Padma 28 for intermittent claudication

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[Intervention Review]

Padma 28 for intermittent claudication

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ABSTRACT

Background

Intermittent claudication (IC) is pain caused by chronic occlusive arterial disease that develops in a limb during exercise and is relieved with rest. Most drug treatments of IC have a limited effect in improving walking distance. Padma 28, a Tibetan herbal preparation, has been used to treat IC, but there is debate as to whether Padma 28 produces a clinical benefit beyond the placebo effect. This is an update of a review first published in 2013.

Objectives

To determine whether Padma 28 is effective, compared with placebo or other medications, in increasing pain-free and maximum walking distance for patients with intermittent claudication.

Search methods

For this update the Cochrane Vascular Trials Search Co-ordinator searched the Specialised Register (September 2015), the Cochrane Register of Studies ((CENTRAL) (2015, Issue 8)) and clinical trials databases.

Selection criteria

Randomised controlled trials of Padma 28 compared with placebo or other pharmacological treatments in people suffering from IC.

Data collection and analysis

All review authors independently assessed the selected studies and extracted the data. Risk of bias was evaluated independently by two review authors. Depending on the data provided in the individual trials, we extracted mean or median walking distance at the end of the trial, or change in walking distance over the course of the trial, or both. Where not provided, and whenever possible, the statistical significance of differences in these parameters between treatment and placebo groups in individual trials was calculated. Where possible, data were combined by meta-analysis.

Main results

No new trials were identified in the search for this review update. In total five trials involving 365 participants were included in this review. All trials compared Padma 28 with placebo for at least 16 weeks of follow-up. Pain-free and maximum walking distances both increased significantly in the groups treated with Padma 28, with no significant change in the placebo group. In general, the studies presented results comparing the treatment arms before and after treatment but made no comparisons between the Padma 28 and placebo

groups. Pooled data of maximum walking distance after treatment with Padma 28 and placebo from two studies (193 participants) indicated a higher maximum walking distance (mean difference (MD) 95.97 m, 95% confidence interval (CI) 79.07 m to 112.88 m, P < 0.00001, very low quality evidence) in the Padma 28 group compared with placebo. The clinical importance of these observed changes in walking distance is unclear as no quality of life data were reported. There was no effect on ankle brachial index (ABI): change in ABI values between baseline and six months follow up MD -0.01, 95% CI -0.07 to 0.05, 1 study, 56 participants, P = 0.72, very low quality evidence). Mild side effects, especially gastrointestinal discomfort, tiredness and skin eruption, were reported but this outcome was not different between the Padma 28 and placebo groups (odds ratio 1.09, 95% CI 0.42 to 2.83, four studies, 231 participants, P = 0.86, very low quality evidence).

Authors' conclusions

Some evidence exists from individual trials to suggest that Padma 28 may be effective in increasing walking distances, at least in the short term (four months), in people with IC. Side effects do not appear to be a problem. However, the longer term effects of treatment are unknown and the clinical significance of the improvements in walking distance are questionable. Moreover, the quality of the evidence is limited by the small sample size of the available trials, limited reporting of statistical analyses that compared treatment groups, and relatively high withdrawal rates that were linked to the outcome. That is, patients were withdrawn if they failed to improve walking distance. There was also evidence of publication bias. We therefore feel there is currently insufficient evidence to draw conclusions regards the effectiveness of Padma 28 in the routine management of IC. Further well-designed research would be required to determine the true effects of this herbal preparation.

PLAIN LANGUAGE SUMMARY

Padma 28 for intermittent claudication

Background

Intermittent claudication (IC) is pain in the leg that occurs on exercise and is relieved by rest. It is caused by an inadequate blood supply to the legs due to blockage of arteries. Conservative drug treatment is commonly used in an attempt to improve walking distance in these patients. Padma 28 is a Tibetan herbal preparation used for treating intermittent claudication.

Study characteristics and key results

This review on the effects of Padma 28 includes five trials with a total of 365 participants (current until September 2015). The review showed that Padma 28 has some beneficial effects in improving maximum and pain-free walking distance. The groups treated with placebo did not show an improved maximum and pain-free walking distance. Unfortunately the studies reported insufficient data to allow the comparison of the change in walking distances in the Padma 28 group with the change in walking distances in the placebo group. Combining the data of maximum walking distance after treatment in two studies showed that there was a longer maximum walking distance in the Padma 28 group compared with the placebo group after 16 weeks of treatment. No change in ankle brachial pressure was observed. Mild side effects such as gastrointestinal discomfort, tiredness and skin eruption were also noted but these were not different between the Padma 28 and placebo groups.

Quality of the evidence

Overall, the quality of the studies was low, with evidence of publication bias, small number of trials, limited reporting of the analyses that compared treatment groups and bias due to a high percentage of withdrawals in the placebo groups because of lack of improvement or deterioration of the overall condition. We therefore feel there is currently insufficient evidence to draw conclusions about the effectiveness of Padma 28 in the routine management of IC. Further well-designed research would be required to determine the true effects of this herbal preparation.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Should Padma 28 versus placebo be used for intermittent claudication?

Patient or population: people with symptomatic intermittent claudication
Setting: outpatient setting
Intervention: Padma 28
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Padma 28				
Pain free walking distance (PFWD) follow up: 4 months	see comment		-	79 (2 RCTs)		Unable to pool data, one of the two studies did not provide variability data. Review authors deemed the limited available data inappropriate for imputation
Change in maximum walking distance (MWD) follow up: 4 months	The mean change in maximum walking distance was - 1.4 metres	The mean change in maximum walking distance in the Padma 28 group was 77.1 metres more (53.41 more to 100.79 more)	-	100 (1 RCT)	⊕⊕◯◯ LOW [12]	
Final value MWD assessed with: treadmill follow up: 4 months	The mean final value maximum walking distance was 77.05 metres	The mean final value maximum walking distance in the Padma 28 group was 95.97 metres more (79.07 more to 112.88 more)	-	193 (2 RCTs)	⊕◯◯◯ VERY LOW [134]	

Adverse effects follow up: 4 months	Study population		OR 1.09 (0.42 to 2.83)	231 (4 RCTs)	⊕◯◯◯ VERY LOW [156]
	99 per 1000	107 per 1000 (44 to 237)			
	Moderate				
	52 per 1000	56 per 1000 (22 to 134)			
Final value ankle brachial index (ABI) follow up: 4 months	The mean final value ankle brachial index was 0.73	The mean final value ankle brachial index in the Padma 28 group was 0.01 fewer (0.11 fewer to 0.09 more)	-	56 (1 RCT)	⊕◯◯◯ VERY LOW [127]
Change in ABI follow up: 4 months	The mean change in ankle brachial index was -0.01	The mean change in ankle brachial index in the Padma 28 group was 0.01 fewer (0.07 fewer to 0.05 more)	-	56 (1 RCT)	⊕◯◯◯ VERY LOW [127]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__ABI:__ Ankle brachial index; __CI:__ Confidence interval; __MWD:__ Maximum walking distance; __RCT:__ Randomised controlled trial __OR:__ Odds ratio; __WD:__ Walking distance

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

[1] possible publication bias as data of one study unavailable - downgraded by one level
[2] one single study, unable to asses inconsistency - downgraded by one level
[3] high withdrawal rate linked to the outcome that is they were withdrawn because of failing to improve WD or as a result of deterioration in overall condition in Smulski 1995 - downgraded by one level

[4] limited reporting of statistical analyses that compared the PADMA 28 and placebo groups: WD after treatment used rather than change in WD. Since the baseline WDs varied between the studies the use of WDs after treatment could have introduced bias - downgraded by one level

[5] differences between studies in baseline characteristics such as smoking: e.g. baseline smoking rates 90% in Mehlsen 1995 and Smulski 1995 but 50% in Sallon 1998 and Schräder 1985 - downgraded by one level

[6] high withdrawal rate linked to the outcome that is they were withdrawn because of failing to improve WD or as a result of deterioration in overall condition in Sallon 1998 and Smulski 1995 - downgraded by one level

[7] high withdrawal rate linked to the outcome that is they were withdrawn because of failing to improve WD or as a result of deterioration in overall condition in Sallon 1998 - downgraded by one level

BACKGROUND

Description of the condition

Peripheral arterial occlusive disease is a leading cause of morbidity in older people. The prevalence of intermittent claudication varies by age and sex. A review of nine studies found age standardised prevalence rates to be consistently higher amongst men than women (men 0.8% to 2.9% versus women 0.6% to 1.6%) (Meijer 1998). In addition, there was a clear increase in prevalence with age, rising from 1.0% in men aged 55 to 59 years to 6.0% in men aged 85 years and older (0.7% and 2.5% respectively for women). Intermittent claudication (IC) presents as the occurrence of pain, ache, cramps, or a sense of fatigue due to inadequate blood supply to locomotor muscles distal to occlusive lesions of the supplying arteries. The pain tends to start after a person has walked a certain distance. The progression of symptoms soon compels the person to stop (Rose 1962). Intermittent claudication per se rarely represents a life-threatening condition. However, it is associated with reduced survival due to generalised arteriosclerosis resulting in high frequencies of heart disease and stroke (Balkau 1994; Cassar 2006; Kannel 1970). Treatment for improving IC is usually conservative (Coffman 1991; Pittler 2005) and includes the avoidance or treatment of risk factors such as smoking, diabetes, hypertension, hypercholesterolaemia, and the promotion of physical activity (Bendermacher 2009; Gardner 1995; Watson 2008). Additionally, pharmacologic interventions are available to treat this condition and in some cases surgery may be beneficial (de Backer 2012; Fowkes 2008; Salhiyyah 2012).

Description of the intervention

There are many types of drugs used for routine risk factor management in peripheral arterial disease (PAD), including antiplatelet agents and lipid-lowering drugs to prevent cardiovascular events. Additionally, some vasoactive drugs have been used for the treatment of symptoms and to improve walking distances.

The use of dietary supplements (especially herbal remedies) has been increasing for the treatment of IC (Melzer 2006; Pittler 2005). This review focuses on the Tibetan herbal preparation Padma 28, based on an ancient Lamaistic formula, which was introduced into Europe by Badmajeff (Kowalewski 1973). The preparation consists of a mixture of 22 different, mainly herbal ingredients, ranging from aconite, calendula, cardamom, camphor, and hydrated calcium sulphate to valerian components (Smulski 1994). It has been sold for about 20 years as an over-the-counter medicine for the treatment of IC, almost exclusively in Switzerland where it is manufactured (Hurlimann 1992). See Appendix 1 for the full product details.

