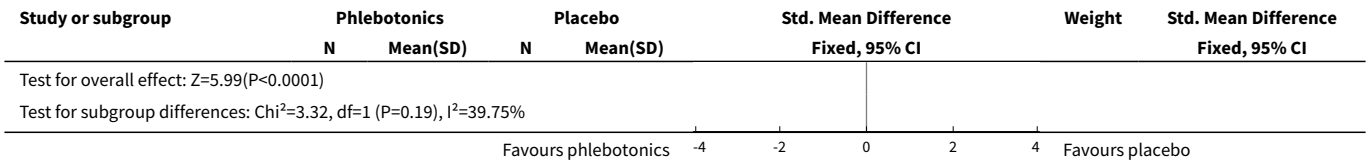
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.2.3 Rutosides							
Cloarec 1996	53	221 (22)	51	225 (19)		8.67%	-4[-11.89,3.89]
Cornu-Thenard 1985	33	226.8 (16.4)	21	224.6 (14)		8.32%	2.2[-6,10.4]
Jongste 1989	41	236 (22)	43	237 (20)		7.45%	-1[-10,8]
MacLennan 1994	41	258 (40)	45	249 (42)		2.83%	9[-8.33,26.33]
Parrado 1999	30	209 (50)	30	243 (48)		1.5%	-34[-58.8,-9.2]
Subtotal ***	**198**		**190**			**28.76%**	**-2.18[-9.79,5.43]**
Heterogeneity: Tau²=38.73; Chi²=9.19, df=4(P=0.06); I²=56.45%							
Test for overall effect: Z=0.56(P=0.57)							
Total ***	**896**		**900**			**100%**	**-3.61[-6.77,-0.45]**
Heterogeneity: Tau²=13.78; Chi²=25.82, df=12(P=0.01); I²=53.53%							
Test for overall effect: Z=2.24(P=0.03)							
Test for subgroup differences: Chi²=1.78, df=1 (P=0.41), I²=0%							



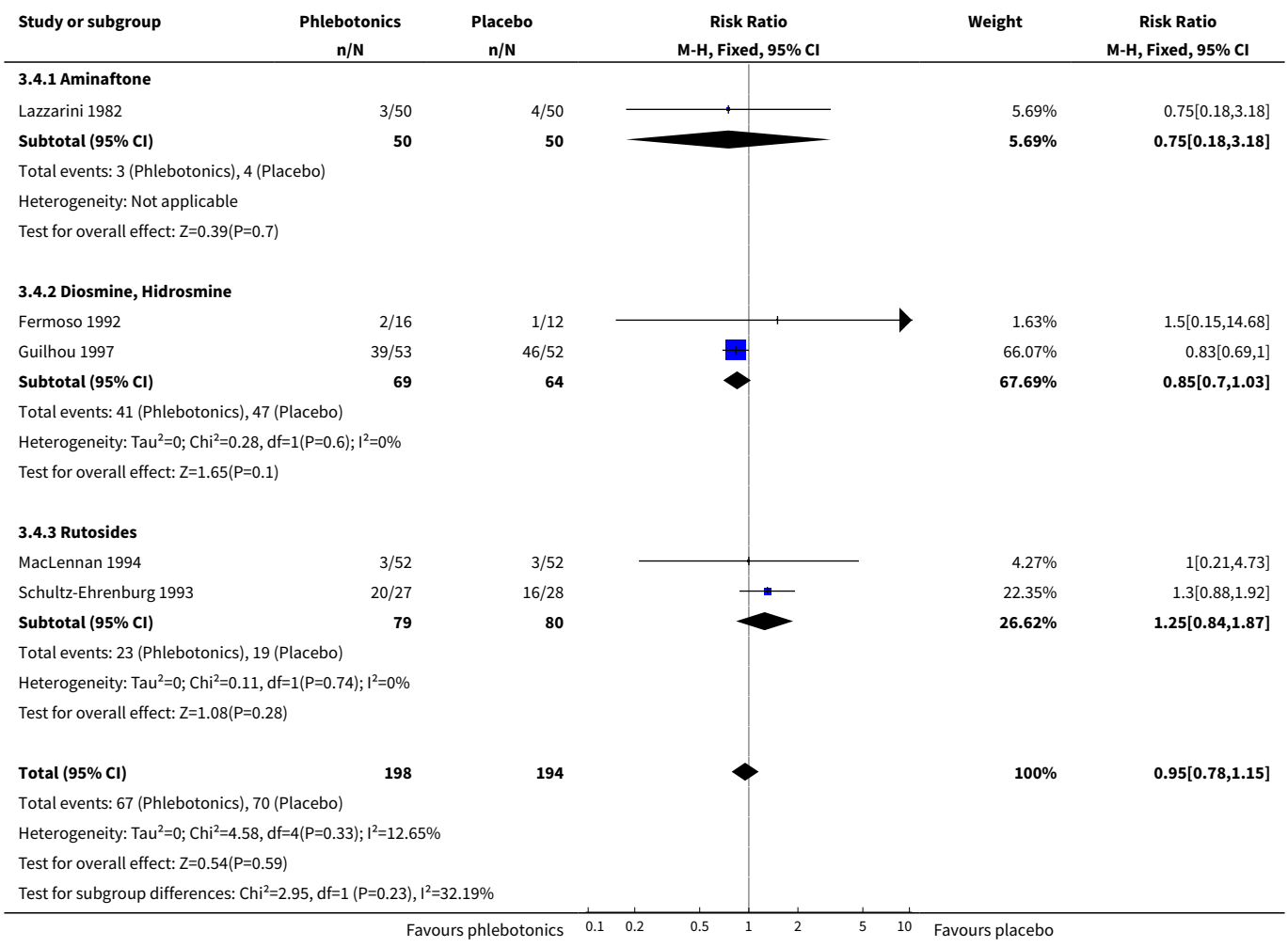
Analysis 3.3. Comparison 3 Sensitivity analysis of published studies only, Outcome 3 Volume of the leg (mL).

Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.3.1 Aminaftone							
Belczak 2014	36	3276.5 (584.6)	43	3391.5 (751.1)		7.69%	-0.17[-0.61,0.28]
Subtotal ***	**36**		**43**			**7.69%**	**-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	15	1097 (93)	15	1205 (104.6)		2.54%	-1.06[-1.83,-0.29]
Rabe 2011	120	-64.7 (111.9)	119	0.8 (152.9)		22.84%	-0.49[-0.74,-0.23]
Widmer 1990	103	-3.8 (6.1)	103	-1.1 (6.1)		19.8%	-0.43[-0.71,-0.16]
Subtotal ***	**238**		**237**			**45.18%**	**-0.5[-0.68,-0.31]**
Heterogeneity: Tau²=0; Chi²=2.26, df=2(P=0.32); I²=11.67%							
Test for overall effect: Z=5.32(P<0.0001)							
3.3.3 Rutosides							
Burnand 1989	24	1098 (157.7)	25	1200 (156.5)		4.57%	-0.64[-1.21,-0.06]
Diebschlag 1994	51	-11.9 (43.4)	50	-4.4 (29.2)		9.89%	-0.2[-0.59,0.19]
Ihme 1996	40	2073 (309)	37	2082 (339)		7.57%	-0.03[-0.47,0.42]
Kiesewetter 1997	37	1992 (367)	44	2111 (541)		7.85%	-0.25[-0.69,0.19]
Vanscheidt 2002a	86	-95.7 (127.9)	93	-44.6 (131.1)		17.25%	-0.39[-0.69,-0.1]
Subtotal ***	**238**		**249**			**47.13%**	**-0.29[-0.47,-0.11]**
Heterogeneity: Tau²=0; Chi²=3.43, df=4(P=0.49); I²=0%							
Test for overall effect: Z=3.22(P=0)							
Total ***	**512**		**529**			**100%**	**-0.38[-0.5,-0.25]**
Heterogeneity: Tau²=0; Chi²=9.01, df=8(P=0.34); I²=11.21%							

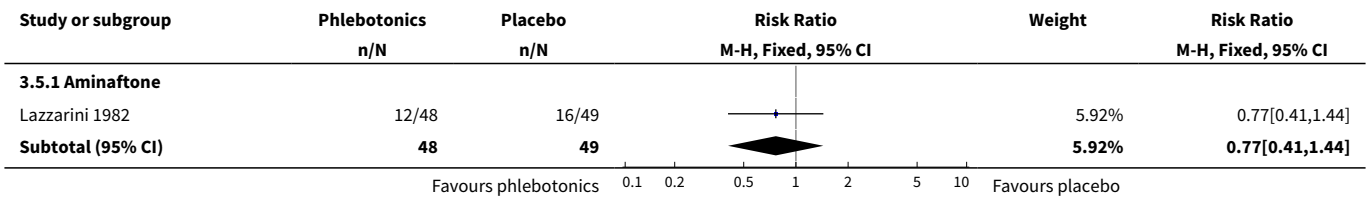


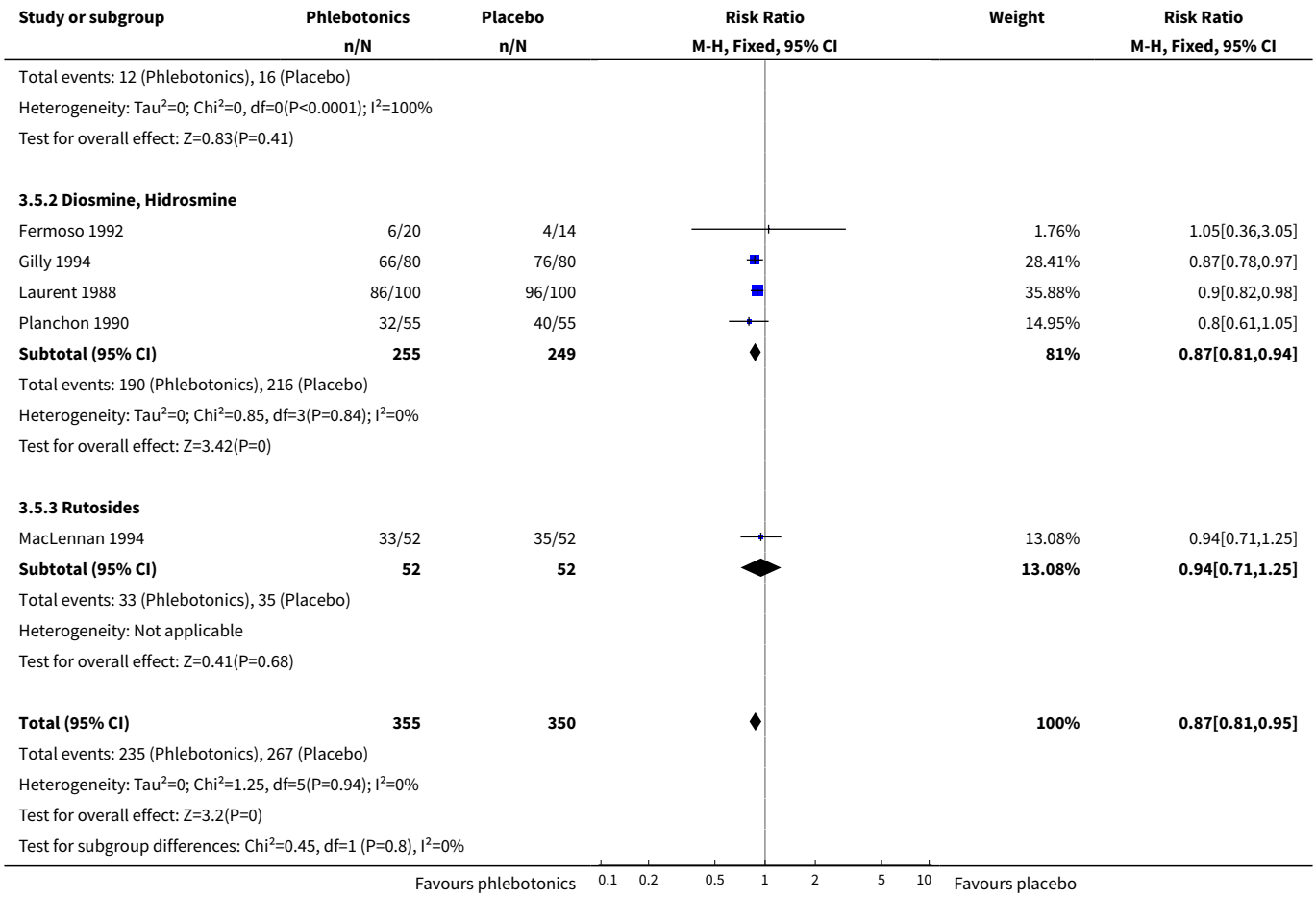


Analysis 3.4. Comparison 3 Sensitivity analysis of published studies only, Outcome 4 Patients with ulcer (dichotomous variable).

