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Effects of Telmisartan and Ramipril on Adiponectin and Blood Pressure in Patients with Type 2 Diabetes

Short title: Adiponectin and blood pressure

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Abstract

Background Adiponectin is secreted by adipose tissue and may play a role in cardiovascular disease. We examined adiponectin levels in patients with type 2 diabetes who participated in the Telmisartan versus Ramipril in Renal Endothelial Dysfunction (TRENDY) study.

Methods Eighty-seven patients were assessed at baseline and following 9 weeks treatment with the angiotensin-receptor blocker telmisartan (final dose, 80 mg; n=45) or the angiotensin-converting enzyme inhibitor ramipril (final dose, 10 mg; n=42). Adiponectin levels were measured in plasma by radioimmunoassay.

Results Adiponectin levels were inversely correlated with systolic (SBP; r=-0.240, P<0.05) and diastolic (DBP; r=-0.227, P<0.05) blood pressure at baseline and following treatment with telmisartan or ramipril (SBP: r=-0.228, P<0.05; DBP: r=-0.286, P<0.05). Changes in adiponectin levels were related to changes in SBP (r=-0.357, P<0.01) and DBP (r=-0.286, P<0.01). There was a significant increase in adiponectin levels in the telmisartan (0.68 [95% CI, 0.27 to 1.10] µg/mL, P<0.01) but not in the ramipril group (0.17 [95% CI, -0.56 to 0.90] µg/mL, P=0.67). Blood pressure reduction in the telmisartan group (ΔSBP: -13.5 [95% CI, -17.0 to -10.0] mmHg; ΔDBP: -7.6 [95% CI, -9.8 to -5.3] mmHg, each P<0.001) was significantly (P=<0.01 for systolic and P<0.01 for diastolic blood pressure) greater than in the ramipril group (ΔSBP: -6.1 [95% CI, -6.2 to -2.0] mmHg; ΔDBP: -2.7 [95% CI, -5.0 to -0.5] mmHg; P<0.01 and P<0.05, respectively).

Conclusion Adiponectin is correlated with blood pressure in patients with type 2 diabetes. Whether increased adiponectin contributes to the blood pressure-lowering effect of telmisartan needs further study.

Introduction

Adiponectin is an adipose tissue-specific plasma protein. Plasma adiponectin levels are decreased in diabetes, metabolic syndrome and coronary artery disease [1-3]. Adiponectin increases insulin sensitivity [4] and stimulates endothelial nitric oxide production [5]. Reduced adiponectin levels therefore provide a link between insulin resistance and endothelial dysfunction in cardiovascular disease (for review see [6-8]).

There is increasing evidence that adiponectin is also involved in the pathogenesis of hypertension. Plasma adiponectin levels have been found to be lower in hypertensive compared to normotensive subjects [9,10]. Hypoadiponectinemia independently predicts development of hypertension in a nondiabetic population cohort [10], and plasma adiponectin levels are inversely related to blood pressure in normotensive men [9]. An adiponectin-knockout mouse exhibits obesity, insulin resistance and hypertension when put on high-fat/high-sucrose/high-salt diet [11]. Similar findings have been described in obese KKAy mice that have low adiponectin levels [12]. Both mouse models respond with amelioration of hypertension to adenovirus-mediated adiponectin replenishment [12]. Potential pathomechanisms include action of adiponectin on endothelial function, sympathetic nervous system and the renin-angiotensin-aldosterone system [13].

Angiotensin receptor blockers (ARBs) and particularly the ARBs telmisartan and irbesartan have been shown to increase plasma adiponectin levels by inducing peroxisome proliferator-activated receptor-γ (PPARγ) activity independent of their AT_1-receptor blocking actions [14,15]. Telmisartan stimulates adiponectin protein expression in adipocytes and preadipocytes via PPARγ activation although the exact mechanisms remain unclear [16-18]. PPARγ-independent stimulation of adiponectin by telmisartan has also been reported [19].

We hypothesised that the blood pressure-lowering effect of telmisartan is related to its potential to increase adiponectin levels. To test our hypothesis we retrospectively analysed data from the Telmisartan versus Ramipril in Renal Endothelial Dysfunction (TRENDY) study [20]. In TRENDY, patients with type 2 diabetes and hypertension, who will particularly benefit from blood

pressure reduction and increase in adiponectin levels, were treated with the ARB telmisartan and the angiotensin-converting enzyme (ACE) inhibitor ramipril.

Methods

Patients

Details of study design, inclusion and exclusion criteria have been published previously [20]. In brief, patients with type 2 diabetes and hypertension were included if systolic blood pressure (SBP) was 140-179 mmHg and/or diastolic blood pressure (DBP) was 90-109 mmHg if untreated, or SBP <180 mmHg and/or DBP <110 mmHg if on antihypertensive medication. Exclusion criteria included poor diabetes control (glycosylated haemoglobin [HbA_{1c}] >9%) and severe diabetes or hypertension-related end organ damage such as proliferative retinopathy and symptomatic cardiovascular disease. Patients with previous intolerance of ACE inhibitors or ARBs, and secondary hypertension including renal artery stenosis were also excluded. Where appropriate, stable dose of metformin during the 12 weeks before enrolment was required. Patients who were on thiazolidinediones were not included. Study participants were not on a controlled diet, but were asked not to change their dietary habits during participation in this study.

The study was a carried out in four study centres and was approved by local ethics committees for each site. Written informed consent was obtained from all participants.

Study protocol

The study protocol has been published previously [20]. There was a 2-week open-label placebo run-in period to improve blood pressure control to the above targets with hydrochlorothiazide and, if required, metoprolol or atenolol. Then randomization to telmisartan (40 mg) or ramipril (5 mg) took place using a parallel-group, double-blind, double-dummy design. After 3 weeks into the study there was forced titration to 80 mg telmisartan or 10 mg ramipril with add-on therapy if blood pressure control remained inadequate (SBP ≥160 mmHg and/or DBP ≥95 mmHg), aiming for a

target blood pressure <130/80 mmHg. The present study is a *post hoc* analysis of the TRENDY study.

Assessment of blood pressure and biochemical parameters

Blood pressure was measured by trained study nurses using a semi automatic device (Dinamap Pro 100, GE Healthcare, Chalfont St. Giles, UK; or Omron HEM 907XL, Omron, Mannheim, Germany). Participants were seated for five minutes before the first measurement was performed. Three measurements were taken and the average of these measurements is given.

Adiponectin was determined in plasma by radioimmunoassay utilizing ^{125}I-labeled murine adiponectin and a multispecies adiponectin rabbit antiserum by the double antibody/PEG technique. (Linco Research, Inc., St. Charles, MO). The limit of sensitivity is 1 ng/mL, whereas the limit of linearity for the Human Adiponectin assay is 200 ng/mL. A 1:500 dilution of samples was therefore required. Quality controls were supplied by the manufacturer. Intra and inter assay coefficients of variation were less than 8% and 7%, respectively. Aldosterone levels were determined in plasma by a commercially available radioimmunoassay (Adaltis Italia S.p.A., Bologna, Italy), and plasma angiotensin II levels were determined by radioimmunoassay (antiserum kindly provided by Prof. D. Ganten, Max Delbrück Zentrum, Berlin, Germany) as previously described [21]. All these analyses were performed in the same run from samples that were frozen and stored at -80 °C immediately after centrifugation. Other laboratory parameters were measured by standard biochemistry methods in local hospital laboratories: glucose, lipids, ALT, AST and creatinine by photometry; CRP and HbA_{1c} by turbidimetry.

Statistical analysis

Normal distribution was tested by Kolmogorov-Smirnov test and visual inspection of Q-Q plots. Data not following normal distribution were log transformed. Data were then compared by paired and unpaired Student's t-test as appropriate. In correlation analyses, Pearson correlation coefficients

are given. Multiple linear regression was used where indicated either will all covariates entered into the model or using a stepwise approach with probabilities of F for entry and removal of 0.05 and 0.10, respectively. In regression models, sex was coded as 1=male and 2=female. Data are given as mean ± standard deviation or median [interquartile range] as appropriate in text and tables and mean ± standard error in figure 2. A *P*-value of ≤0.05 (two-sided) was considered significant. Statistical analyses have been carried out using SPSS version 15 (SPSS Inc., Chicago, IL, USA) and Minitab version 12 (Minitab Inc., State College, PA, USA) software.

Results

Characteristics of the study cohort

Eighty-seven participants were included. Baseline characteristics prior to randomization are displayed in Table 1. There were no significant differences between patients receiving ramipril (n=42) and those receiving telmisartan (n=45). There was a numerical but not statistically significant (*P*=0.064) difference in baseline adiponectin levels between the groups.

Adiponectin and blood pressure at baseline

We first examined which factors are correlated with adiponectin levels at baseline in the whole study cohort (n=87). There were significant correlations between adiponectin levels and age (*r*=0.324, *P*<0.01), sex (*r*=0.323, *P*=<0.01), systolic (*r*=-0.240, *P*<0.05) and diastolic (*r*=-0.227, *P*<0.05) blood pressure, and high-density lipoprotein (HDL) cholesterol levels (*r*=0.399, *P*<0.001). Body mass index (*r*=0.001, *P*=0.99), total (*r*=-0.008, *P*=0.94) and low-density lipoprotein (LDL) cholesterol levels (*r*=-0.040, *P*=0.72), HbA_{1c} (*r*=-0.087, *P*=0.74) and C-reactive protein (CRP) levels (*r*=-0.067, *P*=0.60) were not correlated with adiponectin levels.

We then entered adiponectin levels together with other potential predictors of blood pressure including age, sex, body mass index and 24-hour urinary sodium excretion in a linear regression model. Adiponectin levels were the only predictor of systolic blood pressure (β=-0.287, *P*<0.05)

after adjustment for these covariates using a stepwise regression model (Table 2). The relationship between adiponectin and blood pressure is illustrated in Figure 1.

Effects of telmisartan and ramipril on blood pressure and adiponectin

By treatment with ramipril or telmisartan over a period of 9 weeks the whole study group (n=87) experienced a reduction in systolic and diastolic blood pressure by 9.9 [95% CI, 7.2 to 12.7] mmHg (P<0.001) and 5.2 [95% CI, 3.6 to 6.9] mmHg (P<0.001), respectively, and an increase in adiponectin levels by 0.44 [95%CI, 0.05 to 0.84] µg/mL (P<0.05). Adiponectin levels were also correlated with systolic and diastolic blood pressure after treatment, and changes in adiponectin levels were correlated with changes in blood pressure (Figure 1). In the whole group of patients, change in adiponectin levels were correlated with change in systolic an diastolic blood pressure even after adjustment for treatment (P<0.01 and P<0.05, respectively).

As opposed to the ramipril group there was a significant increase in adiponectin levels in patients treated with telmisartan (ramipril: increase by 0.17 [95% CI, -0.56 to 0.90] µg/mL, P=0.67; telmisartan: increase by 0.68 [95% CI, 0.27 to 1.10] µg/mL, P<0.01) and the difference between the groups was significant (P<0.05) (Table 3). Blood pressure reduction in the telmisartan group (change in systolic and diastolic blood pressure by 13.5 [95% CI, 10.0 to 17.0)] mmHg and 7.6 [95% CI, 5.3 to 9.8)] mmHg, each P<0.001) was significantly (P<0.01 for both systolic and diastolic blood pressure) greater than in the ramipril group (change in systolic and diastolic blood pressure by 6.1 [95% CI, 2.0 to 6.2)] mmHg and 2.7 [95% CI, 0.5 to 5.0)] mmHg; P<0.01 and P<0.05, respectively).

Because of the numerical difference in baseline adiponectin levels between the group assigned to ramipril and telmisartan we examined the effect of treatment on adiponectin in three subsets of patients with baseline adiponectin levels <7 µg/mL (n=34), ≥7 µg/mL but <10 µg/mL (n=25) and ≥10 µg/mL (n=28) to exclude that the observed results are due to regression to the mean. Even in the group with lowest baseline levels, ramipril did not significantly increase adiponectin levels,

whereas in the telmisartan group only patients with the highest baseline levels did not show further increase in adiponectin following treatment (Figure 2). Multiple regression analysis with all variables forced into the analysis confirmed that change in systolic blood pressure was associated with assignment to treatment group (P<0.05) and change in adiponectin levels throughout the treatment period (P<0.01), whereas tertile of basal adiponectin (P=0.91), age (P=0.72), body mass index (P=0.89) and sex (P=0.73) were not related to change in systolic blood pressure in this model (adjusted R^2=12.3%). Similar results have been obtained using a stepwise regression model (variables included in the stepwise model: treatment group [P<0.05] and change in adiponectin levels [P<0.01]; variables not included in the stepwise model: tertile of basal adiponectin (P=0.94), age (P=0.99), body mass index (P=0.91) and sex (P=0.99); adjusted R^2=16.2%).

Associations of treatment with other biochemical parameters are displayed in Table 3. There were no differences between the ramipril and telmisartan group on parameters other than adiponectin and plasma angiotensin II levels. None of the factors were correlated with changes in adiponectin in the whole study group or in the ramipril or telmisartan groups (all P=n.s; data not shown).

Discussion

We have demonstrated an inverse relationship between plasma adiponectin levels and blood pressure in hypertensive patients with type 2 diabetes. Moreover, changes in adiponectin levels were related to reduction in blood pressure following treatment with telmisartan or ramipril. Patients treated with telmisartan experienced a significant increase in plasma adiponectin levels and a more pronounced reduction in blood pressure compared with patients randomized to ramipril.

A subset of ARBs including telmisartan, irbesartan and losartan has been shown to increase adiponectin release from adipocytes independent of the ARBs' action on AT_1-receptors via PPARγ stimulation [14]. There is evidence for both transcriptional [15,16] and post-transcriptional mechanisms involved [17]. In clinical studies telmisartan has been shown to increase circulating adiponectin levels in patients with type 2 diabetes [22,23]. Makita *et al.* [24] recently translated

these findings into clinical routine by demonstrating an association between telmisartan use and adiponectin levels in hypertensive outpatients. In the present study we have shown that, in contrast to the ACE inhibitor ramipril, the ARB telmisartan increases adiponectin plasma levels within a 9-week treatment period. The correlation between blood pressure reduction and increase in adiponectin levels and the greater blood pressure reduction in patients treated with telmisartan compared to those treated with ramipril in our study would be consistent with a role of adiponectin in the hypotensive effect of telmisartan. However, in the absence of data on PPARγ stimulation in the present study further studies are needed to examine this in more detail.

By employing strict inclusion criteria such as a washout period prior to randomization and limiting concomitant hypoglycaemic drugs to metformin together with a relatively large sample size, we were able to demonstrate relationships between adiponectin and blood pressure both at baseline and following treatment. Our study cannot be directly compared with a previous study by Usui *et al.* [25] who also examined metabolic effect of telmisartan in patients with type 2 diabetes and hypertension. In this study [25] telmisartan was administered on top of pre-existing therapy and there were no changes in adiponectin levels during a 6-month treatment period. Similarly, Benndorf *et al.* [26] did not find changes in serum adiponectin levels after 6 weeks of treatment with telmisartan in nondiabetic patients with essential hypertension although telmisartan improved insulin sensitivity. We believe that our present study cohort due to having both conditions, hypertension and type 2 diabetes, is particularly suited to examine the effects of telmisartan on adiponectin levels and blood pressure. Indeed, adiponectin has been demonstrated to have positive effects on insulin sensitivity, inflammation, and atherosclerosis, and insulin-resistance is a feature of essential hypertension [27]. Circulating adiponectin levels have been found to be inversely correlated with insulin resistance in patients with the metabolic syndrome [28], and the ARB candesartan has indeed been found to improve insulin sensitivity [29].

The relationship between adiponectin and blood pressure has been previously described in clinical studies [9,10,13] but has not been uniformly confirmed in other study cohorts [30]. It is an

important feature of our study that we were able to show a relationship between changes in adiponectin levels and changes in blood pressure, although this relationship is not necessarily a causal one. Our data are indeed in line with a report by Negro *et al.* [31] who found a relationship between amelioration of metabolic parameters including adiponectin and blood pressure reduction in obese, insulin resistant, hypertensive patients. The finding that changes in adiponectin levels did not correlate with changes in angiotensin II concentration supports an AT_1-receptor independent stimulation of adiponectin by telmisartan. Our present study, however, does not explain the mechanisms linking adiponectin with blood pressure. Amongst the potential mechanisms improvement of endothelial function by stimulating endothelial nitric oxide release is an attractive hypothesis [13]. We have previously reported improvement of basal nitric oxide activity in the renal vasculature of patients in the present study [20], but the absence of a significant difference in improvement of renal endothelial function between patients on telmisartan and those on ramipril contradicts a direct effect of adiponectin on endothelial function in our patient cohort. Despite evidence from experimental models [5] a recent clinical study by Singhal *et al.* [32] also failed to show a relationship between endothelial function and adiponectin levels. Another possible mechanism involves induction of body visceral fat remodelling by telmisartan [33] which could affect adiponectin production. We could not observe differences in the effect of telmisartan and ramipril on liver enzymes, but have not specifically examined changes in visceral fat content and distribution in our study. We appreciate that the study period was too short in order to examine all metabolic effects in detail. Lastly, it is possible that all blood pressure-lowering effects especially of telmisartan are due to direct interaction with the renin-angiotensin-aldosterone system and that any effect on PPARγ are not directly related to the antihypertensive effects.

Our present study has a number of limitations that should be mentioned. First, the study was originally designed to examine the effect of telmisartan compared to ramipril on renal haemodynamics in patients with type 2 diabetes and hypertension [20], but not specifically designed and powered to examine the relationship between adiponectin and blood pressure. The sample size

was adequate for the primary aim, but may have been too small for the present analysis. Also, data on insulin sensitivity may be useful in interpreting the present findings, but such data have not been collected. This may be particularly important given the sexual dimorphism of adiponectin levels as also observed in our present study. We could not analyze if the study medication affects adiponectin equally in males and females. Secondly, we acknowledge that differential effects of telmisartan and ramipril on blood pressure may simply be due to different potency of these drugs on the renin-angiotensin-aldosterone system. Nevertheless, the differential effect on adiponectin levels between telmisartan and ramipril, which may be related to the differential effect on blood pressure, is at least intriguing and supports the notion that stimulation of adiponectin contributes to the hypotensive effect of telmisartan. Thirdly, adiponectin levels were numerically but not significantly higher in the ramipril group at baseline. Our additional analyses in tertiles of baseline adiponectin levels are evidence against the possibility that the differential effects of telmisartan and ramipril on adiponectin levels are merely due to regression to the mean. Fourthly, although our study includes therapeutic intervention and longitudinal data, we acknowledge that we can show a correlation but cannot prove a causal relationship between adiponectin and blood pressure. Even in case of causality the effect of adiponectin on blood pressure would be moderate as indicated by the modest correlation coefficients and R^2 values. Finally, compared to thiazolidinediones, telmisartan is a relatively weak PPARγ activator. Indeed, in the face of similar effects of telmisartan and ramipril on cardiovascular outcome [34], PPARγ-related effects of telmisartan may not play an immediate role in the majority of patients. Indeed, already in the study by Derosa *et al.* [23], blood pressure reduction was similar in patients treated with telmisartan or irbesartan despite the more pronounced increase in adiponectin in the telmisartan group.

In summary, we have shown that telmisartan was associated with stimulation of adiponectin in hypertensive patients with type 2 diabetes. This could contribute to its blood pressure-lowering effect. It should be tested whether increasing adiponectin levels particularly in patients with low

adiponectin levels offers additional therapeutic benefits. In this scenario telmisartan may be superior to other agents including ramipril.

Disclosure

R.E.S. has received an honorarium for serving on an advisory board and research grants from Boehringer Ingelheim.

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References

1. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; 20:1595-1599.
2. Salmenniemi U, Ruotsalainen E, Pihlajamäki J, Vauhkonen I, Kainulainen S, Punnonen K, Vanninen E, Laakso M. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. *Circulation* 2004; 110:3842-3848.
3. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for

endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; 100:2473-2476.

4. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; 7:941-946.
5. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003; 278:45021-45026.
6. Ritchie SA, Ewart MA, Perry CG, Connell JM, Salt IP. The role of insulin and the adipocytokines in regulation of vascular endothelial function. *Clin Sci (Lond)* 2004; 107:519-532.
7. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin: a key adipocytokine in metabolic syndrome. *Clin Sci (Lond)* 2006; 110:267-278.
8. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol* 2007; 49:531-538.
9. Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, Fu Y, Motone M, Yamamoto K, Matsuo A, Ohashi K, Kihara S, Funahashi T, Rakugi H, Matsuzawa Y, Ogihara T. Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension* 2004; 43:1318-1323.
10. Chow WS, Cheung BM, Tso AW, Xu A, Wat NM, Fong CH, Ong LH, Tam S, Tan KC, Janus ED, Lam TH, Lam KS. Hypoadiponectinemia as a predictor for the development of hypertension: a 5-year prospective study. *Hypertension* 2007; 49:1455-1461.
11. Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, Kumada M, Ohashi K, Okamoto Y, Nishizawa H, Kishida K, Maeda N, Nagasawa A, Kobayashi H, Hiraoka H, Komai

N, Kaibe M, Rakugi H, Ogihara T, Matsuzawa Y. Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension* 2003; 42:231-234.

12. Ohashi K, Kihara S, Ouchi N, Kumada M, Fujita K, Hiuge A, Hibuse T, Ryo M, Nishizawa H, Maeda N, Maeda K, Shibata R, Walsh K, Funahashi T, Shimomura I. Adiponectin replenishment ameliorates obesity-related hypertension. *Hypertension* 2006; 47:1108-1116. Erratum in: *Hypertension* 2007; 49:e14.
13. Wang ZV, Scherer PE. Adiponectin, cardiovascular function, and hypertension. *Hypertension* 2008; 51:8-14.
14. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation* 2004; 109:2054-2057.
15. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension* 2004; 43:993-1002.
16. Fujimoto M, Masuzaki H, Tanaka T, Yasue S, Tomita T, Okazawa K, Fujikura J, Chusho H, Ebihara K, Hayashi T, Hosoda K, Nakao K. An angiotensin II AT1 receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3-L1 adipocytes. *FEBS Lett* 2004; 576:492-497.
17. Clasen R, Schupp M, Foryst-Ludwig A, Sprang C, Clemenz M, Krikov M, Thöne-Reineke C, Unger T, Kintscher U. PPARgamma-activating angiotensin type-1 receptor blockers induce adiponectin. *Hypertension* 2005; 46:137-143.
18. Janke J, Schupp M, Engeli S, Gorzelniak K, Boschmann M, Sauma L, Nystrom FH, Jordan J, Luft FC, Sharma AM. Angiotensin type 1 receptor antagonists induce human in-vitro adipogenesis through peroxisome proliferator-activated receptor-gamma activation. *J Hypertens* 2006; 24:1809-1816.

19. Moriuchi A, Yamasaki H, Shimamura M, Kita A, Kuwahara H, Fujishima K, Satoh T, Fukushima K, Fukushima T, Hayakawa T, Mizuguchi H, Nagayama Y, Abiru N, Kawasaki E, Eguchi K. Induction of human adiponectin gene transcription by telmisartan, angiotensin receptor blocker, independently on PPAR-gamma activation. *Biochem Biophys Res Commun* 2007; 356:1024-1030.
20. Schmieder RE, Delles C, Mimran A, Fauvel JP, Ruilope LM. Impact of telmisartan versus ramipril on renal endothelial function in patients with hypertension and type 2 diabetes. *Diabetes Care* 2007; 30:1351-1356. Erratum in: *Diabetes Care* 2007; 30:2421.
21. Schmieder RE, Langenfeld MR, Friedrich A, Schobel HP, Gatzka CD, Weihprecht H. Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. *Circulation* 1996; 94:1304-1309.
22. Mori Y, Itoh Y, Tajima N. Telmisartan improves lipid metabolism and adiponectin production but does not affect glycemic control in hypertensive patients with type 2 diabetes. *Adv Ther* 2007; 24:146-153.
23. Derosa G, Fogari E, D'Angelo A, Cicero AF, Salvadeo SA, Ragonesi PD, Ferrari I, Gravina A, Fassi R, Fogari R. Metabolic effects of telmisartan and irbesartan in type 2 diabetic patients with metabolic syndrome treated with rosiglitazone. *J Clin Pharm Ther* 2007; 32:261-268.
24. Makita S, Abiko A, Naganuma Y, Moriai Y, Nakamura M. Potential effects of angiotensin II receptor blockers on glucose tolerance and adiponectin levels in hypertensive patients. *Cardiovasc Drugs Ther* 2007; 21:317-318 (letter).
25. Usui I, Fujisaka S, Yamazaki K, Takano A, Murakami S, Yamazaki Y, Urakaze M, Hachiya H, Takata M, Senda S, Iwata M, Satoh A, Sasaoka T, Ak ND, Temaru R, Kobayashi M. Telmisartan reduced blood pressure and HOMA-IR with increasing plasma leptin level in hypertensive and type 2 diabetic patients. *Diabetes Res Clin Pract* 2007; 77:210-214.

26. Benndorf RA, Rudolph T, Appel D, Schwedhelm E, Maas R, Schulze F, Silberhorn E, Böger RH. Telmisartan improves insulin sensitivity in nondiabetic patients with essential hypertension. *Metabolism* 2006; 55:1159-1164.
27. Della Mea P, Lupia M, Bandolin V, Guzzon S, Sonino N, Vettor R, Fallo F. Adiponectin, insulin resistance, and left ventricular structure in dipper and nondipper essential hypertensive patients. *Am J Hypertens* 2005; 18:30-35.
28. Santaniemi M, Kesäniemi YA, Ukkola O. Low plasma adiponectin concentration is an indicator of the metabolic syndrome. *Eur J Endocrinol* 2006; 155:745-750.
29. Furuhashi M, Ura N, Higashiura K, Murakami H, Tanaka M, Moniwa N, Yoshida D, Shimamoto K. Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension* 2003; 42:76-81.
30. Lawlor DA, Davey Smith G, Ebrahim S, Thompson C, Sattar N. Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. *J Clin Endocrinol Metab* 2005; 90:5677-5683.
31. Negro R, Formoso G, Hassan H. The effects of irbesartan and telmisartan on metabolic parameters and blood pressure in obese, insulin resistant, hypertensive patients. *J Endocrinol Invest* 2006; 29:957-961.
32. Singhal A, Jamieson N, Fewtrell M, Deanfield J, Lucas A, Sattar N. Adiponectin predicts insulin resistance but not endothelial function in young, healthy adolescents. *J Clin Endocrinol Metab* 2005; 90:4615-4621.
33. Shimabukuro M, Tanaka H, Shimabukuro T. Effects of telmisartan on fat distribution in individuals with the metabolic syndrome. *J Hypertens* 2007;25: 841-848.
34. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358:1547-1559.

Figure Legends

Figure 1. Adiponectin and blood pressure.

Scatterplots of systolic (SBP) and diastolic blood pressure (DBP) *vs* logarithm of adiponectin levels at baseline (A, B) and after treatment with ramipril or telmisartan (C, D). E and F disply changes in blood pressure due to therapy *vs* changes in adiponectin levels. Subjects randomized to ramipril are indicated by open symbols, subjects randomized to telmisartan by solid symbols. Person's correlation coefficients (*r*) are given.

Figure 2. Effects of telmisartan and ramipril on adiponectin levels.

Changes in plasma adiponectin levels in response to 9 weeks of treatment with ramipril (open bars) or telmisartan (solid bars) in the whole study group and in subgroups according to baseline adiponectin levels are displayed. Cut-off values of adiponectin for the definition of subgroups derived from classification in tertiles with minor adjustments to ensure similar numbers of patients allocated to telmisartan and ramipril in each subgroup. Significant changes in adiponectin levels in treatment groups are indicated by symbols on top of the bars (* $P<0.05$; † $P<0.01$; ‡ $P<0.001$). Note that only in the telmisartan group changes in adiponectin levels were significant. When all patients were considered, effects on adiponectin were significantly different between treatment groups ($P<0.05$). Data are given as mean ± standard error.

Table 1. Baseline Characteristics.

	All Participants	Telmisartan	Ramipril	
	n=87	n=45	n=42	*P*-value
Age (years)	59.2±8.9	59.7±8.7	58.8±9.2	0.64
Male (%)	69	64	74	0.37
Height (cm)	172±9	172±9	173±8	0.78
Weight (kg)	89±17	87±17	91±18	0.23
Body mass index (kg/m²)	30.0±5.3	29.4±5.3	30.6±5.2	0.28
Active smokers (%)	18	20	17	0.79
Duration of diabetes (years)	5 [3;7]	5 [3;9]	5 [3,7]	0.30
Duration of hypertension (years)	11 [6;16]	12 [6;15]	9 [5;22]	0.69
Systolic blood pressure (mmHg)	147±12	149±13	146±11	0.20
Diastolic blood pressure (mmHg)	83±10	84±10	83±9	0.52
HbA_{1c} (%)	6.8±1.0	7.0±1.1	6.6±0.7	0.13
Blood glucose (mg/dL)	168 [130;209]	176 [124;219]	167 [135;197]	0.60
Creatinine (mg/dL)	0.82±0.17	0.81±0.16	0.83±0.18	0.45
Total cholesterol (mg/dL)	215±43	212±43	219±44	0.47
LDL cholesterol (mg/dL)	134±34	134±35	135±34	0.96
HDL cholesterol (mg/dL)	45 [38;53]	47 [38;53]	45 [40;54]	0.85
Triglycerides (mg/dL)	184 [137;263]	170 [142;257]	201 [123;280]	0.71
ALT (U/L)	33 [24;48]	32 [24;39]	37 [26;52]	0.29
AST (U/L)	26 [21;32]	25 [21;30]	26 [19;33]	0.97
CRP (mg/L)	1.9 [0.9;4.0]	1.6 [0.8;4.0]	2.7 [1.3;4.4]	0.32
Plasma adiponectin (µg/mL)	8.1 [5.9;11.4]	7.3 [5.0;10.5]	8.5 [6.3;13.0]	0.064
Plasma angiotensin II (pg/mL)	3.4 [2.3;5.9]	3.5 [2.1;5.5]	3.4 [2.3;6.1]	0.86
Plasma aldosterone (pg/mL)	128 [107;163]	122 [104;156]	129 [108;167]	0.56
Urinary sodium excretion (mmol/d)	104±33	102±32	106±33	0.54

HbA_{1c}, glycosylated haemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine amino transferase; AST, aspartate amino transferase; CRP, C-reactive protein. Blood glucose concentration has been measured 1 to 2 hours after a light breakfast.
Data are given as mean±standard deviation or median [interquartile range] as appropriate. *P*-values refer to comparisons between the ramipril and telmisartan group and derive from Student's t-test, Mann-Whitney U-test and Fisher's exact test for normally distributed, non-normally distributed and categorical data, respectively.

Table 2. Systolic blood pressure and adiponectin at baseline

	All variables entered			Stepwise approach		
	B	β	*P*-value	B	β	*P*-value
Constant	150.08 [122.43 to 177.72]	-	<0.001	152.62 [146.93 to 158.32]	-	<0.001
Sex (1=male, 2=female)	-1.17 [-7.45 to 5.16]	-0.05	0.71	-	-	-
Age (years)	-0.02 [-0.33 to 0.30]	-0.01	0.91	-	-	-
Body mass index (kg/m²)	0.08 [-0.47 to 0.62]	0.03	0.78	-	-	-
Adiponectin (µg/mL)	-0.54 [-1.19 to 0.10]	-0.21	0.098	-0.63 [-1.20 to -0.06]	-0.24	<0.05
24-hour urinary sodium (mmol/d)	0.02 [-0.64 to 0.11]	0.06	0.63	-	-	-

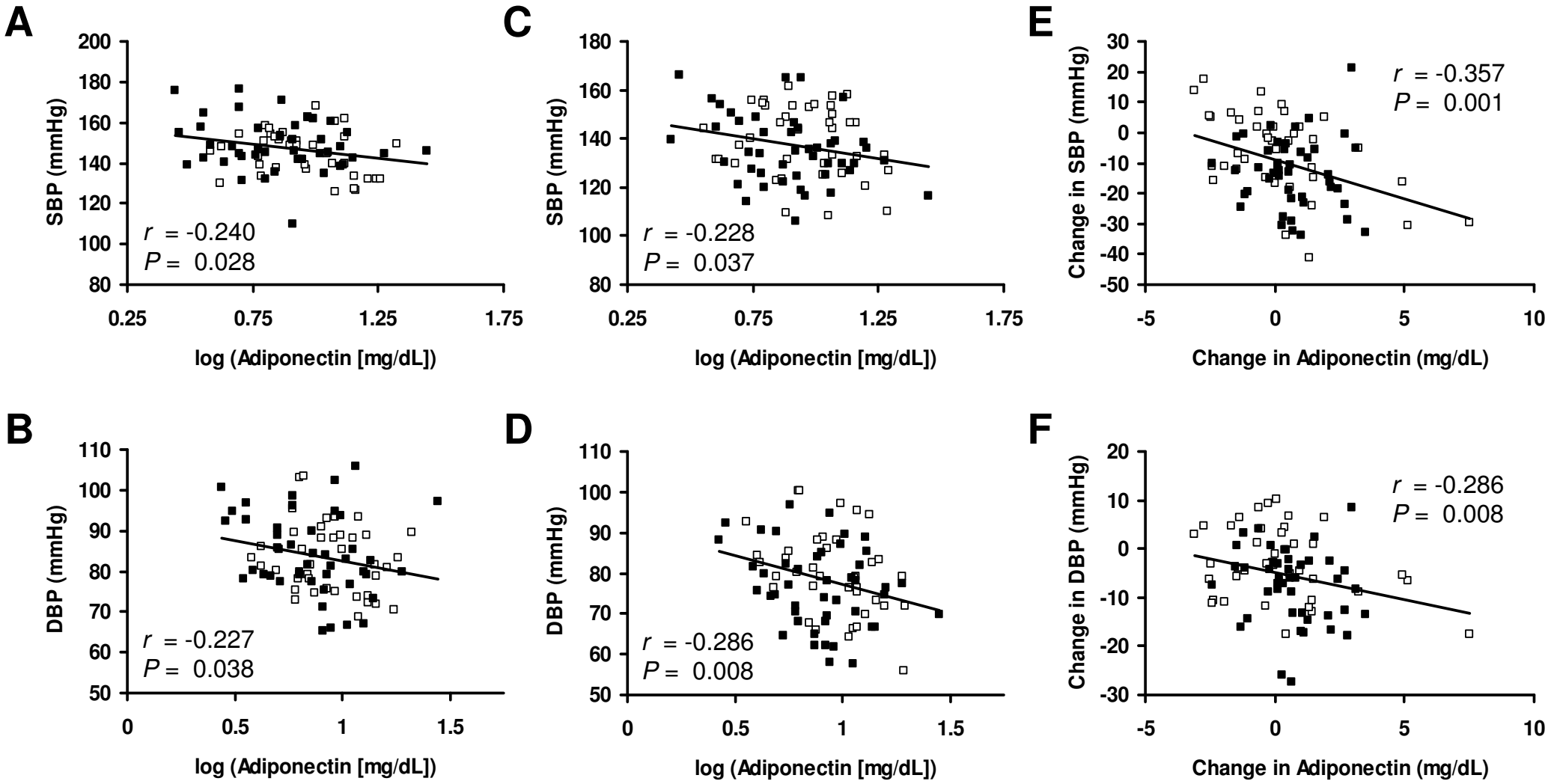
Multiple stepwise regression analysis of the predictive value of sex, age, body mass index, baseline adiponectin levels and 24-hour urinary sodium excretion on baseline systolic blood pressure. A model with all variables forced in (adjusted R^2=0.1%) and a stepwise approach with probabilities of F for entry and removal of 0.05 and 0.10, respectively (adjusted R^2=4.4%), was applied. B denotes unstandardized and β denotes standardized regression coefficients, respectively. 95% confidence intervals are given for B-values.

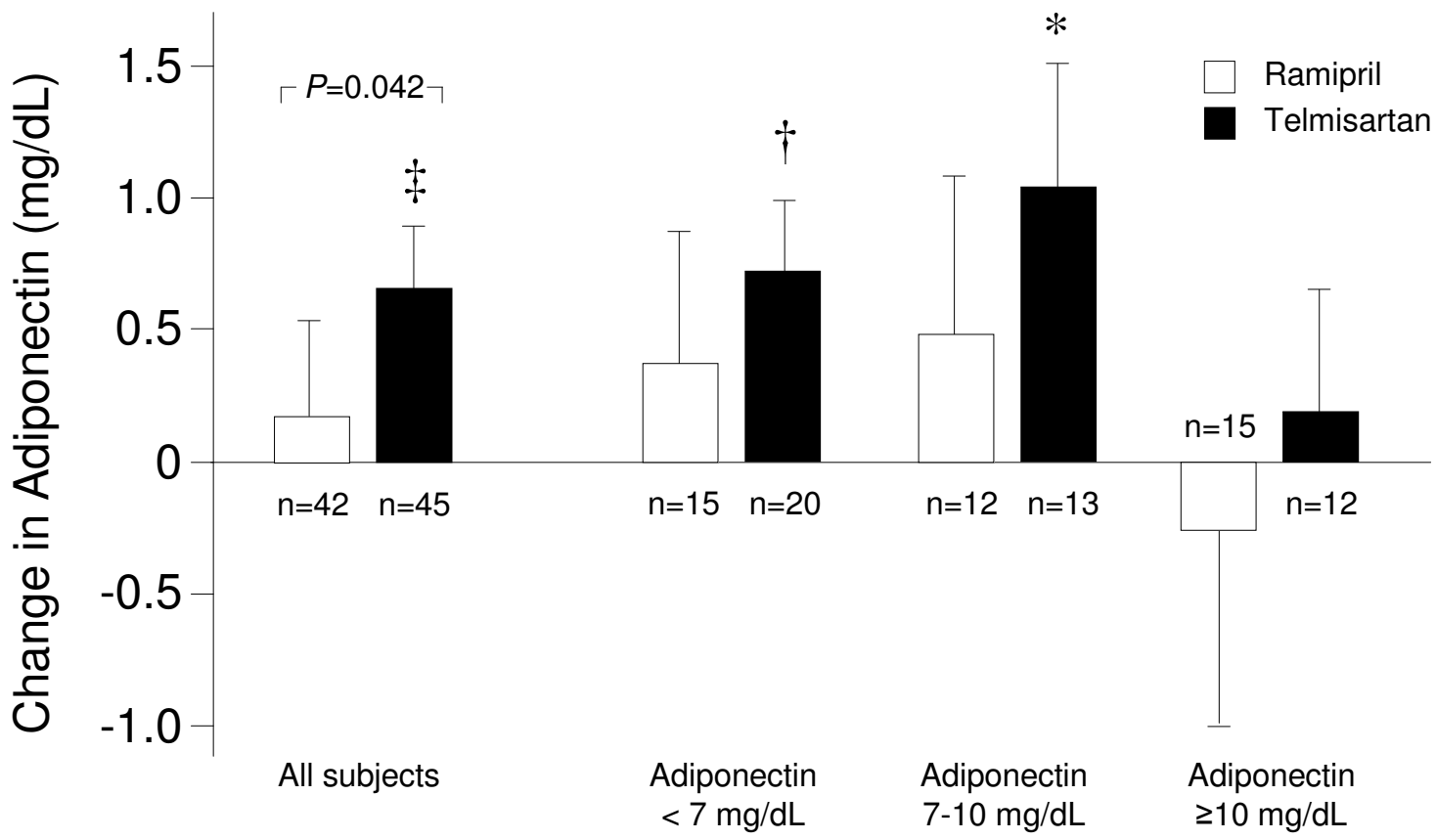
Table 3. Associations of treatment with other biochemical parameters.

	Telmisartan n=45	Ramipril n=42	*P*-value
SBP (mmHg)	-13.5 [-17.0 to -10.0]	-6.1 [-6.2 to -2.0]	<0.01
DBP (mmHg)	-7.6 [-9.8 to -5.3]	-2.7 [-5.0 to -0.5]	<0.05
Body mass index (kg/m²)	-0.3 [-0.5 to 0.0]	+0.1 [-0.1 to 0.3]	0.52
HbA_{1c} (%)	-0.08 [-0.24 to 0.08]	+0.02 [-0.12 to 0.17]	0.32
Blood glucose (mg/dL)	-5.9 [-18.5 to 6.8]	+6.0 [-9.0 to 20.1]	0.22
Creatinine (mg/dL)	+0.03 [0.00 to 0.06] *	+0.02 [-0.01 to 0.06]	0.60
Sodium (mmol/L)	-0.21 [-1.09 to 0.67]	+0.07 [-0.83 to 0.96]	0.65
Potassium (mmol/L)	+0.07 [-0.18 to 0.31]	+0.05 [-0.06 to 0.16]	0.91
Total cholesterol (mg/dL)	+4.3 [-8.9 to 17.5]	+0.8 [-9.4 to 11.0]	0.68
LDL cholesterol (mg/dL)	+6.6 [0.9 to 12.3] *	+4.1 [-3.0 to 11.2]	0.58
HDL cholesterol (mg/dL)	-1.1 [-3.1 to 1.0]	-0.7 [-2.9 to 1.4]	0.82
Triglycerides (mg/dL)	+26.1 [-39.5 to 91.7]	-5.6 [-33.1 to 21.9]	0.74
ALT (U/L)	-1.5 [-5.0 to 1.9]	-2.9 [-9.0 to 3.2]	0.23
AST (U/L)	-1.8 [-4.1 to 0.5]	-2.1 [-4.6 to 0.3]	0.56
CRP (mg/L)	+1.0 [-0.9 to 2.8]	-0.3 [-0.9 to 0.4]	0.66
Plasma adiponectin (µg/mL)	+0.7 [0.3 to 1.1] ‡	+0.2 [-0.6 to 0.9]	<0.05
Plasma angiotensin II (pg/mL)	+6.8 [2.6 to 10.9] ‡	-1.6 [-3.3 to 0.2]	<0.001
Plasma aldosterone (pg/mL)	-18.4 [-30.0 to -7.1] †	-22.5 [-40.1 to -5.0] ‡	0.37
Urinary sodium excretion (mmol/d)	-7.6 [-16.6 to 1.3]	+2.6 [-7.9 to 13.6]	0.14
Urinary potassium excretion (mmol/d)	-1.29 [-5.45 to 2.87]	-1.28 [-5.24 to 2.68]	1.00

SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, glycosylated haemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine amino transferase; AST, aspartate amino transferase; CRP, C-reactive protein. Blood glucose concentration has been measured 1 to 2 hours after a light breakfast.

Data are given as mean [95% confidence interval] irrespective of the distribution of variables to facilitate interpretation of data. *P*-values in the right column refer to comparisons between the ramipril and telmisartan group and derive from Student's t-test or Mann-Whitney U-test as appropriate. Within groups, asterisks (*; $P<0.05$), daggers (†; $P<0.01$) and double daggers (‡; $P<0.001$) denote significant differences in a parameter; these comparisons have been made by paired Student's t-test on native data or on data after log transformation in case of non-normal distribution.


A
SBP (mmHg)
200
180
160
140
120
100
80
r = -0.240
P = 0.028
0.25
0.75
1.25
1.75
log (Adiponectin [mg/dL])
C
SBP (mmHg)
180
160
140
120
100
80
r = -0.228
P = 0.037
0.25
0.75
1.25
1.75
log (Adiponectin [mg/dL])
E
Change in SBP (mmHg)
30
20
10
0
-10
-20
-30
-40
-50
r = -0.357
P = 0.001
-5
0
5
10
Change in Adiponectin (mg/dL)
B
DBP (mmHg)
110
100
90
80
70
60
50
r = -0.227
P = 0.038
0
0.5
1
1.5
log (Adiponectin [mg/dL])
D
DBP (mmHg)
110
100
90
80
70
60
50
r = -0.286
P = 0.008
0
0.5
1
1.5
log (Adiponectin [mg/dL])
F
Change in DBP (mmHg)
20
10
0
-10
-20
-30
r = -0.286
P = 0.008
-5
0
5
10
Change in Adiponectin (mg/dL)


Change in Adiponectin (mg/dL)
1.5
1.0
0.5
0
-0.5
-1.0
P=0.042
‡
†
*
Ramipril
Telmisartan
n=42
n=45
n=15
n=20
n=12
n=13
n=15
n=12
All subjects
Adiponectin
< 7 mg/dL
Adiponectin
7-10 mg/dL
Adiponectin
≥10 mg/dL