How the intervention might work

Various mechanisms of the action of Padma 28 have been postulated including lipid-lowering activity (Samochowiec 1987a; Smulski 1994), inhibition of blood lipid oxidisability (Brunner-La Rocca 2005), an increase in fibrinolytic activity (Winther 1994), inhibition of platelet aggregation (Samochowiec 1987a; Smulski 1994), modulation of neutrophil derived free radicals (Matzner 1995), inhibition of lysozyme release from neutrophils (Matzner 1995), a decrease in the oxidative burst response of monocytes (Winther 1994), inhibition of cellular response to growth factors involved in atherosclerosis and restenosis (Navab 2004), and inhibition of inflammatory cytokine production (Barak 2004) and anti-inflammatory mechanisms in the vessel wall (Exner 2006).

Why it is important to do this review

There has been considerable debate on whether Padma 28 produces a clinical benefit beyond the placebo effect. Additionally, the lack of standardisation and the uncertain bioavailability of the mixture have been criticised. Therefore, a review assessing the evidence on the efficacy of Padma 28 for the treatment of IC is warranted.

OBJECTIVES

To determine whether Padma 28 is effective, compared with placebo or other medications, in increasing pain-free and maximum walking distance for patients with intermittent claudication (IC).

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials of Padma 28 compared with placebo or other pharmacological treatments.

Types of participants

We included participants with symptomatic IC (Fontaine stage II) (Fontaine 1954) due to atherosclerotic disease, diagnosed either clinically or by questionnaire, and considered suitable for conservative treatment.

We excluded studies of participants diagnosed as having lower limb atherosclerosis by clinical examination or questionnaire but who were asymptomatic, that is who did not show symptoms.

Types of interventions

We included all types of Padma 28 regimens versus placebo or other pharmacological treatments.

Types of outcome measures

Primary outcomes

1. Pain-free walking distance (PFWD) or the initial claudication distance (ICD), which is the distance walked on a treadmill before the onset of pain.
2. Maximum walking distance (MWD) or total walking distance (TWD) or the absolute claudication distance (ACD), which is the maximum or absolute distance walked on a treadmill.

Secondary outcomes

1. Proportion of patients experiencing adverse events.
2. Ankle brachial index (ABI), calculated by dividing the systolic blood pressure in the ankle by that in the arm.

Search methods for identification of studies

There was no restriction on language or publication status.

Electronic searches

For this update the Cochrane Vascular Trials Search Co-ordinator (TSC) searched the Specialised Register (September 2015). In addition the TSC searched the Cochrane Register of Studies (CRS) http://www.metaxis.com/CRSWeb/Index.asp ((CENTRAL) (2015, Issue 8)). See Appendix 2 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).

The following trial databases were searched by the TSC for details of ongoing and unpublished studies (September 2015) using the term Padma:

- World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/);
- ClinicalTrials.gov (http://clinicaltrials.gov/);
- ISRCTN registry (http://www.controlled-trials.com/)
- Nederlands Trials Register (http://www.trialregister.nl/trialreg/admin/rctsearch.asp).

Searching other resources

For the original review version published in 2013 we contacted one pharmaceutical company producing Padma 28 (Padma AG, Swizerland) for information on both unpublished and ongoing trials. The company was unwilling to release data for this review and referred to a prior meta-analysis using unpublished data by Melzer 2006. We were unable to obtain any additional data from the authors of this meta-analysis.

Data collection and analysis

Selection of studies

All review authors (JM, HM, MS) independently examined the studies identified by the search strategy for eligibility for inclusion in the review.

Data extraction and management

All review authors (JM, HM, MS) independently extracted data using a standard data extraction form designed by Cochrane Vascular. The information extracted included: study design, method of allocation and concealment, degree of blinding, power calculation, exclusion post-randomisation, number of withdrawals and reasons, country where the study was undertaken, setting, participant numbers, age and sex, inclusion and exclusion criteria, interventions, duration of the study, and primary and secondary outcomes as defined in Types of outcome measures.
Disagreements were resolved by discussion.

Assessment of risk of bias in included studies

Two review authors (JM, MS) independently assessed the sources of systematic bias of the included studies according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion.

We examined five key domains as part of the Cochrane 'Risk of bias' tool: selection bias, performance bias. attrition bias, detection bias, and reporting bias. We assessed and classified these domains as either a low risk of bias or a high risk of bias. Where insufficient detail was reported in a study to assess the risk we reported this as 'unclear'. In addition to the five key domains, we reported any other form of potential bias noted in the study.

Measures of treatment effect

We performed statistical analyses according to the statistical guidelines for review authors by Cochrane Vascular. We analysed the data using the Review Manager 5 software distributed by Cochrane.

We summarised the continuous primary outcome measures PFWD and MWD using metres as the main unit for walking distance. If only time to onset of claudication symptoms or walking cessation was provided, we converted it to walking distance in metres by multiplying the speed of the treadmill (metres per second) by the walking time (seconds). We reported both final walking distance data and change in walking distance data between baseline and follow-up where available.

For the continuous data, we extracted the mean and standard deviation (SD) values where available. Investigation determined that two of the studies that stated that their results were median values were in fact reporting mean values (Samochowiec 1987; Smulski 1995). Where standard errors (SE) were reported (Sallon 1998), we calculated the SD using the agreed formula SD = SE x $\sqrt{N}$ (Higgins 2011).

For the dichotomous secondary outcome relating to experiencing adverse effects we reported the odds ratio (OR) and 95% confidence interval (CI). The secondary outcome ABI was measured as a continuous variable. We reported both final values and change in ABI data between baseline and follow-up where available.

Unit of analysis issues

The individual participant was the unit of analysis.

Dealing with missing data

Where data were missing we attempted to contact the original investigator and requested the missing data, however these were not available.

Where outcome variables were not reported we analysed the available data. For missing data related to loss to follow-up we assumed the data to be missing at random.

Since the validity of the study would be affected by whether the characteristics of those participants with missing data were reported and whether any bias was likely to have occurred, we presented information on missing data for each study in the Characteristics of included studies table. We considered the potential impact of missing data when making the final conclusions. In studies where medians and interquartile ranges (IQRs) were presented and and any skewing was deemed minor from the presented outcome data, the median was assumed to be the mean and the SD was imputed according to chapter 7.7.3.5 of the Cochrane *Handbook for Systematic Reviews for Interventions* (Higgins 2011).

Assessment of heterogeneity

We explored clinical heterogeneity in the studies using the previously identified characteristics of the studies and the quality of the included studies. We used the Chi^2 test to test for heterogeneity where data were pooled. A P value of < 0.10 was deemed to indicate heterogeneity.

Assessment of reporting biases

Reporting biases commonly arise when the nature and direction of research findings are unexpected. When contacting the pharmaceutical company, we obtained a meta-analysis for Padma 28 (Melzer 2006) and one unpublished trial was detected in this meta-analysis. The results of most trials in this meta-analysis showed a positive effect on walking distance whereas, according to Melzer 2006's description, the unpublished study showed a non-significant difference between treatments. We did not draw funnel plots according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) because there were not enough trials included in the review to give a meaningful result.

Data synthesis

Where meta-analyses were possible, data were pooled using a fixed-effect model. Where it was not possible to pool the data, we reported the data as presented by the studies.

Subgroup analysis and investigation of heterogeneity

We did not plan to perform subgroup analysis in this review.

Sensitivity analysis

Sensitivity analyses were performed, where possible, using imputed or converted median final values of walking distance and ABI. If in future updates sufficient studies are included, we will perform a sensitivity analysis to assess the impact of methodological quality of the studies by excluding studies with low methodological quality.

Summary of findings

We created a 'Summary of findings' table according to Higgins 2011 and GRADE (Atkins 2004). We used the GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/) to assist in the preparation of the 'Summary of findings' table.

We reported the following outcomes in the 'Summary of findings' table:

- PFWD
- MWD
- adverse events
- ABI

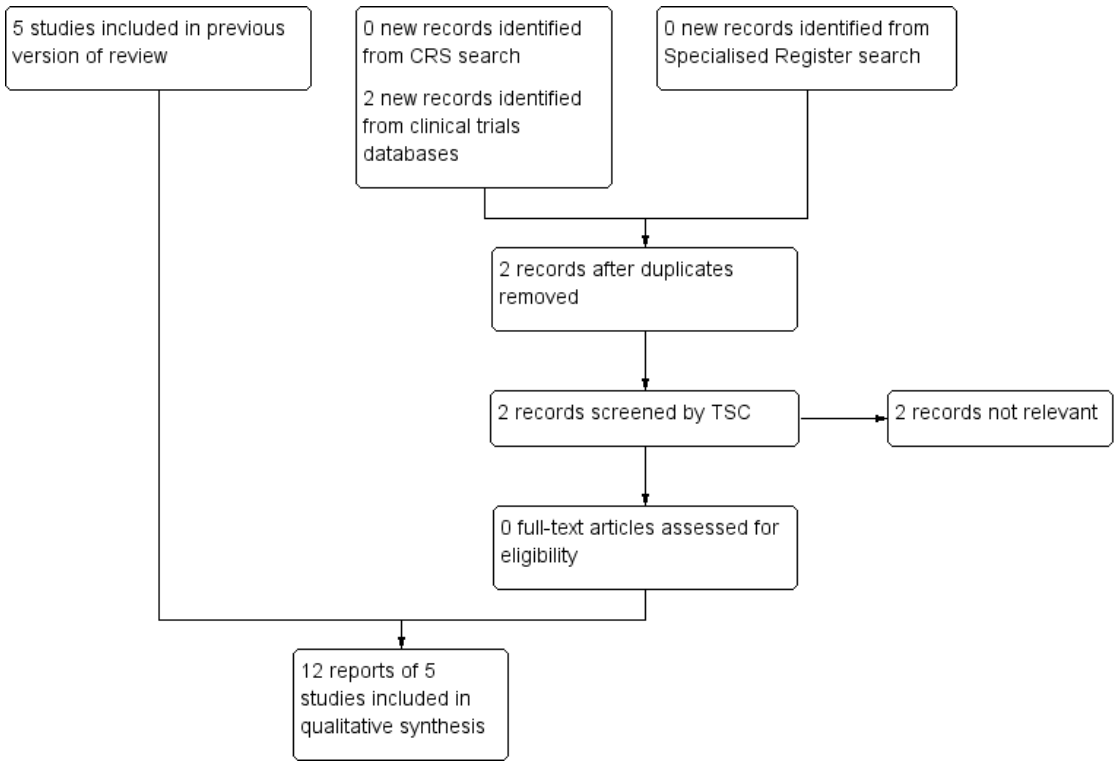
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



No new studies were identified in the search for this review update. The methods described above therefore reflect the work carried out for the original version of this review published in 2013, except for the creation of the 'Summary of findings' table which was newly added to this version of the review.