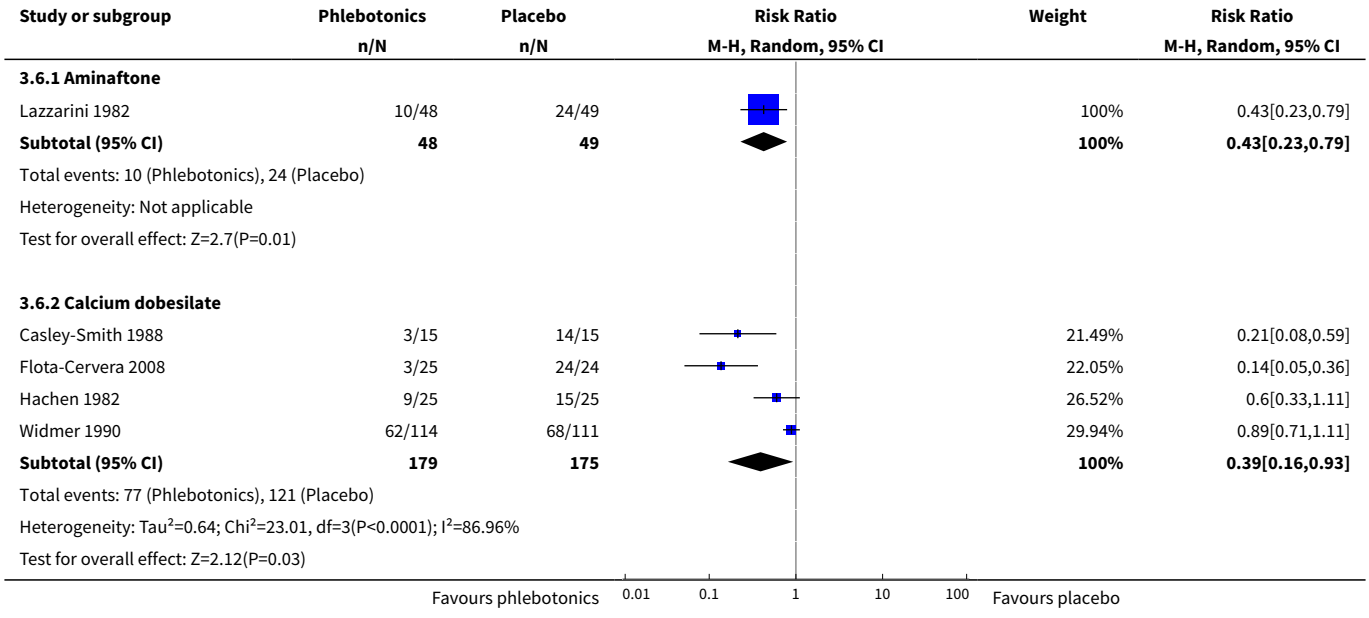


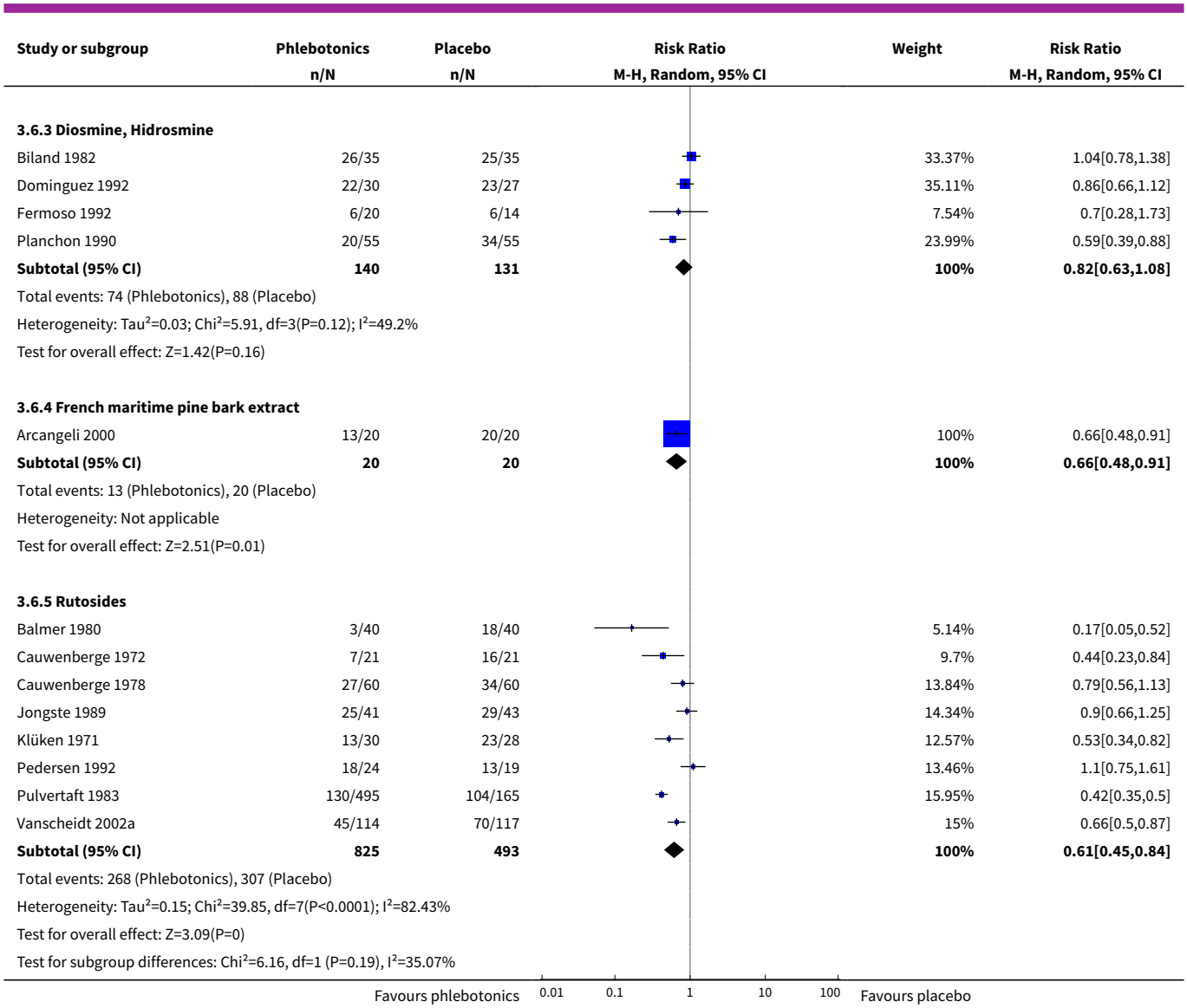
Analysis 3.5. Comparison 3 Sensitivity analysis of published studies only, Outcome 5 Trophic disorders (dichotomous variable).



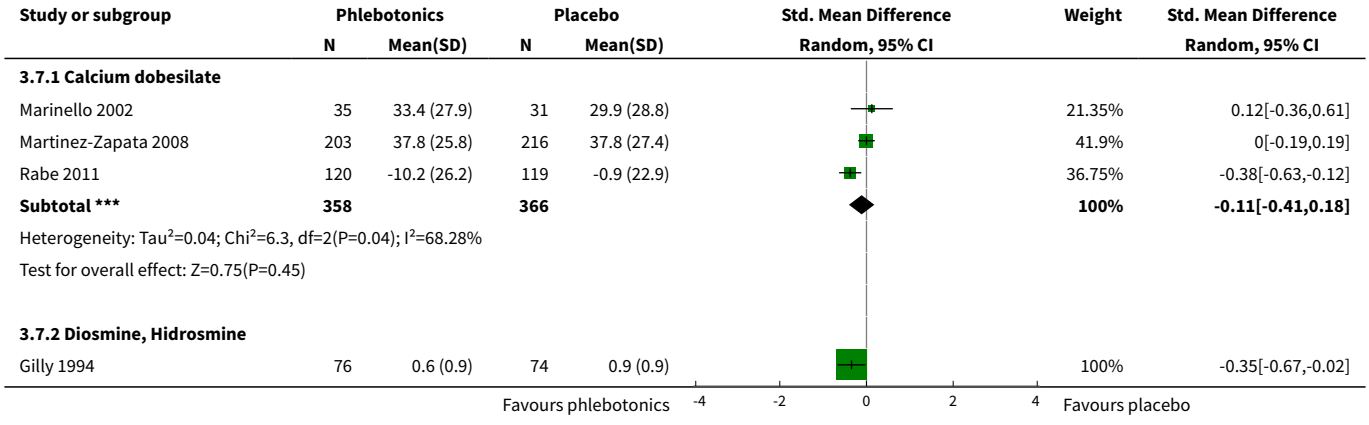


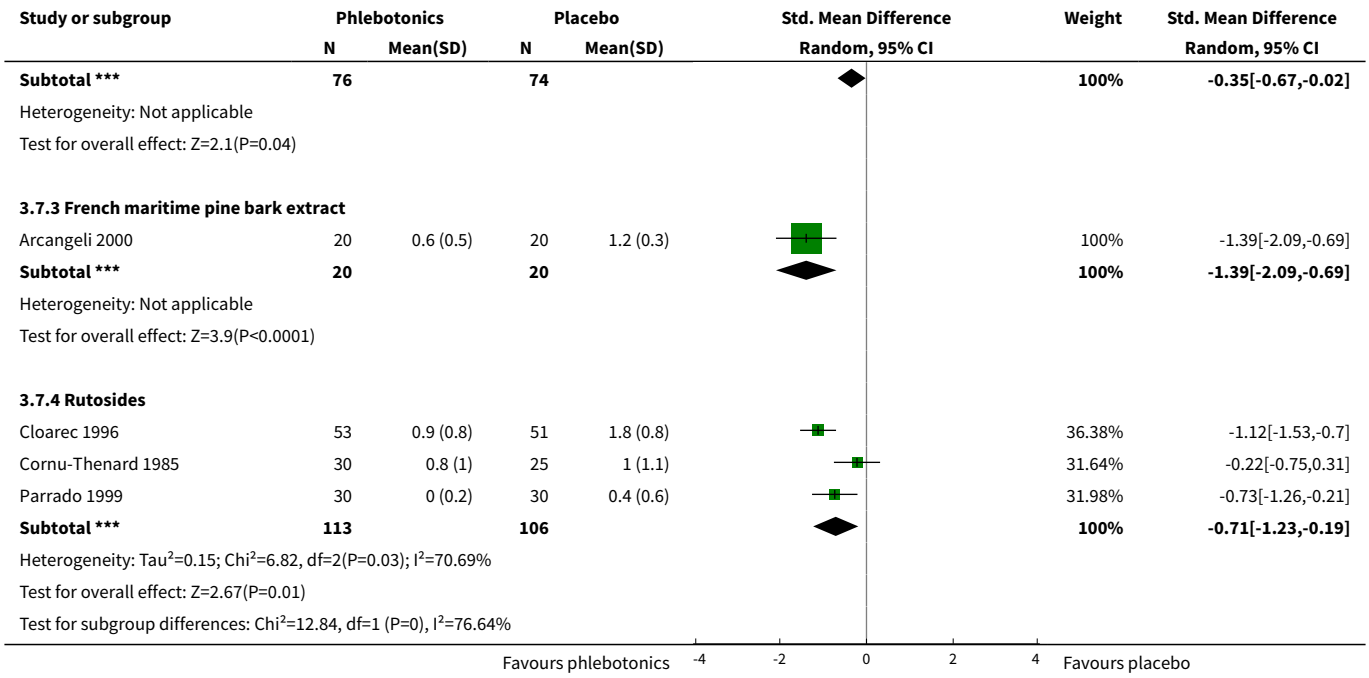
Analysis 3.6. Comparison 3 Sensitivity analysis of published studies only, Outcome 6 Pain in the lower legs (dichotomous variable).



