Meta-analysis of some results of clinical trials on sulodexide therapy in peripheral occlusive arterial disease

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Authors' objectives
The author’s aim was to look at the effect of sulodexide in diabetic and non-diabetic patients with peripheral occlusive arterial disease (POAD), and to determine the effects on the clinical course of claudication or the main risk factors of POAD.

Searching
MEDLINE and EMBASE were searched for articles on sulodexide use in patients with POAD. No search strategy or restrictions (language or dates) were provided, though studies appeared to be limited to Italian research published between 1981 and 1993. The manufacturers were contacted and copies of all published articles on sulodexide were obtained.

Study selection
Study designs of evaluations included in the review
The review included randomised controlled trials.

Specific interventions included in the review
Sulodexide.

Participants included in the review
Patients diagnosed as having POAD, with diagnosis based on clinical and homogeneous criteria. Details of other patient characteristics, such as age and disease status in terms of comorbidities (diabetes and hyperlipidaemia), were provided.

Outcomes assessed in the review
The outcomes evaluated for all studies were fibrinogen (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL). Whole blood and plasma viscosities (centipoise) were evaluated in some of the studies. In addition, descriptive evaluations of the effects of sulodexide or placebo were compared, including: pain-free walking distance (PFWD, m); number of patients with improvement, no effect or worsening of claudication; and the results of clinical instrumental tests (B mode and pulsed Doppler echotomography of the ilio-femoral trunk, strain gauge plethysmography, Windsor index and local pressure evaluations).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The studies were classified according to a hierarchy of evidence and on a journal impact factors according to the 1992 Science Citation Index. All the studies followed a double-blind design and/or with crossover. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
The meta-analysis employed several different statistical methods, including the Mantel-Haenszel method, adopting the Robin formulas, DerSimonian and Laird's method for non-homogeneous groups and the Grand Total method.

How were differences between studies investigated?
Homogeneity was tested using a chi-squared test according to the Grand Total method.

Results of the review
Nineteen studies (849 patients in total) were included in the review, with 427 patients receiving sulodexide and 422 placebo. Seven studies (310 patients) were used to assess PFWD, whilst 8 studies (321 patients) analysed clinical and instrumental results. Fibrinogen levels were assessed in 8 studies (321 patients) after oral administration for 70 to 90 days, and in 6 studies (259 patients) which included both intramuscular and oral administration. Viscosity was assessed in 7 studies (348 patients). No data was provided on the number of studies or patients in the analysis of lipids.

Sulodexide had no significant effect up to 20 days treatment, sulodexide significantly increased PFWD in patients after 70 to 90 days oral treatment, compared to PFWD prior to treatment (t=0: +143.6 m, t=-3.40; 95% confidence interval, CI: -237.6, -9.7, P=0.0066, d.f.=10) and compared to placebo (t=0: +146.2 m, t=3.11, P=0.014; 95% CI: 37.9, 254.4, P=0.014, d.f.=8).

Analysis of clinical and instrumental tests showed 7 of the 8 studies had odds ratios above 1, favouring sulodexide in respect of improving rates and worsening rates. No overall odds ratio or confidence limits are quoted.

Sulodexide had significant effects on fibrinogen after 70 to 90 days oral treatment for intra- and inter-group differences. The case number-weighted average on pooled data for sulodexide at baseline was 346.7 plus or minus (±) 8.3 mg/dL, and at 70 days, 294.0 ± 9.7 mg/dL (P<0.0001 versus baseline). The corresponding value for placebo at baseline was 344.8 ± 9.1 mg/dL (P>0.1 versus sulodexide at baseline), and at 70 days, 345.8 ± 9.5 mg/dL (P>0.1 versus baseline; p<0.01 versus 70 days sulodexide group).

Whole blood, plasma and serum viscosities were unaffected by the placebo treatment, but 5 of the 6 studies showed highly significant declines in plasma and serum viscosities with sulodexide treatment. Whole blood cholesterol was reduced by intramuscular sulodexide in all 6 studies and by oral sulodexide in 3 of the 6 studies.

Sulodexide had a beneficial effect on lipids following 3 months of therapy. Triglycerides declined from 222.1 to 159.4 mg/dL (95% CI: 29.3, 96.2, P>0.015 versus t=0) for the group receiving sulodexide, and from 206.5 to 192.1 mg/dL (95% CI: 35.1, 17.1, P=0.46 versus t=0) for the placebo group. HDL-C levels increased with sulodexide from 38.02 to 47.38 mg/dL (95% CI: ± 4.6, -14.1 P=0.0007 versus t=0) but changed only marginally with placebo from 38.18 to 39.55 mg/dL (95% CI: ± 4.6, +1.9, P=0.38).

Authors' conclusions
The studies reviewed consistently showed that sulodexide is effective in treating and/or preventing POAD. When administered intramuscularly for a short time and then orally for an average of 70 days, increased claudication distance significantly, evaluated as PFWD on a treadmill. Clinical and instrumental results showed beneficial effects from medium-term sulodexide therapy compared to placebo. Medium-term therapy with daily doses of 500 to 1000 LRU (lipoprotein lipase releasing units) decreases claudication effectively in early-stage POAD patients and prevents disease worsening (for at least 6 months), compared to placebo. However, the analysis could not establish the long-term efficacy of intramuscular sulodexide therapy, the effectiveness of short-term treatment with oral sulodexide, and the efficacy of sulodexide in advanced stages of disease.

CRD commentary
Limited information on the literature search strategy is provided in the review, with no specific mention of key search terms or restrictions on search dates and publication language. Selection and validity criteria are discussed within the
review although their application receives little attention. Similarly, methods of data extraction are not discussed. The analysis uses a range of statistical methods for testing for heterogeneity and for pooling results where appropriate. Unfortunately, the presentation of statistics from the individual studies and from the pooling of results appear incomplete and unclear, making interpretation of the evidence difficult. Whether drop-out rates from the studies, or odds ratios and CIs, their exclusion from the analysis is detrimental to the quality of the review. The review uses quality and inclusion criteria and assesses the influence of publication bias, but the strength of the evidence may be affected by the apparently selective literature search.

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