Included studies

Type of studies

There were 12 reports to five studies included in this review (Mehlsen 1995; Sallon 1998; Samochowiec 1987; Schräder 1985; Smulski 1995). All were reported as randomised controlled, double-blinded studies. The trials were carried out in hospitals in Denmark, Germany, Poland, and Israel.

Type of participants

For the five studies a total of 331 participants were included. Three hundred and sixty-five participants were randomised in the studies with 34 subsequently withdrawing or being lost to follow-up. Data were not available to allow last observation carried forward (LOCF) analysis to be carried out. The numbers in each study were as follows (number completing study/number commencing study): Mehlsen 1995 36/40; Sallon 1998 59/72; Samochowiec 1987 100/100; Schräder 1985 43/53; and Smulski 1995 93/100. The trials were published between 1985 and 1998.

Diagnosis of IC was confirmed in all participants by interview for a typical IC history and objective clinical examination. Clinical examination methods varied between the studies, including: ABI (Mehlsen 1995), objective criteria for peripheral arterial occlusive disease Fontaine stage II (Samochowiec 1987; Schräder 1985), or conventional angiography and Doppler ultrasound (Sallon 1998; Smulski 1995).

The distribution of participants' age (mean or median values 54 to 73 years) and sex (men 53% to 77%) were broadly similar in the

five studies. Whether the participants were smokers was indicated in four trials (Mehlsen 1995; Sallon 1998; Schräder 1985; Smulski 1995) with varied proportions: approximately 50% in Schräder 1985 and Sallon 1998 and approximately 90% in Mehlsen 1995 and Smulski 1995. Co-morbidities, surgical history, medication history, and location of peripheral arterial obstruction were similar amongst all five studies.

The baseline maximum walking distance (MWD) differed between studies (150 m to 300 m) although the pain-free walking distances (PFWD) were comparable. Otherwise, the conditions for inclusion and exclusion were similar.

Type of interventions

All five trials compared Padma 28 with a placebo. There was no comparison of Padma 28 with other medications. The dose of Padma 28 provided to the treatment groups in the trials varied between 340 mg and 403 mg per capsule with a total daily dose of between 1360 mg and 2280 mg. All of the studies had a treatment period of 16 weeks or four months with the exception of Sallon 1998 which lasted six months.

Outcomes

MWD was measured in four trials during a four-month or 16-week period of treatment with follow-up assessments every four weeks (Mehlsen 1995; Samochowiec 1987; Schräder 1985; Smulski 1995). Of these four studies, two also investigated PFWD (Mehlsen 1995; Schräder 1985). For the walking test, the studies used a treadmill with a standard intensity (3 km/hour at 13 º as slope) with the exception of one study (Mehlsen 1995), which used a variable condition (2.5 to 4 km/hour and 8 º to 16 º slope).

All five studies reported on the adverse effects of treatment with Padma 28. Smulski 1995 and Mehlsen 1995 found no adverse effects. Samochowiec 1987 did not report numbers of adverse effects or numbers of participants affected by adverse effects. However, Samochowiec 1987 did report that all side effects were mild in nature, that none required special treatment, and that no participants stopped because of adverse effects. In addition, Samochowiec 1987 stated that there was no significant difference between the treatment groups in reported adverse effects. The number of participants experiencing an adverse effect was reported in Sallon 1998 (numbers of each adverse effect) and Schräder 1985 (total number of any adverse events). Only Sallon 1998 compared the prevalence of adverse effects between the treatment and placebo group.

ABI was investigated by Mehlsen and Sallon (Mehlsen 1995; Sallon 1998). The ABI was obtained at baseline and the end of treatment in both trials and not during follow-up. Schräder 1985 measured blood pressure in the upper arm and ankle at rest and after exercise, both before and after treatment. However, the blood pressure measures were reported as differences in blood pressure at rest and after exercise. Therefore, ABI values could not be extracted.

For full details of the included studies see Characteristics of included studies.

Excluded studies

One trial was excluded from this review. This trial explored the efficacy of Padma 28 for peripheral arterial occlusive disease and was a controlled clinical trial but was not randomised (Hurlimann 1978).

See also Characteristics of excluded studies.

Risk of bias in included studies

All five included trials were reported as randomised, controlled double-blinded trials. Some trials did not report the method of randomisation (Samochowiec 1987) or blinding (Samochowiec 1987; Schräder 1985). Only one trial presented a power calculation (Mehlsen 1995). Intention-to-treat analyses were not performed in the included trials with the exception of Samochowiec 1987 in which all participants completed the study.

Full details of each of the domains in the 'Risk of bias' tool are given below and summarised in Figure 2, Figure 3, and Characteristics of included studies.

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

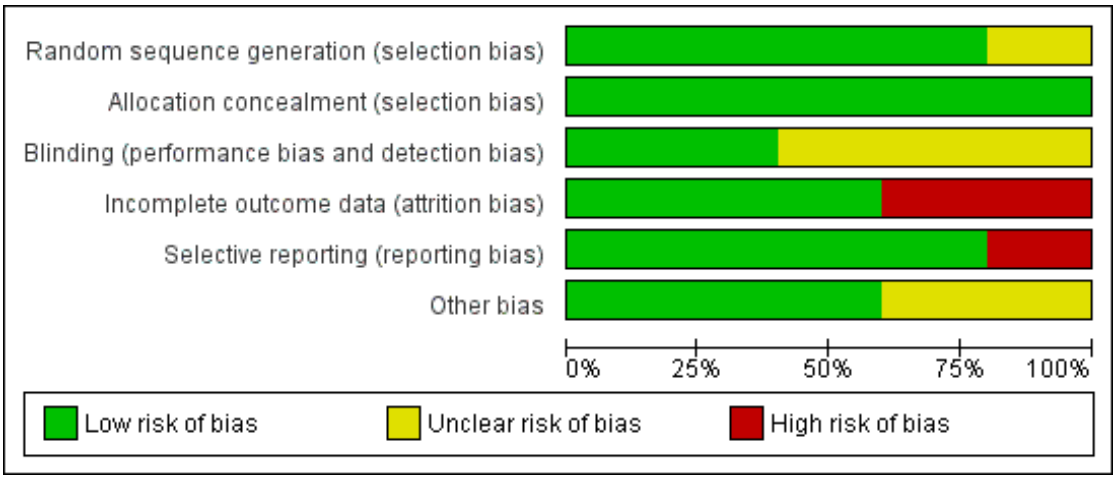
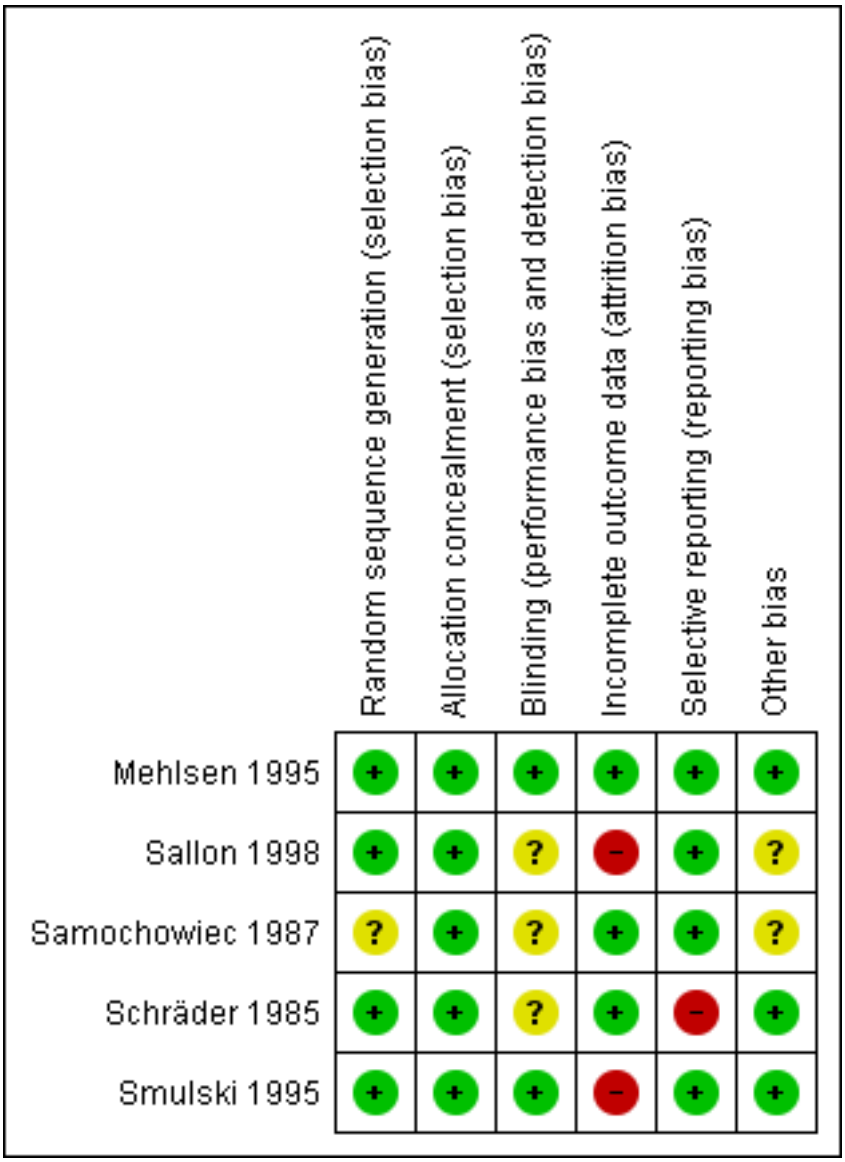


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

For Mehlsen 1995; Sallon 1998; Schräder 1985; Smulski 1995, the allocation sequence was generated by random numbers, permutation list or automated computer lists. Samochowiec 1987 did not report on allocation generation and concealment.

For Mehlsen 1995 and Smulski 1995, in order to conceal the identity of the interventions from both the participants and investigation team, Padma 28 and placebo were identically packaged by the manufacturer, coded, and then handed over to the study teams. Although reported in less detail, Sallon 1998; Samochowiec 1987; and Schräder 1985 appear to have used a similar process of concealment (stating the identical appearance of Padma 28 and placebo and that each had a code on its packaging).

Blinding

Mehlsen 1995 and Smulski 1995 reported that the investigation team, outcome assessors, and participants in the study were blinded while conducting the study. Both Padma 28 and the placebo were identically packaged and coded. The drugs were produced by the manufacturer as capsules that were identical in appearance, taste, and packaging. The randomisation schedule was kept hidden until after the completion of data collection. Sallon 1998 reported that participants and staff were blinded, with no additional details. While both Samochowiec 1987 and Schräder 1985 were reported to be double-blinded trials, the authors did not provide further details of blinding.

Incomplete outcome data

Please see Table 1 for details.

There were no withdrawals from Samochowiec 1987. Mehlsen 1995 reported that four participants, two in the treatment group and two in the placebo group, were excluded within the first month because of insufficient time to attend the study or due to non-attendance. These exclusions were not related to clinical factors. Sallon 1998; Schräder 1985; and Smulski 1995 provided detailed explanations of the withdrawals from their studies. Numbers of withdrawals were equal between the treatments groups for Sallon 1998 and Schräder 1985 but a larger number of withdrawals was shown by Smulski 1995 in the placebo group. Generally, the time points of withdrawals in Sallon 1998; Schräder 1985; and Smulski 1995 were described as before the end of the study period.

In total, one patient in the Padma group (Sallon 1998) and four participants in the placebo groups (three from Sallon 1998 and one from Schräder 1985) withdrew because of no improvement in walking distance. An additional nine participants from the placebo groups (three from Sallon 1998 and six from Smulski 1995) withdrew because of a deterioration in walking distance. These withdrawals were directly related to the walking distance outcomes and make the Sallon 1998 and Smulski 1995 trials at high risk of attrition bias.

Selective reporting

Mehlsen 1995; Sallon 1998; Samochowiec 1987; and Smulski 1995 reported all of the intended outcomes. The main pre-specified outcomes measured on the treadmill, PFWD and MWD, were reported for Schräder 1985 but one additional outcome based on subjective evaluation of effectiveness by both the physician and the participants was not described.

Other potential sources of bias

The Mehlsen 1995 and Schräder 1985 studies stated that the baseline characteristics of participants were not different between the Padma 28 and placebo groups. Smulski 1995 reported that the distribution of patient characteristics was statistically random among the control groups at the time of randomisation. Samochowiec 1987 listed some baseline characteristics but did not report on the differences of the baseline characteristics between the Padma 28 and placebo groups. Sallon 1998 reported that the baseline characteristics of participants were not significantly different. However, confusing reports of the numbers and characteristics of evaluated participants were found. Of a total of 72 participants at baseline the numbers of withdrawals were 13, six from Padma 28 and seven from the placebo group. Thus the evaluated participants were 31 in the treatment group and 28 in the placebo group. ABI was tested on 25 participants, not 28, in the placebo group without any reason being given. Moreover, the measurement requiring exercise on the treadmill (not an outcome in this review) was completed in only 47 participants, 25 in the treatment group and 22 in the placebo group, without reasons being provided.

The review authors are aware of one unpublished study (Sommoggy 1990), as reported in a systematic review by Melzer 2006. Contact with the pharmaceutical company and the authors of the systematic review proved unsuccessful in obtaining the required data. Melzer 2006 reported that this unpublished study provided the only data reported as not supporting a significant effect of Padma 28 compared with placebo. This can be seen as a form of publication bias.

Effects of interventions

See: **Summary of findings for the main comparison** Padma 28 versus placebo

All five included trials compared Padma 28 with a placebo. There was no comparison of Padma 28 with other medications.

Change in walking distance (WD) (PFWD and MWD) was the preferred outcome for this review, especially in light of the dif-

ferences in MWD between treatment groups at the start of the trials. However, limited data were presented on change in mean values, preventing a meta-analysis of the difference in change between the two treatment groups. Therefore, descriptive details of the changes within each study group as well as the mean WD or median WD data after treatment are presented below and in the additional tables.

Details of the available data for each of the included studies are presented by outcome below and in the additional tables.

Padma versus placebo

Pain-free walking distance (PFWD)

PFWD was reported in two studies (Mehlsen 1995; Schräder 1985). Both studies reported PFWD in medians, with Mehlsen 1995 reporting median baseline and follow-up PFWD with interquartile ranges (IQRs) and Schräder 1985 reporting change in median PFWD data as well as baseline and final value PFWD data. It should be noted that the two studies used different intensities of walking tests. See Characteristics of included studies for details.

In Mehlsen 1995 the median PFWD increased from 52 m (IQR 20 to 106) to 86 m (IQR 24 to 164) after four months of treatment in the Padma 28 group (P < 0.01), and from 70 m (IQR 29 to 140) to 71 m (IQR 29 to 120) in the placebo group (P = not significant (NS)). The authors did not report on the change in median PFWD between the placebo and Padma 28 groups but changes in median PFWD were calculated by the review authors to be 34 m (Padma 28) versus 1 m (placebo). Converting median final PFWD values into mean PFWD values and calculating SDs allowed a comparison between the Padma 28 and placebo groups, showing a statistically non-significant mean difference (MD) in PFWD of 15.00 m (95% CI -42.15 to 72.15, P = 0.61) (Analysis 2.1)

Schräder 1985 found that after 16 weeks of treatment, PFWD increased by 66 m in the Padma 28 group (P = 0.002) compared with 30 m in the placebo group (P = 0.01). This difference in change in PFWD between the treatment groups was not statistically significant (P = 0.06). While data on WD at the start and end of the trial were provided, no information on the variability was provided thereby making it not possible for the review authors to pool the final value PFWD data with the Mehlsen 1995 study. In addition, due to the limited data the review authors deemed it inappropriate to impute SDs for changes in PFWD data and to pool the data.

For additional details see Table 2.

Maximum walking distance (MWD)

MWD was evaluated in four trials (Mehlsen 1995; Samochowiec 1987; Schräder 1985; Smulski 1995). The final point of treatment was 16 weeks (four months) in all trials and the intensities of the walking tests were similar with the exception of Mehlsen 1995, as described in Included studies.

Samochowiec 1987 and Smulski 1995 presented the outcome as a median but, as described in Measures of treatment effect, on further investigation it was determined that their results were in fact mean values. Samochowiec 1987 found a statistically significant change in MWD in the Padma 28 group with an improvement of 76 m (from 80.6 m to 156.2 m, P < 0.001). The placebo group did not show a statistically significant change in mean MWD (68.1 m to 66.6 m, P > 0.1). The authors did not report on the difference between the Padma 28 and placebo groups but this could be calculated from the available data, showing a statistically significant increase in MWD of 77.10 m (95% CI 53.41 to 100.79, P < 0.00001, low quality evidence) (Analysis 1.1). In Smulski 1995, the MWD was shown to have risen significantly by 100 m in the Padma 28 group (87.5 m to 187.7 m, P < 0.001) and by 13 m in the placebo group (from 75.0 to 87.5 m, P = NS). Smulski 1995 did not report the SDs for change in mean MWD. The authors did not report on the difference between the Padma 28 and placebo groups. Due to missing SDs for the mean MWD in Smulski 1995, the change in MWD data could not be pooled with the Samochowiec 1987 data. The review authors deemed it was inappropriate to impute the SDs with the limited number of studies included in this review.

The MWD data after treatment from Samochowiec 1987 and Smulski 1995 were pooled showing a statistically significant difference in final MWD values between the Padma 28 and placebo groups (MD 95.97 m, 95% CI 79.07 to 112.88, P < 0.00001, very low quality evidence) (Analysis 1.2). There was no evidence of heterogeneity (Chi^2 test P = 0.055).

Mehlsen 1995 and Schräder 1985 used medians to report the outcome measure and the results were not pooled with Samochowiec 1987 and Smulski 1995. Mehlsen 1995 detected a significant increase in median MWD of 112 m in the Padma 28 group (115 to 227 m, P < 0.001) and an increase of 7 m in the placebo group (125 to 132 m, P = NS). This study also noted differences in effect size within the Padma 28 group with 7/18 participants at least doubling their MWD. Three participants in the Padma 28 group reached > 500 m WD and were no longer restricted by IC in their daily life. In comparison, only one of 18 participants in the placebo group attained a doubling of WD distance and none of the placebo group achieved a WD of > 500 m. The authors did not report the difference between the Padma 28 and placebo groups. Schräder 1985 reported an increase in the median value of MWD by 124 m in the Padma 28 group (P < 0.01) and 27 m (P = NS) in the placebo group. The authors reported that the increase in MWD was significantly different between the Padma 28 and placebo groups (P = 0.03).

The median MWD data after treatment from Mehlsen 1995 were deemed too skewed to pool with the final MWD data analysis of Samochowiec 1987 and Smulski 1995. Due to a lack of studies the review authors deemed the imputation of SDs for Mehlsen 1995;

Schräder 1985; and Smulski 1995 inappropriate and therefore a sensitivity analysis of pooled change in MWD data with imputed data was not performed.
For additional details see Table 3.

Adverse effects of therapy

In the four trials that reported data on side effects (Mehlsen 1995; Sallon 1998; Schräder 1985; Smulski 1995), 24 out of 231 (10%) participants reported at least one adverse effect. Adverse effects from Padma 28 were found in two studies (Sallon 1998; Schräder 1985), with Mehlsen 1995 and Smulski 1995 reporting that there were no adverse effects. The main adverse effects reported were gastrointestinal discomfort, tiredness, and skin eruptions. Pooling the adverse effects data showed there was no statistically significant difference in adverse effects between the Padma 28 and placebo groups (odds ratio (OR) 1.09, 95% CI 0.42 to 2.83, P = 0.86, very low quality evidence) (Analysis 1.3). There was no evidence of heterogeneity (Chi^2 test P = 0.44). Samochowiec 1987 did not report numbers of adverse effects or numbers of participants affected by adverse effects. However, Samochowiec 1987 did report that all side effects were mild in nature and that none required special treatment. In addition, Samochowiec 1987 reported that there was no significant difference between the treatment groups and that no participants stopped treatment because of adverse effects.
See also Table 4.
Of the 34 withdrawals from the five studies, five where technical exclusions such as poor compliance (two) and insufficient time to participate (three); the remainder were patient withdrawals. There were 13/184 (7%) withdrawals from the Padma 28 groups and 21/181 (12%) withdrawals from the placebo groups. From the Padma 28 groups, 8/13 withdrawals were due to clinical concerns: two cardiac problems, three gastrointestinal discomfort, one back pain, one toe amputation, and one bladder carcinoma. In addition, the Padma 28 groups recorded a single death due to myocardial infarction in a participant with a complex cardiovascular history. From the placebo groups, 6/21 withdrawals were due to clinical concerns: two cardiac problems, one stroke, one lumbago, one dyspnoea (shortness of breath), and one gastrointestinal discomfort. In total, one patient in the Padma groups and four participants in the placebo groups withdrew because of no improvement in walking distance, and nine participants from the placebo groups withdrew because of a deterioration in walking distance.
For additional details see Table 1.

Ankle brachial index (ABI)

ABI was extracted from two studies (Mehlsen 1995; Sallon 1998). Mehlsen 1995 reported the median value of ABI after four months with a reduction of 0.03 in the Padma 28 group (0.62 to 0.59) and an increase of 0.02 in the placebo group (0.59 to 0.61), with no differences between baseline and follow-up for the two groups. Mehlsen 1995 did not compare the two groups with each other. Sallon 1998 reported both final ABI values and the change in ABI values for both treatment groups. Sallon 1998 reported no significant change in ABI after six months of treatment for both treatment groups. Sallon 1998 did not analyse the difference between the Padma 28 and placebo groups but the data presented for the final ABI values indicated no significant difference between the two treatment groups for ABI values after treatment (MD -0.01, 95% CI -0.11 to 0.09, P = 0.84, very low quality evidence) (Analysis 1.4) and change in ABI values between baseline and at six months (MD -0.01, 95% CI -0.07 to 0.05, P = 0.72, very low quality evidence) (Analysis 1.5).
A sensitivity analysis was performed in order to combine the ABI data of the Mehlsen 1995 and Sallon 1998 studies. The median ABI data after treatment from Mehlsen 1995 were assumed to be the mean ABI data after treatment and SDs were calculated and pooled, showing no difference in ABI after treatment between the Padma 28 and placebo groups (MD -0.01, 95% CI -0.10 to 0.08, P = 0.79) (Analysis 2.2). Due to the lack of studies presenting change in ABI data, the review authors deemed it inappropriate to impute change in ABI data for the Mehlsen 1995 study.
For additional details see Table 5.

DISCUSSION

Summary of main results

Some evidence exists from individual trials to suggest that patients with intermittent claudication (IC) may benefit from daily Padma 28 in terms of moderate, short term (four month) improvements in walking distances (WDs). Neither Padma 28 nor placebo had any statistically significant effect on ankle brachial index (ABI). Side effects do not appear to be a problem. However, the longer term effects of treatment are unknown and the clinical significance of the improvements in WD are questionable. Moreover, the quality of the evidence is limited by the small sample size of the available trials, lack of detail on key elements required to assess other sources of bias for example around randomisation and blinding, limited reporting of statistical analyses that compared treatment groups, and relatively high withdrawal rates that were linked to outcome. That is, withdrawn if failed to improve walking distance. There was also some evidence of publication bias.

Overall completeness and applicability of evidence

All of the included trials were applicable to the general older population with IC. The participants of all studies were middle aged

or older people (range 35 to 81 years) and were diagnosed by clinical examination or questionnaire and the WDs were tested on standardised equipment such as treadmills.

The clinical significance of the change in WDs is questionable. Typically, the change in median PFWD reflected a doubling in median PFWD, ranging from 1 m to 66 m between the included studies. For change in mean or median MWD, the change in MWD ranged from -1.4 m to 124 m between the included studies.

Quality of the evidence

Overall, the included studies were of limited methodological quality. Two studies (Samochowiec 1987; Schräder 1985) did not report details on participant or study personnel blinding, which could be considered a methodological limitation. Schräder 1985 also did not report on all predefined outcomes for their study, which was therefore considered to be at high risk of selective reporting bias.

Differences between the included studies in baseline participant characteristics such as smoking status of participants (e.g. baseline smoking rates 90% in Mehlsen 1995 and Smulski 1995 but 50% in Sallon 1998 and Schräder 1985) may have had an impact on the outcomes studied.

The included trials were all small and the different reporting styles prevented pooling studies to produce a stronger result. In general, there was limited reporting of statistical analyses that compared the treatment groups. This resulted, in some cases, in the review authors using WDs after treatment rather than changes in WD. Since the baseline WDs varied between the studies the use of WDs after treatment could have introduced bias.

There was a high rate of withdrawals linked to the outcome. That is they were withdrawn because of failing to improve WD or as a result of deterioration in overall condition (Sallon 1998; Smulski 1995), introducing attrition bias.

The quality of the evidence in this review is also limited by the review authors being unable to acquire additional information and data to allow more formal meta-analyses of the primary or secondary outcomes. A meta-analysis undertaken by Melzer 2006 included data from an unpublished study which we were unable to gain access to. This omission has the potential to alter the conclusions of the review (see Agreements and disagreements with other studies or reviews below) and it may reflect previous negative publication bias.

Overall the quality of the evidence according to the GRADE principles is very low, see Summary of findings for the main comparison.

Potential biases in the review process

This review was conducted by following the review question and predefined protocol. Data analysis was undertaken using both narrative and statistical pooling methods in accordance with the available data.

In some cases the review authors assumed that reported median WDs were mean WDs and calculated the corresponding SDs in order to pool the data with other studies. Such assumptions can introduce bias especially when very few studies are available. For this reason, these analyses were presented as sensitivity analyses. For this reason also, the review authors deemed it inappropriate to impute SDs of the change in WD data in order to pool the available change in WD data.

Agreements and disagreements with other studies or reviews

The meta-analysis conducted by Melzer 2006 evaluated evidence on the efficacy and safety of Padma 28 in treating peripheral arterial occlusive disease, Fontaine stage II. The meta-analysis was conducted according to a pre-specified protocol, which the authors reported was guided by Cochrane methodology. Their analysis identified seven trials for investigating WD and then combined five of them. Five of the trials were the same studies as in this Cochrane review. However, Sallon 1998 and Smulski 1995 were excluded from the meta-analysis by Melzer 2006 due to not having MWD data and because of concerns over differences in the baseline characteristics of the two treatment groups, respectively. The additional studies included by Melzer 2006 were an unpublished controlled trial (Sommoggy 1990) and a historical re-analysed non-randomised study (Samochowiec 1987b). Melzer 2006 was able to access original data for nearly all of the studies, allowing a meta-analysis to be undertaken. The results of Sommoggy 1990 were the only data reported as not supporting a significant effect of Padma 28 compared with placebo. Overall, the result of the meta-analysis by Melzer 2006 was consistent with our own, with reporting of a significant difference in change in MWD between the two treatment groups (MWD 63.5 m, 95% CI 27.1 to 99.9 m, $P < 0.001$). However, the clinical significance of this degree of improvement can be questioned.

AUTHORS' CONCLUSIONS

Implications for practice

Some evidence exists from individual trials to suggest that patients with intermittent claudication (IC) may benefit from daily Padma 28 in terms of moderate, short term (four month) improvements in walking distances. Side effects do not appear to be a problem. However, the longer term effects of treatment are unknown and the clinical significance of the improvements in walking distance are questionable. Moreover, the quality of the evidence is very low, limited by the small sample size and difference in baseline

characteristics such as smoking of the available trials, lack of detail on key elements required to assess other sources of bias for example around randomisation and blinding, limited reporting of statistical analyses used to compare treatment groups, and relatively high withdrawal rates that were linked to outcome, that is withdrawn if failed to improve walking distance. There was also evidence of publication bias. We therefore feel there is currently insufficient evidence to draw conclusions regards the effectiveness of Padma 28 in the routine management of intermittent claudication.

Implications for research

Further research into Padma 28 as a treatment for IC would be beneficial in order to formulate a definitive answer. Large methodologically sound trials need to be conducted. The main outcomes of walking distance, ABI, and quality of life are needed for adequate evaluation in order to identify clinically relevant changes. Further trials in which patients are followed up over a long term period are also needed. In addition, any future studies should ensure the outcomes reported include the assessment of change between the treatment groups studied.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Mehlsen 1995

Methods	Study design: Randomised, double-blind, placebo-controlled trial Method of randomisation: Random numbers Concealment of allocation: Coding by manufacturer Blinding: Patient and investigation team Power calculation: Observed SD 47 m; change of parameter 55 m; ß (type II error) 90% Number of participants randomised: 40 Number of participants analysed: 36 Number of exclusions post randomisation: 4 within the first four weeks from the study Timing of study: Not stated
Participants	Country: Denmark Setting: Hospital Number of centres: 1 Number of participants: Padma 28 20; Placebo 20 Median age (IQR): Padma 28 67 yrs (48 - 81 yrs); Placebo 66 yrs (44 - 77 yrs) Sex: 19 male/17 female (Padma 28 9/9; Placebo 10/8) Smoking: Padma 28 15/18; Placebo 17/18 Inclusion criteria: The clinical diagnosis of IC verified by typical IC history confirmed by interview, clinical present for more than six months, MWD between 50 and 300 m and ABI lower than 0.85 Exclusion criteria: Participants with symptoms of chronic lung disease, diabetes mellitus, osteoarthrosis in the lower extremities, or other diseases limiting the walking distance
Interventions	Treatment: Padma 28 (340 mg) two capsules twice a day Control: Placebo Duration: 4 months (F/U 4, 8, 12 and 16 weeks)
Outcomes	1. Bilateral systolic blood pressure at the ankle and first toe 2. Systolic blood pressure on both upper limbs 3. Walking distance: PFWD and MWD 4. ABI
Notes	No intention-to-treat analyses due to dropout in the very early stage of the study Patient not permitted to change medication or life-style during the study period Circumstance of measurement at baseline: treadmill with an elevation 8º to 16º and 2. 5 to 4.0 km/h speed Adverse effects investigated, none reported Reporting of significance level: authors report results are not significant but do not provide definition

Risk of bias

Bias	Authors' judgement	Support for judgement

Mehlsen 1995 (*Continued*)

Random sequence generation (selection bias)	Low risk	Reports: The participants were assigned on the basis of random numbers
Allocation concealment (selection bias)	Low risk	Reports: Medication coding was undertaken by the manufacturer; placebo and Padma 28 were identically packaged; the investigation team were unaware of the coding system
Blinding (performance bias and detection bias) All outcomes	Low risk	Reports: Double-blind methodology; the results were entered prior to decoding; measurements were undertaken by two nurses who were unaware of the randomisation process
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reports: 2/20 missing from intervention group; 2/20 missing from control group. Full details of attrition provided: 3/4 missing participants did not have sufficient time to participate in the study; 1/4 did not attend on the specified date
Selective reporting (reporting bias)	Low risk	Reports: All expected outcomes reported
Other bias	Low risk	Reports: The Padma 28 and placebo groups did not differ by age, sex, smoking, surgical history and duration of illness

Sallon 1998

Methods	Study design: Randomised, double-blind, placebo-controlled trial Method of randomisation: Computer generated Concealment of allocation: Not stated Blinding: Participants and investigators Power calculation: Not stated Number of participants randomised: 72 Number of participants analysed: 59 Number of withdrawals: 13 (6 in intervention group and 7 in placebo group) Timing of study: June 1993 - July 1995
Participants	Country: Israel Setting: Hospital Number of centres: 1 Number of participants: Padma 28 37; placebo 35 Mean age (± SE): Padma 28 72.4 ± 1.6 yrs; placebo 73 ± 1.6 yrs Sex: 42 male/30 female (Padma 28 19/18; Placebo 23/12) Smoking: Padma 28 59.5% (22/37); Placebo 45.7% (16/35) Inclusion criteria: Abnormal wave-form recordings using bidirectional Doppler; a pre-

Sallon 1998 (*Continued*)

	exercise ankle-arm pressure ratio of ≤ 0.85; a post-exercise drop in the ankle-arm pressure ratio $\geq$ 15% compared with the pre exercise ratio; a depressed systolic ankle pressure during 3 minutes post-exercise Exclusion criteria: Lower extremity rest pain; ulceration or need for revascularization; previous peripheral arterial surgery; use of anticoagulant warfarin; active peptic ulcer disease; serious liver or renal disease; mental disease; a significant or serious cardiac condition; carcinoma and other life-threatening condition
Interventions	Treatment: Padma 28 (403 mg) two capsules twice a day Control: Placebo (potato starch) two capsules twice a day Duration: 6 months
Outcomes	1. Resting ABI 2. Pressure drop 3. Pressure recovery time 4. Ischaemic window
Notes	No intention-to-treat analysis or power calculation Participants continued all usual medications except those affecting blood flow and peripheral blood vessels Walking distance measurement method: 2 km/h at a 10º upward incline Adverse events investigated: experienced by 8 participants. The numbers of each adverse event were reported Padma 28 supplier: Padma AG, Zollikon, Switzerland Reporting of significance level: authors report results are not significant but do not provide definition

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reports: "Randomisation lists were generated by an automatic computerized procedure developed to produce two balanced groups by the capsule manufacturer at the factory"
Allocation concealment (selection bias)	Low risk	Reports: "Randomisation was to either Padma 28 or an identical-looking placebo", "patients and staff were blinded as to treatment assignment"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reports: "Patients and staff were blinded as to treatment assignment". There was no information to determine whether the blinding was maintained during study

Sallon 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Reports: Comprehensive attrition data reported; 6/37 missing from intervention group; 7/35 from placebo group. Since six out of the seven withdrawals from the placebo group are outcome-related (no improvement or deterioration in condition) attrition bias has been coded as high risk
Selective reporting (reporting bias)	Low risk	Reports: All expected outcomes reported
Other bias	Unclear risk	Confusing reports of the numbers and characteristics of evaluated participants were found. Of 72 total participants at baseline, the numbers of withdrawals were six from Padma 28 and seven from the placebo group. Thus the evaluated participants were 31 in the Padma 28 group and 28 in the placebo group. ABI was tested on 25 participants, not 28, in the placebo group without a reason being given. Moreover, the measurement requiring exercise on the treadmill (not an outcome in this review) was completed in only 47 participants, 25 in the Padma 28 group and 22 in the placebo group Authors report there were no differences between patient characteristics at time of randomisation

Samochowiec 1987

Methods	Study design: Randomised, double-blind, placebo-controlled trial Method of randomisation: Not stated Concealment of allocation: Not stated Blinding: Not stated Power calculation: Not stated Number of participants randomised: 100 Number of participants analysed: 100 Number of withdrawals: None Timing of study: Not stated
Participants	Country: Poland Setting: Medical centre Number of participants: Padma 28 55; Placebo 45 Mea age (range): Padma 28 57.5 yrs (41 - 69 yrs); Placebo 57 yrs (45 - 65 yrs) Sex: 67 males / 33 females (Padma 28 40/15; Placebo 27/18) Smoking: Not reported Inclusion criteria: Diagnosis of arterial occlusive disease of Fontaine II based on clinical

Samochowiec 1987 (*Continued*)

	criteria; MWD < 150 m; minimum duration of IC of 8 months Exclusion criteria: Stage other than Fontaine II; concomitant disease including - venous disorders, anaemia, significant ill-health (e.g. myocardial infarction) within 8 months, uncontrolled hypertension, kidney or liver insufficiency
Interventions	Treatment: Padma 28 (380 mg) two capsules twice a day Control: Placebo (Lactose 400 mg) two capsules twice a day Duration: 16 weeks (F/U 4,8,12,16 weeks)
Outcomes	1. Blood pressure 2. MWD 3. Serum/plasma testing (biochemistry,electrolytes, liver enzymes, blood cell count)
Notes	Additional study criteria: there was a preliminary period of 2 weeks Participants were requested to stop vasoactive medication Walking distance measurement method: 100 m with 3.2 km/h speed and upward gradient from 13º Adverse event investigation: no formal assessment of adverse effects, reports that mild side effects did not require treatment Additional patient information: location of the vascular obstruction Padma 28: 15 iliac, 35 femorodistal, 5 iliofemoral; Placebo: 12 iliac, 30 femorodistal, 3 iliofemoral Reporting of significance level: authors did not specifically report on significance levels but report P values for their comparisons

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reports: randomised methodology however the sequence generation process was not stated
Allocation concealment (selection bias)	Low risk	Reports: "The patients in the study got the medicine appropriately to their code number", "The medications were made by manufacturer, which were not outwardly different between Padma 28 and placebo"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reports: There were no data missing
Selective reporting (reporting bias)	Low risk	Reports: All expected outcomes reported

Samochowiec 1987 (*Continued*)

Other bias	Unclear risk	The characteristics of evaluated participants between both groups were not described

Schräder 1985

Methods	Study design: Randomised, double-blind, placebo-controlled trial Method of randomisation: Random numbers Concealment of allocation: Not stated Blinding: Not stated Power calculation: Not stated Number of participants randomised: 53 Number of participants analysed: 43 Number of withdrawals: 10 Timing of study: Not stated
Participants	Country: Germany Setting: Not stated Number of participants: Padma 28 27; placebo 26 Mean age: Padma 28 68.6 yrs; placebo 69.3 yrs Sex: 41 male/12 female (Padma 28 21/6; placebo 20/6) Smoking: Padma 28 11/29; placebo 12/24 Inclusion criteria: Diagnosis of PAOD in Fontaine II based on clinical criteria and non invasive examination, MWD < 250 m, duration of illness of at least 8 months, older than 50 years, good compliance Exclusion criteria: Concomitant vasoactive therapy, concomitant serious diseases such as myocardial infarct within the last 8 months, cardiac insufficiency, disease limiting walking distance other than IC, not steady state of PAOD Criteria for formal withdrawal from trial: intolerance of treatment; deterioration of the PAOD (Fontaine stage III or IV); intercurrent significant ill health; change in concomitant medication; change in lifestyle; lack of compliance
Interventions	Treatment: Padma 28 (380 mg) two capsules three times a day Control: Placebo (Lactose 400 mg) two capsules three times a day Duration: 16 weeks
Outcomes	1. Ankle and upper arm blood pressure at rest and after exercise 2. PFWD and MWD 3. Subjective assessment for judging effectiveness of each intervention 4. Compliance and adverse effects
Notes	Additional study criteria: there was a preliminary period of 2 weeks No intention-to-treat analyses Participants were requested to stop vasoactive medications but were able to continue all other usual medications Walking distances measurement method: treadmill set at 100 m with 13° upward gradient and 3 km/h speed Adverse effect reporting: 16 participants experienced adverse effect. The symptoms were

Schräder 1985 (*Continued*)

	reported but the numbers who experienced each symptom were not reported Reporting of significance level: Statistical significance level was reported as P < 0.05

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reports: "The patients were distributed randomly in the two groups" The PVD group contacted the author in 1995 who advised that the methodology was "random numbers"
Allocation concealment (selection bias)	Low risk	Reports: "The medication was coded on packing" Detailed information on the process of allocation concealment was not described, however "coding" is likely to be sufficient
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reports: Full details of attrition were reported; 4/27 missing from Padma 28 group; 6/26 missing from placebo group
Selective reporting (reporting bias)	High risk	Reports: The study included all stated outcomes except subjective effectiveness. PFWD, MWD and ankle arterial BP were given as change scores
Other bias	Low risk	The participants in the two groups were considered statistically identical

Smulski 1995

Methods	Study design: Randomised, double-blind, placebo-controlled trial Method of randomisation: The Rumke and de Jong permutation list Concealment of allocation: Encoded sealed packages Blinding: Participants and examining/treating physician Power calculation: Not stated Number of participants randomised: 100 Number of participants analysed: 93 Number of withdrawals: 7 Timing of study: May 1984 - June 1989

Smulski 1995 (*Continued*)