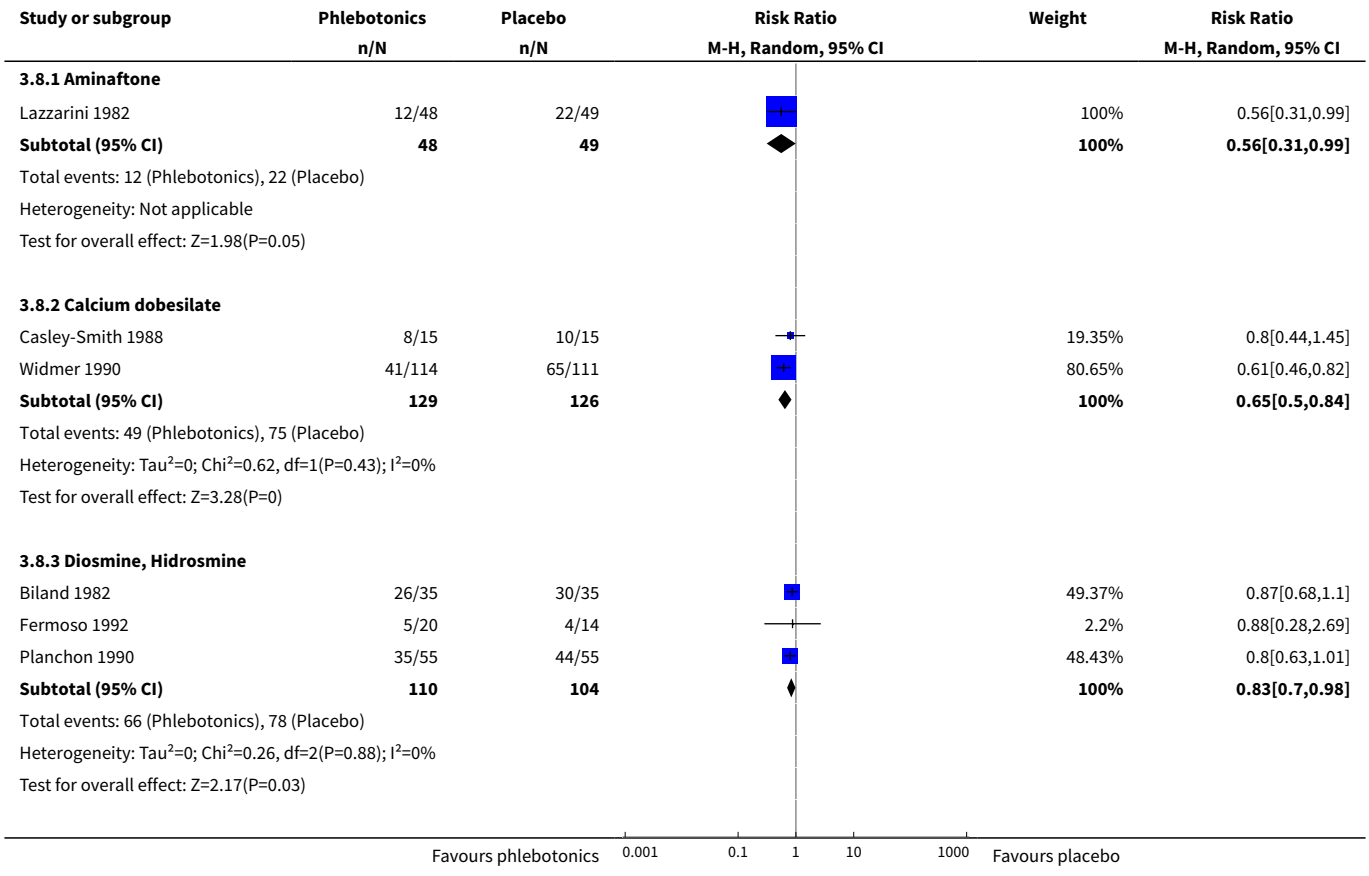


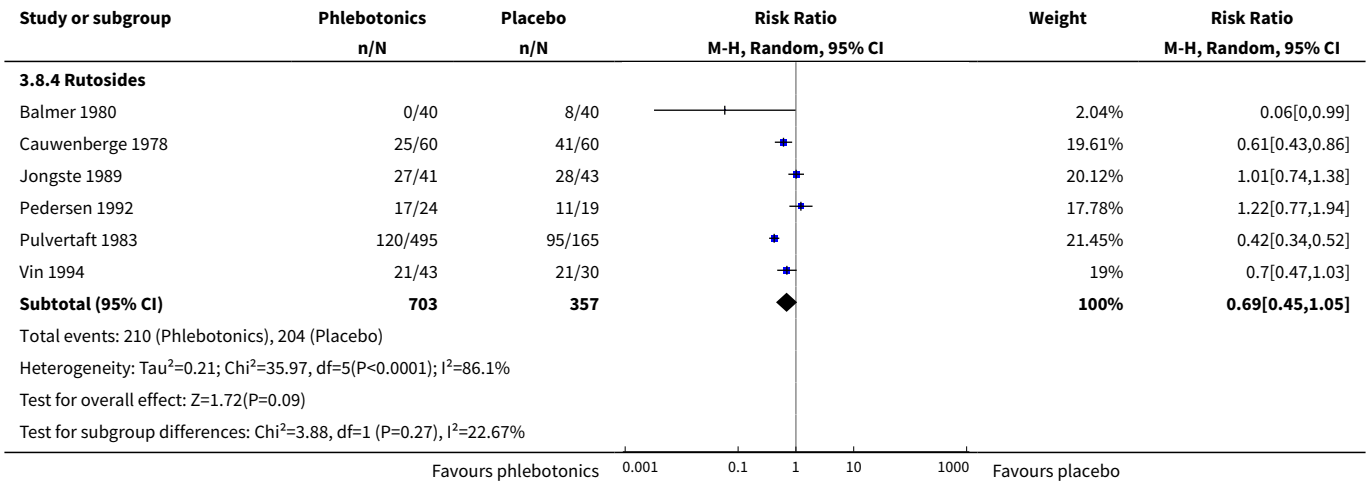
Analysis 3.7. Comparison 3 Sensitivity analysis of published studies only, Outcome 7 Pain in the lower legs (continuous variable).



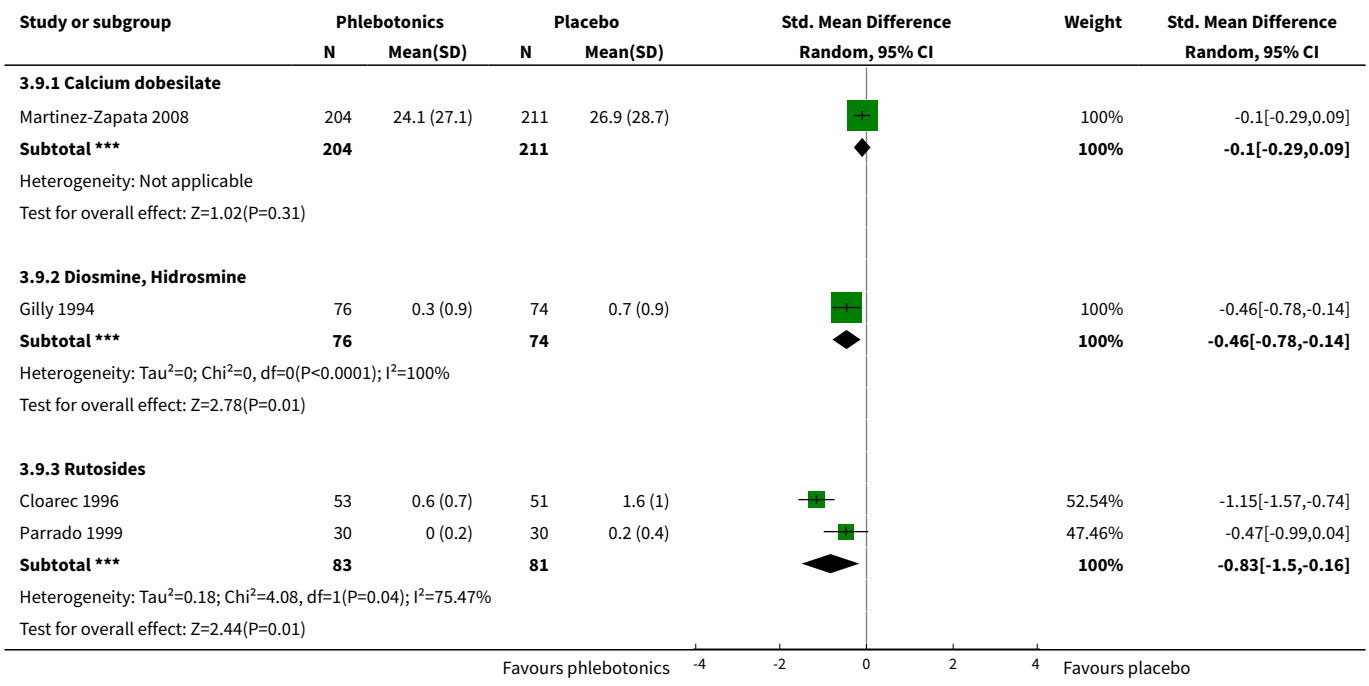


Analysis 3.8. Comparison 3 Sensitivity analysis of published studies only, Outcome 8 Cramps in the lower legs (dichotomous variable).

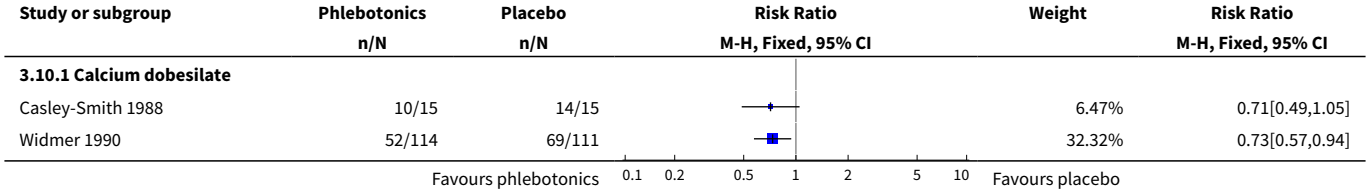


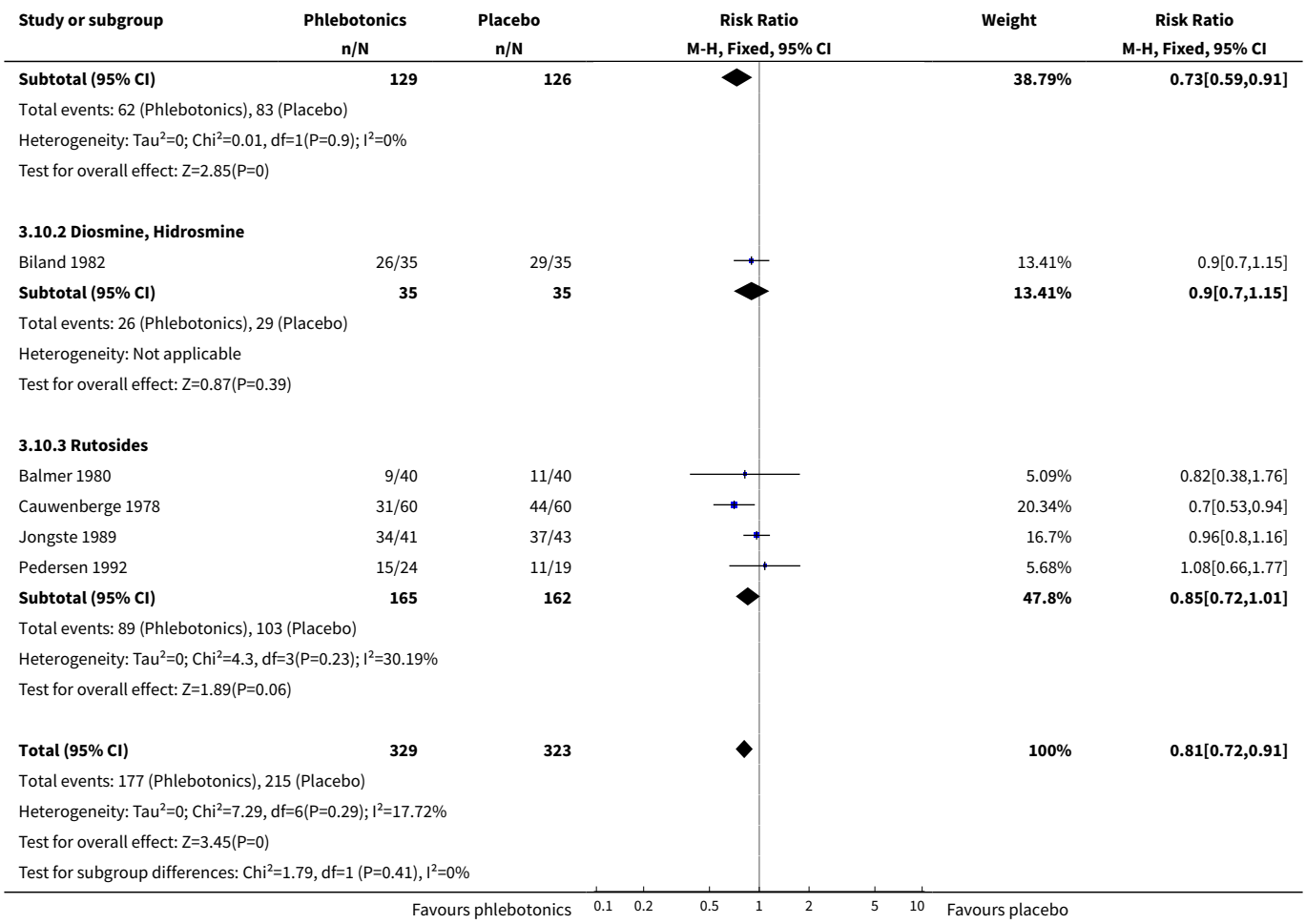


Analysis 3.9. Comparison 3 Sensitivity analysis of published studies only, Outcome 9 Cramps in the lower legs (continuous variable).

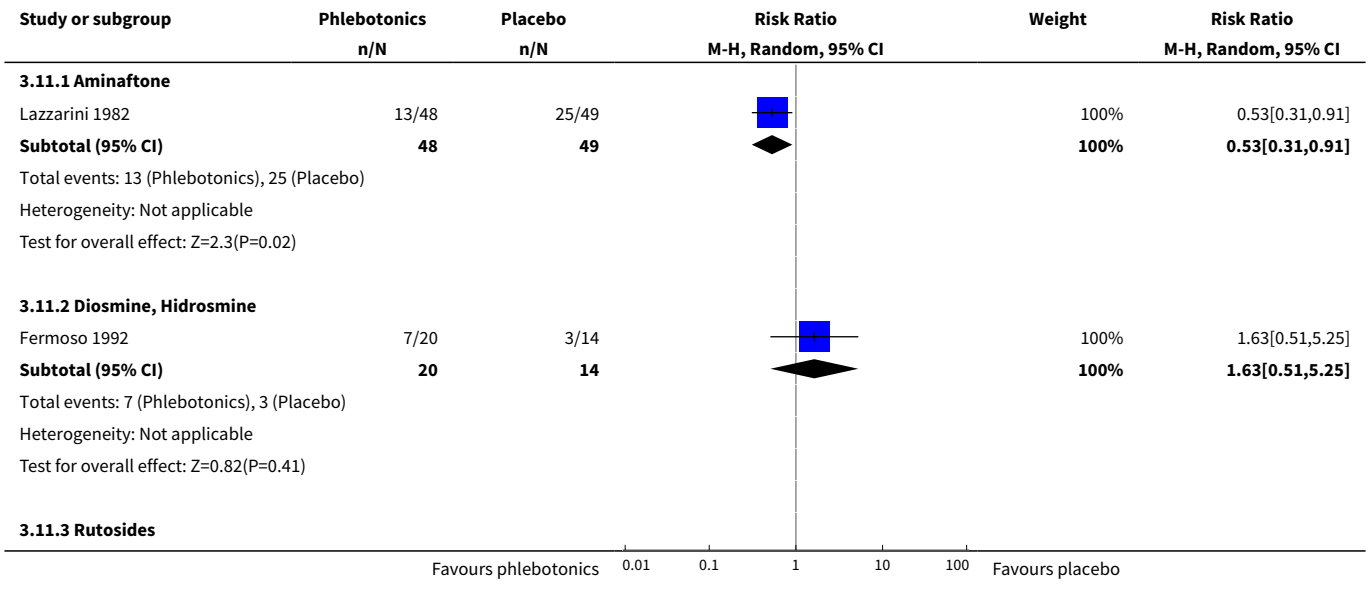


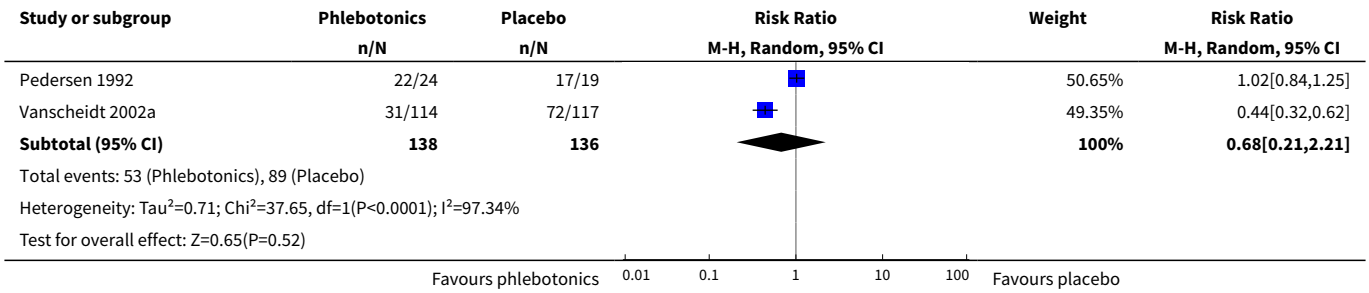
Analysis 3.10. Comparison 3 Sensitivity analysis of published studies only, Outcome 10 Restless legs (dichotomous variable).



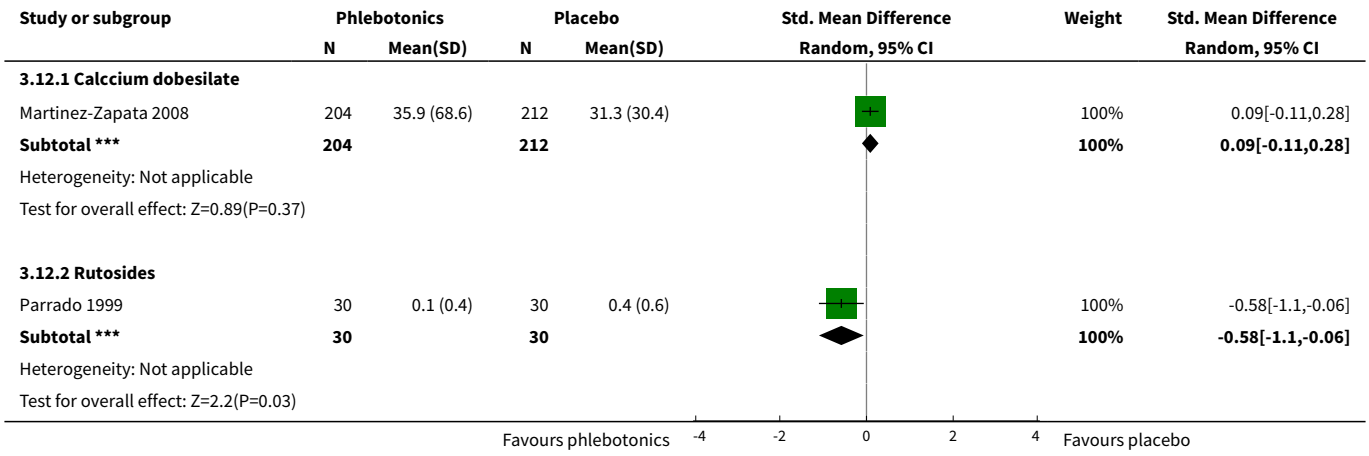


Analysis 3.11. Comparison 3 Sensitivity analysis of published studies only, Outcome 11 Itching in the lower legs (dichotomous variable).

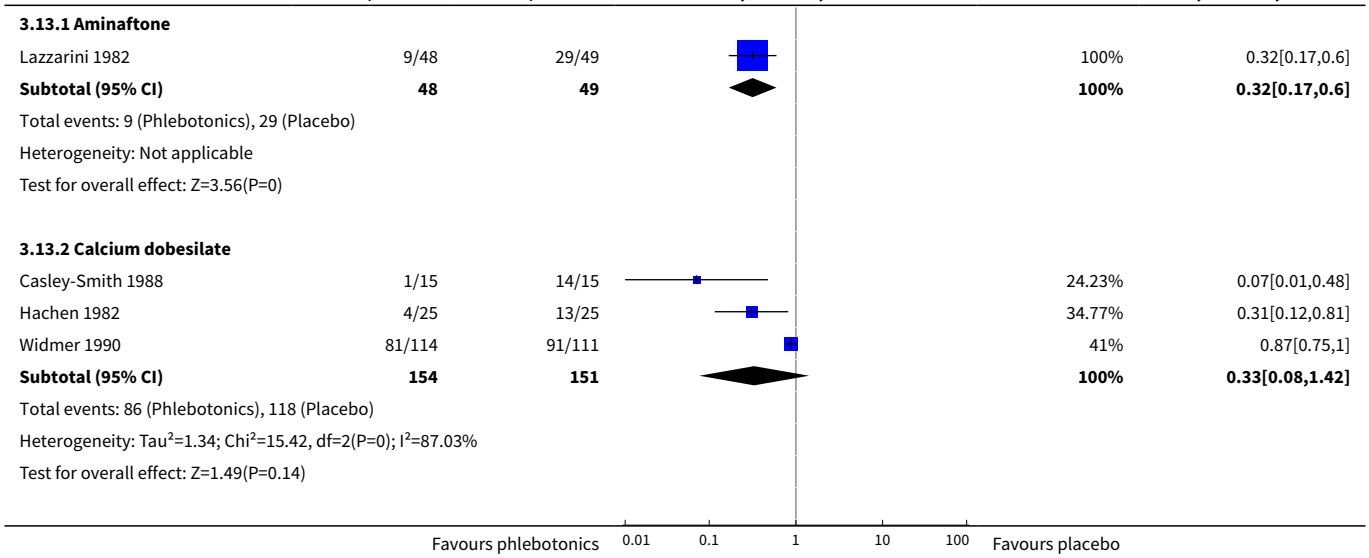


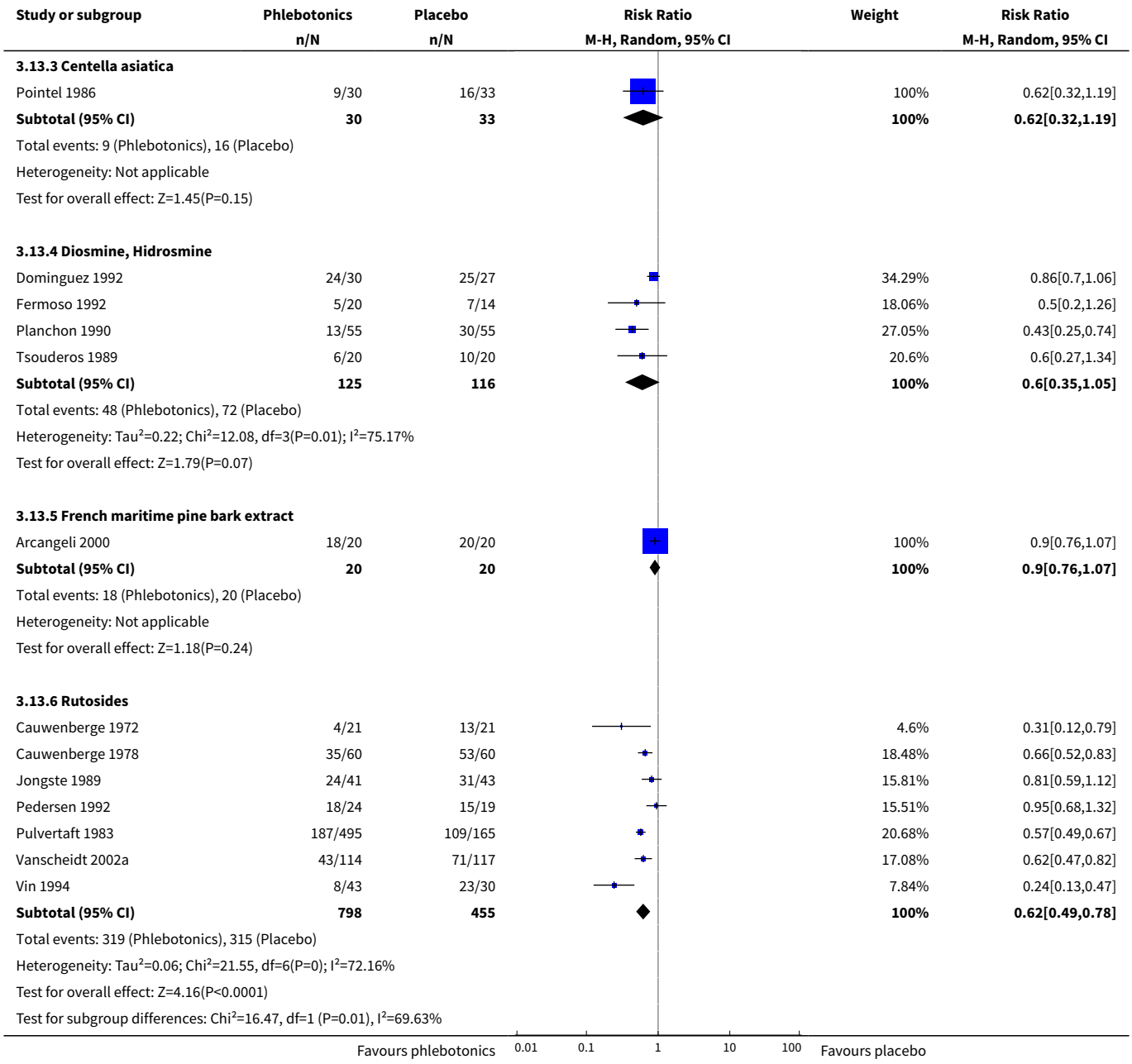


Analysis 3.12. Comparison 3 Sensitivity analysis of published studies only, Outcome 12 Itching in the lower legs (continuous variable).

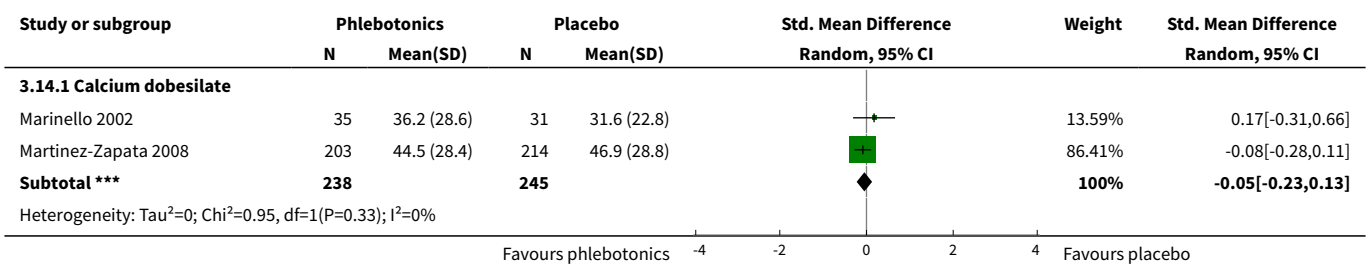


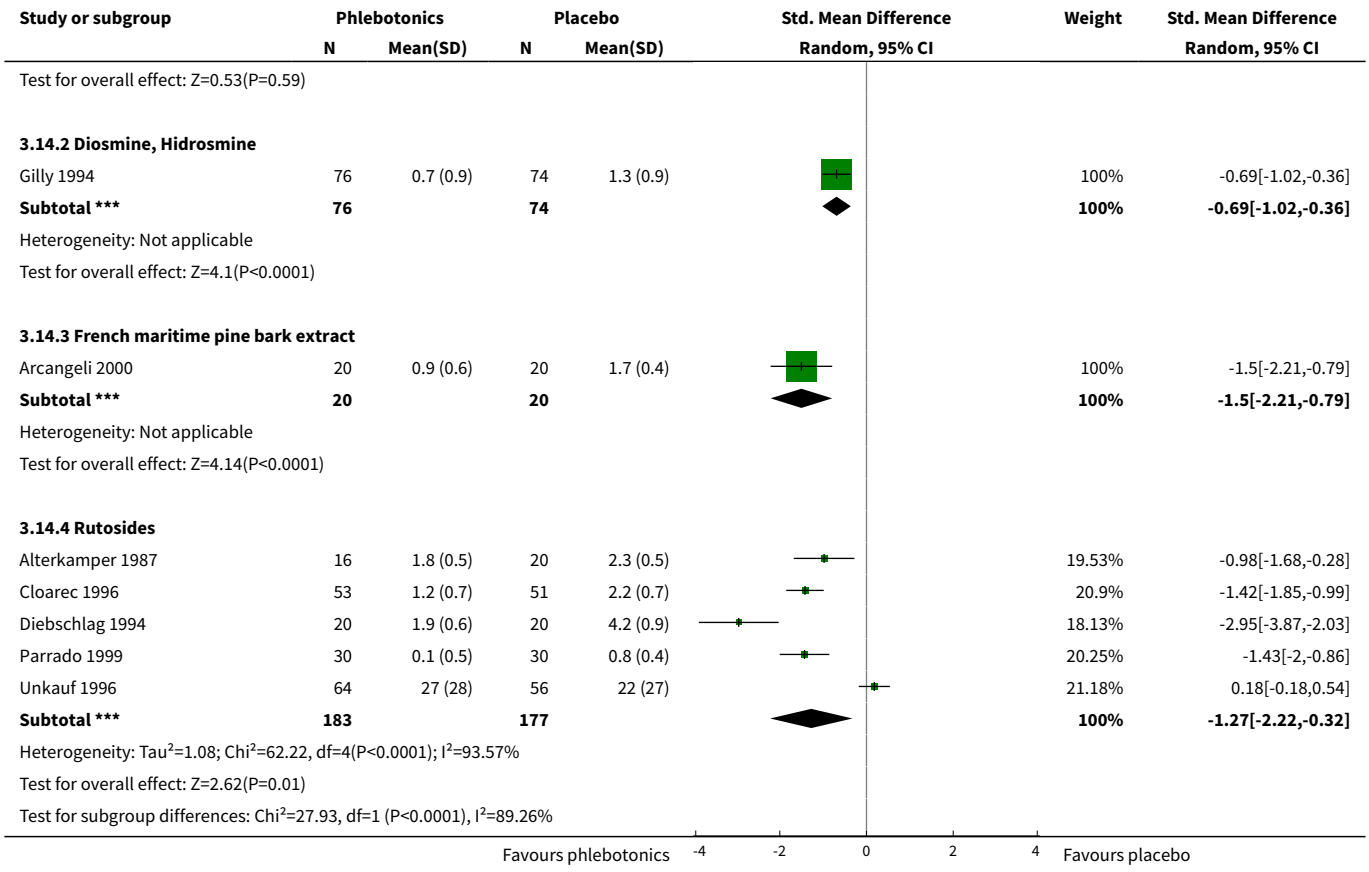
Analysis 3.13. Comparison 3 Sensitivity analysis of published studies only, Outcome 13 Heaviness in the lower legs (dichotomous variable).



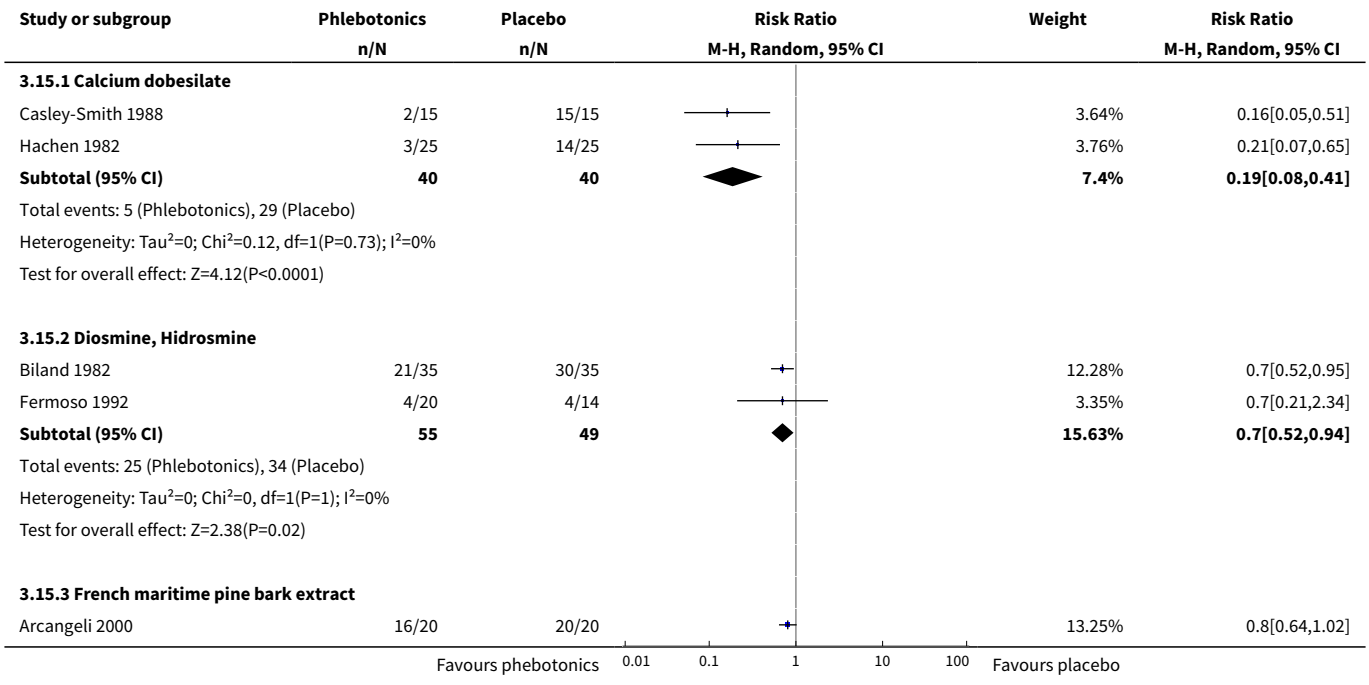


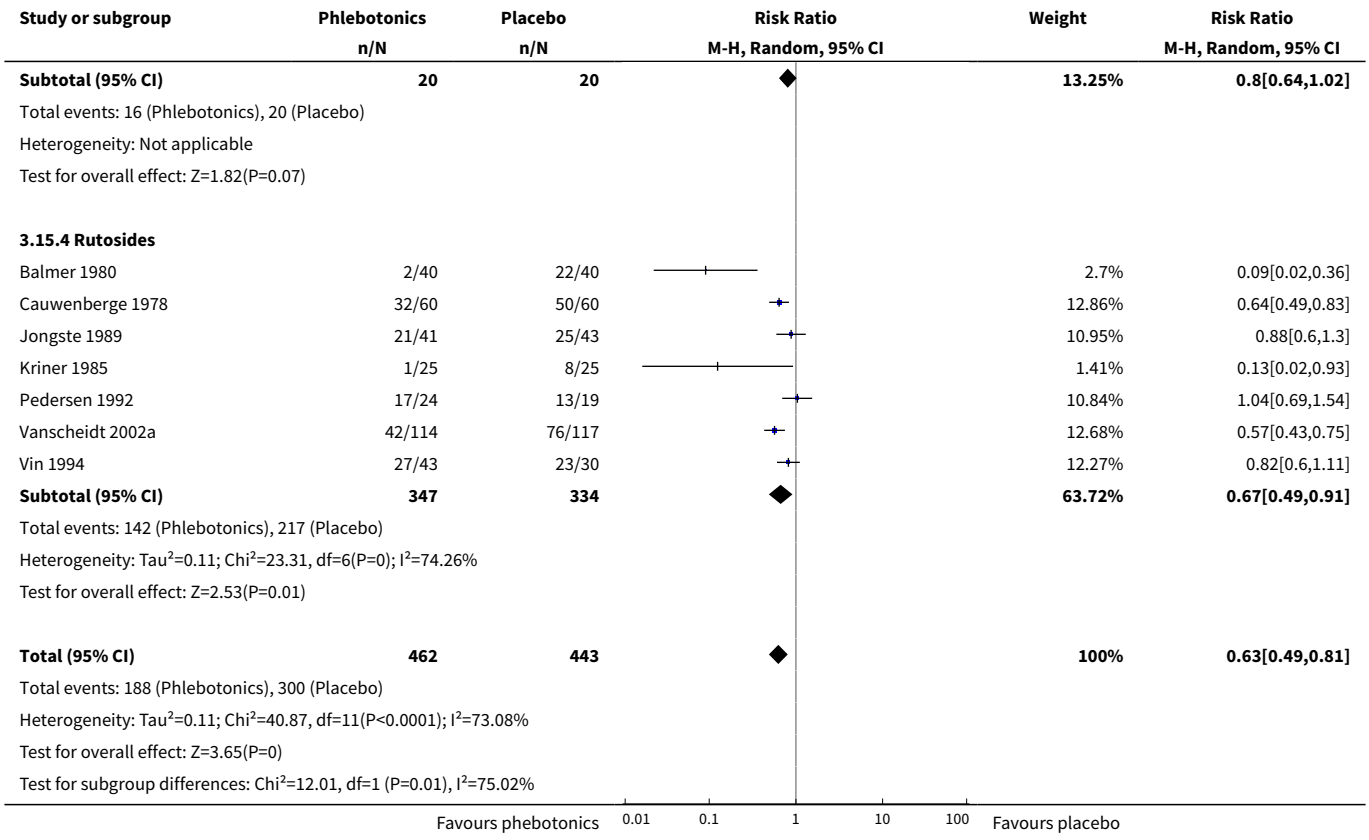
Analysis 3.14. Comparison 3 Sensitivity analysis of published studies only, Outcome 14 Heaviness in the lower legs (continuous variable).



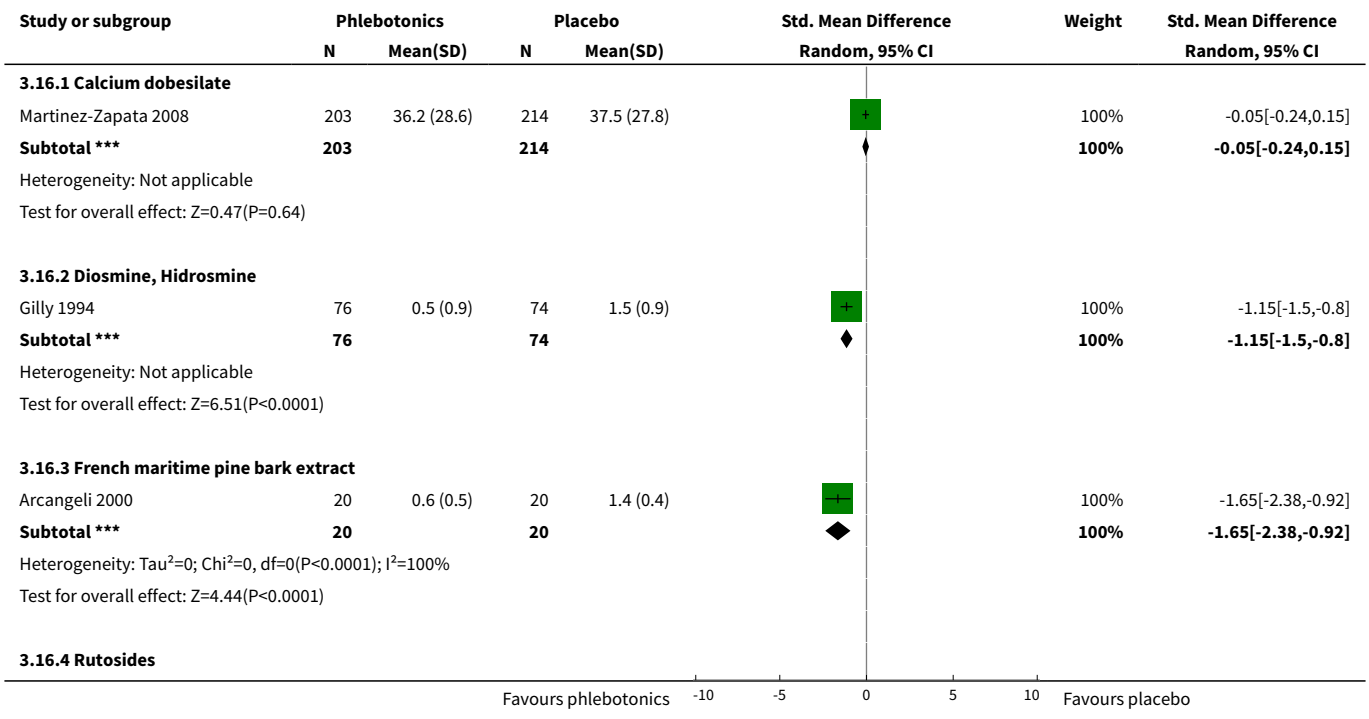


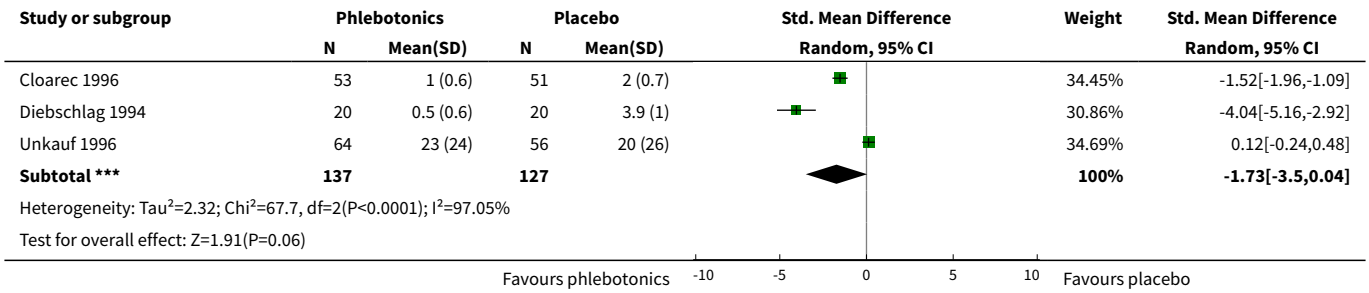
Analysis 3.15. Comparison 3 Sensitivity analysis of published studies only, Outcome 15 Swelling in the lower legs (dichotomous variable).





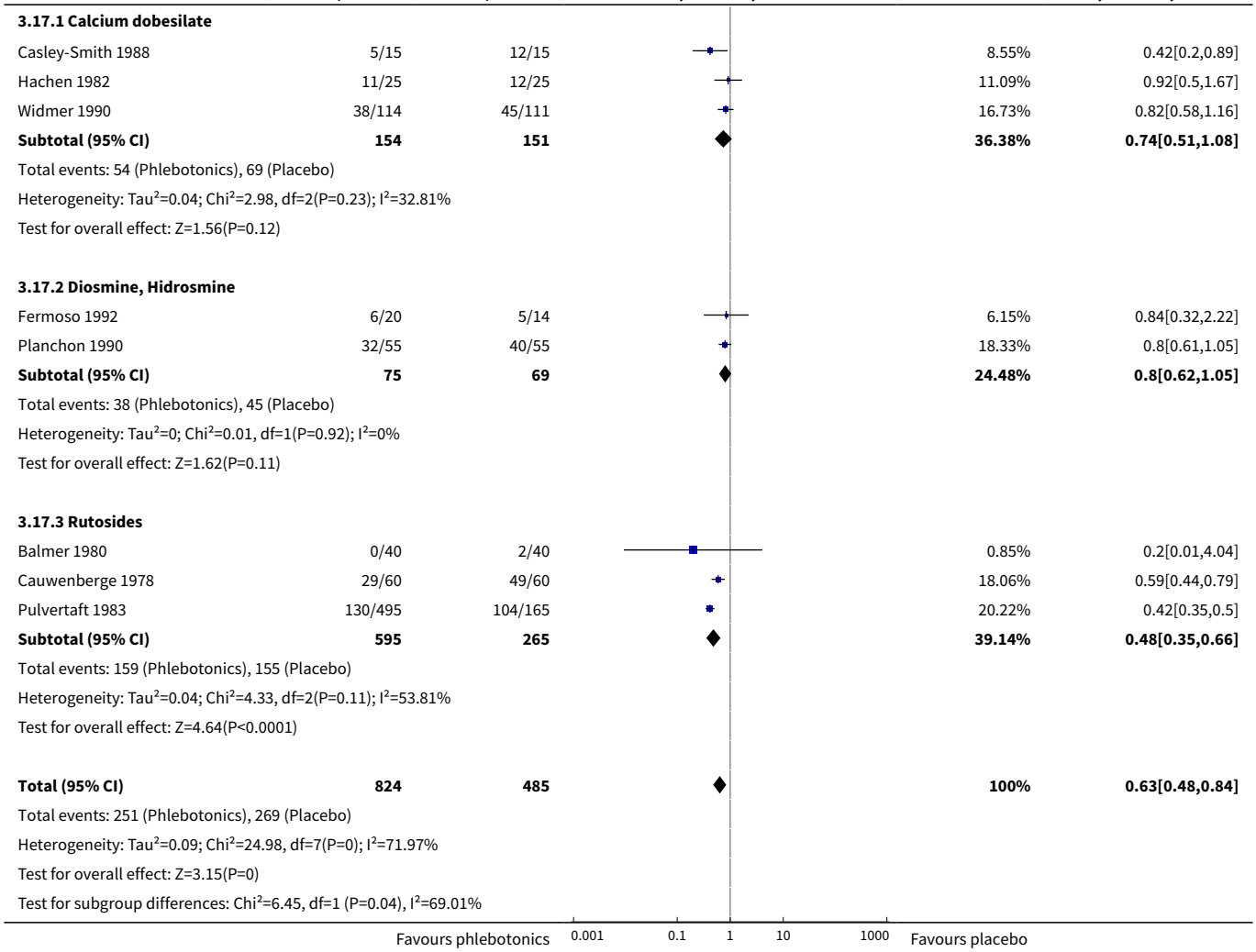
Analysis 3.16. Comparison 3 Sensitivity analysis of published studies only, Outcome 16 Swelling in the lower legs (continuous variable).





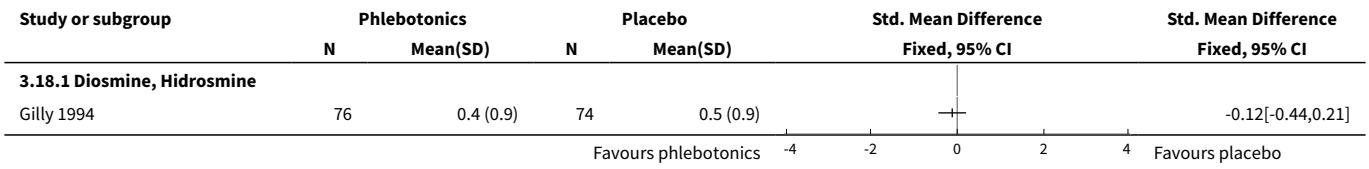
Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Cloarec 1996	53	1 (0.6)	51	2 (0.7)		34.45%	-1.52[-1.96,-1.09]
Diebschlag 1994	20	0.5 (0.6)	20	3.9 (1)		30.86%	-4.04[-5.16,-2.92]
Unkauf 1996	64	23 (24)	56	20 (26)		34.69%	0.12[-0.24,0.48]
Subtotal ***	**137**		**127**			**100%**	**-1.73[-3.5,0.04]**
Heterogeneity: Tau²=2.32; Chi²=67.7, df=2(P<0.0001); I²=97.05%							
Test for overall effect: Z=1.91(P=0.06)							

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

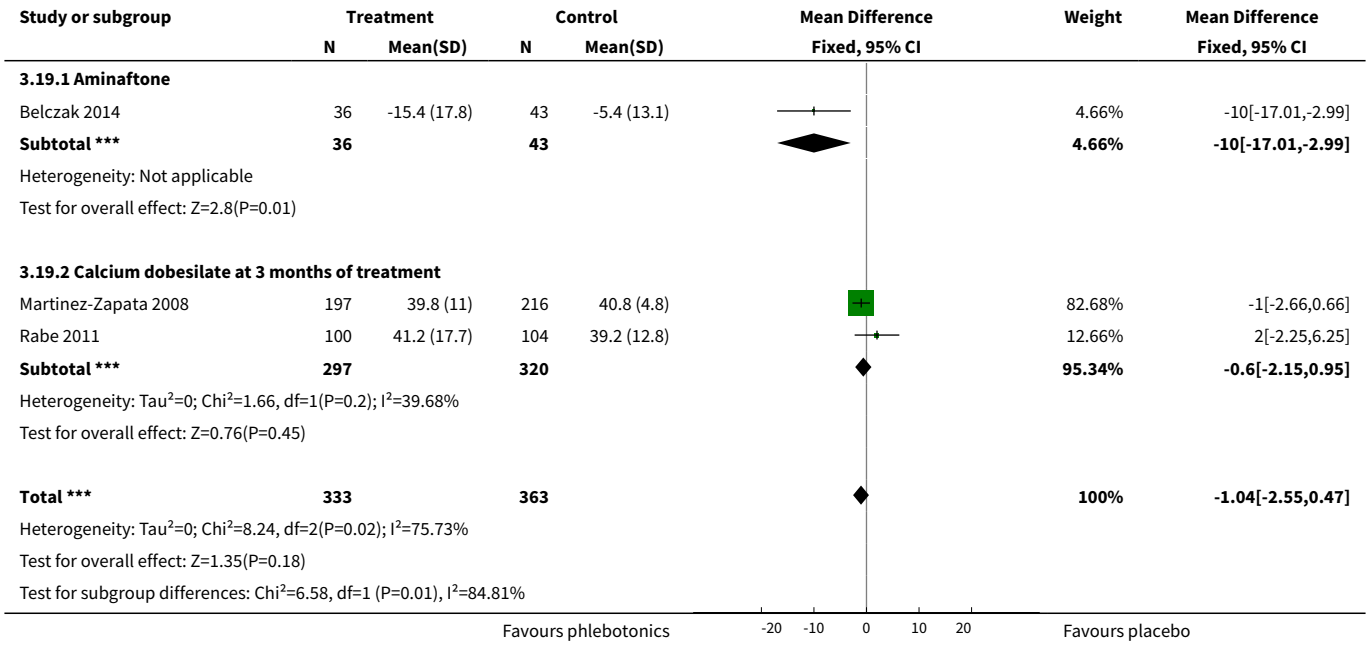


Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.17.1 Calcium dobesilate					
Casley-Smith 1988	5/15	12/15		8.55%	0.42[0.2,0.89]
Hachen 1982	11/25	12/25		11.09%	0.92[0.5,1.67]
Widmer 1990	38/114	45/111		16.73%	0.82[0.58,1.16]
Subtotal (95% CI)	**154**	**151**		**36.38%**	**0.74[0.51,1.08]**
Total events: 54 (Phlebotonics), 69 (Placebo)					
Heterogeneity: Tau²=0.04; Chi²=2.98, df=2(P=0.23); I²=32.81%					
Test for overall effect: Z=1.56(P=0.12)					
3.17.2 Diosmine, Hidrosmine					
Fermoso 1992	6/20	5/14		6.15%	0.84[0.32,2.22]
Planchon 1990	32/55	40/55		18.33%	0.8[0.61,1.05]
Subtotal (95% CI)	**75**	**69**		**24.48%**	**0.8[0.62,1.05]**
Total events: 38 (Phlebotonics), 45 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%					
Test for overall effect: Z=1.62(P=0.11)					
3.17.3 Rutosides					
Balmer 1980	0/40	2/40		0.85%	0.2[0.01,4.04]
Cauwenberge 1978	29/60	49/60		18.06%	0.59[0.44,0.79]
Pulvertaft 1983	130/495	104/165		20.22%	0.42[0.35,0.5]
Subtotal (95% CI)	**595**	**265**		**39.14%**	**0.48[0.35,0.66]**
Total events: 159 (Phlebotonics), 155 (Placebo)					
Heterogeneity: Tau²=0.04; Chi²=4.33, df=2(P=0.11); I²=53.81%					
Test for overall effect: Z=4.64(P<0.0001)					
Total (95% CI)	**824**	**485**		**100%**	**0.63[0.48,0.84]**
Total events: 251 (Phlebotonics), 269 (Placebo)					
Heterogeneity: Tau²=0.09; Chi²=24.98, df=7(P=0); I²=71.97%					
Test for overall effect: Z=3.15(P=0)					
Test for subgroup differences: Chi²=6.45, df=1 (P=0.04), I²=69.01%					

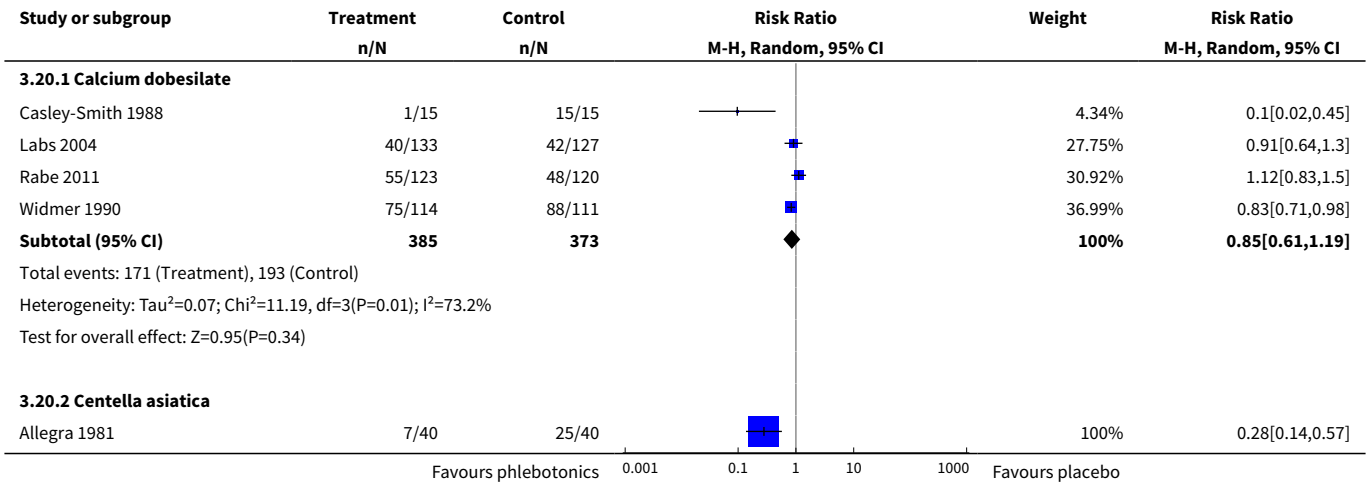
Analysis 3.18. Comparison 3 Sensitivity analysis of published studies only, Outcome 18 Paraesthesias in the lower legs (continuous variable).



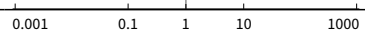
Analysis 3.19. Comparison 3 Sensitivity analysis of published studies only, Outcome 19 Quality of life.



Analysis 3.20. Comparison 3 Sensitivity analysis of published studies only, Outcome 20 Global assessment by the participant (dichotomous variable).

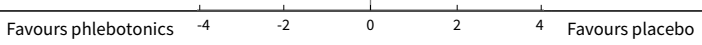


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**40**	**40**		**100%**	**0.28[0.14,0.57]**
Total events: 7 (Treatment), 25 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.49(P=0)					
3.20.3 Diosmine, Hidrosmine					
Biland 1982	23/35	28/35		25.85%	0.82[0.61,1.1]
Chassignolle 1994	24/40	28/40		23.65%	0.86[0.62,1.19]
Danielsson 2002	30/51	34/50		25.37%	0.87[0.64,1.17]
Laurent 1988	35/100	66/100		25.12%	0.53[0.39,0.72]
Subtotal (95% CI)	**226**	**225**		**100%**	**0.75[0.59,0.96]**
Total events: 112 (Treatment), 156 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=7.42, df=3(P=0.06); I^2=59.56%					
Test for overall effect: Z=2.33(P=0.02)					
3.20.4 Rutosides					
Burnand 1989	9/24	12/25		18.74%	0.78[0.4,1.51]
Cloarec 1996	3/53	32/51		13.81%	0.09[0.03,0.28]
Jongste 1989	15/41	26/43		20.65%	0.61[0.38,0.97]
Parrado 1999	0/30	1/30		3.63%	0.33[0.01,7.87]
Pedersen 1992	18/24	10/19		20.51%	1.43[0.88,2.31]
Pulvertaft 1983	116/495	109/165		22.65%	0.35[0.29,0.43]
Subtotal (95% CI)	**667**	**333**		**100%**	**0.5[0.26,0.97]**
Total events: 161 (Treatment), 190 (Control)					
Heterogeneity: Tau^2=0.48; Chi^2=40.6, df=5(P<0.0001); I^2=87.68%					
Test for overall effect: Z=2.04(P=0.04)					
Test for subgroup differences: Chi^2=8.9, df=1 (P=0.03), I^2=66.29%					



Analysis 3.21. Comparison 3 Sensitivity analysis of published studies only, Outcome 21 Global assessment by the participant (continuous variable).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.21.1 Calcium dobesilate							
Rabe 2011	108	15.2 (12.5)	115	20.8 (11.9)		50.16%	-0.46[-0.73,-0.19]
Widmer 1990	114	4.4 (4.4)	111	7.4 (5.7)		49.84%	-0.59[-0.85,-0.32]
Subtotal ***	**222**		**226**			**100%**	**-0.52[-0.71,-0.33]**
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.51); I^2=0%							
Test for overall effect: Z=5.44(P<0.0001)							
3.21.2 Diosmine, Hidrosmine							
Gilly 1994	76	0.5 (0.9)	74	1.2 (0.9)		100%	-0.81[-1.14,-0.47]
Subtotal ***	**76**		**74**			**100%**	**-0.81[-1.14,-0.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.74(P<0.0001)							
3.21.3 Rutosides							
Cesarone 2002	16	3.1 (1.2)	15	6 (2)		21.67%	-1.73[-2.57,-0.89]



