

ORIGINAL ARTICLE

Effects of telmisartan therapy on interleukin-6 and tumor necrosis factor-alpha levels: a meta-analysis of randomized controlled trials

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A recent meta-analysis of randomized head-to-head trials suggests that therapy with telmisartan, an angiotensin II receptor blocker (ARB) and partial agonist of peroxisome proliferator-activated receptor-gamma, may increase adiponectin levels more strongly than other ARB therapies. Therefore, telmisartan would be expected to reduce interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNF- α). To determine whether telmisartan reduces IL-6 or TNF- α , we performed the first meta-analysis of randomized controlled trials of telmisartan therapy. MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched through November 2011. Eligible studies were prospective randomized controlled trials of telmisartan vs. unrestricted control therapy reporting IL-6 or TNF- α levels as an outcome. For each study, data regarding percent changes from baseline to final IL-6 or TNF- α levels in both the telmisartan and control groups were used to generate standardized mean differences (SMDs) and 95% confidence intervals (CIs). Nine reports of randomized trials enrolling a total of 645 patients were identified. Pooled analysis of seven and five trials demonstrated a statistically significant reduction in percent changes of IL-6 (fixed-effects SMD, -0.385 ; 95% CI, -0.581 to -0.189 ; $P < 0.001$; P for heterogeneity = 0.073) and TNF- α levels (random-effects SMD, -0.627 ; 95% CI, -0.945 to -0.308 ; $P < 0.001$; P for heterogeneity = 0.029) with telmisartan relative to control therapy, respectively. In conclusion, based on a meta-analysis of nine randomized controlled trials, telmisartan therapy is likely effective in reducing IL-6 and TNF- α levels.

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INTRODUCTION

Adiponectin is an abundant adipocyte-derived protein with well-established anti-atherogenic, insulin-sensitizing and anti-inflammatory properties.¹ Interleukin-6 (IL-6) is an important adipocytokine linking obesity to vascular disease² and a regulator of hepatic C-reactive protein (CRP) production.³ Adiponectin expression may be negatively regulated by IL-6 in adipose tissue.² Tumor necrosis factor-alpha (TNF- α), another adipocytokine, is thought to be involved in the induction of insulin resistance in obesity and may also have a role in the regulation of hepatic CRP synthesis and induction of IL-6 expression.^{3,4} Adiponectin may indirectly inhibit IL-6 and CRP expression through its ability to inhibit the production of TNF- α .² A meta-analysis⁵ points to a clear increase in adiponectin serum levels after the administration of thiazolidinedione, a peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonist.⁶

Telmisartan, an angiotensin II receptor blocker (ARB), can act as a partial agonist of PPAR- γ .⁷ The results of our recent meta-analysis⁸ of randomized head-to-head trials suggest that telmisartan therapy may increase adiponectin levels more strongly than other ARB therapy.

Therefore, telmisartan would be expected to reduce IL-6 or TNF- α . Although a number of randomized controlled trials of telmisartan therapy for the reduction of IL-6 or TNF- α levels have been published to date, the results have been inconclusive. To determine whether telmisartan reduces IL-6 or TNF- α , we performed the first meta-analysis of randomized controlled trials of telmisartan therapy.

METHODS

Search strategy

All prospective randomized controlled trials of telmisartan therapy were identified using a 2-level search strategy. First, public domain databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched through November 2011 using Web-based search engines (PubMed and OVID). Second, relevant studies were identified through a manual search of secondary sources, including the references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates and further analysis. Keywords included *telmisartan*; *interleukin*, *IL*, *tumor necrosis factor*, or *TNF*; and *randomized*, *randomised*, *randomly*, or *randomization*.

Study selection and data abstraction

Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; the study population consisted of unrestricted patients; the patients were randomly assigned to telmisartan *vs.* unrestricted control therapy (including placebo and no treatment); and the outcomes included IL-6 or TNF- α levels. Data regarding detailed inclusion criteria, duration of follow-up, and IL-6 or TNF- α levels were abstracted (as available) from each individual study.

Statistical analysis

For each study, data regarding percent changes from baseline to final IL-6 or TNF- α levels in both the telmisartan and control groups were used to generate standardized mean differences (SMDs) and 95% confidence intervals (CIs). When standard deviations (SDs) were unavailable and where only baseline and final IL-6 or TNF- α levels were reported, missing SDs were imputed and changes from baseline to final IL-6 or TNF- α levels were obtained according to the Cochrane Handbook,⁹ respectively. As suggested by Follmann *et al.*,¹⁰ we assumed a correlation coefficient of 0.5 between the baseline and final values and equal variances during the trial and between the telmisartan and control groups. Study-specific estimates were separately combined for IL-6 and TNF- α using inverse variance-weighted averages of logarithmic SMDs in both fixed- and random-effects model. Between-study heterogeneity was analyzed by means of standard χ^2 -tests. Where no significant statistical heterogeneity was identified, the fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the pooled SMD estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation and linear regression test. All analyses were conducted using Comprehensive Meta-Analysis version 2 software (Biostat, Englewood, NJ, USA).

RESULTS

Search results

Our comprehensive search identified 12 prospective randomized controlled clinical trials of telmisartan *vs.* control therapy.^{11–22} We excluded trials by Nagel *et al.*²⁰ and Wohl *et al.*²¹ that reported only final IL-6 or TNF- α levels. A trial by Cadeddu *et al.*²² was also eliminated because it enrolled quite different patients with histologically confirmed tumors at different sites, previously untreated, to be treated with an epirubicin-based chemotherapy regimen. In total, our meta-analysis included data on 645 patients from the remaining 9 trials^{11–19} that were randomized to therapy with telmisartan or control (Table 1).

Qualitative findings

Bähr *et al.*¹¹ conducted a 14-week, randomized, double-blind, placebo-controlled, 2-center study with 80 and 160 mg per day telmisartan treatment in patients with metabolic syndrome. In this low-risk patient population, telmisartan treatment did not significantly affect serum IL-6 levels. Derosa *et al.*¹² evaluated type 2 diabetic patients with metabolic syndrome, all of whom had been diabetic for at least 6 months and took a fixed dose of rosiglitazone, and in all of whom glycemic control by the maximum tolerated dietary changes and maximum tolerated dose of oral hypoglycemic agents had been attempted and failed. The authors administered telmisartan or irbesartan in a randomized, controlled, double-blind, clinical manner. Significant decreases in TNF- α levels were observed after 6 months in the telmisartan group and after 12 months in both groups.

Hong *et al.*¹³ compared the effects of telmisartan and valsartan after sirolimus-eluting stent implantation in a prospective, randomized, single-blinded, 8-month follow-up study that included hypertensive patients with significant coronary artery stenosis. After 8 months of

follow-up, only the telmisartan group showed significant decreases in IL-6 and TNF- α . Hong *et al.*¹⁴ compared the effects of telmisartan and valsartan after stenting in a prospective, randomized, 8-month follow-up study that included hypertensive type 2 diabetes with significant coronary stenosis. The decreases from baseline in IL-6 and TNF- α levels were significantly greater in the telmisartan group at 8 months.

In a prospective, randomized study, Huang *et al.*¹⁵ investigated the effects of telmisartan in patients with hypertension and obesity treated with telmisartan or losartan for 16 weeks. The levels of serum TNF- α only improved in the telmisartan group. In a prospective double-blind study by Link *et al.*,¹⁶ patients with hypertension and coronary artery disease were treated with either telmisartan or a placebo for 12 weeks. As expected for normal ranges, TNF- α and IL-6 remained unchanged in both the placebo and telmisartan groups.

Nakamura *et al.*¹⁷ compared the effects of telmisartan and amlodipine in untreated hypertensive chronic kidney disease patients with moderate renal insufficiency randomly assigned to receive telmisartan or amlodipine for 12 months. Plasma levels of IL-6 decreased more strikingly in the telmisartan group than in the amlodipine group. Nakamura *et al.*¹⁸ investigated the effect of telmisartan *vs.* enalapril in patients with hypertensive autosomal dominant polycystic kidney disease with good renal function randomly assigned to telmisartan or enalapril. Although serum IL-6 levels significantly decreased after treatment in both groups, the decrease in serum IL-6 was significantly greater in the telmisartan group than in the enalapril group at 6 and 12 months.

Nakayama *et al.*¹⁹ compared the effects of olmesartan and telmisartan in an open-label, prospective, crossover study to which early-stage type-2 diabetes patients with hypertension who had been treated with valsartan for at least 8 weeks were recruited. At study entry, valsartan was switched to olmesartan or telmisartan and administered for 8 weeks, and the drugs were then switched and treatment was continued for another 8 weeks. The olmesartan treatment resulted in a more significant decrease in serum IL-6. Despite the noted heterogeneity in design between the trials, there was sufficient similarity between the populations and the hypotheses to merit the inclusion of all 11 trials in the quantitative meta-analysis.

Quantitative findings

Pooled analysis of seven and five trials demonstrated a statistically significant reduction in percent changes of IL-6 (fixed-effects SMD, -0.385 ; 95% CI, -0.581 to -0.189 ; $P < 0.001$; random-effects SMD, -0.363 ; 95% CI, -0.658 to -0.069 $P = 0.016$; P for heterogeneity = 0.073 ; Figure 1) and TNF- α levels (random-effects SMD, -0.627 ; 95% CI, -0.945 to -0.308 ; $P < 0.001$; fixed-effects SMD, -0.688 ; 95% CI, -0.869 to -0.506 ; $P < 0.001$; P for heterogeneity = 0.029 ; Figure 2) with telmisartan relative to control therapy, respectively. To assess the impact of qualitative heterogeneity in trial design and patient selection on the pooled effect estimate, we performed several sensitivity analyses. The exclusion of any single trial from the analysis did not substantively alter the overall result of our analysis for IL-6 (Figure 3) or TNF- α (Figure 4).

In the excluded study by Cadeddu *et al.*,²² serum levels of IL-6 rose significantly in the placebo arm at 7 days after reaching the epirubicin dose of 200 mg m^{-2} (68.8 ± 52.6 *vs.* $31 \pm 8.8 \text{ pg ml}^{-1}$; $P < 0.05$) but remained unchanged in the telmisartan arm (27.7 ± 18.1 *vs.* $26 \pm 18.8 \text{ pg ml}^{-1}$). The same trend was shown by TNF- α serum levels, which increased significantly at 7 days after reaching the epirubicin dose of 200 mg m^{-2} in the placebo arm (47.1 ± 4.6 *vs.* $30.1 \pm 9 \text{ pg ml}^{-1}$) but not in the telmisartan arm (22.3 ± 10.6

Table 1 Trial design and baseline values

Trial	Inclusion criteria	Follow-up	Intervention	Number of patients	Baseline values (mean \pm SD)							
					Systolic BP (mm Hg)		hsCRP (mg l ⁻¹)		Interleukin-6 (pg ml ⁻¹)		TNF-alpha (pg ml ⁻¹)	
					Telmisartan	Control	Telmisartan	Control	Telmisartan	Control	Telmisartan	Control
Bähr <i>et al.</i> ¹¹	MeS with normal stress ECG, normal carotid ultrasound, and normal funduscopy	14 weeks	80 mg telmisartan Placebo	17 18	138.8 \pm 8.8 140.0 \pm 9.5	NA NA	2.9 \pm 2.4 (ng ml ⁻¹)	2.1 \pm 1.7 (ng ml ⁻¹)	NA NA	NA NA		
Derosa <i>et al.</i> ¹²	MeS with overweight and poorly controlled T2DM	12 months	160 mg telmisartan 40 mg telmisartan + irbesartan 40 mg telmisartan + telmisartan + irbesartan + 4 mg rosiglitazone 80 mg valsartan	19 92	138.9 \pm 10.8 135 \pm 4	NA NA	2.5 \pm 1.9 (ng ml ⁻¹) NA	NA NA	NA NA	NA 3.0 \pm 0.6 (ng ml ⁻¹)		
Hong <i>et al.</i> ¹³	Essential HT and high-grade CAL treated by SES implantation	8 months	40 mg telmisartan 80 mg valsartan	79	146 \pm 15	142 \pm 15	3.5 \pm 2.2	2.8 \pm 3.0	1.4 \pm 1.3	1.3 \pm 0.7	13.3 \pm 3.0	12.8 \pm 3.6
Hong <i>et al.</i> ¹⁴	Essential HT with de novo CAL requiring stent implantation	8 months	40-80 mg telmisartan	36	140.7 \pm 13.8	143.2 \pm 12.6	3.1 \pm 2.8	2.9 \pm 2.8	1.4 \pm 1.1	1.3 \pm 1.3	14.5 \pm 3.4	13.5 \pm 4.5
Huang <i>et al.</i> ¹⁵	Essential HT with overweight or obese accompanied with insulin resistance	16 weeks	80 mg telmisartan	23	153.6 \pm 9.6	154.1 \pm 6.3	NA	NA	NA	NA	86.5 \pm 28.0	87.4 \pm 24.6
Link <i>et al.</i> ¹⁶	CAD and treated essential HT	12 weeks	40 mg telmisartan Placebo	21	140.0 \pm 13.2	136.5 \pm 14.1	2.5 \pm 2.7	3.8 \pm 6.4	3.1 \pm 2.3	3.0 \pm 2.3	1.8 \pm 0.4	1.2 \pm 0.3
Nakamura <i>et al.</i> ¹⁷	Non-diabetic CKD with HT and moderate renal insufficiency	12 months	40 mg telmisartan	15	162 \pm 10	160 \pm 8	NA	NA	44.6 \pm 8.8	45.0 \pm 10.0	NA	NA
Nakamura <i>et al.</i> ¹⁸	Hypertensive ADPKD with microalbuminuria but good renal function	12 months	80 mg telmisartan	10	158 \pm 6	159 \pm 6	NA	NA	43.5 \pm 16.4	42.3 \pm 15.9	NA	NA
Nakayama <i>et al.</i> ¹⁹	T2DM and HT treated with valsartan	8 weeks	40 mg telmisartan	20	133.6 \pm 12.1		0.76 \pm 0.63		4.95 \pm 5.47	4.95 \pm 5.47	NA	NA
Total				332								

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; CAD, coronary artery disease; CAL, coronary artery lesion; CKD, chronic kidney disease; ECG, electrocardiography; hsCRP, high-sensitivity C-reactive protein; HT, hypertension; MeS, metabolic syndrome; NA, not available; SD, standard deviation; SES, sirolimus-eluting stent; TNF, tumor necrosis factor; T2DM, type 2 diabetes mellitus.

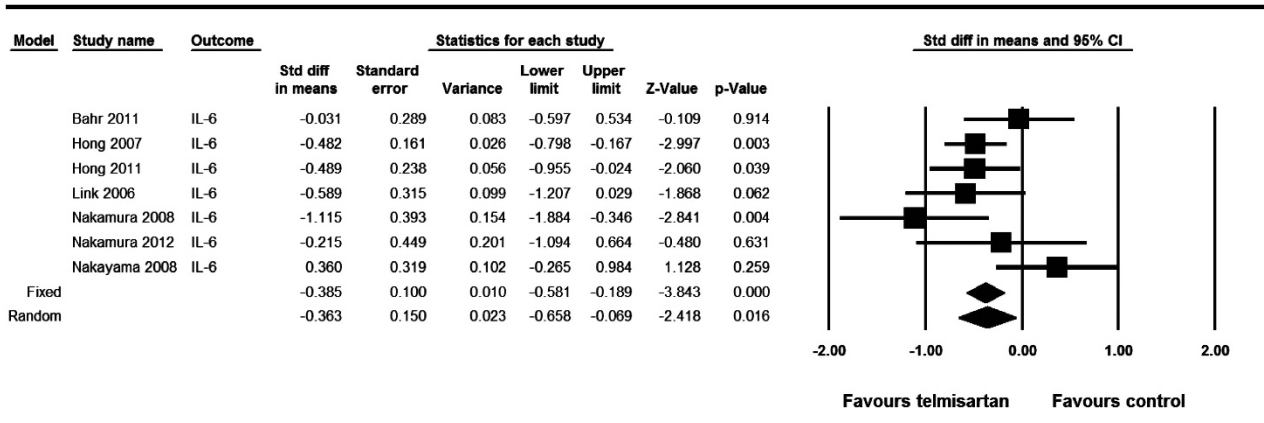


Figure 1 Percent changes in interleukin-6 (IL-6) levels among patients randomized to telmisartan vs. control therapy. CI, confidence interval.

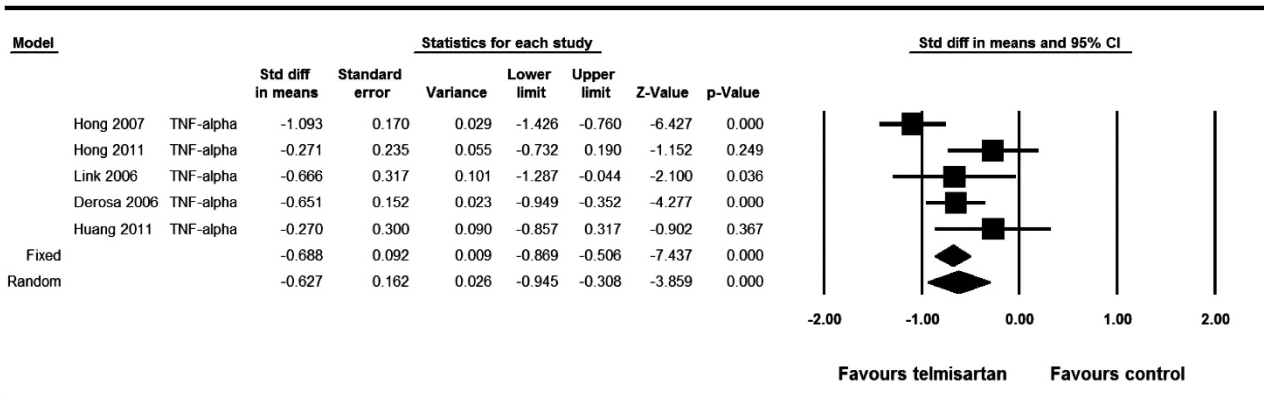


Figure 2 Percent changes in tissue necrosis factor-alpha (TNF- α) levels among patients randomized to telmisartan vs. control therapy. CI, confidence interval.

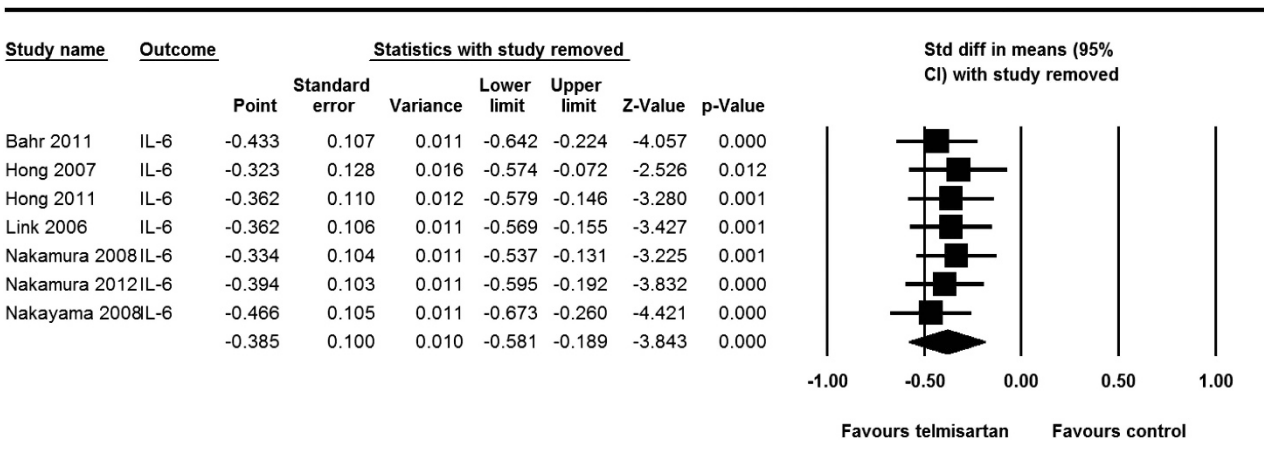


Figure 3 One-study-removed meta-analysis of percent changes in interleukin-6 (IL-6) levels among patients randomized to telmisartan vs. control therapy. CI, confidence interval.

vs. 23.5 ± 5.5 pg ml⁻¹). When these results were added to a primary meta-analysis, pooled analysis of eight and six trials demonstrated a statistically significant reduction in changes of IL-6 (random-effects SMD, -0.435; 95% CI, -0.725 to -0.146; $P=0.003$; P for heterogeneity=0.040) and TNF- α levels (random-effects SMD,

-0.780; 95% CI, -1.169 to -0.391; $P<0.001$; P for heterogeneity=0.001) with telmisartan relative to control therapy, respectively.

Two trials^{20,21} were eliminated from the present meta-analysis because of unavailable percent changes in IL-6 or TNF- α levels.

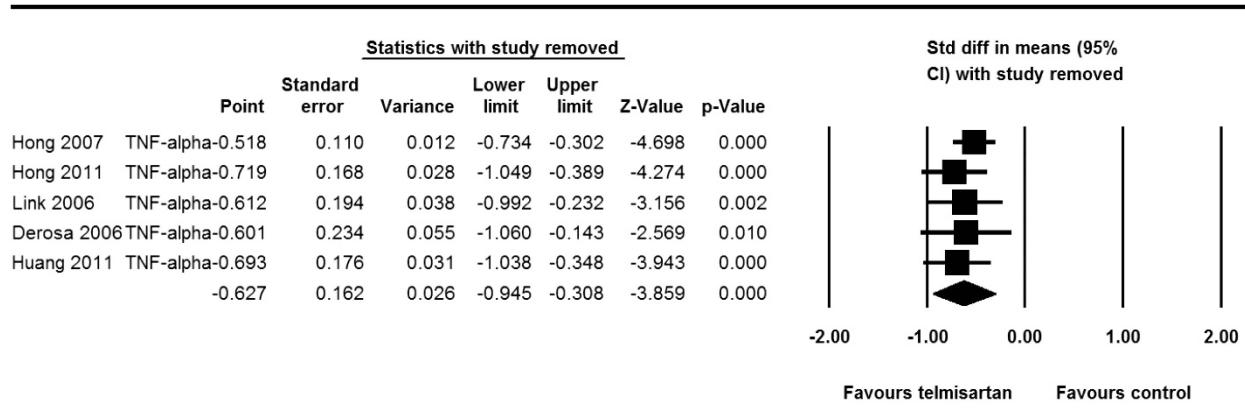


Figure 4 One-study-removed meta-analysis of percent changes in tissue necrosis factor- α (TNF- α) levels among patients randomized to telmisartan vs. control therapy. CI, confidence interval.

Nagel *et al.*²⁰ evaluated the effect of 12 weeks of telmisartan in subjects with insulin resistance in a randomized, placebo-controlled, double-blind, crossover study, and IL-6 concentrations were unchanged during telmisartan treatment compared with placebo (1.80 ± 1.02 vs. 1.66 ± 0.92 pg dl⁻¹; $P=0.96$). Wohl *et al.*²¹ evaluated the effect of telmisartan in a double-blind, randomized, crossover trial in which patients with impaired fasting glucose received telmisartan or a placebo for 3 weeks and *vice versa* with a 2-week washout period. During the hyperinsulinemic euglycemic clamp at the end of each period, TNF- α was decreased after telmisartan treatment (7.4 ± 0.9 vs. 8.6 ± 1.0 pg dl⁻¹; $P<0.05$).

Publication bias

To assess publication bias, we generated a funnel plot of the logarithm of effect size vs. the standard error for each trial (data not shown). There was no evidence of significant publication bias ($P=0.764$ and 0.779 for IL-6; $P=1.000$ and 0.360 for TNF- α ; by the adjusted rank-correlation and linear regression test, respectively).

DISCUSSION

The results of our analysis suggest that telmisartan therapy may reduce both IL-6 and TNF- α levels over control therapy; this finding was robust in sensitivity analyses. On the basis of cellular assays of PPAR- γ activation, Benson *et al.*⁷ have found that the angiotensin II receptor antagonist telmisartan is also a partial agonist of PPAR- γ , a well-known target of insulin-sensitizing drugs used to treat type 2 diabetes. In contrast, none of the other ARBs affected PPAR- γ activity, with the possible exception of irbesartan, which appeared to cause a modest activation of the receptor.⁷

The meta-analysis by Riera-Guardia and Rothenbacher⁵ that included 19 studies examined the effect of the intake of thiazolidinedione, a PPAR- γ agonist,⁶ on adiponectin serum concentrations in various subjects with different comorbidities. The thiazolidinedione treatment was clearly associated with an increase in adiponectin serum concentrations independent of the baseline population characteristics, and subjects treated with thiazolidinedione had average levels that were ~ 1 SD higher compared with the control group.⁵ Thus, telmisartan, a partial agonist of PPAR- γ ,⁷ may increase adiponectin.

Indeed, we recently performed a meta-analysis of 11 randomized head-to-head trials (representing 1088 patients) and demonstrated a statistically significant increase in the percent changes of adiponectin

levels (random-effects mean difference, 15.74%; 95% CI, 4.95–26.52%; $P=0.004$) with telmisartan relative to other ARB therapy.⁸ There is an inverse correlation between plasma adiponectin and IL-6 concentrations.^{23,24} Adiponectin and TNF- α mutually inhibit each other's production in adipose tissue, and adiponectin can counteract the proinflammatory effects of TNF- α in vascular cells.^{25–28} It has been observed that chronic administration of troglitazone, a selective ligand for PPAR- γ , is associated with a greatly attenuated responsiveness toward inducers of hepatic TNF- α and IL-6 production.²⁹ Additionally, IL-6 concentration is elevated in the plasma of diabetic rabbits and significantly diminished after treatment with pioglitazone, a high-affinity ligand of PPAR- γ .³⁰ Pioglitazone significantly reduces serum TNF- α levels in hypercholesterolemic rabbits independent of its metabolic actions, which may at least partly be due to its direct inhibition of TNF- α expression and secretion in adipocytes.³¹

These findings regarding PPAR- γ agonists could explain the reduction in IL-6 and TNF- α levels with telmisartan therapy demonstrated in the present meta-analysis. Tian *et al.*³² examined whether telmisartan inhibits the expression of IL-6 in vascular smooth muscle cells. Telmisartan, but not valsartan, attenuated IL-6 mRNA expression induced by TNF- α . Because the suppression of IL-6 mRNA expression was prevented by pretreatment with a specific PPAR- γ antagonist, PPAR- γ may be involved in the process. Telmisartan also attenuated serum IL-6 levels in TNF- α -infused mice and IL-6 production from rat aorta stimulated with TNF- α *ex vivo*.

These data suggest that telmisartan, but not valsartan, suppresses TNF- α -induced IL-6 expression in a PPAR- γ -dependent manner.³² Furthermore, both IL-6 and TNF- α are important pro-inflammatory adipokines that contribute to the regulation of CRP production in liver.³ Our recent meta-analysis³³ of 17 randomized controlled trials (representing 2632 patients) demonstrated a statistically significant reduction in percent changes of high-sensitivity CRP levels with telmisartan relative to control therapy (fixed-effects mean difference, -10.80% ; 95% CI, -16.15% to -5.45% ; $P<0.0001$). Thus, telmisartan may reduce CRP via reducing IL-6 and TNF- α .

Recently, Barnabe *et al.*³⁴ sought to systematically assess the association between anti-TNF- α therapy in rheumatoid arthritis and cardiovascular event rates. Anti-TNF- α therapy is associated with a reduced risk of all cardiovascular events, myocardial infarction, and cerebrovascular accident in observational cohorts. Although the point estimate of the effect from randomized controlled trials is

underpowered with wide 95% CIs, and cardiovascular events were secondary outcomes, randomized trials also demonstrated a trend toward decreased risk.³²

Raised levels of markers of acute inflammatory response after stroke are associated with poor outcomes. The odds ratios (ORs) for the association of markers and poor outcome (comparing the upper and the lower third) were IL-6, 3.1 (95% CI, 1.9–5.0); CRP, 1.9 (95% CI, 1.2–3.1); fibrinogen, 1.5 (95% CI, 1.0–2.36); white cell count, 2.1 (95% CI, 1.3–3.4); and glucose, 1.3 (95% CI, 0.8–2.1).³⁵ In addition, long-term IL-6 levels are associated with coronary heart disease risk (OR per 2 SD increase in baseline IL-6, 1.61; 95% CI, 1.42–1.83; OR per 2 SD increase in usual (long-term average) IL-6 levels, 3.34; 95% CI, 2.45–4.56) approximately as strongly as are some major established risk factors,³⁶ but causality remains uncertain. To determine whether unique properties of telmisartan are responsible for better clinical outcomes in cardiovascular disease prevention through the reductions in IL-6 and TNF- α , large clinical trials are needed.

In conclusion, we found that based on a meta-analysis of nine randomized controlled trials, telmisartan therapy is likely effective in reducing IL-6 and TNF- α levels. The reduction of inflammatory cytokines by telmisartan shown in the present meta-analysis may be beneficial for the treatment of not only hypertension but also atherosclerotic cardiovascular diseases. However, large clinical trials are needed to determine whether these unique properties of telmisartan are responsible for better clinical outcomes in cardiovascular disease prevention.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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