Participants	Country: Poland Setting: Hospital Number of participants: Padma 28 50; Placebo 50 Mean age: Padma 28 58 yrs; Placebo 54 yrs Sex: 60 males/40 females (Padma 28 30/20; Placebo 30/20) Smoking: Padma 28 47/50; Placebo 46/50 Inclusion criteria: Written agreement by the patient to participate in the study; Fontaine II; positive history of typical IC with walking distance until onset of calf pain; missing or deficient pulse on back of foot; MWD < 250 m; minimum 6 month duration of IC; good compliance and availability for follow-up Exclusion criteria: PAOD other than Fontaine II concomitant severe diseases or disease impeding walking ability; deficient steady state of PAOD II Criteria for formal withdrawal from trial: Intercurrent severe illness; changes in lifestyle; changes in medication therapy for concomitant disease; intolerance to administered medication; poor compliance; failure to attend follow-up studies
Interventions	Treatment: Padma 28 (380 mg) two capsules twice a day Control: Placebo (Lactose 400 mg) two capsules twice a day Duration: 16 weeks (F/U: 4, 8, 12 weeks)
Outcomes	Primary outcome: MWD with clinical relevance Secondary outcomes: 1. Patient's subjective evaluation 2. Upper arm BP 3. Serum lipids (total lipid, cholesterol, triglycerides, LDL) and platelet aggregation
Notes	No intention-to-treat analysis Participants received conventional angiography or Doppler ultrasound tonometry to verify the clinical diagnosis Participants were requested to stop vasoactive medications (washout period 2 weeks) but were able to continue all other usual medications Walking distances measurement method: treadmill set at 13º incline and a speed of 3.2 km/h Adverse event reporting: Adverse events were investigated and none occurred Additional patient information: location of the vascular obstruction - 70% femorodistal, 20% iliofemoral, 10% iliac Manufacturer: Padma AG, Zurich Reporting of significance level: "The significance limits for all tests were determined at the 5% level (two-sided test)"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reports: "The randomisation schedule was compiled by the study coordinator in accordance with the Rumke and de Jong permutation list"

Smulski 1995 (*Continued*)

Allocation concealment (selection bias)	Low risk	Report: "He (2nd author) encoded sealed packages and handed them to the examining and treating physician."
Blinding (performance bias and detection bias) All outcomes	Low risk	Reports: "The randomisation schedule was kept confidential until the collection of data was complete.", "He did not disclose randomisation schedule, particularly not to patients nor to the examining and treating physician."
Incomplete outcome data (attrition bias) All outcomes	High risk	Report: Full attrition data reported; 1/50 missing from Padma 28 group due to newly diagnosed bladder carcinoma; 6/50 missing from placebo group (all due to deterioration in their overall condition). As all withdrawals in placebo group were treatment related, attrition bias classed as high risk
Selective reporting (reporting bias)	Low risk	Reports: All expected outcomes reported
Other bias	Low risk	Authors report the distribution of patient characteristics was statistically random among the control groups at time of randomisation

ABI: ankle brachial index
BP: blood pressure
F/U: follow-up
IC: intermittent claudication
IQR: interquartile range
LDL: low density lipoprotein
m: metres
mg: milligram
MWD: maximum walking distance
PAOD: peripheral arterial occlusive disease
PFWD: pain-free walking distance
SD: standard deviation
SE: standard error
yrs: years

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

Study	Reason for exclusion
Hurlimann 1978	Controlled clinical trial

DATA AND ANALYSES

Comparison 1. Padma 28 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in MWD	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Final value MWD	2	193	Mean Difference (IV, Fixed, 95% CI)	95.97 [79.07, 112.88]
3 Adverse effects	4	231	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.42, 2.83]
4 Final value ankle brachial index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Change in ankle brachial index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Padma 28 versus placebo sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free walking distance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Imputed final value data	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Ankle brachial index	2	92	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.10, 0.08]
2.1 Final value data	1	56	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.11, 0.09]
2.2 Imputed final value data	1	36	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.21, 0.17]

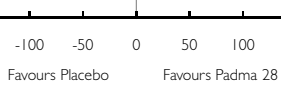
Analysis 1.1. Comparison 1 Padma 28 versus placebo, Outcome 1 Change in MWD.

Review: Padma 28 for intermittent claudication

Comparison: 1 Padma 28 versus placebo

Outcome: 1 Change in MWD

Study or subgroup	Padma 28 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Samochowiec 1987	55	75.7 (89.3)	45	-1.4 (7)		77.10 [53.41, 100.79]



Analysis 1.2. Comparison 1 Padma 28 versus placebo, Outcome 2 Final value MWD.

Review: Padma 28 for intermittent claudication

Comparison: 1 Padma 28 versus placebo

Outcome: 2 Final value MWD

Study or subgroup	Padma 28 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Samochowiec 1987	55	156.2 (93.1)	45	66.6 (36.1)		39.9 %	89.60 [62.83, 116.37]
Smulski 1995	49	187.7 (69.6)	44	87.5 (33.1)		60.1 %	100.20 [78.40, 122.00]
Total (95% CI)	**104**		**89**			**100.0 %**	**95.97 [79.07, 112.88]**

Heterogeneity: $Chi^2 = 0.36$, df = 1 (P = 0.55); I^2 =0.0%

Test for overall effect: Z = 11.13 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Padma 28 versus placebo, Outcome 3 Adverse effects.

Review: Padma 28 for intermittent claudication

Comparison: 1 Padma 28 versus placebo

Outcome: 3 Adverse effects

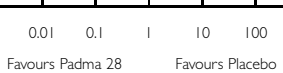
Study or subgroup	Padma 28 n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Mehlsen 1995	0/18	0/18			Not estimable
Sallon 1998	5/30	3/29		31.3 %	1.73 [0.37, 8.03]
Schräder 1985	8/23	8/20		68.7 %	0.80 [0.23, 2.76]
Smulski 1995	0/49	0/44			Not estimable
Total (95% CI)	**120**	**111**		**100.0 %**	**1.09 [0.42, 2.83]**

Total events: 13 (Padma 28), 11 (Placebo)

Heterogeneity: $Chi^2 = 0.59$, df = 1 (P = 0.44); I^2 =0.0%

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable



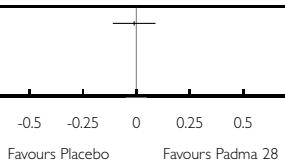
Analysis 1.4. Comparison 1 Padma 28 versus placebo, Outcome 4 Final value ankle brachial index.

Review: Padma 28 for intermittent claudication

Comparison: 1 Padma 28 versus placebo

Outcome: 4 Final value ankle brachial index

Study or subgroup	Padma 28 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Sallon 1998	31	0.72 (0.17)	25	0.73 (0.2)		-0.01 [-0.11, 0.09]



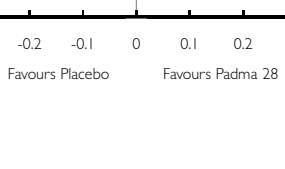
Analysis 1.5. Comparison 1 Padma 28 versus placebo, Outcome 5 Change in ankle brachial index.

Review: Padma 28 for intermittent claudication

Comparison: 1 Padma 28 versus placebo

Outcome: 5 Change in ankle brachial index

Study or subgroup	Padma 28 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Sallon 1998	31	-0.02 (0.11)	25	-0.01 (0.1)		-0.01 [-0.07, 0.05]

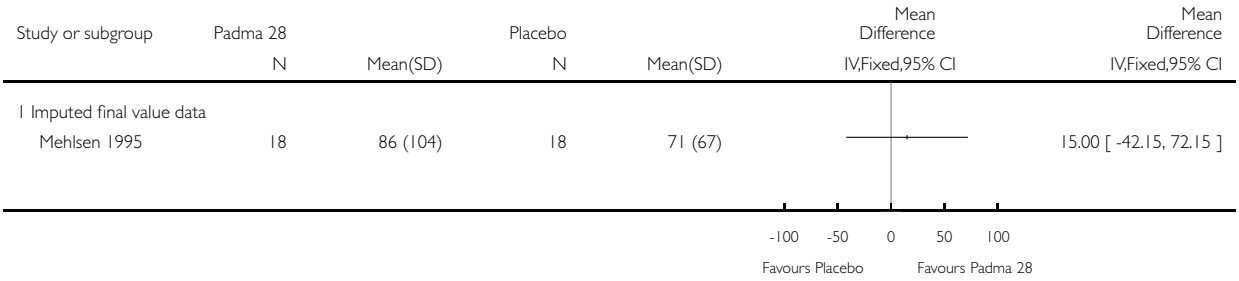


Analysis 2.1. Comparison 2 Padma 28 versus placebo sensitivity analysis, Outcome 1 Pain-free walking distance.

Review: Padma 28 for intermittent claudication

Comparison: 2 Padma 28 versus placebo sensitivity analysis

Outcome: 1 Pain-free walking distance

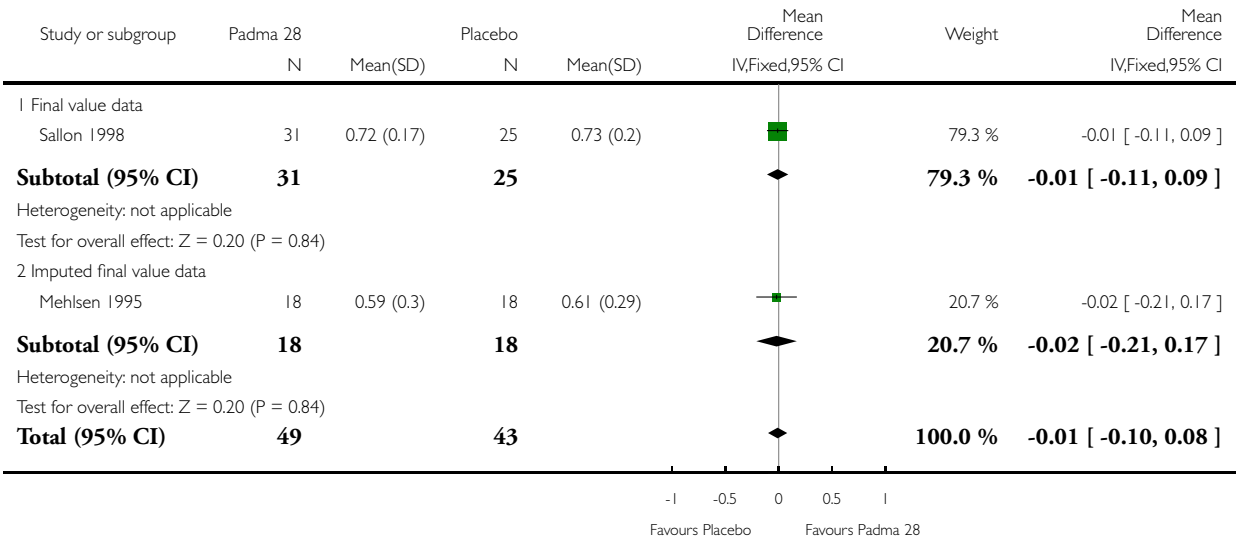


Analysis 2.2. Comparison 2 Padma 28 versus placebo sensitivity analysis, Outcome 2 Ankle brachial index.