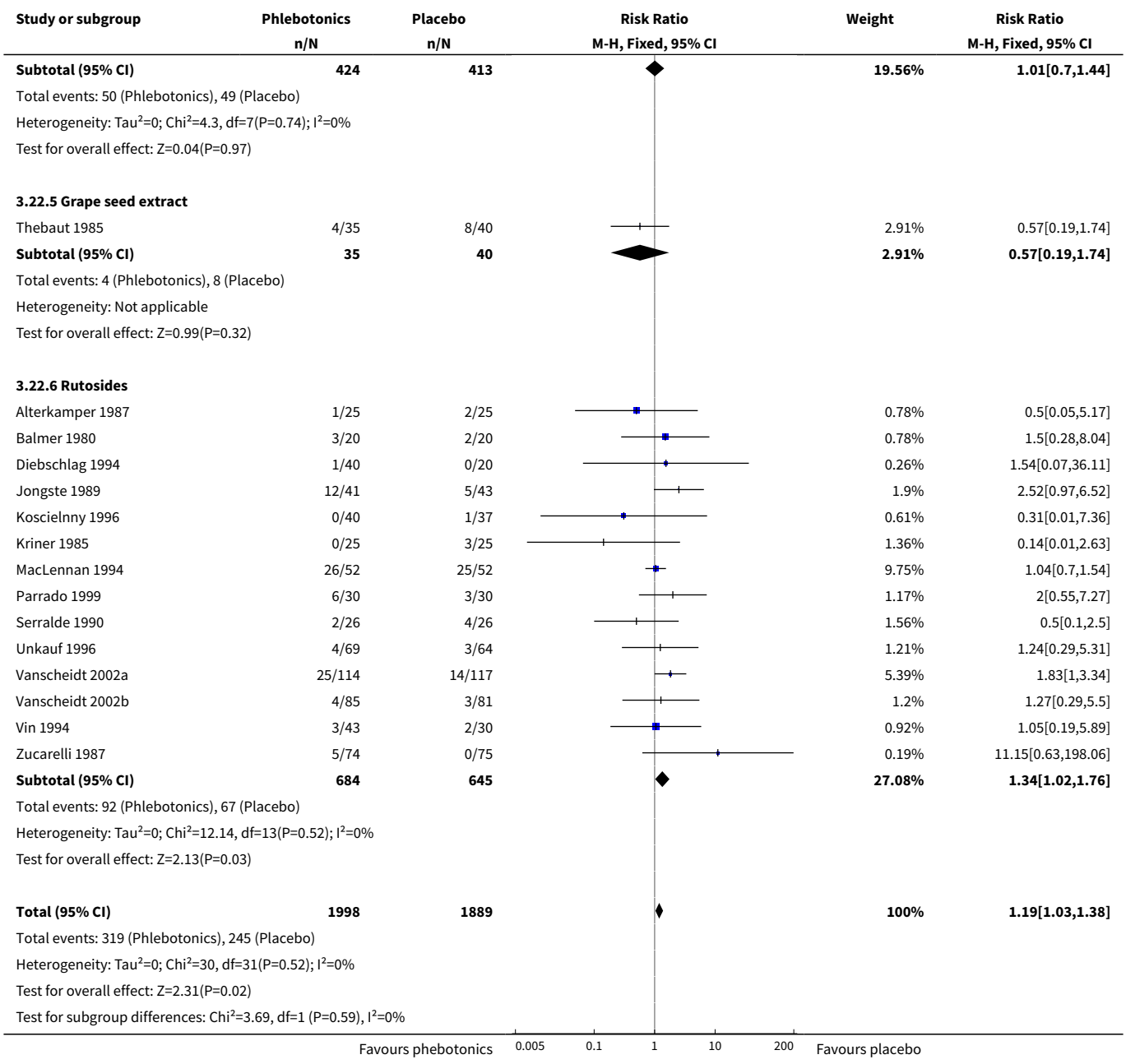
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Cloarec 1996	53	4.3 (2.5)	51	9.5 (3.3)		26.26%	-1.77[-2.22,-1.31]
Ihme 1996	36	2.2 (1.4)	31	2.4 (1.7)		26%	-0.13[-0.61,0.35]
Kiesewetter 1997	37	1.5 (1.1)	44	3 (1.4)		26.07%	-1.17[-1.64,-0.69]
Subtotal * **	**142**		**141**			**100%**	**-1.18[-1.96,-0.39]**
Heterogeneity: Tau²=0.56; Chi²=26.15, df=3(P<0.0001); I²=88.53%							
Test for overall effect: Z=2.93(P=0)							
Test for subgroup differences: Chi²=4.11, df=1 (P=0.13), I²=51.31%							

Favours phlebotonics — Favours placebo

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

Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.22.1 Aminaftone					
Belczak 2014	1/36	2/43		0.71%	0.6[0.06,6.32]
Subtotal (95% CI)	**36**	**43**		**0.71%**	**0.6[0.06,6.32]**
Total events: 1 (Phlebotonics), 2 (Placebo)					
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		0.4%	0.96[0.06,14.5]
Hachen 1982	1/25	0/25		0.19%	3[0.13,70.3]
Labs 2004	9/133	8/127		3.19%	1.07[0.43,2.7]
Marinello 2002	32/82	18/41		9.36%	0.89[0.57,1.38]
Martinez-Zapata 2008	46/246	45/263		16.96%	1.09[0.75,1.59]
Rabe 2011	33/133	10/124		4.03%	3.08[1.58,5.98]
Widmer 1990	31/114	28/111		11.06%	1.08[0.69,1.67]
Subtotal (95% CI)	**758**	**715**		**45.19%**	**1.23[0.99,1.53]**
Total events: 153 (Phlebotonics), 110 (Placebo)					
Heterogeneity: Tau²=0; Chi²=10.58, df=6(P=0.1); I²=43.3%					
Test for overall effect: Z=1.87(P=0.06)					
3.22.3 Centella asiatica					
Pointel 1986	19/61	9/33		4.55%	1.14[0.58,2.23]
Subtotal (95% CI)	**61**	**33**		**4.55%**	**1.14[0.58,2.23]**
Total events: 19 (Phlebotonics), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
3.22.4 Diosmine, Hidrosmine					
Biland 1982	11/35	12/35		4.68%	0.92[0.47,1.79]
Danielsson 2002	6/51	2/50		0.79%	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		0.23%	2.14[0.09,49.08]
Gilly 1994	12/80	9/80		3.51%	1.33[0.6,2.99]
Guilhou 1997	4/53	5/52		1.97%	0.78[0.22,2.76]
Laurent 1988	9/100	13/100		5.07%	0.69[0.31,1.55]
Planchon 1990	6/55	8/55		3.12%	0.75[0.28,2.02]

Favours phebotonics — Favours placebo



Comparison 4. Sensitivity analysis based on low risk of bias

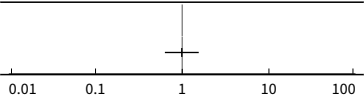
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oedema in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Calcium dobesilate	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Ankle perimeter circumference (mm)	3	867	Mean Difference (IV, Random, 95% CI)	-2.34 [-8.79, 4.11]
2.1 Calcium dobesilate	3	867	Mean Difference (IV, Random, 95% CI)	-2.34 [-8.79, 4.11]
3 Volume of the leg (mL)	2	418	Mean Difference (IV, Fixed, 95% CI)	-59.08 [-84.40, -33.76]
3.1 Calcium dobesilate	1	239	Mean Difference (IV, Fixed, 95% CI)	-65.48 [-99.47, -31.49]
3.2 Rutosides	1	179	Mean Difference (IV, Fixed, 95% CI)	-51.1 [-89.06, -13.14]
4 Pain in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Pain in the lower legs (continuous variable)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Calcium dobesilate	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Cramps in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Itching in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Itching in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Heaviness in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Heaviness in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Swelling in the lower legs (dichotomous variable)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Rutosides	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Swelling in the lower legs (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Quality of life	2	617	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
13.1 Calcium dobesilate at 3 months of treatment	2	617	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.15, 0.95]
14 Global assessment by the participant (dichotomous variable)	2	476	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.32]
14.1 Calcium dobesilate	2	476	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.32]
15 Global assessment by the participant (continuous variable)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Calcium dobesilate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Adverse events	4	1257	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.97, 2.63]
16.1 Calcium dobesilate	3	1026	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.76, 3.09]
16.2 Rutosides	1	231	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.00, 3.34]

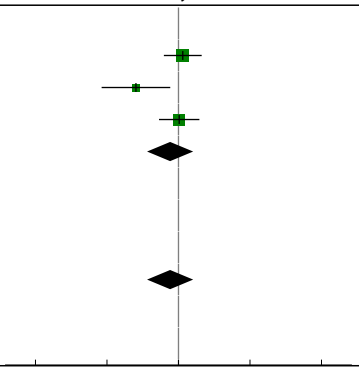
Analysis 4.1. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 1 Oedema in the lower legs (dichotomous variable).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Calcium dobesilate				
Labs 2004	30/133	29/127		0.99[0.63,1.55]



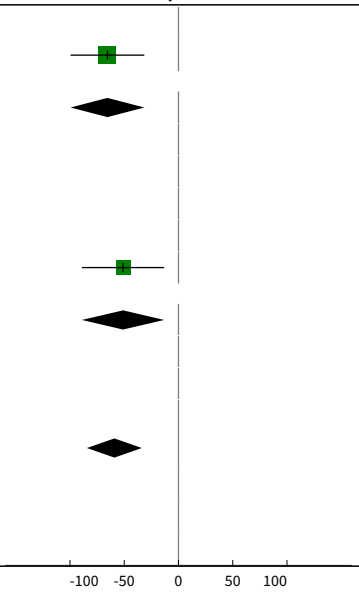
Analysis 4.2. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 2 Ankle perimeter circumference (mm).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.2.1 Calcium dobesilate							
Labs 2004	124	229.5 (22.7)	123	228.3 (19.6)		38.58%	1.2[-4.09,6.49]
Martinez-Zapata 2008	193	254.9 (43.2)	203	266.8 (53.9)		24.19%	-11.9[-21.5,-2.3]
Rabe 2011	109	240.9 (21.3)	115	240.7 (21.8)		37.23%	0.2[-5.44,5.84]
Subtotal ***	**426**		**441**			**100%**	**-2.34[-8.79,4.11]**
Heterogeneity: Tau²=20.8; Chi²=5.79, df=2(P=0.06); I²=65.47%							
Test for overall effect: Z=0.71(P=0.48)							
Total ***	**426**		**441**			**100%**	**-2.34[-8.79,4.11]**
Heterogeneity: Tau²=20.8; Chi²=5.79, df=2(P=0.06); I²=65.47%							
Test for overall effect: Z=0.71(P=0.48)							



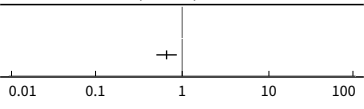
Analysis 4.3. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 3 Volume of the leg (mL).

Study or subgroup	Favours phlebotonics N	Favours phlebotonics Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.3.1 Calcium dobesilate							
Rabe 2011	120	-64.7 (111.9)	119	0.8 (152.9)		55.49%	-65.48[-99.47,-31.49]
Subtotal ***	**120**		**119**			**55.49%**	**-65.48[-99.47,-31.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.78(P=0)							
4.3.2 Rutosides							
Vanscheidt 2002a	86	-95.7 (127.9)	93	-44.6 (131.1)		44.51%	-51.1[-89.06,-13.14]
Subtotal ***	**86**		**93**			**44.51%**	**-51.1[-89.06,-13.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.64(P=0.01)							
Total ***	**206**		**212**			**100%**	**-59.08[-84.4,-33.76]**
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%							
Test for overall effect: Z=4.57(P<0.0001)							
Test for subgroup differences: Chi²=0.31, df=1 (P=0.58), I²=0%							



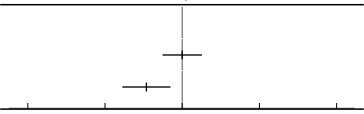
Analysis 4.4. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 4 Pain in the lower legs (dichotomous variable).

Study or subgroup	Phlebotonics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Rutosides				
Vanscheidt 2002a	45/114	70/117		0.66[0.5,0.87]



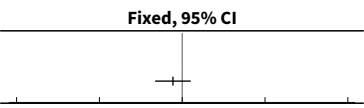
Analysis 4.5. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 5 Pain in the lower legs (continuous variable).

Study or subgroup	Phlebotonics N	Phlebotonics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
4.5.1 Calcium dobesilate						
Martinez-Zapata 2008	203	37.8 (25.8)	216	37.8 (27.4)		0[-5.09,5.09]
Rabe 2011	120	-10.2 (26.2)	119	-0.9 (22.9)		-9.28[-15.52,-3.04]



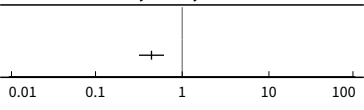
Analysis 4.6. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 6 Cramps in the lower legs (continuous variable).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.6.1 Calcium dobesilate						
Martinez-Zapata 2008	204	24.1 (27.1)	211	26.9 (28.7)		-2.8[-8.17,2.57]



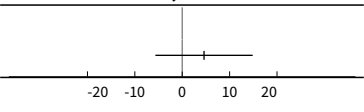
Analysis 4.7. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 7 Itching in the lower legs (dichotomous variable).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	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	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.8.1 Calcium dobesilate						
Martinez-Zapata 2008	204	35.9 (68.6)	212	31.3 (30.4)		4.6[-5.66,14.86]

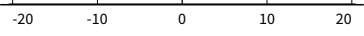


Analysis 4.9. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 9 Heaviness in the lower legs (dichotomous variable).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.9.1 Rutosides				
Vanscheidt 2002a	43/114	71/117		0.62[0.47,0.82]

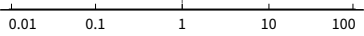
Analysis 4.10. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 10 Heaviness in the lower legs (continuous variable).

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.10.1 Calcium dobesilate						
Martinez-Zapata 2008	203	44.5 (28.4)	214	46.9 (28.8)		-2.4[-7.89,3.09]



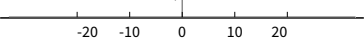
Analysis 4.11. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 11 Swelling in the lower legs (dichotomous variable).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.11.1 Rutosides				
Vanscheidt 2002a	42/114	76/117		0.57[0.43,0.75]



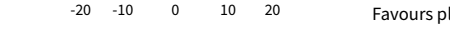
Analysis 4.12. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 12 Swelling in the lower legs (continuous variable).

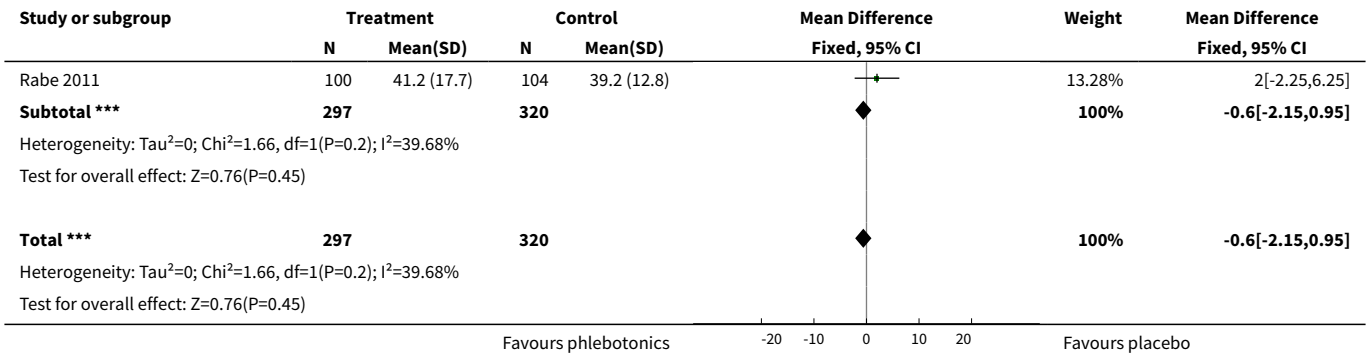
Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.12.1 Calcium dobesilate						
Martinez-Zapata 2008	203	36.2 (28.6)	214	37.5 (27.8)		-1.3[-6.72,4.12]



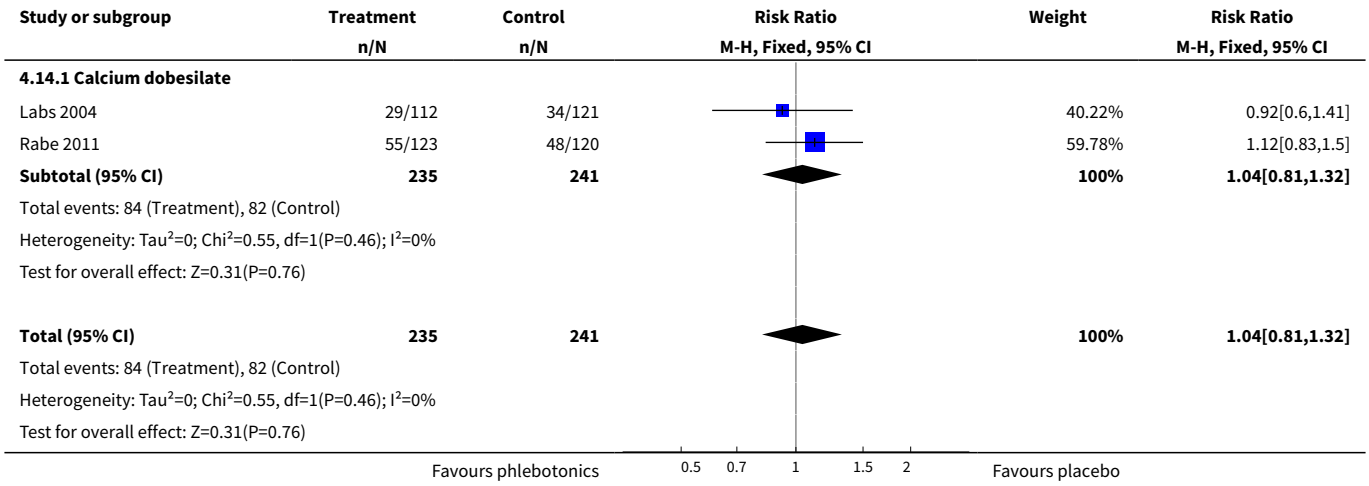
Analysis 4.13. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 13 Quality of life.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.13.1 Calcium dobesilate at 3 months of treatment							
Martinez-Zapata 2008	197	39.8 (11)	216	40.8 (4.8)		86.72%	-1[-2.66,0.66]

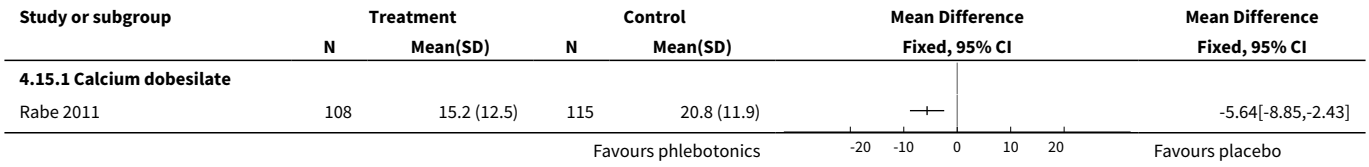




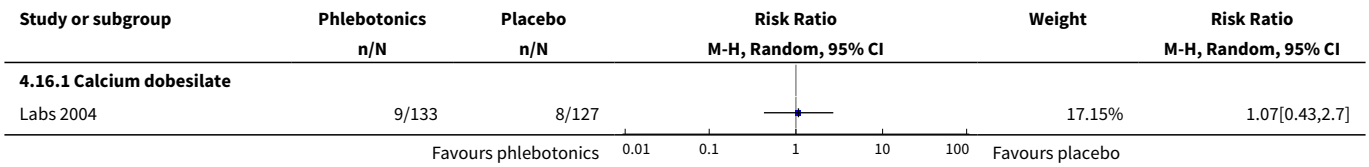
Analysis 4.14. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 14 Global assessment by the participant (dichotomous variable).

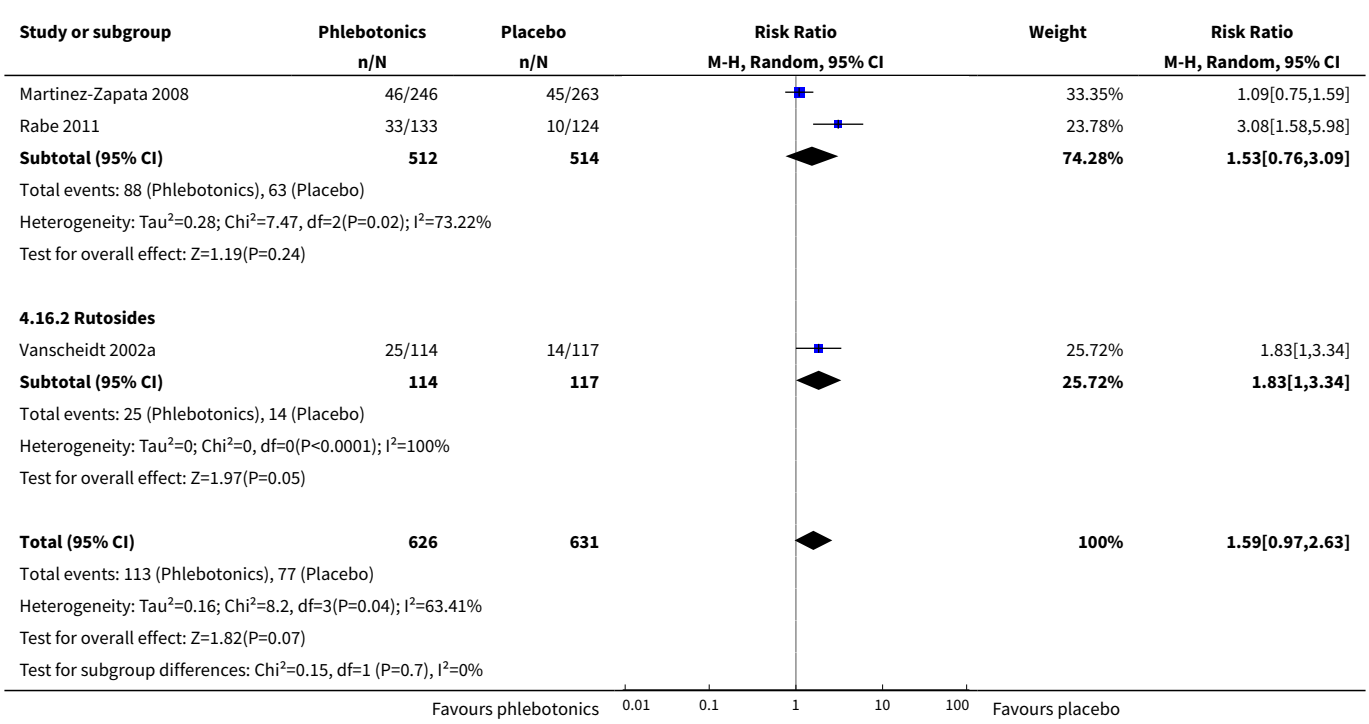


Analysis 4.15. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 15 Global assessment by the participant (continuous variable).



Analysis 4.16. Comparison 4 Sensitivity analysis based on low risk of bias, Outcome 16 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 -0.38 (-0.50 to -0.25)
Ulcer cured	NS	-
Trophic disorders	RR 0.87 (0.81 to 0.95)	-
Pain	-	-
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)	-

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

Paraesthesia	RR 0.67 (0.50 to 0.88)	NS
Quality of life	-	-
Global assessment by the participant	-	-
Adverse events	RR 1.21 (1.05 to 1.40)	-
Note: No measures of effect are specified when I^2 was > 75% for the subgroup		

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

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

Table 3. Results by pharmacological group: calcium dobesilate

Variables	Dichotomous	Continuous
Oedema	-	-
Oedema (mm)	-	NS
Oedema (volume)	-	SMD -0.50 (-0.68 to -0.31)
Ulcer cured	NS	-

Table 3. Results by pharmacological group: calcium dobesilate *(Continued)*

Pain	RR 0.39 (0.16 to 0.93)	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	NS	-
Note: No measures of effect are specified when I^2 was > 75% for the subgroup		

NS: non-significant
RR: risk ratio
SMD: standardised 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 analysed		

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 -0.35 (-0.67 to -0.02)

Table 5. Results by pharmacological group: diosmine, hidrosmine *(Continued)*

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
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: standardised 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 analysed		

NS: non-significant
RR: risk ratio
SMD: standardised 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 analysed		

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 -0.29 (-0.11 to -0.47)
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 1.41 (1.08 to 1.83)	-
Note: No measures of effect are specified when I^2 was > 75%		

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

APPENDICES

Appendix 1. CRS search strategy

Search run on Fri Aug 21 2015		
#1	MESH DESCRIPTOR Venous Insufficiency EXPLODE ALL TREES	333
#2	(insuffic* or insufic* or CVI or isch* or incompet*):TI,AB,KY	29524
#3	(saphenous or vein* or veno*):TI,AB,KY	21111
#4	#1 OR #2 OR #3	48620

(Continued)

#5	MESH DESCRIPTOR Flavonoids EXPLODE ALL TREES	1732
#6	MESH DESCRIPTOR Saponins EXPLODE ALL TREES	149
#7	MESH DESCRIPTOR Calcium Dobesilate	37
#8	*rutin*:TI,AB,KY	516
#9	*rutoside*:TI,AB,KY	183
#10	(*escin* or *aescin* or *essaven*):TI,AB,KY	196
#11	(*rosskastani* or *aesculus*):TI,AB,KY	23
#12	(horse near3 (chestnut or chest-nut)):TI,AB,KY	42
#13	(calcium near2 dobesilate):TI,AB,KY	81
#14	(naftazone* or aminaftone* or aminaphtone* or chromocarbe*):TI,AB,KY	18
#15	(bark* near3 extract):TI,AB,KY	80
#16	(*french* near3 maritime*):TI,AB,KY	26
#17	(*grape* near3 *seed*):TI,AB,KY	67
#18	(disodium* near2 flavodate*):TI,AB,KY	3
#19	(*dioxium* or hidrosmin* or *diosmin*):TI,AB,KY	102
#20	(*venostasin* or *venorutin* or pycnogenol*):TI,AB,KY	86
#21	(*flavono* or *flaven* or centella or aminaftone):TI,AB,KY	1007
#22	*phlebotonic*:TI,AB,KY	8
#23	(*quercetin or hesperidin or saponosides or saponin*):TI,AB,KY	465
#24	daflon:TI,AB,KY	70
#25	#5 OR #6 OR #7 OR #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	3207
#26	#4 AND #25	513

WHAT'S NEW

Date	Event	Description
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

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

HISTORY

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

Date	Event	Description
8 July 2008	Amended	Converted to new review format
14 November 2006	Amended	Edited update. CDSR citations updated

CONTRIBUTIONS OF AUTHORS

All reviewers contributed to development of the protocol, selected and assessed clinical trials and evaluated their quality. In the first version of this SR:

- MJ Martinez, RM Moreno and D Capellà extracted data for the first version of this SR. SM Uriona and RWM Vernooij extracted data from new studies and assessed risk of bias of all included studies;
- RM Moreno provided clinical experience and insight on the protocol and review reports;
- MJ Martinez was responsible for statistical and methodological aspects and for overall compiling of this SR; and
- MJ Martinez, RWM Vernooij, SM Uriona, AT Stein, RM Moreno, E Vargas, D Capellà and X Bonfill Cosp were responsible for manuscript development and revision of this SR.

DECLARATIONS OF INTEREST

Dr D Capellà, Dr X Bonfill Cosp, Dr RM Moreno and Dr E Vargas were part of an advisory group of the Safety Committee of the Spanish Drug Agency, whose objective was to assess the efficacy and safety of phlebotonics during 2002. Dr MJ Martínez assisted with technical work for this group.

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 sponsored 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 MJ Martínez-Zapata: none known.
Dr RWM Vernooij: none known.
Dr SM Uriona Tuma: none known.
Dr AT Stein: none known.
Dr RM Moreno: none known.
Dr E Vargas: none known.
Dr D Capellà: chair of the Independent Drug Monitoring Committee of the clinical trial "Neurodegeneration as an early event in the pathogenesis of diabetic retinopathy: a multicentric, prospective, phase II-III, randomised controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest diabetic retinopathy", carried out by the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR) with support from the European Commission, FP7-HEALTH-2011-GA No. 278040 and sponsored by BCN Peptides.
Dr X Bonfill Cosp: none known.

SOURCES OF SUPPORT

Internal sources

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External sources

- The Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.
- Instituto de Salud Carlos III, Spain.

  Dr. Mª José Martinez Zapata is funded by a Miguel Servet research contract from the Instituto de Salud Carlos III (CP15/00116).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have noted some differences between the protocol and this systematic review (SR), specifically in the following items.

- In the previous version of this SR, we made different assumptions to examine adverse events. In this current SR, we have 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 previous version of this SR, 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 SR, we used only the current Cochrane criteria to assess risk of bias (Higgins 2011).
- In the previous version of this SR, we considered statistical heterogeneity of P value < 0.1 as a reason for not pooling results of the studies. In this current SR, we used the I^2 statistic and considered I^2 > 75% a reason for not pooling the results of RCTs.
- In the previous version of this SR, we specified to use a random-effects statistical model in all analyses. In this current SR, however, we used this model only when I^2 was between 50% and 75%.
- In the previous version of this SR, we performed a sensitivity analysis by level of quality of studies according to the Cochrane criteria (Clarke 2003). In this current SR, 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 previous version of this SR, assessment of publication bias was not specified. In this current SR, we constructed a funnel plot to explore publication bias.
- In the previous version of this SR, the quality of evidence was assessed by the Cochrane criteria. In this current SR, 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 for the main comparison).

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans