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# Sulodexide improves pain-free walking distance in patients with lower extremity peripheral arterial disease: A systematic review and meta-analysis

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**Abstract**

Peripheral arterial disease is associated with very high cardiovascular risk. The main symptom is intermittent claudication, which strongly affects the quality of life. Therefore, treatment goals in peripheral arterial disease consist of the reduction of cardiovascular events and the relief of symptoms. An increase in pain-free walking distance, evaluated based on the Initial Claudication Distance, was also a strong positive prognostic factor in patients with peripheral arterial disease. Our objective was to reassess whether sulodexide is effective in improving Initial Claudication Distance. For this, we searched the literature according to the PRISMA checklist for double blind clinical trials assessing the improvement in the Initial Claudication Distance after 90 days of standard therapeutic regimen with sulodexide in adult patients with peripheral arterial disease. We found and assessed for bias in 11 studies eligible for review and meta-analysis. Data extracted from those studies favoured the sulodexide group, showing an overall difference in Initial Claudication Distance of +68.9 (CI 95%; ± 11.9 m) at the end of treatment ($p < 0.001$). According to this review, sulodexide is effective in improving Initial Claudication Distance and consequently the quality of life in patients with peripheral arterial disease. Further studies are needed to assess the effects of this drug on disease progression in asymptomatic patients with peripheral arterial disease.

**Keywords**

Peripheral arterial disease, lower extremity arterial disease, drug therapy, intermittent claudication, meta-analysis, walking distance

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## Introduction

Lower extremity peripheral arterial disease (PAD) is a medical condition mainly secondary to atherosclerosis; deficiency in blood supply might lead to intermittent claudication, rest pain, cutaneous ulcerations, and rarely, to gangrene. PAD represents a global health problem; in Europe, nearly 40 million people are estimated to be affected by this disease.[1] The prevalence of PAD, diagnosed by ankle-brachial index test (ABI) – a quick, non-invasive test, able to detect significant stenosis in major leg arteries[a] – ranges from 8% in the general population[2] to approximately 20% in high-risk populations.[3,4] In the last decade, the total number of

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individuals with PAD has increased by 23%, mostly due to population growth, global aging, diabetes mellitus, and smoking habits in low- and middle-income countries.[1]

Most patients with PAD are asymptomatic. Intermittent claudication (IC) is a lead symptom in approximately 20% of the people affected.[5] Claudication is a reproducible discomfort (pain and/or weakness) of a defined group of muscles of the lower limbs. The obstruction of one or more vessels causes IC to reduce the blood flow in the lower extremities muscles.[6,7] Exercise, typically walking, elicits IC, while rest relieves the symptom. In up to 70–80% of cases of PAD with IC, the evolution is benign, without progression to limb-threatening lower extremity ischemia.[8] Consequently, indications for revascularization in patients with IC are still under debate and restricted to specific categories; thus, conservative treatment remains the main therapeutic approach.[3,9,10]

Patients with PAD are included in the very high category of cardiovascular risk.[6,10–13] The evolution of this disease is characterized by increased rates of myocardial infarction, stroke or aortic complication; death occurs in three quarters of cases due to a vascular event in another territory than the lower extremity arteries.[11–13] Therefore, first-line therapy in PAD, in symptomatic and asymptomatic patients, must be addressed to reduce the global cardiovascular risk. This goal includes risk factor control (smoking cessation, control of arterial hypertension or diabetes mellitus) and pharmacological therapy. A significant amount of data – as per the guidelines currently in use[3,10] – sustain the use of antiplatelet therapy (aspirin[14,15] and clopidogrel[16]) or lipid-lowering therapy (statins[17]) for the reduction of cardiovascular events, specifically in patients with PAD.

Statins,[18] evolocumab,[19] and rivaroxaban in low doses added to aspirin[20] seems to reduce major adverse limb events. However, there is no evidence that these drugs can improve the walking distance in IC, while an augmented risk of bleeding was reported for the latter.[21]

Nevertheless, for patients with IC, symptom relief represents an important therapeutic goal.

A measurable target of treatment is the increment of the pain-free walking distance (PFWD),[4–6] namely, the length a patient can walk before pain forces him or her to stop. Improvement in the Initial Claudication Distance (ICD) and in the Absolute Claudication Distance (ACD), particularly in debilitate patients,[7] is considered a positive prognostic factor.

Supervised exercise programmes are known to give the most convincing benefits.[22–28] In fact, lifestyle modifications, particularly exercise (walking, intensive walking, and supervised exercise), are effective in increasing the ICD[18–22]: supervised exercise programmes can increase the ICD by 81.2–143.8 m, whereas free exercise shows inferior results.[23,24]

According to the therapeutic algorithms currently in use, patients with IC start treatment with supervised exercised programmes; drugs are added in cases of insufficient improvement after three to six[3,7,9,10] months.

Recently, new approaches have also been tried: surgical treatment, such as percutaneous transluminal angioplasty (PTA) and revascularization;[8–11] use of autologous, stem and embryogenic cells for critical limb ischemia;[12,13] mixed surgical and pharmacological intervention, such as drug-eluting balloons;[8,14,15] new resorbable stent;[16] or promising extracorporeal shockwave therapy (ESW).[17]

Medical treatments used for cardiovascular risk control, such as statins, might slightly contribute to ICD improvement.[29] Along with these, data from randomized trials and meta-analyses indicate three drug therapies as symptom relievers in patients with IC: cilostazol,[30–33] naftidrofuryl[33] and pentoxifylline.[34,35] Cilostazol is a phosphodiesterase inhibitor that suppresses platelet aggregation and has direct vasodilatory activity.[36] It has serious side effects and is contraindicated in heart failure of any grade.[37] Naftidrofuryl is a 5-hydroxytryptamine-2-receptor antagonist whose mechanism of action is still unclear; it might promote glucose uptake and increase adenosine triphosphate levels.[38] Pentoxifylline is a rheologic modifier; it increases red cell deformability, reduces blood viscosity and decreases platelet aggregation.

In one meta-analysis, cilostazol appeared slightly less effective than naftidrofuryl but more effective than pentoxifylline.[32]

In addition, a fourth drug has shown a significant effect on IC. Sulodexide is a highly purified glycosaminoglycan. It is a combination of heparin sulfate (80%), with a molecular weight of 7000 Da and affinity for antithrombin III, and dermatan sulfate (20%) with a molecular weight of 25,000 Da and affinity for the heparin II cofactor.[39] Previous studies have demonstrated a noteworthy improvement of IC parameters in patients treated with this drug. Sulodexide seems effective in reducing fibrinogen and circulating lipoprotein levels.[40,41] These mechanisms, as well as the antithrombotic effect of this drug, help improve the PFWD in patients with IC.

To better understand the effectiveness of this drug in treating IC, we thus performed a systematic review to evaluate the effect of sulodexide on ICD and, consequently, on the improvement in the quality of life of affected patients.

## Materials and methods

The study was performed according to the recommendations of the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) statement.[42,43] We published the complete protocol in PROSPERO[44,b] (ID=CRD42017076473).

### Eligibility criteria and search strategy

As per our protocol, we searched from December 2017 to September 2018 PubMed, Embase, and Cochrane Library, Clinicaltrials.gov, WanFang, VIP, and China National Knowledge Infrastructure databases for clinical trials on the sulodexide effect on vascular diseases (all types).

A combination of the following key words (including Medical Subject Headings 2017)[c] was applied for each selected database: sulodexide (including sulodexide, soludexide, sulodexiden, sulodexid, Sulodeksid) AND atherosclerosis (arteriosclerosis and MESH UNIQUE ID D050197 and D001161 (MeSH C14.907.137.126.307 and C14.307.320).

### Data extraction and quality assessment

Two authors independently assessed trials for selection and independently extracted data. Disagreements were resolved by discussion. We also considered those articles originally published in languages different from English when a translation was available.

Studies that did not specifically include patients with IC were excluded. We performed the quality assessment adopting the Cochrane Collaboration Tools;[45] the JADAD score was evaluated by the Oxford QSS.[d]

### Outcome measures and statistical analysis

We set the ICD (sometimes named in the retrieved articles as PFWD) as the primary outcome because this index is commonly used to evaluate the IC.[46–49] Furthermore, it relates to the quality of life of patients affected by IC,[50] and it is strongly linked with its prognosis expressed as the progression of the disease according to Leriche-Fontaine staging classification.[51]

ICD was also considered a primary outcome in other systematic reviews aimed at evaluating the effectiveness of other drugs used in the treatment of IC.[33,34,52] We set the duration at 90 days of treatment according to the indications that came from the literature that we analysed. However, as per our protocol, we consider the ICD at 60 days of treatment as well.

We did not include the absolute claudication distance (ACD, or maximum walking distance) because this measure cannot be standardized and is considered a less relevant endpoint.

We set as exclusion criteria in our meta-analysis studies of a lower quality, thus potentially biased, defined as studies with JADAD score $< 3$.

We performed the meta-analysis with fixed-effects and random-effects models to evaluate the overall pooled ICD (yielding equivalent results).[53,54] We used a random effect model when $I^2$ was $> 50\%$; otherwise, we used a fixed effect model, as suggested by a recent Cochrane meta-analysis on ICD in patients with claudication.[33] When useful, we followed the recommendations of Zwetsloot:[55] using raw mean differences instead of standardized difference of means by estimate of precision funnel plots. Statistics were computed by Comprehensive Meta Analysis Rel. 2.2.064.

Although not specifically expressed in our research protocol, we analysed other comparable measurements considered of interest in the articles eligible for our review, as recommended by recent publications on the clinical evaluation of peripheral vascular disease (PVD); among those, the ABI[56,57] and the number of patients with a clinical improvement were expressed according to other indexes.[40,58]

### Methodological and ethical issues

We checked for ethical approval of the papers included in the study. Some of the oldest publications may not explicitly state whether the ethical authorization was granted because of the different laws in use at the time of the studies. The studies included in the meta-analysis appear to be deontologically sound.

## Results

### Study selection for meta-analysis and quality assessment

A total of 723 publications were found from different literature sources: 444 (61,4%) were letters, editorials, review and other papers without original data in humans; 199 (27,5%) articles were excluded as no relevant in terms of patient included, outcomes or treatment used (Figure 1).

Eighty studies (Figure 1) are relevant on the basis of published study protocol[44] (humans, sulodexide therapy, patients with atherosclerosis). Of those, 23 did not measure ICD or had been performed on patients without a clear diagnosis of PVD; 32 studies on patients with PVD outcomes were measured in terms of modification of laboratory values with no relevant data on IC. Twelve studies were excluded because they used an open protocol without a control group or because of an inadequate protocol.

Table 1 shows the demographic characteristics of the included studies: Bodula,[59] Bonalumi,[60] Borreani,[61] Coccheri,[40] Corsi,[58] Cospite,[62] Della Marchina,[63] Di Stefano,[64] Liguori,[65] Palmieri,[66] Shustov.[67]

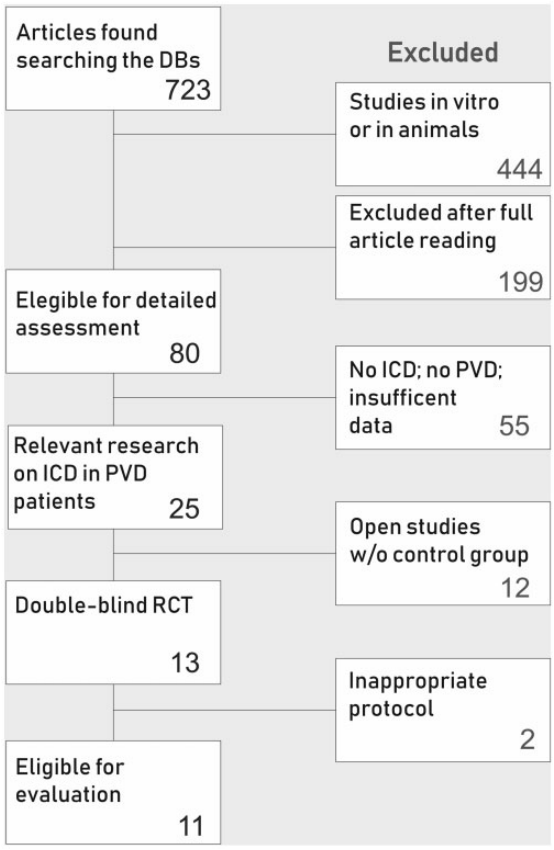


**Figure 1.** Flowchart of the study number identified and included in the meta-analysis.
ICD: Initial Claudication Distance; PVD: Peripheral Vascular Disease; RCT: randomized controlled trial.

All the studies included in the table refer to patients with type II IC according to Leriche-Fontaine; in two studies,[61,66] patients with type III IC were also included. All the studies clearly specify PVD patients' inclusion and exclusion criteria.

In two studies (Table 2), the inclusion criteria are only summarized. The Borreani study excluded patients with diabetes or hyperlipoproteinemia;[61] in the Della-Marchina study, patients with diabetes were included,[63] whereas the Palmieri study included patients with hyperlipoproteinemia only (phenotype IV or IIb according to Fredrickson).[66] In this same study, demographic data collected before randomization were reported (overall mean age of 42.5 years and sex distribution, namely male = 16 and female = 14). The Cospite study[62] also enrolled patients with atheromasia in district other than the lower limbs (carotids, coronary) or without IC, and those were excluded from analysis. Sex distribution was the same in both groups, while the prevalence of diabetes and hyperlipoproteinemia was the same ($p > 0.1$), although it was not analytically reported in the three subgroups considered (coronary, cerebral and peripheral vasculopathy). The Bodula study reports lipid levels in the two groups without significant differences in LDLc or HDLc triglycerides;[59] the prevalence of hyperlipoproteinemia is not stated.

## *Effect size of ICD differences between and within groups*

*Baseline value of ICD (m).* Sulodexide group= 183,7 ± 49,6 m.; placebo Groups= 191,0 ± 55,4 m; Hedges' g for fixed effect 0,07 ± 0,060, $p = 0{,}308$, $I^2 = 0{,}0\%$ (no heterogeneity, forest plot and funnel plot not shown). Identical results were obtained, including in the effect size analysis the two studies against pentoxyphilline (sulodexide = 166,3 ± 62,0 m; Controls= 174,1 ± 65,4, $p > 0{,}1$, Hedges'g 0,092 ± 0,064, $p = 0{,}153$, $I^2 = 0{,}0\%$).

*Mean difference of ICD in the sulodexide group after three months of therapy.* First explorative analysis included all available data regardless of the dose administered or the control group used by the different authors (the Bodula and the Shustov studies were also included). The random effect size evaluated on raw data (absolute differences in meters) showed an overall difference of +68,9 m., ± 11,9, $z = 5{,}76$, $p < 0{,}001$ with an $I^2 = 52{,}9\%$. The forest plot is shown in Figure 2.

We performed a random effect on studies with placebo as a control with a JADAD score >3, a comparable dose and length of therapy: the ICD difference resulted of +91.4 m (SEM = 17.52, $z = 5.21$, $p < 0.001$). Taking into account the heterogeneity of the results in some of the studies (i.e. higher rise of Delta-ICD in sulodexide treated patients in the Bonalumi[60] paper), we analysed intra-group ICD differences with the leave-one-out meta-analysis method (Figure 3).

The leave-one out analysis demonstrates the absence of individual studies with a crucial effect on comprehensive results. Meta-regression analysis of mean daily doses on difference in means was not significant ($z = 1.159$ $p = 0.246$), although two studies with very low doses (50 mg/day),[65] and a very short administration period[59] showed the lowest result in ICD improvement after sulodexide administration (both < 55 m).

*Effect size analysis of the mean difference in ICD in the control groups after three months of therapy.* The ICD mean difference (raw data) in placebo-treated patients was +5.37 ± 2,77 m ($z = 1.935$, $p = 0.053$, $I^2 = 20.2\%$), both with fixed and random effect size analysis. Two studies with active drugs as a control (pentoxifylline) with JADAD Score 2 were also included in the forest plot shown in Figure 4. The delta ICD values (in m) were +22.09 ± 8.8 (fixed model) and +27.09 ± 20.9 (random

**Table 1.** Eligible trials, characteristics and demographics.

| Author | Year | Control | Patient enrolled (N) | | Patient analysed (N) | | Patient analysed (%} | | Age (mean–SD/range) | | Age (mean-SD/range) | | Males (%) | | Diabetes (%) | | Hyperlipoproteinemias (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | S | C | S | C | S | C | S | | C | | S | C | S | C | S | C |
| Bonalumi, F. | 1986 | Placebo | 15 | 15 | 15 | 15 | 100,0 | 100,0 | 60,1 | 8,6 | 60,4 | 9,6 | 93,3 | 73,3 | 40,0 | 33,3 | 93,3 | 86,7 |
| Borreani, B. | 1993 | Placebo | 50 | 50 | 50 | 50 | 100,0 | 100,0 | 67,1 | 5,1 | 68,1 | 4,9 | 76,0 | 70,0 | no | no | no | no |
| Coccheri, S. | 2002 | Placebo | 143 | 143 | 141 | 143 | 98,6 | 100,0 | 64,7 | 7,6 | 66,2 | 7,5 | 83,9 | 76,9 | 25,2 | 23,8 | 46,9 | 55,2 |
| Corsi, C. | 1985 | Placebo | 15 | 15 | 15 | 15 | 100,0 | 100,0 | 65,8 | 11,1 | 69,8 | 12,6 | 80,0 | 66,7 | no | no | 73,3 | 80,0 |
| Cospite, M. | 1985 | Placebo | 9 | 8 | 9 | 8 | 100,0 | 100,0 | 59,0 | 40–72 | 57,0 | 40–72 | na | na | na | na | na | na |
| Della Marchina, M. | 1992 | Placebo | 35 | 35 | 27 | 29 | 77,1 | 82,9 | 65,4 | 59–74 | 63,8 | 55–81 | 54,3 | 57,1 | 100,0 | 100,0 | 60,0 | 57,1 |
| Di Stefano, F. | 1984 | Placebo | 15 | 15 | 15 | 15 | 100,0 | 100,0 | 66,9 | 55–75 | 68,2 | 55–75 | 73,3 | 66,7 | 26,7 | 13,3 | 60,0 | 60,0 |
| Liguori, L. 25 b.i.d . | 1993 | Placebo | 62 | 62 | 60 | 61 | 96,8 | 98,4 | 67,7 | 7,8 | 66,4 | 8,6 | 71,0 | 74,2 | 11,3 | 8,1 | 21,0 | 19,4 |
| Liguori, L. 100 q.d . | 1993 | Placebo | 62 | 62 | 58 | 61 | 93,5 | 98,4 | 67,8 | 8,5 | 66,4 | 8,6 | 69,4 | 74,2 | 14,5 | 8,1 | 24,2 | 19,4 |
| Liguori, L. 50 b.i.d . | 1993 | Placebo | 62 | 62 | 61 | 61 | 98,4 | 98,4 | 69,3 | 8,5 | 66,4 | 8,6 | 59,7 | 74,2 | 11,3 | 8,1 | 24,2 | 19,4 |
| Palmieri, G. 84 | 1984 | Placebo | 15 | 15 | 11 | 10 | 73,3 | 66,7 | na | 20–60 | na | 20–60 | 53,3 | 53,3 | no | no | 100,0 | 100,0 |
| Bodula, A . | 2010 | Pentoxyphylline | 23 | 17 | 23 | 17 | 100,0 | 100,0 | 53,6 | 18,7 | 53,3 | 9,1 | 82,6 | 65,2 | 73,9 | 47,8 | na | na |
| Shustov, S.B. | 1997 | Pentoxyphylline | 60 | 60 | 56 | 51 | 93,3 | 85,0 | 71,1 | 10,8 | 69,8 | 17,0 | 70,0 | 66,7 | 31,7 | 26,7 | 40,0 | 41,7 |
| Sum/raw means (placebo, n=12) | | | 483 | 482 | 462 | 468 | 94,3 | 95,0 | 65,4 | 8,2 | 65,3 | 8,6 | 71,4 | 68,7 | 32,7 | 27,8 | 55,9 | 55,2 |
| Sum/raw means (active control, n=2) | | | 83 | 77 | 79 | 68 | 96,7 | 92,5 | 62,4 | 14,8 | 61,6 | 13,1 | 76,3 | 65,9 | 52,8 | 37,2 | 40,0 | 41,7 |
| Sum, raw means (all, n=14) | | | 566 | 559 | 541 | 536 | 94,7 | 94,6 | 64,9 | 9,6 | 64,6 | 9,6 | 72,2 | 68,2 | 37,2 | 29,9 | 54,3 | 53,9 |
| Sum, weighted means (all, n=14) | | | | | | | 95,6 | 95,9 | 66,3 | | 66,1 | | 73,1 | 71,3 | 29,4 | 24,4 | 40,0 | 40,7 |

Note: Weighted means were evaluated excluding studies with missing data). The Liguori paper[65] presented results from three distinct studies in which different clusters of patients and different protocols were used; findings from these studies were summarized in a single published paper.
Na: not assessed; no: not included.

**Table 2.** Assessment for bias in each study included in the review and the quality of those same studies.

| Author | JADAD score | Study design | Intention to treat | Homogeneity check | Inclusion criteria description | Randomization bias | Allocation concealment | Performance bias | Detection bias | Attrition bias | Reporting bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bonalumi, F. | 3 | DB | ITT | Yes | Sufficient | Low | Low | Low | Low | Low | Low |
| Borreani, B. | 3 | DB | ITT | Yes | Sufficient | Low | Low | Low | Low | Low | High |
| Coccheri, S. | 5 | DB MC | ITT PP | Yes | Good | Low | Low | Low | Low | Low | Low |
| Corsi, C. | 5 | DB | ITT | Yes | Good | Low | Low | Low | Low | Low | Low |
| Cospite, M. | 5 | DB | ITT | NA | Sufficient | Low | Low | Low | Low | Low | Unclear |
| Della Marchina, M. | 3 | DB | PP | Yes | Good | Low | Low | Low | Low | Low | Low |
| Di Stefano, F. | 4 | DB | ITT | Yes | Good | Low | Low | Low | Low | Low | Low |
| Liguori, L. 25 b.i.d. | 4 | DB MC DD | ITT PP | Yes | Good | Low | Low | Low | Low | Low | Low |
| Liguori, L. 100 q.d. | 4 | DB MC DD | ITT PP | Yes | Good | Low | Low | Low | Low | Low | Low |
| Liguori, L. 50 b.i.d. | 4 | DB MC DD | ITT PP | Yes | Good | Low | Low | Low | Low | Low | Low |
| Palmieri, G. 84 | 3 | DB | ITT | NA | Good | Low | NA | Low | NA | Low | Low |
| Bodula, A. | 2 | CO | NA | Yes | Good | NA | NA | High | NA | Low | Low |
| Shustov, S.B. | 2 | CO | PP | Yes | Good | Low | NA | High | NA | Low | Low |

Note: Assessment was also done for every study according to the JADAD scale. JADAD is scored according to the Oxford Quality Scoring System (http://www.pmidcalc.org/?sid=8721797&newtest=Y).
DB: double blind; MC: multicenter research trial; DD: double dummy; CO: cross Over; ITT: intention to treat; PP: per-protocol; NA: not available.

model) with $Z = 2.6$, $p = 0.008$ and $z = 1.29$, $p = 0.195$, respectively. In the Bodula study, the protocols were not comparable. The analysis considerably favours sulodexide when compared with placebo; the effect of pentoxifylline, described in other studies, is not comparable.[32,68] The Borreani study[61] was excluded because it did not report data for effect size evaluation in the placebo group (mean value without SEM/SD or paired p value).

### *ICD differences between the sulodexide and control groups after three months of therapy*

**Sulodexide versus placebo.** As stated before, we exclude the Borreani study[61] in the analysis because of high heterogeneity among data (overall, placebo and pentoxifenilline as controls, $I^2 = 94.2\%$); moreover, a funnel plot of precision by raw difference in means also confirms the presence of publication bias (Figure 5).

We first performed a random effect meta-analysis with inclusion of all the available data, regardless of the dose of sulodexide used, including the group treated with $25 \times 2$ mg/day published in the Liguori study. The random effect size evaluated on raw data (absolute differences in meters of ICD) in all published papers resulted of + 80,91 m ±5,72, favouring sulodexide ($z = 9{,}34$, $p < 0{,}001$). We tried to reduce heterogeneity excluding individual studies: the random effect size evaluation after exclusion of the outliers (Bonalumi and Liguori dose finding study with low-dose sulodexide[60,65]), resulted in $+58.2 \pm 15.7$ m, favouring sulodexide ($z = 3.709$, $p = 0.001$; $I^2$ 72.7%).

The leave-one-out analysis (Figure 6) revealed an effect on the comprehensive effect size by removing the Coccheri study (from $58.2 \pm 15.6$ to $69.5 \pm 18.6$ m of the raw ICD difference) and the Di Stefano trial (decrease from 58.2 to $41.2 \pm 12.8$ m)

**Sulodexide versus pentoxifylline.** No differences were observed in effect size (fixed model, no heterogeneity) of delta ICD between pentoxifylline and sulodexide $+2.84 \pm 9.00$, $z = 0.318$, $p = 0.752$. However, further studies are needed for a proper evaluation.

### *Surrogate outcome analysis*

**Number of patients with relevant improvement of ICD.** The absolute number of patients markedly improved (see Materials and methods) after administration of sulodexide or placebo is reported only in six surveys. The data are heterogeneous ($I^2 = 82\%$); however, the absolute rates are very different: 177 out of 328 (53.9%) patients markedly improved in the sulodexide-treated group, 24 out of 319 (7.2%) in placebo-treated controls. The random effect size evaluated on the log of odds ratio (OR) favoured

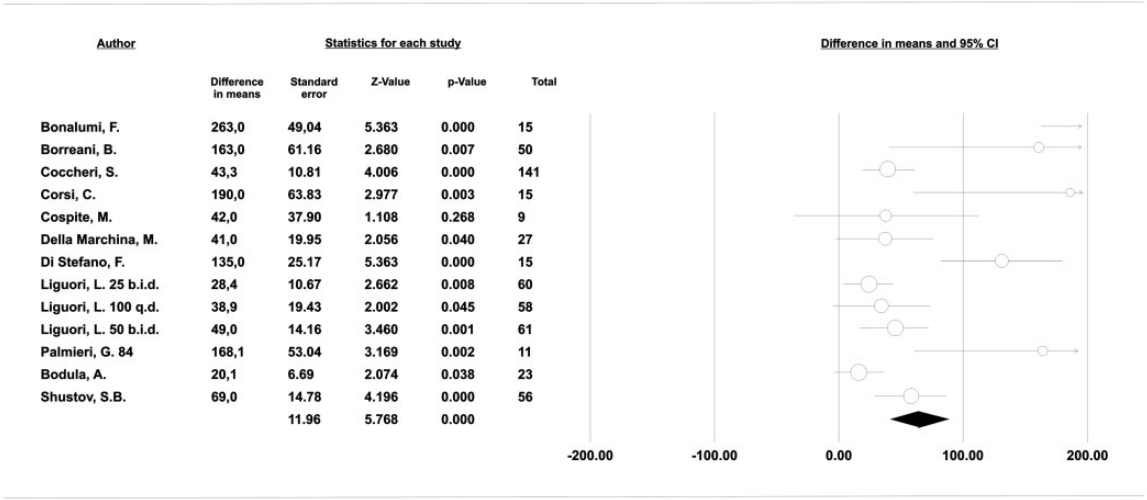


**Figure 2.** ICD mean difference (raw data) with ICD calculated in m in sulodexide-treated patients. The forest plot shows the mean difference between 0 and + 3 months of treatment. The results favour treatment with sulodexide.

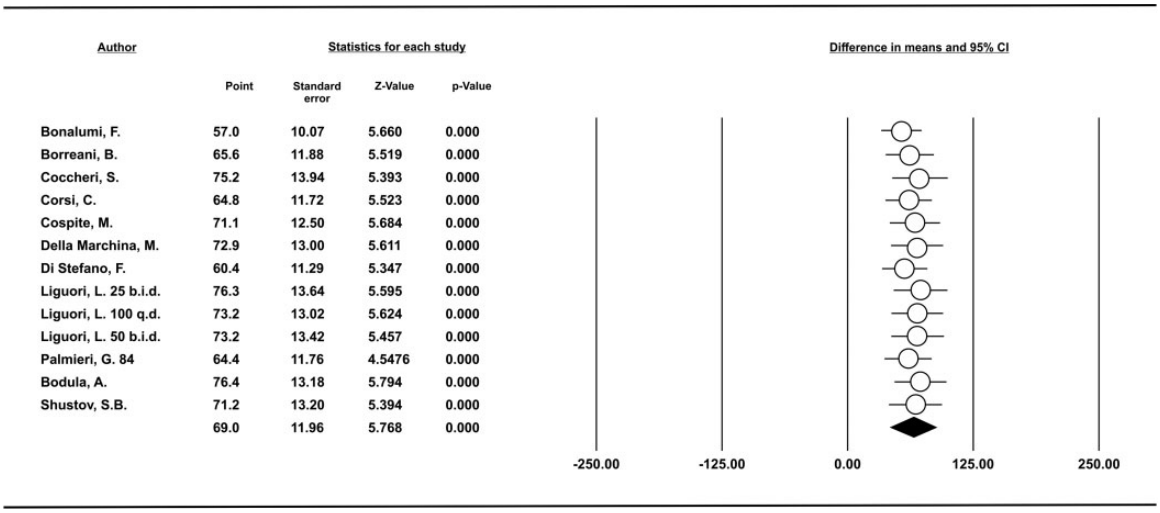


**Figure 3.** Leave-one-out analysis of ICD improvement measured in m in the sulodexide group. The plot shows the results on computed random effect size (raw difference in means and 95% interval of confidence) calculated removing one study at a time. The analysis indicates that the influence and the weight of each individual study are very light.

sulodexide: OR $\log = 3.345 \pm 0.837$, $z = 3.997$, $p < 0.0001$) (Figure 7)

Ankle-brachial (Winsor) index. The ankle-brachial (Winsor) index was evaluated in seven surveys with placebo as a control (plus one with pentoxifylline, which we do not considered in our analysis). Several authors reported only the p values at end (paired p within group and/or independent sample t and p values at the end of the study). The data resulted in homogenous and fixed effect meta-analysis demonstrating an improvement of the Winsor index in sulodexide-treated patients (Hedge's $0.346 \pm 0.078$, $z = 4.0531$, $p < 0.0001$).

*Long-term period variations of ICD.* Four studies reported data on ICD differences after six months of sulodexide therapy (three versus placebo and one versus pentoxifylline). Funnel plot analysis revealed the presence of publication bias; however, the mean effect size evaluated with or without predicted values is still the same. The overall analysis of effect size (fixed effect, $I^2=0\%$) on raw ICD within group differences in sulodexide group resulted in $89.0 \pm 13.71$ m, $z= 6.491$, $p < 0.001$.

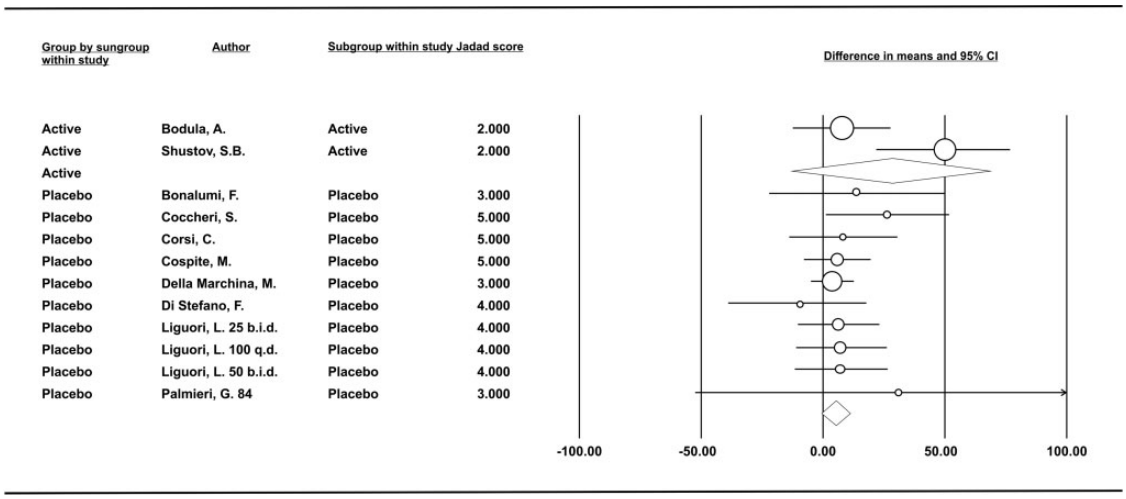


**Figure 4.** ICD mean difference (raw data) in pentoxifylline (top diamond) and placebo (bottom diamond)-treated patients. The graphs show the forest plot of the mean difference between 0 and + 3 months of treatment.

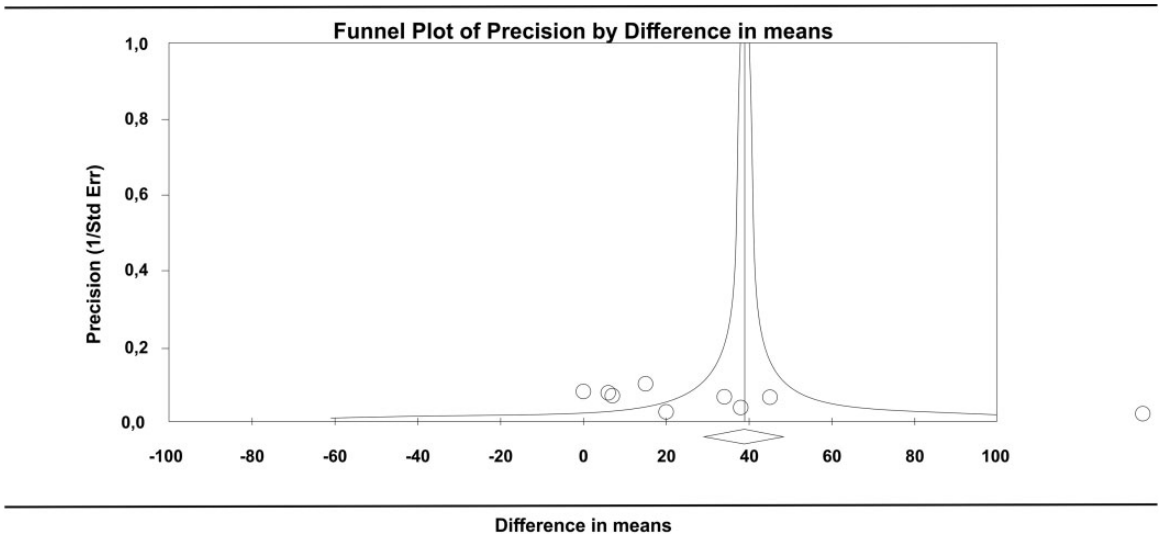


**Figure 5.** Funnel plot of precision by ICD difference in means. The graph shows a remarkable deviation from the funnel distribution, highlighting the possible presence of publication bias in the Borreani study.

*Miscellanea*

Adverse events/side effect. No serious or clinically relevant side effects were described in the surveys included in this review. The Shustov study reports lower side effects, referred ad minor complaints, in the pentoxifylline group ($p < 0.05$).

## Discussion

Our meta-analysis aimed to evaluate the effect size of sulodexide on ICD improvement in patients with well-established peripheral vascular disease (particularly in stage IIa and IIB according to Leriche classification). After three months of therapy, the effect size was 70–90 m; this is an increase of the PFWD of approximately 45%, which is significantly higher than the placebo controls (+3%). There are no sufficient data available to compare sulodexide with other drugs; we found only two studies where sulodexide was compared with pentoxifylline. These two studies formally show similar results in the raw ICD difference effect size.

The one-study influence and cumulative analyses reflect the stability of the effect-size results reported above.

As stated before, we also found a slight rise of ICD in placebo-treated controls; several studies reported in other reviews[33,69] show a slight increment in patients

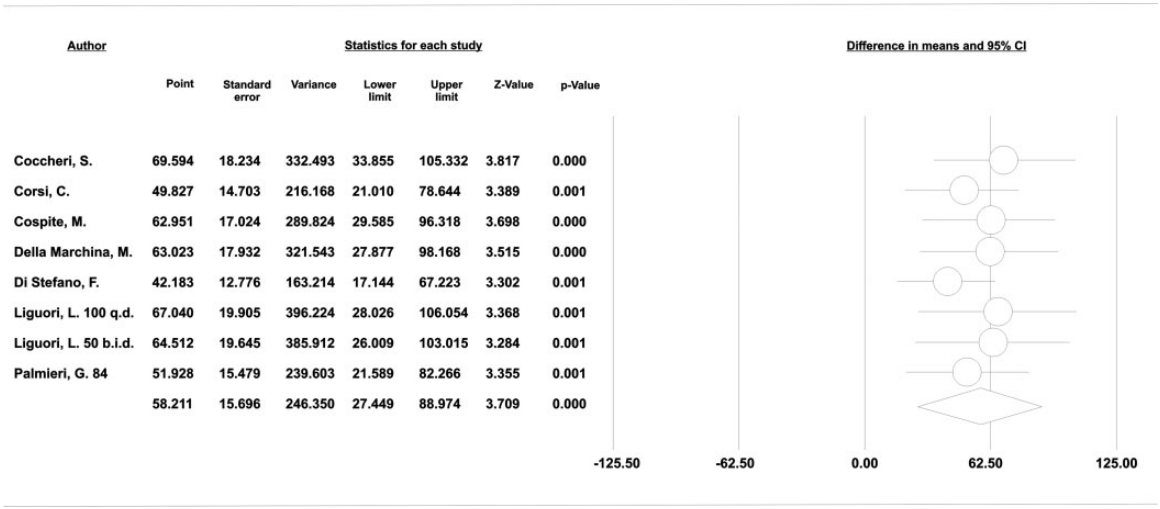


**Figure 6.** Forest plot of raw ICD difference between sulodexide and placebo, with the leave-one-out method (details in the text).

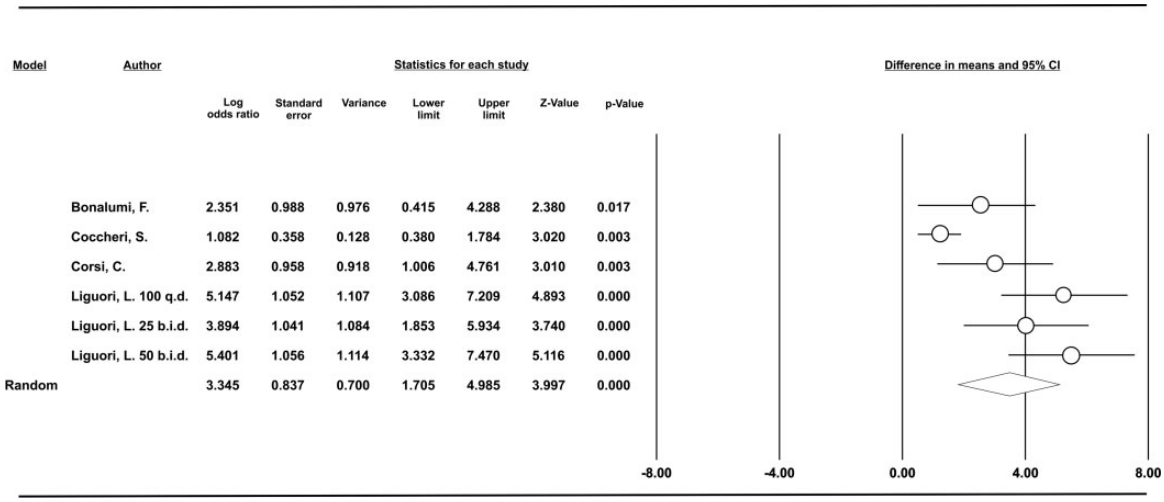


**Figure 7.** The forest plot shows the random effect size evaluated on the log of OR of number of patients with marked ICD improvement in sulodexide- or placebo-treated groups. The results favour the sulodexide group.

treated with placebo, which refers to improvement in the lifestyle or in the physical activities of the patients when assessed for confounders;[27,70] this was particularly evident when the placebo group went through supervised and personalized physical activity programmes[26,71] or the optimization of concomitant treatments.

In the studies that we included in our final review, concomitant treatments were homogeneous in the sulodexide group and in the control group, with no specific activity programmes in place, as suggested by guidelines;[51,72] in one study, a progressive walking programme was strongly recommended.[40]

The number of patients who improved their medical condition after treatment with sulodexide suggests that this drug can be useful in the management of IC.

The Momsen systematic review[73] on drugs for improvement of walking distance in claudication, according to European guidelines, states that an improvement of 30% or more of the ICD is clinically meaningful to help maintain essential daily living activities. In addition, a walking distance of 70 m without leg pain enables patients to work in non-physical jobs. The Momsen review shows results close to the upper limit of these cut-offs when statins, cilostazol, indobrufen and naftidrofuryl were used.[73] Momsen cited only one article on sulodexide stating that "of the individual drugs, the effect estimate pointed to sulodexide as the most effective with an increase in MWD of 86 meters (95%IC 83–89)".

Similar results are described for pentoxifylline, although some studies show a negative or non-

significant effect: Girolami, in a recent meta-analysis,[68] confirms significant inhomogeneities in the results when pentoxifylline is considered, with a mild improvement of the ICD (+44, IC95% 14–74 m when compared with the placebo group).

Our meta-analysis, with only two studies in which pentoxifylline was used in the control groups (both with a JADAD score of 2), does not add any information. We can speculate that the inclusion of these studies – namely, the raw ICD difference in pentoxifylline-treated patients of +7 m ($p > 0.05$) and +49 m ($p < 0.01$) in Bodula[59] and in Shustov[67] study, respectively – in the Girolami meta-analysis would not have modified its conclusions.

In addition, recent guidelines include cilostazol among the drugs suggested for the treatment of IC. Nonetheless, there are no recommendations related to the use of pentoxifylline, although a recent review published in the Cochrane database showed significant differences among cilostazol and pentoxifylline, as also stated by FDA;[33] a further analysis concluded that cilostazol is not cost-effective, suggesting that naftidrofuryl oxalate is the only vasoactive drug for PAD, which is likely to be cost-effective.[74] According to the ESC guidelines, however, there is no evidence that cilostazol, naftidrofuryl, pentoxifylline, buflomedil, carnitine and propionyl-L-carnitine can improve the walking distance in IC.[3]

In terms of increment of ICD, the naftidrofuryl (nafronyl) had a better ranking,[32,68] with a percentage increase of ICD similar to that of sulodexide as per our meta-analysis.[5]

In this meta-analysis, there is a good concordance among other indexes used to measure the effectiveness of sulodexide on claudication, which is also indirectly expressed in terms of improvement of the ABI. Nevertheless, some discrepancies remain evident in the protocols of individual studies, so that both the number of patients that showed some improvements and the data on ABI are not properly reported; however, it is easy to measure and to standardize. Thus, an in-depth analysis is not possible. Data on the Winsor index are not relevant. Recent literature suggests that future high quality studies are required to objectively define the best training programme to facilitate ABI teaching and learning,[75] considering also that ABI can make diagnosis of PAD even when symptoms are not present yet and can give valuable information in relation to its prognosis and to the prediction of the overall cardiovascular complications of the atherosclerosis.[56,76]

The lack of homogenous data collection is an interpretative limitation of this meta-analysis, as also seen in a similar review of patients with PAD.

However, the comparison of the different drugs available to treat or improve IC is not the aim of this review.

Considering the social implications and the impact of PAD on the quality of life, and the lack of effective programmes for the screening and early diagnosis of this disease – as also highlighted by a recent review by the Cochrane Collaboration[77] – further clinical trials including patients with poor or no symptoms, are highly recommended.

The improvement of ICD in symptomatic patients in stage II and higher according to the Leriche staging scale remains a major target to improve the quality of life of these patients.

According to our review, a three-month treatment with sulodexide resulted in an effective improvement in ICD with an effect size higher than those reported for other medications currently in use or suggested in the international guidelines for the treatment of PAD. For these reasons, we suggest that sulodexide should be considered as the primary choice in the treatment of IC.

## Conclusions

This review indicates that treatment with sulodexide 60 to 100 mg/day for three months can significantly increase ICD in patients with stage IIa/IIb PAD, according to the Leriche classification. The magnitude of the ICD increase was 70–90 m in the intragroup analysis and 60–80 m when compared with the placebo. These results are consistent with other data reported in the literature.

Few studies have followed the effects of a six-month treatment with sulodexide and have found even a higher increment of ICD (90 m on the average).

Our results show that improvement of ICD with sulodexide can reach equal or higher values than other symptomatic treatments in PAD, e.g., cilostazol. This meta-analysis is not able to provide data on the comparison between sulodexide and pentoxifylline effects in PAD.

Further research is needed to clarify whether a longer duration of treatment with sulodexide – 6 to 12 months – can bring a higher benefit for ICD improvement and to assess the effect of this drug in asymptomatic patients with PAD.

### Contributorship

AVG designed the research protocol, assessed the studies, extracted data, wrote the statistical analysis plan, analysed the data and drafted and revised the paper. FC designed the research protocol, assessed the studies, extracted data, drafted and revised the paper. ROD analysed the data and drafted and revised the paper. SF reviewed data analysis,

drafted and revised the paper. OFG-F monitored data analysis and analysed the data, and drafted and revised the paper.

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## Notes

a. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease.[70]
b. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017076473
c. https://meshb.nlm.nih.gov/search
d. http://www.pmidcalc.org/?sid=8721797&newtest=Y
e. comparable data: studies versus placebo, with measurement of ICD in meters in patients with PVD in stage II: Naftidrofuryl raw difference of ICD +49% (95%IC=23–81), cilostazol 13% (95%IC= 2–26), pentoxifylline 9% (95%IC=–2–22), sulodexide 49% (95%IC= 26–72).

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