Brie, D, Sahebkar, A, Penson, P, Dinca, M, Ursoniu, S, Serban, M-C, Zanchetti, A, Howard, G, Ahmed, A, Aronow, WS, Muntner, P, Lip, GYH, Wong, ND, Rysz, J and Banach, M

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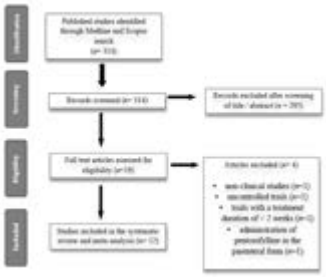

Effects of Pentoxifylline on Inflammatory Markers and Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Short Title: Pentoxifylline & Inflammatory Markers

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Conflicts of Interest and Source of Funding

This work was produced without any specific funding. The authors do not have any conflicts of interest to declare

Word count (including references, but not tables and legends): 5336

Number of tables: 2

Number of figures: 8

Number of supplementary digital content files: 0

Abstract

Introduction: Pentoxifylline is a xanthine derivative with potential cardiovascular benefits.

Aim: To evaluate the impact of pentoxifylline on blood pressure and plasma tumor necrosis factor-α, C-reactive protein and interleukin-6 through a systematic review and meta-analysis of randomized controlled trials.

Methods: The protocol was registered (PROSPERO: CRD42016035988). The search included PUBMED, ProQuest, Scopus, and EMBASE until September 1st 2015 to identify trials reporting blood pressure or inflammatory markers during pentoxifylline therapy. Quantitative data synthesis was performed using a random-effects model, with weighted mean difference and 95% confidence intervals as summary statistics.

Results: 15 studies (16 treatment arms) were found to be eligible for inclusion. Meta-analysis did not suggest any effect of pentoxifylline on either systolic or diastolic blood pressure. Pentoxifylline treatment was associated with a significant reduction in plasma concentrations of tumor necrosis factor-α (weighted mean difference: -1.03 pg/mL, 95% confidence interval: -1.54, -0.51, $p < 0.001$, 11 treatment arms) and C-reactive protein (weighted mean difference: -1.39 mg/L, 95% confidence interval: -2.68, -0.10, $p = 0.034$, 5 treatment arms). No alteration in plasma interleukin-6 concentration was observed. The impact of pentoxifylline on plasma tumor necrosis factor-α levels was found to be positively associated with treatment duration (slope: 0.031; 95% confidence interval: 0.004, 0.057; $p = 0.023$) but independent of pentoxifylline dose (slope: -0.0003; 95% confidence interval: -0.002, 0.001; $p = 0.687$).

Conclusions: Pentoxifylline did not alter blood pressure or plasma interleukin-6 concentration, but significantly reduced circulating tumor necrosis factor-α and C-reactive protein concentrations.

Keywords: pentoxifylline, C reactive protein, interleukin-6, TNF-α, blood pressure.

No. of words: 242

Condensed abstract

Pentoxifylline is a xanthine derivative with potential cardiovascular benefits. This study evaluated the impact of pentoxifylline on blood pressure, plasma tumor necrosis factor-α, C-reactive protein and interleukin-6 through a systematic review and meta-analysis of randomized controlled trials. No effect of pentoxifylline on either systolic or diastolic blood pressure or interleukin-6 was observed. Pentoxifylline treatment was associated with a statistically significant reduction in plasma concentrations of tumor necrosis factor-α and C-reactive protein. The impact of pentoxifylline on plasma tumor necrosis factor-α levels was found to be positively associated with treatment duration but independent of pentoxifylline dose.

No. of words: 95

INTRODUCTION

Pentoxifylline is a methylxanthine derivative and a non-selective phosphodiesterase inhibitor with hemorheological activity. Its primary use is for treating the symptoms of claudication, a manifestation of peripheral artery disease which results

in muscle pain [1]. In common with other methylxanthines such as theobromine, aminophylline, theophylline and caffeine, many of the pharmacological activities of pentoxifylline can be explained by inhibition of phosphodiesterases [2]. This group of enzymes is responsible for the breakdown of the intracellular second-messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Thus the methylxanthines increase intracellular concentrations of cAMP and cGMP in a wide variety of tissues [2]. Pentoxifylline increases erythrocyte flexibility, reduces blood viscosity, increases microcirculatory flow and tissue perfusion and decreases the potential for platelet aggregation and thrombus formation [3, 4]. It has been reported that pentoxifylline might also influence the function of immune cells and the production of cytokines [5, 6]. Interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines involved in inflammatory diseases in humans including rheumatoid arthritis, inflammatory bowel disease, graft-vs-host disease and many others. Administration of these inflammatory cytokines in humans results in fever, inflammation, tissue destruction, and, in some cases, shock and death [7]. Reduction of the biological activities of IL-1, TNF-α and other inflammatory cytokines is an important target for the treatment of many pathologies. C-Reactive Protein (CRP) is a marker of systemic inflammation and is useful in cardiovascular risk prediction [8, 9]. The increasing recognition of the role of inflammation in atherosclerosis, has led to the development and testing of anti-inflammatory agents for the prevention of cardiovascular events [10].

Experimental and animal studies have shown that pentoxifylline administration causes immune modulation in a dose-dependent manner. This is exemplified by increased leukocyte deformability and chemotaxis, decreased endothelial leukocyte

adhesion, neutrophil degranulation, TNF-α production and NK cell activity [5, 11, 12]. Moreover, pentoxifylline is able to suppress the synthesis of TNF-α in cell cultures, and *in vivo*, and to protect experimental animals against endotoxin shock [13]. At high concentrations, pentoxifylline has been shown to suppress TNF-α production by stimulating alveolar macrophages. However, in the same study, pentoxifylline did not affect the production of IL-1β, IL-6 or GM-CSF. In peripheral blood monocyte cultures it inhibited the production of TNF-α and GM-CSF, at all concentrations which were tested [14].

Phosphodiesterase inhibitors such as pentoxifylline cause a range of physiological changes which have the potential to modulate blood pressure. Clinical trials have shown variable effects of phosphodiesterase inhibitors in humans on systemic arterial blood pressure, with most trials finding little or no effect [15]. However, trials may have been underpowered to detect such a difference.

Because of the inconsistent data in published studies, we have performed the present meta-analysis to evaluate the impact of oral pentoxifylline therapy on systemic arterial blood pressure and on pro-inflammatory cytokines, when compared with placebo in randomized clinical trials. We discuss the possible future implications of therapy using pentoxifylline as an anti-inflammatory drug.

METHODS

Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [16] and was registered in the PROSPERO database (CRD42016035988). SCOPUS

(http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed), and ProQuest (http://www.proquest.com) and EMBASE (http://www.embase.com) databases were searched using the following search terms in titles and abstracts (and in combination with MESH terms in Pubmed/Medline): ("blood pressure" OR systolic OR diastolic OR SBP OR DBP OR hypertension OR hypertensive OR hypotension OR hypotensive OR anti-hypertensive) AND (pentoxifylline OR oxpentifylline OR torental OR trental OR agapurin OR oxpentifylline OR PENTOX OR PENTOXIL OR FLEXITAL). The wild-card term ‘‘*’’ was used to increase the sensitivity of the search strategy. No language restrictions were used in the literature search. The search was limited to studies in human. The literature was searched from inception to September 1st 2015. Two reviewers evaluated each article separately. Disagreements were resolved by agreement and discussion with a third party. The bibliographies of selected articles were hand searched to identify further relevant studies.

Study Selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized controlled trial with either parallel or cross-over design, (ii) investigating the impact of oral pentoxifylline on at least one of the biomarkers of systemic inflammation including serum/plasma CRP and pro-inflammatory cytokines or blood pressure iii) presenting sufficient information on baseline and end-trial concentrations (or differences) of inflammatory parameters in both pentoxifylline and control groups. Exclusion criteria were (i) non-clinical studies, (ii) uncontrolled trials, iii) trials with a treatment duration of < 2 weeks, and iv) administration of pentoxifylline in the parenteral form.

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) inclusion criteria; 5) number of participants in the pentoxifylline and control groups; 6) age, gender and body mass index (BMI) of study participants; 7) circulating concentrations of CRP and pro-inflammatory cytokines at baseline and at the end of treatment; 8) systolic and diastolic blood pressures; and 9) prevalence of smoking, type 2 diabetes, dyslipidemia, hypertension and CHD.

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [17]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding of subjects and personnel, blinding of outcome assessment, treatment of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias.

Quantitative Data Synthesis

Meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [18]. Plasma concentrations of CRP and pro-inflammatory cytokines were collated in mg/L and pg/mL, respectively. Systolic and diastolic blood

pressure were recorded as mmHg. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [$(SD_{pre\text{-}treatment})^2$ + $(SD_{post\text{-}treatment})^2$ – (2R × $SD_{pre\text{-}treatment}$ × $SD_{post\text{-}treatment}$)], assuming a correlation coefficient (R) = 0.5. When studies reported SEM, SD was estimated using the following formula: SD = SEM × sqrt (*n*), where *n* is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel trials, as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). A random-effects model and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of design, pentoxifylline dose, duration of treatment, and demographic characteristics of individual trials (underlying disease, age, gender and etc). In order to avoid double-counting of subjects and consequent unit-of-analysis error the trials with more than 1 treatment arm, the control group was evenly (where possible) divided into appropriate subgroups. Effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method (i.e. removing one study each time and repeating the analysis).

Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated WMD in plasma concentrations of inflammatory factors with dose and duration of treatment with pentoxifylline.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication bias [19].

RESULTS

Search results and trial flow

The searches uncovered 314 articles. The initial screening for potential relevance removed 295 articles in whose titles and/or abstracts were obviously irrelevant. Among the 19 full text articles assessed for eligibility, 4 papers were excluded for the following reasons: non-clinical studies (*n*=1), uncontrolled trials (*n*=1), trials with a treatment duration of < 2 weeks (*n*=1), administration of pentoxifylline in the parenteral form (*n*=1) (**Figure 1**).

Characteristics of included studies

After assessment, 15 RCTs achieved the inclusion criteria and were used for the final meta-analysis [20-34] and these reported 18 treatment arms. A total of 739 individuals participated in the selected trials and 377 of them were allocated to the pentoxifylline group and 362 subjects to control group. The number of participants in these trials ranged from 23 to 100. Included studies were published between 1998 and 2015, and were conducted in South Africa (3 studies), USA (3 studies), Spain (2 studies), Germany, India, Brazil, Turkey, Iran, and Egypt. All the studies used 400 or

600 mg pentoxifylline tablets and the doses ranged from 400 mg/day to 1200 mg/day. Duration of treatment with pentoxifylline ranged between 1 month and 12 months. All trials were designed as parallel-group studies. Baseline and demographic characteristics of included studies are summarized in **Table 1**.

Quality assessment

Some of the studies included reported insufficient information about the random sequence generation and allocation concealment. The majority of selected studies were double-blind, although five trials [21, 22, 25, 27, 28] were not blinded. Details of the quality assessment are shown in **Table 2**.

Quantitative data synthesis

Overall, the impact of pentoxifylline treatment on plasma concentrations of TNF-α [20, 22, 25, 28, 30-34], CRP [21, 25-27, 32] and IL-6 [20, 23, 26, 33] was reported in 11, 5 and 5 treatment arms, respectively. Meta-analysis showed a significant effect of pentoxifylline treatment in reducing plasma concentrations of TNF-α (WMD: -1.03 pg/mL, 95% CI: -1.54, -0.51, $p < 0.001$) (**Figure 2**) and CRP (WMD: -1.39 mg/L, 95% CI: -2.68, -0.10, $p = 0.034$) (**Figure 3**). However, no significant alteration was observed in plasma IL-6 concentrations following pentoxifylline treatment (WMD: 1.17 pg/mL, 95% CI: -1.28, 3.62, $p = 0.350$) (**Figure 4**). The meta-analyses on changes in plasma TNF-α and IL-6 concentrations were robust in the leave-one-out sensitivity analysis; however, the meta-analysis of CRP concentrations was sensitive to studies by Maiti *et al.*[27], Sliwa *et al.* [32], Demir *et al.[21]* and Goicochea *et al*. [25] (**Figure 3, lower panel**).

Meta-analysis of 9 RCTs (10 treatment arms) [20, 21, 24, 25, 28-32] did not suggest any significant effect of pentoxifylline on SBP (WMD: 0.82 mmHg, 95% CI: -1.70, 3.34, *p* = 0.523) **(Figure 5)**. Meta-analysis of 8 RCTs (9 treatment arms) [20, 21, 24, 25, 28, 29, 31, 32] did not suggest any significant effect of pentoxifylline on DBP (WMD: 0.09 mmHg, 95% CI: -1.29, 1.47, *p* = 0.895) **(Figure 6)**. Both analyses (SBP and DBP) were robust in the leave-one-out sensitivity analysis **(Figures 5 and 6, lower plots)**. Because the trial conducted by Goicochea *et al*. [25] was the only trial to report the change in BP after pentoxifylline treatment in a hypertensive population (Mean SBP >140 mmHg), we repeated this analysis with the data from Goicochea *et al*. excluded. Thus, the effects of pentoxifylline treatment on a population which were normal as baseline was as follows: SBP: WMD = 0.91; 95% = -1.90, 3.72; p = 0.524; DBP: WMD = 0.27; 95% = -1.15, 1.69; p = 0.708 **(Figures 5 and 6, lower plots)**.

Meta-regression

Meta-regression analysis was conducted to evaluate the association between changes in plasma TNF-α concentrations and potential confounder variables including dose and duration of treatment with pentoxifylline. The impact of pentoxifylline on plasma TNF-α levels was found to be positively associated with treatment duration (slope: 0.031; 95% CI: 0.004, 0.057; *p* = 0.023) but independent of pentoxifylline dose (slope: -0.0003; 95% CI: -0.002, 0.001; *p* = 0.687) (**Figure 7**).

Publication bias

Visual inspection of the funnel plot of the study precision (inverse SEM) by effect size (mean difference) suggested an asymmetry in the meta-analysis of the effect of pentoxifylline on plasma TNF-α concentration that was addressed by the imputation of 3 studies on the right side of the mean using trim-and-fill method. The imputed effect size was -0.95 pg/mL (95% CI: -1.45, -0.45), showing a significant effect after imputation of potentially missing studies. There was no sign of publication bias according to either Begg's rank correlation (Kendall's Tau with continuity correction = -0.11, z = 0.47, two-tailed p-value = 0.640) and Egger's linear regression (intercept = 0.05, 95% CI = -1.18, 1.29, t = 0.096, df = 9.00, two-tailed p = 0.926) test. Funnel plot of the impact of pentoxifylline treatment on plasma TNF-α concentration is illustrated in **Figure 8**.

DISCUSSION

Our meta-analysis showed that pentoxifylline treatment was associated with a statistically significant reduction in the concentrations of TNF-α and CRP in plasma. However, no significant alteration of plasma IL-6 concentrations was observed following pentoxifylline treatment.

Four studies investigated the effect of pentoxifylline in patients with dilated cardiomyopathy with various causes (ischemic etiology in Sliwa et al. 2004 and Bahrmann et al. 2004; idiopathic in Sliwa et al. 1998, Skudicky et al. 2001 and Bahrmann et al. 2004, hypertensive in Bahrmann et al. 2004) [20, 30-32]. Sliwa et al. 1998 investigated the effect of pentoxifylline on left ventricular performance in idiopathic dilated cardiomyopathy and concluded that pentoxifylline treatment reduced the concentration of TNF-alpha in plasma and was associated with improvement of

symptoms and left ventricular systolic function [31]. This was in contrast to the studies performed by Skudicky et al. 2001 [30] and Bahrmann et al. 2004 [20] which included patients with idiopathic cardiomyopathy. In these studies, treatment with pentoxifylline was not associated with significant changes in TNF-alpha [20, 30] and IL-6 [20] concentrations. Significant improvements in symptoms and left ventricular function were seen in one trial [30] but not the other [20]. However in this negative study, the results are complicated by the fact patients in this study were treated with a beta-blocker (carvedilol) for the 3 months prior to initiation of pentoxifylline therapy. Functional improvement by beta-blockers in heart failure is well documented as well as the potential of these drugs to reduce concentrations of circulating inflammatory cytokines [35]. Thus a 'ceiling' beneficial effect may have been reached before pentoxifylline treatment began.

In patients with ischemic cardiomyopathy, adding pentoxifylline to standard therapy (which included beta blockers) was associated with reduction in plasma concentration of inflammatory markers TNF-alpha and CRP, marker of apoptosis (Fas/Apo-1) and correlated with improvement of left ventricular ejection fraction [32].

Three studies investigated the effect of pentoxifylline in patients with non-alcoholic steatohepatitis (NASH) [22, 33, 34]. In studies conducted by Van Wagner et al. 2011 [33] and Zein et al. 2011 [34], pentoxifylline treatment did not alter serum TNF-α, concentrations, but improved liver enzymes and histology in patients with NASH, but did not appear to offer substantial benefit over placebo [33] with some benefit in liver fibrosis at one year [34]. But pentoxifylline therapy reduced hepatic

expression of collagen-1, an important fibrogenic gene, and TIMP-1, which is also involved in fibrosis, however the latter effect was not statistically significant. Thus pentoxifylline could have potential benefit on fibrosis. Both studies concluded that pentoxifylline treatment is well tolerated [33, 34]. When pentoxifylline was added to fenofibrate treatment in patients with NASH (El-Haggar et al. 2015) [22], patients receiving both drugs showed significantly lower TNF-α concentrations than that detected with fenofibrate treated group. The author concluded that the combination of pentoxifylline and fenofibrate has a beneficial effect on liver markers of fibrosis, liver stiffness, insulin resistance and inflammatory pathways implicated in NASH [22].

Two studies investigated the anti-inflammatory effect of pentoxifylline in patients with type 2 diabetes mellitus. In study conducted by Navarro et al in 2005, pentoxifylline therapy was added to angiotensin II receptor blocker (ARB) therapy in normotensive patients with diabetes and residual albuminuria despite adequate therapy with an ARB [28]. The study showed that pentoxifylline added to ARB therapy was associated with a significant reduction of concentrations of TNF-α in serum and urine. This modulation of inflammatory responses could explain the supplementary antiproteinuric effect observed [28]. It has also been demonstrated that in hypertensive patients with type 2 diabetes mellitus pentoxifylline treatment improved inflammatory markers, oxidative stress and platelet-aggregation. In this trial, however, hsCRP was used as a marker for inflammation and TNF-α was not reported. [27]

In patients with coronary artery disease, pentoxifylline treatment has been shown to be associated with a statistically significant reduction in pro-inflammatory response (decreased CRP and TNF-α) and a trend towards increased concentrations of

the anti-inflammatory mediator TGF-beta1. Although this study was small and did not measure clinical events, it nevertheless showed an anti-inflammatory effect of pentoxifylline treatment [23].

The mechanisms by which phosphodiesterase inhibitors such as pentoxifylline can elicit anti-inflammatory effects have been comprehensively reviewed elsewhere [36, 37]. In particular, the inhibition of the isozyme phosphodiesterase-4 is likely to be important. Phosphodiesterase 4 highly expressed in inflammatory cells including neutrophils, macrophages, T cells and endothelial cells [38]. Insights from the respiratory system have shown that inhibition of phosphodiesterase 4 in immune cells and the subsequent elevation of cAMP results in an anti-inflammatory effect [38-40]. Specific inhibitors of this isoenzyme are being developed for use in the treatment of a wide range of disease states with an inflammatory component, including dermatological, neurological and respiratory conditions [38, 41-46]. With respect to the reduction in TNF-α by pentoxifylline observed in this study, Shaw [11] has comprehensively reviewed the potential mechanisms which include: Suppression of TNF-α gene transcription by pentoxifylline [47], attenuation of the response of TNF-α to endotoxin [48], and attenuation of Interleukin-2, a cytokine which stimulates TNF-α production [6],

Primarily used to treat peripheral arterial disease patients due to the improved circulation obtained through its ability to alter erythrocyte deformability, pentoxifylline also enhances capillary microcirculation [2, 11]. We examined the potential of this methylxanthine derivate as a blood pressure (BP) lowering agent in a range of studies, including those that reported its effects in hypertensive patients [20, 27] . Blood

pressure was similar in pentoxifylline and control groups and no significant differences were observed during the follow-up period in systolic blood pressure or diastolic blood pressure.

The lack of effect of pentoxifylline on systemic arterial blood pressure seen in this study supports previous observations with pentoxifylline [49] and other phosphodiesterase inhibitors [15] where little or no effect on blood pressure was observed. It is important to note that in all but one of the studies which measured the effect of pentoxifylline on blood pressure, the participants were normotensive at baseline. It would be difficult to demonstrate a hypotensive effect of a drug in such a population. Nevertheless, the study performed by Goicochea *et al*.[25] which enrolled a hypertensive population (mean SBP >140 mmHg) did not demonstrate an effect of pentoxifylline on BP, and exclusion of this study from the meta-analysis did not affect the result. The ubiquity of cAMP (and cGMP) signaling, modulated by phosphodiesterases, results in multiple and complex physiological effects when these enzymes are inhibited. In the vasculature, the accumulation of cAMP promotes vasodilation and a reduction in peripheral resistance [50, 51] which would be expected to be associated with a hypotensive effect. However, the dose required for this effect may be higher the usual clinical dose [52]. Conversely, in the myocardium, phosphodiesterase inhibition and elevation of cAMP have been shown to elicit positive chronotropic [53] and inotropic [54] responses which would be expected to increase blood pressure. Thus the effects of pentoxifylline in the heart and the vasculature would appear to have small, functionally opposite effects on blood pressure, and the overall effect would appear to be a ‘zero sum’. An antihypertensive effect of pentoxifylline would be desirable in the treatment of cardiovascular disease.

However, the fact that no pressor effect of pentoxifylline has been demonstrated, means that it can be used for its anti-inflammatory effects without concerns about an adverse effect on blood pressure. Further investigations into the effects of this drug on blood pressure in a hypertensive population are warrented.

The present meta-analysis has several limitations. Most importantly, there were only a small number of eligible RCTs and most of them included relatively small populations. Furthermore, these studies were heterogeneous regarding population characteristics, study design, and pathology of patients involved. A conservative random-effects model was used to account for the heterogeneity between the studies and sensitivity analysis was performed to examine the impact of each individual study on the overall effect size.

Conclusion

In conclusion, our meta-analysis has shown a significant anti-inflammatory effect of pentoxifylline treatment, exemplified by reduced concentrations of TNF-α and CRP in plasma in a range pathologies including coronary artery disease, type 2 diabetes mellitus, idiopathic and ischemic cardiomyopathy and chronic kidney disease. Pentoxifylline treatment was associated with anti-inflammatory effects when given alone or when added to standard therapy. This is not a licensed indication for pentoxifylline. We did not detect any effect of pentoxifylline on Il-6 or systemic arterial blood pressure. None of the randomized controlled trials (RCT) gave any cause to doubt the safety of pentoxifylline treatment. This raises the possibility that pentoxifylline may have therapeutic benefit in diseases where inflammatory pathways (characterized by

elevated by TNF-α and CRP) play an important role. These may include rheumatoid arthritis, asthma and atherosclerotic cardiovascular disease. Further outcomes- based RCTs are warranted to test the effect of pentoxifylline in such circumstances.

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Table 1. Baseline and demographic characteristics of the included studies

Study		Bahrmann et al [$]	Demir et al.	El-Haggar et al	Fernandes et al	Ghorbani et al.	Goicoechea et al	Gupta et al	Maiti et al	Navarro et al	Shahidi et al.	Skudicky et al	Sliwa et al	Sliwa et al.	Van Wagner et al	Zein et al
Reference		[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]
Year		2004	2006	2015	2008	2012	2012	2013	2007	2005	2015	2001	1998	2004	2011	2011
Location		Germany	Turkey	Egypt	Brazil	Iran	Spain	USA	India	Spain	Iran	South Africa	South Africa	South Africa	USA	USA
Design		Double-blind randomized placebo controlled trial	Randomized controlled trial.	Randomized controlled trial.	Double-blind randomized placebo contr	Double-blind randomized controlled trial	Randomized placebo controlled trial	Double-blind randomized placebo contr	Randomized open add-on clinical	Randomized placebo controlled trial	Double Blind parallel-group randomized	Double-blind randomized placebo controlled trial	Double-blind randomized placebo controlled trial	Double-blind randomized placebo controlled trial	Double-blind randomized placebo contr	Double-blind randomized placebo contr

					olled trial			olled trial	trial with parallel controls		contr olled trial				olled trial	olled trial
Experimental groups	Case	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifyllin e	pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline	Usual treatment + pentoxifylline
	Control	Usual treatment + Placebo	Usual treatment only	Usual treatment only	Usual treatment + Place	Usual treatment only	Usual treatment only	Placebo	Usual treatment only	Usual treatment only	Usual treatment + Place	Usual treatment + Placebo	Usual treatment + Placebo	Usual treatment + Placebo	Usual treatment + Place	Usual treatment + Place

					bo						bo				bo	bo
Duration of trial		6 months	3 months	6 months	6 months	6 months	12 months	2 months	1 month	4 months	6 months	6 months	6 months	6 months	12 months	12 months
Inclusion criteria		(1) age between 18 and 70 years, (2) stable New York Heart Association (NYHA) class	(1)Patients who had received a renal transplant from a living donor more than	Patients who had persistently abnormal aminotransferase levels in two separate occasi	Patients between 18 and 80 years with non-ST-segment elevation ACS,	Patients with type 2 diabetes mellitus and diabetic nephropathy (persistent	(1) presence of CKD, defined as an estimated glomerular filtration rate (eGFR	HIV-infected participants not on ART.b	Patients with type 2 diabetes mellitus with hypertension aged 45	Diabetic nephropathy, defined by persistent albuminuria >300 mg/24 h in two	Patients aged >18 years. GFR > 60 ml/min/1.73 m^2. Blood pressure <140/90	(1) age ≥18 and ≤70 years, (2) stable NYHA functional class II or III congestive heart	age between 18 and 70 years; stable New York Heart Association (NYHA) functional	(1) age≥ 18 and ≤70 years; (2) stable New York Heart Association functional class	Subjects between the ages of 18 and 65 without evidence of other liver diseas	(1) daily alcohol intake of <30 g for males and <15 g for femal es; (2)

		II or III CHF due to ischemic and hypertensive cardiomyopathy or idiopathic-dilated cardiomyopathy, (3) left ventric	6 months before recruitment. (2) Symptom-free (3) Serum creatinine levels < 1.8 mg/dl	ons over the past six months.	elevated cardiac markers (defined as troponin I > 0.1 ng/mL) and at least one other high-risk	proteinuria > 150mg/24hr in 3 consecutive measurements. No other kidney or renal tract diseas	) lower than 60 ml/min per 1.73 m^2, (2) stable clinical condition defined as no hospitalizati		years and older; the patients were free from other significant morbidity specially infection, infest	consecutive determinations, no other kidney or renal tract disease, and presence of diabetic retinopathy	mmHg (using beta-blockers, ARBs or ACEI, on a diet with protein intake < 0.8 g/Kg/d, HbA1	failure of unknown cause, (3) LV ejection fraction (LVEF) < 40% by radionuclide angiography, (4) sinus rhythm, and (5)	class II or III congestive heart failure of unknown aetiology; a left ventricular ejection fraction of 40% or less as measur	II or III congestive heart failure secondary to coronary artery disease, as defined by the presence of ≥2-vessel disease on angiogr	e and an initial biopsy evaluation (within 6 months of entry) with steatohepatitis defined by the	appropriate exclusion of other liver diseases; (3) age between 18 and 70 years and (4) the

		ular ejection fraction (LVEF) less or equal than 40% assessed by contrast 2D echocardiography and (4) sinus			criteria: an episode of angina at rest lasting longer than 20 min in the preceding 24 h; rest	e. Insufficient response to adequate therapy with losartan and enalapril in at least 3 months	ons or cardiovascular events within the 3 months before screening, (3) stable renal function (baseline		ations, inflammatory or neoplastic diseases.	and normal BP (≤140/90 mmHg); treatment with the recommended doses of ARB for >1 yr;	c < 8%, spot urine albumin-creatinine ratio < 300 mg/g in 3 consecutive measurements over 3	eligible patients in whom high-quality echocardiographic images could be obtained.	ed by radionuclide angiography; sinus rhythm; and possibility of obtaining high-quality echocardiographic images.	aphy; (3) left ventricular ejection fraction < 40% by radionuclide scintigraphy; (4) sinus rhythm; and (5) eligible patients	presence of steatosis, inflammation and ballooning.	ability to give informed consent. Patients with diabetes mellitus type 2 (DM) were inclu

		rhythm.			angina with dynamic ST changes ≥0.1 mV; angina with hypotension, pulmonary edem	before recruitment.	serum creatinine had to have not increased by 50% in the 3 months before screening) and (4) no chang			normal renal function, defined as a GFR ≥90 ml/min (calculated using the Modification of Diet in	months.			in whom high-quality echocardiographic images could be obtained.		ded only if their therapeutic regimen was limited to oral agents including sulfonylureas

					a or ventricular tachycardia or a TIMI score ≥5.		es in concomitant medication during the study.			Renal Disease study equation) ; and insufficient response to conventional therapy, defined as album						(e.g. glipizide and glyburide) and/or biguanides (e.g. metformin), was stable (defined by no chang

										inuria >400 mg/24 h in three consecutive measurements in the 3 months before inclusion in the study.						es in oral agents or their dose for at least 6 months), and with relatively adequate glucose

																control as defined by HgbA1C < 8%.
Pentoxifylline intervention		1200 mg daily	1200 mg daily	1200 mg daily	1200 mg daily	400 mg daily	800 mg/day	1200 mg daily	800 mg/day	1200 mg/day	1200 mg/day	1200 mg daily	1200 mg daily	1200 mg daily	1200 mg daily	1200 mg daily
Participants	Case	21	22	45	29	50	34	10	25	30	20	16	14	19	19	23
	Control	20	20	45	28	50	36	13	26	31	20	16	10	14	7	26
Age	Ca	55±12	33±1	45.3±5	60.6±	56±7.	NR	40±1	56.37	58.6±	50.3±	50±9	49.1±8	57±10	48±2	50.5±

(years)	se		2	.34	1.7	6		1.6	6±8.6	9.0	9				12.7
	Control	58±12	35±12	43.78±6.30	60.9±1.7	58±8.0	NR	34±10.9	53.81±7.21	58.8±6.0	55.6±10.7	47±12	55.7±12	53±11	53±2	49.6±9.6
Male (%)	Case	87	64	71.11	63	56	NR	62	50	53.34	40.9	50	50	75	38	69
	Control	100	70	66.67	69	52	NR	85	66.67	48.38	33.3	86	85.7	67	62	69.2
BMI Kg/m^2)	Case	28±3	NR	27.14 ± 1.27	27.5±0.7	32.06	NR	NR	26.45 ±4.25	NR	30.51 ±7.13	NR	NR	NR	34.0 ± 0.9	32.9 ± 4.6
	Contr	28±5	NR	27.26 ± 1.06	27.8±0.8	31.84	NR	NR	25.19 ±3.01	NR	30.75 ±4.22	NR	NR	NR	35.1 ± 2.6	34.0 ± 5.4

	ol															
SBP (mm Hg)	Case	125± 12	127 ± 9.2	NR	NR	122.2	148 ± 24	NR	144.5 ±12.95	134.4 ± 6.0	115.68±11.16	120± 18	121	119±19	NR	NR
	Control	118± 13	128 ± 8.4	NR	NR	124.4	147 ± 16	NR	139.55±10.39	132.1 ± 6.2	115.28±9.15	111± 22	115	117±18	NR	NR
DBP (mm Hg)	Case	77± 9	84 ± 3.9	NR	NR	72.3	77 ± 15	NR	86.0± 7.70	83.3± 6.7	75.45 ±8.15	76 ±11	73	77±14	NR	NR
	Control	73± 10	85 ± 4.1	NR	NR	74.6	76± 13	NR	82.71 ±6.35	81.5 ±7.6	77.29 ±8.26	70± 13	70	74±13	NR	NR
TNF-α pg/ml	Case	11± 7	4.2 ± 2.1	5.67±1.24	2.5(3.9) *	NR	6.6±1.9¥	NR	NR	6.4(2.1 to 9.7)	NR	2.5±1.9	6.5±3.0	7.0±3.4	NR	7.4±2.0

	Control	9± 5	4.0 ± 2.2	5.39±1.04	3.0 (4.2) *	NR	7±1.6¥	NR	NR	5.1(1.4 to 10)	NR	2.16±1.9	10.8±9.1	7.9±3.9	NR	7.6±1.7
hs - CRP mg/l	Case	NR	NR	NR	9.6(19) *	NR	4.7(2.0-8.4) ¥	1.78(3.72)€	1.39± 0.9	NR	NR	NR	NR	11.0±5.6	NR	NR
	Control	NR	NR	NR	8.8(24) *	NR	3.0(1.8-7.5) ¥	1.86(2.57) €	1.22± 0.9	NR	NR	NR	NR	6.9±5.7	NR	NR
IL-6 pg/ml	Case	12± 30	1.81 ± 0.6	NR	5.7(6.8) *	NR	NR	2.61(2.59) €	NR	NR	NR	NR	NR	NR	NR	NR

	Control	7± 6	2.12 ± 0.6	NR	4.4(6.9) *	NR	NR	1.91 (1.53) €	NR	NR	NR	NR	NR	NR	NR	NR

Values are expressed as mean ± SD; ≠-Values represent relative means ± SEM; *Values represent median (interquartile range); €-Values represent as means (standard deviation); ¥-Data are expressed as mean ± standard deviation or median (interquartile range); $ The trial conducted by Bahrmann et al included two treatment arms which represented two populations: Group A, Patients with ischemic dilated and hypertensive cardiomyopathy; Group B: Patients with idiopathic dilated cardiomyopathy.

Abbreviations: ACEI-angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; BNP-brain natriuretic peptide; CRP- C reactive protein; GFR-glomerular filtration rate; IL-interleukin; LVEF-left ventricle ejection fraction; NR-not reported; NYHA-New York Heart Association; PAI-1- Plasminogen activator inhibitor-1; sTNFRI-soluble tumor necrosis factor receptor; TGF-tumor growth factor; TNF-tumor necrosis factor;

Table 2 Assessment of risk of bias in the included studies using Cochrane criteria.

Study	Ref	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Bahrmann et al. 2004	**[20]**	**U**	**U**	**L**	**L**	**L**	**L**	**L**
Demir et al. 2006	**[21]**	**H**	**H**	**H**	**H**	**L**	**L**	**L**
El-Haggar et al. 2015	**[22]**	**U**	**U**	**H**	**H**	**L**	**L**	**L**
Fernandes 2008	**[23]**	**L**	**L**	**L**	**U**	**L**	**L**	**L**
Ghorbani et al. 2012	**[24]**	**L**	**L**	**U**	**U**	**L**	**L**	**L**
Goicoechea et al 2012	**[25]**	**L**	**L**	**H**	**H**	**L**	**L**	**L**

Gupta et al.2013	**[26]**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Navarro et al. 2005	**[28]**	**L**	**L**	**H**	**H**	**L**	**L**	**L**
Maiti et al. 2007	**[27]**	**U**	**U**	**H**	**H**	**L**	**L**	**L**
Shahidi et al. 2015	**[29]**	**L**	**L**	**L**	**U**	**L**	**L**	**L**
Skudicky et al. 2001	**[30]**	**U**	**U**	**L**	**L**	**L**	**L**	**L**
Sliwa et al. 1998	**[31]**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Sliwa et al. 2004	**[32]**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Van Wagner et al. 2011	**[33]**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Zein et al. 2011	**[34]**	**L**	**L**	**L**	**l**	**L**	**L**	**L**

L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

Figures

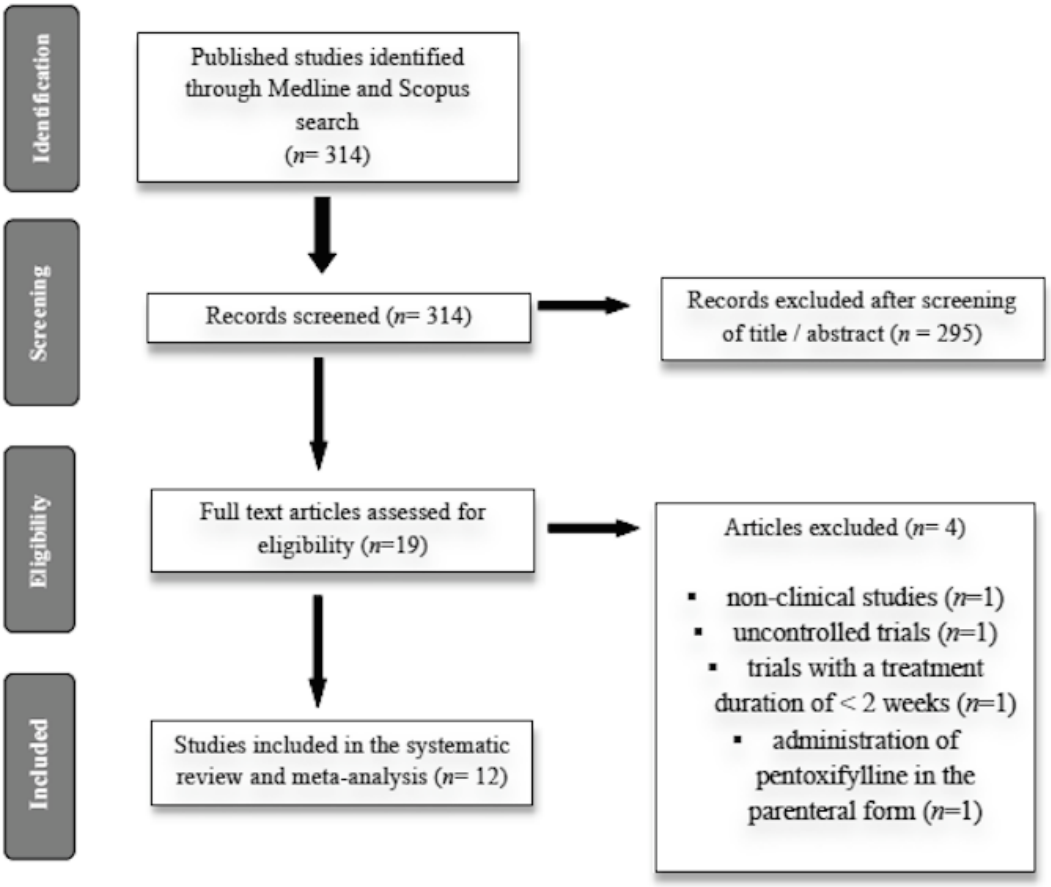

Figure 1. Flow diagram of the study selection procedure.

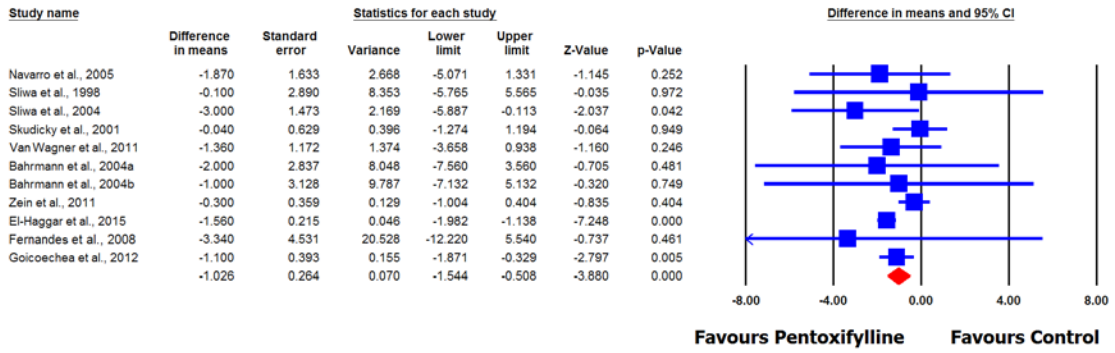

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pentoxifylline treatment on plasma TNF-α concentrations. The trial conducted by Bahrmann et al included two treatment arms which represented two populations: Group A, Patients with ischemic dilated and hypertensive cardiomyopathy; Group B: Patients with idiopathic dilated cardiomyopathy.

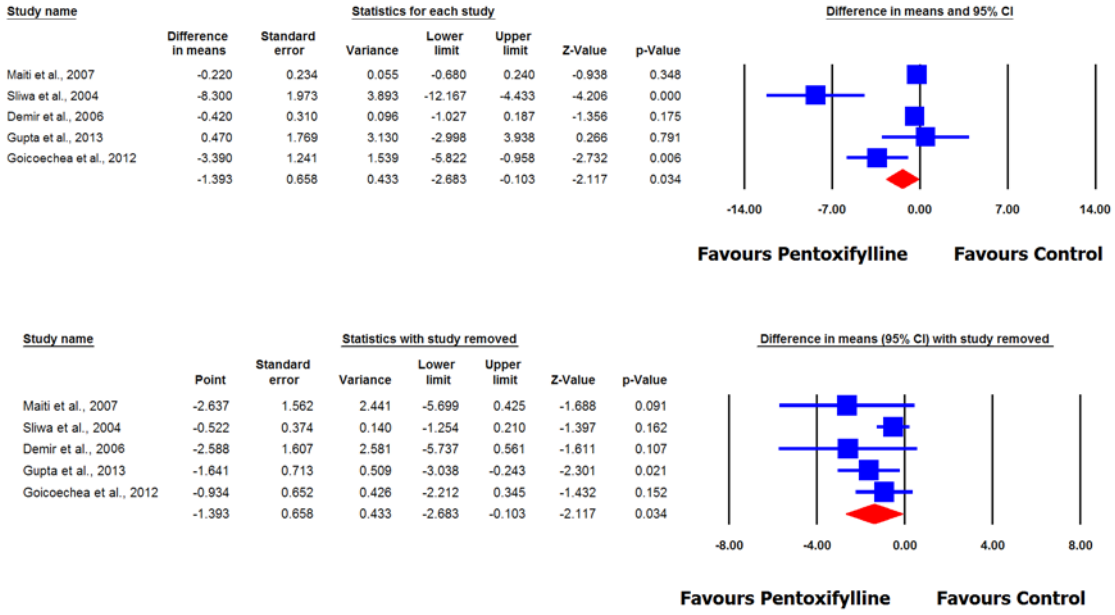

Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pentoxifylline treatment on plasma CRP concentrations. The lower plot shows the results of leave-one-out sensitivity analysis.

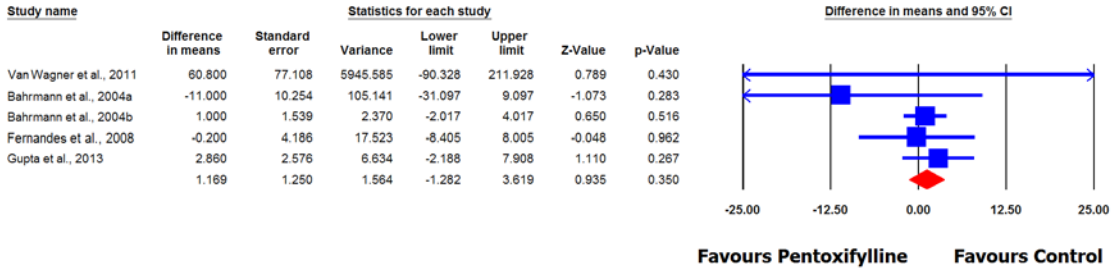

Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pentoxifylline treatment on plasma IL-6 concentrations. The trial conducted by Bahrmann et al included two treatment arms which represented two populations: Group A, Patients with ischemic dilated and hypertensive cardiomyopathy; Group B: Patients with idiopathic dilated cardiomyopathy.

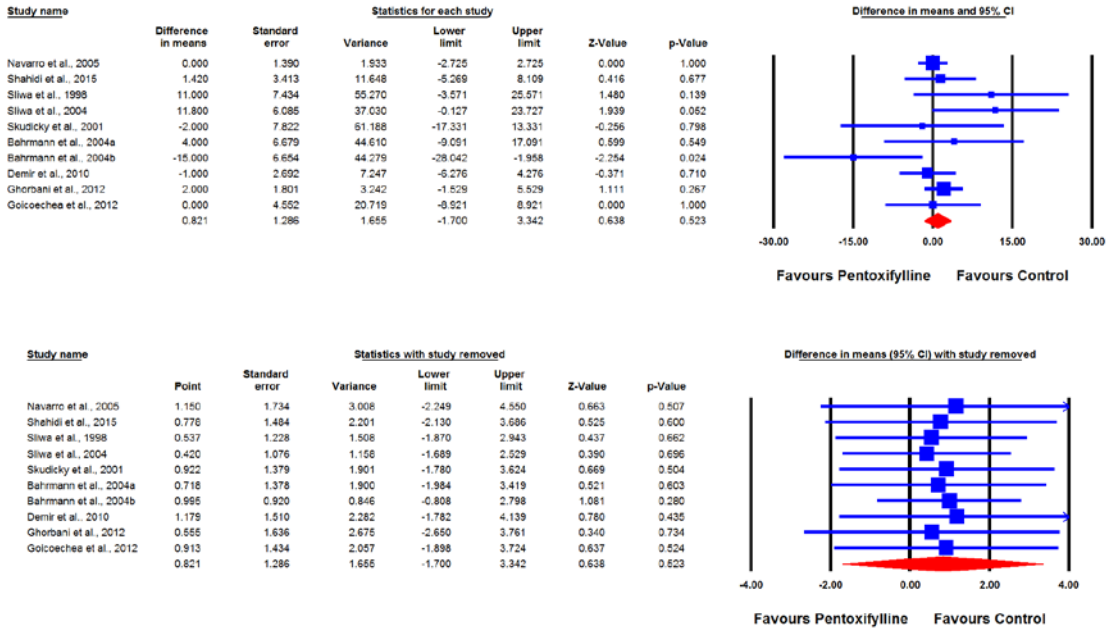

Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pentoxifylline treatment on systolic blood pressure. The lower plot shows the results of leave-one-out sensitivity analysis. The trial conducted by Bahrmann et al included two treatment arms which represented two populations: Group A, Patients with ischemic dilated and hypertensive cardiomyopathy; Group B: Patients with idiopathic dilated cardiomyopathy. N.B. The result is unaffected by the exclusion of the study by Goicoechea which included hypertensive participants.

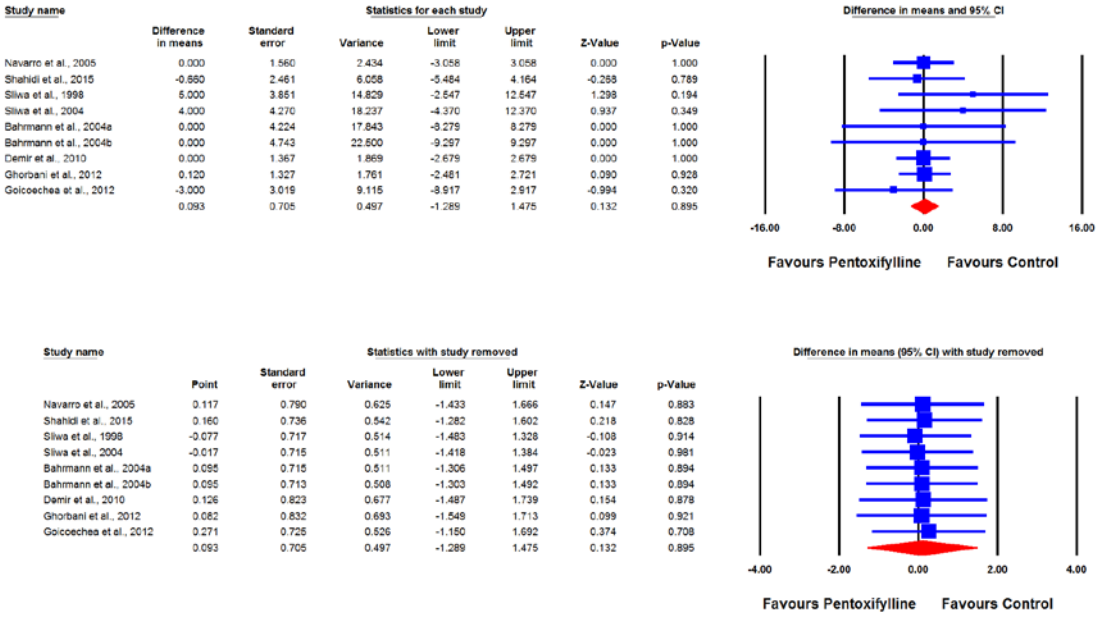

Figure 6. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pentoxifylline treatment on diastolic blood pressure. The lower plot shows the results of leave-one-out sensitivity analysis. The trial conducted by Bahrmann et al included two treatment arms which represented two populations: Group A, Patients with ischemic dilated and hypertensive cardiomyopathy; Group B: Patients with idiopathic dilated cardiomyopathy. N.B. The result is unaffected by the exclusion of the study by Goicoechea which included hypertensive participants.

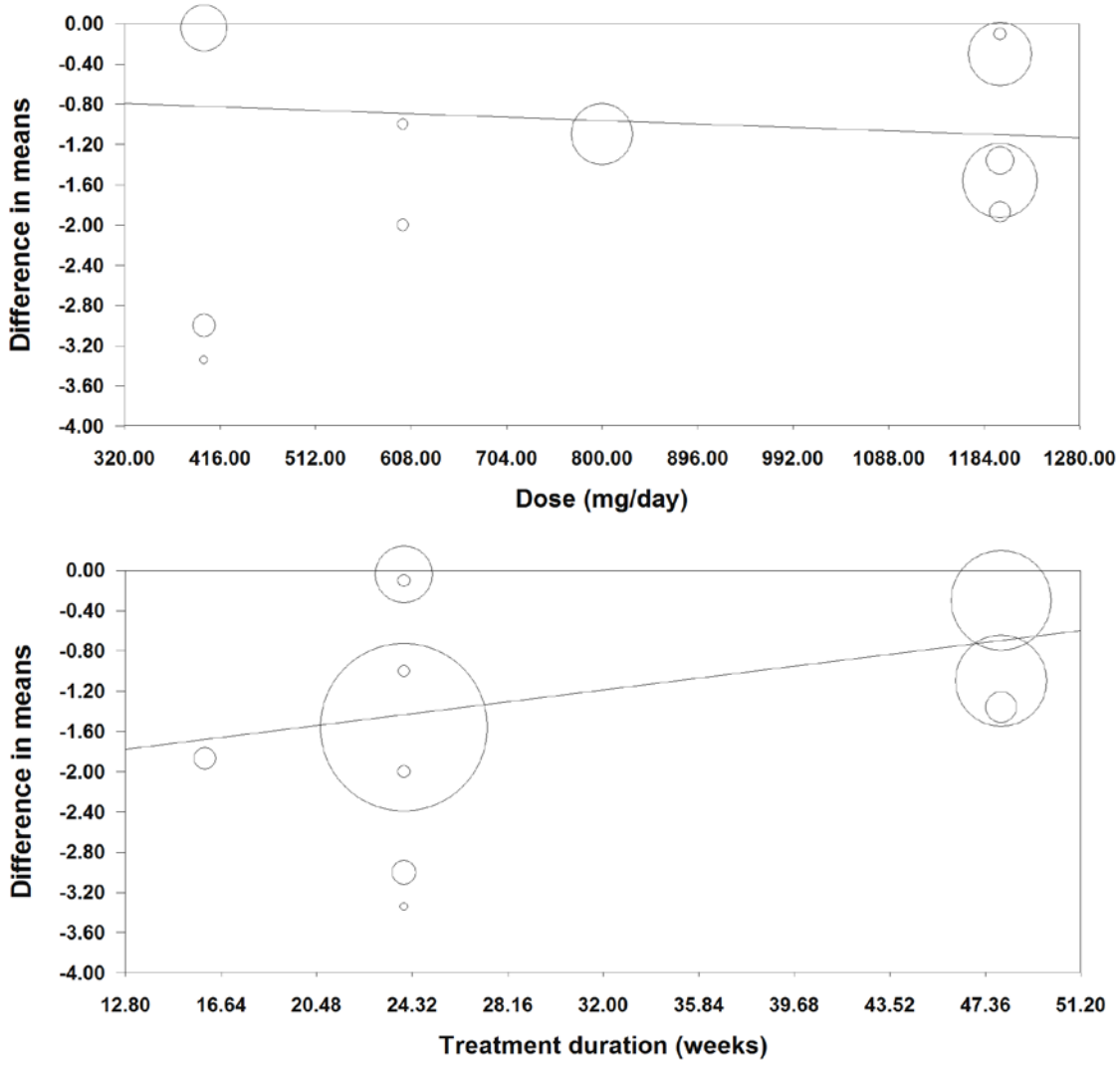

Figure 7. Meta-regression plots of the association of mean changes in plasma TNF-α concentrations with dose and duration of pentoxifylline treatment. The size of each circle is inversely proportional to the variance of change.

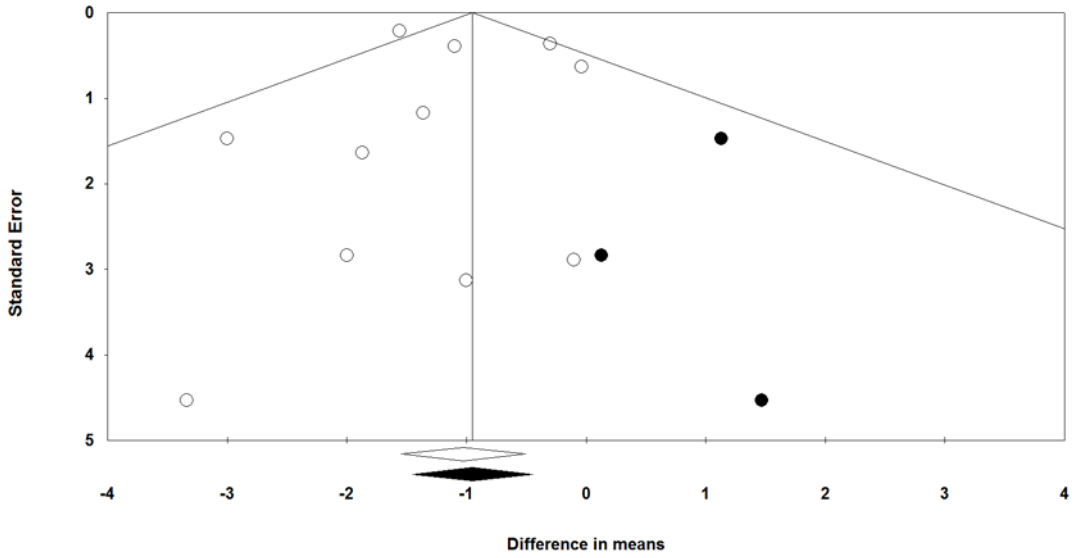

Figure 8. Funnel plot detailing publication bias in the meta-analysis of the impact of pentoxifylline treatment on plasma TNF-α concentrations. Trim and fill method was used to impute for potentially missing studies. Open circles represent observed published studies; closed circles represent imputed unpublished studies.