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[Intervention Review]

Ginkgo biloba for intermittent claudication

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ABSTRACT

Background

People with intermittent claudication (IC) suffer from pain in the muscles of the leg occurring during exercise which is relieved by a short period of rest. Symptomatic relief can be achieved by (supervised) exercise therapy and pharmacological treatments. Ginkgo biloba is a vasoactive agent and is used to treat IC.

Objectives

To assess the effect of Ginkgo biloba on walking distance in people with intermittent claudication.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (March 2013) and CENTRAL (2013, Issue 2).

Selection criteria

Randomised controlled trials of Ginkgo biloba extract, irrespective of dosage, versus placebo in people with IC.

Data collection and analysis

Two authors independently assessed trials for selection, assessed study quality and extracted data. We extracted number of patients, mean walking distances or times and standard deviations. To standardise walking distance or time, caloric expenditures were used to express the difference between the different treadmill protocols, which were calculated from the speed and incline of the treadmill.

Main results

Fourteen trials with a total of 739 participants were included. Eleven trials involving 477 participants compared Ginkgo biloba with placebo and assessed the absolute claudication distance (ACD). Following treatment with Ginkgo biloba at the end of the study the ACD increased with an overall effect size of 3.57 kilocalories (confidence interval (CI) -0.10 to 7.23, $P = 0.06$), compared with placebo. This translates to an increase of just 64.5 (CI -1.8 to 130.7) metres on a flat treadmill with an average speed of 3.2 km/h. Publication bias leading to missing data or "negative" trials is likely to have inflated the effect size.

Authors' conclusions

Overall, there is no evidence that Ginkgo biloba has a clinically significant benefit for patients with peripheral arterial disease.

PLAIN LANGUAGE SUMMARY***Ginkgo biloba for people with leg pain while walking (intermittent claudication)***

The main symptom of peripheral arterial disease (PAD) is leg pain in one or both calves while walking. Typically, this pain occurs during walking and is relieved by a short period of rest. This clinical phenomenon is called intermittent claudication (IC). Peripheral arterial disease is caused by progressive narrowing of the arteries in one or both legs and is a manifestation of systematic atherosclerosis, possibly leading to cardiovascular events. Conservative treatment consists of treatment for cardiovascular risk factors and symptomatic relief by exercise therapy and pharmacological treatments. One of the pharmacotherapeutical options is Ginkgo biloba extract, which is derived from the leaves of the Ginkgo biloba tree and has been used in traditional Chinese medicine for centuries. It is a vasoactive agent which is believed to have a positive effect on walking ability in patients with PAD. This review shows that people using Ginkgo biloba could walk 64.5 metres further, which was a non-significant difference compared with the placebo group. Overall, there is no evidence that Ginkgo biloba has a clinically significant benefit for patients with PAD.

BACKGROUND

Description of the condition

Patients with peripheral arterial disease (PAD) suffer from a progressive narrowing and hardening of the arteries in one or both legs (atherosclerosis). The most common symptom of PAD is intermittent claudication (IC) defined as pain in the muscles of the leg occurring during exercise which is relieved by a short period of rest. This clinical phenomenon affects 1.6% to 4.5% of all people in the general population (Fowkes 1991; Hooi 1998; Meijer 1998; Murabito 2002).

Description of the intervention

Basic conservative treatment for patients with IC includes risk-factor modification and exercise therapy. Intermittent claudication is a manifestation of systemic atherosclerosis, thus all patients with this symptom should be treated with medical therapy for cardiovascular risk factors. Glucose and cholesterol metabolism and blood pressure should be optimised and, as smoking is considered the most important modifiable vascular risk factor, attention should be paid to smoking cessation. Antiplatelet therapy is indicated for all patients with IC to reduce the risk of a cardiovascular event (ATC 2002). Exercise therapy can improve the absolute claudication distance (ACD) by 150% (Leng 2004) and should be prescribed for symptom relief. A supervised exercise programme has more clinical benefits than an unsupervised exercise programme. A recent Cochrane review showed approximately a 150 metre difference in increased walking distance after three months in favour of supervised exercise therapy programmes compared with non-supervised therapy (Bendermacher 2006). Pharmacological treatments reported to be associated with improvement of leg symptoms include cilostazol, pentoxifylline, naftidrofuryl, statins, angiotensin-converting enzyme inhibitors and Ginkgo biloba extract (Bendermacher 2005; Hankey 2006).

How the intervention might work

Ginkgo biloba extract is derived from the leaves of Ginkgo biloba, the only surviving species of the Ginkgoaceae family of trees. It has been used in traditional Chinese medicine for centuries. In the western world Ginkgo biloba extract is prescribed mainly for IC, cerebral insufficiency and tinnitus. The extract is made from dried leaves, and preparations for use are standardised to contain the same ingredients in similar doses of 24% ginkgo flavonoids and 6% terpenoids. Flavonoids are believed to contribute to Ginkgo's antioxidant properties. In vitro studies of Ginkgo biloba demonstrated free-radical scavenging properties (Pincemail 1989) and prolongation of the half-life of endothelial-derived relaxing factor (Robak 1988) resulting in improved microcirculation by inducing relaxation of contracted blood vessels (Kleijnen 1992). In other in vitro experiments, the ginkgolides, components of the terpenoids, inhibit the activity of platelet-activating factor (Korth 1988), resulting in diminished platelet aggregation, neutrophil degranulation and oxygen-free radical production (Kleijnen 1992). Based on the use of Ginkgo biloba in traditional Chinese medicine and the vasoactive properties of Ginkgo biloba, Ginkgo biloba is being used in Western medicine for the relief of symptoms of PAD.

Why it is important to do this review

To establish the clinical effect in patients with PAD we performed a systematic review. Possible problems with such a review of Ginkgo biloba extract is the potential for small unpublished studies, especially from relatively inexperienced and small research groups. Moreover, strong beliefs and financial interest could hamper the publication of negative trials. Hence, it is important to explore the possibility of publication bias in detail.

OBJECTIVES

To determine the effect of Ginkgo biloba extract on the walking capacity of people with intermittent claudication.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of Ginkgo biloba extract versus placebo in people with IC (stage II according to Fontaine (Fontaine 1954); stages 1 to 3 according to Rutherford (Rutherford 1997).

Types of participants

Adults (18 years and older) with IC, according to Fontaine stage II or Rutherford stages 1 to 3.

Types of interventions

Ginkgo biloba extract was compared with placebo for IC. Included studies used standardised Ginkgo biloba extracts. All studies were included irrespective of dosage.

Types of outcome measures

Primary outcomes

The primary outcome measurement was the absolute claudication distance (ACD) at the end of the study.

Secondary outcomes

Secondary outcomes were initial claudication distance (ICD), ankle brachial index (ABI), quality of life (QoL) and adverse reactions.

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (March 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 2, part of *The Cochrane Library*, (www.thecochranelibrary.com). See [Appendix 1](#) for details of the search strategy used to search CENTRAL. 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 Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

For the previous version of the review the authors searched MEDLINE/PUBMED (January 1966 to May 2008) and EMBASE (January 1985 to May 2008) using the search strategy described in [Appendix 2](#) which was adapted for each database.

Searching other resources

We checked the reference lists of all retrieved articles. In addition, we attempted to identify unpublished studies and contacted manufacturers of Ginkgo biloba products to ask for information about any published and unpublished studies. We did not apply any language restrictions.

Data collection and analysis

Selection of trials

For the 2013 update, two authors (RS and PB) independently assessed trials identified by the literature search. In the previous version, two authors (SN and LK) independently selected eligible trials identified by the literature search.

Quality of trials

Two authors (SN and LK) independently assessed the selected trials for methodological quality using The Cochrane Collaboration tool for assessing risk of bias ([Higgins 2008](#)). Trials were assessed with respect to sequence generation, allocation concealment and blinding in each group. We resolved discrepancies by discussion, or, if this failed, by consulting authors MP and JT. The results were checked for accuracy by BB.

Data extraction

Two authors (SN and LK) independently extracted data using standardised data extraction forms.

Data analysis

Data were analysed using Review Manager (RevMan 5) software. Treadmill testing is the main assessment used to quantify therapy effect and walking ability in patients with PAD. In studies concerning medical therapy for PAD, the change in walking distance is assessed by different treadmill protocols that vary in speed and incline of the treadmill. Owing to the diverse workloads of different protocols, it is difficult to compare increases in walking distance (metres) or time. To standardise walking distance caloric expenditure is used to express the difference. This was calculated from the speed and incline of the treadmill.

We explored publication bias by relating the observed treatment effect to the standard error of the mean difference. We used meta-regression to assess statistically the effect of publication bias. For this purpose the square root of the size of the study was introduced as a covariate in the assessment of the size of the treatment effect. Three domains of quality assessment were applied according to The Cochrane Collaboration tool for assessing risk of bias ([Figure 1](#); [Figure 2](#)) ([Higgins 2008](#)). As many studies were assessed as unclear risk of bias, all studies were included in the primary analysis (see Risk of Bias section). Additionally, we explored dose-effect relationship using meta-regression.

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)
Bauer 1984	?	?	?
Blume 1996	+	?	+
Blume 1998	?	?	?
Bulling 1991	?	?	?
Diehm 1990	+	?	?
Drabæk 1996	?	?	?
Gardner 2008	+	?	+
Mouren 1994	+	?	?
Natali 1985	?	?	?
Peters 1998	?	?	?
Salz 1980	+	?	?
Schoop 1997	?	?	?
Thomson 1990	?	?	?
Wang 2007	+	+	+

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

RESULTS

Description of studies

Results of the search

See [Appendix 1](#).

No additional studies were identified for inclusion in this update. One additional study was excluded ([Sandreau 1989](#)).

Included studies

For details of included studies see [Characteristics of included studies](#).

We included 14 randomised controlled trials; 11 published trials and three unpublished trials. Five of the published articles were published in German ([Bauer 1984](#); [Blume 1996](#); [Blume 1998](#); [Bulling 1991](#); [Salz 1980](#)); five in English ([Gardner 2008](#); [Mouren 1994](#); [Peters 1998](#); [Thomson 1990](#); [Wang 2007](#)); and one in Danish ([Drabaek 1996](#)). One clinical trial was published as an abstract ([Schoop 1997](#)). Two internal reports with unpublished data ([Diehm 1990](#); [Natali 1985](#)) which were mentioned in other published meta-analyses ([Horsch 2004](#); [Letzel 1992](#); [Pittler 2000](#); [Schneider 1992](#)) were requested from the manufacturers. We contacted all authors of trials who did not report means and standard deviation for walking distances. However, we only received additional data for one trial ([Gardner 2008](#)). The two most recent trials were published in 2007 and 2008 ([Gardner 2008](#); [Wang 2007](#)). The remaining 12 trials were published between 1984 and 1998.

The fourteen included trials involved a total of 739 participants. All these studies compared Ginkgo biloba with placebo in people with IC. The trials were conducted in Germany (8), France (2), Denmark (1), United States of America (1), United Kingdom (1) and Australia (1). The number of participants included in each trial varied between 18 and 209. The majority of trials included less than 50 participants and only two trials included more than 100 patients ([Peters 1998](#); [Schoop 1997](#)). The mean age of the participants in the included trials varied between 60.9 and 71.6 years. Eleven trials included male and female participants. In three trials the gender of the participants was not described ([Drabaek 1996](#); [Mouren 1994](#); [Thomson 1990](#)).

In one trial maximal trained participants who did not further improve after a walking program of three to four times per

week were included ([Blume 1996](#)). In another trial all participants received exercise therapy in combination with participation in the study ([Bulling 1991](#)), and one trial offered exercise therapy to all patients ([Peters 1998](#)). In this trial no information was given regarding how many patients actually participated in the exercise training program.

Inclusion criteria

In all 14 trials the patients had PAD according to Fontaine stage II ([Fontaine 1954](#)). Six trials mentioned that the situation should have been stable for a given period (three months to one year) ([Bauer 1984](#); [Blume 1998](#); [Drabaek 1996](#); [Mouren 1994](#); [Natali 1985](#); [Wang 2007](#)), and in three trials the diagnosis was confirmed by angiography ([Blume 1996](#); [Blume 1998](#); [Peters 1998](#)). Four trials applied an age restriction; 40 to 75 years ([Diehm 1990](#)); 35 to 75 years ([Mouren 1994](#)); 30 to 75 years ([Natali 1985](#)); and 50 to 80 years ([Wang 2007](#)). In nine studies an upper limit of the ACD or ICD was used as an inclusion criterion. Inclusion criterion for the ACD were an ACD < 300 metres ([Bauer 1984](#)), ACD between 50 and 500 metres ([Drabaek 1996](#); [Gardner 2008](#)) or an ACD between 100 and 500 metres ([Mouren 1994](#)) as assessed by treadmill testing. Inclusion criteria for the ICD were an ICD < 150 metres ([Blume 1996](#); [Peters 1998](#)), ICD < 300 metres ([Thomson 1990](#)) or an ICD between 50 and 200 metres ([Bulling 1991](#); [Diehm 1990](#)).

Exclusion criteria

The exclusion criteria were slightly variable between trials (see [Characteristics of included studies](#)). In all studies patients with PAD according to Fontaine stage III or IV were excluded. Patients with other reasons for a limited walking distance, e.g. cardiopulmonary or orthopaedic co-morbidities were also excluded.

Dosage and duration of treatment

There were no dose-related restrictions to the included trials in this review. Six trials included a comparison of 120 mg Ginkgo biloba daily versus placebo ([Bauer 1984](#); [Blume 1996](#); [Diehm 1990](#); [Drabaek 1996](#); [Peters 1998](#); [Schoop 1997](#)) and three trials included the comparison of 160 mg Ginkgo biloba daily versus placebo ([Blume 1998](#); [Natali 1985](#); [Salz 1980](#)). Three trials, including the two most recent ones, compared daily dosages of 240 mg ([Wang 2007](#)), 300 mg ([Gardner 2008](#)) and 320 mg ([Mouren 1994](#)) Ginkgo biloba extract with placebo. The maximal follow-up period of eight trials was 24 weeks, of one trial 16 weeks, of three trials 12 weeks, of one trial six weeks, and of one trial four weeks.

Outcome measurements

The primary outcome measurement of the study was ACD. In 13 trials walking distances were mentioned. Data on the walking distances could not be retrieved from one trial (Mouren 1994). In two other studies, only data from ICD were presented (Schoop 1997; Thomson 1990). In 12 trials treadmill testing with different protocols was used to assess the ACD and/or ICD. In one trial (Salz 1980) walking distance was measured by walking on a flat floor with two steps per second.

In six trials data from ankle brachial index (ABI) or ankle pressures were presented (Bauer 1984; Bulling 1991; Drabaek 1996; Gardner 2008; Thomson 1990; Wang 2007). Only one study reported quality of life as administered by the MOS SF-36 questionnaire (Gardner 2008). Four trials presented data of a Visual Analogue Scale (VAS-scale) for the subjective estimate of pain (Bauer 1984; Blume 1996; Drabaek 1996; Thomson 1990) and one trial presents a VAS-scale for functional impairment (Mouren 1994). Nine trials reported on tolerance and adverse reactions of the medication and the placebo (Bauer 1984; Blume 1996; Blume 1998; Bulling 1991; Diehm 1990; Natali 1985; Peters 1998; Schoop 1997; Thomson 1990).

Excluded studies

For this update one additional study (Sandreau 1989) was excluded because it only included patients diagnosed with PAD stage III according to Fontaine. Twelve randomised controlled trials were excluded from analysis in 2009. Five of these trials compared Ginkgo biloba with another pharmacological treatment; dextran (Baitsch 1986), buflomedil (Berndt 1987), pentoxifylline (Bohmer 1988), naftidrofuryl (Horsch 1998), and the combination of Ginkgo biloba extract with magnesium and Levo-arginine compared with acetylsalicylic acid (Michelin 1998). In four trials, conducted in 1975, 1977 and 1981, the inclusion criterion to include patients only with PAD stage II according to Fontaine was not met and separate data for patients diagnosed with PAD stage II according to Fontaine were not available (Ambrosi 1975; Courbier 1977; Frileux 1975; Garzya 1981). In one trial the primary aim was to compare diabetic and non-diabetic PAD patients (Li 1998) and one double blind randomised cross-over study evaluated the short term effect

(within 60 minutes) of Ginkgo biloba extract versus placebo in patients with PAD stage II according to Fontaine (Rudofsky 1987). One study compared two dosages of Ginkgo biloba extract without a placebo group (Schweizer 1999).

Risk of bias in included studies

Allocation

All 14 trials were randomised trials, however explicit generation of the allocation sequence was only described in six trials (Blume 1996; Diehm 1990; Gardner 2008; Mouren 1994; Salz 1980; Wang 2007) where a random number generator was used.

Blinding

Only one trial explicitly described an adequate allocation concealment. In this trial the allocation sequence was administered by a third party who was not involved in the study (Wang 2007). All trials were reported to be double blinded. However, only three trials describe explicitly how this blinding was performed and stated that participants and trial personnel were blinded to treatment assignment until the end of the study (Blume 1996; Gardner 2008; Wang 2007). Because most of the studies were assessed as unclear risk of bias, all studies were included in the primary analysis (Figure 1; Figure 2).

Effects of interventions

Absolute claudication distance

Data for the ACD at the end of the study were available in 11 trials with a total sample size of 477 participants. The effect was calculated after standardisation of the presented walking distances. The total caloric expenditure was calculated from the speed and incline of the treadmill and if possible the weight of the participants. At the end of the study the ACD increased with an overall effect size of 3.57 kcal (confidence interval (CI) -0.10 to 7.23, $P = 0.06$) (Figure 3), in favour of the Ginkgo biloba group, using a random-effects model. For a 70 kg weighted person this can be translated to an increase of 64.5 metres (CI -1.8 to 130.7) on a flat treadmill with an average speed of 3.2 km/h, which is most comparable with walking in daily life.

Figure 3. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.1 Absolute claudication distance (expressed as kilocalories) at the end of the study.

Furthermore, the effect size was calculated for 24 weeks of treatment (Figure 4), 12 to 16 weeks of treatment (Figure 5) and 6 to 8 weeks of treatment (Figure 6) with Ginkgo biloba extract versus placebo. After a follow-up period of 24 weeks, data for six trials for ACD were available with a sample size of 321 participants. The ACD was increased with an overall effect size of 4.72 kcal (CI 2.27 to 7.16, $P = 0.0002$), in favour of the Ginkgo biloba group, using a

random-effects model. This can be translated to 85.3 metres (CI 41.0 to 129.4) on a flat treadmill with an average speed of 3.2 km/h. After 12 to 16 weeks of follow-up data of eight trials ($n = 339$) present an increase in ACD with an overall effect size of 1.36 kcal (CI -2.63 to 5.36, $P = 0.50$). This was comparable with the overall effect size of 2.19 kcal (CI -0.62 to 4.99, $P = 0.13$) after 6 to 8 weeks of follow up ($n = 236$).

Figure 4. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.2 Absolute claudication distance (expressed as kilocalories) after 24 weeks.

Figure 5. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.3 Absolute claudication distance (expressed as kilocalories) after 12 to 16 weeks.

Figure 6. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.4 Absolute claudication distance (expressed as kilocalories) after 6 to 8 weeks.

Initial claudication distance

Data for the ICD were present in 13 trials at the end of the study within a total of 723 participants (Figure 7). The ICD increased with a overall effect size of 1.84 kcal (CI -0.92 to 4.61, $P = 0.19$) with a random-effects model in favour of the Ginkgo biloba group. This

corresponds with an increase in 33.3 metres (CI -16.7 to 83.3) for a 70 kg weighted adult with 3.2 km/h on a flat treadmill. After 24 weeks of treatment the overall effect size was 2.15 kcal (CI -2.06 to 6.36, $P = 0.32$) in favour of the Ginkgo biloba group (Figure 8). After 12 to 16 weeks (Figure 9) and 6 to 8 weeks (Figure 10) the overall effect

sizes were 1.54 kcal (CI -0.04 to 3.12, $P = 0.06$) and 2.72 kcal (CI 0.75 to 4.69, $P = 0.007$), respectively.

Figure 7. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.5 Initial claudication distance (expressed as kilocalories) at the end of the study.

Figure 8. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.6 Initial claudication distance (expressed as kilocalories) after 24 weeks.

Figure 9. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.7 Initial claudication distance (expressed as kilocalories) after 12 to 16 weeks.

Figure 10. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.8 Initial claudication distance (expresses as kilocalories) after 6 to 8 weeks. **Ankle brachial index**

In three trials the ABI (Drabaek 1996; Gardner 2008; Wang 2007) and in three trials ankle pressures (Bauer 1984; Bulling 1991;

Thomson 1990) were presented. Therefore, the standardised mean differences were used to show an overall effect size of -0.22 (CI -0.58 to 0.15, $P = 0.25$) on the ABI or ankle pressures in favour of the placebo group (Figure 11).

Figure 11. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.9 Ankle brachial index and ankle pressure at the end of study. **Quality of life**

One study collected QoL data using the standardised MOS SF-36 questionnaire (Gardner 2008). This study showed a significant improvement for the “role physical” domain in favour of the Ginkgo

biloba study group ($P = 0.03$). The subjective assessment of pain and functional impairment administered by a VAS scale increased with an overall effect of 0.38 (CI -0.94 to 1.70, $P = 0.57$) in the Ginkgo biloba group (Bauer 1984; Blume 1996; Drabaek 1996; Mouren 1994; Thomson 1990) (Figure 12).

Figure 12. Forest plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.10 Quality of life (expressed as a Visual Analogue Scale for complaints). **Adverse reactions**

Most common side effects of Ginkgo biloba included gastro-intestinal complaints, headache, allergic skin reactions. Furthermore, Ginkgo biloba may increase the risk of bleeding. Nine out of 14 studies reported tolerance on Ginkgo biloba, as assessed

by adverse reactions. In five trials no side effects were observed (Blume 1998; Bulling 1991; Diehm 1990; Peters 1998; Schoop 1997). In the other four trials the following side effects were reported; nausea (2), gastro-intestinal complaints (2), blood in the urine (1), headache (1) (Bauer 1984; Blume 1996; Natali 1985; Thomson

1990). Overall, a low percentage of adverse reactions, which were all minor side effects, were found.

Assessment of publication bias

To explore publication bias two funnel plots in which the standard error of the mean difference was plotted against the mean

difference were performed. The funnel plots for the ACD at the end of the study and the ACD after 24 weeks of follow up suggested publication bias as many smaller studies had more positive results. (Figure 13; Figure 14).

Figure 13. Funnel plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.1 Absolute claudication distance (expressed as kilocalories) at the end of the study. On the horizontal axis the effect estimate of Ginkgo biloba versus placebo on the absolute claudication distance at the end of the study is presented as the mean difference. The vertical axis presents the standard error of the intervention effect on a reversed scale.

Figure 14. Funnel plot of comparison: 1 Ginkgo biloba versus placebo, outcome: 1.2 Absolute claudication distance (expressed as kilocalories) after 24 weeks. On the horizontal axis the effect estimate of Ginkgo biloba versus placebo on the absolute claudication distance after 24 weeks is presented as the mean difference. The vertical axis presents the standard error of the intervention effect on a reversed scale.

Dosage of Ginkgo biloba

Meta-regression analysis did not show a significant effect on the effect of Ginkgo biloba on walking distance; neither did the dosage of the Ginkgo biloba extract.

DISCUSSION

Summary of main results

Eleven included trials with a total sample size of 477 patients did reveal non significant increases in ACD at the end of the study with a total effect size of 3.57 kcal. This corresponds with an increase of 64.5 metres on a flat treadmill (average speed 3.2 km/h). However, in clinical studies, most frequently a treadmill protocol of 3.2 km/h and 10% incline is used to assess therapy effect. Applying this protocol, 3.57 kcal represents an increase of 31 metres.

After 24 weeks of treatment we found a significant improvement in ACD with an overall effect size of 4.72 kcal, corresponding with 85.3 metres. However, in this analysis the number of patients who contributed was smaller, $n = 321$, and this analysis is likely to be more prone to publication bias (Figure 14).

For comparison, exercise therapy which is the main conservative treatment for symptomatic relief, is associated with 150% overall improvement of the ACD (Leng 2004). This translates into a benefit

of 19.1 to 39.9 kcal, depending on the applied treadmill protocol to assess the improvement in walking distance. (19.1 kcal for 3.2 km/h and 0% increase, 39.9 kcal for 3.2 km/h and 10%, energy expenditures of graded protocols lie in between both). Hence, the effect of exercise therapy can be estimated to be approximately 5 to 10 times greater than that of Ginkgo biloba extract. Moreover, supervised exercise therapy programs have an additional and significantly greater benefit than non-supervised regimens (Bendermacher 2006).

Other meta-analyses comparing pharmacological therapy (cilostazol, buflomedil, pentoxifylline and naftidrofuryl) with placebo for IC show similar results (Robless 2008; de Backer 2008; de Backer 2008a; Girolami 1999; Moher 2000). Possibly, the results on walking distance for buflomedil are most conclusive. Although all these comparisons are indirect, they support the generally accepted view that (supervised) exercise therapy is the main conservative therapy for patients with IC.

Clinical relevance

The clinical relevance of a non significant improvement of 64.5 metres in ACD is questionable. Quality of life, which is probably more important than the regained walking distance (for the patients' well being), was evaluated in only one trial. In this single study there was a borderline significant improvement of QoL (Gardner 2008). However, five trials assessed subjective assessment

of pain and functional impairment by a VAS scale, which failed to show a statistically significant effect (Bauer 1984; Blume 1996; Drabaek 1996; Mouren 1994; Thomson 1990).

Limitations of this review

Eleven out of fourteen studies reported data on ACD. Authors of the three other studies were contacted for the walking distances. However, they did not respond (Mouren 1994; Schoop 1997; Thomson 1990). In two articles only the median was presented with the corresponding 95% confidence intervals (CI) (Blume 1996; Drabaek 1996). The authors were contacted but did not reply and the median was used instead of the mean and the standard deviation was calculated from the 95% CI. In one study the standard deviations were not directly available and had to be derived from the reported P values (Blume 1998). Unfortunately, in two studies only the differences to the ACD at the start of the study were available with the corresponding P values. The ACD at baseline was calculated with the known proportions of the ICD and ACD in the other included studies (Peters 1998; Salz 1980).

Figure 13 and Figure 14 suggested publication bias as many smaller studies had more positive results. This publication bias leading to missing data or "negative" trials is likely to have inflated the effect size. Furthermore, most included studies were performed with a small sample size; the majority included less than 50 participants.

Special attention should be paid for a more recent study by Wang et al. (Wang 2007) that presented data of 17 participants and is the only study that reported results contrary to the other studies (Figure 3).

AUTHORS' CONCLUSIONS

Implications for practice

Ginkgo biloba has no significant effect on walking distance in people with IC. Even if the small positive point estimate of the effect could be documented to be statistically significant in a larger trial, this effect would be marginal to the effect of (supervised) exercise therapy. Hence, currently no evidence supports the use of Ginkgo biloba in the treatment of PAD.

Implications for research

Before Ginkgo biloba can be advised for the use in clinical practice further research would be required. However, given the small absolute summary effect in the reported trials, it is unlikely that the effect of Ginkgo biloba will ever be clinically relevant.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bauer 1984

Methods	<p>Study design: double blind randomised clinical trial.</p> <p>Method of randomisation: divided at random.</p>
Participants	<p>Country: Germany.</p> <p>Setting: outpatient setting.</p> <p>Number randomised: 79 (treatment group: 44, control group: 35).</p> <p>Age: mean 60.9 years.</p> <p>Sex: 61 males and 18 females.</p> <p>Inclusion criteria: patients with PAD (stage IIb according to Fontaine), predominantly on one site, lasting > 1 year; ACD less than or equal to 300 metres.</p> <p>Exclusion criteria: Unco-operative patients; patients with other vaso-active medication; other stage of Fontaine's classification; concomitant illness: pathology of the veins; anaemia; non compensated cardiac insufficiency; recent myocardial infarction; uncontrolled hypertension; other causes of walking impairment; poorly controlled diabetes; important kidney or hepatic insufficiency; recent treatment with anticoagulant drugs.</p>
Interventions	<p>Treatment: 40 mg GbE three times daily. (Coated tablets containing 40 mg GbE. Manufacturer: Intersan, Institut für pharmazeutische und Klinische Forschung GmbH, Ettlingen, Germany)</p> <p>Control: placebo.</p> <p>Duration: 24 weeks.</p>
Outcomes	<p>Walking distance: ACD and ICD by treadmill testing (3 km/h and 10% incline); subjective estimate of pain by a VAS; plethysmography; systolic ankle pressures at rest and after exercise; tolerance.</p>
Notes	<p>In three other articles the clinical course is described of the treatment group after 1 year (Bauer 1986a), 2 years (Bauer 1986b) and 3 years (Bauer 1986c). However, the control group is not mentioned.</p> <p>Funding: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were divided at random into 2 equal groups.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The placebo group received matching placebo tablets which were taken in the same manner.

Blume 1996

Methods	<p>Study design: double blind randomised clinical trial.</p> <p>Method of randomisation: EPD number generator.</p>
Participants	<p>Country: Germany.</p> <p>Setting: ambulant patient seeking consultation at a angiological practice.</p> <p>Number randomised: 60 (treatment group: 30, control group: 30).</p> <p>Age: aged between 47 and 82, median treatment group 71 (95% CI 65.2 to 74.8), median control group 68.6 (95% CI 65.5 to 73.2).</p> <p>Sex: 42 males and 18 females.</p> <p>Inclusion criteria: patients with PAD (stage IIb according to Fontaine) angiographically confirmed; stable walking distance in spite of constant walking training; ICD less than 150 metres.</p> <p>Exclusion criteria: age < 18 years; cardiac infarction during the preceding 6 months; NYHA stage III or IV cardiac insufficiency; diastolic pressure > 120 mmHg; renal insufficiency; functional hepatic disorders; respiratory insufficiency or orthopaedic disorder as limiting factor of the walking distance; venous insufficiency stage II (Basle Classification); badly manageable diabetes mellitus; anaemia; hematocrit > 48%; fibrinogen > 500 mg/dl; use of platelet aggregation inhibitor; anti-inflammatory agents or analgesics; pregnancy or expected insufficient compliance.</p>
Interventions	<p>Treatment: 40 mg Ginkgo biloba special extract GbE 761 three times daily. (40 mg film-coated tablet containing dry extract from Ginkgo biloba leaves (50:1) 40 mg, adjusted at 9.6 mg Ginkgo flavone glycosides and 2.4 mg terpene lactones (ginkgolides, bilobalide). Manufacturer: Dr. Wilmar Schwabe Arzneimittel / Pharmaceuticals, Karlsruhe, Germany).</p> <p>Control: placebo.</p> <p>Duration: 24 weeks.</p>
Outcomes	<p>Walking distance: ACD and ICD by treadmill testing (3 km/h and 12% incline); ABI; subjective estimate of pain by a VAS; adverse drug reactions.</p>
Notes	<p>Maximum level trained patients with IC.</p> <p>Funding: not stated.</p> <p>Conflicts of interests: One of the authors is employed by one of the manufacturers Dr. Willmar Schwabe, Karlsruhe, Germany.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned using an EPD random number generator was used for allocation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	There was an externally indistinguishable placebo and neither the patient nor the examiner or any other person directly involved in the study was able to see which group a patient belonged to.

Blume 1998

Methods	Study design: double blind randomised clinical trial. Method of randomisation: not stated.
Participants	Country: Germany. Setting: not stated. Number randomised: 41 (treatment group 21, control group 20). Age: mean treatment group 66.4, mean control group 68.2. Sex: treatment group 14 males and 7 females, control group 15 males and 4 females. Inclusion criteria: patients with PAD (stage IIb according to Fontaine) angiographically confirmed. PAD > 6 months present. Exclusion criteria: not stated.
Interventions	Treatment: 80 mg Ginkgo biloba special extract EgB 761 two times daily. (80 mg film-coated tablet containing dry extract from Ginkgo biloba leaves (35-67:1) 80 mg, standardised at 19.2 mg Ginkgo flavone glycosides and 4.8 mg terpene lactones (ginkgolides, bilobalide). Manufacturer: Dr. Wilmar Schwabe Arzneimittel / Pharmaceuticals, Karlsruhe, Germany). Control: placebo. Duration: 24 weeks.
Outcomes	Walking distance: ACD and ICD by treadmill testing (3 km/h and 12% incline); tolerance of Ginkgo biloba special extract EgB 761.
Notes	Funding: not stated. Conflicts of interests: One of the authors is employed by one of the manufacturers Dr. Willmar Schwabe, Karlsruhe, Germany.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information

Bulling 1991

Methods	Study design: double blind randomised clinical trial. Method of randomisation: not stated.
Participants	Country: Germany. Setting: outpatient setting.

Ginkgo biloba for intermittent claudication (Review)

Bulling 1991 (Continued)

Number randomised: 36, 33 were evaluated, treatment group 17, control group 16.

Age: mean treatment group 62.8, mean control group 63.3.

Sex: treatment group; 12 males and 5 females, control group; 12 males and 4 females.

Inclusion criteria: patients with PAD (stage IIb according to Fontaine); ICD at least 50 metres and at most 200 metres.

Exclusion criteria: venous complaints; anaemia; decompensated cardiac insufficiency; unstable angina pectoris; coronary heart disease; respiratory insufficiency; non-controlled hypertension; recent myocardial infarction; badly adjustable diabetes; disease of liver and kidneys; orthopaedic reason for walking restriction.

Interventions	<p>Treatment: standardised Ginkgo biloba extract 761. (The drug extract ratio is 50:1, the standardised content of flavone glycosides is 24% (9.6 mg/40 mg extract), and that of terpene lactones 6% (2.4 mg/40 mg extract) Rökan®)</p> <p>Control: placebo.</p> <p>Duration: 24 weeks.</p>
Outcomes	Walking distance: ACD and ICD by treadmill testing (3 km/h and 10% incline); number of "tip-toe" stands; systolic ankle pressure in the posterior tibial artery; plasma viscosity and haematocrit; adverse reactions.
Notes	<p>All patients received exercise therapy in combination with participation in this trial.</p> <p>Funding: not stated.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The placebo tablets had an identical appearance.

Diehm 1990

Methods	<p>Study design: double blind randomised clinical trial.</p> <p>Method of randomisation: computerised randomisation program.</p>
Participants	<p>Country: Germany.</p> <p>Setting: not stated.</p> <p>Number randomised: 40, treatment group 22, control group 18.</p> <p>Age: mean treatment group 62.2, mean control group 63.0.</p> <p>Sex: treatment group; 21 males and 1 female, control group; 17 males and 1 female.</p>

Diehm 1990 (Continued)

Inclusion criteria: Patients with PAD (stage IIb according to Fontaine); ICD of 50 to 200 m; age between 40 and 75 years; precisely reproducible pain localization under exercise; pressure in posterior tibial artery > 50 mmHg; ABI < 0.85; Broca deviation < 30 %; abstinence from nicotine.

Exclusion criteria: myocardial infarction within half a year before enrolment; heart failure NYHA III or IV; severe chronic venous insufficiency; insufficiently controllable diabetes mellitus; malabsorption; liver disorder: transaminase levels above 3 times the upper limit of the normal range; renal disorder: serum creatinin level above 3.0 mg/dl; gait impairment due to orthopaedic or neurological diseases; respiratory insufficiency limiting walking distance; angina pectoris limiting walking distance; uncontrolled hypertension.

Interventions	Treatment: 120 mg Ginkgo biloba special extract EgB 761 daily. Control: placebo. Duration: 12 weeks.
Outcomes	Walking distance: ACD and ICD by treadmill testing (5 km/h and 10% incline); adverse reactions.
Notes	Conflicts of interests: Internal rapport of Dr. Wilmar Schwabe Arzneimittel/Pharmaceuticals, Karlsruhe, Germany.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised with a computerised randomisation program.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Tablets of identical appearance, packed and labelled in identical way.

Drabaek 1996

Methods	Study design: double blind randomised cross-over study. Method of randomisation: not stated.
Participants	Country: Denmark. Setting: Not stated. Number randomised: 18. Age: 59 to 82 years (median age 74). Sex: not stated. Inclusion criteria: Stable form of IC more than 6 months; ACD 50 to 500 metres; ABI < 0.85. Exclusion criteria: Chronic obstructive pulmonary disease; diabetes mellitus; artrosis; angina pectoris; cardiac insufficiency.
Interventions	Treatment: 120 mg GbE GB 8 daily.

Drabaek 1996 (Continued)

Control: placebo.

Duration: 6 months, 3 months treatment and 3 months placebo.

Outcomes	Walking distance: ACD and ICD by treadmill testing (individual speed (2.5 to 4 km/h) and incline (8 to 16% incline); ABI; subjective estimate of pain by a VAS; cognitive functions: concentration and short term memory.
Notes	Only the first study period (3 months) before the cross-over is considered. Funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.

Gardner 2008

Methods	Study design: double blind randomised clinical trial. Method of randomisation: computerised randomisation program.
Participants	Country: USA. Setting: patients recruited from the local community through advertisement. Number randomised: 62, treatment group 31, control group 31. Age: mean treatment group 69, mean control group 70. Sex: treatment group 13 males and 18 females, control group 24 males and 7 females. Inclusion criteria: Patients with a resting ABI < 0.90; ACD between 1 and 10 minutes; drop in ABI after exercise of at least 25%. (For diabetics all ABI values were allowed). Exclusion criteria: major surgery; chronic disease in the last three months; use of pentoxifylline, carnitine, arginine, prostacycline, dietary antioxidant supplements, supplements containing Ginkgo biloba.
Interventions	Treatment: 300 mg standardised Ginkgo biloba extract 761 daily (180 mg with breakfast and 120 mg with dinner). (60 mg tablet standardised at 24% Ginkgo flavone glycosides and 6% terpene lactones. Manufacturer: Dr. Wilmar Schwabe Arzneimittel/Pharmaceuticals, Karlsruhe, Germany). Control: placebo. Duration: 4 months.
Outcomes	ABI; walking distance: ACD and ICD by treadmill testing (3.2 km/h and 10% incline); flow-mediated vasodilatation of the brachial artery; antibodies to epitopes of oxidized LDL; walking impairment questionnaire; QoL: MOS SF-36 questionnaire.

Ginkgo biloba for intermittent claudication (Review)

Gardner 2008 (Continued)

Notes

Funding: NIH grant R01 AT002004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by generating random numbers assigned to treatment and control and assigning each new participant the next number in sequence.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Subjects, study staff, and laboratory technicians were blinded to treatment assignments until the conclusions of the trial.

Mouren 1994

Methods	Study design: double blind randomised clinical trial. Method of randomisation: not stated
Participants	Country: France. Setting: patients recruited from the outpatient clinic. Number randomised: 20. Age: not stated. Sex: not stated. Inclusion criteria: patients between the ages of 35 and 75 years suffering from IC (stage II according to Fontaine); diagnosed for more than 1 year; stable for three months; ACD on treadmill (3.2 km/h and 10% incline) > 100 metres and < 500 metres; transcutaneous partial pressure of oxygen in rest > 40 mmHg. Exclusion criteria: Patients with stage III and IV arterial disease; recent acute arterial occlusion; any form of peripheral circulatory insufficiency due to causes other than atherosclerosis; planned surgical revascularisation; decompensated heart failure; coronary insufficiency; poorly controlled hypertension; locomotor handicap.
Interventions	Treatment: 160 mg EGb 761 two times daily. Control: placebo. Duration: 4 weeks.
Outcomes	Transcutaneous partial pressure of oxygen in rest; transcutaneous partial pressure of oxygen after exercise; functional impairment by VAS.
Notes	Although walking distances were not reported, functional impairment as measured by a VAS was used for the analysis. Funding: not stated

Risk of bias
Ginkgo biloba for intermittent claudication (Review)

Mouren 1994 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by random number generation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.

Natali 1985

Methods	Study design: double blind randomised clinical trial. Method of randomisation: not stated.	
Participants	Country: France. Setting: outpatient setting. Number randomised: 18, treatment group 9, control group 9. Age: treatment group 60.8, control group 66.2. Sex: treatment group 7 males and 2 females, control group 8 males and 1 female. Inclusion criteria: Patients with PAD (stage IIb according to Fontaine); age 30 to 75 years; occlusive lesions of deep femoral arteries verified by arteriography; stable condition. Exclusion criteria: non co-operative patient; significant psychiatric disorder; physical condition that does not allow exercise tests to be performed; any other ailment that could influence the course of the PAD or interfere with the assessment of treatment effects (e.g. Parkinson's disease, tumours); treatment of the same type as the product studied; treatment that could interfere with the assessment of treatment effects.	
Interventions	Treatment: 160 mg Ginkgo biloba special extract EgB 761 daily. Control: placebo. Duration: 6 months.	
Outcomes	Walking distance: ACD and ICD by treadmill testing (3 km/h and 5% incline); adverse reactions.	
Notes	Conflicts of interests: Internal rapport of Dr. Wilmar Schwabe Arzneimittel/Pharmaceuticals, Karlsruhe, Germany	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.

Ginkgo biloba for intermittent claudication (Review)

Natali 1985 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	The intervention and the placebo were presented the same way.
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Peters 1998

Methods	Study design: double blind randomised clinical trial. Method of randomisation: assigned at random.
Participants	Country: Germany. Setting: multicenter study. Number randomised: 109, treatment group 52, control group 59. Age: mean treatment group 62.8, mean control group 61.2. Sex: treatment group 29 males and 23 females, control group 34 males and 23 females. Inclusion criteria: Patients with PAD (stage IIb according to Fontaine) angiographically confirmed; older than 18 years; IC for more than 6 months; ICD < 150 metres. Exclusion criteria: severe impairment of heart, liver and/or kidney; walking limitation due to respiratory insufficiency or orthopaedic disorder; poorly controlled diabetes; pathologically altered hemorrheology; drugs for the same indication as the test substance; use of platelet aggregation inhibitors; anti-inflammatories; or analgesics.
Interventions	Treatment: 40 mg standardised Egb 761 three times daily. (1 film-coated tablet contains 40 mg special extract EGb 761 from Ginkgo biloba leaves (35-67:1), standardised to 9.6 mg (24%) of ginkgo flavone glycosides and 2.4 (6%) to terpene lactones. Manufacturer: Dr. Wilmar Schwabe Arzneimittel/Pharmaceuticals, Karlsruhe, Germany). Control: placebo. Duration: 24 weeks.
Outcomes	Walking distance: ACD and ICD by treadmill testing (3 km/h and 12% incline); ABI; subjective assessment of therapeutic outcome using VAS; tolerance.
Notes	During the course of the study, participation in a walking exercise program was offered for all patients. Funding: Not stated. Conflicts of interests: One of the authors is employed by one of the manufacturers Dr. Willmar Schwabe, Karlsruhe, Germany.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned at random.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias)	Unclear risk	Insufficient information.

Ginkgo biloba for intermittent claudication (Review)

Peters 1998 (Continued)

All outcomes

Salz 1980

Methods	Study design: double blind randomised cross-over study. Method of randomisation: assigned at random.
Participants	Country: Germany. Setting: not stated. Number randomised: 29, treatment group 13, control group 13. Age: mean age males 69.0, mean age females 64.4. Sex: 11 males and 18 females. Inclusion criteria: Patients with PAD (stage IIb according to Fontaine) in both legs. Exclusion criteria: not stated.
Interventions	Treatment: 40 mg standardised Egb 761 two times daily 2 tablets. (Rökan®). Control: placebo. Duration: two times 6 week cross-over study.
Outcomes	Walking distance: ACD and ICD assessed by walking with 2 steps per second; Ratschow-test; maximal time of toe-standing; temperature of the skin; laboratory parameters.
Notes	Only the first study period (6 weeks) before the cross-over is considered. Funding: Not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned to the trial according to a random code van 1 to 30 in a consecutive way.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.

Schoop 1997

Methods	Study design: double blind randomised clinical trial. Method of randomisation: not stated.
Participants	Country: Germany.

Schoop 1997 (Continued)

Setting: not stated.

Number randomised: 205, treatment group 105, control group 100.

Age: mean treatment group 64.3, mean control group 67.2.

Sex: treatment group 80 males and 25 females, control group 77 males and 23 females.

Inclusion criteria: Patients with PAD (stage IIb according to Fontaine).

Exclusion criteria: not stated.

Interventions	Treatment: 40 mg standardised GbE three times daily. (1 film-coated tablet contains 40 mg dry extract from Ginkgo biloba leaves (50:1), standardised to 9.6 mg of ginkgo flavone glycosides and 2.4 to ter-pene lactones. (ginkgolides, bilobalide). Manufacturer: not stated). Control: placebo. Duration: 24 weeks.
Outcomes	Walking distance: ICD by treadmill testing (3 km/h and 12% incline); tolerance.
Notes	Funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information.

Thomson 1990

Methods	Study design: double blind randomised clinical trial. Method of randomisation: randomly allocated.
Participants	Country: United Kingdom. Setting: not stated. Number randomised: 49, treatment group 25, control group 24. Age: not stated. Sex: not stated. Inclusion criteria: Patients with PAD (stage IIb according to Fontaine) affecting the iliac or femoral arter-ies, involving predominantly one leg. Exclusion criteria: ICD > 300 metres; alternating side of pain; poorly controlled diabetes; significant concomitant illness.

Thomson 1990 (Continued)

Interventions	Treatment: Ginkgo biloba extract (Tanakan®). Control: placebo. Duration: 24 weeks.
Outcomes	Walking distance: ICD by treadmill testing (4 km/h and 10 degrees (= 17.6% incline)); recovery times; systolic ankle pressure at rest and after exercise; tolerance.
Notes	Funding: The work was supported and assisted by Ipsen International (one of the manufacturers).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Randomisation to Ginkgo biloba or placebo was made in a double blind manner.

Wang 2007

Methods	Study design: double blind randomised clinical trial. Method of randomisation: randomly allocated.
Participants	Country: Australia. Setting: not stated. Number randomised: 22, treatment group 11, control group 11. Age: mean treatment group 71.6, mean control group 71.2. Sex: treatment group 9 males and 2 females, control group 11 males. Inclusion criteria: Patients with stable IC for at least 6 months; 50-80 years of age; ABI at rest < 0.90 and after exercise < 0.80. Exclusion criteria: resting ischaemic pain; ulceration; gangrene; unable to walk on treadmill with 3.2 km/h, exercise capacity limited by angina; congestive heart failure; chronic obstructive pulmonary disease or arthritis.
Interventions	Treatment: 240 mg standardised GbE 761 daily. (The Ginkgo biloba tablets were standardized to 26.7% ginkgo flavone glycosides and 6.7% terpenoids (ginkgolides or bilobalide). Manufacturer: not stated). Control: placebo. Duration: 12 weeks.
Outcomes	Walking distance: ACD and ICD by treadmill testing (3.2 km/h and 0% incline); ABI in rest and after exercise; plasma viscosity; whole blood viscosity; peak VO ₂ ; walking economy.

Wang 2007 (Continued)

Notes

Only the first 12 weeks of the study in which Ginkgo biloba treatment was compared with placebo is considered. The second part was a 12-week supervised treadmill walking programme, while the subjects continued taking the same dosage of Ginkgo biloba or placebo.

Funding: The Ginkgo biloba and placebo tablets were kindly donated by Mayne Health Consumer Products, Australia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subjects were randomly allocated following a randomisation code. The code was created by a computerised program.
Allocation concealment (selection bias)	Low risk	The code was administered by a third party who was not involved in the study.
Blinding (performance bias and detection bias) All outcomes	Low risk	The code was revealed to the subject and the researcher after the database of the study was completed.

ABI: ankle brachial index

ACD: absolute claudication distance

GbE: Ginkgo biloba extract

ICD: initial claudication distance

LDL: low density lipoprotein

PAD: peripheral arterial disease

VAS: visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ambrosi 1975	Separate data for patients diagnosed with PAD stage II according to Fontaine were not available.
Baitsch 1986	This study compares Ginkgo biloba extract with dextran in patients with PAD stage IV according to Fontaine.
Berndt 1987	Ginkgo biloba extract is compared with buflomedil.
Bohmer 1988	(According to Fontaine), diagnosed for more than 1 year.
Coubier 1977	Separate data for patients diagnosed with PAD stage II according to Fontaine were not available.
Frileux 1975	Separate data for patients diagnosed with PAD stage II according to Fontaine were not available.
Garzya 1981	Separate data for patients diagnosed with PAD stage II according to Fontaine were not available.
Horsch 1998	Ginkgo biloba extract is compared with naftidrofuryl in patients with PAD stage III and IV according to Fontaine.
Li 1998	Primary aim of this study was to compare diabetic and non-diabetic PAD patients.
Michelini 1998	This study compares the combination of Ginkgo biloba extract, magnesium and Levo-arginine with acetylsalicyl acid.

Study	Reason for exclusion
Rudofsky 1987	Double blind randomised cross-over study evaluating the short term effect (60 minutes) of Ginkgo biloba extract versus placebo in patients with PAD stage II according to Fontaine.
Sandreau 1989	This study only included patients diagnosed with PAD stage III according to Fontaine.
Schweizer 1999	This study compares two dosages of Ginkgo biloba extract without a placebo group.

DATA AND ANALYSES

Comparison 1. Ginkgo biloba versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absolute claudication distance (expressed as kilocalories) at the end of the study	11	477	Mean Difference (IV, Random, 95% CI)	3.57 [-0.10, 7.23]
2 Absolute claudication distance (expressed as kilocalories) after 24 weeks	6	321	Mean Difference (IV, Random, 95% CI)	4.72 [2.27, 7.16]
3 Absolute claudication distance (expressed as kilocalories) after 12 to 16 weeks	8	339	Mean Difference (IV, Random, 95% CI)	1.36 [-2.63, 5.36]
4 Absolute claudication distance (expressed as kilocalories) after 6 to 8 weeks	5	236	Mean Difference (IV, Random, 95% CI)	2.19 [-0.62, 4.99]
5 Initial claudication distance (expressed as kilocalories) at the end of the study	13	723	Mean Difference (IV, Random, 95% CI)	1.84 [-0.92, 4.61]
6 Initial claudication distance (expressed as kilocalories) after 24 weeks	8	564	Mean Difference (IV, Random, 95% CI)	2.15 [-2.06, 6.36]
7 Initial claudication distance (expressed as kilocalories) after 12 to 16 weeks	9	441	Mean Difference (IV, Random, 95% CI)	1.54 [-0.04, 3.12]
8 Initial claudication distance (expresses as kilocalories) after 6 to 8 weeks	6	335	Mean Difference (IV, Random, 95% CI)	2.72 [0.75, 4.69]
9 Ankle brachial index and ankle pressure at the end of study	6	274	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.58, 0.15]
10 Quality of life (expressed as a Visual Analogue Scale for complaints)	5	208	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.94, 1.70]

Analysis 1.1. Comparison 1 Ginkgo biloba versus placebo, Outcome 1 Absolute claudication distance (expressed as kilocalories) at the end of the study.

Analysis 1.2. Comparison 1 Ginkgo biloba versus placebo, Outcome 2 Absolute claudication distance (expressed as kilocalories) after 24 weeks.

Analysis 1.3. Comparison 1 Ginkgo biloba versus placebo, Outcome 3 Absolute claudication distance (expressed as kilocalories) after 12 to 16 weeks.

Analysis 1.4. Comparison 1 Ginkgo biloba versus placebo, Outcome 4 Absolute claudication distance (expressed as kilocalories) after 6 to 8 weeks.

Analysis 1.5. Comparison 1 Ginkgo biloba versus placebo, Outcome 5 Initial claudication distance (expressed as kilocalories) at the end of the study.

Analysis 1.6. Comparison 1 Ginkgo biloba versus placebo, Outcome 6 Initial claudication distance (expressed as kilocalories) after 24 weeks.

Analysis 1.7. Comparison 1 Ginkgo biloba versus placebo, Outcome 7 Initial claudication distance (expressed as kilocalories) after 12 to 16 weeks.

Analysis 1.8. Comparison 1 Ginkgo biloba versus placebo, Outcome 8 Initial claudication distance (expresses as kilocalories) after 6 to 8 weeks.

Analysis 1.9. Comparison 1 Ginkgo biloba versus placebo, Outcome 9 Ankle brachial index and ankle pressure at the end of study.

Analysis 1.10. Comparison 1 Ginkgo biloba versus placebo, Outcome 10 Quality of life (expressed as a Visual Analogue Scale for complaints).

APPENDICES

Appendix 1. 2013 CENTRAL search strategy

#1	MeSH descriptor: [Arteriosclerosis] this term only	893
#2	MeSH descriptor: [Arteriolosclerosis] this term only	0
#3	MeSH descriptor: [Arteriosclerosis Obliterans] this term only	71
#4	MeSH descriptor: [Atherosclerosis] this term only	382
#5	MeSH descriptor: [Arterial Occlusive Diseases] this term only	755
#6	MeSH descriptor: [Intermittent Claudication] this term only	711
#7	MeSH descriptor: [Ischemia] this term only	753
#8	MeSH descriptor: [Peripheral Vascular Diseases] explode all trees	2150
#9	MeSH descriptor: [Vascular Diseases] this term only	381
#10	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	17195
#11	(arter*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	4872
#12	(vascular) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1378
#13	(vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	713
#14	(veno*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	976
#15	(peripher*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1358
#16	peripheral near/3 dis*	3243
#17	arteriopathic	10
#18	(claudic* or hinken*)	1436
#19	(isch* or CLI)	16827
#20	dysvascular*	14
#21	leg near/4 (obstruct* or occlus* or steno* or block* or obliter*)	176
#22	limb near/4 (obstruct* or occlus* or steno* or block* or obliter*)	228
#23	(lower near/3 extrem*) near/4 (obstruct* or occlus* or steno* or block* or obliter*)	137
#24	(aort* or iliac or femoral or popliteal or femoropop* or fempop* or crural) near/3 (obstruct* or occlus*)	322
#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	39158

(Continued)

#26	MeSH descriptor: [Ginkgo biloba] this term only	231
#27	(ginkgo* or ginkgo* or ginkco* or ginko* or gingho or gincosan):ti,ab,kw	654
#28	(bilobalid* or tebonin* or kaveri* or tanakan or tanakene or tebokan or rokan or supergin* or (li next 1370)):ti,ab,kw	57
#29	(EGB761 or "EGB 761" or EGB-761):ti,ab,kw	134
#30	#26 or #27 or #28 or #29	670
#31	#25 and #30 in Trials	90

Appendix 2. Search strategy used by authors to search MEDLINE and EMBASE

#1 Peripheral arterial disease
#2 Peripheral arterial occlusive disease
#3 PAD
#4 Intermittent claudication
#5 (#1 OR #2 OR #3 OR #4)
#6 Ginkgo biloba
#7 Egb 761
#8 Taveonin
#9 Tebonin
#10 Roka
#11 (#6 OR #7 OR #8 OR #9 OR #10)
#12 (#5 AND #11)

WHAT'S NEW

Date	Event	Description
6 December 2019	Review declared as stable	This Cochrane review has been marked stable and will only be updated if new studies are identified

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 2, 2009

Date	Event	Description
13 March 2013	New search has been performed	Searches were rerun. No new studies were included. One new study was excluded.
13 March 2013	New citation required but conclusions have not changed	Searches were rerun. No new studies were included. One new study was excluded. Minor copy edits made. Two authors added to review team. Conclusions not changed.
15 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Saskia Nicolai and Lotte Kruidenier independently selected trials for inclusion, assessed study quality and extracted data. Bianca Bendermacher checked all results for accuracy. Martin Prins and Joep Teijink resolved disagreements. For the 2013 update, Rutger Stokmans and Pieter Broos independently selected trials for inclusion.

DECLARATIONS OF INTEREST

MP reports his institution has received funds for his Board membership of clinical studies and invited speaker activities from Bayer, Pfizer, Leo, Daichi Sankyo and Sanofi-Aventis. These were not related to this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

The PVD Group editorial base is supported by the Chief Scientist Office.

NOTES

This review has been marked stable and will only be updated if new studies are identified.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ginkgo biloba; *Phytotherapy; Intermittent Claudication [*drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans