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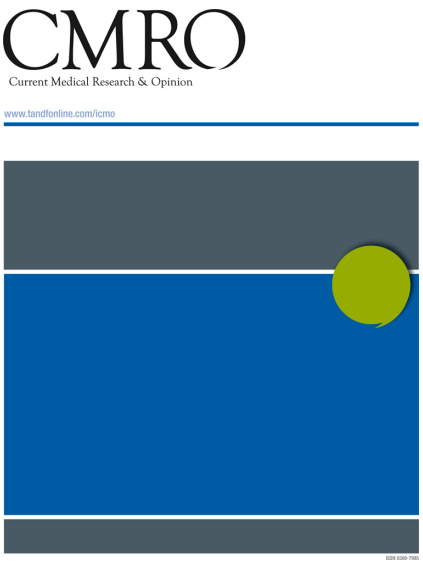

Effects of telmisartan on fat distribution: a meta-analysis of randomized controlled trials

Geun Joo Choi, Hyun Min Kim, Hyun Kang, Jaetaek Kim

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Abstract

Objectives: Several meta-analyses confirmed the positive metabolic effects of telmisartan, an angiotensin II receptor blocker that can also act as a partial peroxisome proliferator-activated receptor-γ agonist, compared to those of other angiotensin II receptor blocker. These effects include decreased fasting glucose, glycosylated hemoglobin, interleukin-6, and tumor necrosis factor-α levels. However, no systemic analysis of telmisartan's effects on body fat distribution has been performed. We performed a meta-analysis of randomized controlled telmisartan trials to investigate its effects on body weight, fat distribution, and visceral adipose reduction.

Research design and methods: A literature search was performed using Embase, MEDLINE, and Cochrane Library between January 1966 and November 2013. Randomized controlled trials in English and meeting the following criterion were included: random assignment of hypertensive participants with overweight/obesity, metabolic syndrome, or glucose intolerance to telmisartan or control therapy group.

Results: Of 651 potentially relevant reports, 15 satisfied the inclusion criterion. While visceral fat area was significantly lower in the telmisartan group than in the control group (weighted mean difference = -18.13 cm^2, 95% CI = -27.16 to -9.11, P_{chi}^2 = 0.19, I^2 = 41%), subcutaneous fat area was similar (weighted mean difference = 2.94 cm^2, 95% CI = -13.01 to 18.89, P_{chi}^2 = 0.30, I^2 = 17%). Total cholesterol levels were significantly different between the groups (standardized mean difference = -0.24, 95% CI = -0.45 to -0.03, P_{chi}^2 = 0.0002, I^2 = 67%).

Limitations: Limitations include (1)) limited number of studies, especially those evaluating fat distribution., (2) different imaging modalities to assess VFA and SFA, (3) observed heterogeneity.

Conclusion: The findings suggest that telmisartan affected fat distribution, inducing visceral fat reduction, and thus, could be useful in hypertensive patients with obesity/overweight, metabolic syndrome, or glucose intolerance.

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Effects of telmisartan on fat distribution: a meta-analysis of randomized controlled trials

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Key words: Telmisartan, Body fat distribution, Hypertension, Obesity

[Running Title: Telmisartan's effects on fat distribution]

ABSTRACT

Objectives: Several meta-analyses confirmed the positive metabolic effects of telmisartan, an angiotensin II receptor blocker that can also act as a partial peroxisome proliferator-activated receptor-γ agonist, compared to those of other angiotensin II receptor blocker. These effects include decreased fasting glucose, glycosylated hemoglobin, interleukin-6, and tumor necrosis factor-α levels. However, no systemic analysis of telmisartan's effects on body fat distribution has been performed. We performed a meta-analysis of randomized controlled telmisartan trials to investigate its effects on body weight, fat distribution, and visceral adipose reduction.

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Limitations: Limitations include (1)) limited number of studies, especially those evaluating fat distribution., (2) different imaging modalities to assess VFA and SFA, (3) observed heterogeneity.

Conclusion: The findings suggest that telmisartan affected fat distribution, inducing visceral fat reduction, and thus, could be useful in hypertensive patients with obesity/overweight, metabolic syndrome, or glucose intolerance.

INTRODUCTION

In the last decade, the prevalence of obesity has more than doubled in populations worldwide. Obesity increases the risk of comorbidities, such as type 2 diabetes, dyslipidemia, cardiovascular disease, cancer, and mortality[1,2]. Adipose tissue is an endocrine organ that is known to release a variety of cytokines and bioactive mediators such as leptin, adiponectin, interleukin (IL)-6, and tumor necrosis factor (TNF)-α[3]. These functions affect not only energy homeostasis but also insulin resistance, glucose intolerance, lipid metabolism, chronic inflammation, and atherosclerosis in obese patients[4]. In particular, visceral adipose tissue is considered a pathogenic fat depot, and plays a key role in metabolic syndrome.

Telmisartan, an angiotensin II receptor blocker (ARB), can also function as a partial agonist of peroxisome proliferator–activated receptor (PPAR)-γ and shows pleiotropic effects on not only blood pressure but also glucose and lipid profiles[5-7]. Recently, several meta-analyses confirmed the positive metabolic effects of telmisartan compared to those of other ARBs. Takagi *et al.* showed that telmisartan therapy improved metabolic parameters, including fasting plasma glucose, fasting insulin, glycosylated hemoglobin, adiponectin, inflammatory cytokines, and endothelial function assessed by flow-mediated dilatation[8-13]. However, few randomized controlled trials (RCTs) have evaluated the effect of telmisartan therapy on body fat composition, especially the reduction of visceral fat.

We performed a meta-analysis of RCTs of telmisartan to investigate its effect on body weight,

fat distribution, and visceral fat reduction in hypertensive patients with obesity/overweight, metabolic syndrome, or glucose intolerance.

METHODS

We performed a systematic review following the guidelines of the Preferred Reporting Items of Systematic Review and Meta-Analyses statement[14].

Literature search

A systematic review of literature concerning the effect of telmisartan on fat distribution and metabolism was conducted according the protocol recommended by the Cochrane Collaboration. The literature search was performed using Embase, MEDLINE and the Cochrane Library between January 1966 and November 2013 by 2 authors (G.J.C. and H.M.K.). The reference list of the identified literature was also searched manually. Search terms are presented in the Appendix.

Study selection

We included RCTs in English that met the following criterion: hypertensive participants with overweight/obesity, metabolic syndrome, or glucose intolerance randomly assigned to telmisartan versus control therapy (including placebo). We excluded studies in which existing treatments were switched to the study medicine. Two authors (G.J.C. and H.M.K.) independently selected eligible studies, and they discussed any differences of opinion to arrive at a consensus as to whether a study should be included or excluded. Disagreement over inclusion and exclusion was settled in discussion with 2 senior authors (H.K. and J.T.K.) who were blinded to the evaluation of the first 2 authors.

Data extraction

Two authors (G.J.C. and H.M.K) independently evaluated all the included studies and performed data extraction using a data collection form specifically developed for this review. Discrepancies were resolved by discussion between 2 senior authors (H.K. and J.T.K.). Data

extracted from studies included the following: name of the first author; year of publication; number of participants; body mass index (BMI); waist circumference; medication with dosages of the intervention group and control group; duration of follow-up; fat area (visceral and subcutaneous); abdominal visceral fat area (VFA) and subcutaneous fat area (SFA) with their diagnostic methods; and lipid profile including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Data were initially extracted from tables or text. For data not available in tables, the data were abstracted from available figures. Continuous data were recorded using mean and standard deviation.

We considered all medications, including placebo, in comparison with the telmisartan group as a control group. When telmisartan was compared with 2 medications in a single study (including placebo), we included each pair-wise comparison separately, but with the shared telmisartan group divided into 2 approximately even groups[15]. When the durations of follow-up were diverse, we retrieved the data near 6 months or 24 weeks.

Assessment of risk of bias

The quality of eligible studies was assessed independently by 2 authors (G.J.C. and H.M.K.) using the "risk of bias" tool according to Review Manager software (version 5.1, The Cochrane Collaboration, Oxford, UK). The quality was evaluated based on the following 6 potential sources of bias: random sequence generation, allocation concealment, blinding of the participants, outcome assessors, incomplete outcome data, and selective reporting. The methodology of each trial was graded as "high," "low," or "unclear," to reflect a high risk of bias, low risk of bias, and uncertainty of bias, respectively.

Data synthesis and analysis

We computed weighted mean difference (WMD) or standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) for continuous variables using Review

Manager software (version 5.1, The Cochrane Collaboration, Oxford, UK). We used the Chi^2 test for homogeneity and the I^2 test for heterogeneity. We regarded a level of 10% significance ($P < 0.1$) in the Chi^2 statistic or an I^2 greater than 50% as considerable heterogeneity. We pooled data using both the fixed-effect model and the random-effect model. Funnel plots were drawn for each data set as a measure of publication bias across studies, which were assessed visually for symmetry[15].

RESULTS

The present review was described according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[14].

Search results and study characteristics

Of 651 potentially relevant reports identified by the search strategy, 25 were retrieved for a more detailed assessment. Ten studies did not meet the inclusion criteria, 3 of which were studies where the existing treatments were switched to study medications. Finally, 15 studies satisfied the inclusion criteria (Figure 1). The study characteristics of the included studies are summarized in table 1. Overweight or obese was defined as BMI value $\geq$ 23 kg/m^2 in one trial[16], and BMI value $\geq$ 27 kg/m^2 in non-Asians and $\geq$ 24 kg/m^2 in Asians in one trial[17]. Glucose intolerance includes the conditions of impaired fasting glucose (defined as free plasma glucose (FPG) $\geq$100 mg/dL), impaired glucose tolerance (defined as 2-hour values in the oral glucose tolerance test (OGTT) of $\geq$ 140 mg/dl, but <200 mg/dl), and type 2 diabetes mellitus. Diabetes was diagnosed as FPG $\geq$126 mg/dl, 2-hour values in the OGTT of $\geq$ 200 mg/dl, HbA1c >= 6.5% or taking antidiabetic agents. Metabolic syndrome was defined according to the diagnostic criteria of the National Cholesterol Education Program Adult III Treatment Panel (NCEP-ATP III) in 3 trials[18-20], the criteria of the International Diabetes Federation in 2 trials[21,22], the criteria of Japan Society for the Study of Obesity in 2 trials[23,24], and the criteria of the World Health Organization in one trial[25], respectively. In one study[26],

insulin resistance was defined as having an insulin sensitivity index below the 25th percentile of the general population[27].

Risk of bias

All studies mentioned randomization, but 7 studies described the method used for sequence generation[16,17,19,20,24,25,28]. Two studies reported allocation concealment[19,28]. Three studies described blinding of participants[17,19,20], and 4 studies had blinding of outcome assessors[19,20,22,28]. Nine studies showed incomplete outcome data[17-20,22-24,28,29].

Results of the meta-analysis

Three studies investigated abdominal VFA and SFA[16,22,24], which were determined by abdominal computed tomography scans in 2 studies[22,24], and magnetic resonance imaging in one[16]. While VFA was significantly lower in the telmisartan group than in the control group (WMD = -18.13 cm^2, 95% CI = -27.16 to -9.11, P_{chi}^2 = 0.19, I^2 = 41%; figure 2), SFA was similar between the 2 groups (WMD = 2.94 cm^2, 95% CI = -13.01 to 18.89, P_{chi}^2 = 0.30, I^2 = 17%; figure 2). There were no intergroup differences in BMI in 10 studies[19-24,28-31], and in waist circumference in 5 studies[16,18,22,24,30] (WMD = -0.16 kg/m^2, 95% CI = -0.65 to 0.32, P_{chi}^2 = 0.004, I^2 = 62%; WMD = -1.92 cm, 95% CI = -4.68 to 0.84, P_{chi}^2 = 0.03, I^2 = 62%, respectively). TC was evaluated in 13 studies[16-25,28-31], TG in 13 [16-24,28-31], LDL in 9 [16-19,21,24,28,29,31], and HDL-C in 12 [16-19,21-24,28-31]. TC showed a significant difference between the 2 groups (SMD = -0.24, 95% CI = -0.45 to -0.03, P_{chi}^2 = 0.0002, I^2 = 67%; figure 3). TG, LDL, and HDL-C were similar between the 2 groups (SMD = -0.10, 95% CI = -0.20 to 0.00, P_{chi}^2 = 0.53, I^2 = 0%; SMD = -0.17, 95% CI = -0.38 to 0.04, P_{chi}^2 = 0.03, I^2 = 51%; SMD = 0.02, 95% CI = -0.08 to 0.12, P_{chi}^2 = 0.14, I^2 = 30%, respectively). Funnel plots were applied for every comparison, all of which showed a symmetric appearance.

DISCUSSION

The present study is the first meta-analysis to investigate the effect of telmisartan on fat

distribution. Our results revealed that telmisartan treatment may decrease visceral fat, without changing body weight, waist circumference, and subcutaneous fat. We also confirmed that telmisartan therapy improved the lipid profile and decreased total cholesterol compared to other ARBs, calcium channel blockers (CCBs), or placebo in hypertensive patients with obesity/overweight, metabolic syndrome, or glucose intolerance.

Because ARBs are highly effective and well tolerated in most people, these medications have become quite popular, especially in patients with diabetes or kidney disease. The antihypertensive effect of telmisartan is known to be comparable to that of another ARB from several meta-analyses[32-34]. In addition to its blood pressure lowering effect, many trials supported its metabolic effects in patients with hypertension. Takagi *et al.* and other have shown that telmisartan therapy decreased fasting glucose levels, glycosylated hemoglobin, fasting insulin levels, homeostasis model assessment index[9], triglyceride levels[11], C-reactive protein levels[35], TNF-α levels, IL-6 levels[8], and increased the anti-inflammatory adipokine and adiponectin levels[12]. Furthermore, when evaluating the metabolic effects of combining statins with ARBs in patients with metabolic syndrome, telmisartan improved insulin sensitivity and hs-CRP[36]. Because the negative effect of statin treatment on glucose metabolism is known, co-treatment of telmisartan with statin might be more helpful when considering antihypertensive agents in patients with metabolic syndrome, dyslipidemia, or glucose intolerance. Despite strong evidence for the metabolic benefits of telmisartan, however, the exact mechanisms and causal relationship remain unclear.

Over the last several decades, abdominal adiposity has attracted attention, because of its close association with chronic metabolic disorders[37]. Today, adipose tissue is recognized as an endocrine organ that plays an active role in energy homeostasis[3]. Abdominal adipose tissue in the human body can be categorized according to its location in 2 major compartments, subcutaneous and visceral fat. Among these, visceral fat seems to releases various cytokines

and bioactive mediators, including leptin, adiponectin, IL-6, and TNF-α, and is considered to play a pivotal role in the development and progression of obesity, insulin resistance, glucose intolerance, dyslipidemia, inflammation, and atherosclerosis[38]. Further, visceral fat is an independent predictor of insulin resistance[39], dyslipidemia[40,41], type 2 diabetes[41], microalbuminuria[42], and all-cause mortality[43]. Recently, Britton *et al.* showed that visceral adiposity is still associated with cardiovascular disease and cancer after adjustment for clinical risk factors and generalized adiposity represented by BMI from the Framingham Heart Study[44].[45] These data suggest that ectopic fat, including visceral fat, is a trigger point for signaling cascades mediating metabolic disturbances, termed "metaflammation"[45]. Thus, alterations in body fat distribution by reducing visceral fat may play a key role in the prevention or treatment of chronic metabolic disorders[46].

Along with non-pharmacological intervention, including diet control or exercise, and pharmacological therapies, such as weight loss drugs or growth hormone treatment, thiazolidinediones (TZDs), a family of anti-diabetic agents, consistently show favorable effects on fat distribution[47-49]. TZDs are insulin sensitizers, and are widely used to treat type 2 diabetes. These agents bind to and activate the nuclear receptor PPAR-γ, which is a ligand-dependent transcription factor expressed predominantly in adipose tissue[49]. PPAR-γ is a key transcription factor in the regulation of adipogenesis[50]. Thus, TZDs stimulate adipogenesis, particularly in the subcutaneous fat, thereby recruiting new small adipocytes to accommodate excess lipids[51,52]. Several clinical studies in patients with type 2 diabetes mellitus showed that TZDs redistribute adipose tissue from the abdominal visceral to the subcutaneous compartment, which is considered a more metabolically favorable profile[47,48,52]. Further, recent data from the DREAM trial (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) showed that rosiglitazone is associated with relatively less visceral fat after 3.5 years of treatment in people with pre-diabetes[53].

Because telmisartan acts as a partial PPAR-γ agonist[5], telmisartan could partly affect fat distribution. Fat redistribution induced by PPAR-γ agonists is characterized by the differentiation of pre-adipocytes into small fat cells in subcutaneous fat depots and apoptosis of differentiated large adipocytes in visceral fat depots[54]. In animal studies, telmisartan reduced adipocyte size and protected against obesity and steatohepatitis compared to valsartan[55], furthermore, showed cardio-protective effect in rats with hypertensive left ventricular hypertrophy[56]. This change in fat distribution could explain the favorable effects of telmisartan on reducing pro-inflammatory cytokines, like IL-6 and TNF-α levels, and increasing adiponectin levels. Recently, several studies suggested that telmisartan-induced PPAR-δ activation could be involved in its insulin sensitizing effect in an animal model or human mesangial cells[57-59]. However, the effects of partial PPARγ agonists should be differentiated from the effects of full PPARγ agonist. Especially on lipid metabolism, rosiglitazone, one of the most potent full PPARγ agonists, increased TG and LDL-C[60]. The different effects on gene expression patterns between two kinds of agonist could explain this point of difference[61,62] For example, in the previous experimental study, Telmisartan affected the expression of acetyl coenzyme A carboxylase, a key gene involved in the regulation of muscle fatty acid metabolism, but rosiglitazone did not[5]. Therefore, the detailed mechanisms of fat redistribution by telmisartan need to be verified, and furthermore the cardiovascular outcome following the reduction of visceral fat and inflammatory cytokines should be clarified in clinical studies.

There are several limitations in this study. First, the number of trials is limited, especially those evaluating fat distribution. Additionally, the imaging modalities to assess VFA and SFA were not identical, as one studied used magnetic resonance imaging, whereas the others used computed tomography scans. Although computed tomography scans are commonly used and

considered the gold standard technique for measuring VFA and SFA[63], magnetic resonance imaging is a powerful and accurate tool for visceral fat quantification, and its use has increased in recent years[64]. Because an early study showed that fat areas from the transverse scans by computed tomography and magnetic resonance imaging were comparable[65], it is possible to include studies with both imaging tools in this analysis.

In conclusion, the present study showed that telmisartan therapy could affect the fat distribution, with a significant reduction in visceral fat. This change could explain the effects of telmisartan on reducing pro-inflammatory cytokines levels, including IL-6 and TNF-α, and increasing adiponectin levels. Further, this meta-analysis confirmed the beneficial effect on lipid profile compared to other hypertensive agents and placebos. The additional benefits of this antihypertensive drug might be helpful, especially when patients have multiple cardiovascular risk factors. We propose that telmisartan therapy could be useful as an antihypertensive agent, especially in the hypertensive patients with obesity/overweight, metabolic syndrome, or glucose intolerance. However, more clinical trials are warranted to confirm this relationship and to further understand the effect of visceral fat reduction on cardiovascular outcomes.

Transparency

Declaration of funding:

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Declaration of financial/other interests:

The Authors have no relevant conflicts of interest to declare. CMRO Peer Reviewer 1 has disclosed he is on the Speakers' Bureaus of AstraZeneca, MSD, Pfizer, Abbott, Boehringer Ingleheim, Eli Lilly and GSK. Peer Reviewer 2 has given talks, attended conferences and participated in trials sponsored by MSD, Sanofi, and Amgen. Peer Reviewer 3 has no relevant

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Table 1. Trial design and baseline characteristics for the enrolled patients.

Trial	Intervention		Number of patients		Follow-up duration
	Telmisartan	Control	Telmisartan	Control	
Bahadir 2006	80 mg	Losartan 50 mg	21	21	8 weeks
de Luis 2010	80 mg	Olmesartan 40 mg	34	31	3 months
Derosa 2004	40 mg	Nifedipine GITS 20 mg	58	58	12 months
Derosa 2006	40 mg	Irbesartan 150 mg	23	26	6 months
Derosa 2004	40 mg	Eprosartan 600 mg	40	39	6 months
		Placebo		40	6 months
Georgescu 2009	20 mg	Placebo	28	26	20 months
Huang 2011	80 mg	Losartan 100 mg	23	22	16 weeks
Ichikawa 2007	20 mg	Valsartan 40 mg	26	27	4 weeks
Lan 2011	80 mg	Amlodipine 5 mg	27	27	6 months
Makita 2008	40 or 80 mg	Candesartan 8 /12 mg	46	44	6 months
Mori 2012	80 mg	Elmisartan 40 mg	34	34	3 months

		Amlodipine 5 mg			
Murakami 2012	40 mg	Valsartan 80 mg	9	10	24 weeks
Sharma 2007	80 mg + HTCZ 12.5 mg	Valsartan 160 mg + HCTZ 12.5 mg	428	412	10 weeks
Shimabukuro 2007	20-40 mg	Amlodipine 2.5-5 mg	27	26	24 weeks
Vitale 2005	80 mg	Losartan 50 mg	20	20	3 months

Figure 1. Flow diagram of trials identified and selected.

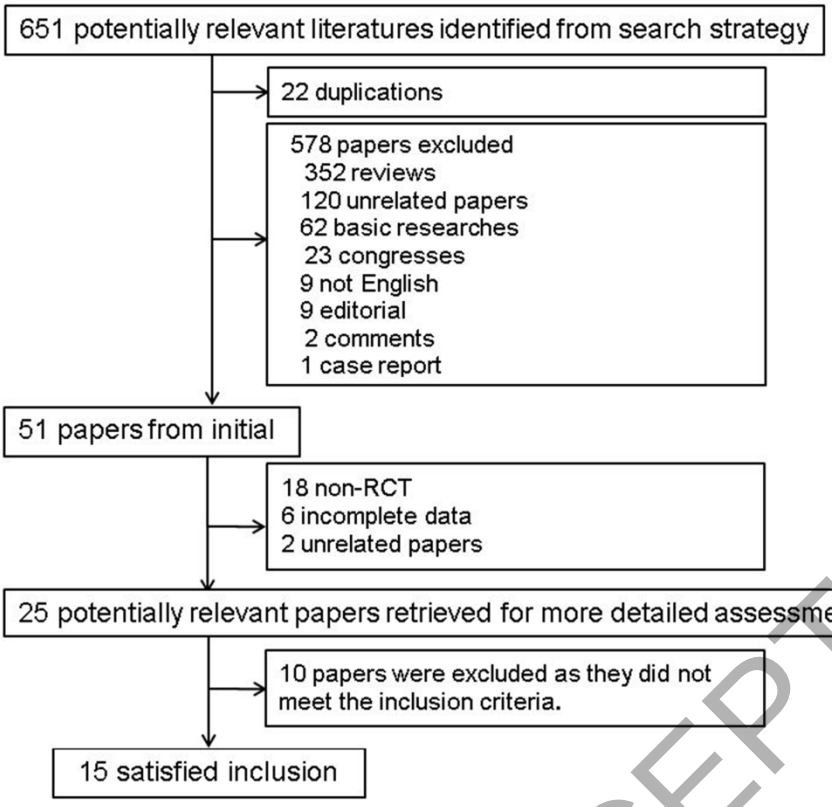

Figure 2. Final SFA and VFA among patients randomized to telmisartan versus control therapy. CI, Confidence interval; IV, inverse variance; SD, standard deviation.

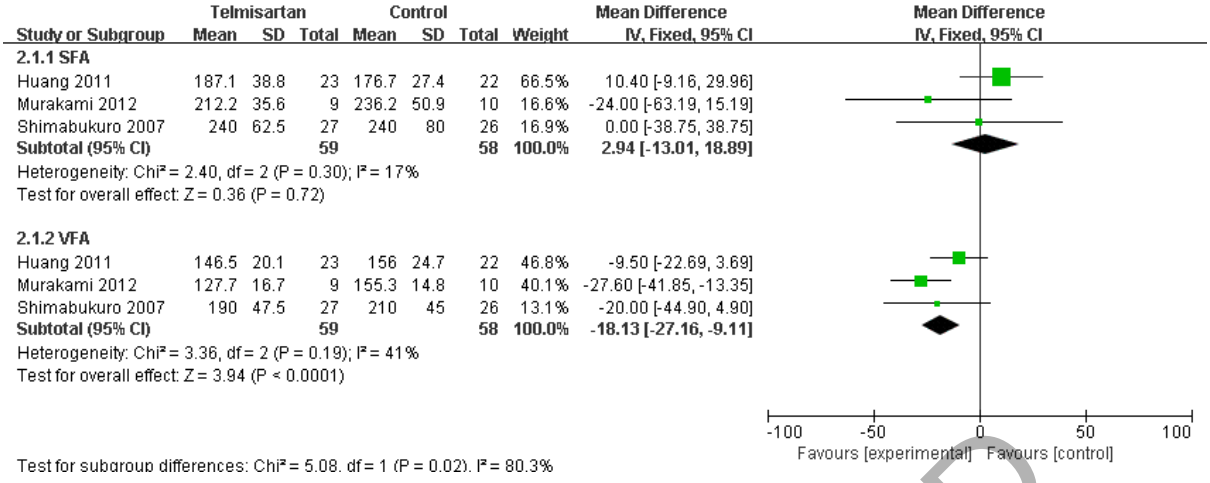

Figure 3. Final TC among patients randomized to telmisartan versus control therapy. CI, Confidence interval; IV, inverse variance; SD, standard deviation.