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# Meta-analyses of sulodexide and other drugs in prevention and treatment of post-thrombotic syndrome

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**Abstract. – OBJECTIVE: Post-thrombotic syndrome (PTS) is a common chronic complication of deep vein thrombosis. Elastic compression (ECS) is the common pillar for PTS prevention and treatment, while the pharmacological approach for PTS includes direct oral anticoagulants (DOACs) and venoactive drugs (VADs) for prevention and treatment, respectively. Sulodexide can be used both in long-term prevention and in the treatment of PTS. To better understand the efficacy of the main drugs used in the prevention (sulodexide or DOACs) and treatment of PTS (sulodexide or VADs), pairwise meta-analyses of observational studies and RCTs were conducted.**

**MATERIALS AND METHODS: A literature search in MEDLINE, Embase, and Cochrane Library for observational studies and RCTs was performed. Incidence of PTS, reduction in PTS signs or symptoms and proportion of patients with complete venous ulcers healing were the primary outcomes for prevention and treatment of PTS, respectively. Fixed and Random effect model meta-analyses were performed. Heterogeneity and publication bias were assessed. R® software was used for the analysis.**

**RESULTS: 893 articles were identified during the search. 8 observational studies (6 for DOACs and 2 for sulodexide) and 2 RCTs for sulodexide, out of the 11 studies included in the qualitative synthesis, were included for the prevention and treatment of PTS, respectively. Meta-analyses of observational studies showed an overall incidence of PTS of 15% (95% CI, 11-19) for sulodexide, and a 50% reduction of PTS signs and/or symptoms for rivaroxaban compared to warfarin (OR, 0.50; 95% CI, 0.38-0.65). The overall estimate of the two sulodexide RCTs showed a significant improvement in complete ulcer healing, with an OR of 2.32 (95% CI, 1.49-3.63).**

**CONCLUSIONS: In prevention of PTS, sulodexide and rivaroxaban showed a low incidence and reduced risk of PTS respectively, while in PTS treatment, sulodexide was significantly effective in the complete ulcers healing. These results confirm the need to move from the traditional single-pillar approach with elastic compression stockings to a more effective multi-pillar approach, tailoring the treatment to each individual patient.**

*Key Words:*
*Post-thrombotis syndrome, PTS, Sulodexide, DOACs, Venoactive drug, Prevention, Treatment, Ulcer.*

## Introduction

Post-thrombotic syndrome (PTS) is a common chronic complication of deep vein thrombosis (DVT), which develops in 20-50% of patients after proximal DVT[1] and has a moderate to severe intensity in approximately 15% of cases, with an associated worsening of quality of life (QoL) after DVT[2]. PTS is a long-term consequence of chronic venous hypertension produced by reflux alone or combined with persisting outflow obstruction[3]. Venous hypertension is associated with chronic inflammation affecting not only the vein wall but also the microcirculation, producing excessive capillary leakage and impairment of skin nutrition[4], with fibrotic remodeling of the vessel wall due to medial cell proliferation, matrix protein changes, self-sustained leukocyte influx, and action by proteinases as matrix metalloproteinases and growth factors leading to further damage of valves with resulting reflux[5,6]. Some studies[7,8] have shown raised levels of IL-6 and C-reactive protein in patients with PTS.

In addition to chronic venous hypertension, thrombus remodeling plays a key role in the pathogenesis of PTS. As some studies have shown, the appearance of residual vein thrombosis within the first 3-6 months after acute proximal DVT may predict the development of PTS[9,10] and, while the



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process leading to the formation of new thrombus and its resolution is relatively known, it is unclear why in over one-third of patients a complete recanalization does not occur.

Among the main known risk factors for PTS[11], proximal (e.g., iliofemoral) location of the index DVT and a history of prior ipsilateral DVT seem to be the most important factors as each of them increases the risk by up to 6 times[12]. In patients with acute lower-limb DVT, a study from the international RIETE Registry found that prior history of VTE, diabetes, pre-existing leg varicosities and male sex independently increased the risk for PTS ulcer at one year[13]. Identification of DVT patients at increased risk of developing severe PTS signs and/or symptoms as well as new predictors, such as markers of inflammation, could likely serve as targets for potential new treatments.

The clinical presentation of PTS is characterized by edema and skin changes such as venous ectasia, redness, eczema, and hyperpigmentation, with all the clinical signs of PTS caused by increased venous pressure[12]. In severe cases, fibrosis of the subcutaneous adipose tissue and chronic venous ulcers develop. The diagnosis of PTS is mainly based on clinical grounds in patients with signs of chronic venous insufficiency (CVI) and a previous episode of DVT at least 3 months before. The Villalta scale[14] is recommended as the most appropriate measure for PTS diagnosis by the International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation. Treatment options are based on both prevention and treatment of PTS. Given the proven association between recurrent DVT and a higher risk for PTS, the prevention of DVT recurrences should reduce the prevalence of PTS because the persistence of signs and symptoms one month after the onset of DVT are highly predictive of the subsequent development of PTS[15]. Pharmacological prevention treatments include anticoagulants (DOACs - direct oral anticoagulants), although current guidelines do not recommend any specific anticoagulant after DVT[11,16], neither vitamin K antagonists (VKAs) nor low-molecular-weight heparins (LMWH) or DOACs[16,17].

Sulodexide, a heparin-like substance that is active both parentally and orally showed anti-inflammatory and endothelial protective effects in two important observational studies, reducing significantly the incidence of recurrent DVT and better preventing the development of PTS than their control groups[18,19]. In Luzzi et al[19], the incidence of PTS was lower in the sulodexide subgroup (12.17%) than in the two other subgroups [18.23% in standard management (SM) with elastic compression stockings (ECS) and 23.5% in SM + aspirin 23.5%, respectively]. For this reason, sulodexide might be a novel approach in the long-term prevention of PTS after initial anticoagulant therapy for DVT.

As to the treatment of PTS, besides physical activity, ECS and pharmacologic therapy are the most important approaches. The main goal is to prevent stasis in the limb alleviating symptoms and improving limb functioning. However, the evidence is limited to only two RCTs that showed contrasting results[20,21]. Active principles, such as venoactive drugs [e.g., micronized purified flavonoid fraction (MPFF) or hydroxy-ethyl-rutosides], are currently used for the treatment of PTS, but their evidence is limited as it has been shown in two meta-analyses[22,23]. Sulodexide can be used in the treatment of PTS; in particular, in the treatment of venous ulcers[24,25]. To better understand the efficacy of the main drugs used in the prevention (sulodexide or DOACs) and the treatment of PTS (sulodexide or venoactive drugs), a pairwise meta-analysis of observational studies and one of RCTs were conducted, respectively. In PTS prevention only the observational studies were considered because none of the pivotal randomized clinical trials (RCTs) included the incidence of PTS as an outcome, while RCTs were used to perform a meta-analysis for the treatment of PTS.

## Materials and Methods

### Search Strategy and Selection Criteria

This work was registered in the International Prospective Register for Systematic Reviews. The literature search was conducted in Medline (through PubMed interface), EMBASE, and Cochrane Library, according to the PICO (Patient/Population, Intervention, Comparison/Control, Outcome) statement through the proper search strategy, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[26] (**Supplementary Table I**). For a meta-analysis of observational studies for PTS prevention, cohort and case-control studies have been included and following PICO criteria were considered: (P) adult population diagnosed with lower extremity DVT, regardless of the methods of diagnosis treated with drugs for at least 4

weeks; (I) sulodexide *vs.* DOACs (rivaroxaban, dabigatran, apixaban, edoxaban); (C) placebo *vs.* other drugs; (O) incidence of PTS after treatment or as risk to develop PTS. Furthermore, no limitation for use of compression measures was imposed and English language restrictions were adopted. Only the full text was considered for inclusion. For RCTs, a PICO was built up to perform pairwise meta-analysis of sulodexide *vs.* venoactive drugs in PTS treatment (**Supplementary Table II**).

### Data Extraction and Assessment of Risk of Bias

Two reviewers (GP, ID) extracted the following data independently: first author, year of publication, study design, characteristics of patients, and outcomes. The quality of included studies was evaluated according to the Cochrane Collaboration's tool for assessing the risk of bias[27] and the ROBINS-I tool was used to assess the quality of the non-randomized studies[28]. A third reviewer (MM or RP) was consulted in case of disagreement.

### Statistical Analysis

The incidence or the risk of developing PTS of sulodexide or DOACs in the prevention of post-thrombotic syndrome were measured as proportion or odds ratio. In the meta-analysis of RCTs the proportion of patients with complete ulcer healing was considered.

The fixed and random effect models were applied, and the potential for publication bias was assessed by conducting Begg's funnel plot test and Egger's test in both meta-analyses. Heterogeneity in the meta-analysis was assessed using $I^2$ statistics: it was considered not important when $I^2$ was 0-40%; moderate when $I^2$ was 30-60%; substantial heterogeneity with $I^2$ range 50-90%, and considerable heterogeneity when $I^2$ was 75-100%[29]. The meta-analyses for sulodexide were performed using R software (version R 4.2.0, The R Foundation for Statistical Computing, Vienna, Austria)[30].

## Results

### Systematic Literature Review

893 articles were identified during the literature search 74 of which were duplicates, and 772 were excluded for different reasons. Thus, 47 articles were reviewed for eligibility, and 11 studies were included in the qualitative synthesis covering a period from 1950 to 2022 (9 observational studies[19,31-38] for prevention of PTS and 2 RCTs[24,25] for treatment of PTS) (Figure 1) (**Supplementary Table III**).

### Prevention

6[31-36] out of 9 studies for PTS prevention evaluated the treatment effect of rivaroxaban compared to warfarin, and all reported a significant reduction in PTS development for the former and were included in meta-analysis. A cross-sectional follow-up study[37], which included 166 out of 349 patients treated with dabigatran and 183 with warfarin, showed a crude odds ratio (OR) of 1.1 (95% CI; 0.6-1.8) for PTS in patients treated with dabigatran compared with warfarin, meaning a similar effectiveness in prevention PTS for dabigatran and warfarin. Two observational studies[19,38] for the prevention of PTS were included in the meta-analysis for sulodexide, with both studies reporting a significantly lower occurrence of PTS than that observed with the placebo group[38], and standard management (SM)[19], respectively.

### Treatments

Following the exclusion criteria reported in the PICO for RCTs, four abstracts were excluded[39-41,44] two for rutosides[39,40] and two for MPFF[41,44]. In particular, one abstract[39] for rutosides in 84 patients reported an improvement in the clinical symptoms and a significative circumference reduction of the calf and ankle at the 8th week in the HR [0-(β.hydroxyethyl)-rutosides] group compared to control, and the other one[40] reported an improvement of PTS (Villalta Scale) in HR and ECS group in 120 patients followed-up for 12 months. For MPFF, one abstract[41] reported improvement of some objective venous measures (such as capacity distensibility, outflow time and tone) and the other one[42] found an improvement in PTS symptoms in patients receiving MPFF compared to conservative treatment alone. Another RCT[43] previously considered by Li et al[44], that evaluated MPFF in combination with rivaroxaban compared to rivaroxaban alone in patients with femoropopliteal DVT, was also excluded because it evaluated the prevention of PTS and therefore did not meet the PICO criteria. Two RCTs[24,25] for sulodexide were included in pairwise meta-analysis, with a total of 329 patients investigated. Both studies for sulodexide found a significant effect on healing ulcers.

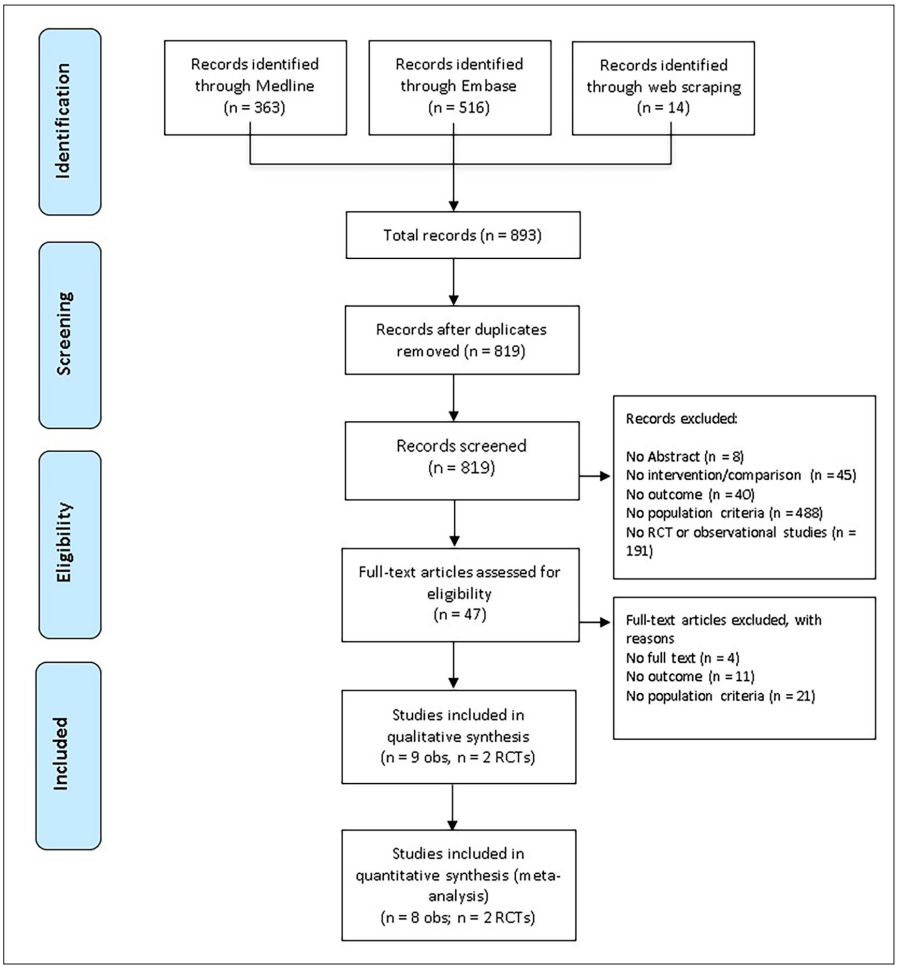


**Figure 1.** PRISMA diagram.

## *Meta-Analysis of Observational Studies for Prevention of PTS*

### *Sulodexide*

The two observational studies[19,38] for sulodexide were included in the meta-analysis. The overall effect estimate, evaluated on 346 patients, reported an incidence of PTS of 15% (Random effect model, 95% CI, 11-19) showing that sulodexide was effective in preventing PTS (Figure 2).

### *Rivaroxaban*

All six studies[31-36] reported in the qualitative synthesis were included in the meta-analysis. Patients receiving rivaroxaban for DVT had a

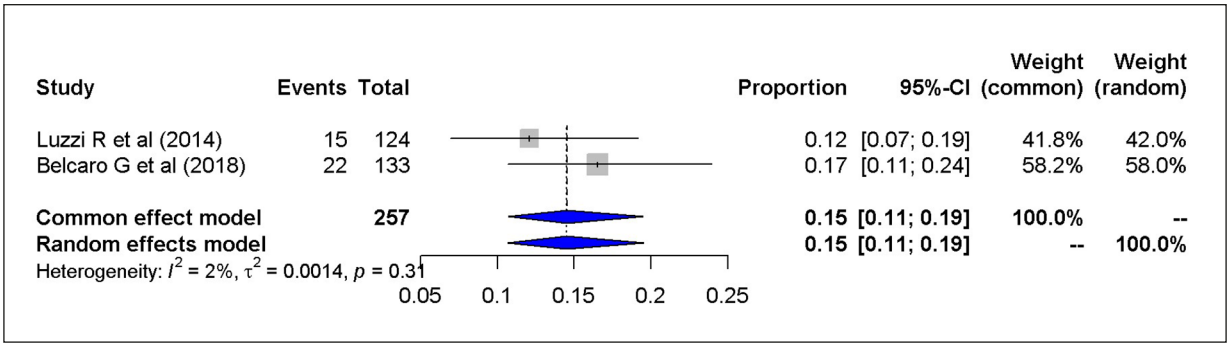


**Figure 2.** Pairwise meta-analysis of observational studies of sulodoxide.

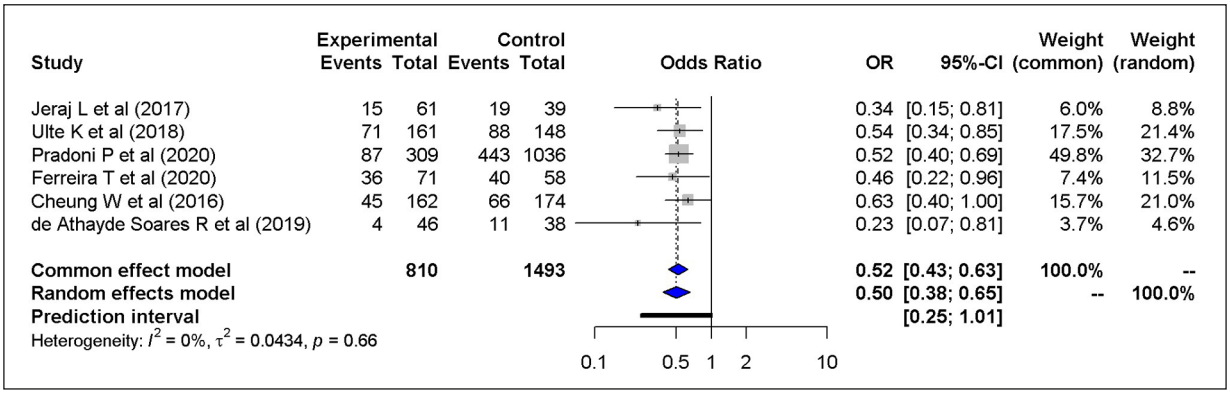


**Figure 3.** Pairwise meta-analysis of observational studies of rivaroxaban.

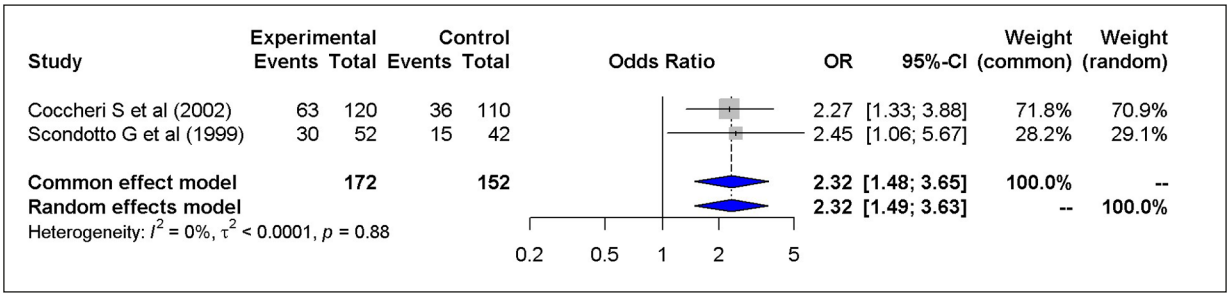


**Figure 4.** Pairwise meta-analysis of RCTs of sulodexide.

significant reduction in PTS signs and/or symptoms compared to patients receiving warfarin (OR=0.50; 95% CI, 0.38-0.65). The heterogeneity of the included studies was low ($I^2$=0%; $p$=0.66) (Figure 3).

### *Meta-Analysis of RCTs for Sulodexide*

The overall estimate of two RCTs of sulodexide for complete ulcer healing found a significant improvement, with an OR of 2.32 (95% CI, 1.49-3.63), meaning that sulodexide was more effective (2.32 times) than the control (Figure 4). The heterogeneity was zero as both studies had the same level of agreement, showing that sulodexide was more effective than the control groups (Figure 5).

### *Assessment of Risk and Publication Bias*

Both RCTs included in the meta-analysis found an unclear risk of selection bias, while Scondotto et al[25] reported an elevated risk of execution bias. Thus, the overall assessment was a low and unclear risk of bias for Coccheri et al[24] and Scondotto et al[25] respectively (Figure

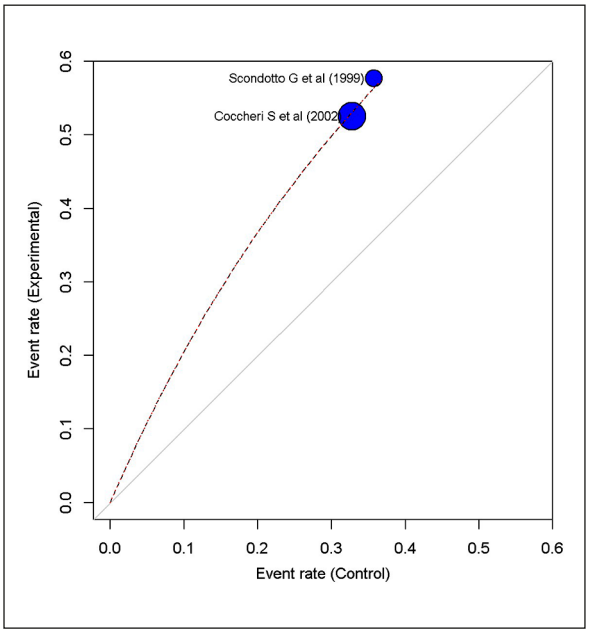


**Figure 5.** Visual inspection through Abbé plot. RCTs in which the experimental treatment proves better than the control will be in the upper left of the plot, between the y axis and the solid line of equality.

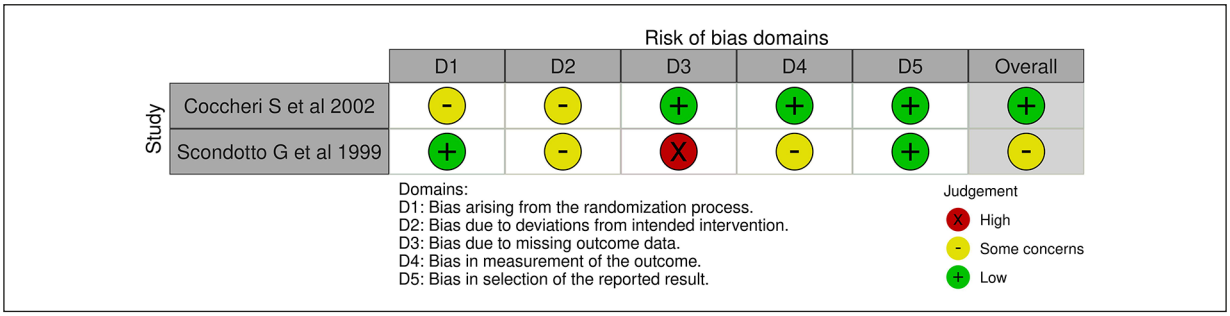


**Figure 6.** Risk of bias summary for RCTs of sulodexide.

6 and Figure 7). The risk of bias for the observational studies included in meta-analyses was evaluated as moderate in both cases (**Supplementary Figure 1** and **Supplementary Figure 2**). A funnel plot was developed to ascertain the publication bias of RCTs of sulodexide included in the pairwise meta-analysis: no publication bias was observed (**Supplementary Figure 3**). However, it must be considered that at least ten studies are needed to detect the asymmetry of the funnel plot[45].

## Discussion

To date, pharmacological therapy, early thrombus removal, and ECS have been considered the main therapeutic approaches for preventing PTS after DVT, with ECS being considered as the mainstay. However, compression therapy has been considered to have a low class 2B recommendation in the AHA statement on PTS, and an even lower grade 2C recommendation for ECS and 2B for intermittent pneumatic compression (IPC) in the ACCP guidelines[17,46]. Other non-pharmacological approaches include invasive strategies of clot removal or stenting, thrombolysis, and stent placement in patients with chronic PTS[47]. Clot removal has been used to prevent venous reflux, venous outflow restriction and thereby PTS when impaired fibrinolysis may result in inadequate thrombus resolution. Thrombolysis is an adjunctive treatment to swiftly remove the thrombus in the acute phase of the DVT, with a few data[47] supporting the net clinical benefit. Stenting may maintain long-term venous patency and relieve symptoms, but it is still unclear how to manage anticoagulant therapy in patients with venous stenting[47]. The pharmacological strategy to prevent PTS after lower-limb DVT is mainly based on the use of DOACs, VKAs or LMWH. Studies[11,16] with DOACs suggested that the type and quality of the specific DOAC may influence the risk of PTS, though the incidence and severity of PTS were not included among the outcomes in the Phase III clinical trials with DOACs, VKAs seem to be associated with both VTE recurrences and PTS[17] while LMWHs have been found to be more effective than VKAs[16], with a meta-analysis[48] of 5 RCTs confirming a significant risk

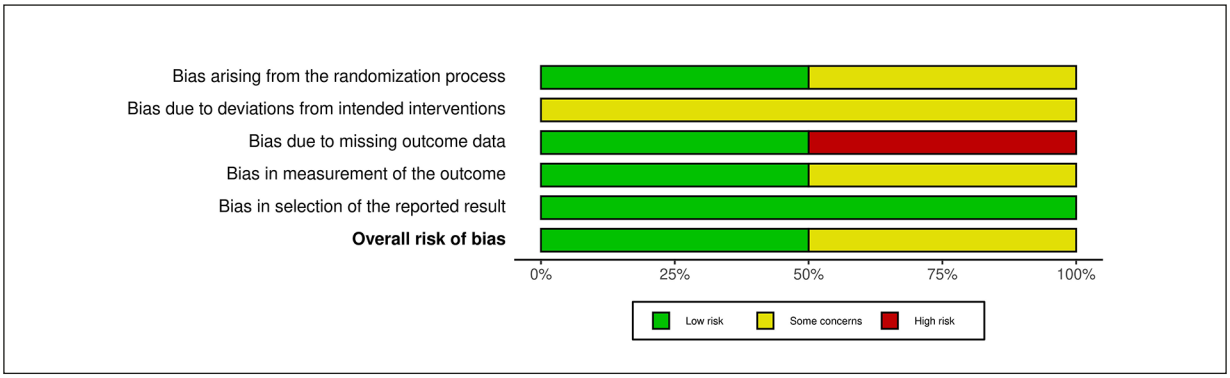


**Figure 7.** Risk of bias graph for RCTs of sulodexide.

reduction of both PTS and residual vein thrombosis. The adjunctive therapy with statins may help to reduce the incidence of PTS, as found in a RCT comparing LMWH monotherapy *vs.* LMWH plus a statin (rosuvastatin)[49]. Patients also receiving rosuvastatin were at a lower risk for PTS at 3 months (38.3% *vs.* 48.5%, $p$=0.02), but we are still waiting for the results of the SAVER pilot study to better understand the impact of statins to prevent PTS (available at: ClinicalTrials.gov; Identifier: NCT02679664). Regarding the treatment of PTS, few RCTs[22,23] are available for MPFF and rutosides that explicitly included patients with PTS among the inclusion criteria, and a review[50] evaluating healed ulcers in patients receiving flavonoids did not consider a specific PTS population. In meta-analyses of observational studies, we found a low incidence of PTS, with 9% of patients presenting PTS among patients receiving sulodexide and a 50% reduction in the risk of PTS in patients receiving rivaroxaban. These findings highlight the need for a shift from the traditional single-pillar approach towards a multi-pillar approach tailoring the treatment for every individual patient[47], also in the light of a recent meta-analysis that found a low benefit with the use of ECS in preventing PTS[51]. Furthermore, for DOACs, it needs to be considered that Ginsberg et al[20] did not find a pleiotropic effect that could benefit the vessel walls. In addition, the use of sulodexide was associated to an extremely low risk of bleeding. This is in line with the recent new European Venous Forum (EVF) guidelines, which states that secondary prophylaxis should be based on estimates of the risk of recurrences *vs* the risk of bleeding to select the most appropriate drug[52].

For the treatment of PTS, a meta-analysis of two RCTs found sulodexide to be 2.32 more effective than the control group (placebo + ECS) in healing ulcers (OR=2.32, 95% CI, 1.49-3.63). Although indirect comparisons between sulodexide and its comparators cannot be performed due to a lack of appropriate studies, an indication of the therapeutic potential of sulodexide compared to rutosides may be derived from a meta-analysis included in the Cochrane review[22] which reported an OR for rutoside for PTS improvement of 1.29 (0.69-2.41). Though few studies[19,24,25,38] are availablefor sulodexide in the prevention[19,38] and treatment of PTS[24,25], its anticoagulant, antithrombotic, profibrinolytic, anti-inflammatory and hemodynamic properties are well known[53-58].

### Limitations

There are several limitations regarding the potential bias introduced by performance and selection bias in some of the included RCTs; the lack of RCTs for sulodexide in the prevention of PTS makes the quality of evidence low, just as the absence of RCTs for the treatment of other signs and symptoms of PTS besides ulcers does not allow the benefit of sulodexide to be extended to the treatment of PTS as a whole.

## Conclusions

This study found that sulodexide and rivaroxaban seem to be effective in preventing PTS, showing a low percentage of patients developing PTS and a reduced risk of PTS, respectively. Sulodexide reported a clinically effective in treating the most severe sign of PTS such as ulcers, appearing to be an important pillar in both the prevention and treatment of PTS. However, due to the low quality of the studies on the prevention of PTS[19,31-36,38] and the lack of head-to-head studies for the treatment of PTS, the findings of this study need to be validated by further good quality studies.

This is the first study to jointly evaluate the evidence for sulodexide in the prevention and treatment of PTS. A quantitative synthesis of the evidence is not only important for assessing the impact of sulodexide in PTS, but is also useful for addressing clinicians in their treatment choices and, more generally, for understanding what further studies should be conducted to fill the missing evidence.

### Conflict of Interest

DI is the CEO of ISHEO s.r.l. and has received grants from Abbvie, Merck Serono, Bristol Myers Squibb, Pierre Fabre, Eli Lylli, Boehringer Ingelheim, Angelini, Fidia Pharma, and AlfaSigma. Other authors declare no conflict of interest.

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### Authors' Contribution

GP, MM and RP performed literature search and reviewed articles for inclusion. GP and DI wrote the first draft of the review. All authors reviewed and edited the manuscript and approved the final version.

### Ethics Committee and Informed Consent

Not applicable.

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