The Effect of Sulodexide on the Incidence of Cardiovascular Outcomes in Patients With Vascular Disorders

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Abstract

BACKGROUND AND OBJECTIVES: Among patients with macrovascular and microvascular disease, we investigated the association between sulodexide and cardiovascular (CV) outcomes and adverse events.

METHODS: We conducted a meta-analysis of randomized control trials (RCTs) reporting CV outcomes and adverse events in patients with vascular disease receiving sulodexide for any indication versus control. The following outcomes were investigated: any CV event, myocardial infarction, CV death, bleeding events and gastrointestinal symptoms.

RESULTS: Twelve studies with a total of 8,436 patients were included. Sulodexide resulted in a significant reduction in CV events (OR 0.51 [95% confidence interval 0.41-0.73]; p<0.0001) and CV death (OR 0.63 [CI 0.48-0.81]; p = 0.0004). This effect was mainly related to a lower risk of CV events (OR 0.55, CI 0.41-0.73) and CV death (OR 0.60, CI 0.45-0.79) in the macrovascular disease arm. Similarly, patients with macrovascular disease on sulodexide had significantly lower rates of myocardial infarction (OR 0.68 CI 0.50-0.94; p = 0.02) compared to control. The effects of sulodexide were nonsignificant among patients with microvascular disease in terms of overall CV event, myocardial infarction and mortality reduction. The risk of bleeding and gastrointestinal adverse events was not significantly different between sulodexide and control.

CONCLUSION: Sulodexide has a beneficial effect among patients with macrovascular disease in terms of reducing the risk for MI, overall CV mortality and CV events. Larger RCTs are needed to corroborate these findings.

KEYWORDS: Sulodexide, microvascular disease, macrovascular disease, cardiovascular outcomes

BACKGROUND

The endothelium connects all organs in the body. Its dysfunction is transmitted to all tissues with arterial, venous and capillary vessels. There are evidences of interconnectivity between all vascular disorders and also evidences of shared risk factors. For example, increasing age, family history, physical inactivity, hypertension and obesity are shared risk factors for chronic venous disease and coronary artery disease. Furthermore, literature suggests that if one vascular bed is diseased, the other vascular beds are also involved. For example, in the TROMSO study where 1,853 patients with myocardial infarction were observed, there was 51% increased risk of venous thromboembolism.[1] In another large cohort of 25,199 patients with previous deep vein thrombosis (DVT), there was 60% increase in incidence of myocardial infarction.[2] In the REACH Registry, 2,485 patients with peripheral artery disease (PAD) had 61% risk of myocardial infarction.[3] In a cohort of patients with diabetic retinopathy, a twofold increase in incidence of myocardial infarction was observed.[4] In patients with chronic kidney disease, the risk of myocardial infarction was 51% higher.[5] In elderly patients with albuminuria, there

was 74% increased risk of myocardial infarction.[6] Another study showed that in patients with chronic venous insufficiency, there was 40% risk of myocardial infarction.[7] These studies suggest that there may be an underlying pathophysiologic process where prior or concomitant arterial vascular disease can predispose the development of venous diseases and vice versa.

Several RCTs have suggested this interconnectivity among all the vascular beds. In the HOPE 1 study, which included patients at elevated risk for cardiovascular events, it showed that treatment with ramipril resulted in 32% relative risk reduction of myocardial infarction (MI), stroke and CV death. Overt nephropathy was also reduced by 22% suggesting that protecting the coronary vascular bed also positively affects renal vasculature.[8] In the SPARCL study, stroke or transient ischemic attack (TIA) patients given high-dose statins had 16% reduction in stroke recurrence. Incidentally, the overall incidence of MI was 49% and cardiovascular events also reduced by 3.5%.[9] Similarly, in the SHARP study, 9,438 patients with advanced chronic kidney disease who received intensive lipid lowering agents had relative risk reduction of 18% for developing major atherosclerotic events, defined as the combination of MI, coronary death, ischemic stroke or any revascularization procedure.[10] In the same manner, the PEGASUS trial showed 15% relative reduction in the risk of major adverse cardiovascular events (MACE), and stroke was also reduced by 25%.[11] In the ASCOT study, total MI was not reduced significantly, but occurrence of PAD was reduced by 35%.[12] Lastly, in patients with venous thromboembolism (VTE), pulmonary embolism (PE) and atrial fibrillation (AF) who received non-vitamin K antagonists, stroke and systemic embolism were reduced by 18%-21%, while myocardial infarction was reduced by 33%-53%.[13] All of these data suggest that there was interconnectivity between the vascular beds, therefore protecting one bed may translate to protection of the rest of the vascular system.

Both microvascular and macrovascular diseases are independently associated with a 10-year risk of MACE, microvascular events and death. However, this is more established among patients with diabetes mellitus, which is one of the more common causes of both microvascular and macrovascular disease.[14] Microvascular disease has been associated with increased risks of developing macrovascular complications at a later time. Macrovascular disease is well-known to predispose or even coexist with involvement of a different macrovascular territory. However, no study has provided comparison on the extent of vasoactive medication effect like sulodexide between microvascular and macrovascular disease subgroups in reducing cardiovascular events, death and MI.

The endothelium of blood vessels has a lining called glycocalyx, which is composed of proteoglycans, dermatan, heparan and chondroitin.[15] They exist as hair-like structures along the endothelium, maintain fluidity of blood and control transport of molecules between the blood and tissues. Glycocalyx damage leads to endothelial dysfunction and eventual atherosclerosis and thrombosis.[16] Restoring the glycocalyx can reverse endothelial dysfunction by continuously supplying back its components glycosaminoglycans, specifically dermatan and heparan. One of the naturally occurring glycosaminoglycans is sulodexide. Sulodexide was investigated in several clinical trials on various vascular disorders both involving venous and arterial diseases. In this study, the authors looked into the effect of sulodexide on the incidence of MI when given to patients with various vascular disorders.

RESEARCH QUESTION

Among patients diagnosed with any vascular disorder, what is the effect of sulodexide on the incidence of MI and cardiovascular death?

Objectives

General Objective: To determine the effect of sulodexide on the incidence of MI and cardiovascular mortality when given to patients with macrovascular and microvascular disease: chronic venous disease, DVT, venous thromboembolism, nephropathy, retinopathy and PAD.

Specific Objectives:

1. To determine the effect of sulodexide when given to adult patients with macrovascular and microvascular disease on the incidence of:
   a. Total MI
   b. Cardiovascular mortality
   C. Any cardiovascular event
2. To determine the adverse effects of sulodexide when given to adult patients with macrovascular or microvascular disease on the incidence of:
   a. Any bleeding
   b. Gastrointestinal symptoms

Definition of Terms

Cardiovascular mortality – defined as death from any of the following: acute coronary syndrome, MI, decompensated heart failure, cardiac arrhythmias, stroke, acute limb ischemia, aortic dissection.

Cardiovascular event – defined as follows: acute coronary syndrome, MI, heart failure hospitalization, decompensated heart failure, cardiac arrhythmias, TIA, stroke, acute limb ischemia, aortic dissection.

METHODS

Selection Criteria

We included: (1) all RCTs assessing the efficacy of sulodexide versus no sulodexide or placebo for any indication among patients with vascular disease, AND (2) studies reporting the MI event, cardiovascular events, and/or cardiovascular death, OR (3) the study reported bleeding rate and gastrointestinal symptoms. We excluded studies that did not meet the above criteria and those that could not be retrieved in full text. No

limitations to journal, language, or date of publication were imposed.

Types of Patients
Patients aged 18 years and above with vascular disease were included:

1. Microvascular disease: Retinopathy, nephropathy manifesting as microalbuminuria or macroalbuminuria, peripheral neuropathy.
2. Macrovascular disease: Coronary artery disease, PAD, cerebrovascular disease, chronic venous insufficiency, DVT.

Interventions
All studies included should have at least one treatment arm treated with sulodexide orally with or without initial parenteral dosing (intramuscular/intravenous doses) at any dosage and for any duration.

Outcome Measures
The studies were assessed if any of the following outcome measures were included:

1. MI
2. Any cardiovascular event: Includes MI, reinfarction, stroke, arrhythmia, acute limb ischemia or acute aortic syndrome
3. Cardiovascular mortality: Death from MI, stroke, arrhythmia, acute limb ischemia or acute aortic syndrome
4. Gastrointestinal symptoms
5. Any bleeding

Search Methods
Medline, EMBASE, Cochrane and CINAHL searches using free text and MeSH headings of the following words: "sulodexide", "myocardial infarction", "cardiovascular events", "major adverse cardiovascular events", "gastrointestinal bleeding", "bleeding", "diabetes complications", "chronic venous insufficiency", "peripheral arterial disease", "diabetes mellitus", "acute coronary syndrome". Review of article references retrieved and communications with pharmaceutical companies for unpublished studies were also done. The complete search was concluded on 29 October 2022.

Data Collection and Extraction
Using predefined inclusion and exclusion criteria, two reviewers independently reviewed the titles and abstracts, and assessed the eligibility of studies identified by searches. Full text articles of potentially relevant clinical studies were then reviewed to confirm eligibility for inclusion. Two authors then independently extracted data from the studies. Throughout the process, any disagreements or discrepancies were reconciled by consensus with all authors.

Assessment of Risk of Bias of Included Studies
Quality assessment of randomized trials was done by each author using the Cochrane's Collaboration tool for assessment of risk of bias and is based on four domains: selection, performance, attrition and detection bias. Quality analysis grading was done by the authors as follows: A, if there is low risk of bias; B, if there is unclear risk of bias; and C, if there is high risk of bias.

Data Analysis
Dichotomous data was analyzed using risk ratio and 95% confidence interval using the Mantel-Haenszel method with random-effects model using the Review Manager version 5.3. The software and statistical formula are available from Cochrane Collaboration. The tools for quality assessment are available online.

RESULTS
Search Results
Among the 21 full text articles evaluated, nine studies excluded did report outcome measures or adverse events. Overall, 12 studies considered in this review included 8,436 patients with a mean age of 52.5 years, 72% of which were males. Two studies did not explicitly report the mean age and gender proportions.[17,18]

Risk of Bias
The overall risk of bias evaluation is shown in Figure 1, which shows that most of the studies have low risk of bias. The detailed evaluation of risks of bias specifically on random sequence generation, allocation, concealment, blinding, incomplete outcome data and selective reporting can be found in the supplementary material. The three main concerns were blinding of participants, incomplete outcome data and selective reporting. The first was associated with initial parenteral dosing (intramuscular injections) prior to oral doses, wherein no placebo was set for parenteral doses.[19,20] Incomplete outcome data was encountered in two trials with significant dropout rates and one trial which was terminated early.[21–23] Allocation concealment was not explicitly stated in two of the trials.[23,24] Overall, most trials included had low risk of bias and were considered high quality studies. Nine out of 21 studies assessed for eligibility were excluded because they contained no quantitative data that was extractable or did not report any of the chosen outcome measures.

There were four trials which investigated patients with macrovascular disease, including MI, chronic venous insufficiency, PAD and DVT.[21,22] Seven trials included patients with microvascular disease, particularly those with retinopathy and nephropathy.[17,18,23–27]

Myocardial Infarction
Among a total of 7,674 patients with vascular disease, there was no significant difference in overall risk of MI with sulodexide use (OR 0.78; CI 0.51-1.19). This was mainly driven by the nonsignificant difference in MI events among those with microvascular disease (n=2,787). However, among 165 patients with macrovascular disease, sulodexide had a statistically significant benefit in reducing risk of developing MI (OR 0.68; CI 0.50-0.94). No significant heterogeneity was seen among the subgroups (I^2 0%) and overall (I^2 11%) (See Figure 2).

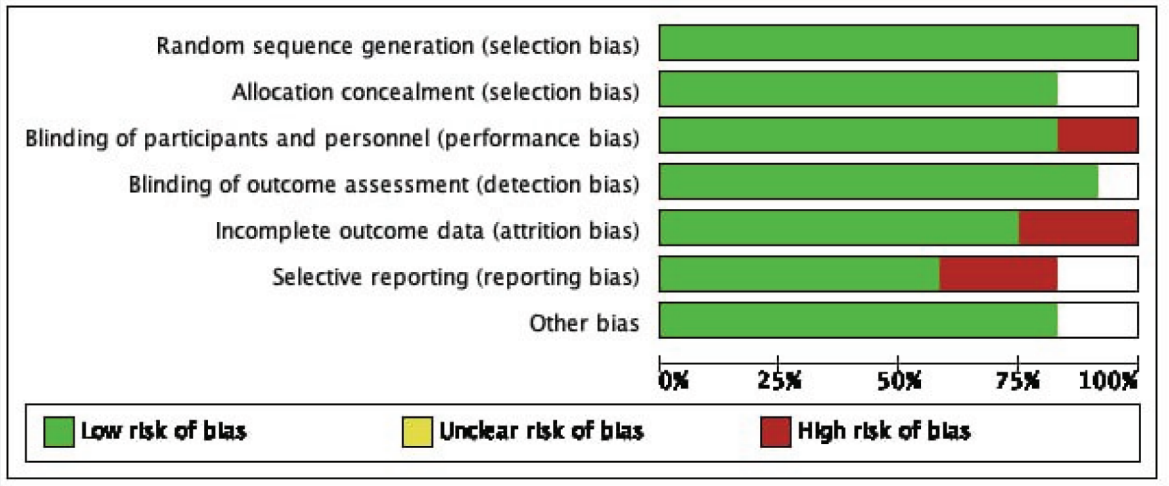

Figure 1. Overall evaluation of the risk of bias in RCTs included in quantitative synthesis.

Cardiovascular Events

Cardiovascular events reported in the studies were nonfatal MI, heart failure hospitalization, TIA, stroke, revascularization and reinfarction. Among a total of 7,342 patients with vascular disease, there was a statistically significant benefit with sulodexide use in reducing overall risk for cardiovascular events (OR 0.66; CI 0.46-0.94) [Figure 3]. This was mainly driven by the statistically significant benefit of sulodexide use in reducing CV events among patients with macrovascular disease (OR 0.55, CI 0.41-0.73). For those with microvascular disease, no significant difference was noted in overall CV events. No significant heterogeneity was noted in the subgroups and overall.

Cardiovascular Mortality

Events leading to cardiovascular death that were noted among the studies included acute lower limb ischemia, fatal acute coronary syndrome, fatal arrhythmia, decompensated heart failure and reinfarction. Similar to the findings in cardiovascular events, among 6,748 patients with vascular disease, there was a statistically significant benefit with sulodexide use in reducing CV mortality (OR 0.63; CI 0.48-0.81). This was driven again by statistically significant CV mortality reduction in 4,887 patients with macrovascular disease (OR 0.60, CI 0.45-0.79). No significant heterogeneity was noted in the subgroups and overall.

Gastrointestinal Symptoms

Gastrointestinal involvement was one of the most common adverse events observed across all studies. This includes epigastric pain, nausea, vomiting, diarrhea and gastrointestinal bleeding. Among 7,582 patients with vascular disease, there was no statistically significant difference in gastrointestinal adverse events between sulodexide and placebo (OR 0.98, CI 0.57-1.67).

Any Bleeding

In terms of bleeding, clinical events included hematoma formation at the injection site, gross hematuria and gastrointestinal bleeding. Among the 6,322 patients with vascular diseases, use of sulodexide and placebo had no significant difference in developing any bleeding complications (OR 2.0 CI 0.53-7.59). There was a trend towards increased bleeding risk with sulodexide use, but accounting for overall event rates, it was still relatively low overall (1.9% in sulodexide, 0.07% in placebo).

DISCUSSION

In this meta-analysis, the use of sulodexide compared to control (placebo or no treatment), across the spectrum of patients with vascular disease was associated with reduced odds of CV events and CV mortality. These results were consistent with another meta-analysis by Bikdeli, et al. (2020) which included 7,956 patients and showed reduced odds of all-cause mortality, CV mortality and MI.[28] Although their study also included patients with vascular disease, no subgroup analysis was done to determine the treatment effect among those with microvascular and macrovascular disease. Patients with macrovascular disease are well-known to have concomitant involvement of other macrovascular beds. In fact, for patients with diagnosed macrovascular disease (ie, coronary artery disease and peripheral vascular disease), guidelines recommend screening for concomitant involvement of other macrovascular territory.[29] Furthermore, prior macrovascular disease (whether venous or arterial bed involvement) could also predispose to increased risk of a future CV event and CV death. Interestingly, although microvascular disease confers increased risks of developing MI, CV events and CV mortality, our findings did not show a significant reduction in these outcomes with sulodexide use among this subgroup. In contrast, among the macrovascular disease subgroup analysis, a statistically significant reduction was seen consistently in reduction of MI, CV death and CV events.

The safety profile of sulodexide is generally well-tolerated. Both treatment and control arms had <5% adverse event rates in terms of bleeding and gastrointestinal symptoms. The trend towards increased bleeding risk with sulodexide was attributed

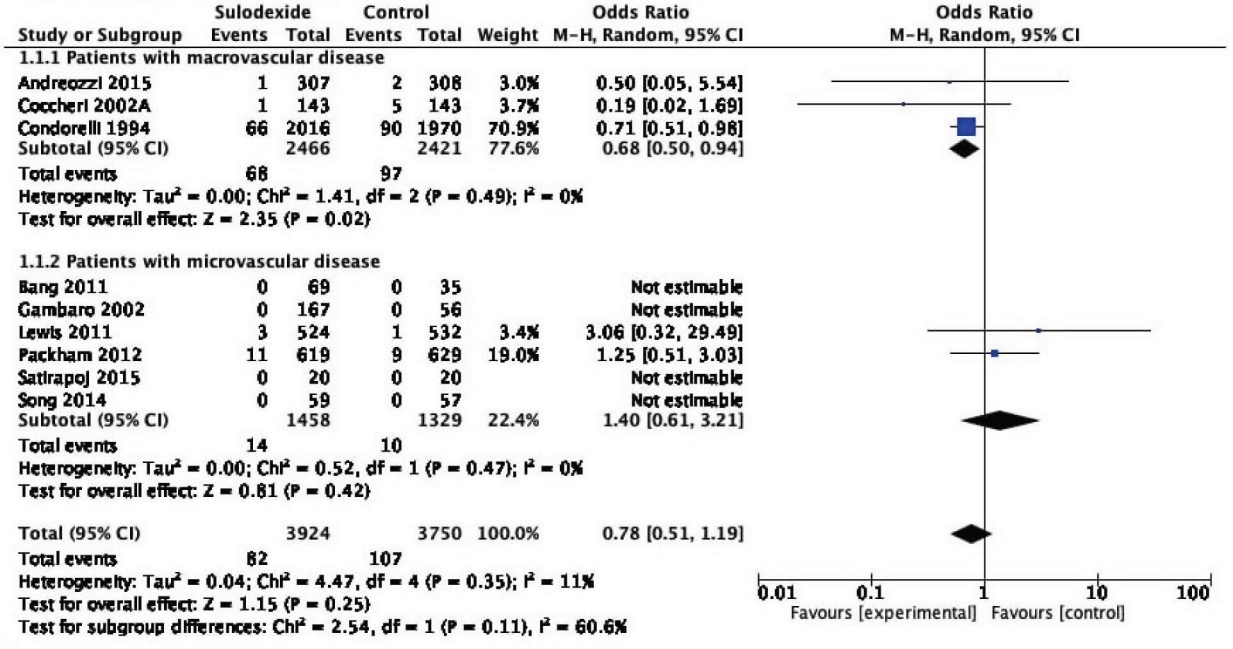

Figure 2. Forest plot of comparison: Sulodexide versus controls in reducing risks of myocardial infarction among patients with vascular disease.

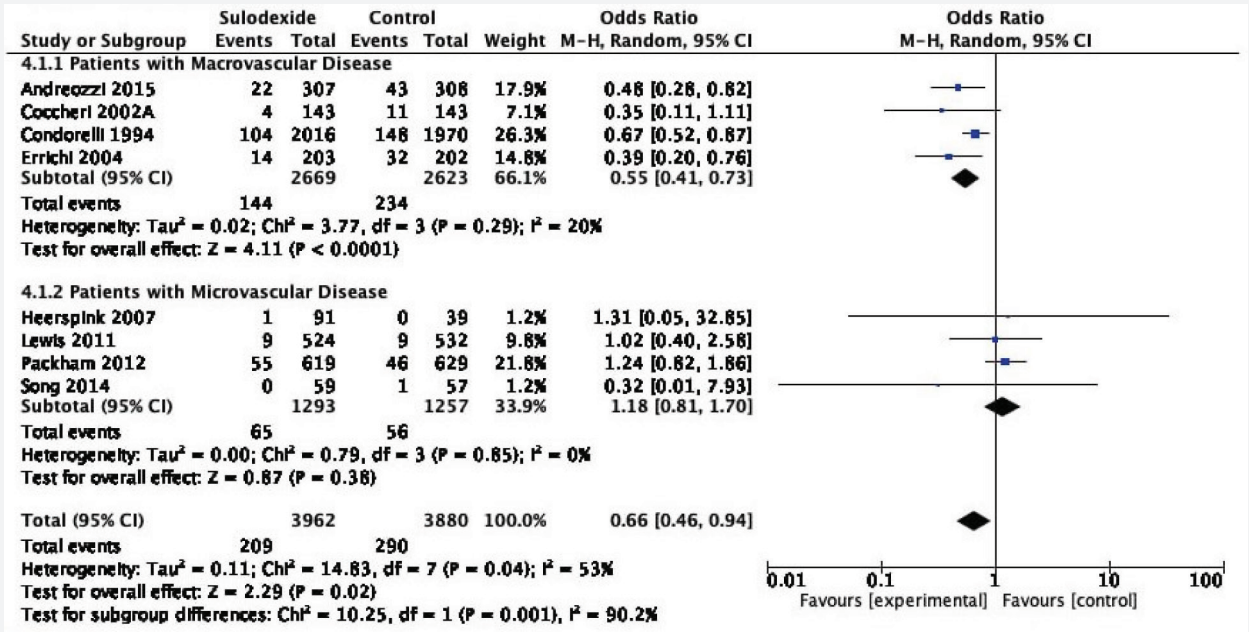

Figure 3. Forest plot of comparison: Sulodexide versus controls in reducing risks of cardiovascular events among patients with vascular disease.

to its mechanism of action and anticoagulant contents. In several pharmacokinetic studies, oral sulodexide has not yet been demonstrated to achieve a plasma level capable of factor Xa inhibition.[24,30] An interesting perspective about this review was that sulodexide conferred reduction in thrombotic events and CV complications despite not increasing rates of bleeding events. This may suggest alternative unknown pharmacophysiologic mechanisms to explain this phenomenon. Prior studies have suggested the role of sulodexide in thrombomodulation and further may also work on targets unrelated to thrombotic mechanisms to deploy favorable effects on cardiovascular complications.[28,31] These proposed mechanisms include heparanase inhibition, vascular endothelial growth factor inhibition, interference with metabolic stress,

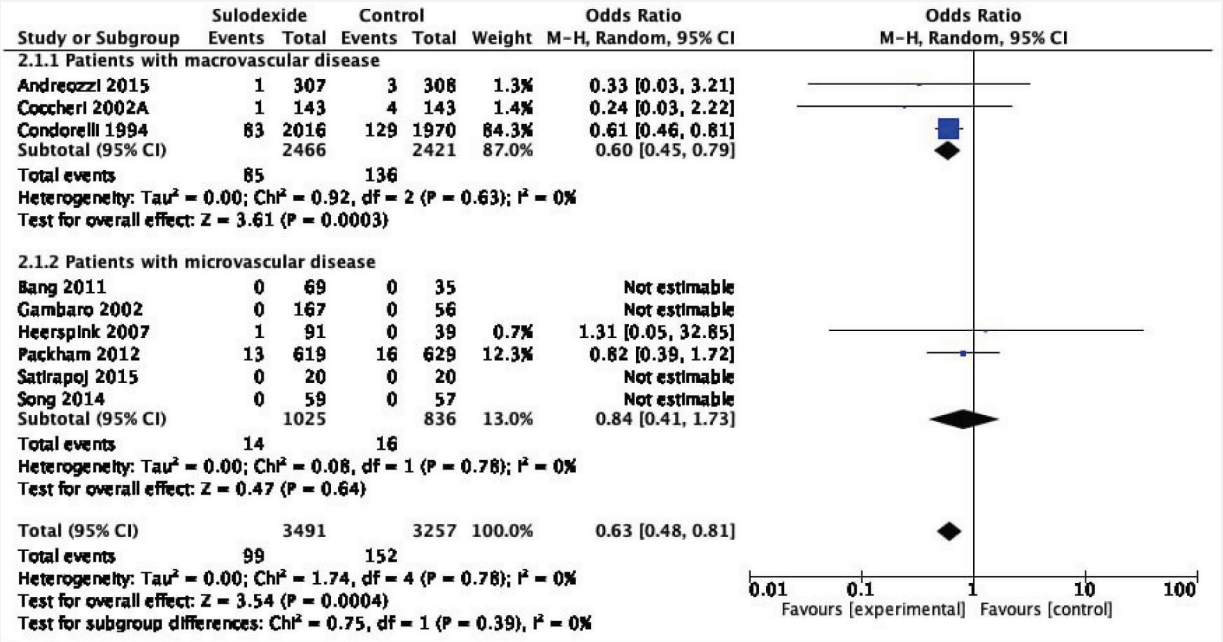

Figure 4. Forest plot of comparison: Sulodexide versus controls in reducing risks of cardiovascular death among patients with vascular disease.

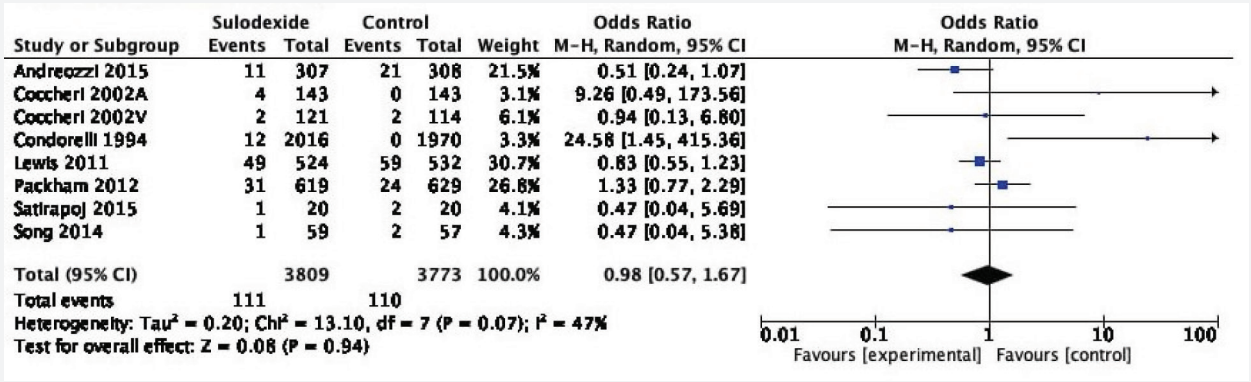

Figure 5. Forest plot of comparison: Sulodexide versus controls and gastrointestinal adverse events among patients with vascular disease.

endothelial nitric oxide synthesis and anti-inflammatory, anti-proteolytic and antioxidant effects.[32–41]

Prior systematic reviews have also raised the issue of appropriate administration route and dosing recommendations for sulodexide which also varied in our findings. We found that earlier studies usually had an initial parenteral dosing followed by subsequent oral dosing.[19,21,22] Later studies involved oral administration with daily doses ranging from 50 mg to 400 mg [1 mg = 10 lipasemic releasing units (LRU)]. A meta-analysis involving 2,143 patients investigating the mode of sulodexide administration and renal complications found no significant difference between these subgroups.[31]

It is important to note that clinical trials included in this systematic review spanned over a 20-year period. During this time, there have been several advances and developments in the standard of care for different vascular conditions. Therefore, the standard of care among control groups across the studies included also varied with time and disease conditions. There was also varying proportions of comorbidities, with some studies excluding patients with chronic kidney disease and advanced heart failure, which are established independent prognostic factors for development of CV events and MI.[17,20,28]

In the Philippines, there is still common use of sulodexide for a variety of vascular indications, although it has not been included as recommendations in both local and international guidelines. Local studies include sulodexide use among patients with acute coronary syndrome and vasculopathic cranial nerve palsies.[42,43] It's use was mostly geared towards patients who had increased bleeding risk in combination with standard therapy for vascular diseases because of its good safety profile.

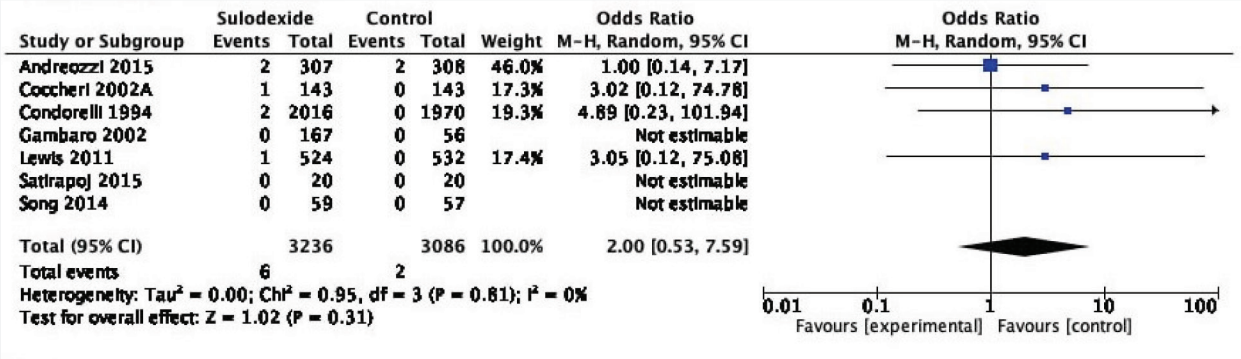

Figure 6. Forest plot of comparison: Sulodexide versus controls and bleeding among patients with vascular disease.

Table 1. Studies on the effects of sulodexide on MI and fatal CHD

Study/ author and year	Design	Population	Mean Age (years)	Males %	Vascular Disease	Interventions (Dosage)	Duration
Condorelli 1994	RCT	3986	59	82	Acute myocardial infarction	Sulodexide + standard therapy vs standard therapy (60 mg IM for 1 month, then 100 mg/d PO thereafter)	13 months
Coccheri 2002A	RCT	286	64	84	Peripheral arterial disease	Sulodexide vs placebo (60 mg IM for first 20 days, then 100 mg/d PO)	6.5 months
Coccheri 2002V	RCT	235	63	43	Chronic venous insufficiency	Sulodexide vs placebo (60 mg IM daily x 20 days, then by 100 mg/d PO x 70 days).	3 months
Gambaro 2002	RCT	223	47	-	Nephropathy	Sulodexide vs placebo (50 mg/d, 100 mg/d, 200 mg/d PO)	4 months
Errichi 2004	RCT	405	53	49	Deep venous thrombosis	Sulodexide vs None (50 mg/d PO)	6 months
Heerspink 2007	RCT	149	61	72	Nephropathy	Sulodexide vs Placebo (200 mg/d, 400 mg/d PO)	24 months
Bang 2011	RCT	70	41	46	Nephropathy	Sulodexide vs placebo (75 mg/d, 150 mg/d PO)	6 months
Lewis 2011	RCT	1056	62	76	Nephropathy	Sulodexide vs placebo (200 mg/d PO)	6.5 months
Packham 2012	RCT	1248	62	60	Nephropathy	Sulodexide vs placebo. (200 mg/d PO)	12 months
Song 2014	RCT	130	-	-	Retinopathy	Sulodexide vs placebo (50 mg/d PO)	12 months
Andreozzi 2015	RCT	615	55	54	Venous thromboembolism	Sulodexide vs placebo + elastic stockings (100 mg/d PO)	24 months
Satirapoj 2015	RCT	40	63	63	Nephropathy	Sulodexide vs placebo (100 mg/d PO)	3.5 months

**1 mg = 10 Lipasemic releasing units (LRU); IM – intramuscular injection; PO – per orem*

Limitations of This Meta-Analysis

The study population of included studies was not homogenous to say the least. They had varying degrees of atherosclerosis, prior CV events, severity of baseline renal dysfunction and diabetes mellitus. The primary outcomes of interest we investigated were not the initial outcome of interest in the trials included since they had different indications for sulodexide. Moreover, most of the studies included were not designed to compare the rates of MI, CV events and CV death. Unpublished studies that may not have been detected during our literature search were not included in this study.

Implication to Practice and Research

Given the issues of differences in baseline clinical characteristics of individuals included, route of administration, dosing, standard of care definition, the statistically significant findings in this study must be confirmed with future larger RCTs. We recommend that the following be taken into account in designing future studies: subgroup analysis of patients with micro- and macro-vascular disease, inclusion of chronic kidney disease and advanced heart failure, standardization of dosage and administration and with updated standard of care.

CONCLUSION

In this meta-analysis of 12 RCTs, the use of sulodexide compared to control (placebo or no treatment), across the spectrum of patients with vascular disease, was associated with reduced odds of CV events and CV mortality. Odds of MI, CV events and CV mortality was consistently reduced among patients with macrovascular disease given sulodexide. This statistically significant benefit was not consistently seen among the sulodexide arm in the microvascular disease subgroup. Sulodexide use did not confer statistically significant difference of developing adverse events, particularly bleeding and gastrointestinal symptoms, when compared to placebo.

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Supplementary Figure 7: Evaluation of the risk of bias among included studies.