Review: Padma 28 for intermittent claudication

Comparison: 2 Padma 28 versus placebo sensitivity analysis

Outcome: 2 Ankle brachial index



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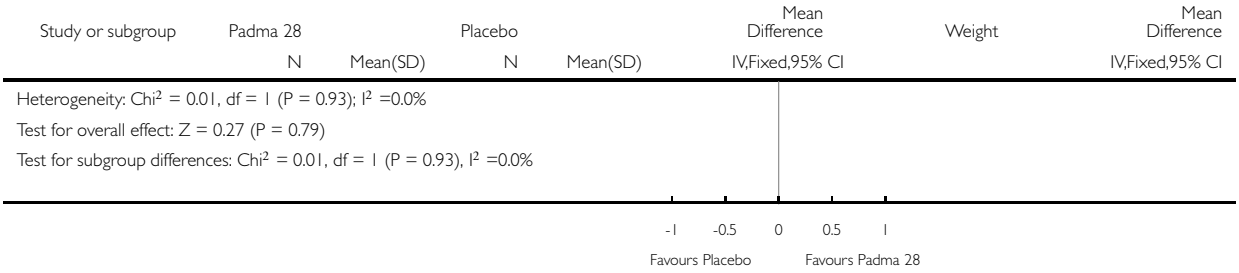

ADDITIONAL TABLES

Table 1. Reasons for withdrawal

	Mehlsen 1995	Sallon 1998	Samochowiec 1987	Schräder 1985	Smulski 1995
Padma 28	4/40 withdrawals: 3 insufficient time to participate 1 non-attendance	6/37 withdrawals: 3 gastrointestinal discomfort 1 poor compliance 1 failure to improve 1 death due to MI and CVA	0/50 withdrawals	4/27 withdrawals: 2 cardiac concerns 1 toe amputation 1 back pain	1/50 withdrawals: 1 bladder carcinoma
Placebo		7/35 withdrawals: 1 gastrointestinal discomfort 3 no improvement 3 worsening conditions	0/50 withdrawals	6/26 participants: 2 cardiac concerns 1 dyspnoea 1 stroke 1 lumbago 1 other (no 'steady state' achieved after 4 weeks)	6/50 withdrawals: 6 deterioration in overall condition

CVA: cerebrovascular accident
MI: myocardial infarction

Table 2. Pain-free walking distance

Study	*Group*	*Median baseline PFWD (m)*	*IQR*	*Median final PFWD (m)*	*IQR*	*Change in median PFWD (m)*	*P**
Mehlsen 1995	Padma 28	52	20 - 106	86	24 - 164	34	< 0.01

Table 2. Pain-free walking distance (*Continued*)

	Placebo	70	29 - 140	71	29 - 120	1	NS
Schräder 1985	Padma 28	65		131		66	0.002
	Placebo	65		95		30	0.01

*P value refers to difference between baseline and follow-up PFWD values
IQR: interquartile range
m: metres
NS: not significant
PFWD: pain-free walking distance

Table 3. Maximum walking distance

Study	*Group*	*Mean baseline MWD (m)*	*SD*	*Mean final MWD (m)*	*SD*	*Change in mean MWD (m)*	*SD*	*P**
Samochowiec 1987	Padma 28	80.6	38.8	156.2	93.1	75.7	89.3	< 0.001
	Placebo	68.1	37.0	66.6	36.1	-1.4	7.0	> 0.1
Smulski 1995	Padma 28	87.5	30.0	187.7	69.6	100.2		< 0.001
	Placebo	75.0	27.8	87.5	33.1	12.5		NS
Study	*Group*	*Median baseline MWD (m)*	*IQR*	*Median final MWD (m)*	*IQR*	*Change in median MWD (m)*		*P*
Mehlsen 1995	Padma 28	115	72 - 218	227	73 - > 1000	112		< 0.001
	Placebo	125	59 - 285	132	64 - 336	7		NS
Schräder 1985	Padma 28	127		251		124		< 0.01
	Placebo	141		168		27		NS

*P value refers to difference between baseline and follow up MWD values
IQR: interquartile range
m: metres
MWD: maximum walking distance
SD: standard deviation
NS: not significant

Table 4. Adverse effects

	Mehlsen 1995	Sallon 1998	Schräder 1985	Smulski 1995
Padma 28	0 reported	5 participants: 3 gastrointestinal discomfort 2 tiredness	8 in Padma 28 and 8 in placebo: stomach pain, gastrointestinal symptoms, and skin eruption	0 reported
Placebo	0 reported	3 participants: 1 gastrointestinal discomfort 2 tiredness		0 reported

Table 5. Ankle brachial index

Study	*Group*	*Mean baseline ABI*	*SD*	*Mean final ABI*	*SD*	*Change in mean ABI*	*SD*	*P**
Sallon 1998	Padma 28	0.73	0.11	0.72	0.17	-0.02	0.11	NS
	Placebo	0.74	0.15	0.73	0.2	-0.01	0.1	NS
Study	***Group***	***Median baseline ABI***	***IQR***	***Median final ABI***	***IQR***	***Change in median ABI***		***P****
Mehlsen 1995	Padma 28	0.62	0.42 - 0.83	0.59	0.43 - 0.82	-0.03		NS
	Placebo	0.59	0.39 - 0.77	0.61	0.39 - 0.78	0.02		NS

*P value refers to difference between baseline ABI and final ABI values
ABI: ankle brachial index
IQR: interquartile range
NS: not significant
SD: standard deviation

APPENDICES

Appendix 1. PADMA 28 ingredients

PADMA AG, Wiesenstrasse 5, 8603 Schwerzenbach, Switzerland. One capsule / one tablet contains: Columbine 15 mg, valerian root 10 mg, d-camphor 4 mg, aconite 1 mg, lettuce leaf 6 mg, clove 12 mg, golden cinquefoil 15 mg, kaempferia galanga rhizome 10 mg, costus root 40mg, Iceland moss 40 mg, cardamom fruit 30 mg, Bengal quince 20 mg, myrobalan fruit 30 mg, calcium sulphate 20 mg, allspice 25 mg, neem fruit 35 mg, calendula flower 5 mg, red sandalwood 30 mg, heart-leaved sida 10 mg, ribwort plantain 15 mg, liquorice root 15 mg, knotgrass 15 mg and Excipients.

Appendix 2. CRS search strategy

Search run on Thu Sep 17 2015		
#1	MESH DESCRIPTOR Arteriosclerosis	863
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	69
#4	MESH DESCRIPTOR Atherosclerosis	493
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	695
#6	MESH DESCRIPTOR Intermittent Claudication	669
#7	MESH DESCRIPTOR Ischemia	720
#8	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2080
#9	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	7943
#10	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	6730
#11	(peripheral near3 dis*):TI,AB,KY	2888
#12	(claudic* or IC):TI,AB,KY	2626

(*Continued*)

#13	(isch* or CLI):TI,AB,KY	20212
#14	arteriopathic or leriche*:TI,AB,KY	54
#15	dysvascular*:TI,AB,KY	9
#16	(leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	78
#17	(limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	117
#18	((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	71
#19	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1062
#20	MESH DESCRIPTOR Iliac Artery	135
#21	MESH DESCRIPTOR Popliteal Artery	248
#22	MESH DESCRIPTOR Femoral Artery	725
#23	MESH DESCRIPTOR Tibial Arteries	30
#24	(((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*))):TI,AB,KY	929
#25	#1 OR #2 OR #3 OR #4 OR #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	37825
#26	MESH DESCRIPTOR Medicine, Tibetan Traditional EXPLODE ALL TREES	3

(*Continued*)

#27	Tibetan:TI,AB,KY	46
#28	Padma*:TI,AB,KY	22
#29	#26 OR #27 OR #28	60
#30	#25 AND #29	14
#31	* NOT SR-PVD:CC AND 30/04/2013 TO 30/09/2015:DL	200160
#32	#30 AND #31	0

WHAT'S NEW

Last assessed as up-to-date: 17 September 2015.

Date	Event	Description
17 May 2016	Review declared as stable	This Cochrane review has been marked stable and will only be updated when new studies are identified

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 7, 2013

Date	Event	Description
20 September 2015	New citation required but conclusions have not changed	Searches rerun, no new trials identified. Review updated according to current Cochrane guidelines. 'Summary of findings' table added. No change in conclusions
20 September 2015	New search has been performed	Searches rerun, no new trials identified

CONTRIBUTIONS OF AUTHORS

JM: selected trials, assessed trial methodology, extracted data, and wrote the text of the review

HM: selected trials, assessed trial methodology, extracted data, and contributed to the text of the review

MS: selected trials, assessed trial methodology, extracted data, and contributed to the text of the review

DECLARATIONS OF INTEREST

MS: none known. MS is a member of Cochrane Vascular's editorial staff. To prevent any conflict of interest issues editorial decisions and activities related to this review were carried out by other editorial staff where appropriate

JM: supported by a Diabetes UK Clinical Training Fellowship, a fellowship grant covering research costs and salary between 2011 and 2015. This research grant does not conflict with this review

HM: none known

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Internal sources

- No sources of support supplied

External sources

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

According to updated Cochrane guidance, a GRADE 'Summary of findings' table was added in this review using the *Cochrane Handbook for Systematic Reviews of Interventions* guidelines (Higgins 2011) and GRADE recommendations (Atkins 2004).

INDEX TERMS

Medical Subject Headings (MeSH)

*Walking; Intermittent Claudication [*drug therapy]; Placebo Effect; Plant Extracts [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans