

# Additive Beneficial Effects of Fenofibrate Combined With Candesartan in the Treatment of Hypertriglyceridemic Hypertensive Patients

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**OBJECTIVE** — Mechanisms underlying fibric acid and angiotensin II type 1 receptor blocker therapies differ. Signaling from peroxisome proliferator-activated receptor  $\alpha$  may cross-talk with the angiotensin II system. We investigated vascular and metabolic responses to these therapies either alone or in combination in hypertriglyceridemic hypertensive patients.

**RESEARCH DESIGN AND METHODS** — This was a randomized, double-blind, placebo-controlled, cross-over trial with three treatment arms (each 2 months) and two washout periods (each 2 months). Forty-four patients were given 200 mg fenofibrate and placebo, 200 mg fenofibrate and 16 mg candesartan, or 16 mg candesartan and placebo daily during each treatment period.

**RESULTS** — Fenofibrate, combined therapy, or candesartan therapy significantly reduced blood pressure. However, combined therapy significantly reduced blood pressure more than fenofibrate or candesartan alone ( $P < 0.001$  by ANOVA). When compared with candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde, high-sensitivity C-reactive protein, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared with monotherapy ( $P < 0.001$ ,  $P = 0.002$ ,  $P = 0.050$ , and  $P = 0.032$  by ANOVA, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitude of these increases were not significantly different among the three therapies ( $P = 0.246$  and  $P = 0.153$  by ANOVA, respectively).

**CONCLUSIONS** — Fenofibrate combined with candesartan improves endothelial function and reduces inflammatory markers to a greater extent than monotherapy in hypertriglyceridemic hypertensive patients.

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**Abbreviations:** ARB, angiotensin II type 1 receptor blocker; AT<sub>1</sub>R, angiotensin II type 1 receptor; MDA, malondialdehyde; PPAR, peroxisome proliferator-activated receptor; QUICKI, quantitative insulin sensitivity check index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**H**ypertriglyceridemia and hypertension are major public health problems that are frequently treated with fenofibrate and angiotensin II type 1 receptor (AT<sub>1</sub>R) blockers (ARBs), respectively. Although the mechanisms of action for these two classes of drugs differ, both classes have beneficial effects on the vasculature. Large-scale clinical studies have demonstrated that micronized fenofibrate, fibric acid, and losartan, an ARB, prevent and retard the progression of coronary heart disease (1,2). Hypertension and coronary heart disease are frequently associated with insulin resistance and disorders of metabolic homeostasis such as obesity and type 2 diabetes. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance and the pathophysiology of diabetes and its vascular complications (3). Indeed, large-scale clinical studies have demonstrated that candesartan reduces the onset of type 2 diabetes (4). The mechanisms of this benefit may relate to the ability of these therapies to reduce insulin resistance (5–7).

Fibric acids and ARBs both improve endothelium-dependent dilation, reduce vascular inflammation, and reduce cardiovascular events in randomized clinical trials (5–8). This may be because the pathophysiology of atherosclerosis and cardiovascular diseases depends upon multiple etiological mechanisms. The epidemic of obesity, hyperlipidemia, hypertension, insulin resistance, and the metabolic syndrome is creating a huge population at risk for atherosclerosis and cardiovascular diseases. Thus, it is imperative to design more effective therapeutic strategies for these diseases. We reasoned that distinct biological actions of fibric acids and ARB therapies on lipoproteins and the angiotensin system may improve endothelium-dependent vascular function by different mechanisms such that combination therapy may be of benefit.

Fenofibrate, a synthetic ligand of peroxisome proliferator-activated receptor (PPAR)  $\alpha$ , reduces triglycerides and increases HDL cholesterol (6,9). It improves

endothelial function via stimulation of nitric oxide (NO) synthase activity and mediates antioxidant effects that result in enhanced NO bioactivity (10,11). ARBs also improve endothelial function, in part, by diminishing intracellular production of superoxide anions (12). Decreased production of superoxide anions contributes to increased NO bioactivity by limiting oxidation of NO (13). In addition, cross-talk between PPAR $\alpha$  and angiotensin II signaling exists (14–17). Indeed, angiotensin II mediates activation of nuclear factor- $\kappa$ B resulting in induction of proinflammatory genes and downregulation of PPAR $\alpha$  and PPAR $\gamma$ . This promotes vascular inflammation and acceleration of atherosclerosis (15). Cross-talk also occurs when PPAR $\gamma$  suppresses AT $_1$ R gene expression and ARBs induce PPAR $\gamma$  activity (14,16,17).

Endothelial dysfunction associated with diabetes, obesity, metabolic syndrome, and other insulin-resistant states is characterized by impaired NO release from endothelium with decreased blood flow and reduced delivery of substrates (18). Thus, improvement in endothelial function is predicted to improve insulin sensitivity, and this may be one mechanism by which candesartan decreases the incidence of new-onset diabetes. Adiponectin is one of a number of proteins secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance (19). In humans, plasma levels of adiponectin are negatively correlated with adiposity and decreased plasma adiponectin levels are observed in patients with diabetes (20). Thus, decreased levels of adiponectin may play a key role in the development of insulin resistance.

Therefore, we hypothesized that combined therapy may have additive beneficial effects that are greater than those observed with either fenofibrate or candesartan therapy alone in hypertriglyceridemic hypertensive patients.

## RESEARCH DESIGN AND METHODS

Forty-six hypertriglyceridemic hypertensive Korean patients (triglyceride levels  $\geq 150$  mg/dl) participated in this study. We defined hypertension as systolic and diastolic blood pressure  $\geq 140$  or  $\geq 90$  mmHg, respectively. We excluded patients with severe hypertension, unstable angina, or acute myocardial infarction. No patient had taken any lipid-lowering agent, ACE in-

hibitors, or ARBs during the preceding 2 months. Blood pressure measured in the right arm in the sitting position using a standard sphygmomanometer with appropriate-sized cuff was recorded as the mean of two successive readings (subjects were seated for at least 10 min before measurements [5,8]). To minimize acute side effects due to candesartan, study medication was titrated from 8 to 16 mg upwards over a 2-week period if no hypotension (systolic blood pressure  $< 100$  mmHg) was noted. At the end of this time, participants were receiving either placebo or 16 mg candesartan per day. Forty-four of 46 patients tolerated 16 mg candesartan with regard to maintaining systolic blood pressure  $> 100$  mmHg for 3 h after drug administration and experienced no adverse effects from therapy. One patient who was hypotensive and another who suffered from a dry cough were withdrawn from the study. Thus, data from a total of 44 patients were analyzed. The mean age of our subjects was  $52 \pm 1$  years, and the male-to-female proportion was 26:18. The mean BMI was  $26.0 \pm 0.5$  kg/m $^2$ . The number of current smokers was 14 (32%). Six (14%) and four (9%) patients were taking  $\beta$ -adrenergic blockers or calcium channel blockers, respectively, to control blood pressure. Patients were randomly assigned to one of three treatments: 200 mg micronized fenofibrate and placebo, 200 mg micronized fenofibrate and 16 mg candesartan, or 16 mg candesartan and placebo daily during 2 months. This was a randomized, double-blind, placebo-controlled, cross-over trial with three treatment arms (each 2 months) and two washout periods (each 2 months). Patients were seen at 14-day intervals (or more frequently) during the study. Calcium channel or  $\beta$ -adrenergic blockers were withheld for  $\geq 48$  h before the study to avoid the effects of these drugs. The study was approved by the Gil Hospital Institute Review Board, and all participants gave written informed consent.

## Laboratory assays

Blood samples for laboratory assays were obtained at  $\sim 8:00$  A.M. following overnight fasting before and at the end of each 2-month treatment period. These samples were immediately coded so that investigators performing laboratory assays were blinded to subject identity or study sequence. Assays for lipids, glucose, and plasma malondialdehyde (MDA), soluble CD40L, and adiponectin were performed in duplicate by ELISA (Bioxytech LPO-

586; OxisResearch, Portland, OR; R&D Systems, Minneapolis, MN) and assays for high-sensitivity C-reactive protein levels by latex agglutination [CRP-Latex(II); Denka-Seiken, Tokyo, Japan] as previously described (5–8,12). Assays for plasma insulin levels were performed in duplicate by immunoradiometric assay (Insulin-Riabeed II; SRL, Tokyo, Japan). The interassay and intra-assay coefficients of variation were  $< 6\%$ . Quantitative insulin sensitivity check index (QUICKI), a surrogate index of insulin sensitivity, was calculated as follows (insulin is expressed in  $\mu$ U/ml and glucose in mg/dl): QUICKI =  $1/[\log(\text{insulin}) + \log(\text{glucose})]$  (21).

## Vascular studies

Imaging studies of the right brachial artery were performed using an ATL HDI 3000 ultrasound machine (Bothell, WA) equipped with a 10-MHz linear array transducer, based on a previously published technique (5–8,12). Measurements were performed by two independent investigators (S.H.H. and W.-J.C.) blinded to the subject's identity and medication status.

## Statistical analysis

Data are expressed as means  $\pm$  SE or median (range 25–75%). After testing data for normality, we used Student's paired *t* or Wilcoxon signed-rank test to compare values before and after each treatment and the relative changes in values in response to treatment, as reported in Table 1. The effects of the three therapies on vascular function, markers of oxidant stress and inflammation, and insulin sensitivity relative to baseline values were analyzed by one-way repeated-measures ANOVA or Friedman's repeated ANOVA on ranks. After demonstration of significant differences among therapies by ANOVA, post hoc comparisons between treatment pairs were made by use of the Student-Newman-Keuls multiple comparison procedures. Pearson correlation coefficient analysis was used to assess associations between measured parameters. We calculated that 30 subjects would provide 80% power for detecting an absolute increase of  $\geq 2.1\%$  in flow-mediated dilation of the brachial artery between baseline and candesartan, with  $\alpha = 0.05$  based on our previous studies (12). The comparison of endothelium-dependent dilation among the three treatment schemes was prospectively designated as the primary end point of the study. All

other comparisons were considered secondary. A value of  $P < 0.05$  was considered to be statistically significant.

**RESULTS** — When baseline values before each treatment period were compared among the three treatment arms, no significant differences were noted in any of the parameters measured (Table 1). To rule out the possibility of a carryover effect from one treatment period to the next, we compared baseline values before the first treatment period to those before the second and third treatment periods. There were no significant differences in any of the measured parameters in this analysis.

### Effects of therapies on blood pressure and lipids

Fenofibrate, combined therapy, or candesartan all significantly reduced systolic and diastolic blood pressure after 2 months administration when compared with baseline. However, combined therapy significantly reduced blood pressure more than fenofibrate or candesartan alone ( $P < 0.001$  by ANOVA; Fig. 1). Fenofibrate alone or combined therapy significantly lowered total cholesterol, triglycerides, apolipoprotein B, and non-HDL cholesterol levels (all  $P < 0.001$ ) and increased HDL cholesterol levels ( $P < 0.001$ ) when compared with baseline. These reductions were significantly greater than those observed with candesartan alone ( $P < 0.001$  by ANOVA; Fig. 1; Table 1). However, there were no significant differences between fenofibrate alone and combined therapy for these parameters (Table 1).

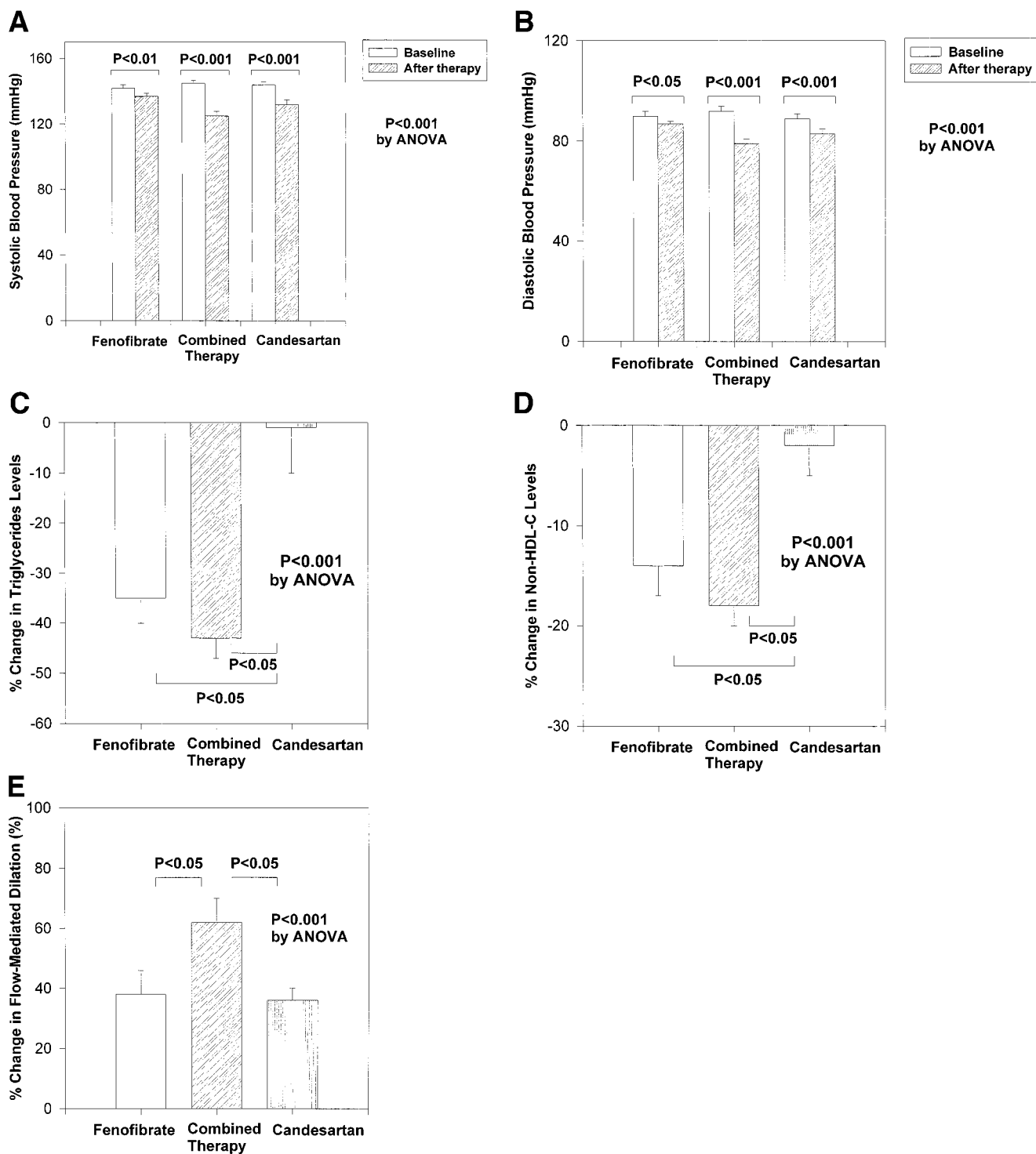
### Effects of therapies on vasomotor function and malondialdehyde

Fenofibrate, combined therapy, or candesartan significantly improved the percent flow-mediated dilator response to hyperemia relative to baseline measurements by  $38 \pm 8\%$ ,  $62 \pm 8\%$ , and  $36 \pm 4\%$ , respectively (all  $P < 0.001$ ). Importantly, combined therapy significantly improved this response more than fenofibrate or candesartan alone ( $P < 0.001$  by ANOVA; Fig. 1; Table 1). The brachial artery dilator response to nitroglycerin was similar for all therapies and was not significantly changed from respective baseline values. Combined therapy significantly decreased the plasma MDA levels relative to baseline measurements by  $11 \pm 4\%$  ( $P < 0.001$ ), and the magnitude of this reduction was significantly greater

**Table 1—Effects of fenofibrate, combined therapy, and candesartan in hypertriglyceridemic hypertensive Korean patients**

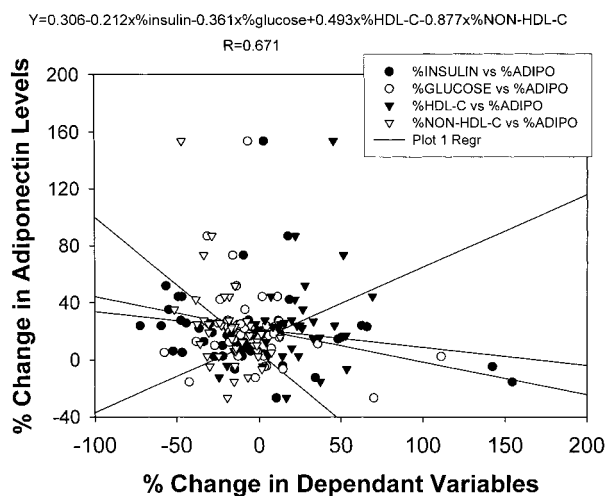
Variables	Fenofibrate (F, 44)		Fenofibrate and candesartan (C, 44)		Candesartan (A, 44)		P value	ANOVA		
	Baseline 1	Treatment	Baseline 2	Treatment	Baseline 3	Treatment		F/C	F/A	C/A
BMI (kg/m <sup>2</sup> )	26.02 ± 0.46	26.04 ± 0.47	26.01 ± 0.46	26.02 ± 0.43	26.03 ± 0.47	26.02 ± 0.47				
Lipids (mg/dl)										
Total cholesterol	204 ± 4	186 ± 5*	208 ± 5	184 ± 4*	198 ± 5	195 ± 6	0.006	NS	<0.05	<0.05
Triglycerides	228 ± 15	149 ± 17*	255 ± 21	130 ± 10*	226 ± 23	190 ± 17†	<0.001	NS	<0.05	<0.05
LDL cholesterol	114 ± 4	106 ± 4†	112 ± 6	107 ± 3	108 ± 6	111 ± 6	0.400			
Apolipoprotein B	110 ± 3	92 ± 3*	108 ± 3	91 ± 3*	106 ± 3	105 ± 4	<0.001	NS	<0.05	<0.05
HDL cholesterol	44 ± 2	49 ± 2*	45 ± 1	51 ± 2*	45 ± 2	46 ± 2	0.076			
Apolipoprotein A-I	150 ± 3	152 ± 4	147 ± 3	155 ± 3†	147 ± 4	144 ± 4	0.036	NS	NS	<0.05
Non-HDL cholesterol	160 ± 4	136 ± 5*	163 ± 5	133 ± 4*	153 ± 5	149 ± 6	<0.001	NS	<0.05	<0.05
Vasomotor function										
Flow-mediated dilation (%)	4.26 ± 0.24	5.63 ± 0.36*	4.17 ± 0.24	6.45 ± 0.36*	4.19 ± 0.23	5.62 ± 0.32*	<0.001	<0.05	NS	<0.05
MDA (μmol/l)	1.02 ± 0.06	1.07 ± 0.06	1.05 ± 0.05	0.91 ± 0.05*	1.08 ± 0.07	1.04 ± 0.06	0.002	<0.05	NS	<0.05
Inflammation										
C-reactive protein (mg/l)	0.85 (0.40–1.70)	0.60 (0.20–1.10)	1.00 (0.50–1.85)	0.55 (0.20–0.90)*	0.90 (0.40–1.85)	0.50 (0.30–1.20)	0.050	<0.05	NS	NS
CD40L (ng/ml)	2.30 ± 0.39	1.86 ± 0.41	2.97 ± 0.38	1.98 ± 0.30*	2.66 ± 0.52	2.12 ± 0.30	0.032	NS	<0.05	<0.05
Insulin resistance										
Adiponectin (μg/ml)	3.1 ± 0.4	3.3 ± 0.3	3.0 ± 0.3	3.5 ± 0.4*	3.0 ± 0.3	3.4 ± 0.3*	0.246			
Insulin (μU/ml)	5.32 ± 0.61	4.32 ± 0.48	4.74 ± 0.46	4.21 ± 0.46	5.84 ± 0.36	5.76 ± 0.61	0.693			
Glucose (mg/dl)	92 ± 2	87 ± 2	89 ± 2	85 ± 3	92 ± 2	90 ± 2	0.769			
QUICKI	0.415 ± 0.015	0.460 ± 0.026†	0.403 ± 0.010	0.422 ± 0.011†	0.395 ± 0.005	0.412 ± 0.009†	0.153			

Data are means ± SE or median (25th to 75th percentile). There were no significant differences among each baseline values. \* $P < 0.001$  for comparison with each baseline value; † $P < 0.05$ ; ‡ $P < 0.01$ . QUICKI =  $1/\log(\text{insulin}) + \log(\text{glucose})$  (21). C/A, combined therapy versus candesartan; F/A, fenofibrate versus combined therapy; NS, not significant.



**Figure 1**—A: Change in systolic blood pressure at respective pretreatment baseline and after treatment with fenofibrate alone, combined therapy, and candesartan alone ( $P < 0.001$  by ANOVA). SE is identified by bars. B: Change in diastolic blood pressure at respective pretreatment baseline and after treatment with fenofibrate alone, combined therapy, and candesartan alone ( $P < 0.001$  by ANOVA). SE is identified by bars. C: Percent change in triglyceride levels from respective pretreatment values after treatment with fenofibrate alone, combined therapy, and candesartan alone ( $P < 0.001$  by ANOVA). SE is identified by bars. D: Percent change in non-HDL cholesterol levels from respective pretreatment values after treatment with fenofibrate alone, combined therapy, and candesartan alone ( $P < 0.001$  by ANOVA). SE is identified by bars. E: Percent change in flow-mediated dilatation from respective pretreatment values after treatment with fenofibrate alone, combined therapy, and candesartan alone ( $P < 0.001$  by ANOVA). SE is identified by bars.





**Figure 2**—Scatter plots showing the significant correlation between the changes in adiponectin levels and the changes in insulin ( $\beta = -0.212$ ,  $P = 0.024$ ), glucose ( $\beta = -0.361$ ,  $P = 0.025$ ), HDL cholesterol ( $\beta = 0.493$ ,  $P = 0.005$ ), and non-HDL cholesterol ( $\beta = -0.877$ ,  $P = 0.001$ ) by multiple linear regression analysis. The line shows the predicted regression line.

than with fenofibrate or candesartan treatment alone ( $P = 0.002$  by ANOVA; Table 1).

#### Effects of therapies on markers of inflammation

Combined therapy significantly decreased the plasma high-sensitivity C-reactive protein and soluble CD40L levels relative to baseline measurements by  $32 \pm 8\%$  and  $21 \pm 8\%$  (both  $P < 0.001$ ), respectively, and the magnitude of these reductions was significantly greater than with fenofibrate or candesartan therapy alone ( $P = 0.050$  and  $P = 0.032$  by ANOVA, respectively; Table 1).

#### Effects of therapies on adiponectin and insulin resistance

There were inverse correlations between baseline adiponectin levels and baseline triglyceride levels ( $r = -0.318$ ,  $P = 0.036$  before fenofibrate;  $r = -0.403$ ,  $P = 0.007$  before combined therapy; and  $r = -0.276$ ,  $P = 0.070$  before candesartan). There were positive correlations between baseline adiponectin levels and baseline HDL cholesterol levels ( $r = 0.365$ ,  $P = 0.015$  before fenofibrate;  $r = 0.214$ ,  $P = 0.164$  before combined therapy; and  $r = 0.421$ ,  $P = 0.004$  before candesartan). There were significant inverse correlations between baseline adiponectin levels and baseline insulin levels ( $r = -0.318$ ,  $P = 0.036$  before fenofibrate;  $r = -0.348$ ,  $P = 0.021$  before combined therapy; and  $r = -0.302$ ,  $P = 0.047$  before candesartan). Combined therapy or candesartan alone significantly increased the plasma adiponectin levels relative to baseline measurements by  $22 \pm 4\%$  and  $22 \pm 5\%$  (both  $P < 0.001$ ), respectively. However, the magnitude of

these increases was not significantly different among the three therapies ( $P = 0.246$  by ANOVA; Table 1). The three therapies did not have significantly different baseline insulin and glucose levels, and these levels did not significantly change after any of the therapies. Fenofibrate, combined therapy, or candesartan alone significantly increased QUICKI relative to baseline measurements by  $11 \pm 4\%$  ( $P = 0.037$ ),  $5 \pm 2\%$  ( $P = 0.007$ ), and  $4 \pm 2\%$  ( $P = 0.021$ ), respectively. However, the magnitude of increase was not significantly different among three therapies ( $P = 0.153$  by ANOVA; Table 1). There were correlations between percent changes in adiponectin levels and percent changes in total cholesterol ( $r = -0.312$ ,  $P = 0.039$ ), apolipoprotein B ( $r = -0.289$ ,  $P = 0.057$ ), non-HDL cholesterol ( $r = -0.465$ ,  $P = 0.002$ ), HDL cholesterol ( $r = 0.381$ ,  $P = 0.011$ ), apolipoprotein A-I ( $r = 0.307$ ,  $P = 0.043$ ), insulin ( $r = -0.275$ ,  $P = 0.071$ ), and QUICKI ( $r = 0.301$ ,  $P = 0.047$ ) following combined therapy. The changes in adiponectin levels were investigated in a multiple regression setting with other predictors (insulin, glucose, QUICKI, HDL cholesterol, and non-HDL cholesterol). Changes in adiponectin levels persisted as an independent predictor of changes in insulin ( $\beta = -0.212$ ,  $P = 0.024$ ), glucose ( $\beta = -0.361$ ,  $P = 0.025$ ), HDL cholesterol ( $\beta = 0.493$ ,  $P = 0.005$ ), and non-HDL cholesterol ( $\beta = -0.877$ ,  $P = 0.001$ ) (Fig. 2) but not percent changes in QUICKI ( $\beta = -0.771$ ,  $P = 0.099$ ).

We investigated whether changes in the percent flow-mediated dilator response to hyperemia, serological markers of oxidant stress and inflammation, and

insulin resistance were mediated by reduction of systolic or diastolic blood pressure. There were no significant correlations between these changes and reduction of systolic blood pressure ( $-0.105 \leq r \leq 0.307$ ) or between these changes and reduction of diastolic blood pressure ( $-0.268 \leq r \leq 0.247$ ). Following combined therapy, improvement in flow-mediated dilation correlated with changes in total cholesterol ( $r = -0.317$  and  $P = 0.036$ ), apolipoprotein B ( $r = -0.361$  and  $P = 0.016$ ), and non-HDL cholesterol levels ( $r = -0.349$  and  $P = 0.020$ ).

Improvement in flow-mediated dilation was investigated in a multiple regression setting with other predictors (total cholesterol, non-HDL cholesterol, apolipoprotein B, and glucose). Improvement in flow-mediated dilation persisted as an independent predictor of changes in apolipoprotein B ( $\beta = -1.580$ ,  $P = 0.008$ ) and glucose ( $\beta = 0.584$ ,  $P = 0.036$ ) but not percent changes in total cholesterol ( $\beta = -0.161$ ,  $P = 0.910$ ) and non-HDL cholesterol ( $\beta = -0.462$ ,  $P = 0.742$ ).

**CONCLUSIONS**— In our hypertriglyceridemic hypertensive cohort, fenofibrate therapy alone significantly improved the lipid profile, while candesartan therapy alone significantly lowered blood pressure as expected. Comparable beneficial effects on both lipids and blood pressure were observed with combination therapy. We reasoned that distinct biological actions of fenofibrate and candesartan therapies on lipoproteins and the angiotensin system may improve endothelium-dependent vascular function by different mechanisms. Indeed, while monotherapy with fenofibrate or candesartan significantly lowered blood pressure and improved endothelial function and inflammatory markers (assessed by flow-mediated dilation, MDA levels, C-reactive protein levels, and CD40L levels), combined therapy had additional substantial and significant beneficial effects on these parameters over those seen with monotherapy for either drug. Since there are multiple etiologies for atherosclerosis and cardiovascular diseases, combination therapy with drugs that have distinct and separate mechanisms of action may confer more benefit in the treatment of cardiovascular diseases than individual monotherapies. Indeed, we have demonstrated that combination therapy with simvastatin/losartan or ramipril has beneficial additive effects

on endothelial function and inflammatory markers in hypercholesterolemic hypertensive patients (5,8), and combination therapy with atorvastatin/fenofibrate has beneficial additive effects on endothelial function and inflammatory markers in combined hyperlipidemia (7). This may be due to combined effects of the respective monotherapies to further improve endothelial function and reduce inflammation.

The additional beneficial effects of combined fenofibrate/candesartan therapy may be the result of several interacting mechanisms. Indeed, recent experimental studies have demonstrated cross-talk between PPAR $\alpha$  and angiotensin II (14–17). Interestingly, angiotensin II, through activation of nuclear factor- $\kappa$ B, stimulates proinflammatory gene expression and downregulation of PPAR $\alpha$  and PPAR $\gamma$ . This promotes vascular inflammation and acceleration of atherosclerosis in apolipoprotein E knockout mice (15). PPAR $\gamma$  ligands reduce AT $_1$ R messenger RNA and protein (14). Thus, PPAR $\gamma$  ligands may inhibit angiotensin II–induced cell growth and hypertrophy in vascular smooth muscle cells by suppressing AT $_1$ R expression. This may be beneficial for treatment of diabetic patients with hypertension and atherosclerosis. ARBs induce PPAR $\gamma$  activity, thereby promoting PPAR $\gamma$ -dependent differentiation in adipocytes. The activation of PPAR $\gamma$  provides a potential mechanism for insulin-sensitizing/antidiabetic effects of ARBs (16,17).

Angiotensin II is a very potent endogenous vasoconstrictor, while PPAR $\alpha$  activator attenuated the development of hypertension, corrected structural abnormalities, and improved endothelial dysfunction induced by angiotensin II (11). Furthermore, the effect of fenofibrate to reverse the elevated blood pressure response to angiotensin II infusion is accompanied by decreased oxidative stress and inflammation in the vascular wall (11). PPAR $\alpha$  expression is increased in blood vessels of spontaneously hypertensive rats (22), and fenofibrate lowers blood pressure in these rats (11,23). Fenofibrate also prevents cardiac fibrosis in mineralocorticoid-dependent hypertensive rats (24). C-reactive protein upregulates AT $_1$ R in vascular smooth muscle cells, and these effects are attenuated by losartan (25). The additive beneficial effects of combined therapy in the present study are consistent with these experimental studies. In our previous and current studies, fenofibrate did not change

plasma levels of nitrate and malondialdehyde (9). Although we did not measure prostaglandin F $_{2\alpha}$ , there is an excellent correlation between prostaglandin F $_{2\alpha}$  and MDA levels (26). Thus, fenofibrate may not have antioxidant effect in humans and the beneficial effects on endothelial function may be mediated by another mechanism.

With regard to the effects of fenofibrate on inflammation, we observed that combined therapy reduced C-reactive protein and soluble CD40L levels more than fenofibrate or candesartan alone.

Adiponectin is an adipose-derived factor that augments and mimics metabolic actions of insulin. Increasing adiponectin levels would be predicted to improve both insulin sensitivity and endothelial function by multiple mechanisms. Regulation of metabolic homeostasis and hemodynamic homeostasis may be coupled by vascular actions of insulin to stimulate production of NO (27). By contrast with effects of combination therapy on flow-mediated dilation, MDA, C-reactive protein, and CD40L, the beneficial effects of fenofibrate or candesartan therapy on adiponectin levels, insulin levels, and insulin sensitivity did not increase further with combination therapy. There may be additional mechanisms for the therapy to improve insulin sensitivity that are independent of endothelial function. For example, PPAR $\alpha$  activators improve insulin sensitivity and reduce adiposity in rodent models (28). Recently, Chinetti et al. (29) found that AdipoR2, an adiponectin receptor, was induced by both PPAR $\alpha$  and PPAR $\gamma$ . Moreover, we observed that fenofibrate therapy significantly increased plasma adiponectin levels and insulin sensitivity in primary hypertriglyceridemic patients (6). In cell culture studies, angiotensin II does not inhibit the expression of adiponectin. However, in our current study, candesartan significantly increased plasma levels of adiponectin. Thus, there may be additional mechanisms for candesartan to improve insulin sensitivity that are independent of endothelial function. For example, it is known that angiotensin II receptor cross-talk with insulin signaling pathways may cause insulin resistance (30). In addition, candesartan may have direct effects to augment insulin-stimulated glucose uptake, promote adipogenesis (31), and induce PPAR $\gamma$  activity that promotes differentiation of adipocytes (16,17). On the other hand, combined therapy may reduce insulin resistance by

multiple mechanisms such as lipoprotein changes and reduced oxidant stress that also contribute to NO bioavailability.

In the current study, we observed significant correlations between the degree of changes in adiponectin levels and non-HDL cholesterol, HDL cholesterol, and insulin levels following combined therapy. However, we did not see significant correlations between the degree of changes in adiponectin levels and C-reactive protein or CD40L levels. Each 2-month treatment increased adiponectin levels without a change in body weight or BMI. This raises the possibility that drug therapy is directly altering adiponectin levels independent of adiposity. Thus, it is possible that increased adiponectin levels are contributing to improvement in insulin sensitivity rather than simply reflecting a change in adiposity.

In summary, our study suggests that combination therapy with fenofibrate/candesartan has beneficial additive effects on endothelial function and inflammatory markers. This may be due to combined effects of the respective monotherapies to improve lipid profile, blood pressure, adiponectin levels, and insulin sensitivity. The additive beneficial effects of combined therapy are predicted to reduce cardiovascular events in hypertriglyceridemic hypertensive patients more than monotherapy with either drug alone.

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