Combination Pravastatin and Valsartan Treatment Has Additive Beneficial Effects to Simultaneously Improve Both Metabolic and Cardiovascular Phenotypes Beyond That of Monotherapy With Either Drug in Patients With Primary Hypercholesterolemia

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Statin and angiotensin II type 1 receptor blocker therapy improves endothelial dysfunction using distinct mechanisms. We evaluated simultaneous vascular and metabolic responses to pravastatin and valsartan therapy, alone or in combination, in hypercholesterolemic patients. Forty-eight hypercholesterolemic patients (23 had metabolic syndrome) were given pravastatin 40 mg and placebo, pravastatin 40 mg and valsartan 160 mg, or valsartan 160 mg and placebo daily during each 2-month treatment period in a randomized, single-blind, placebo-controlled, crossover trial with three treatment arms and two washout periods (each 2 months). Brachial artery flow-mediated dilation and C-reactive protein improved to a greater extent with combined therapy compared with either monotherapy. Importantly, we also observed simultaneous improvement in metabolic phenotypes, with all three treatments causing increased plasma adiponectin levels, reduced fasting insulin levels, and increased insulin sensitivity relative to baseline measurements. For the first time in a statin combination trial, pravastatin combined with valsartan therapy increased plasma adiponectin, lowered fasting insulin levels, and improved insulin sensitivity in an additive manner when compared with monotherapy alone. In contrast to other statins, hydrophilic pavastatin may be combined with other drugs to safely reach lipid target levels while simultaneously improving the metabolic and cardiovascular phenotype of patients at high risk. ***Diabetes*** **62:3547–3552, 2013**

Hypercholesterolemia and hypertension are major public health problems that are frequently treated with statins and angiotensin II type 1 receptor blockers, respectively. Although the mechanisms of action for these two classes of drugs differ, both classes have beneficial effects on the vasculature by reducing LDL cholesterol and blood pressure, respectively (1,2).

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Hypercholesterolemia and hypertension are frequently associated with insulin resistance and disorders of metabolic homeostasis such as obesity and type 2 diabetes mellitus. The endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance and the pathophysiology of diabetes and its vascular complications (3). However, it has recently been recognized that statin therapy, one of the mainstays of treatment for hypercholesterolemia that reduces coronary heart disease and atherosclerosis, may have adverse consequences for glucose homeostasis, such as increased risk for diabetes and insulin resistance (4). This is particularly problematic from a therapeutic standpoint, since the presence of diabetes and insulin resistance increases the risk for cardiovascular diseases including coronary heart disease (5) and cancer mortality (6). Indeed, simvastatin and atorvastatin worsened insulin sensitivity by decreasing adiponectin levels despite improvement in endothelial function (7,8). Therefore, we did not observe additive metabolic improvement with combination therapy in hypercholesterolemic patients. Since pravastatin may differ from other statins in that it is nonlipophilic and has beneficial effects on metabolic phenotypes (4,9,10), we reasoned that a combination trial of pravastatin plus valsartan may cause simultaneous additive benefit to both endothelial function and metabolic phenotypes that are greater than those observed with either pravastatin or valsartan therapy alone in hypercholesterolemic patients.

RESEARCH DESIGN AND METHODS

Study population and design. Fifty-one hypercholesterolemic patients (LDL cholesterol levels ≥130 mg/dL) participated in this study. We excluded patients with overt liver disease, chronic renal failure, uncontrolled diabetes (HbA_{1c} >9% or 75 mmol/mol), severe hypertension, or alcohol abuse. A research nurse counted pills at the end of treatment to monitor compliance. In order to minimize acute side effects to valsartan, study medication was titrated from 80 to 160 mg upwards over a 2-week period. Two patients were hypotensive, and the other one suffered from dry cough. Thus, data from a total of 48 patients were analyzed. Patients were randomly assigned to one of the three treatments: pravastatin 40 mg and placebo, pravastatin 40 mg and valsartan 160 mg, or valsartan 160 mg and placebo daily during 2 months. This study design was randomized, single-blind, placebo-controlled, with three treatment arms (each 2 months), and crossover with two washout periods (each 2 months). Allocation concealment was achieved by using envelopes with the collaboration of a statistician. Twenty-three patients among 48 had metabolic syndrome (11). 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 ~8:00 A.M. following overnight fasting before and at the end of each 2-month treatment period. Assays for lipids, glucose, and plasma adiponectin were

performed in duplicate by ELISA (R&D Systems, Minneapolis, MN), assays for high-sensitivity C-reactive protein (hsCRP) levels by latex agglutination [CRP-Latex(II); Denka-Seiken, Tokyo, Japan] and assays for plasma insulin levels by immunoradiometric assay (Insulin Riabead II; SRL, Inc, Tokyo, Japan) and assays for HbA_{1c} by high performance liquid chromatography assay (VARIANT II TURBO; Bio-Rad, Hercules, CA) as previously described (7–9,12–14). The interassay and intra-assay coefficients of variation were <6%. Quantitative Insulin-Sensitivity Check Index (QUICKI) was calculated (15,16). Imaging studies of the right brachial artery were performed using an ATL HDI 3000 ultrasound machine (ATL Philips, Bothell, WA) equipped with a 10-MHz linear-array transducer, based on a previously published technique (7–9,12–14). The intraobserver variability for repeated measurement of maximum diameter was 0.01 ± 0.06 mm. The intraobserver variability for repeated measurement of percent flow-mediated dilation (FMD) was 0.13 ± 1.33%.

Statistical analysis. Data are expressed as mean ± SEM or median (range 25–75%). After testing data for normality, we used the Student 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 Tables 1 and 2. The effects of the three therapies were analyzed by one-way repeated-measures ANOVA or Friedman repeated ANOVA on ranks. Post hoc comparisons, Pearson, or Spearman correlation coefficient analysis was used. We calculated that 40 subjects would provide 80% power for detecting an absolute increase of ≥1.7% in FMD between baseline and pravastatin, with $\alpha = 0.05$ based on our previous studies (9). 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

No significant differences among baseline values were noted in any of the parameters measured (Tables 1 and 2). There was no carryover effect from one treatment period to the next treatment period.

Effects of therapies on blood pressure and lipids. Valsartan alone or combined therapy significantly reduced systolic and diastolic blood pressure after 2 months' administration when compared with baseline. These reductions were significantly greater than those observed with pravastatin alone ($P < 0.05$ by ANOVA). However, there were no significant differences between valsartan alone and combined therapy for these parameters (Table 1). Pravastatin alone or combined therapy significantly lowered total cholesterol (both $P < 0.001$), triglycerides (both $P < 0.05$), LDL cholesterol (both $P < 0.001$), and apolipoprotein B levels (both $P < 0.001$) when compared with baseline. These reductions were significantly greater than those observed with valsartan alone ($P < 0.05$ by ANOVA). However, there were no significant differences between pravastatin alone and combined therapy for these parameters (Table 1).

Effects of therapies on vasomotor function and marker of inflammation. Pravastatin, combined therapy, or valsartan significantly improved the percent FMD relative to baseline measurements by 37 ± 2, 47 ± 3, and 32 ± 2%, respectively (all $P < 0.001$); however, combined therapy significantly improved this response more than pravastatin or valsartan alone ($P < 0.001$ by ANOVA; Fig. 1 and Table 1). Pravastatin, combined therapy, or valsartan lowered plasma hsCRP levels relative to baseline measurements from 0.85 to 0.60 ($P < 0.001$), 1.00 to 0.65 ($P < 0.001$), and 1.10 to 0.80 mg/L ($P = 0.158$), respectively; however, combined therapy significantly lowered plasma hsCRP levels more than pravastatin or valsartan alone ($P = 0.019$ by ANOVA on ranks; Fig. 1 and Table 1).

Effects of therapies on adiponectin and insulin resistance. Pravastatin, combined therapy, or valsartan significantly increased the plasma adiponectin levels relative to baseline measurements from 2.97 to 3.38 ($P = 0.007$), 2.81 to 3.73 ($P < 0.001$), and 2.96 to 3.45 μg/mL ($P = 0.002$), respectively. Of note, combined therapy significantly increased the plasma adiponectin levels more than pravastatin or valsartan alone in an additive fashion ($P = 0.003$ by ANOVA on ranks; Fig. 2*A* and Table 1). Pravastatin, combined therapy, or valsartan lowered plasma insulin levels relative to baseline measurements from 10.90 to 9.35 ($P = 0.012$), 10.16 to 7.78 ($P < 0.001$), and 9.62 to 8.67 μU/mL ($P = 0.103$), respectively; however, combined therapy significantly lowered plasma insulin levels more than pravastatin or valsartan alone ($P = 0.049$ by ANOVA on ranks; Fig. 2*B* and Table 1). Pravastatin, combined therapy, or valsartan significantly increased QUICKI relative to baseline measurements by 3 ± 1 ($P = 0.020$), 6 ± 1 ($P < 0.001$), and 2 ± 1% ($P = 0.053$), respectively. Of note, combined therapy significantly increased QUICKI more than pravastatin or valsartan alone ($P = 0.049$ by ANOVA; Fig. 2*C* and Table 1). The three therapies did not significantly change fasting glucose or HbA_{1c} levels relative to baseline measurements.

There were correlations between percent changes in adiponectin levels and percent changes in QUICKI ($r = 0.521$, $P < 0.001$ after pravastatin; $r = 0.437$, $P = 0.002$ after combined therapy; and $r = 0.297$, $P = 0.040$ after valsartan). There were inverse correlations between percent changes in adiponectin levels and percent changes in insulin levels ($r = -0.284$, $P = 0.050$ after pravastatin; $r = -0.373$, $P = 0.009$ after combined therapy; and $r = -0.258$, $P = 0.077$ after valsartan).

We investigated whether pravastatin- or valsartan-induced changes in the percent FMD, serological markers of inflammation, and insulin resistance were mediated by changes of lipoprotein or blood pressure levels. There were no significant correlations. Of note, following combined therapy, improvement in FMD correlated with changes in QUICKI ($r = 0.397$; $P = 0.005$) and insulin levels ($r = -0.292$; $P = 0.040$).

Effects of therapies in patients with metabolic syndrome. We analyzed 23 patients with metabolic syndrome, as reported in Table 2. Overall, compared with the effects of each therapy in 48 hypercholesterolemic patients, we observed similar results in 23 patients with metabolic syndrome. When compared with baseline, all three treatment arms improved endothelial dysfunction as assessed by FMD. Of note, FMD improved to a greater extent with combined therapy versus either monotherapy ($P = 0.008$ by ANOVA). Combined therapy reduced hsCRP levels compared with valsartan therapy ($P = 0.003$ by ANOVA). We also observed simultaneous improvement in metabolic phenotypes, with combined therapy causing increased plasma adiponectin levels, reduced fasting plasma insulin levels, and increased insulin sensitivity in an additive manner when compared with either monotherapy alone ($P = 0.009$, $P = 0.065$, and $P = 0.070$ by ANOVA on ranks, respectively). Following combined therapy, improvement in FMD correlated with changes in QUICKI ($r = 0.499$; $P = 0.015$) and insulin levels ($r = -0.480$; $P = 0.021$).

DISCUSSION

In our hypercholesterolemic cohort, pravastatin therapy alone significantly improved the lipid profile, while valsartan therapy alone significantly lowered blood pressure. Comparable beneficial effects on both lipids and blood pressure were observed with combination therapy. We reasoned that distinct biological actions of pravastatin and valsartan therapies on lipoproteins and the angiotensin system may improve endothelium-dependent vascular

TABLE 1
Effects of pravastatin, combination, and valsartan in 48 hypercholesterolemic patients

Variables	Pravastatin (P)		Pravastatin plus valsartan (C)		Valsartan (V)		ANOVA	*P* value		
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment		P/C	C/V	P/V
Age (years)	56 ± 1									
Sex (male/female)	29/19									
BMI (kg/m^2)	25.66 ± 0.43	25.51 ± 0.39	25.50 ± 0.46	25.37 ± 0.44	25.48 ± 0.47	25.38 ± 0.45	0.880			
Heart rate	78 ± 2	79 ± 2	80 ± 2	78 ± 2	78 ± 2	80 ± 2	0.377			
Systolic BP	138 ± 2	134 ± 2*	134 ± 2	123 ± 2‡	138 ± 2	127 ± 2‡	0.002	<0.05	NS	<0.05
Diastolic BP	85 ± 2	83 ± 2	82 ± 2	76 ± 1‡	83 ± 2	77 ± 1‡	0.033	<0.05	NS	<0.05
Lipids (mg/dL)										
Total cholesterol	233 ± 6	192 ± 5‡	234 ± 5	185 ± 4‡	229 ± 6	229 ± 5	<0.001	NS	<0.05	<0.05
Triglycerides	151 ± 9	132 ± 11*	164 ± 10	143 ± 11+	158 ± 12	165 ± 13	0.018	NS	<0.05	<0.05
LDL cholesterol	151 ± 5	109 ± 4‡	148 ± 4	105 ± 3‡	146 ± 5	144 ± 5	<0.001	NS	<0.05	<0.05
Apolipoprotein B	121 ± 3	93 ± 2‡	119 ± 3	91 ± 2‡	118 ± 3	116 ± 3	<0.001	NS	<0.05	<0.05
HDL cholesterol	53 ± 1	53 ± 2	51 ± 1	52 ± 1	52 ± 2	51 ± 1	0.759			
Apolipoprotein A1	146 ± 3	146 ± 3	147 ± 2	151 ± 3	145 ± 3	145 ± 2	0.440			
Vasomotor										
FMD dilation (%)	5.71 ± 0.25	7.67 ± 0.28‡	5.68 ± 0.23	8.24 ± 0.30‡	5.89 ± 0.24	7.65 ± 0.28‡	<0.001	<0.05	<0.05	NS
NTG dilation (%)	17.02 ± 0.51	17.02 ± 0.66	17.14 ± 0.52	16.57 ± 0.62	17.10 ± 0.54	17.23 ± 0.70	0.716			
Inflammation										
hsCRP (mg/L)	0.85 (0.50–1.60)	0.60 (0.30–1.25)‡	1.00 (0.63–1.80)	0.65 (0.40–0.98)‡	1.10 (0.50–1.78)	0.80 (0.60–1.50)	0.019	<0.05	<0.05	NS
Insulin resistance										
ADP (μg/mL)	2.97 (2.09–4.80)	3.38 (2.38–5.82)+	2.81 (1.96–5.03)	3.73 (2.42–5.73)‡	2.96 (1.92–5.45)	3.45 (2.15–6.14)+	0.003	<0.05	<0.05	NS
Insulin (μU/mL)	10.90 ± 0.80	9.35 ± 0.75*	10.16 ± 0.75	7.78 ± 0.77‡	9.62 ± 0.85	8.67 ± 0.70	0.049	<0.05	<0.05	NS
Glucose (mg/dL)	102 ± 1	102 ± 2	105 ± 2	103 ± 2	103 ± 2	101 ± 2	0.601			
QUICKI	0.340 ± 0.006	0.351 ± 0.006*	0.341 ± 0.005	0.363 ± 0.007‡	0.346 ± 0.005	0.354 ± 0.006*	0.049	<0.05	<0.05	NS
HbA_{1c} [% (mmol/mol)]	5.81 ± 0.05 (40 ± 0.5)	5.84 ± 0.06 (40 ± 0.7)	5.91 ± 0.07 (41 ± 0.8)	5.85 ± 0.06* (40 ± 0.7)	5.89 ± 0.07 (41 ± 0.8)	6.03 ± 0.14 (42 ± 1.5)	0.239			

Data are means ± SEM or median (25th percentile–75th percentile). There were no significant differences among baseline values. QUICKI = 1/(log [insulin] + log [glucose]) (15,16). ADP, adiponectin; BP, blood pressure; C/V, combination vs. valsartan; NTG, nitroglycerin; P/C, pravastatin vs. combination; P/V, pravastatin vs. combination. *$P < 0.05$, ‡$P < 0.001$, +$P < 0.01$ for comparison with each baseline value.

TABLE 2
Effects of pravastatin, combination, and valsartan in 23 hypercholesterolemic patients with metabolic syndrome

Variables	Pravastatin (P)		Pravastatin plus valsartan (C)		Valsartan (V)		ANOVA	*P* value		
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment		P/C	C/V	P/V
Age (years)	58 ± 2									
Sex (male/female)	12/11									
BMI (kg/m^2)	27.33 ± 0.56	27.04 ± 0.53	27.29 ± 0.58	27.12 ± 0.56	27.29 ± 0.58	27.05 ± 0.53	0.649			
Heart rate	81 ± 2	80 ± 2	78 ± 2	77 ± 2	79 ± 3	78 ± 2	0.963			
Systolic BP	139 ± 3	134 ± 3*	136 ± 4	123 ± 3‡	137 ± 3	127 ± 3‡	0.124			
Diastolic BP	87 ± 2	84 ± 2*	84 ± 2	77 ± 2‡	83 ± 3	77 ± 2+	0.528			
Lipids (mg/dL)										
Total cholesterol	243 ± 9	194 ± 7‡	240 ± 8	189 ± 6‡	236 ± 9	240 ± 8	<0.001	NS	<0.05	<0.05
Triglycerides	169 ± 14	160 ± 19	190 ± 16	165 ± 18	190 ± 20	197 ± 23	0.231			
LDL cholesterol	159 ± 8	110 ± 6‡	152 ± 7	108 ± 5‡	151 ± 9	151 ± 8	<0.001	NS	<0.05	<0.05
Apolipoprotein B	126 ± 5	97 ± 4‡	122 ± 4	96 ± 3‡	122 ± 4	125 ± 4	<0.001	NS	<0.05	<0.05
HDL cholesterol	51 ± 2	49 ± 3	49 ± 2	49 ± 2	49 ± 3	49 ± 2	0.589			
Apolipoprotein A1	144 ± 4	143 ± 4	145 ± 3	147 ± 4	144 ± 4	146 ± 4	0.606			
Vasomotor										
FMD dilation (%)	5.86 ± 0.37	7.70 ± 0.36‡	5.76 ± 0.30	8.18 ± 0.39‡	5.85 ± 0.33	7.69 ± 0.35‡	0.008	<0.05	<0.05	NS
NTG dilation (%)	17.47 ± 0.65	18.23 ± 0.88	17.76 ± 0.64	17.58 ± 0.86	17.74 ± 0.71	18.27 ± 1.01	0.502			
Inflammation										
hsCRP (mg/L)	1.00 (0.60–1.90)	0.60 (0.50–1.30)‡	1.10 (0.70–1.80)	0.70 (0.50–1.00)‡	1.20 (0.50–1.90)	1.10 (0.60–1.60)	0.003	NS	<0.05	<0.05
Insulin resistance										
ADP (μg/mL)	2.73 (1.81–6.38)	2.91 (2.25–6.29)	2.64 (1.78–5.44)	2.84 (2.37–6.76)‡	2.86 (1.81–5.70)	2.79 (1.87–6.18)	0.009	<0.05	<0.05	NS
Insulin (μU/mL)	11.4 (6.3–17.5)	9.6 (8.3–16.0)	10.7 (6.3–16.2)	7.3 (4.6–10.6)+	9.8 (7.4–16.5)	9.8 (5.9–13.4)*	0.065			
Glucose (mg/dL)	106 ± 2	107 ± 2	106 ± 2	104 ± 3	108 ± 3	106 ± 3	0.751			
QUICKI	0.33 (0.31–0.35)	0.33 (0.31–0.34)	0.33 (0.31–0.35)	0.35 (0.33–0.37)‡	0.33 (0.31–0.35)	0.34 (0.32–0.36)+	0.070			
HbA_{1c} [% (mmol/mol)]	5.86 ± 0.09 (41 ± 1.0)	5.97 ± 0.11 (42 ± 1.2)	5.94 ± 0.11 (41 ± 1.2)	5.90 ± 0.09 (41 ± 1.0)	5.97 ± 0.12 (42 ± 1.3)	6.20 ± 0.28 (44 ± 3.1)	0.552			

Data are means ± SEM or median (25th percentile–75th percentile). There were no significant differences among each baseline values. QUICKI = 1/[log (insulin) + log (glucose)] (15,16). ADP, adiponectin; BP, blood pressure; C/V, combination vs. valsartan; NTG, nitroglycerin; P/C, pravastatin vs. combination; P/V, pravastatin vs. combination. *$P < 0.05$, ‡$P < 0.001$, +$P < 0.01$ for comparison with each baseline value.

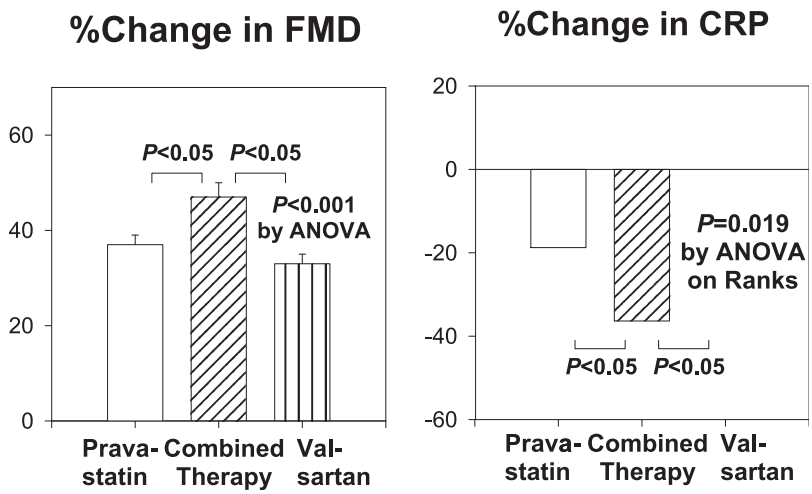

FIG. 1. Percent change in flow-mediated dilation (*left*) and percent change in hsCRP levels (*right*) from respective pretreatment values after treatment with pravastatin alone, combined therapy, and valsartan alone (the median was zero for valsartan). Mean with SEM (*left*) or median (*right*) values are provided.

function by different mechanisms. Indeed, while monotherapy with pravastatin or valsartan improved endothelial function and inflammatory markers (assessed by FMD and hsCRP levels), combined therapy had additional significant beneficial effects on these parameters over those seen with monotherapy for either drug.

In all of our previous intervention studies combining simvastatin or atorvastatin with losartan, ramipril or fenofibrate, we observed beneficial additive effects on endothelial function but not on metabolic parameters (12–14). We reasoned that these results may be explained by direct adverse metabolic consequences of these statins that masked the beneficial metabolic effects expected from improved endothelial function (2–4). Indeed, in head-to-head comparisons of simvastatin or rosuvastatin with pravastatin at equal lipid-lowering doses, we observed effects of simvastatin and rosuvastatin to worsen insulin resistance and related metabolic parameters, while pravastatin had beneficial metabolic actions to lower fasting insulin levels, increase adiponectin levels, and improve insulin sensitivity (9,17). Moreover, therapy with high-dose atorvastatin causes glucose intolerance (8). Our small clinical intervention studies are consistent with larger multicenter outcome studies that suggest most statins, except for pravastatin, cause an increase in the incidence of new onset diabetes (10,18,19). This has recently led to the Food and Drug Administration requiring a label warning for statins regarding the increased risk of diabetes. Thus, we reasoned that combination therapy of pravastatin with valsartan would result in simultaneous additive beneficial effects on both cardiovascular and metabolic parameters that was lacking in our previous statin combination intervention studies.

Recent large-scale clinical studies and meta-analyses have demonstrated that some statins, particularly at high dose, increase the rate of new-onset diabetes (10,20–22). Pravastatin would not suffer from this potential downside. Pravastatin retarded the progression of glucose intolerance

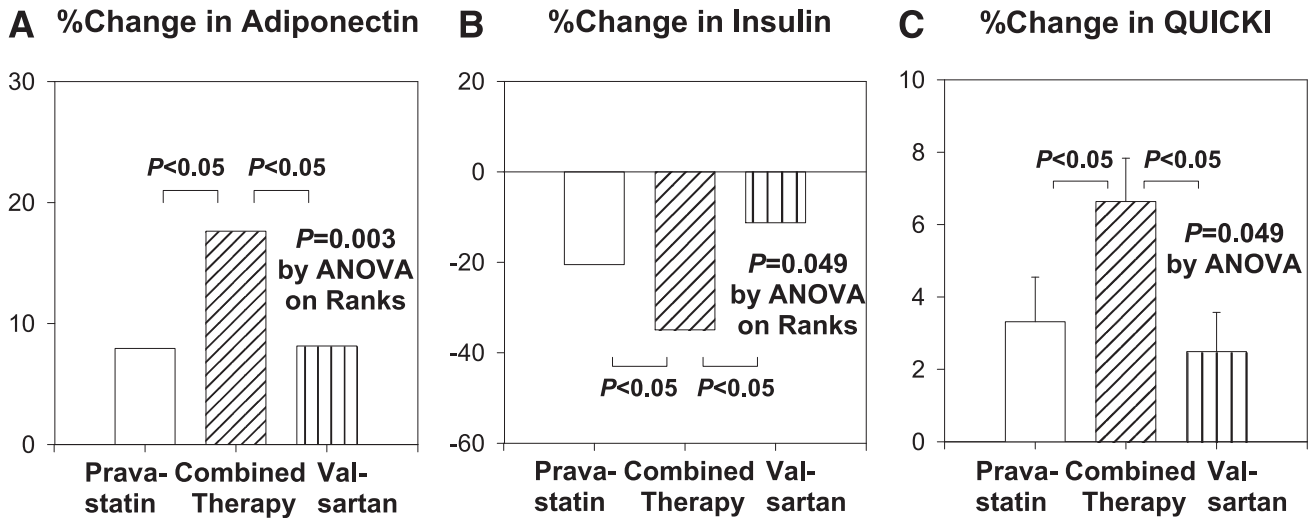

FIG. 2. Percent change in adiponectin levels (*A*), percent change in insulin levels (*B*), and percent change in QUICKI (*C*) from respective pretreatment values after treatment with pravastatin alone, combined therapy, and valsartan alone. Median values (*A* and *B*) or mean with SEM (*C*) are provided.

in diabetes model (23). Pravastatin enhances adiponectin secretion from 3T3-L1 adipocytes and causes an increase in adiponectin mRNA and plasma adiponectin levels with enhanced insulin sensitivity (24). Indeed, pravastatin significantly increases plasma adiponectin levels and insulin sensitivity in hypercholesterolemic patients (9,17).

In the current study, we observed correlations between percent changes in adiponectin levels and percent changes in QUICKI and inverse correlations between percent changes in adiponectin levels and percent changes in insulin levels following each therapy. We also observed significant correlations between improvement in FMD and changes in QUICKI and insulin levels following combined therapy. We observed similar results in a subgroup of 23 patients with the metabolic syndrome. Thus, our study may have the same implication for the treatment of patients with the metabolic syndrome.

One caveat in the use of pravastatin for lipid treatment is that it has weaker lipid-lowering effects than other lipophilic statins. Thus, other statins tend to save lives even in diabetic populations. However, one wonders whether even more lives might be saved if lipid targets could be reached without causing diabetes or even diminishing diabetes (2,4,25).

In summary, our study demonstrates for the first time that a combination trial with a statin (pravastatin) and valsartan simultaneously improved endothelial function and insulin sensitivity to a greater extent than monotherapy in hypercholesterolemic patients. This may be due to combined effects of the respective monotherapy to improve lipid profile, blood pressure, endothelial function, adiponectin levels, and insulin sensitivity.

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K.K.K., S.L., and M.J.Q. designed, researched data, wrote the manuscript, and reviewed, edited, and approved the final version of the manuscript. H.C. researched data and reviewed and approved the final version of the manuscript. Y.L. undertook statistical analysis and interpretation of the results and reviewed and approved the final version of the manuscript. S.H.H., K.L., P.C.O., I.S., and E.K.S. reviewed, edited, and approved the final version of the manuscript. K.K.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. Cardiovasc Res 2000;47:648–657
2. Koh KK, Han SH, Oh PC, Shin EK, Quon MJ. Combination therapy for treatment or prevention of atherosclerosis: focus on the lipid-RAAS interaction. Atherosclerosis 2010;209:307–313
3. Han SH, Quon MJ, Koh KK. Reciprocal relationships between abnormal metabolic parameters and endothelial dysfunction. Curr Opin Lipidol 2007; 18:58–65
4. Koh KK, Sakuma I, Quon MJ. Differential metabolic effects of distinct statins. Atherosclerosis 2011;215:1–8
5. Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension 2004;43:963–969
6. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care 2012;35:1835–1844
7. Koh KK, Quon MJ, Han SH, et al. Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients. Diabetes Care 2008;31:776–782
8. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. J Am Coll Cardiol 2010;55:1209–1216
9. Koh KK, Quon MJ, Han SH, et al. Differential metabolic effects of pravastatin and simvastatin in hypercholesterolemic patients. Atherosclerosis 2009;204: 483–490
10. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ 2013;346:f2610
11. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–3421
12. Koh KK, Quon MJ, Han SH, et al. Additive beneficial effects of losartan combined with simvastatin in the treatment of hypercholesterolemic, hypertensive patients. Circulation 2004;110:3687–3692
13. Koh KK, Son JW, Ahn JY, et al. Simvastatin combined with ramipril treatment in hypercholesterolemic patients. Hypertension 2004;44:180–185
14. Koh KK, Quon MJ, Han SH, et al. Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. J Am Coll Cardiol 2005;45:1649–1653
15. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402–2410
16. Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes 2005;54:1914–1925
17. Koh KK, Quon MJ, Sakuma I, et al. Differential metabolic effects of rosuvastatin and pravastatin in hypercholesterolemic patients. Int J Cardiol 2013;166:509–515
18. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001;103:357–362
19. Coleman CI, Reinhart K, Kluger J, White CM. The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2008;24:1359–1362
20. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305:2556–2564
21. Waters DD, Ho JE, DeMicco DA, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. J Am Coll Cardiol 2011;57:1535–1545
22. Waters DD, Ho JE, Boekholdt SM, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. J Am Coll Cardiol 2013;61:148–152
23. Yu Y, Ohmori K, Chen Y, et al. Effects of pravastatin on progression of glucose intolerance and cardiovascular remodeling in a type II diabetes model. J Am Coll Cardiol 2004;44:904–913
24. Takagi T, Matsuda M, Abe M, et al. Effect of pravastatin on the development of diabetes and adiponectin production. Atherosclerosis 2008; 196:114–121
25. Lim S, Sakuma I, Quon MJ, Koh KK. Potentially important considerations in choosing specific statin treatments to reduce overall morbidity and mortality. Int J Cardiol 15 November 2012 [Epub ahead of print]